BJA British Journal of Anaesthesia

Volume 123, Number 1, July 2019

British Journal of Anaesthesia, 123 (1): e11–e13 (2019)
doi: 10.1016/j.bja.2019.03.010
Advance Access Publication Date: 11 April 2019

EDITORIALS

Optimising diagnostics in perioperative allergy

Morten S. Opstrup[1,2,*] and Lene Heise Garvey[1,3]

[1]Danish Anaesthesia Allergy Centre, Allergy Clinic, Department of Dermatology and Allergy, Copenhagen University Hospital, Gentofte, Denmark, [2]Department of Dermatology, Zealand University Hospital, Roskilde, Denmark and [3]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

*Corresponding author. E-mail: morten.schjoerring.opstrup@regionh.dk

Perioperative allergic reactions are rare, but often present with a sudden and unexpected onset of severe symptoms, requiring rapid recognition and treatment. As anaphylaxis is a clinical diagnosis and symptoms mimic other perioperative events, making the diagnosis can be challenging to anaesthesiologists. There is currently no diagnostic test that can distinguish between anaphylaxis and other relevant differential diagnoses during or immediately after the reaction. However, results of blood samples drawn in close proximity to the reaction are useful during subsequent allergy testing, which takes place a few weeks or months later.

In this issue of the *British Journal of Anaesthesia*, Takazawa and colleagues[1] review the principles, benefits, and limitations of available *in vitro* tests—both for the acute phase and for subsequent diagnostic work up. In the acute phase, both basophils and mast cells degranulate, releasing many different mediators, of which so far only histamine and tryptase have been suggested to be relevant for the diagnosis of anaphylaxis. The plasma concentration of histamine peaks only minutes after the onset of the allergic reaction, and rapidly declines to normal values. As handling of the sample is complicated, this test is not used routinely, and only recommended for use by a few specialised centres.[2] In contrast, the serum concentration of tryptase peaks 1–2 h after the onset of the allergic reaction and remains elevated for up to several hours.[3,4] This means that blood sampling can be done after the patient has been stabilised, which is feasible in a clinical setting. An elevated concentration of tryptase at the time of reaction is a sensitive marker of anaphylaxis, when compared with a baseline concentration measured later in the same patient. Consequently, measuring serum tryptase 1 h after a suspected allergic reaction is recommended in guidelines for the investigation of perioperative allergic reactions.[2,4,5]

After the patient has been stabilised and a blood sample for tryptase has been sent for analysis, the next question arises: what caused the reaction? It is tempting to guess the culprit drug simply by looking at the time of administration of each drug in relation to symptom onset. However, this approach is not recommended in a complex perioperative setting. Indeed, by using this approach, previous studies have shown that the correct allergen is missed in a substantial number of patients.[6,7] Consequently, systematic allergy investigations are needed to identify and avoid additional exposure to the culprit allergen.

Allergists generally agree that provocation testing is the gold standard test in drug allergy testing. However, in the setting of suspected perioperative allergic reactions, it is not that simple. This has been addressed in detail in another article this issue.[8,9] First, provocation tests do not have a sensitivity and specificity of 100%, thus a negative test cannot always rule out allergy.[10] Second, full dose provocation testing is not possible for all perioperative drugs such as neuromuscular blocking agents (NMBAs), anaesthetic agents, or opioids, because of their pharmacological and adverse effects, and there are no standardised provocation tests for substances such as latex, chlorhexidine, or ethylene oxide. Third, provocation testing is very time consuming and demanding on resources in perioperative allergy investigation, where testing

DOIs of original article: 10.1016/j.bja.2019.03.018, 10.1016/j.bja.2019.03.038, 10.1016/j.bja.2019.01.002, 10.1016/j.bja.2019.04.002.

comprises many drugs and substances. Fourth, drug provocation testing is a high-risk procedure that can result in anaphylaxis, and thus requires relevant emergency back-up. For all these reasons, drug provocation testing is rarely used in testing for perioperative allergy. There is a continuous need for optimisation of other diagnostic tests such as skin tests and *in vitro* tests.

Skin testing (skin prick testing and intradermal testing) are the recommended first line tests in perioperative allergy. Skin prick testing is easy to perform but is considered less sensitive than intradermal testing, which in contrast carries a higher risk of inducing an allergic reaction during testing. Interpretation of the intradermal test is not as simple as for the skin prick test; currently there is no international consensus regarding the criteria for a positive test.[11] In addition, there is a risk of both false positive (most commonly attributable to the drug causing irritation in the skin)[12] and false negative results (e.g. if the test concentration is too low) affecting specificity and sensitivity of the test. As there are limitations to both provocation testing and skin testing, there is room for *in vitro* testing in the diagnostic work up. The most obvious benefit of *in vitro* tests is that they can be performed without putting the patient at risk.

Takazawa and colleagues[1] address the potential and limitations of quantification of specific immunoglobulin E (IgE) in plasma and the basophil activation test (BAT). Quantification of specific IgE is only commercially available for a small number of drugs and substances used in the perioperative setting. For some drugs (e.g. chlorhexidine) both sensitivity and specificity are high,[13] but for most other drugs sensitivities and specificities are considered relatively low. Takazawa and colleagues[1] propose that in patients with a suspected perioperative allergic reaction, where an early surgical re-intervention is needed, concentrations of specific IgE to suspected allergens can be measured to aid diagnosis. As concentrations of specific IgE increase in the first few weeks to months after the allergic reaction, testing should be repeated after 1–2 months if negative at the time of reaction.[14] An important limitation of quantification of specific IgE is that plasma concentrations decline over time for some drugs (e.g. penicillins, chlorhexidine, and ethylene oxide) if exposure is avoided, making it difficult to detect if testing is performed years after the allergic reaction.[14,15] However, for penicillins and chlorhexidine, re-exposure in patients previously positive but now negative for specific IgE can result in an allergic reaction.[14,16] Therefore a negative specific IgE result can never be used to rule out allergy.

BAT takes advantage of the different surface markers on the basophil granulocyte in the resting and activated states. When an allergic reaction takes place, basophils are activated and begin to upregulate and express markers on the surface membrane, including CD63 and CD203c. In the laboratory, using flow cytometric analysis, this upregulation and expression of surface markers can be detected and quantified. Overall, BATs have high specificity (>90%) and relatively high sensitivity (50–90%) when performed in specialist centres with great experience in BAT, but values vary between studies and allergens.[17] A major limitation of BAT is that it is not commercially available and standardisation is currently lacking. Moreover, 6–17% of the population are non-responders, meaning that basophil granulocytes remain unresponsive to stimuli under standard BAT conditions, potentially leading to false negative results.[18] Finally, it is a limitation that testing has to be done within 3 h of blood sampling.[19] Overall, BAT has great potential, but primarily in a few highly specialised centres with a large catchment area.

Insufficient testing, interpretation of tests, or both can lead to a culprit being overlooked. This has very serious potential consequences if the patient is re-exposed to the overlooked allergen. For this reason, the highest possible sensitivity should be aimed for in perioperative allergy investigation which can only be achieved by combining different tests for the same drug. Combining several different test results leads to a decrease in specificity, because of increased risk of false positive testing, which in turn can lead to unnecessary restrictions in the choice of drugs for future anaesthesia.

If a provocation model is available, the result of this test is considered decisive. However, for drugs with no available provocation model, the decision on which tests to perform can be difficult. Takazawa and colleagues[1] propose a diagnostic algorithm for investigation of suspected NMBA allergy in the current review. Based on this algorithm, a relevant clinical history in combination with one positive test (skin prick test, intradermal test, or BAT) leads to an allergy diagnosis. This is a simple algorithm and can be useful in a clinical setting; however, it is worth noting that this algorithm has some limitations. Especially for NMBAs, there is a high risk of false-positive skin test results[20,21] that can lead to the wrong 'culprit' drug being identified. BAT does not have a specificity of 100% either, and by using this algorithm, relying on a positive test result in a single test modality, there is a risk of incorrectly diagnosing patients with allergy to NMBAs. In addition, after identifying an NMBA as the allergen, there is a risk that allergists will stop looking for other allergens, which can result in overlooking the real culprit drug.

It has previously been suggested that the allergy diagnosis for drugs in the perioperative setting should be based on a relevant clinical history in combination with a minimum of two positive tests (skin prick test, intradermal test, specific IgE, BAT).[22] In the Danish Anaesthesia Allergy Center, the national reference centre for perioperative allergy investigation in Denmark, this approach is used for all drugs and substances in the perioperative setting.[11] With this approach, the risk of incorrectly diagnosing patients with an allergy is reduced. In a few cases where clinical suspicion is high, the diagnosis can be made on the basis of a single positive test result, but in the majority of cases, two or more positive tests are identified. Currently, there is no evidence that one of the two proposed algorithms is better than the other, but we encourage future research to optimise and standardise test methods to help establish the best possible diagnostic pathway for drugs investigated in the perioperative setting.

Authors' contributions

First draft: MSO.
Equal contribution to all subsequent revisions: both authors.

Declarations of interest

LHG is a consultant and adjudication committee member for Merck, NJ, USA and Novo Nordisk A/S, Denmark. MSO has no conflicts of interest.

References

1. Takazawa T, Sabato V, Ebo D. In vitro diagnostic tests for perioperative hypersensitivity: potential, limitations and perspectives. *Br J Anaesth* 2019: e117–25

2. Mertes PM, Malinovsky JM, Jouffroy L, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2011; **21**: 442–53
3. Krishna MT, York M, Chin T, et al. Multi-centre retrospective analysis of anaphylaxis during general anaesthesia in the United Kingdom: aetiology and diagnostic performance of acute serum tryptase. *Clin Exp Immunol* 2014; **178**: 399–404
4. Kroigaard M, Garvey LH, Gillberg L, et al. Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Anaesthesiol Scand* 2007; **51**: 655–70
5. Garvey LH, Dewachter P, Hepner DL, et al. Management of suspected immediate perioperative allergic reactions – an international overview and consensus recommendations. *Br J Anaesth* 2019; **123**: 3–9
6. Kroigaard M, Garvey LH, Menne T, Husum B. Allergic reactions in anaesthesia: are suspected causes confirmed on subsequent testing? *Br J Anaesth* 2005; **95**: 468–71
7. Christiansen IS, Krøigaard M, Mosbech H, Skov PS, Poulsen LK, Garvey LH. Clinical and diagnostic features of perioperative hypersensitivity to cefuroxime. *Clin Exp Allergy* 2015; **45**: 807–14
8. Garvey LH, Ebo DG, Krøigaard M, et al. The challenge of drug provocation testing in the investigation of suspected immediate perioperative allergic reactions. *Br J Anaesth* 2019; **123**: e126–34
9. van Cuilenborg VR, Hermanides J, Bos EME, Hollmann MW, Kooij FO, Terreehorst I. Awake intravenous provocation with small doses of neuromuscular blocking agent in patients with suspected allergy: experiences from the Dutch Perioperative Allergy Centre (DPAC). *Br J Anaesth* 2019; **123**: e153–5
10. Demoly P, Romano A, Botelho C, et al. Determining the negative predictive value of provocation tests with beta-lactams. *Allergy* 2010; **65**: 327–32
11. Opstrup MS, Malling H-J, Krøigaard M, et al. Standardized testing with chlorhexidine in perioperative allergy–a large single-centre evaluation. *Allergy* 2014; **69**: 1390–6
12. Garvey LH, Krøigaard M, Poulsen LK, et al. IgE-mediated allergy to chlorhexidine. *J Allergy Clin Immunol* 2007; **120**: 409–15
13. Anderson J, Rose M, Green S, Fernando SL. The utility of specific IgE testing to chlorhexidine in the investigation of perioperative adverse reactions. *Ann Allergy Asthma Immunol* 2015; **114**. 425–426.e1
14. Opstrup MS, Poulsen LK, Malling HJ, Jensen BM, Garvey LH. Dynamics of plasma levels of specific IgE in chlorhexidine allergic patients with and without accidental re-exposure. *Clin Exp Allergy* 2016; **46**: 1090–8
15. Bommer J, Ritz E. Ethylene oxide (ETO) as a major cause of anaphylactoid reactions in dialysis (a review). *Artif Organs* 1987; **11**: 111–7
16. Hjortlund J, Mortz CG, Stage TB, Skov PS, Dahl R, Bindslev-Jensen C. Positive serum specific IgE has a short half-life in patients with penicillin allergy and reversal does not always indicate tolerance. *Clin Transl Allergy* 2014; **4**: 34
17. Ebo DG, Faber M, Elst J, et al. In vitro diagnosis of immediate drug hypersensitivity during anesthesia: a review of the literature. *J Allergy Clin Immunol Pract* 2018; **6**: 1176–84
18. Hoffmann HJ, Santos AF, Mayorga C, et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. *Allergy* 2015; **70**: 1393–405
19. McGowan E. Update on the performance and application of basophil activation tests. *Curr Allergy Asthma Rep* 2013; **13**: 101–9
20. Berg CM, Heier T, Wilhelmsen V. Rocuronium and cisatracurium-positive skin tests in non-allergic volunteers: determination of drug concentration thresholds using a dilution titration technique. *Acta Anaesthesiol Scand* 2003; **47**: 576–82
21. Claudius C, Garvey LH, Viby-Mogensen J. The undesirable effects of neuromuscular blocking drugs. *Anaesthesia* 2009; **64**(Suppl. 1): 10–21
22. Leysen J, Bridts CH, De Clerck LS, et al. Allergy to rocuronium: from clinical suspicion to correct diagnosis. *Allergy* 2011; **66**: 1014–9

British Journal of Anaesthesia, 123 (1): e13–e15 (2019)
doi: 10.1016/j.bja.2019.05.001
Advance Access Publication Date: 21 May 2019

Suspected perioperative allergic reactions: nomenclature and terminology

Vito Sabato[1,*], Peter Platt[2], Tomaz Garcez[3] and Peter Cooke[4]

[1]Department of Immunology, Allergology and Rheumatology, University Antwerp, Antwerp University Hospital, Antwerp, Belgium, [2]Anaesthesiology, Sir Charles Gairdner Hospital, Anaesthetic Allergy Referral Centre of Western Australia, Perth, Western Australia, Australia, [3]Manchester University NHS Foundation Trust, Manchester, UK and [4]Department of Anaesthesia and Perioperative Medicine, Auckland City Hospital, Auckland, New Zealand

*Corresponding author. E-mail: vito.sabato@uantwerpen.be

2. Mertes PM, Malinovsky JM, Jouffroy L, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2011; **21**: 442–53
3. Krishna MT, York M, Chin T, et al. Multi-centre retrospective analysis of anaphylaxis during general anaesthesia in the United Kingdom: aetiology and diagnostic performance of acute serum tryptase. *Clin Exp Immunol* 2014; **178**: 399–404
4. Kroigaard M, Garvey LH, Gillberg L, et al. Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Anaesthesiol Scand* 2007; **51**: 655–70
5. Garvey LH, Dewachter P, Hepner DL, et al. Management of suspected immediate perioperative allergic reactions – an international overview and consensus recommendations. *Br J Anaesth* 2019; **123**: 3–9
6. Kroigaard M, Garvey LH, Menne T, Husum B. Allergic reactions in anaesthesia: are suspected causes confirmed on subsequent testing? *Br J Anaesth* 2005; **95**: 468–71
7. Christiansen IS, Krøigaard M, Mosbech H, Skov PS, Poulsen LK, Garvey LH. Clinical and diagnostic features of perioperative hypersensitivity to cefuroxime. *Clin Exp Allergy* 2015; **45**: 807–14
8. Garvey LH, Ebo DG, Krøigaard M, et al. The challenge of drug provocation testing in the investigation of suspected immediate perioperative allergic reactions. *Br J Anaesth* 2019; **123**: e126–34
9. van Cuilenborg VR, Hermanides J, Bos EME, Hollmann MW, Kooij FO, Terreehorst I. Awake intravenous provocation with small doses of neuromuscular blocking agent in patients with suspected allergy: experiences from the Dutch Perioperative Allergy Centre (DPAC). *Br J Anaesth* 2019; **123**: e153–5
10. Demoly P, Romano A, Botelho C, et al. Determining the negative predictive value of provocation tests with beta-lactams. *Allergy* 2010; **65**: 327–32
11. Opstrup MS, Malling H-J, Krøigaard M, et al. Standardized testing with chlorhexidine in perioperative allergy–a large single-centre evaluation. *Allergy* 2014; **69**: 1390–6
12. Garvey LH, Krøigaard M, Poulsen LK, et al. IgE-mediated allergy to chlorhexidine. *J Allergy Clin Immunol* 2007; **120**: 409–15
13. Anderson J, Rose M, Green S, Fernando SL. The utility of specific IgE testing to chlorhexidine in the investigation of perioperative adverse reactions. *Ann Allergy Asthma Immunol* 2015; **114**. 425–426.e1
14. Opstrup MS, Poulsen LK, Malling HJ, Jensen BM, Garvey LH. Dynamics of plasma levels of specific IgE in chlorhexidine allergic patients with and without accidental re-exposure. *Clin Exp Allergy* 2016; **46**: 1090–8
15. Bommer J, Ritz E. Ethylene oxide (ETO) as a major cause of anaphylactoid reactions in dialysis (a review). *Artif Organs* 1987; **11**: 111–7
16. Hjortlund J, Mortz CG, Stage TB, Skov PS, Dahl R, Bindslev-Jensen C. Positive serum specific IgE has a short half-life in patients with penicillin allergy and reversal does not always indicate tolerance. *Clin Transl Allergy* 2014; **4**: 34
17. Ebo DG, Faber M, Elst J, et al. In vitro diagnosis of immediate drug hypersensitivity during anesthesia: a review of the literature. *J Allergy Clin Immunol Pract* 2018; **6**: 1176–84
18. Hoffmann HJ, Santos AF, Mayorga C, et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. *Allergy* 2015; **70**: 1393–405
19. McGowan E. Update on the performance and application of basophil activation tests. *Curr Allergy Asthma Rep* 2013; **13**: 101–9
20. Berg CM, Heier T, Wilhelmsen V. Rocuronium and cisatracurium-positive skin tests in non-allergic volunteers: determination of drug concentration thresholds using a dilution titration technique. *Acta Anaesthesiol Scand* 2003; **47**: 576–82
21. Claudius C, Garvey LH, Viby-Mogensen J. The undesirable effects of neuromuscular blocking drugs. *Anaesthesia* 2009; **64**(Suppl. 1): 10–21
22. Leysen J, Bridts CH, De Clerck LS, et al. Allergy to rocuronium: from clinical suspicion to correct diagnosis. *Allergy* 2011; **66**: 1014–9

British Journal of Anaesthesia, 123 (1): e13–e15 (2019)
doi: 10.1016/j.bja.2019.05.001
Advance Access Publication Date: 21 May 2019

Suspected perioperative allergic reactions: nomenclature and terminology

Vito Sabato[1,*], Peter Platt[2], Tomaz Garcez[3] and Peter Cooke[4]

[1]Department of Immunology, Allergology and Rheumatology, University Antwerp, Antwerp University Hospital, Antwerp, Belgium, [2]Anaesthesiology, Sir Charles Gairdner Hospital, Anaesthetic Allergy Referral Centre of Western Australia, Perth, Western Australia, Australia, [3]Manchester University NHS Foundation Trust, Manchester, UK and [4]Department of Anaesthesia and Perioperative Medicine, Auckland City Hospital, Auckland, New Zealand

*Corresponding author. E-mail: vito.sabato@uantwerpen.be

Standardising nomenclature facilitates diagnostic and therapeutic algorithms, improves comparisons of data in scientific research and reduces misunderstanding. Here, we propose a nomenclature for suspected perioperative allergic reactions.

Importance of harmonised nomenclature

Nomenclature in medicine changes over time and is based on understandings of scientific reality. The acceptance of harmonised consensus nomenclature facilitates the usefulness of diagnostic and therapeutic algorithms, promotes the ability to compare data in scientific research, and reduces misunderstanding. Although uniformity has been recommended by allergy-related scientific societies,[1,2] variation in the usage of key terminology remains. For example, the words hypersensitivity, allergy, and anaphylaxis are frequently used interchangeably without uniformity in their meaning, as are allergy-like, pseudoallergy, and anaphylactoid.

Adverse drug reactions after administration of a compound for diagnostic, prophylactic, or therapeutic purposes can be classified as type A (dose-dependent, predictable, non-immune mediated) and type B (dose-independent, unpredictable, possibly immune-mediated), but some drug reactions may have features that overlap these categories.

The term hypersensitivity encompasses reproducible symptoms or signs resulting from effects beyond the predicted pharmacological targets (intended therapeutic or side-effects) of a compound and implies involvement of immune system/cells or inflammatory mechanisms. Non-allergic hypersensitivity implies involvement of immune cells and release of mediators by direct mechanisms but does not include the adaptive (specific) immune system response. Allergic hypersensitivity implies specific involvement of the adaptive immune system and is further categorised according to the Gell and Coombs[3] classification. Pichler[4] has subsequently substratified type IV (T-cell mediated) reactions. From a clinical point of view hypersensitivity reactions are also categorised as immediate or non-immediate. Immediate reactions occur within 2 h (usually within minutes), and the clinical presentation varies from single organ system features (e.g. urticaria, bronchospasm) to anaphylaxis.

Anaphylaxis is a potentially life-threatening clinical condition resulting from either specific (allergic) or non-specific (non-allergic) activation of mast cells/basophils, inflammatory pathways, or both. It is characterised by the rapid onset of a number of signs and symptoms after exposure to a trigger (Table 1). The National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network[5] consensus meeting defined three clinical scenarios that make the classic presentation of anaphylaxis likely, but these are not necessarily useful in the perioperative context.[6,7]

Non-immediate reactions occur more than 2 h after the exposure (often 48–72 h later) and include maculopapular exanthema, serious cutaneous adverse reactions, drug rash (or reaction) with eosinophilia and systemic symptoms (DRESS), and severe exanthems such as Stevens–Johnson syndrome and toxic epidermal necrolysis. Although some overlap exists, the effector cells involved in immediate reactions are mast cells and basophils, whereas the effector cells involved in non-immediate reactions are T cells.

A sequence of events does not infer causality

When reporting and evaluating adverse events after exposure to a medication, one has to consider that causality cannot necessarily be inferred from a sequence of events. For example, urticaria occurring during a course of penicillin does not mean that penicillin is the cause. This concept is particularly true in the perioperative context where symptoms and signs could be explained by pharmacological or pathophysiological responses. For example, severe hypotension could be either the consequence of an immediate hypersensitivity reaction or surgical complication (i.e. bleeding); and bronchospasm could be either the consequence of an immediate hypersensitivity reaction or a consequence of tracheal intubation in a patient with hyper-reactive airways. Therefore, detailed documentation of signs and symptoms together with time between exposure to the medication and onset of the symptoms is of utmost importance. As clinical presentations of different underlying mechanisms of immediate drug hypersensitivity reactions are indistinguishable, it is not appropriate to assume a mechanism until an allergological work-up has been completed.

'Suspected perioperative allergic reactions' as a pragmatic clinical descriptor

We concur with Cook and colleagues[8] that in the current context it is appropriate to define the perioperative period as the time when the patient is under the care of an anaesthetist, rather than from the moment of contemplation of surgery until full recovery.[9] During the perioperative period, when clinical features compatible with immediate hypersensitivity occur, for example hypotension, the best descriptor may be 'suspected perioperative allergic reaction' (Fig. 1).[10] The clinical features could be related to (1) the pharmacological effect of the medication or to surgical factors; (2) specific activation

Table 1 Definitions of key terms.

Anaphylaxis	Severe, life-threatening generalised or systemic hypersensitivity reaction which is characterised by being rapid in onset with life-threatening airway, breathing or circulatory problems, usually associated with skin and mucosal changes.
Hypersensitivity reaction	Reproducible clinical features resulting from effects beyond the pharmacological activity of a medication. It implies activation of immune cells, inflammatory pathways, or both.
Allergic hypersensitivity	Clinical features resulting from specific activation of immune cells.
Non-allergic hypersensitivity	Clinical features resulting from non-specific activation of immune cells, inflammatory pathways, or both.

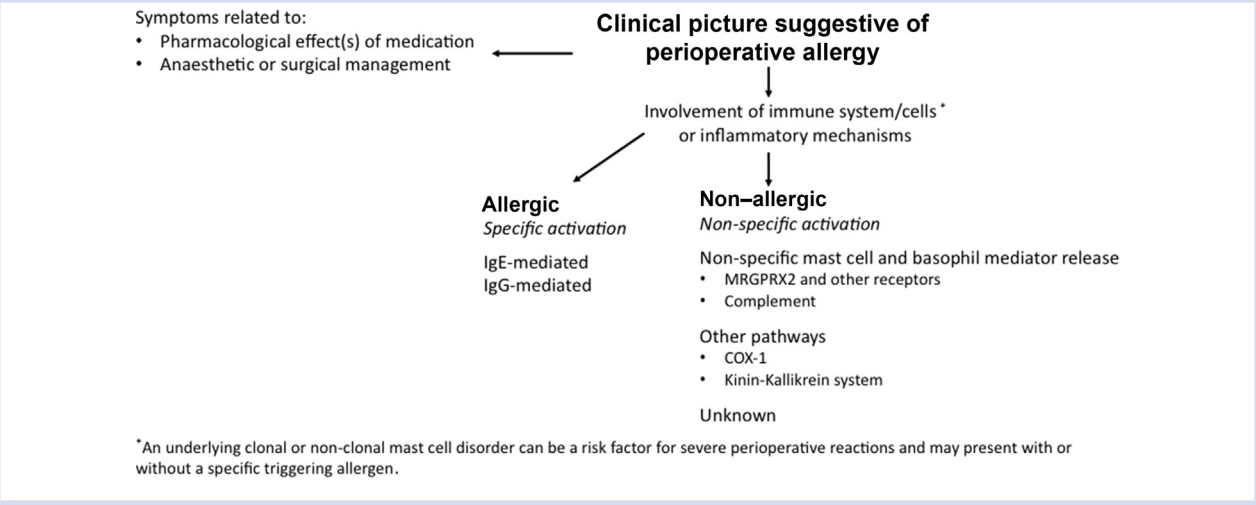


Fig 1. Possible pathomechanisms for clinical picture suggestive of perioperative allergy.

(immunoglobuin [Ig] E/IgG) mediated by mast cells/basophils, namely allergy; or (3) non-specific activation of immune cells (mast cells and basophils) or inflammatory mechanisms (see earlier discussion of mechanisms). Although clinical manifestations of allergic and non-allergic mechanisms are indistinguishable, they follow different rules in terms of risk of re-occurrence, risk of cross-reactivity with related compounds, the role of facilitating factors, and the response to desensitisation. Therefore a clinically oriented, comprehensive allergological evaluation of those patients is mandatory.

The subsequent categorisation of suspected perioperative allergic reactions relies on evaluation of the clinical picture and the allergological investigation. The investigation includes analysis of markers of mast cell release (serum tryptase is the most used and accessible) and deduction of the underlying immunological mechanisms by undertaking skin tests, specific IgE measurement, basophil activation testing, and when indicated drug provocation testing.

Authors' contributions

Conception, design, and drafting of paper: all authors.
Approval of the final version of the paper: all authors.

Declaration of interest

The authors declare that they have no conflict of interests.

References

1. Johansson SG, Hourihane JO, Bousquet J, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001; **56**: 813–24
2. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the nomenclature review committee of the world allergy organization, October 2003. *JACI* 2004; **113**: 832–6
3. Gell PGH, Coombs RRA. *Clinical aspects of immunology*. 2nd edn. Edinburgh: Blackwell Scientific; 1963
4. Pichler W. Drug hypersensitivity reactions: classification and relationship to T-cell activation. In: Pichler WJ, editor. *Drug hypersensitivity*. Basel: Karger; 2007. p. 168–89
5. Sampson HA, Munoz-Furlong A, Bock SA, et al. Symposium on the definition and management of anaphylaxis: summary report. *J Allergy Clin Immunol* 2005; **115**: 584–91
6. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
7. Hopkins PM, Cooke PJ, Clarke RC, et al. Consensus clinical scoring for suspected perioperative immediate hypersensitivity reactions. *Br J Anaesth* 2019; **123**: e29–37
8. Cook TM, Harper NJN, Farmer L, et al. Anaesthesia, surgery, and life-threatening allergic reactions: protocol and methods of the 6th national audit project (NAP6) of the royal college of anaesthetists. *Br J Anaesth* 2018; **121**: 124–33
9. Grocott MP, Mythen MG. Perioperative medicine: the value proposition for anesthesia?: a UK perspective on delivering value from anesthesiology. *Anesthesiol Clin* 2015; **33**: 617–28
10. Garvey LH, Dewachter P, Hepner DL, et al. Management of suspected immediate perioperative allergic reactions—an international overview and consensus recommendations. *Br J Anaesth* 2019; **123**: e50–64.

BJA

British Journal of Anaesthesia, 123 (1): e16–e28 (2019)

doi: 10.1016/j.bja.2019.01.027
Advance Access Publication Date: 4 March 2019
Review Article

EPIDEMIOLOGY AND MECHANISMS

Comparative epidemiology of suspected perioperative hypersensitivity reactions

Paul Michel Mertes[1,*,#,†], Didier G. Ebo[2,#,†], Tomaz Garcez[3,#,†], Michael Rose[4,5,#,†], Vito Sabato[2,#,†], Tomonori Takazawa[6,#,†], Peter J. Cooke[7,†], Russell C. Clarke[8,9,†], Pascale Dewachter[10,11,†], Lene H. Garvey[12,13,†], Anne B. Guttormsen[14,15,†], David L. Hepner[16,†], Phil M. Hopkins[17,†], David A. Khan[18,†], Helen Kolawole[19,20,†], Peter Kopac[21,†], Mogens Krøigaard[12,†], Jose J. Laguna[22,†], Stuart D. Marshall[19,20,†], Peter R. Platt[8,9,†], Paul H. M. Sadleir[8,9,23,†], Louise C. Savic[24,†], Sinisa Savic[25,†], Gerald W. Volcheck[26,†] and Susanna Voltolini[27,†]

[1]Department of Anesthesia and Intensive Care, Hôpitaux Universitaires de Strasbourg, Nouvel Hôpital Civil, Strasbourg, France, [2]Department of Immunology, Allergology and Rheumatology, University of Antwerp, Antwerp University Hospital, Antwerp, Belgium, [3]Department of Immunology, Manchester University NHS Foundation Trust, Manchester, UK, [4]Northern Clinical School, University of Sydney, Sydney, Australia, [5]Department of Anaesthesia, Royal North Shore Hospital, Sydney, Australia, [6]Intensive Care Unit, Gunma University Hospital, Gunma, Japan, [7]Department of Anaesthesia and Perioperative Medicine, Auckland City Hospital, Auckland, New Zealand, [8]Department of Anaesthesia, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia, [9]Anaesthetic Allergy Referral Centre of Western Australia, Sir Charles Gairdner Hospital, Perth, Australia, [10]Department of Anesthesiology and Intensive Care, Groupe Hospitalier de Paris-Seine-Saint-Denis, Assistance Publique-Hôpitaux de Paris, Paris, France, [11]Université Paris 13, Sorbonne-Paris-Cité, Paris, France, [12]Danish Anaesthesia Allergy Centre, Allergy Clinic, Department of Dermatology and Allergy, Copenhagen University Hospital, Gentofte, Denmark, [13]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, [14]Department of Anaesthesia and Intensive Care, Haukeland University Hospital, Bergen, Norway, [15]Department of Clinical Medicine, University of Bergen, Bergen, Norway, [16]Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Boston, MA, USA, [17]Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK, [18]Department of Internal Medicine, Division of Allergy and Immunology, University of Texas Southwestern Medical Center, Dallas, TX, USA, [19]Department of Anaesthesia and Perioperative Medicine, Monash University, Melbourne, Australia, [20]Department of Anaesthesia, Peninsula Health, Melbourne, Australia, [21]Division of Allergology, University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia, [22]Allergy Unit, Allergo-Anaesthesia

Editorial decision date: 15 January 2019; **Accepted:** 15 January 2019

Unit, Hospital Central de la Cruz Roja, Faculty of Medicine, Alfonso X El Sabio University, ARADyAL, Madrid, Spain, [23]Department of Pharmacology, University of Western Australia, Crawley, Australia, [24]Anaesthetic Department, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [25]Department of Clinical Immunology and Allergy, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [26]Division of Allergic Diseases, Mayo Clinic College of Medicine, Rochester, MN, USA and [27]Allergy Unit, S. Martino Policlinic Hospital, Genoa, Italy

*Corresponding author. E-mail: paul-michel.mertes@chru-strasbourg.fr

#These authors contributed equally.
†The authors are members of the ISPAR (International Suspected Perioperative Allergic Reaction) Group.

Summary

Suspected perioperative hypersensitivity reactions are rare but contribute significantly to the morbidity and mortality of surgical procedures. Recent publications have highlighted the differences between countries concerning the respective risk of different drugs, and changes in patterns of causal agents and the emergence of new allergens. This review summarises recent information on the epidemiology of perioperative hypersensitivity reactions, with specific consideration of differences between geographic areas for the most frequently involved offending agents.

Keywords: antibiotics; blood products; chlorhexidine; latex; neuromuscular blocking agents; perioperative anaphylaxis; perioperative hypersensitivity; sugammadex

Perioperative hypersensitivity (POH) reactions are, in most cases, completely unexpected and unpredictable critical events presenting suddenly without warning. Reactions may be either of allergic or non-allergic origin.[1,2] Severity of reactions ranges from mild to severe, and, in extreme cases, may be fatal despite prompt recognition, prolonged adequate resuscitation, and treatment. After pioneering work conducted in Australia,[3] the UK,[4] and France,[5] our knowledge about the epidemiology of perioperative anaphylaxis has substantially improved. Data are now available from large numbers of clinical practice publications, clinical databases, and allergen surveys from many countries.[6–17]

Although surveillance and analysis of rare and random adverse drug reactions represent statistical challenges, we now have clear evidence that differences between countries do exist. Several factors may contribute to these differences, such as gene–environment interactions, but also differences in anaesthesiology practice, variability in clinical recognition of potential POH reactions, and subsequent referral or variability in the comprehensiveness of the allergy evaluation. However, we have learned to take advantage of these differences to increase our knowledge about hypersensitivity reactions,[18] either concerning the respective risk of different drugs or the changing patterns of causal agents and the emergence of new allergens. Recent publications have highlighted these changes in the respective risks for antibiotics,[12,19] neuromuscular blocking agents (NMBAs) and sugammadex,[8,11,12,19,20] natural latex,[19] dyes,[12,19,21] and chlorhexidine.[12,22] This review summarises important recent information on the epidemiology of POH, with specific consideration to geographical differences for the most frequently involved causal agents.

Methods

A literature search was performed in the US National Center for Biomedical Information PubMed database with MeSH terms relevant to epidemiologic aspects of POH/anaphylaxis including triggers, geographical differences, and trends. Additional reports of interest identified by the writing group were included. Retrieved results were then reviewed to summarise the current knowledge of POH epidemiology.

Global incidence and mortality: similarities and regional differences

Several series from different countries have estimated the incidence of POH to be in the range of one in 18 600 to one in 353 anaesthetic procedures with substantial geographical variability.[11,17,19,20,23–31] In the recent 6th National Audit Project (NAP6) of the Royal College of Anaesthetists, the incidence of severe life-threatening anaphylaxis (grades 3 and 4 POH) was estimated at one in 10 000 anaesthetic procedures. Because of methodology limitations the true incidence of severe reactions was estimated to be 70% higher.[12]

Anaphylaxis is often thought to be allergic, that is mediated by drug-specific immunoglobulin E (IgE) antibodies.[32] However, other immune and non-immune mechanisms such as IgG antibodies, non-specific direct histamine release, contact phase or complement activation and off-target occupation of mast cell MRGPRX2 (Mas-related G-protein coupled receptor member X2) receptors may be involved[33,34]; these account for 40% of the cases in some series.[19,20,35] Moreover, POH might even occur independently of mast cell and basophil activation, for example by interference with enzymes such as cyclo-oxygenase 1 (COX1). The incidence of presumed IgE-mediated reactions during anaesthesia has been estimated to be in the range of one in 5000 to one in 13 000.[3,36] These data should be interpreted cautiously, as a positive skin test does not necessarily reflect a genuine IgE-mediated reaction.[37]

The most powerful incidence estimate was reported in France, where a combined analysis of three different independent databases using a capture–recapture method allowed a nationally based estimation of the incidence of

immediate allergic (IgE-mediated) reactions of all grades occurring during anaesthesia, according to sex, age, and causal substance. This report has confirmed the general view that immediate-type hypersensitivity reactions are largely underreported, the incidence of allergic reactions being estimated at 100.6 (76.2–125.3) per million procedures (one in 10 000), a result that is very similar to that reported in NAP6.[12,38]

POH, including anaphylaxis, occur in a monitored setting, and recent studies have shown that recognition of anaphylaxis was generally prompt.[39,40] If anaesthesiologists were considered reluctant to administer epinephrine (adrenaline) in Denmark,[41] this does not seem to be the case in the UK and France.[39,40] In both countries, most patients with severe reactions were adequately managed with rapid administration of epinephrine; however, fluid administration was sometimes regarded as insufficient. Despite adequate resuscitation, per-case mortality was estimated at one in 26.6 cases in the UK, a result very similar to that observed in France for mortality related to NMBA anaphylaxis.[39,40] Even after well treated anaphylactic reactions, adverse sequelae were seen in one-third of cases.[40]

A very similar perioperative mortality rate of 4–4.76% has been recorded for all causative drugs in the USA and Japan, respectively.[42,43] This contrasts with the low rate of 0–1.4% recently reported for Western Australia (2000–9).[25]

Causal agents

Neuromuscular blocking agents and sugammadex

In many countries, NMBAs are by far the most frequently incriminated culprit, and represent the first[3,8,16,19,20,44,45] or the second[12,13] most common cause of POH. Significant differences are observed concerning the frequency of alleged IgE-mediated reactions to NMBAs between countries. Reactions have been reported with a high frequency in France,[19,20,38,46–48] Australia and New Zealand,[8] the UK,[12] Norway,[7] Belgium,[44,45] South Korea,[49] and Spain.[13,27] The incidence of IgE-mediated reactions has been estimated at 184.0 per million (95% confidence interval,139.3–229.7) anaesthetics, reaching 250.9 per million (189.8–312.9) for women in France.[38] POH reactions to NMBAs seem to be less frequent in Sweden,[18] Denmark,[6] and the USA.[50–52] Although the incidence seems to remain relatively stable in France,[35] a significant decrease has been observed in Norway since the withdrawal of the antitussive pholcodine, which may play a role in NMBA sensitisation.[53,54]

Structure–activity studies have established that the IgE recognition site of NMBAs involves the tertiary and quaternary substituted ammonium groups and their molecular environment.[55,56] This could explain the frequent but not constant skin cross-sensitivity between different NMBAs observed in patients allergic to NMBAs, and variability between patients.[57] An alternative explanation for cross-sensitivity in drug naïve patients could relate to off-target occupancy of the MRGPRX2 receptor by various NMBAs.[34,37] Cross-sensitivity to all NMBAs is unusual; only ~7% of patients in the last French study.[19] Patients suffering from anaphylaxis to succinylcholine cross-react with *cis*-atracurium in 10% of cases and with rocuronium in 20% of cases. Cross-sensitivity is most frequently observed with rocuronium and less frequently with *cis*-atracurium.[8,19,44,58] Cross-sensitivity between *cis*-atracurium and atracurium is frequent but not constant, observed in ~50% of patients suffering from anaphylaxis to one of these two drugs.[19,58] These cross-sensitivity results strongly support the absolute necessity of a systematic cross-sensitivity investigation in patients who survive anaphylaxis to an NMBA in order to identify a possible safe drug for the future.[33,59,60]

Differences have been reported regarding the relative risk of allergic reactions with the various NMBAs available.[61] Several studies report succinylcholine and rocuronium to be associated with a higher risk of anaphylaxis, whereas pancuronium and *cis*-atracurium are reported to be the NMBAs associated with the lowest incidence of anaphylaxis.[8,10,38,44,46,47,49,62] This was not found in the NAP6 survey where only succinylcholine was considered at higher risk, with similar risk shared by the other NMBAs. However, in the UK, the market share of *cis*-atracurium was only 1.6%, and 40.6% for rocuronium.[12] Thus, comparison of the respective allergic risk of rocuronium and *cis*-atracurium in this report cannot be accurately assessed.

Sensitisation may occur during previous anaesthesia but the majority of patients are drug naïve, that is they do not report previous exposure.[44,56] This suggests that there must be alternative, probably environmental, factors that play a role in cross-sensitising patients to NMBAs. Sensitisation resulting from exposure to compounds containing tertiary substituted ammonium group, quaternary substituted ammonium group, or both, such as cosmetics or disinfectants, has been hypothesised.[56] This hypothesis is supported by a recent study conducted on hairdressers demonstrating a significant increase in IgE sensitisation to NMBAs and quaternary ammonium ion compounds,[63] although the clinical significance of this increase remains to be demonstrated. An attractive alternative hypothesis arises from the work published by Florvaag and colleagues,[64] who provided repeated evidence for a connection between the consumption of pholcodine, an opioid antitussive, and IgE-mediated anaphylactic reactions to NMBAs.[64–67] Nevertheless, patients with a genuine pholcodine allergy can have congruent negative skin tests and basophil activation tests to NMBAs, suggesting that allergy to this opioid does not necessarily preclude use of NMBAs.[45] Johansson and colleagues[68] showed, retrospectively, that pholcodine withdrawal from the Swedish market was associated with a decrease in the prevalence of sensitisation against ammonium groups in the general population. Their observations have led to the withdrawal of pholcodine from the Norwegian market. This resulted in a progressive decrease in IgE antibodies to quaternary substituted ammonium in the population and in the number of reports of allergic reactions to NMBAs.[53,54] A prospective 4 yr case–control study (the ALPHO study: ALlergie aux curares et exposition à la PHOlcodine) designed to confirm this possible link between pholcodine exposure and sensitisation to NMBAs in France was initiated in 2015.

The NMBA reversal drug sugammadex was launched in the USA (December 2015) much later than in Europe (2008) or Japan (2010) because of US Food and Drug Administration (FDA) concerns about hypersensitivity reactions. As the use of sugammadex in Europe is limited (probably because of its high cost), occurrence of immediate sugammadex-induced anaphylaxis seems rare.[12] In contrast, the incidence of sugammadex-induced anaphylaxis was recently reported as about one in 2500 administrations (0.039%) based on a retrospective observational study conducted in a single Japanese hospital.[69] Sugammadex usage in Japan in 2010, in terms of monetary value, was more than four times higher than that in Spain, the country with the second-highest usage.[11] The popularity of sugammadex in Japan is such that it has been administered to approximately 10% of the total Japanese population during the 8 yr period since its release.[70] This

suggests that the difference in sugammadex-induced anaphylaxis between countries can be explained, at least in part, by differences in the total amount of sugammadex used. The authors of the Japanese study referred to a previous observational study reported from New Zealand that showed that the estimated incidence of anaphylaxis caused by succinylcholine and rocuronium was 0.048% and 0.04%, respectively,[10] and concluded that the incidence of sugammadex-induced anaphylaxis is roughly equivalent to that induced by succinylcholine or rocuronium.[69] Based on this speculation, one can estimate that the total incidence of intraoperative anaphylactic events will increase by at least one-third with the full-scale introduction of sugammadex.[71]

Two recent reports conducted in healthy non-anaesthetised subjects receiving sugammadex at doses of either 4 or 16 mg kg^{-1}, or placebo, repeated twice at weekly intervals, showed an unexpected and dose-related high rate of immediate hypersensitivity reactions after sugammadex administration. The incidence of confirmed hypersensitivity was determined to be 0.7% in the 4 mg kg^{-1} group, 4.7% in the 16 mg kg^{-1} group, and 0% in the placebo group in one study.[72] In the second study, the incidence of hypersensitivity was 6.6% in the 4 mg kg^{-1} group, 9.5% in the 16 mg kg^{-1} group, and 1.3% of the placebo group.[73] These high rates of reactions contrasts with the number of reactions reported in clinical practice, and highlights the need for a careful survey of sugammadex-related hypersensitivity reactions. Based on current knowledge, sugammadex cannot be recommended as appropriate in the treatment of suspected rocuronium allergy.[74]

Although the mechanism of sugammadex-induced anaphylaxis remains elusive, various hypotheses have been proposed. As sugammadex is a modified γ-cyclodextrin, which is also used for food additives, exposure to γ-cyclodextrin may be the sensitising trigger.[75] Cyclodextrin is frequently used in foods and cosmetics because it can change the physical properties of various compounds by their encapsulation within the cyclic structure. The average person is thought to ingest about 4 g of γ-cyclodextrin per day from food.[76] Therefore, even people who have never received sugammadex may be sensitised by food and cosmetics. None of 12 patients who suffered anaphylaxis to sugammadex had a history of previous sugammadex exposure.[77] If this hypothesis is correct, the incidence of sugammadex-induced anaphylaxis may vary from country to country because the use of food containing cyclodextrins in each country is likely to differ. Another hypothesis is that sugammadex causes anaphylaxis only after it complexes with rocuronium, based on several clinical cases[78–82] in which rocuronium and sugammadex alone had negative results by skin test, but were positive when combined. These cases suggest that sugammadex may change its structure and become an antigenic determinant after forming a complex with rocuronium.

Hypnotics

Historically hypnotic agents were responsible for a significant proportion of cases of perioperative anaphylaxis, but discontinuation of agents using Cremophor EL as a solvent and declining use of thiopental has dramatically changed this. In the most recent GERAP (Groupe d'Etude des Reactions Anaphylactiques Perioperatoires) survey of anaphylaxis in France, hypnotics were responsible for 2.2% of cases, with propofol and ketamine being responsible for five reactions each and midazolam a single reaction.[19] The recent NAP6 survey in the UK identified only a single case of hypnotic anaphylaxis.[12] This reaction was to propofol, and the authors highlighted the relative safety of propofol given that approximately 2 million patients are administered propofol annually in the UK.[12]

There has been ongoing debate about whether it is safe to administer propofol in cases of egg, soy, and peanut allergy. Studies in Denmark and Spain in recent years suggest that it is.[83,84] There has been a case report of anaphylaxis to propofol in a patient without clinical history of soy allergy but latent sensitisation demonstrable by positive specific IgE (sIgE).[85] A single report of a child with egg allergy who experienced urticaria and erythema after propofol and had a borderline positive skin test[86] led Harper[87] to suggest that propofol is safe for use in adults with peanut, soy, or egg allergy.

Opioids

Opioids include (1) naturally occurring opiate alkaloids derived from opium (the liquid released by scratched immature seed pods of the opium poppy, *Papaver somniferum*) such as morphine and codeine; (2) semisynthetic opioids such as pholcodine, hydrocodone, hydromorphone, and diamorphine; and (3) synthetic compounds that are chemically not related to opiates such as methadone, pethidine, fentanyl, and tramadol. Many natural and (semi)synthetic opioids are potent non-specific liberators of histamine. Non-allergic histaminic reactions are much more prevalent than IgE-mediated hypersensitivity to these drugs and they probably result from off-target occupation of the MRGPRX2 receptor[88,89] rather than from binding to the opioid μ-receptor.[90] Data suggest that many patients labelled with opioid/opiate allergy do not have a genuine IgE-mediated allergy.[91,92] The reason for this mislabelling is often the uncertainties associated with the use of skin tests[93] with these potent non-specific histamine releasers and unavailability of validated or reliable sIgE assays.[94] Indeed, allergic reactions to these substances are exceedingly rarely reported despite their ubiquitous use during anaesthesia.[6,7,12,13,44,95,96]

Local anaesthetics

Local anaesthetics are commonly used in the perioperative environment, yet no cases of proven local anaesthetic allergy were reported in the NAP6 survey[12] or two other recent studies of perioperative anaphylaxis.[19,97] True hypersensitivity reactions to local anaesthetic drugs are considered rare.[98–100] Many reports of allergy prove to be spurious, often related to side-effects of injections in awake patients (e.g. vasovagal reactions) or adverse effects of rapid absorption of vasopressor or toxic serum levels of local anaesthetic. Excipients in local anaesthetic preparations may also be responsible for suspected local anaesthetic hypersensitivity reactions, such as chlorhexidine in urethral gels. Delayed hypersensitivity can also occur with local anaesthetics.

The ester group of local anaesthetics (e.g. procaine, tetracaine) is considered to be more antigenic than the amide group (e.g. lidocaine, bupivacaine, ropivacaine). The *para*-aminobenzoic acid metabolite of esters is thought to be responsible for much of the antigenicity of this group.[33,101] Assessment of suspected immediate hypersensitivity to local anaesthetics should involve skin tests and subcutaneous challenge tests.[97,99]

Antibiotics

Antibiotics, mainly β-lactam antibiotics such as amoxicillin/clavulanic acid, cefazolin, and cefuroxime, constitute another

significant cause of perioperative anaphylaxis.[6,7,12,13,19,20,38,44,45,50,52,95,96,102,103] In most patients, diagnosis of β-lactam allergy is readily established by skin tests, which still merit a place as the primary diagnostic tool.[104–106] However, for some compounds there appears to be room for considerable improvement, mainly in optimising the concentration of drug to be used for skin tests.[107] The potential and limitations of *in vitro* tests in the diagnostic management of β-lactam antibiotics have been reviewed recently.[108]

The NAP6 allergen exposure survey[109] showed that choice of antibiotic prophylaxis was influenced by preoperative penicillin allergy history in 25% of the patients who received teicoplanin or vancomycin, and thereby probably contributed to the high incidence of teicoplanin-induced anaphylaxis in the UK.[12] Other frequently applied alternatives are vancomycin and clindamycin. With the knowledge that history of penicillin allergy is wrong in more than 90% of cases, effective de-labelling is mandatory to optimise appropriate antibiotic administration.[110,111] Obsolete historic data and statistics suggesting extensive cross-reactivity between penicillins and first-generation cephalosporins such as cephalothin and cephaloridine continue to influence modern practice. Therefore, many patients with unverified β-lactam allergy are labelled as 'pan-β-lactam' allergic, leading to the withholding of penicillins, cephalosporins, and monobactams. However, during the past few decades, evidence has accumulated that this 'pan-β-lactam' allergy label is false in most cases. For example, cefazolin allergy is generally selective,[107] and rarely associated with cross-reactivity to penicillins or other cephalosporins. It appears that cefazolin is generally safe in patients with an IgE-mediated or non-IgE-mediated penicillin allergy, especially when the history is vague.[112–114] Cefazolin does not share an R1 and R2 group with any other β-lactam antibiotic.[115] There are limited data on cefazolin safety in patients with a history of a significant reaction to penicillin or positive skin testing to penicillin. There is no evidence that the administration of a 'test dose' of an antibiotic reduces the severity of an ensuing reaction,[12] and current guidelines are advising against this practice.[116] In contrast, there are different arguments for antibiotics to be systematically administered before induction of anaesthesia.[12] This is likely to improve the detection of unknown allergies, simplify treatment, and orientate the diagnostic investigation.

Hevea latex

Since the discovery of the vulcanisation process by Goodyear and Hayward in the mid-19th century, natural rubber latex (NRL) from *Hevea brasilensis* has been used in medical devices for its elastic properties. The first cases of allergy to NRL were reported in 1927 by Stern[117] and Grimm.[118] In 1984, Turjanmaa and colleagues[119] reported the first cases of perioperative anaphylaxis attributed to NRL in healthcare workers (nurses) who underwent surgery. In 1989, Slater[120] reported the case of NRL allergy in two children with spina bifida. In 1990, Moneret-Vautrin and colleagues[121] confirmed an increased risk in patients with a spina bifida associated with the detection of specific IgE against NRL and recommended an NRL-free environment for these patients during surgery.

The number of reported cases of allergy to NRL rapidly increased in the 1980s and reached its peak during the 1990s. The prevailing hypothesis to explain this rapid increase in NRL sensitisation is that the implementation of high hygiene standards after the human immunodeficiency virus (HIV) epidemic led to an increased demand for NRL gloves. To respond to this demand, producers had to change their manufacturing process by reducing the leaching steps of NRL, leading to the release of higher protein content products. High protein content increased antigen exposure and extractable proteins leading to NRL sensitisation.[122] Moreover, donning glove powder absorbs most NRL proteins and facilitates their airborne dissemination increasing the risk of sensitisation for healthcare workers and patients.[123]

Several populations at risk have been identified including children with spina bifida,[124,125] those with a history of multiple surgeries, especially during childhood,[126] healthcare workers,[127] and non-healthcare workers frequently exposed to NRL.[128] Atopy has been associated with a higher risk of NRL allergy in the general population and among healthcare workers.[129] However, a recent population-based study showed no significant association between atopy and NRL allergy when exposure is low.[130] Some allergies to fruits and vegetable have been associated with a higher risk of NRL allergy, but this may reflect cross-sensitisation that is not always clinically relevant. Chestnut, avocado, banana, and kiwi are the most frequently associated with NRL allergy, a condition referred as the latex-fruit syndrome.[131,132]

Two Italian studies reported an increased risk of NRL sensitisation in pregnant women when compared with women having gynaecological surgery,[133,134] results that need to be confirmed.

The incidence of NRL-related perioperative IgE-mediated reactions was estimated at 59.1 reactions (44.8–73.6) per 1 million anaesthetics in France between 1997 and 2004 with an increased incidence in women (91.0 [68.9–113.4]).[38] More recent studies in many countries show a marked decrease in NRL anaphylaxis when compared with other causes of IgE-mediated POH. In a large multicentre study of more than 31 000 paediatric anaesthetic procedures performed in Europe between 2014 and 2015, only one complication was attributed to NRL allergy.[135]

This reduction of NRL sensitisation observed in the general population[136] can be attributed to efforts made by manufacturers and healthcare providers during the past 10 yr to reduce NRL exposure. Primary prevention is based on increased awareness of the risk of NRL allergy, NRL avoidance in at-risk populations, particularly children, use of powder-free latex gloves, and recognition of clinical signs. Interestingly, in Thailand, where the sensitisation to NRL was previously low, the continued use of powdered gloves led to increased sensitisation to NRL in healthcare workers.[137]

Nonsteroidal anti-inflammatory drugs

NSAIDs are COX inhibitors commonly used in perioperative settings during general anaesthesia and after operation for analgesia. They are a rare but well recognised cause of POH.[19,138] Hypersensitivity to multiple NSAIDs with dissimilar structures is mediated by inhibition of the COX-1 isoenzyme.[32] It is most likely to feature exacerbations of respiratory disease in susceptible patients, urticaria, or angioedema.[139,140] Less commonly, true anaphylaxis occurs to NSAIDs and is the result of an IgE-mediated allergic reaction to a particular NSAID. In this situation, cross-reactivity may occur to NSAIDs that belong to the same chemical subgroup of NSAIDs, but the majority of NSAIDs will be non-reactive.

Paracetamol is another rare cause of anaphylaxis,[140] particularly in the perioperative setting. The intravenous

preparation may contain mannitol that has been responsible for one such reaction that goes undetected by oral drug challenge.[141] Hypersensitivity resulting from COX-1 isoenzyme inhibition is also possible at high doses.[142]

Disinfectants

Chlorhexidine is known as a major cause of POH. Since the first case of proven chlorhexidine-induced anaphylaxis reported in 1989,[143] numerous further cases have been reported mostly related to anaesthesia and surgery. Chlorhexidine products are recommended increasingly to reduce infection risks for patients. For example, national UK guidelines recommend use of 2% chlorhexidine in 70% isopropyl alcohol as the skin disinfectant of choice for central venous catheter insertion and for urethral catheterisation. The use of a chlorhexidine-containing urethral lubricant for catheterisation is also suggested.[144] According to the Medicines and Healthcare Products Regulatory Agency licensing records, the percentage of products containing chlorhexidine has significantly increased over the past 20 yr.[145] Moreover, even in non-medical environments, chlorhexidine is found in many commercially available products, including mouthwashes, antiseptic creams, toothpaste, and plasters. This increase in chlorhexidine containing products in both medical and non-medical environments clearly identifies its popularity, which may explain the increasing susceptibility to sensitisation followed by the high incidence of chlorhexidine-induced anaphylaxis.

Although chlorhexidine represented 9% of culprit drugs for POH in the NAP6 study,[12] regional differences are large in the incidence of chlorhexidine-induced anaphylaxis. Chlorhexidine is frequently incriminated in the UK,[146] Belgium,[45] Australia,[147] and Denmark,[6,22] which are countries where chlorhexidine is routinely tested in all patients investigated for suspected perioperative allergy. Reactions are relatively rare in France, probably because of a limited use of chlorhexidine as a disinfectant in the operating room.[20] The causative chlorhexidine product was reportedly chlorhexidine-containing lubricant for urinary catheter (44%), chlorhexidine-impregnated central venous catheters (35%), and topical chlorhexidine (16%) in a recent review.[147] Chlorhexidine-induced anaphylaxis predominantly occurs in males (~80%).[145,147] This may be because of the more frequent use of urethral lubricant in males. The first case of chlorhexidine-impregnated catheter anaphylaxis was reported in 1997,[148] and acute anaphylactic shock during anaesthesia has been reported in Japanese and European patients after insertion of chlorhexidine-impregnated catheters. Such adverse events prompted government warnings in Japan,[143] the USA,[149] and Australia.[150] These led to Japan withdrawing all chlorhexidine-impregnated central venous catheters.[151] Although it is not common, POH caused by topical chlorhexidine has also been reported.[143,152,153] A high rate of reactions to topical chlorhexidine was reported in Japan, and as a result specific recommendations regarding the maximum chlorhexidine concentration to be used were issued.[143] Additional warnings concerning urethral gels have been issued. In contrast, the guideline published by the US Centers for Disease Control and Prevention recommends skin preparation with a >0.5% chlorhexidine solution with alcohol before central venous catheter and peripheral arterial catheter insertion[154]; even more concentrated (2%) chlorhexidine is recommended for the same purpose in the UK.[155] Although the incidence of anaphylaxis caused by topical chlorhexidine in the USA is unknown, one can expect a high incidence there as well. Collaborative international studies to compare the usage of chlorhexidine in each country with the incidence of anaphylaxis caused by chlorhexidine would be beneficial. Taken together, the incidence of anaphylaxis caused by chlorhexidine is likely to be underestimated, and clinicians should be aware that chlorhexidine is one of the 'hidden' causes of POH.[138] The problem of chlorhexidine allergy in the perioperative setting is discussed in greater depth by Rose and colleagues.[156]

A few cases of anaphylaxis caused by povidone–iodine have been also reported,[157,158] although it is notably less than that caused by chlorhexidine.

Dyes

Blue dyes have long been associated with anaphylaxis in the perioperative period, first described in the 1960s.[159,160] They are frequently used by surgeons in combination with radioactive isotope to facilitate mapping of lymphatic drainage and identification of sentinel lymph nodes (SLNs) in cases of breast cancer and melanoma. Anaphylaxis to dyes is often delayed in onset compared with i.v. perioperative antigens,[12,21] probably as a result of slow absorption from subcutaneous tissue and lymphatics,[21,161] delay of recognition, or both because of interference with pulse oximetry with (prolonged) artificial lowering of readings.[21,162] The two most commonly used blue dyes for SLN identification are patent blue V (also known as E-131, commonly used in Europe and Australia) and isosulfan blue (commonly used in the USA). The close structural relationship between these two vital dyes (isosulfan blue is a structural isomer of patent blue which is often confused with its hydroxylated relative, patent blue V) means that cross-reactivity has been described and should be assumed.[163] In contrast, methylene blue is structurally dissimilar and would not be expected to cross-react, although this has been described.[21,164] Allergy to dyes is mainly documented by skin testing, but basophil activation testing can help to identify safe alternatives.[165]

Controversy about the incidence of reactions to these dyes has existed for years. Barthelmes and colleagues[166] looked at several studies of isosulfan blue allergy and reported an allergy rate of 1.42% with severe reactions requiring vasopressor support in 0.44%. In contrast, their own large study of patent blue V reported a lower allergy rate of 0.86% with 0.06% severe using the same criteria. The largest series involving skin test-proven hypersensitivity to patent blue V recorded a rate of 0.34%.[161] In the last survey published in France, blue dyes were the third largest cause of POH of all severity grades.[19] Similarly, the recent NAP6 survey in the UK found that patent blue V was the fourth most prevalent cause of perioperative allergy after antibiotics, NMBAs, and chlorhexidine,[12] and was calculated to occur in one out of 6863 exposures. This value is lower than those in previously mentioned studies, but in perspective is a higher incidence than that calculated for antibiotics, NMBAs, and chlorhexidine once exposure rates are considered. Some centres have begun screening patients using skin tests for detection of hypersensitivity to blue dyes before exposure[167] or advocating consenting patients specifically about risks of hypersensitivity with their use.[166–168]

Methylene blue has been considered a lower allergy risk than patent blue V or isosulfan blue but is theoretically less useful in SLN localisation because of the lack of a sulphonic acid group that would allow lymphatic uptake. Methylene blue

is also less suitable for subcutaneous injection because of the risk of skin and fat necrosis. Recent evidence suggests that it may be equally suitable at detecting SLN as patent blue V.[169] Isolated case reports of hypersensitivity to methylene blue exist.[170–172]

Colloids

The epidemiology of hypersensitivity reactions to colloids has changed because of the withdrawal of some colloids from the market and restrictions in the use of others. Only a few studies are relevant to the epidemiology of currently used colloids.

Synthetic colloids are associated with the higher risk of hypersensitivity reactions.[173] In a study in which human albumin was used as a reference, the estimated risk of hypersensitivity reaction to gelatin was 12 times higher, hydroxyethyl starch four times higher, and dextrans two times higher per administration.[174] However, hydroxyethyl starch 130/0.4 was not evaluated in this study and old modified fluid gelatins (Haemaccel®, Piramal Healthcare, Mortpeth, Northumberland, UK), with histamine-releasing properties,[175] are no longer used in Western countries.

Allergic reactions to dextrans are mainly IgG-mediated[173] and can be prevented in most cases by hapten inhibition.[176] As this product is no longer used for vascular filling, these reactions are no longer seen in the perioperative setting.

Hypersensitivity reactions to newer modified fluid gelatins account for 0.6% of POH in the last GERAP study in France and for 1.2% in Norway.[7,19] In the UK, 2.8% of anaesthetists reported seeing a POH caused by colloids.[177] In the NAP6 study, only three cases of gelatin-induced reaction were reported.[12]

In the USA, the use of hydroxyethyl starch was associated with a risk of hypersensitivity reactions with an odds ratio of 1.29 (1.02–1.62).[17] Because of the recent restrictions applied to the use of hydroxyethyl starch, hypersensitivity reactions to this fluid were not described in the last GERAP study in France nor in the NAP6 survey in the UK.[12,19]

Blood products

Hypersensitivity reactions occur to a heterogeneous group of blood components that vary in their risk of causing serious hypersensitivity reactions. The genesis of true hypersensitivity reactions to blood products is complex and is best divided into recipient- and donor-related aetiologies. In the first of these, a recipient's antibody reacts with an antigen in the blood product. The best known of these is anti-A in a patient who is IgA deficient although many antibodies have been described. For example, traces of drug in the unit can react with the patient's antibodies, which is the reason for measurement of recipient IgA levels in the investigation of possible blood transfusion anaphylaxis.[178] Donor-related reactions include the transfer of antibodies or lymphocytes in the blood product that react to antigens present in the patient.[179]

The NAP6 survey identified two cases of anaphylaxis (one to cryoprecipitate and one to fresh frozen plasma) in an estimated 84 000 perioperative blood product administrations.[12] This may reflect a local haemovigilance scheme but equally may reflect the difficulty in diagnosing perioperative blood product reactions in the absence of a confirmatory skin test and with multiple other suspect antigens. Furthermore, shock during the administration of blood products may result from non-anaphylactic causes such as ABO incompatibility (acute haemolytic transfusion reaction), bacterial contamination of blood products, bradykinin accumulation,[180] and hypovolaemia.

The incidence of hypersensitivity reactions to blood products overall is estimated as 0.6 per 1000 transfusions.[179] The risk of individual components of blood varies substantially with estimates that platelets cause 1.1 allergic reactions (of all severities) per 1000 transfusions compared with 0.68 and 0.04 for plasma transfusions and red cell concentrates, respectively. Allergic reactions to platelets were likely to be more severe than with other blood components.[181] A report from France suggested that methylene blue treated fresh frozen plasma (introduced as a pathogen reduction strategy) could carry a higher risk of allergic reactions than non-treated units,[171] but this increased risk has not been confirmed in other studies.[182]

Others

Aprotinin, a polypeptide isolated from bovine lung, is capable of stimulating a specific IgE antibody in humans, and has been shown to cause anaphylaxis. Although the incidence seems to be low,[12] sporadic cases of anaphylaxis caused by aprotinin contained in fibrin glue[183,184] and aprotinin used as an anticoagulant during cardiac surgery[185,186] have been reported. The risk of hypersensitivity reaction is low after primary exposure to aprotinin. However, application of aprotinin carries a high risk 4–30 days after previous exposure and cannot be recommended for the first 6 months.[185]

Protamine sulphate is a polypeptide that is used to reverse heparin anticoagulation and retard absorption of insulin, often as neutral protamine Hagedorn (NPH). The polypeptide is extracted from salmon milt. In addition to IgE-mediated anaphylaxis, protamine can produce multiple adverse reactions, including non-immune mast cell degranulation, complement activation, or IgG-mediated responses that account for the systemic effects.[187] If anaphylaxis occurs during protamine administration when cardiopulmonary bypass is readily available, the method of managing anticoagulation and potential reversal after reheparinisation is an unsolved issue.[188] Fortunately, the incidence of protamine-induced anaphylaxis appears to be low in most countries.[12,20] Patients who receive protamine-containing insulins are at the greatest risk with an incident rate of adverse effects of 0.6–2% (10–30 times more than other patients) in NPH insulin-dependent diabetics undergoing cardiac surgery.[189,190]

Discussion

The overall incidence of POH ranges from one in 18 600 to one in 353 with substantial geographical variability (Box 1). Several factors explain these differences including the definition of hypersensitivity or anaphylaxis used and the mechanism and severity of the reactions included. The recent NAP6 survey conducted in the UK included only severe grade 3–5 cases, and the incidence was estimated to be at least one in 10 000 anaesthetics, but was likely underestimated.[12] This incidence is similar to that of IgE-mediated POH of all grades in France, which was based on a combined analysis of two independent databases representing a cohort of 2516 cases.[38]

There is also substantial geographical variability regarding the different drugs or substances involved. There are a large number of variables that can have an impact on the most common causes of perioperative anaphylaxis from country to country. These variables include the ability to identify possible

Box 1
Key points.

- Perioperative hypersensitivity (POH) reactions may be allergic or non-allergic.
- The incidence of POH of all severity grades varies between countries and ranges from one in 18 600 to one in 353 procedures.
- The proportion of presumed POH being immunoglobulin E-mediated allergic reactions seems to be relatively similar between countries (50–60%).
- Mortality ranges from 1.4% to 4.8% depending on series and countries.
- Substantial geographical variability regarding the causative drugs or substances involved is reported.
- Reactions involving neuromuscular blocking agents are the first or second cause in several countries.
- Reactions involving antibiotics are increasing and represent the most frequently incriminated drugs in several countries.
- Reactions involving dyes or chlorhexidine are reported with high and increasing frequency, whereas reactions to natural rubber latex are rapidly decreasing in most series.
- Regional differences and progressive changes in the substances incriminated are a strong incentive for repeated epidemiological surveys in different countries.
- Building a worldwide network dedicated to the investigation of POH will enable a higher standard of patient care and provide valuable data on geographical differences and new or emerging allergen sources

POH and initiate referral, the severity of the reactions that are included, the type of NMBA and antibiotics used by region, the comprehensiveness of the evaluation (i.e. inclusion of all potential allergens the patient was exposed to, such as chlorhexidine, sealants), possible sensitising substances in a region and availability of *in vitro* testing.[35]

Hypersensitivity reactions to NMBAs remain a major cause in most, but not all, countries. Reactions to NRL have been decreasing over the past 20 yr. Reactions involving antibiotics are rapidly increasing, now being more common than NRL and the most common culprit in some series.[12,19]

This increase in antibiotic anaphylaxis may reflect increasing antibiotic sensitisation in the population, but may also be influenced by the type of antibiotics used for prophylaxis. Thus, reactions to teicoplanin appear to be frequent in the UK but not in France.[12] Reactions to cephalosporins represent half of the reactions in France.[19] The use of teicoplanin for prophylaxis is not recommended in France, whereas it is frequently used as an alternative in cases of suspected penicillin allergy in the UK.

Reactions involving chlorhexidine are now being reported with increased frequency.[12,22] It may be difficult to correctly diagnose because of a lack of exposure recognition as exposure to chlorhexidine is rarely documented on anaesthetic charts.[138] Therefore, systematic testing for a possible chlorhexidine allergic reaction seems prudent in cases of POH, even in countries where usage appears to be low.

Allergic reactions involving dyes are also being reported with a high frequency, representing the third most commonly responsible allergen in France. Clinical diagnosis may be difficult as these reactions are usually delayed after dye injection.[21] Reactions to hypnotics, local anaesthetics, and NSAIDs remain uncommon in the perioperative environment.

Conclusions

Owing to the rare occurrence of POH, it is mandatory that collaborations are established both within and across specialties to form centres that can build up and report expertise in this highly specialised field. Building a worldwide network dedicated to the investigation of these reactions will not only enable a higher standard of patient care, but will also lead to research collaborations and provide invaluable data on geographical differences, changes in patterns of causal agents, and new or emerging allergen sources.

Authors' contributions

Design of the study: PMM, DE, TG, MR, VS, TT.
Drafting of manuscript: PMM, DE, TG, MR, VS, TT.
Study conception; data collection, analysis, and interpretation; revising paper: all authors.

Declarations of interest

PD receives lecture and travel fees from MSD France (Courbevoie, France) and from Bracco Imaging France (Courcouronnes, France), support from Agence Nationale de Sécurité du Médicament et des Produits de Santé (Saint-Denis, France), expert for a task force on 'neuromuscular blocking agents and anaphylactic reactions' (until 2016), and is a MSD Expert Board on 'neuromuscular blocking agents and fast-tracking anesthesia' (until October 2019); LHG is a consultant and adjudication committee member for Merck, NJ, USA and for Novo Nordisk Denmark; PMH is an Editorial Board Member of the *British Journal of Anaesthesia*; PMM is a scientific advisor for the ALPHO study (NCT02250729) funded by a consortium of pharmaceutical companies: Zambon, Urgo, Pierre Fabre, Boots, Hepatoum, Biocodex, Sanofi, LBR, GSK, APL, Bells Healthcare, Pinewood, T & R, Ernest Jackson; PK receives lecture fees from Novartis Pharma Services Inc. and Shire Pharmaceuticals Group Plc.; SM has a Australian National Health and Medical Research Council (NHMRC) ECR Fellowship for investigation of cognitive aids in emergencies. All other authors confirm that they have no interests to declare.

References

1. Sabato V, Platt P, Garcez T, Cooke P. Suspected perioperative allergic reactions: nomenclature and terminology. *Br J Anaesth* 2019; **123**: e13–5
2. Johansson SG, Hourihane JO, Bousquet J, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001; **56**: 813–24
3. Fisher MM, More DG. The epidemiology and clinical features of anaphylactic reactions in anaesthesia. *Anaesth Intensive Care* 1981; **9**: 226–34
4. Watkins J, Clarke RS. Report of a symposium: adverse responses to intravenous agents. *Br J Anaesth* 1978; **50**: 1159–64

5. Vignon H, Gay R, Laxenaire MC. Clinical observations of per- and post-anesthetic anaphylactoid complications. Results of an a posteriori survey. *Ann Anesthesiol Fr* 1976; **17**: 117–21
6. Garvey LH, Roed-Petersen J, Menne T, Husum B. Danish anaesthesia allergy centre — preliminary results. *Acta Anaesthesiol Scand* 2001; **45**: 1204–9
7. Harboe T, Guttormsen AB, Irgens A, Dybendal T, Florvaag E. Anaphylaxis during anesthesia in Norway: a 6-year single-center follow-up study. *Anesthesiology* 2005; **102**: 897–903
8. Sadleir PH, Clarke RC, Bunning DL, Platt PR. Anaphylaxis to neuromuscular blocking drugs: incidence and cross-reactivity in Western Australia from 2002 to 2011. *Br J Anaesth* 2013; **110**: 981–7
9. Fisher MM, Jones K, Rose M. Follow-up after anaesthetic anaphylaxis. *Acta Anaesthesiol Scand* 2011; **55**: 99–103
10. Reddy JI, Cooke PJ, van Schalkwyk JM, Hannam JA, Fitzharris P, Mitchell SJ. Anaphylaxis is more common with rocuronium and succinylcholine than with atracurium. *Anesthesiology* 2015; **122**: 39–45
11. Takazawa T, Mitsuhata H, Mertes PM. Sugammadex and rocuronium-induced anaphylaxis. *J Anesth* 2016; **30**: 290–7
12. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
13. Lobera T, Audicana MT, Pozo MD, et al. Study of hypersensitivity reactions and anaphylaxis during anesthesia in Spain. *J Investig Allergol Clin Immunol* 2008; **18**: 350–6
14. Ebo DG, Hagendorens MM, Bridts CH, De Clerck LS, Stevens WJ. Allergic reactions occurring during anaesthesia: diagnostic approach. *Acta Clin Belg* 2004; **59**: 34–43
15. Mota I, Gaspar A, Benito-Garcia F, Correia M, Chambel M, Morais-Almeida M. Drug-induced anaphylaxis: seven-year single-center survey. *Eur Ann Allergy Clin Immunol* 2018; **50**: 211–6
16. Lapisatepun W, Charuluxananan S, Kusumaphanyo C, Ittichaikulthol W, Suksompong S, Ratanachai P. The Thai anesthesia incident monitoring study of perioperative allergic reactions: an analysis of 1996 incidents reports. *J Med Assoc Thai* 2008; **91**: 1524–30
17. Saager L, Turan A, Egan C, et al. Incidence of intraoperative hypersensitivity reactions: a registry analysis: a registry analysis. *Anesthesiology* 2015; **122**: 551–9
18. Florvaag E, Johansson SG, Oman H, et al. Prevalence of IgE antibodies to morphine. Relation to the high and low incidences of NMBA anaphylaxis in Norway and Sweden, respectively. *Acta Anaesthesiol Scand* 2005; **49**: 437–44
19. Tacquard C, Collange O, Gomis P, et al. Anaesthetic hypersensitivity reactions in France between 2011 and 2012: the 10th GERAP epidemiologic survey. *Acta Anaesthesiol Scand* 2017; **61**: 290–9
20. Dong SW, Mertes PM, Petitpain N, Hasdenteufel F, Malinovsky JM. Hypersensitivity reactions during anesthesia. Results from the ninth French survey (2005–2007). *Minerva Anestesiol* 2012; **78**: 868–78
21. Mertes PM, Malinovsky JM, Mouton-Faivre C, et al. Anaphylaxis to dyes during the perioperative period: reports of 14 clinical cases. *J Allergy Clin Immunol* 2008; **122**: 348–52
22. Garvey LH, Kroigaard M, Poulsen LK, et al. IgE-mediated allergy to chlorhexidine. *J Allergy Clin Immunol* 2007; **120**: 409–15
23. Galletly DC, Treuren BC. Anaphylactoid reactions during anaesthesia. Seven years' experience of intradermal testing. *Anaesthesia* 1985; **40**: 329–33
24. Savic LC, Kaura V, Yusaf M, et al. Incidence of suspected perioperative anaphylaxis: a multicenter snapshot study. *J Allergy Clin Immunol Pract* 2015; **3**: 454–5. e1
25. Gibbs NM, Sadleir PH, Clarke RC, Platt PR. Survival from perioperative anaphylaxis in Western Australia 2000–2009. *Br J Anaesth* 2013; **111**: 589–93
26. Charuluxananan S, Punjasawadwong Y, Suraseranivongse S, et al. The Thai Anesthesia Incidents Study (Thai Study) of anesthetic outcomes: II. Anesthetic profiles and adverse events. *J Med Assoc Thai* 2005; **88**: S14–29
27. Escolano F, Valero A, Huguet J, et al. Prospective epidemiologic study of perioperative anaphylactoid reactions occurring in Catalonia (1996–7). *Rev Esp Anestesiol Reanim* 2002; **49**: 286–93
28. Mitsuhata H, Matsumoto S, Hasegawa J. The epidemiology and clinical features of anaphylactic and anaphylactoid reactions in the perioperative period in Japan. *Masui* 1992; **41**: 1664–9
29. Laxenaire MC, Moneret-Vautrin DA, Boileau S, Moeller R. Adverse reactions to intravenous agents in anaesthesia in France. *Klin Wochenschr* 1982; **60**: 1006–9
30. Watkins J. Adverse anaesthetic reactions. An update from a proposed national reporting and advisory service. *Anaesthesia* 1985; **40**: 797–800
31. Berroa F, Lafuente A, Javaloyes G, et al. The incidence of perioperative hypersensitivity reactions: a single-center, prospective, cohort study. *Anesth Analg* 2015; **121**: 117–23
32. Dea Ebo. Molecular mechanisms and pathophysiology of perioperative hypersensitivity and anaphylaxis. *Br J Anaesth* 2019; **123**: e38–49
33. Volcheck GW, Mertes PM. Local and general anesthetics immediate hypersensitivity reactions. *Immunol Allergy Clin North Am* 2014; **34**: 525–46 [viii]
34. McNeil BD, Pundir P, Meeker S, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature* 2015; **519**: 237–41
35. Mertes PM, Volcheck GW, Garvey LH, et al. Epidemiology of perioperative anaphylaxis. *Presse Med* 2016; **45**: 758–67
36. Laxenaire MC. [Epidemiology of anesthetic anaphylactoid reactions. Fourth multicenter survey (July 1994–December 1996)]. *Ann Fr Anesth Reanim* 1999; **18**: 796–809 (in French)
37. Spoerl D, Nigolian H, Czarnetzki C, Harr T. Reclassifying anaphylaxis to neuromuscular blocking agents based on the presumed patho-mechanism: IgE-mediated, pharmacological adverse reaction or "innate hypersensitivity"? *Int J Mol Sci* 2017; **18**
38. Mertes PM, Alla F, Trechot P, Auroy Y, Jougla E. Anaphylaxis during anesthesia in France: an 8-year national survey. *J Allergy Clin Immunol* 2011; **128**: 366–73
39. Reitter M, Petitpain N, Latarche C, et al. Fatal anaphylaxis with neuromuscular blocking agents: a risk factor and management analysis. *Allergy* 2014; **69**: 954–9
40. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: management and outcomes in the 6th National Audit Project (NAP6). *Paediatr Anaesth* 2018; **121**: 172–88
41. Garvey LH, Belhage B, Kroigaard M, Husum B, Malling HJ, Mosbech H. Treatment with epinephrine (adrenaline) in

suspected anaphylaxis during anesthesia in Denmark. *Anesthesiology* 2011; **115**: 111–6
42. Mitsuhata H, Hasegawa J, Matsumoto S, Ogawa R. The epidemiology and clinical features of anaphylactic and anaphylactoid reactions in the perioperative period in Japan: a survey with a questionnaire of 529 hospitals approved by Japan Society of Anesthesiology. *Masui* 1992; **41**: 1825–31
43. Hepner DL, Castells MC. Anaphylaxis during the perioperative period. *Anesth Analg* 2003; **97**: 1381–95
44. Antunes J, Kochuyt AM, Ceuppens JL. Perioperative allergic reactions: experience in a Flemish referral centre. *Allergol Immunopathol (Madr)* 2014; **42**: 348–54
45. Leysen J, De Witte L, Bridts CH, Ebo DG. Anaphylaxis during general anaesthesia: a 10-year survey at the University hospital of Antwerp. *P Belg Roy Acad Med* 2013; **2**: 12
46. Laxenaire MC, Mertes PM. Anaphylaxis during anaesthesia. Results of a two-year survey in France. *Br J Anaesth* 2001; **87**: 549–58
47. Mertes PM, Laxenaire MC. Anaphylactic and anaphylactoid reactions occurring during anaesthesia in France. Seventh epidemiologic survey (January 2001–December 2002). *Ann Fr Anesth Reanim* 2004; **23**: 1133–43
48. Mertes PM, Laxenaire MC, Alla F. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999–2000. *Anesthesiology* 2003; **99**: 536–45
49. Cho YJ, Ju JW, Sim H, et al. Intraoperative anaphylaxis to neuromuscular blocking agents: the incidence over 9 years at two tertiary hospitals in South Korea: a retrospective observational study. *Eur J Anaesthesiol* 2016; **33**: 368–78
50. Gurrieri C, Weingarten TN, Martin DP, et al. Allergic reactions during anesthesia at a large United States referral center. *Anesth Analg* 2011; **113**: 1202–12
51. Guyer AC, Saff RR, Conroy M, et al. Comprehensive allergy evaluation is useful in the subsequent care of patients with drug hypersensitivity reactions during anesthesia. *J Allergy Clin Immunol Pract* 2015; **3**: 94–100
52. Gonzalez-Estrada A, Pien LC, Zell K, Wang XF, Lang DM. Antibiotics are an important identifiable cause of perioperative anaphylaxis in the United States. *J Allergy Clin Immunol Pract* 2015; **3**: 101–105.e1
53. de Pater GH, Florvaag E, Johansson SG, Irgens A, Petersen MN, Guttormsen AB. Six years without pholcodine; Norwegians are significantly less IgE-sensitized and clinically more tolerant to neuromuscular blocking agents. *Allergy* 2017; **72**: 813–9
54. Florvaag E, Johansson SG, Irgens A, de Pater GH. IgE-sensitization to the cough suppressant pholcodine and the effects of its withdrawal from the Norwegian market. *Allergy* 2011; **66**: 955–60
55. Baldo BA, Fisher MM. Substituted ammonium ions as allergenic determinants in drug allergy. *Nature* 1983; **306**: 262–4
56. Baldo BA, Fisher MM, Pham NH. On the origin and specificity of antibodies to neuromuscular blocking (muscle relaxant) drugs: an immunochemical perspective. *Clin Exp Allergy* 2009; **39**: 325–44
57. Mertes PM, Aimone-Gastin I, Gueant-Rodriguez RM, et al. Hypersensitivity reactions to neuromuscular blocking agents. *Curr Pharm Des* 2008; **14**: 2809–25
58. Petitpain N, Argoullon L, Masmoudi K, et al. Neuromuscular blocking agents induced anaphylaxis: results and trends of a French Pharmacovigilance survey from 2000 to 2012. *Allergy* 2018
59. Chiriac AM, Tacquard C, Fadhel NB, et al. Safety of subsequent general anaesthesia in patients allergic to neuromuscular blocking agents: value of allergy skin testing. *Br J Anaesth* 2018; **120**: 1437–40
60. Tacquard C, Laroche D, Stenger R, et al. Diagnostic procedure after an immediate hypersensitivity reaction in the operating room. *Presse Med* 2016; **45**: 784–90
61. Mertes PM, Volcheck GW. Anaphylaxis to neuromuscular-blocking drugs: all neuromuscular-blocking drugs are not the same. *Anesthesiology* 2015; **122**: 5–7
62. Guttormsen AB. Allergic reactions during anaesthesia — increased attention to the problem in Denmark and Norway. *Acta Anaesthesiol Scand* 2001; **45**: 1189–90
63. Dong S, Acouetey DS, Gueant-Rodriguez RM, et al. Prevalence of IgE against neuromuscular blocking agents in hairdressers and bakers. *Clin Exp Allergy* 2013; **43**: 1256–62
64. Florvaag E, Johansson SG. The Pholcodine Case. Cough medicines, IgE-sensitization, and anaphylaxis: a devious connection. *World Allergy Organ J* 2012; **5**: 73–8
65. Harboe T, Johansson SG, Florvaag E, Oman H. Pholcodine exposure raises serum IgE in patients with previous anaphylaxis to neuromuscular blocking agents. *Allergy* 2007; **62**: 1445–50
66. Johansson SG, Florvaag E, Oman H, et al. National pholcodine consumption and prevalence of IgE-sensitization: a multicentre study. *Allergy* 2010; **65**: 498–502
67. Katelaris CH, Kurosawa M, Moon HB, Borres M, Florvaag E, Johansson SG. Pholcodine consumption and immunoglobulin E-sensitization in atopics from Australia, Korea, and Japan. *Asia Pac Allergy* 2014; **4**: 86–90
68. Johansson SG, Oman H, Nopp A, Florvaag E. Pholcodine caused anaphylaxis in Sweden 30 years ago. *Allergy* 2009; **64**: 820–1
69. Miyazaki Y, Sunaga H, Kida K, et al. Incidence of anaphylaxis associated with sugammadex. *Anesth Analg* 2018; **126**: 1505–8
70. Takazawa T, Lida H. Current status of sugammadex usage and the occurrence of sugammadex-induced anaphylaxis in Japan. *APSF Newsl* 2018; **33**: 11–2
71. Corda D. The anaphylactic risk. *APSF Newsl* 2018; **33**: 11–2
72. de Kam PJ, Nolte H, Good S, et al. Sugammadex hypersensitivity and underlying mechanisms: a randomised study of healthy non-anaesthetised volunteers. *Br J Anaesth* 2018; **121**: 758–67
73. Min KC, Bondiskey P, Schulz V, et al. Hypersensitivity incidence after sugammadex administration in healthy subjects: a randomised controlled trial. *Br J Anaesth* 2018; **121**: 749–57
74. Savic L, Savic S, Hopkins PM. Sugammadex: the sting in the tail? *Br J Anaesth* 2018; **121**: 694–7
75. Hotta E, Tamagawa-Mineoka R, Masuda K, et al. Anaphylaxis caused by gamma-cyclodextrin in sugammadex. *Allergol Int* 2016; **65**: 356–8
76. Munro IC, Newberne PM, Young VR, Bar A. Safety assessment of gamma-cyclodextrin. *Regul Toxicol Pharmacol* 2004; **39**: S3–13
77. Tsur A, Kalansky A. Hypersensitivity associated with sugammadex administration: a systematic review. *Anaesthesia* 2014; **69**: 1251–7

78. Ho G, Clarke RC, Sadleir PH, Platt PR. The first case report of anaphylaxis caused by the inclusion complex of rocuronium and sugammadex. *A A Case Rep* 2016; **7**: 190–2
79. Yamaoka M, Deguchi M, Ninomiya K, Kurasako T, Matsumoto M. A suspected case of rocuronium–sugammadex complex-induced anaphylactic shock after cesarean section. *J Anesth* 2017; **31**: 148–51
80. Okuno A, Matsuki Y, Tabata M, Shigemi K. A suspected case of coronary vasospasm induced by anaphylactic shock caused by rocuronium–sugammadex complex. *J Clin Anesth* 2018; **48**: 7
81. Kim GH, Choi WS, Kim JE, et al. Anaphylactic shock after sugammadex administration, induced by formation of a sugammadex–rocuronium complex. *Korean J Anesthesiol* 2018
82. Baldo BA. Anaphylaxis caused by sugammadex–rocuronium inclusion complex: what is the basis of the allergenic recognition? *J Clin Anesth* 2018; **54**: 48–9
83. Asserhoj LL, Mosbech H, Kroigaard M, Garvey LH. No evidence for contraindications to the use of propofol in adults allergic to egg, soy or peanutdagger. *Br J Anaesth* 2016; **116**: 77–82
84. Molina-Infante J, Arias A, Vara-Brenes D, et al. Propofol administration is safe in adult eosinophilic esophagitis patients sensitized to egg, soy, or peanut. *Allergy* 2014; **69**: 388–94
85. Richard C, Beaudouin E, Moneret-Vautrin DA, Kohler C, Nguyen-Grosjean VM, Jacquenet S. Severe anaphylaxis to Propofol: first case of evidence of sensitization to soy oil. *Eur Ann Allergy Clin Immunol* 2016; **48**: 103–6
86. Murphy A, Campbell DE, Baines D, Mehr S. Allergic reactions to propofol in egg-allergic children. *Anesth Analg* 2011; **113**: 140–4
87. Harper NJ. Propofol and food allergy. *Br J Anaesth* 2016; **116**: 11–3
88. Lansu K, Karpiak J, Liu J, et al. In silico design of novel probes for the atypical opioid receptor MRGPRX2. *Nat Chem Biol* 2017; **13**: 529–36
89. Navines-Ferrer A, Serrano-Candelas E, Lafuente A, Munoz-Cano R, Martin M. MRGPRX2-mediated mast cell response to drugs used in perioperative procedures and anaesthesia. *Sci Report 8* 2018; **8**: 11628
90. Blunk JA, Schmelz M, Zeck S, Skov P, Likar R, Koppert W. Opioid-induced mast cell activation and vascular responses is not mediated by mu-opioid receptors: an in vivo microdialysis study in human skin. *Anesth Analg* 2004; **98**: 364–70 [table of contents]
91. Baldo BA, Pham NH. Histamine-releasing and allergenic properties of opioid analgesic drugs: resolving the two. *Anaesth Intensive Care* 2012; **40**: 216–35
92. Swerts S, Van Gasse A, Leysen J, et al. Allergy to illicit drugs and narcotics. *Clin Exp Allergy* 2014; **44**: 307–18
93. Nasser SM, Ewan PW. Opiate-sensitivity: clinical characteristics and the role of skin prick testing. *Clin Exp Allergy* 2001; **31**: 1014–20
94. Van Gasse AL, Hagendorens MM, Sabato V, Bridts CH, De Clerck LS, Ebo DG. IgE to poppy seed and morphine are not useful tools to diagnose opiate allergy. *J Allergy Clin Immunol Pract* 2015; **3**: 396–9
95. Fisher MM, Baldo BA. The incidence and clinical features of anaphylactic reactions during anesthesia in Australia. *Ann Fr Anesth Reanim* 1993; **12**: 97–104
96. Lieberman P. Anaphylactic reactions during surgical and medical procedures. *J Allergy Clin Immunol* 2002; **110**: S64–9
97. Kvisselgaard AD, Mosbech HF, Fransson S, Garvey LH. Risk of Immediate-type allergy to local anesthetics is overestimated—results from 5 years of provocation testing in a Danish allergy clinic. *J Allergy Clin Immunol Pract* 2018; **6**: 1217–23
98. Fisher MM, Bowey CJ. Alleged allergy to local anaesthetics. *Anaesth Intensive Care* 1997; **25**: 611–4
99. Malinovsky JM, Chiriac AM, Tacquard C, Mertes PM, Demoly P. Allergy to local anesthetics: reality or myth? *Presse Med* 2016; **45**: 753–7
100. Saff RR. Immediate local anesthetic reactions: too quick to point the finger? *J Allergy Clin Immunol Pract* 2018; **6**: 1224–5
101. Mertes PM, Lambert M, Gueant-Rodriguez RM, et al. Perioperative anaphylaxis. *Immunol Allergy Clin North Am* 2009; **29**: 429–51
102. Christiansen IS, Kroigaard M, Mosbech H, Skov PS, Poulsen LK, Garvey LH. Clinical and diagnostic features of perioperative hypersensitivity to cefuroxime. *Clin Exp Allergy* 2015; **45**: 807–14
103. Chong YY, Caballero MR, Lukawska J, Dugue P. Anaphylaxis during general anaesthesia: one-year survey from a British allergy clinic. *Singapore Med J* 2008; **49**: 483–7
104. Torres MJ, Blanca M, Fernandez J, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003; **58**: 961–72
105. Kim MH, Lee JM. Diagnosis and management of immediate hypersensitivity reactions to cephalosporins. *Allergy Asthma Immunol Res* 2014; **6**: 485–95
106. Macy E. Penicillin allergy: optimizing diagnostic protocols, public health implications, and future research needs. *Curr Opin Allergy Clin Immunol* 2015; **15**: 308–13
107. Uyttebroek AP, Decuyper II , Bridts CH, et al. Cefazolin hypersensitivity: toward optimized diagnosis. *J Allergy Clin Immunol Pract* 2016; **4**: 1232–6
108. Ebo DG, Faber M, Elst J, et al. In vitro diagnosis of immediate drug hypersensitivity during anesthesia: a review of the literature. *J Allergy Clin Immunol Pract* 2018; **6**: 1176–84
109. Marinho S, Kemp H, Cook TM, et al. Cross-sectional study of perioperative drug and allergen exposure in UK practice in 2016: the 6th National Audit Project (NAP6) Allergen Survey. *Br J Anaesth* 2018; **121**: 146–58
110. Krishna MT, Huissoon AP, Li M, et al. Enhancing antibiotic stewardship by tackling "spurious" penicillin allergy. *Clin Exp Allergy* 2017; **47**: 1362–73
111. Trubiano JA, Thursky KA, Stewardson AJ, et al. Impact of an integrated antibiotic allergy testing program on antimicrobial stewardship: a multicenter evaluation. *Clin Infect Dis* 2017; **65**: 166–74
112. Novalbos A, Sastre J, Cuesta J, et al. Lack of allergic cross-reactivity to cephalosporins among patients allergic to penicillins. *Clin Exp Allergy* 2001; **31**: 438–43
113. Haslam S, Yen D, Dvirnik N, Engen D. Cefazolin use in patients who report a non-IgE mediated penicillin allergy: a retrospective look at adverse reactions in arthroplasty. *Iowa Orthop J* 2012; **32**: 100–3
114. Savic, et al. Management of the surgical patient with a label of penicillin allergy. *Br J Anaesth* 2019; **123**: e82–94

115. Trubiano JA, Stone CA, Grayson ML, et al. The 3 Cs of antibiotic allergy—classification, cross-reactivity, and collaboration. *J Allergy Clin Immunol Pract* 2017; **5**: 1532–42
116. Harper NJ, Dixon T, Dugue P, et al. Suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia* 2009; **64**: 199–211
117. Stern G. Überempfindlichkeit gegen Kautschuk als Ursache von Urticaria und Quinckeschem Ödem. *Klin Wochenschr* 1927; **6**: 1096–7
118. Grimm A. Überempfindlichkeit gegen Kautschuk als Ursache von Urticaria und Quinckeschem Ödem. *Klin Wochenschr* 1927; **6**: 1479
119. Turjanmaa K, Reunala T, Tuimala R, Karkkainen T. Severe IgE-mediated allergy to surgical gloves. *Allergy* 1984; **39**: 35
120. Slater JE. Rubber anaphylaxis. *N Engl J Med* 1989; **320**: 1126–30
121. Moneret-Vautrin DA, Mata E, Gueant JL, Turgeman D, Laxenaire MC. High risk of anaphylactic shock during surgery for spina bifida. *Lancet* 1990; **335**: 865–6
122. Raulf-Heimsoth M, Rihs HP, Rozynek P, et al. Quantitative analysis of immunoglobulin E reactivity profiles in patients allergic or sensitized to natural rubber latex (*Hevea brasiliensis*). *Clin Exp Allergy* 2007; **37**: 1657–67
123. Raulf M. The latex story. *Chem Immunol Allergy* 2014; **100**: 248–55
124. Michael T, Niggemann B, Moers A, Seidel U, Wahn U, Scheffner D. Risk factors for latex allergy in patients with spina bifida. *Clin Exp Allergy* 1996; **26**: 934–9
125. Ausili E, Tabacco F, Focarelli B, Nucera E, Patriarca G, Rendeli C. Prevalence of latex allergy in spina bifida: genetic and environmental risk factors. *Eur Rev Med Pharmacol Sci* 2007; **11**: 149–53
126. Cremer R, Lorbacher M, Hering F, Engelskirchen R. Natural rubber latex sensitisation and allergy in patients with spina bifida, urogenital disorders and oesophageal atresia compared with a normal paediatric population. *Eur J Pediatr Surg* 2007; **17**: 194–8
127. Bousquet J, Flahault A, Vandenplas O, et al. Natural rubber latex allergy among health care workers: a systematic review of the evidence. *J Allergy Clin Immunol* 2006; **118**: 447–54
128. Charous BL, Hamilton RG, Yunginger JW. Occupational latex exposure: characteristics of contact and systemic reactions in 47 workers. *J Allergy Clin Immunol* 1994; **94**: 12–8
129. Meglio P, Arabito E, Plantamura M, Businco L. Prevalence of latex allergy and evaluation of some risk factors in a population of atopic children. *J Investig Allergol Clin Immunol* 2002; **12**: 250–6
130. Wudy AE, Negro C, Adami A, Larese Filon F. Atopic status and latex sensitization in a cohort of 1,628 students of health care faculties. *Ann Allergy Asthma Immunol* 2017; **118**: 603–7
131. Wagner S, Breiteneder H. The latex-fruit syndrome. *Biochem Soc Trans* 2002; **30**: 935–40
132. Blanco C. Latex-fruit syndrome. *Curr Allergy Asthma Rep* 2003; **3**: 47–53
133. Draisci G, Nucera E, Pollastrini E, et al. Anaphylactic reactions during cesarean section. *Int J Obstet Anesth* 2007; **16**: 63–7
134. Draisci G, Zanfini BA, Nucera E, et al. Latex sensitization: a special risk for the obstetric population? *Anesthesiology* 2011; **114**: 565–9
135. Habre W, Disma N, Virag K, et al. Incidence of severe critical events in paediatric anaesthesia (APRICOT): a prospective multicentre observational study in 261 hospitals in Europe. *Lancet Respir Med* 2017; **5**: 412–25
136. Blaabjerg MS, Andersen KE, Bindslev-Jensen C, Mortz CG. Decrease in the rate of sensitization and clinical allergy to natural rubber latex. *Contact Dermat* 2015; **73**: 21–8
137. Supapvanich C, Povey AC, De Vocht F. Latex sensitization and risk factors in female nurses in Thai governmental hospitals. *Int J Occup Med Environ Health* 2014; **27**: 93–103
138. Garvey LH. Old, new and hidden causes of perioperative hypersensitivity. *Curr Pharm Des* 2016; **22**: 6814–24
139. Kowalski ML, Asero R, Bavbek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy* 2013; **68**: 1219–32
140. de Paramo BJ, Gancedo SQ, Cuevas M, Camo IP, Martin JA, Cosmes EL. Paracetamol (acetaminophen) hypersensitivity. *Ann Allergy Asthma Immunol* 2000; **85**: 508–11
141. Jain SS, Green S, Rose M. Anaphylaxis following intravenous paracetamol: the problem is the solution. *Anaesth Intensive Care* 2015; **43**: 779–81
142. Mertes PM, Malinovsky JM, Jouffroy L, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2011; **21**: 442–53
143. Okano M, Nomura M, Hata S, et al. Anaphylactic symptoms due to chlorhexidine gluconate. *Arch Dermatol* 1989; **125**: 50–2
144. Infection control NICE. Prevention of healthcare-associated infections in primary and community care. *Natl Inst Health Clin Excell Guidance 2003* 2012. Available from: https://www.nice.org.uk/Guidance/CG139. [Accessed 12 August 2018]
145. Odedra KM, Farooque S. Chlorhexidine: an unrecognised cause of anaphylaxis. *Postgrad Med J* 2014; **90**: 709–14
146. Krishna MT, York M, Chin T, et al. Multi-centre retrospective analysis of anaphylaxis during general anaesthesia in the United Kingdom: aetiology and diagnostic performance of acute serum tryptase. *Clin Exp Immunol* 2014; **178**: 399–404
147. Sharp G, Green S, Rose M. Chlorhexidine-induced anaphylaxis in surgical patients: a review of the literature. *ANZ J Surg* 2016; **86**: 237–43
148. Oda T, Hamasaki J, Kanda N, Mikami K. Anaphylactic shock induced by an antiseptic-coated central venous [correction of nervous] catheter. *Anesthesiology* 1997; **87**: 1242–4
149. Nightingale SL. From the food and drug administration. *Jama* 1998; **279**: 1684
150. Therapeutic Goods Administration (TGA). *Medicines Saf Update* June 2012; **3**(Number 3). Available from: https://www.tga.gov.au/publication-issue/medicines-safety-update-volume-3-number-3-june-2012. [Accessed 19 September 2018]
151. Terazawa E, Shimonaka H, Nagase K, Masue T, Dohi S. Severe anaphylactic reaction due to a chlorhexidine-impregnated central venous catheter. *Anesthesiology* 1998; **89**: 1296–8
152. Peutrell JM. Anaphylactoid reaction to topical chlorhexidine during anaesthesia. *Anaesthesia* 1992; **47**: 1013
153. Ohtoshi T, Yamauchi N, Tadokoro K, et al. IgE antibody-mediated shock reaction caused by topical application of chlorhexidine. *Clin Allergy* 1986; **16**: 155–61
154. *Guidelines for the prevention of intravascular catheter-related infections* 2011. Available from: https://www.cdc.gov/infectioncontrol/guidelines/pdf/bsi/bsi-guidelines-H.pdf. [Accessed 12 August 2018]

155. Bahal S, Sharma S, Garvey LH, Nagendran V. Anaphylaxis after disinfection with 2% chlorhexidine wand applicator. *BMJ Case Rep* 2017; **2017**
156. Rose MA, Garcez T, Savic S, et al. Chlorhexidine allergy in the perioperative setting: a narrative review. *Br J Anaesth* 2019; **123**: e95–103
157. Caballero MR, Lukawska J, Dugue P. A hidden cause of perioperative anaphylaxis. *J Investig Allergol Clin Immunol* 2010; **20**: 353–4
158. Le Pabic F, Sainte-Laudy J, Blanchard N, Moneret-Vautrin DA. First case of anaphylaxis to iodinated povidone. *Allergy* 2003; **58**: 826–7
159. Kopp WL. Anaphylaxis from alphazurine 2G during lymphography. *JAMS* 1966; **198**: 668–9
160. Sinclair DJ, Perera FA. Allergic reactions: following patent blue dye injection. *Can Med Assoc J* 1969; **101**: 100–1
161. Brenet O, Laloureey L, Queinnec M, et al. Hypersensitivity reactions to Patent Blue V in breast cancer surgery: a prospective multicentre study. *Acta Anaesthesiol Scand* 2013; **57**: 106–11
162. Ishiyama T, Kotoda M, Asano N, et al. The effects of Patent Blue dye on peripheral and cerebral oxyhaemoglobin saturations. *Anaesthesia* 2015; **70**: 429–33
163. Scherer K, Studer W, Figueiredo V, Bircher AJ. Anaphylaxis to isosulfan blue and cross-reactivity to patent blue V: case report and review of the nomenclature of vital blue dyes. *Ann Allergy Asthma Immunol* 2006; **96**: 497–500
164. Keller B, Yawalkar N, Pichler C, Braathen LR, Hunger RE. Hypersensitivity reaction against patent blue during sentinel lymph node removal in three melanoma patients. *Am J Surg* 2007; **193**: 122–4
165. Ebo DG, Wets RD, Spiessens TK, Bridts CH, Stevens WJ. Flow-assisted diagnosis of anaphylaxis to patent blue. *Allergy* 2005; **60**: 703–4
166. Barthelmes L, Goyal A, Newcombe RG, McNeill F, Mansel RE. Adverse reactions to patent blue V dye — the NEW START and ALMANAC experience. *Eur J Surg Oncol* 2010; **36**: 399–403
167. Platt P, Roberts L. Anaphylaxis to patent blue dye—misadventure or misdemeanour? *Anaesth Intensive Care* 2011; **39**: 166–7
168. Montgomery LL, Thorne AC, Van Zee KJ, et al. Isosulfan blue dye reactions during sentinel lymph node mapping for breast cancer. *Anesth Analg* 2002; **95**: 385–8 [table of contents]
169. Paulinelli RR, Freitas-Junior R, Rahal RM, et al. A prospective randomized trial comparing patent blue and methylene blue for the detection of the sentinel lymph node in breast cancer patients. *Rev Assoc Med Bras* 1992; **2017**: 118–23
170. Rzymski P, Wozniak J, Opala T, Wilczak M, Sajdak S. Anaphylactic reaction to methylene blue dye after laparoscopic chromopertubation. *Int J Gynaecol Obstet* 2003; **81**: 71–2
171. Mertes PM, Demoly P, Alperovitch A, et al. Methylene blue-treated plasma: an increased allergy risk? *J Allergy Clin Immunol* 2012; **130**: 808–12
172. Dewachter P, Mouton-Faivre C, Trechot P, Lleu JC, Mertes PM. Severe anaphylactic shock with methylene blue instillation. *Anesth Analg* 2005; **101**: 149–50 [table of contents]
173. Laxenaire MC, Charpentier C, Feldman L. Anaphylactoid reactions to colloid plasma substitutes: incidence, risk factors, mechanisms. A French multicenter prospective study. *Ann Fr Anesth Reanim* 1994; **13**: 301–10
174. Barron ME, Wilkes MM, Navickis RJ. A systematic review of the comparative safety of colloids. *Arch Surg* 2004; **139**: 552–63
175. Lorenz W, Duda D, Dick W, et al. Incidence and clinical importance of perioperative histamine release: randomised study of volume loading and antihistamines after induction of anaesthesia. Trial Group Mainz/Marburg. *Lancet* 1994; **343**: 933–40
176. Hedin H, Ljungstrom KG. Prevention of dextran anaphylaxis. Ten years experience with hapten dextran. *Int Arch Allergy Immunol* 1997; **113**: 358–9
177. Kemp HI, Cook TM, Thomas M, Harper NJN. UK anaesthetists' perspectives and experiences of severe perioperative anaphylaxis: NAP6 baseline survey. *Br J Anaesth* 2017; **119**: 132–9
178. Tacquard C, Boudjedir K, Carlier M, Muller JY, Gomis P, Mertes PM. Hypersensitivity transfusion reactions due to IgA deficiency are rare according to French hemovigilance data. *J Allergy Clin Immunol* 2017; **140**: 884–5
179. Mertes PM, Bazin A, Alla F, et al. Hypersensitivity reactions to blood components: document issued by the allergy committee of the French medicines and healthcare products regulatory agency. *J Investig Allergol Clin Immunol* 2011; **21**: 171–8
180. Squires JE. Risks of transfusion. *South Med J* 2011; **104**: 762–9
181. Rapport ANSM. *d'activité hémovigilance* 2016. Available from: https://ansm.sante.fr/var/ansm_site/storage/original/application/878213f5896bb59ca330bca39164ee16.pdf. [Accessed 8 December 2018]
182. Muniz-Diaz E, Puig L. Allergic and anaphylactic reactions to methylene-blue-treated plasma in Catalonia in the period 2008–2013. *Blood Transfus* 2014; **12**: 628–30
183. Mitsuhata H, Horiguchi Y, Saitoh J, et al. An anaphylactic reaction to topical fibrin glue. *Anesthesiology* 1994; **81**: 1074–7
184. Oswald AM, Joly LM, Gury C, Disdet M, Leduc V, Kanny G. Fatal intraoperative anaphylaxis related to aprotinin after local application of fibrin glue. *Anesthesiology* 2003; **99**: 762–3
185. Dietrich W, Ebell A, Busley R, Boulesteix AL. Aprotinin and anaphylaxis: analysis of 12,403 exposures to aprotinin in cardiac surgery. *Ann Thorac Surg* 2007; **84**: 1144–50
186. Beierlein W, Scheule AM, Dietrich W, Ziemer G. Forty years of clinical aprotinin use: a review of 124 hypersensitivity reactions. *Ann Thorac Surg* 2005; **79**: 741–8
187. Levy JH, Adkinson Jr NF. Anaphylaxis during cardiac surgery: implications for clinicians. *Anesth Analg* 2008; **106**: 392–403
188. Valchanov K, Falter F, George S, et al. Three cases of anaphylaxis to protamine: management of anticoagulation reversal. *J Cardiothorac Vasc Anesth* 2019; **33**: 482–6
189. Levy JH, Schwieger IM, Zaidan JR, Faraj BA, Weintraub WS. Evaluation of patients at risk for protamine reactions. *J Thorac Cardiovasc Surg* 1989; **98**: 200–4
190. Levy JH, Zaidan JR, Faraj B. Prospective evaluation of risk of protamine reactions in patients with NPH insulin-dependent diabetes. *Anesth Analg* 1986; **65**: 739–42

Handling editor: H.C. Hemmings Jr

BJA

British Journal of Anaesthesia, 123 (1): e29–e37 (2019)

doi: 10.1016/j.bja.2019.02.029
Advance Access Publication Date: 24 April 2019
Special Article

Consensus clinical scoring for suspected perioperative immediate hypersensitivity reactions

P. M. Hopkins[1,2,*,†,#], P. J. Cooke[3,#,†], R. C. Clarke[4,5,#,†], A. B. Guttormsen[6,7,#,†], P. R. Platt[4,5,#,†], P. Dewachter[8,9,†], D. G. Ebo[10,†], T. Garcez[11,†], L. H. Garvey[12,13,†], D. L. Hepner[14,†], D. A. Khan[15,†], H. Kolawole[16,17,†], P. Kopac[18,†], M. Krøigaard[12,†], J. J. Laguna[19,†], S. D. Marshall[16,17,†], P. M. Mertes[20,†], M. A. Rose[21,†], V. Sabato[10,†], L. C. Savic[2,†], S. Savic[22,†], T. Takazawa[23,†], G. W. Volcheck[24,†], S. Voltolini[25,†] and P. H. M. Sadleir[4,5,26,#,†]

[1]Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK, [2]Anaesthetic Department, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [3]Department of Anaesthesia and Perioperative Medicine, Auckland City Hospital, Auckland, New Zealand, [4]Department of Anaesthesia, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia, [5]Anaesthetic Allergy Referral Centre of Western Australia, Nedlands, Western Australia, Australia, [6]Department of Anaesthesia and Intensive Care, Haukeland University Hospital, Bergen, Norway, [7]Department of Clinical Medicine, University of Bergen, Bergen, Norway, [8]Service d'Anesthésie-Réanimation, Groupe Hospitalier de Paris-Seine-Saint-Denis, Assistance Publique-Hôpitaux de Paris, Paris, France, [9]Université Paris 13, Sorbonne-Paris-Cité, Paris, France, [10]Department of Immunology, Allergology and Rheumatology, University of Antwerp, Antwerp University Hospital, Belgium, [11]Department of Immunology, Manchester University NHS Foundation Trust, Manchester, United Kingdom, [12]Danish Anaesthesia Allergy Centre, Allergy Clinic, Department of Dermatology and Allergy, Copenhagen University Hospital, Gentofte, Denmark, [13]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, [14]Department of Anesthesiology, Brigham and Women's Hospital, Boston, MA, USA, [15]Department of Internal Medicine, Division of Allergy and Immunology, University of Texas Southwestern Medical Center, Dallas, TX, USA, [16]Department of Anaesthesia and Perioperative Medicine, Monash University, Melbourne, Australia, [17]Department of Anaesthesia, Peninsula Health, Melbourne, Australia, [18]University Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia, [19]Allergy Unit, Allergo-Anaesthesia Unit, Hospital Central de la Cruz Roja, Faculty of Medicine, Alfonso X. El Sabio University, ARADyAL, Madrid, Spain, [20]Department of Anesthesia and Intensive Care, Hôpitaux Universitaires de Strasbourg, Nouvel Hôpital Civil, Strasbourg, France, [21]Department of Anaesthesia, Royal North Shore Hospital, University of Sydney, Sydney, NSW, Australia, [22]Department of Clinical Immunology and Allergy, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [23]Intensive Care Unit, Gunma University Hospital, Maebashi, Gunma, Japan, [24]Division of Allergic Diseases, Mayo Clinic College of Medicine, Rochester, MN, USA, [25]Allergy Unit, Policlinic Hospital San

Accepted: 28 February 2019

Martino, Genoa, Italy and [26]Department of Pharmacology, University of Western Australia, Crawley, Western Australia, Australia

*Corresponding author. E-mail: p.m.hopkins@leeds.ac.uk

#These authors contributed equally.
†The authors are members of the ISPAR (International Suspected Perioperative Allergic Reaction) Group.

Abstract

Background: Grading schemes for severity of suspected allergic reactions have been applied to the perioperative setting, but there is no scoring system that estimates the likelihood that the reaction is an immediate hypersensitivity reaction. Such a score would be useful in evaluating current and proposed tests for the diagnosis of suspected perioperative immediate hypersensitivity reactions and culprit agents.
Methods: We conducted a Delphi consensus process involving a panel of 25 international multidisciplinary experts in suspected perioperative allergy. Items were ranked according to appropriateness (on a scale of 1–9) and consensus, which informed development of a clinical scoring system. The scoring system was assessed by comparing scores generated for a series of clinical scenarios against ratings of panel members. Supplementary scores for mast cell tryptase were generated.
Results: Two rounds of the Delphi process achieved stopping criteria for all statements. From an initial 60 statements, 43 were rated appropriate (median score 7 or more) and met agreement criteria (disagreement index <0.5); these were used in the clinical scoring system. The rating of clinical scenarios supported the validity of the scoring system. Although there was variability in the interpretation of changes in mast cell tryptase by the panel, we were able to include supplementary scores for mast cell tryptase.
Conclusion: We used a robust consensus development process to devise a clinical scoring system for suspected perioperative immediate hypersensitivity reactions. This will enable objectivity and uniformity in the assessment of the sensitivity of diagnostic tests.

Keywords: allergy; anaesthesia; anaphylaxis; drug hypersensitivity; perioperative period; surgery

Editor's key points

- A panel of 25 international multidisciplinary experts in suspected perioperative allergy used a Delphi consensus process to develop a clinical scoring system for suspected perioperative immediate hypersensitivity reactions.
- Of 60 initial statements, 43 were rated appropriate and met agreement criteria for inclusion in the clinical scoring system, which included supplementary scores for mast cell tryptase levels.
- Rating of clinical scenarios supported the validity of the scoring system.
- This new clinical scoring system should be useful for diagnosis of suspected perioperative immediate hypersensitivity reactions and for assessing the sensitivity of diagnostic tests.

Adverse perioperative events that meet published criteria for suspected immediate hypersensitivity reactions (IHRs) have been reported in up to one per353 general anaesthetics.[1,2] The clinical diagnosis of an IHR (allergic or non-allergic) is difficult in the perioperative patient because many of the clinical features occur frequently at various grades of severity through non-immune mechanisms. In addition, patients under general anaesthesia are unable to report symptoms.[3] If an IHR is diagnosed, identifying the culprit agent can be difficult because of the routine almost simultaneous exposure of multiple potential culprits.[4] The diagnosis of an IHR in the perioperative period is important because it has implications for the provision of safe anaesthesia for the patient in the future. Furthermore, having identified that a patient has had an IHR, identification of the mechanism and culprit agent along with safe alternative drugs within the same class of the culprit is required to enable the goal of safe future anaesthesia.

Guidelines for the investigation of suspected perioperative IHRs emphasise the need to combine clinical information, measurement of biomarkers of acute allergic responses, and skin testing.[5–10] *In vitro* tests to improve diagnosis[11–13] are reviewed in detail elsewhere in this issue of the *British Journal of Anaesthesia*.[14,15] A key requirement for the interpretation of any test is an understanding of its accuracy.[16] The accuracy of a test is described most simply in terms of its sensitivity (the proportion of truly positive patients or samples that have a positive test) and specificity (the proportion of truly negative patients or samples that have a negative test). Calculation of sensitivity and specificity with different cut-off values can be used to determine the optimum cut-off values for diagnosis. In combination with an estimate of *a priori* likelihood of a condition, sensitivity and specificity can be used to calculate the positive and negative predictive values of a test.

To estimate the sensitivity of any test to confirm an IHR or identify a culprit agent, it is necessary to evaluate the test in patients known to have had an IHR, that is true positives. To be an unbiased evaluation, identification of true positive cases should be independent of the results of the test or related tests

to avoid circular arguments.[17–20] This requires an objective approach to identifying true perioperative IHRs with a high degree of likelihood based on clinical information alone. Some researchers have used classification systems of allergic reactions for this purpose,[21–25] mostly based on the Ring and Messmer[26] classification. There are newer systems proposed by Niggemann and Beyer[27] (primarily for food allergy) and, specifically for perioperative reactions, by Rose and colleagues[28] and Cook and colleagues[29] to classify severity of reactions. However, none of these classification systems describe how likely a reaction is to be an IHR. Indeed, the assumption underlying such classification systems is that the patient is having an allergic reaction because there is no likely alternative explanation. This is a reasonable assumption in the absence of all of the potential confounding factors present in the perioperative period. For example, no account is taken for alternative causes of bronchospasm or hypotension[30] with classification systems derived from Ring and Messmer.[26] Therefore, we aimed to generate a clinical scoring system to assess the likelihood of an adverse event in the perioperative period being an IHR.

Methods

Although this paper does not represent development of a guideline *per se*, the methodology shares several aspects of guideline development. We therefore used the AGREE (Appraisal of Guidelines, Research, and Evaluation) checklist,[31] where relevant, to advise our approach.

Panel selection

An international multidisciplinary panel of allergists, anaesthetists, and immunologists with a track record of publication in the field of perioperative anaphylaxis was formed. From within the panel, a 'writing group' was created from those members of the panel expressing a specific interest in taking an additional role with this project.

Literature search

We used the PICO (population, intervention, comparators, outcomes) framework to formulate our literature search strategy as follows:

Population/problem: patients undergoing an operative procedure for diagnosis or treatment involving care from an anaesthetist.

Intervention: diagnosis of suspected IHR in the perioperative period.

Comparators: confounding factors for diagnosis of suspected IHR.

Outcomes: clinical diagnosis, classification, or grading of suspected perioperative IHR.

We searched PubMed and Embase databases and included publications from 1997 to [actual date] and key publications (first reports of paradigms that remain central to the PICO criteria) before 1997.

Modified Delphi process

We adopted the approach of Fitch and colleagues[32] in which statements are rated for appropriateness on a scale of 1 (completely inappropriate) to 9 (completely appropriate). Disagreement was determined using the disagreement index (DI), where the lower the value below 1, the greater is the consensus, and values >1 are considered to represent lack of consensus.[33] 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). 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.[34] The Delphi process was managed by the convener of the writing group (PMH); all other members of the panel were invited to participate in each round and were given at least 2 weeks to respond.

Round 1

A series of statements describing clinical manifestations of suspected IHRs was generated by the writing group based on relevant publications identified from the literature search and their clinical experience. The statements were sent to panel members using an online questionnaire tool (Google forms), in which panel members were asked to rate each statement on the appropriateness scale (1–9). Panel members had the option of responding N/A (not applicable) to statements that they felt to be outside their expertise. Panel members were also invited to provide freehand comments on the wording of existing statements or to propose new statements.

Round 2 and subsequent rounds

Before 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. Median appropriateness values were also calculated separately for panel members who were anaesthetists and those who were either allergists or immunologists and these values were also circulated to panel members.

In generating the statements for Round 2, the writing group reviewed the responses to the statements in Round 1, including freehand comments, and agreed whether each statement should be included unchanged, included in amended form, or not included in Round 2. The revised statements were formatted as an online questionnaire as for Round 1, which the panel members were invited to complete. If the stopping criteria were not met after Round 2, the process for subsequent rounds would follow that of Round 2.

Generation of the clinical scoring system

The results of the final round of the Delphi process were used to rank clinical features as to their contribution to predicting the likelihood of an IHR based first on the median appropriateness rating and then on the DI. These rankings were used to assign points within the scoring system, such that clinical features increasing the likelihood of an IHR were assigned positive values and those decreasing the likelihood (confounding features) were assigned negative values. The relative points allocation within positive and negative categories was made on the basis of the Delphi rankings supplemented by the clinical experience of the writing group that agreed on the initial scoring scheme. The content validity of the scoring scheme was initially assessed subjectively by the writing group before

testing for criterion and discriminant validity using the whole panel. For this exercise, a series of hypothetical case scenarios of suspected perioperative IHRs was developed, and panel members were asked to independently rate the likelihood of the case as 'almost certain', 'very likely', 'likely', or 'unlikely' to be an IHR. The case scenarios were compiled by the writing group convener (PMH) and were designed to evaluate how experts assessed the relative discriminant ability of items within and between scoring system categories and their combination. Minor adjustments of the points allocation within the scoring system were made in order to maximise its discriminant validity before the median likelihood ratings of the panel were used to calibrate the scoring system.

In addition to asking panel members to rate the case scenarios on clinical features alone, they were also asked to rate the scenarios when accompanied by mast cell tryptase results. This intended to assess how experts assessed: (a) 'borderline' tryptase increase; (b) the impact of no or minimal tryptase change on their evaluation of a clinical scenario with relatively high likelihood of being an IHR; and (c) the impact of a large tryptase increase on their evaluation of a clinical scenario with relatively low likelihood of being an IHR. These responses were used to produce and calibrate a scheme for supplementing the clinical scoring system when tryptase results are available (and assuming that the purpose of generating the score is not to evaluate the sensitivity of tryptase changes themselves).

Results

We approached by e-mail 33 international experts in suspected perioperative allergic reactions of which 18 were anaesthetists, 14 allergists or immunologists, and one dually accredited in anaesthesia and allergy. Of these, 15 anaesthetists, nine allergists/immunologists, and the dually accredited colleague agreed to participate. The affiliations of panel members are provided in the list of authors. The six members of the writing group are all anaesthetists.

Delphi process

From the review of the literature (literature search terms and results are provided in Supplementary Appendix 1) and their clinical experience, the writing group generated a list of 60 statements to be used in Round 1. Twenty-three of 24 members (96%) of the panel responded (the final panel member, PMH, managed the Delphi process): 39 of the statements were rated as appropriate, 20 as of uncertain appropriateness, and one inappropriate. The DI was <0.5 for 41 statements, 0.5–1 for 18 statements, and >1 for one statement ('Patients with a history of allergy are at increased risk of developing an IHR in the perioperative period'). This latter statement was one of only eight statements where the median appropriateness scores for anaesthetists differed by more than 2 from that of non-anaesthetists (Supplementary Appendix 2). Panel members contributed a total of 17 freehand comments in Round 1 although no completely new statements were proposed.

In Round 2, 32 of the statements were unchanged from Round 1, 17 statements were amended, and 11 statements were excluded with 24 members (100%) of the panel responding. Supplementary Appendix 3 shows the Round 2 statements ranked in order of highest median appropriateness score and then by the lowest DI. All statements met one or other stopping criteria for the iterative Delphi process. All but six of the statements had a median appropriateness score of 7 or more and a DI <0.5. The remaining statements were considered for use in construction of the clinical scoring system.

From Supplementary Appendix 3 it can be seen that clinical features associated with the cardiovascular system, respiratory system, and skin or mucous membranes were perceived to have value in predicting the likelihood of a perioperative IHR. Within each of these systems several confounding factors were identified that reduced the likelihood of a perioperative IHR (Supplementary Appendix 3). Supplementary Appendix 3 also highlights the high ratings for appropriateness and consensus for co-occurrence of features from more than one system. The other aspect that the writing group reflected in the initial clinical scoring system was the timing of the onset of clinical features in relation to administration of a potential culprit agent.

In transforming the consensus statements into the clinical scoring system, we realised that clinical terms needed to be defined so that the scoring system had construct validity and could be applied reproducibly. The writing group developed a series of definitions of clinical features and tested these for appropriateness with a single round Delphi process involving all panel members. Table 1 shows the definitions agreed and the high level of appropriateness and consensus of the panel for these definitions in this context.

The writing group structured the scoring system based on key areas of consensus from the Delphi process. These were: positive and confounding features within each of cardiovascular, respiratory, and dermal/mucosal categories; the added weight of combinations of features from more than one of these categories; the importance of timing of onset of features in relation to exposure to potential triggers, except for dermal or mucosal features. The writing group agreed on a provisional scoring system before conducting a validity-testing exercise involving the whole panel. The clinical scenarios used in this exercise are presented in Supplementary Appendix 4 along with the ratings of the panel members presented for the whole group and also for anaesthetists separately.

The writing group used the feedback from the clinical scenario ratings of panel members to make minor adjustments to the clinical scoring system while maintaining the principles derived from the initial consensus exercise. The final clinical scoring system is shown in Table 2. The median clinical scenario ratings were used to calibrate the clinical scoring system by converting scoring ranges to indicate almost certain, very likely, likely, or unlikely IHRs. During writing of the manuscript it was agreed to subdivide the 'likely' category into 'likely' and 'possible', as we think this will aid clinical utility. The likelihood categories are shown in Table 3.

In order to incorporate changes in mast cell tryptase concentration into the clinical scoring system, we evaluated the impact of various tryptase changes on the clinical likelihood rating by panel members. Ratings are shown in Supplementary Appendix 4. If the peak tryptase after a suspected IHR showed no change from the baseline value, most panel members considered this to have a negative impact on their assessment of the likelihood of an IHR. A change in tryptase of (1.2×baseline)+2 ng ml^{-1} with the peak tryptase remaining within the reference range was considered a better indicator of a likely IHR than a smaller relative change even if the peak tryptase was outside the reference range (>upper 95% confidence limit of the reference range). If a relative change of (1.2×baseline)+2 ng ml^{-1} was combined with a peak value greater than the upper limit of the reference range, tryptase level was considered to have a greater impact on likelihood of an IHR. An even greater relative change combined with the

Table 1 Definitions for clinical terms used in the clinical scoring scheme. DI, disagreement index; Median, median appropriateness score.

Clinical term	Definition	Median	DI
Hypotension	A fall in systolic blood pressure to <70 mm Hg (at induction or during maintenance of anaesthesia) or by >20% from a previously stable value (during maintenance of anaesthesia)	8	0.140
Severe hypotension	A fall in systolic blood pressure to <60 mm Hg (at induction or during maintenance of anaesthesia) or by >40% from a previously stable value (during maintenance of anaesthesia)	8	0.132
Cardiac arrest	The requirement for cardiopulmonary resuscitation not explained by the surgical pathology, complications of the surgical procedure, co-existing medical problems or drugs, malignant hyperthermia or technical anaesthetic problems	8	0.292
Tachycardia	An otherwise unexplained increase in heart rate of 50% or more from a previously stable value	8	0.074
Bronchospasm	The onset of wheeze on auscultation, any manifestation of otherwise unexplained increased airway resistance, or both	8	0.074
Severe bronchospasm	Bronchospasm associated with SpO_2 <85%	7.5	0.164
Urticaria	A skin rash characterised by raised pink or white raised areas of skin (wheals)	9	0.132
Angioedema	Dermal or mucosal swelling	8.5	0.132

peak being outside the normal range had the greatest impact. These rankings were used to produce an algorithm for increasing points allocation to tryptase changes to supplement the clinical scoring system, when appropriate (Table 4).

Discussion

We used an established methodological approach to generate consensus from an international multidisciplinary panel of experts in suspected perioperative allergic reactions for clinical criteria that have predictive value for estimating the likelihood that an adverse perioperative event was the result of an IHR. We used the ranking of appropriateness and consensus of the criteria to construct a clinical scoring system and went on to ensure its content, construct, criterion, and discriminant validity.

One of the key differences between previously published classification systems and our clinical scoring system is that we have enabled the impact of potential confounding factors and the time interval between potential culprit exposure and onset of signs to be assimilated. Although this increases the complexity of the final scoring system, it reflects the complexity that can be involved in forming an expert clinical judgement of the potential cause of an adverse perioperative event. The need to exclude other causes of suspected adverse drug reactions is an accepted and integral part of causality assessment used in pharmacovigilance.[35] Our validity assessments suggest that the scoring system will be able to identify with high likelihood IHRs that present with relatively subtle features involving two or more systems and IHRs with more severe features confined to a single system. The scoring system also implicitly reflects the expert consensus that timing of skin manifestations is a poor discriminator as these may be obscured by surgical drapes or delayed in appearance until a shocked patient has been resuscitated.

The value of the availability of a clinical scoring system for rare perioperative adverse reactions has been demonstrated by the enduring use of the Larach clinical grading scale for malignant hyperthermia which was developed using a Delphi consensus approach.[36] This has been used to great effect to evaluate the sensitivity of the two principally applied protocols for the laboratory diagnosis of malignant hyperthermia susceptibility[37,38] and in studies of the epidemiology of malignant hyperthermia.[39,40] As with our scoring system for IHRs, the Larach clinical grading scale was not intended for use in real-time clinical diagnosis, which for both IHR and malignant hyperthermia should be based on early pattern recognition of clinical features and rapid evaluation of differential diagnoses with a relatively low threshold for initiating treatment.

Implementation of the IHR clinical scoring system requires experience of interpretation of perioperative records, including anaesthetic charts, in order to accurately extract the data needed. Our recommendation is that this is done by an individual with the necessary expertise who was not involved directly with the case in order to minimise subconscious bias. The relevant and sufficient information to apply the scoring system to cases of suspected perioperative allergic reactions should be routinely available when patients are assessed in a specialist anaesthetic allergy clinic setting. However, the scoring should be done blinded to the results of subsequent investigations to avoid hindsight bias.

The definitions of various clinical terms, such as hypotension, bronchospasm, and tachycardia, that we have adopted for use in the clinical scoring system (Table 1) are intended to maximise the utility of the scoring system. Using hypotension as an example, our definitions differ from the physiological definition, definitions used in the context of allergy in general[41] and even definitions used elsewhere in the context of perioperative allergy.[42,43] It is inevitable that our definitions will exclude clinical features that occur in some true IHRs from contributing to the score for that reaction. It is our collective view that such subtle changes in the perioperative context have too low a predictive value for our purpose. Similarly, although a low end-tidal CO_2 has been shown to be a superior predictor of the severity of an IHR for hypotension,[44] our expert consensus was that this sign did not add to the discriminant ability of hypotension and bronchospasm to distinguish between hypersensitivity and non-hypersensitivity reactions, while potentially introducing additional confounders such as iatrogenic hyperventilation, hypothermia, pulmonary embolus, or right-to-left shunt.

A potential advantage of using a scoring system generated by expert consensus is that it is likely to reduce the potential

Table 2 The clinical scoring system. Items contributing to the clinical score for suspected perioperative immediate hypersensitivity reactions (IHRs). Points are awarded within five categories, with features suggestive of an IHR (pink cells) having positive points values and features against an IHR (green cells) having negative points values. How points may be allocated to items is indicated for each category. The overall clinical score is the sum of the net scores of all categories. *For a score from one of the three organ systems, cardiovascular (CVS), respiratory (RS), dermal/mucosal (D/M) to contribute to a combination score, the net score for that system must be >2. The net score is the sum of scores for positive features minus the sum of scores for confounders within scores for that system. For definitions, see Table 1.

1. Cardiovascular **(choose hypotension, severe hypotension, or cardiac arrest if appropriate, then any other items that apply)**	**Points**
Hypotension	4
Severe hypotension	6
Cardiac arrest	9
Tachycardia	2
A poor or unsustained response of hypotension to standard doses of sympathomimetics used to treat pharmacological hypotension during anaesthesia (e.g. ephedrine, phenylephrine, metaraminol)	2
A point-of-care echocardiogram showing a hyperdynamic and poorlyfilled heart	2
Recurrence or worsening of hypotension after a further dose of a drug given before the initial event	1
Cardiovascular confounders (in the presence of hypotension or cardiac arrest choose any that apply)	
Excessive dose of anaesthetic drug or drugs	–2
Surgically induced hypovolaemia or relative hypovolaemia from prolonged fasting/dehydration	–1
Acute illness predisposing to hypotension	–1
Medications affecting cardiovascular responses during anaesthesia	–2
Neuraxial regional anaesthesia (epidural/spinal)	–1
Onset of hypotension after development of increased peak airway pressure during mechanical ventilation of the lungs	–2
2. Respiratory **(choose bronchospasm or severe bronchospasm if appropriate, then any other items that apply)**	
Bronchospasm	2
Severe bronchospasm	4
Recurrence or worsening of bronchospasm after a further dose of a drug given before the initial event	1
Bronchospasm occurring before airway instrumentation (having excluded airway obstruction)	2
Respiratory confounders (in the presence of bronchospasm choose any that apply)	
Respiratory disease associated with reactive airways	–1
Prolonged or multiple attempts at tracheal intubation	–1
Inadequate dose of drugs to obtund airway responses before airway instrumentation	–1
3. Dermal/mucosal **(choose any items that apply)**	
A generalised rash is itchy in the awake patient who has not received epidural/spinal opioids	1
Angioedema	3
Generalised erythema	3
Generalised urticaria	4
Dermal/mucosal confounder	
Angioedema in a patient taking an ACE inhibitor	–3
4. Combinations **(choose a maximum of one item)***	
CVS>2 and RS > 2	5
CVS>2 and D/M >2	5
RS>2 and D/M >2	5
CVS>2 and RS>2 and D/M >2	8
5. Timings **(choose a maximum of one item)**	
Onset of cardiovascular or respiratory features within 5 min of possible IV trigger	7
Onset of cardiovascular or respiratory features within 15 min of possible IV trigger	3
Onset of cardiovascular or respiratory features within 60 min of possible non-IV trigger	2
Onset of cardiovascular or respiratory features more than 60 min after possible non-IV trigger	–1

inter-rater variability inherent in forming an assessment of causality from an unstructured review of clinical information. The 6th National Audit Project (NAP6) of the Royal College of Anaesthetists addressed this issue by using a large multidisciplinary panel to assess each potential case of anaphylaxis.[29,45,46] Although we have not formally assessed inter-rater variability for application of the clinical scoring system, our validity exercise demonstrated the variability of an opinion-based assessment of some relatively straightforward clinical scenarios. We had anticipated that this variability would be greatest when comparing anaesthetists and non-anaesthetists. However, on the whole this was not the case with within-specialty variability being similar to between-specialty variability; this is likely to reflect the common factor of expertise in perioperative allergy.

Our evaluation of expert opinion of the interpretation of changes in mast cell tryptase indicates that uncertainty persists in how such changes impact on the clinical evaluation of suspected perioperative IHRs. The majority of laboratories use the same supplier for mast cell tryptase testing kits and

Table 3 Clinical grading scale for interpretation of clinical score for suspected perioperative immediate hypersensitivity reactions (IHRs).

Interpretation	Total (net) score
Almost certain to be an IHR	>21
Very likely to be an IHR	15–21
Likely to be an IHR	11–14
Possible IHR	8–10
Unlikely to be an IHR	<8

Table 4 Algorithm for allocating points for mast cell tryptase changes to supplement the clinical scoring system. Points should be subtracted from or added to the net score from the clinical scoring system (Table 2) with the resulting score interpreted as defined in Table 3. Criteria for mast cell tryptase changes: (a) Formula +ve: Peak tryptase is >[(1.2×baseline tryptase)+2 ng ml^{-1}]; (b) Formula −ve: Peak tryptase is < [(1.2×baseline tryptase)+2 ng ml^{-1}]; (c) ULN: upper 95% confidence limit of the reference range (11.4 ng ml^{-1}); and (d) >2×BL: peak tryptase is >2×baseline tryptase.

Mast cell tryptase change	Points
No criteria	−4
Formula −ve but > ULN	−2
Formula +ve and < ULN	0
Formula +ve and > ULN	4
>2×BL and >ULN	12

reagents. The test has a low coefficient of variation with a high level of reproducibility between laboratories.[47] This makes it even more surprising perhaps that there is not better agreement on the interpretation of acute changes in the perioperative period. One of the issues may be the lack of robust estimates for the sensitivity and specificity of mast cell tryptase changes in suspected perioperative allergic reactions. For many years, it was assumed that if the peak tryptase in the 1–2 h after a suspected perioperative allergic reaction was within the normal reference range, then the tryptase result was 'negative'. In the meantime, Brown and colleagues[48] investigated tryptase changes in volunteers in whom allergic reactions were provoked in a controlled experimental setting with venom. Such studies showed that relative change from baseline was perhaps more important in detecting mast cell activation than the absolute value of the peak tryptase concentration. Garvey and colleagues[49] found that the upper 95% confidence interval for relative change in tryptase during elective orthopaedic surgery was 39%. A consensus process was used to develop a criterion for mast cell activation based on the principle of relative change.[47] It is clear from the responses of our expert panel to the hypothetical tryptase changes presented alongside clinical scenarios that not all expert opinion is confident that the use of this formula in the perioperative setting is discriminatory. Egner and colleagues[50] conducted perhaps the largest evaluation of mast cell tryptase in suspected perioperative allergic reactions. Their data, although having to rely on the Ring and Messmer[26] classification, suggest that smaller changes in tryptase in the perioperative setting may indeed be relevant if the sensitivity of tryptase changes is to be optimised. Baretto and colleagues[51] produced similar findings but used the World Allergy Organisation criteria[52] for identifying their 'true positive' cases, which again do not account for confounding factors. We propose that evaluation of tryptase changes in a large cohort of patients categorised as 'almost certain' by our clinical scoring system would provide the best estimate to date of the sensitivity of tryptase changes in identifying perioperative IHRs. We should emphasise that the time of sampling for peak tryptase (ideally 1–2 h after onset of the reaction) is extremely important, especially when considering discrete increases.

Limitations

Although we have demonstrated several aspects of the validity of the scoring system, independent external validation was not possible within the constraints of this project. The main purpose of external validation of such a tool is to ensure that it is generalisable, but we expect that inclusion of global representation on our expert panel makes generalisability of the scoring system likely. One possible means of independent validation of the scoring system would be to utilise the NAP6 cases and compare their scores with the ratings of the NAP6 panel.[29,46] A further potential limitation is that we do not expect the clinical scoring system to be reliable when relevant clinical information is missing, emphasising the necessity to include copies of all perioperative records when referring a patient with a suspected IHR for investigation.[7,8,45]

When applying the clinical scoring system to evaluate the sensitivity of mast cell tryptase changes or skin test results, the score makes no presumption about the mechanism of the suspected IHR. This means that one can evaluate a test for its sensitivity to detect an IHR but not IHRs with a defined mechanism (allergic or non-allergic). Therefore, any test that can identify only IHRs with an allergic mechanism, for example, may not achieve 100% sensitivity to detect IHRs even though it has 100% sensitivity to detect allergic reactions. We can only guess what proportion of IHRs are allergic because mast cell tryptase changes and skin test results have been used to define a reaction as allergic, even in the absence of a clear clinical history of an IHR. We now know that both mast cell tryptase and skin tests can be 'positive' through non-allergic and even non-immune mechanisms.[53–56] From a pragmatic clinical perspective we need to know the sensitivity of tests to detect an IHR of any mechanism, because non-allergic and allergic IHRs can occur with re-exposure to the culprit agent.

Conclusions

Our clinical scoring system, with or without the incorporation of tryptase results as appropriate, has the potential to better assess the sensitivity of currently used tests that are intended to confirm that an IHR has occurred and the agent responsible. It can also provide a consistent framework for the evaluation in research settings of proposed new tests. A robust estimate of sensitivity of skin tests, for example, will also aid interpretation of investigations of cross-reactivity of chemically and pharmacologically related agents.

Authors' contributions

Study design: PMH, PC, ABG, PS, RC, PP.
Writing paper: PMH, PC, ABG, PS, RC, PP.
Revising paper and approval of final version: all authors.

Declarations of interest

PD has received lecture and travel fees from MSD France (Courbevoie, France); lecture and travel fees from Bracco Imaging France (Courcouronnes, France); 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); and is a member of MSD Expert Board on 'neuromuscular blocking agents and fast-tracking anesthesia' (until October 2019). LHG is a consultant and adjudication committee member for Merck, NJ, USA and Novo Nordisk Denmark. PMH is an editorial board member of *British Journal of Anaesthesia*. PMM is a scientific advisor for the ALPHO study (NCT02250729), funded by a consortium of pharmaceutical companies: Zambon, Urgo, Pierre Fabre, Boots, Hepatoum, Biocodex, Sanofi, LBR, GSK, APL, Bells Healthcare, Pinewood, T & R, and Ernest Jackson. PK has received lectures fees from Novartis Pharma Services Inc. and Shire Pharmaceuticals Group Plc.

Funding

SM is in receipt of an Australian National Health and Medical Research Council (NHMRC) ECR Fellowship for the investigation of cognitive aids in emergencies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2019.02.029.

References

1. Savic LC, Kaura V, Yusaf M, et al. Incidence of suspected perioperative anaphylaxis: a multicenter snapshot study. *J Allergy Clin Immunol Pract* 2015; **3**: 454–455 e1
2. Berroa F, Lafuente A, Javaloyes G, et al. The incidence of perioperative hypersensitivity reactions: a single-center, prospective, cohort study. *Anesth Analg* 2015; **121**: 117–23
3. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: diagnostic approach. *Allergy* 2007; **62**: 471–87
4. Hunting AS, Nopp A, Johansson SG, Andersen F, Wilhelmsen V, Guttormsen AB. Anaphylaxis to patent blue V: I. Clinical aspects. *Allergy* 2010; **65**: 117–23
5. Kolawole H, Marshall SD, Crilly H, Kerridge R, Roessler P. Australian and New Zealand anaesthetic allergy group/ Australian and New Zealand College of anaesthetists perioperative anaphylaxis management guidelines. *Anaesth Intensive Care* 2017; **45**: 151–8
6. Scolaro RJ, Crilly HM, Maycock EJ, et al. Australian and New Zealand anaesthetic allergy group perioperative anaphylaxis investigation guidelines. *Anaesth Intensive Care* 2017; **45**: 543–55
7. Harper NJ, Dixon T, Dugue P, et al. Suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia* 2009; **64**: 199–211
8. Ewan PW, Dugue P, Mirakian R, Dixon TA, Harper JN, Nasser SM. BSACI guidelines for the investigation of suspected anaphylaxis during general anaesthesia. *Clin Exp Allergy* 2010; **40**: 15–31
9. Kroigaard M, Garvey LH, Gillberg L, et al. Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Anaesthesiol Scand* 2007; **51**: 655–70
10. Mertes PM, Malinovsky JM, Jouffroy L, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2011; **21**: 442–53
11. Sudheer PS, Hall JE, Read GF, Rowbottom AW, Williams PE. Flow cytometric investigation of peri-anaesthetic anaphylaxis using CD63 and CD203c. *Anaesthesia* 2005; **60**: 251–6
12. Uyttebroek AP, Sabato V, Leysen J, Bridts CH, De Clerck LS, Ebo DG. Flowcytometric diagnosis of atracurium-induced anaphylaxis. *Allergy* 2014; **69**: 1324–32
13. Ebo DG, Faber M, Elst J, et al. In vitro diagnosis of immediate drug hypersensitivity during anesthesia: a review of the literature. *J Allergy Clin Immunol Pract* 2018; **6**: 1176–84
14. Takazawa T, Sabato V, Ebo DG. In vitro diagnostic tests for perioperative hypersensitivity: potential, limitations and perspectives. *Br J Anaesth* 2019; **123**: e117–25
15. Opstrup MS, Garvey LH. Optimizing diagnostics in perioperative allergy. *Br J Anaesth* 2019; **123**: e11–3
16. Brockow K. Dilemmas of allergy diagnosis in perioperative anaphylaxis. *Allergy* 2014; **69**: 1265–6
17. Krishna MT, York M, Chin T, et al. Multi-centre retrospective analysis of anaphylaxis during general anaesthesia in the United Kingdom: aetiology and diagnostic performance of acute serum tryptase. *Clin Exp Immunol* 2014; **178**: 399–404
18. Leysen J, Uyttebroek A, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Predictive value of allergy tests for neuromuscular blocking agents: tackling an unmet need. *Clin Exp Allergy* 2014; **44**: 1069–75
19. Ramirez LF, Pereira A, Chiriac AM, Bonnet-Boyer MC, Demoly P. Negative predictive value of skin tests to neuromuscular blocking agents. *Allergy* 2012; **67**: 439–41
20. Aalberse RC, Kleine Budde I, Mulder M, et al. Differentiating the cellular and humoral components of neuromuscular blocking agent-induced anaphylactic reactions in patients undergoing anaesthesia. *Br J Anaesth* 2011; **106**: 665–74
21. Fisher MM, Bowey CJ. Intradermal compared with prick testing in the diagnosis of anaesthetic allergy. *Br J Anaesth* 1997; **79**: 59–63
22. Karila C, Brunet-Langot D, Labbez F, et al. Anaphylaxis during anesthesia: results of a 12-year survey at a French pediatric center. *Allergy* 2005; **60**: 828–34
23. Laroche D, Gomis P, Gallimidi E, Malinovsky JM, Mertes PM. Diagnostic value of histamine and tryptase concentrations in severe anaphylaxis with shock or cardiac arrest during anesthesia. *Anesthesiology* 2014; **121**: 272–9
24. Mertes PM, Laxenaire MC, Alla F. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999–2000. *Anesthesiology* 2003; **99**: 536–45
25. Tacquard C, Collange O, Gomis P, et al. Anaesthetic hypersensitivity reactions in France between 2011 and 2012: the 10th GERAP epidemiologic survey. *Acta Anaesthesiol Scand* 2017; **61**: 290–9
26. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977; **1**: 466–9
27. Niggemann B, Beyer K. Time for a new grading system for allergic reactions? *Allergy* 2016; **71**: 135–6

28. Rose MA, Green SL, Crilly HM, Kolawole H. Perioperative anaphylaxis grading system: 'making the grade. *Br J Anaesth* 2016; **117**: 551–3
29. Cook TM, Harper NJN, Farmer L, et al. Anaesthesia, surgery, and life-threatening allergic reactions: protocol and methods of the 6th National Audit Project (NAP6) of the Royal College of Anaesthetists. *Br J Anaesth* 2018; **121**: 124–33
30. Garvey LH. Perioperative hypersensitivity reactions: diagnosis, treatment and evaluation. *Curr Treat Options Allergy* 2016; **3**: 113–28
31. Brouwers MC, Kerkvliet K, Spithoff K. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. *BMJ* 2016; **352**: i1152
32. Fitch K, Bernstein SJ, Aguilar MD, et al. *The RAND/UCLA appropriateness method user's manual*. Santa Monica, CA: RAND; 2001
33. Maverakis E, Wang EA, Shinkai K, et al. Stevens–Johnson syndrome and toxic epidermal necrolysis standard reporting and evaluation guidelines: results of a national institutes of Health working group. *JAMA Dermatol* 2017; **153**: 587–92
34. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol* 2014; **67**: 401–9
35. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000; **356**: 1255–9
36. Larach MG, Localio AR, Allen GC, et al. A clinical grading scale to predict malignant hyperthermia susceptibility. *Anesthesiology* 1994; **80**: 771–9
37. Ording H, Brancadoro V, Cozzolino S, et al. In vitro contracture test for diagnosis of malignant hyperthermia following the protocol of the European MH Group: results of testing patients surviving fulminant MH and unrelated low-risk subjects. The European Malignant Hyperthermia Group. *Acta Anaesthesiol Scand* 1997; **41**: 955–66
38. Allen GC, Larach MG, Kunselman AR. The sensitivity and specificity of the caffeine–halothane contracture test: a report from the North American malignant hyperthermia registry. The North American malignant hyperthermia registry of MHAUS. *Anesthesiology* 1998; **88**: 579–88
39. Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB. Cardiac arrests and deaths associated with malignant hyperthermia in North America from 1987 to 2006: a report from the north american malignant hyperthermia registry of the malignant hyperthermia association of the United States. *Anesthesiology* 2008; **108**: 603–11
40. Brandom BW, Larach MG, Chen MS, Young MC. Complications associated with the administration of dantrolene 1987 to 2006: a report from the North American malignant hyperthermia registry of the malignant hyperthermia association of the United States. *Anesth Analg* 2011; **112**: 1115–23
41. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—second national institute of allergy and infectious disease/food allergy and anaphylaxis network symposium. *J Allergy Clin Immunol* 2006; **117**: 391–7
42. Harboe T, Guttormsen AB, Irgens A, Dybendal T, Florvaag E. Anaphylaxis during anesthesia in Norway: a 6-year single-center follow-up study. *Anesthesiology* 2005; **102**: 897–903
43. Gurrieri C, Weingarten TN, Martin DP, et al. Allergic reactions during anesthesia at a large United States referral center. *Anesth Analg* 2011; **113**: 1202–12
44. Gouel-Chéron A, de Chaisemartin L, Jönsson F, et al. Low end-tidal CO_2 as a real-time severity marker of intra-anaesthetic acute hypersensitivity reactions. *Br J Anaesth* 2017; **119**: 908–17
45. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: management and outcomes in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 172–88
46. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
47. Valent P, Akin C, Arock M, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol* 2012; **157**: 215–25
48. Brown SG, Blackman KE, Heddle RJ. Can serum mast cell tryptase help diagnose anaphylaxis? *Emerg Med Australas* 2004; **16**: 120–4
49. Garvey LH, Bech B, Mosbech H, et al. Effect of general anesthesia and orthopedic surgery on serum tryptase. *Anesthesiology* 2010; **112**: 1184–9
50. Egner W, Sargur R, Shrimpton A, York M, Green K. A 17-year experience in perioperative anaphylaxis 1998–2015: harmonizing optimal detection of mast cell mediator release. *Clin Exp Allergy* 2016; **46**: 1465–73
51. Baretto RL, Beck S, Heslegrave J, et al. Validation of international consensus equation for acute serum total tryptase in mast cell activation: a perioperative perspective. *Allergy* 2017; **72**: 2031–4
52. Simons FE, Ardusso LR, Bilo MB, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *World Allergy Organ J* 2011; **4**: 13–37
53. Berg CM, Heier T, Wilhelmsen V, Florvaag E. Rocuronium and cisatracurium-positive skin tests in non-allergic volunteers: determination of drug concentration thresholds using a dilution titration technique. *Acta Anaesthesiol Scand* 2003; **47**: 576–82
54. Spoerl D, Nigolian H, Czarnetzki C, Harr T. Reclassifying anaphylaxis to neuromuscular blocking agents based on the presumed patho-mechanism: IgE-mediated, pharmacological adverse reaction or "innate hypersensitivity"? *Int J Mol Sci* 2017; **18**: 1223
55. Sprung J, Weingarten TN, Schwartz LB. Presence or absence of elevated acute total serum tryptase by itself is not a definitive marker for an allergic reaction. *Anesthesiology* 2015; **122**: 713–4
56. Sprung J, Larson KJ, Divekar RD, Butterfield JH, Schwartz LB, Weingarten TN. Refractory intraoperative hypotension with elevated serum tryptase. *Asia Pac Allergy* 2015; **5**: 47–50

Handling editor: H.C. Hemmings Jr

BJA

British Journal of Anaesthesia, 123 (1): e38–e49 (2019)

doi: 10.1016/j.bja.2019.01.031
Advance Access Publication Date: 8 March 2019
Review Article

Molecular mechanisms and pathophysiology of perioperative hypersensitivity and anaphylaxis: a narrative review

Didier G. Ebo[1,*], Russell C. Clarke[2], Paul-Michel Mertes[3], Peter R. Platt[2], Vito Sabato[1] and Paul H. M. Sadleir[2,4]

[1]Department of Immunology, Allergology and Rheumatology, University Antwerp, Antwerp University Hospital, Antwerpen, Belgium, [2]Anaesthetic Allergy Referral Centre of Western Australia, Department of Anaesthesia, Sir Charles Gairdner Hospital, Perth, Australia, [3]Department of Anesthesia and Intensive Care, Hôpitaux Universitaires de Strasbourg, Nouvel Hôpital Civil, Strasbourg, France and [4]Department of Pharmacology, University of Western Australia, Perth, Australia

*Corresponding author. E-mail: immuno@uantwerpen.be

Summary

Perioperative hypersensitivity reactions (POH) constitute a clinical and diagnostic challenge, a consequence of heterogeneous clinical presentations, and multiple underlying pathomechanisms. POH do not necessarily involve an allergen-specific immune response with cross-linking of specific immunoglobulin E (sIgE) antibodies on mast cells and basophils. POH can also result from alternative specific and non-specific effector cell activation/degranulation such as complement-derived anaphylatoxins and off-target occupancy of mast cell, basophil, or both surface receptors. Moreover, POH and anaphylaxis can occur independent from mast cell and basophil degranulation.

The manifestations of POH primarily affect the cardiovascular, respiratory, and integumentary systems. POH present within the context of surgical or procedural pathology and the effects of surgical and anaesthetic techniques on pre-existing physiological reserve. The majority of cases of appropriately-treated intraoperative anaphylaxis can be considered a compensated cardiovascular anaphylaxis. With increasing severity of anaphylaxis, maldistribution and hypovolaemia lead to reduced venous return and circulatory failure. Treatment with a combination of epinephrine and i.v. fluid is critical for successful resuscitation, although the excessive use of epinephrine without adequate volume expansion may be deleterious. Neural control of the airways is important in the pathophysiology of bronchospasm. Anticholinergic drug premedication is beneficial in patients with hyperreactive airways. Pulmonary oedema can result from a combination of pulmonary capillary hypertension, incompetence of the alveolocapillary membrane, or both. Angioedema can be distinguished mechanistically into histaminergic and non-histaminergic (e.g. bradykinin-mediated). An understanding of the molecular mechanisms and pathophysiology of POH are essential for the immediate management and subsequent investigation of these cases.

Keywords: anaesthesia; anaphylaxis; angioedema; bronchospasm; drug hypersensitivity; perioperative outcomes; shock

Editorial decision: 15 January 2019; **Accepted:** 15 January 2019

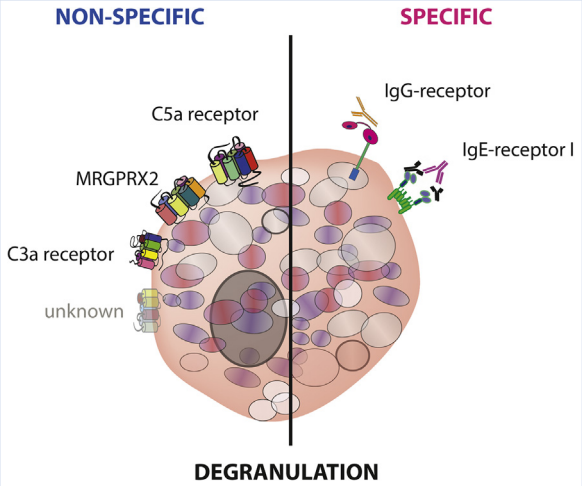


Fig 1. Mast cell, basophil, or both activation can occur via non-specific or specific pathways. Non-specific activation mainly involves occupation of complement receptors C3aR and C5aR by the anaphylatoxins C3a and C5a that are generated through activation of the complement system. Another mechanism of non-specific mast cell activation involves occupation of the Mas-related G protein-coupled receptor MRGPRX, which is not constitutively expressed by basophils. Specific activation of basophils requires activation of B lymphocytes of the adaptive immune system, with production of allergen-specific IgE antibodies.

Molecular mechanisms and pathophysiology of perioperative hypersensitivity and anaphylaxis

According to the revised nomenclature of allergy,[1] the term *hypersensitivity* is currently used as an umbrella term to cover all unexpected but reproducible reactions to exposure to a defined substance that are tolerated by normal subjects, and that go beyond the primary pharmacological actions. Importantly, this definition does not take into account the underlying pathophysiological process, and it was proposed to use the terms *allergic* and *non-allergic hypersensitivity* to denote an immune or non-immune mechanism, respectively. Similarly, the term *anaphylaxis* should not be reserved for immune, mainly IgE/high-affinity IgE receptor (FcεRI)-dependent reactions, but extend to all rapidly developing, life-threatening, generalised, or systemic reactions, irrespective of the mechanistic endotype.[2] The term *allergic anaphylaxis* is proposed when an immunologic mechanism is demonstrable, and all other situations should be referred as *non-allergic anaphylaxis*. An anaphylactic reaction mediated by cross-linking of allergen-specific IgE bound to FcεRI on mast cells and basophils may be called IgE-mediated anaphylaxis. The terms anaphylactoid and pseudo-allergic should be abandoned, especially as novel specific and non-specific hypersensitivity mechanisms have been identified that can explain IgE/FcεRI-independent effector cell degranulation. Nevertheless, many authors still use these obsolete terms, which does not benefit harmonisation of classification and deepening insights into mechanisms. Here we review the molecular mechanisms and pathophysiology of perioperative hypersensitivity and anaphylaxis resulting from IgE/FcεRI-dependent and -independent effector cell activation.

Specific and nonspecific mast cell and basophil activation mechanisms

Mast cells and basophils are the key effector cells of POH and anaphylaxis. Degranulation of these cells can be triggered by various specific and non-specific mechanisms (Fig. 1). Classically, degranulation is considered to be a reaction involving activation of the adaptive immune system with production and secretion of allergen-specific IgE (sIgE) antibodies by plasma cells. Subsequently, these circulating homocytotropic sIgE antibodies bind to their high-affinity receptors (FcεRI) present on the surface membrane of both effector cell types. Encounter of a specific allergen that cross-links sIgE/FcεRI-complexes present on the surface membrane of both effector cells induces a complex downstream signalling cascade that culminates in compounded degranulation with release of aggregates of secretory granules. The presence of sIgE antibodies is essential, but does not suffice for an effective cross-linking of FcεRI complexes resulting in degranulation. Those requirements are not yet fully elucidated, but the number of IgE binding sites on the allergen (epitopes) and the number and duration of cross-links per mast cell or basophil are key elements.[3] Unlike protein allergens, small drug allergens are usually monovalent and require haptenization or other forms of protein binding to become complete allergens.[4–6]

The signalling mechanisms that govern mast cell and basophil activation/degranulation and inhibition, and the exocytic pathways are beyond the scope of this review and have been extensively described.[7,8] However, as elegantly reviewed by Finkelman and colleagues[9] and Reber and colleagues,[10] activation/degranulation of these effector cells can also occur independently from allergen-sIgE antibodies. A first putative mechanism of sIgE/FcεRI-independent degranulation includes allergen-specific cross-linking of IgG/FcγR complexes. However, evidence for IgG-mediated anaphylaxis is mainly provided by animal models, and there have been no unequivocal examples of IgG-mediated POH published. Clinical evidence for human IgG-mediated anaphylaxis is currently restricted to a few observations involving the parental administration of significant quantities of (protein) allergen. For example, potential IgG-dependent anaphylaxis has been described to different chimeric, humanized, and even fully human monoclonal antibodies such as infliximab[11–13] and adalimumab,[13] dextrans,[14,15] or aprotinin.[16,17] However, the relevance of some of these observations remains uncertain,[17,18] as in some cases (low) titres of drug-sIgE were demonstrable.

Mast cell and basophil activation can also occur via antibody-independent mechanisms. Complement activation with generation of anaphylatoxins C3a and C5a that bind to their specific G-protein-coupled receptors C3aR and C5aR on mast cells and basophils, can occur in reactions to iodinated contrast media,[19] and in reactions to over-sulphated chondroitin sulphate contaminated heparin.[20] Other potential causes for complement-related hypersensitivity reactions, called C activation-related pseudo-allergy (CARPA). CARPA represents a novel subcategory of acute hypersensitivity reactions that might be preventable by appropriate precautions. Rarely, it can be severe or even lethal.[21,22] CARPA mainly involves liposomal and micelle-solubilised drugs. The best-known liposomal drugs are ambisome, a charged non-PEGylated liposome and liposomal doxorubicin sulphate

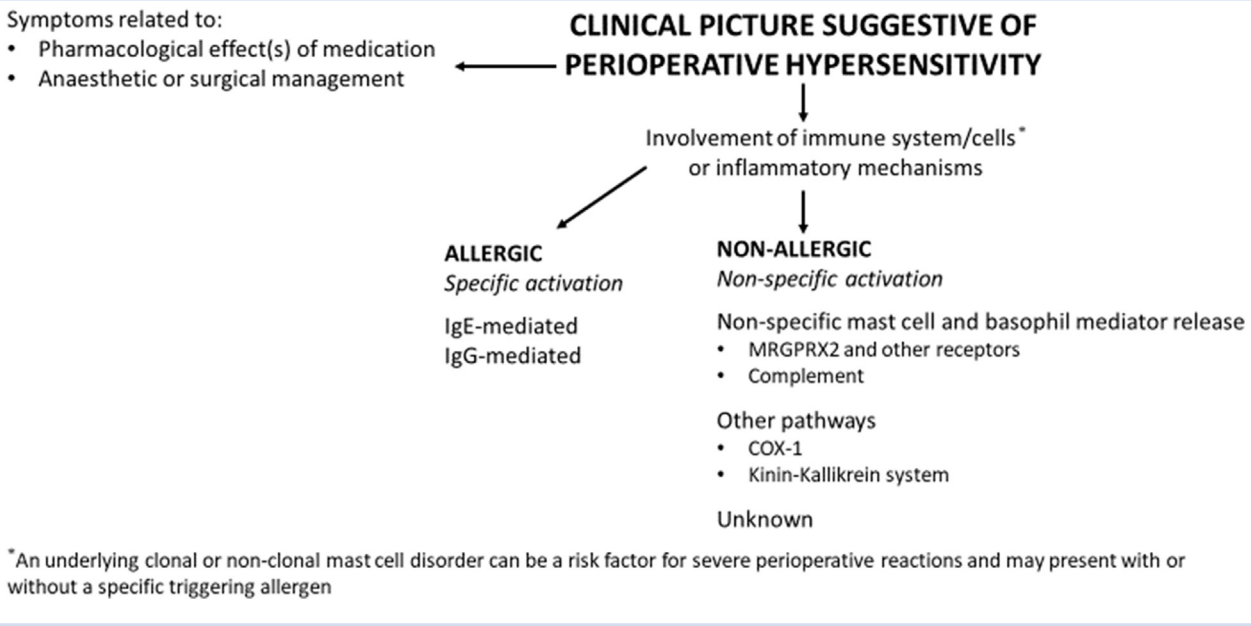


Fig 2. Pathomechanisms for clinical picture suggestive of perioperative hypersensitivity reactions (Garvey et colleagues, unpublished).

(Doxil®), a poly(ethylene glycol)—phospholipid (PEG-PL) engineered nanomedicine.[23] A well-known micelle-solubilised-drug is paclitaxel (Taxol®).

Mast cell activation can also result from engagement of the Mas-related G protein-coupled receptor MRGPRX2.[24] Since the first description,[25] evidence has accumulated that off-target occupation of this receptor by various drug classes such as neuromuscular blocking agents (NMBA) and opioids could constitute an additional mechanism of non-immune immediate drug hypersensitivity reactions (IDHR).[26] Alternatively, opioid receptors may be involved in hypersensitivity to some opiates and semisynthetic opioids.[27]

Mast cell and basophil degranulation products

Degranulation of mast cells and basophils results in release of mediators that are classified as preformed (i.e. histamine, proteases), newly synthesised lipid mediators [prostaglandin, leukotrienes, platelet activating factor (PAF)] usually generated over minutes, and newly synthesised cytokines, chemokines, and growth factors usually generated over hours. Because of variability, redundancy, and ethical issues in inducing anaphylaxis in humans, it is difficult and challenging to judge the specific effect of each single factor. However, there is evidence that histamine, leukotrienes, and PAF are involved in vasodilatation, capillary leak, and bronchospasm. Depending on the underlying trigger, mast cells and basophils release their mediators in different spatiotemporal manners. For example, sIgE/FcεRI cross-linking results in compound exocytosis, that is a 'delayed' but sustained process with release of large, stable, granules with a high content of inflammatory mediators. In contrast, MRGPRX2 engagement results in rapid but transient release of unstable granules with a low content of inflammatory mediators by the kiss and run mechanism.[28,29] The precise mechanisms and clinical repercussion in the context of POH and drug hypersensitivity in general need to be elucidated. Further studies are also important on the roles, activation processes, and mediators of cells other than mast cells and basophils such as neutrophils, monocyte/macrophages, and T cells in POH. It seems that neutrophils are involved mainly in IgG-dependent anaphylaxis with PAF as a key mediator.

Perioperative hypersensitivity reactions resulting from enzyme interference

Perioperative hypersenstivity reactions can also occur independent from mast cell and basophil activation (Fig. 2). Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the major causes of immediate drug hypersensitivity reactions (IDHRs) that can mechanistically be classified in two groups. Most frequently, reactions are induced by non-immunological non-specific mechanisms (non-allergic or cross-intolerance reactions) that encompass different clinical phenotypes such as NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD), and NSAID-induced urticaria/angioedema (NIUA). Far rarer, reactions result from specific immunological mechanisms (allergic or selective reactions) designated as single NSAID-induced urticaria/angioedema or anaphylaxis in which interclass cross-reactivity is virtually absent. The pathogenesis of the non-immunological NSAID hypersensitivity syndromes (NERD, NECD, NIUA) is related to their pharmacodynamic properties, that is inhibition of cyclo-oxygenase (COX)-1. Blocking COX-1 blocks prostaglandin synthesis and increases leukotriene production, and can cause NERD, NECD, and NIUA.[30]

Angiotensin-converting enzyme (ACE) is a key component of the renin-angiotensin system that converts angiotensin I to angiotensin II. It is also responsible for the degradation of

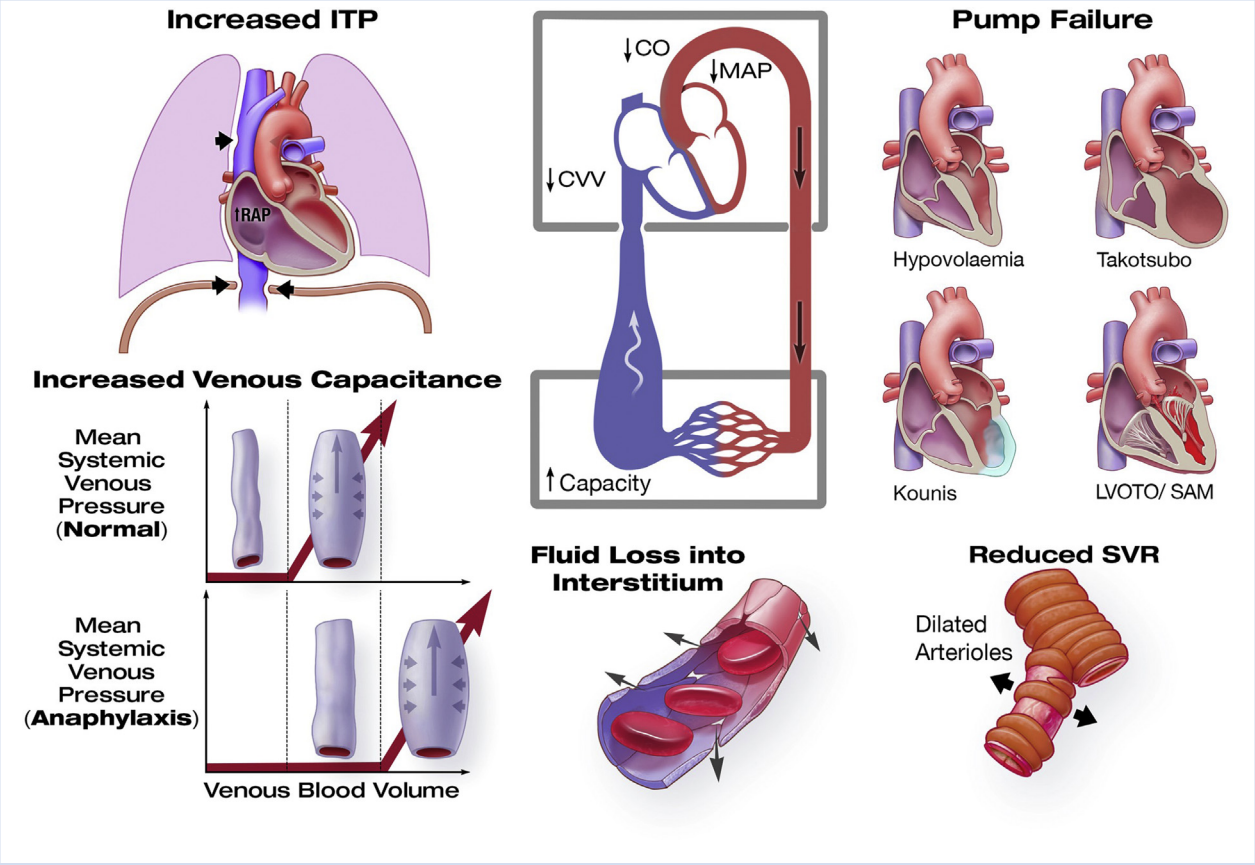


Fig 3. The five causes of cardiovascular anaphylactic shock. Severe anaphylactic shock may result from any or all of the five mechanisms indicated. CVV, central vascular volume; CO, cardiac output; ITP, intrathroacic pressure; LVOTO/SAM, left ventricular outflow tract obstruction and systolic anterior motion of the mitral valve leaflets; MAP, mean arterial blood pressure; RAP, right atrial opressure; SVR, systemic vascular resistance. Copyright P Sadleir, R Clarke, and P Platt.

bradykinin, which is generated from high molecular weight kininogen by kallikrein. Activation of bradykinin 2 receptors by bradykinin affects vascular permeability and stimulates release of substance P, a peptide that causes vasodilation and fluid extravasation into tissues. Inhibition of ACE and subsequent blockade of bradykinin degradation is a likely explanation for the sometimes life-threatening ACE inhibitor (ACEI)-induced angioedema. Angioedema can occur at any time during treatment with ACEIs and may continue weeks after the medication is discontinued. In the context of POH, ACEIs have been assumed to trigger isolated angioedema, that is angioedema without accompanying symptoms, mainly of the oropharynx because of mechanical stress because of (difficult) intubation.[31,32] There is no information on impairment of aminopeptidase P and dipeptidyl peptidase IV as risk factors for perioperative angioedema.

MRGPRX2: a new player in perioperative hypersensitivity/anaphylaxis?

Mast cells and basophils are equipped with various surface receptors, providing them with an intrinsic capacity to respond to different stimuli independent from aggregation of IgE/FcεRI complexes by specific allergens. Unfortunately, some of these receptors can also be activated by different drug classes, resulting in detrimental and harmful IDHRs. However, for most of these alternative activation mechanisms, clinical data are limited, especially in the context of POH (including perioperative anaphylaxis). Apart from IgE/FcεRI cross-linking, the main mechanism assumed to be implicated in POH and anaphylaxis probably relates to off-target occupancy of the MRGPRX2 receptor by drugs such as NMBA (aminosteroids and benzylisoquinolines),[25,33–36] opiates/opioids,[35,37] and some antibiotics such as fluoroquinolones[25,33] and vancomycin.[35,38] Moreover, by challenging the value of skin testing to discriminate between IgE/FcεRI- and MRGPRX2-dependent mast cell activation, some authors have proposed to reclassify NMBA hypersensitivity as an adverse pharmacological event or innate hypersensitivity reaction.[39] However, data are mainly from animal and *in vitro* models and findings are not universal. For example Lansu and colleagues[37] could not confirm mast cell degranulation by rocuronium, atracurium, ciprofloxacin, or moxifloxacin. Navines-Ferrer and colleagues[35] failed to demonstrate human mast cell degranulation in response to rocuronium amongst several other drugs. The explanation for the divergences between mice and human mast cells

has probably to be sought in adaptive changes of the MRGPRX2 gene in human evolution,[40] making the human receptor less susceptible to rocuronium than its murine orthologue Mrgprb2.[25,35] It seems difficult to ignore congruent results from complementary basophil activation experiments and drug-specific sIgE assays that point to genuine IgE/FcεRI-dependent reactions to rocuronium[41–43] and atracurium[44,45] in most of our patients. Collectively, these data indicate that next to IgE/FcεRI-cross-linking, off-target occupation of the MRGPRX2 receptor by NMBA might constitute an alternative pathomechanism for POH. MRGPRX2-dependendent reactions would be clinically indistinguishable from allergic POH resulting from IgE/FcεRI-cross-linking, and additional *in vitro* tests are required to distinguish between these mechanisms because of uncertainties associated with skin tests. This assumption also applies to immediate opiate hypersensitivity reactions[46] that might require additional *in vitro* testing to discriminate between IgE/FcεRI- and MRGPRX2-dependent reactions.[47,48]

Pathophysiology of intraoperative anaphylaxis: clinical implications

The phenotypically indistinguishable POH endotypes interact with patients' comorbid diseases, surgical pathology, and anaesthetic and surgical techniques to create a myriad of presenting syndromes that evolve according to the patients' physiological reserve and the effectiveness of clinician intervention. Most anaesthetic drugs have both a direct depressant effect on the heart and circulation, and an indirect effect to reduce sympathetic activity. If cessation of spontaneous ventilation occurs, the favourable effect of the thoracic pump on venous return is lost. IPPV, usually accompanied with PEEP, results in increased mean intrathoracic pressure, further reducing the pressure gradient for right atrial filling. Instrumentation of the airway is common, potentially exacerbating bronchospasm and contributing to airway trauma, but also ensuring that airway swelling from angioedema and bronchospasm are not as critical as in the community where they are commonly reported causes of mortality.

There have been many animal models of anaphylaxis studied, but those findings are not necessarily applicable to man because of the dramatically different effects of anaphylaxis between species. Knowledge gained from the collective experience of managing human anaphylaxis in the operating theatre has been critical in understanding the physiological effects, set out below, that are responsible for changing an often benign process into a lethal one. Most cases of anaphylaxis respond rapidly to treatment and are not associated with long term sequelae. Some cases are unresponsive to treatment, shock supervenes, and cardiopulmonary resuscitation is required that can be unsuccessful in 1–9% of cases.[49–51]

Compensated cardiovascular anaphylaxis

Hypotension is the most common presenting feature of perioperative anaphylaxis, and is frequently associated with tachycardia.[52] Nonetheless, in the majority of cases of appropriately treated intraoperative anaphylaxis, cardiac output is maintained or increased.[55] Hypotension is a consequence of reduced cardiac preload and afterload rather than myocardial dysfunction, although there are multiple causes of cardiovascular anaphylactic shock (Fig. 3), and myocardial dysfunction can complicate any cause of hypoperfusion. Two reports of grade III, human intraoperative anaphylaxis, in which invasive monitoring had been incidentally applied, indicated that hypotension was initially associated with a reduction in systemic vascular resistance and pulmonary capillary wedge pressure. Left ventricular stroke volume was maintained or increased as a consequence of large compensatory increases in ejection fraction, although both end-diastolic and -systolic volumes were severely decreased. With compensatory tachycardia, cardiac output was maintained or increased. Endogenous epinephrine and norepinephrine blood concentrations became elevated 5.5 and 3.5 times baseline, respectively, counteracting to some extent the cardiovascular effects of histamine.[53,54]

Chronotropicity

Tachycardia is more common than bradycardia during intraoperative anaphylaxis, a consequence of the direct myocardial effects of histamine on cardiac H2-receptors, endogenous catecholamine effects on cardiac β-receptors, and reflex sympathetic activation.[55] However, in the less common cases of anaphylaxis complicated by cardiac arrest, bradycardia was more common.[52] A postulated explanation is a precipitous reduction in venous return causing a vasodepressor response, the Bezold-Jarisch reflex. The afferent limb of the reflex involves cardiac mechanoreceptors in response to cardiac underfilling, and paradoxical arterial baroreceptor discharge in response to severe hypotension ('collapse firing').[56] The more frequent observation of bradycardia in severe anaphylaxis therefore suggests that in these cases, a lack of venous return is a key feature.

Shock

In increasingly severe or prolonged anaphylaxis, the ability to maintain cardiac output and arterial pressure will be compromised by an unpredictable combination of distributive, hypovolaemic, obstructive, or less commonly, cardiogenic causes of shock. In animal models, regional blood flows are altered and the abolition of cerebral autoregulation results in pressure-dependent flow.[57] Clinical features to suggest inadequate perfusion include a reduction in end-tidal expired carbon dioxide partial pressure, poor peripheral perfusion resulting in failure of oximetry readings, or a delay in the appearance of skin manifestations of anaphylaxis. In ventilated patients suffering intraoperative anaphylactic shock to NMBAs, end-tidal CO_2 tensions were reduced in 57% of grade III cases.[58]

Maldistribution and hypovolaemia

Reduction in venous return and preload is secondary to fluid loss and redistribution of blood between vascular compartments. Extravasation of fluid from systemic capillaries is enhanced by both an increase in blood flow, as a result of vasodilatation, and disruption of the endothelial barrier by histamine and PAF.[59] The magnitude of fluid loss has been estimated by observing the degree of haemoconcentration as a decrease in blood volume of 30–37% in unresuscitated anaphylaxis.[60]

Reduced preload can only be compensated for by reducing the left ventricular end-systolic volume until a mechanical limit is reached, thus volume replacement is essential; in the severest cases, resuscitation is impossible if replacement is inadequate. Venous return is determined by the gradient between the mean systemic pressure, itself determined by the stressed volume in the venous compartment,[61] and right atrial pressure. Raised intrathoracic pressure and a reduction in

stressed volume combine to severely compromise the pressure gradient that drives cardiac filling. The primacy of circulatory failure, rather than myocardial dysfunction, has been demonstrated by a case of human anaphylaxis during cardiopulmonary bypass.[62] Gelofusine® anaphylaxis was immediately associated with a reduction in return of venous blood from the patient to the circuit reservoir, requiring addition of 73% of the patient's estimated blood volume by weight (51 ml kg^{-1} of fluid) in the subsequent 15 min to maintain extracorporeal flow. The contribution of reduced venous return, as a result of venous maldistribution in this case, was similar to that of fluid extravasation, although the site of this maldistribution has not been clearly elucidated in man. In dog and rat models of anaphylaxis, sequestration of blood in the venous compartments of organs drained by the portal system is associated with acute increases in portal venous pressures.[63–65] Regardless, severe circulatory failure may occur despite the presence in this case of a functional (extracorporeal) pump, and is consistent with the majority of patients suffering grade IV anaphylactic shock who do not have pre-existing myocardial comorbidities.

Further supporting observations implicating maldistribution and hypovolaemia in severe anaphylactic shock include upright posture and lack of volume resuscitation in fatal cases, and the efficacy of reversal of neuromuscular block and external chest compressions in resurrecting severe cases. Pumphrey[66] reported a pattern of sudden death after a change to the upright posture in four patients suffering out-of-hospital anaphylactic shock, with at least 10 out of 38 patients who died in a series of community anaphylactic shock cases being resuscitated while positioned in an upright posture. This 'fatal' posture was also noted in a high proportion of anaphylaxis fatalities in Australia.[67]

Intraoperative echocardiography in severe or non-responsive anaphylactic shock almost universally demonstrates hyperdynamic left and right ventricles with low end-diastolic and extremely low (negligible) end-systolic volumes. In these circumstances, the primary correctable defect is lack of venous return to the heart. In a European series of three fatal cases of NMBA anaphylaxis, volume expansion was absent or inadequate.[68]

There is a dichotomy between continuing reports of the beneficial use and a lack of plausible mechanism for sugammadex in rocuronium-induced IgE-mediated anaphylactic shock. *In vivo* and *in vitro* experimental evidence indicates that sugammadex does not influence the extent or duration of the immunological response to rocuronium in patients with immediate hypersensitivity to rocuronium.[68,69] It is equally effective in ameliorating severe anaphylactic shock induced by IgE-mediated POH triggered by either rocuronium or cephazolin, suggesting that the most likely mechanism is non-immunological.[70] The onset of exercise has been demonstrated to result in an immediate increase in the mean circulatory filling pressure as a consequence of the effect of muscle contraction on venous capacitance in exercising muscle and the abdomen. The volume shift has been estimated to be of the order of 500–1100 ml (8–16 ml kg^{-1}); a similar autotransfusion during anaphylaxis could explain observed clinical improvements.[71] Reversal of neuromuscular block by sugammadex in anaphylaxis, regardless of the trigger, would be expected to similarly increase muscular tone and cause a reduction in venous capacitance.

The resumption of spontaneous (negative-pressure) ventilation may also ameliorate anaphylactic shock. Obstruction to venous return as a consequence of raised intrathoracic pressures from positive pressure ventilation, with or without bronchospasm, further impairs cardiac filling in the setting of hypovolaemia and increased venous compliance. Vena caval compression may occur, and any increase in intrathoracic pressure increases right atrial pressure. Administration of sugammadex and conversion from positive- to negative-pressure respiration may widen the gradient for flow between mean systemic filling pressure and right atrial pressure. A similar principle has been used to explain the return of spontaneous circulation in cases of circulatory arrest during dynamic hyperinflation of the lungs after cessation of resuscitative efforts ('Lazarus phenomenon').

Distinct from this previous example, neurological deficit-free survival from pulseless electrical activity (PEA) during POH is unexpectedly high.[72] Diastolic (organ-perfusing) pressure during external chest compressions must therefore be higher than would be expected of a pure vasoplegic state. If PEA results from the inability of the passively-filled heart to maintain cardiac output, external chest compressions might result in effective arterial pressure by overcoming the impediment to venous return to the right ventricle by creating negative intrathoracic pressure (suction) during the decompressive phase of external chest compressions (thoracic pump mechanism). There will also be increased left ventricular filling as a consequence of reduced pulmonary vascular capacitance during the compressive phase.[73]

The discussion above relates to impaired biventricular filling. There are multiple mediators that have either vasodilatory or constrictive effects on the pulmonary circulations and may cause impairment only of left ventricular filling. In dogs and mice, acute pulmonary hypertension and right heart failure has been observed, with reduction in left ventricular preload.[74,75] This has not been observed in man except after IgE-independent anaphylaxis, such as a type III, immune-complex reaction to protamine.

Myocardial depression

Intraoperative anaphylaxis occurs most commonly in patients who do not have reduced myocardial reserve, as are the majority of patients in which cardiac arrest is a complication.[72] However, there will be some patients with pre-existing cardiac disease in whom hypotension and increased myocardial work (from tachycardia) result in secondary cardiac dysfunction because of inadequate myocardial perfusion. Myocardial ischaemia during anaphylaxis has been reported secondary to a number of different causes. These have been collectively described as Kounis syndrome[76] that includes three variants: coronary vasospasm with normal coronary vasculature, plaque erosion or rupture leading to myocardial infarction, and stent thrombosis. These syndromes are not commonly seen during anaesthesia.

Takatsubo's cardiomyopathy is a rare condition characterised by reversible left ventricular dysfunction attributable to regional wall motion abnormalities predominantly affecting the apex of the heart. Because of its association with emotional stress, it may alternatively be called 'broken heart syndrome'. There is a complex interaction between the brain and the cardiovascular system that, if dysfunctional through neurological injury such as subarachnoid haemorrhage or emotional processing, can lead to both circulating and myocardial catecholamines reaching damaging concentrations.[77] Although ST-segment elevation, T-wave inversion, or both can occur with normal or marginally elevated troponin

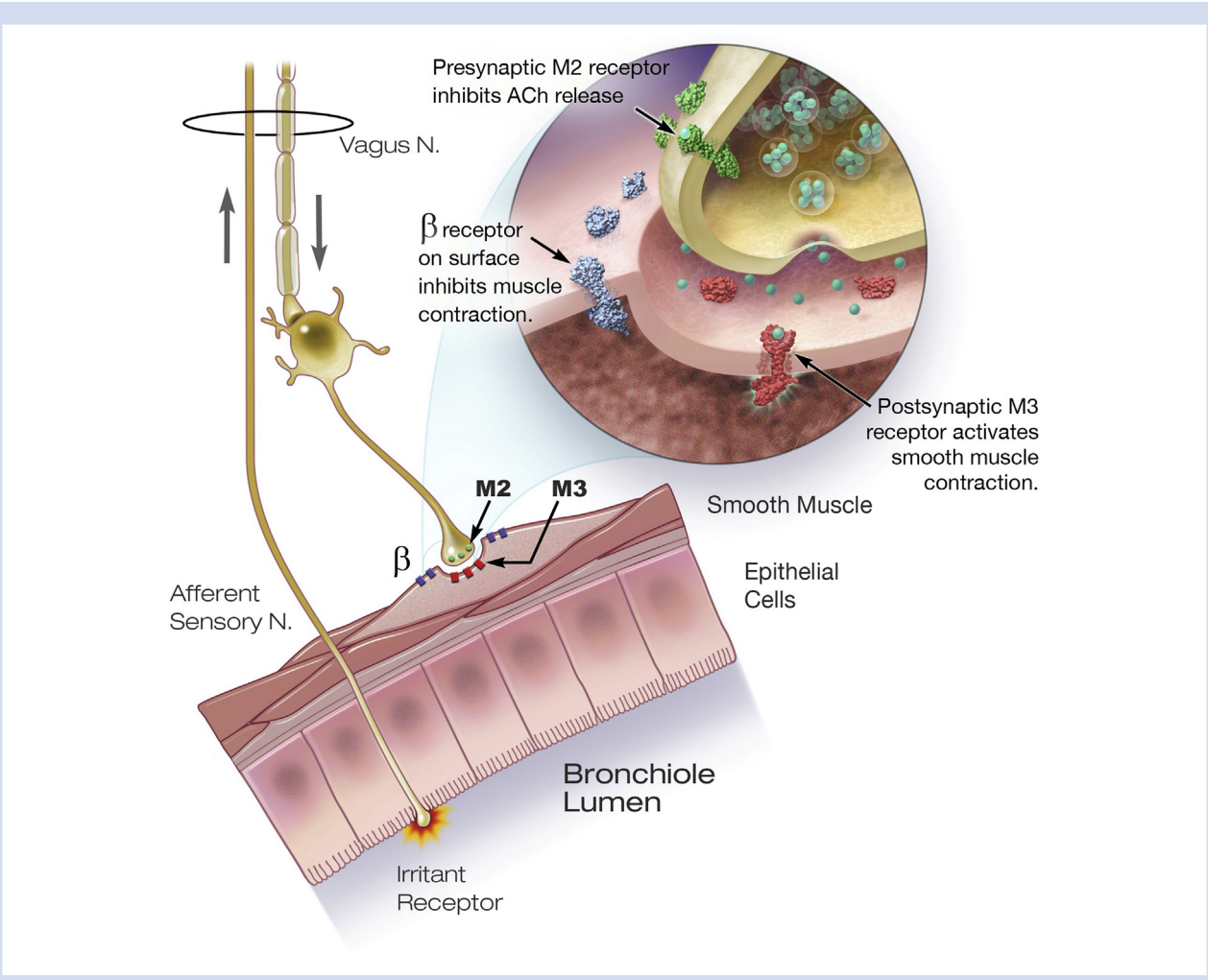


Fig 4. Irritant receptor–vagal reflex. Neuromuscular junction acetylcholine stimulates postsynaptic bronchial smooth muscle (bronchoconstriction) via M_3 receptors, an action limited by its effect on inhibitory, presynaptic M_2 receptors which impede exocytosis of further acetylcholine. Copyright P Sadleir, R Clarke, and P Platt.

concentrations, coronary angiography usually demonstrates normal coronary vasculature. Takatsubo's cardiomyopathy associated with anaphylaxis is more commonly reported in non-anaesthetised patients presenting to emergency departments from the community. Anaesthesia will obtund the effects of the heart-brain axis and thus Takatsubo's cardiomyopathy is uncommon with anaphylaxis in the anaesthetised patient, but may be a cause in this setting by over-aggressive treatment with epinephrine. The most plausible hypothesis to explain Takatsubo cardio-depression is that is it caused by the action of epinephrine on β2-adrenoreceptors that are more prevalent in the apex of the heart.[78] Norepinephrine, having less β2 activity, does not cause the same contractile effects in animal models.

Left ventricular outflow obstruction causing obstructive shock

Excessive use of epinephrine in association with inadequate volume replacement can result in a hyperdynamic, underfilled heart that results in dynamic left ventricular outflow obstruction with systolic anterior motion of the mitral valve and severe mitral regurgitation.[79] This condition is most commonly seen with anatomical abnormalities of the outflow tract of the left ventricle, such as hypertrophic obstructive cardiomyopathy, but in association with anaphylaxis, they can occur with normal cardiac anatomy. It is exacerbated by positive pressure ventilation, inadequate fluid resuscitation, and positive inotropes. Continued use of epinephrine in this situation is likely to worsen the condition and may be fatal, in which case there would be no evidence of the cause of death at post-mortem.

It can therefore be seen that the cardiovascular manifestations of anaphylaxis are not stereotypical and the individual response depends on the reserve of each component of the cardiovascular system. This, in turn, is influenced by the surgical procedure being performed, the stage of the procedure, surgical pathology, anaesthetic techniques, and clinician interventions. Finally, patient comorbidities and pharmaceutical treatments (beta-blockers, antihypertensives, or antihistamines) can exacerbate or ameliorate the presentation.

Pathophysiology of bronchospasm

Many patients presenting for surgery have a predisposition to bronchospasm. Some of these will not admit to, or ignore, asthma symptoms. Asthma medication is often mistakenly omitted particularly before emergency surgery. Neither sedative nor anticholinergic medications are now fashionable as premedication before surgery. Anxiety, irritant volatile anaesthetics, airway instrumentation, and many histamine-releasing drugs can cause bronchospasm in these patients. POH is not the most common cause of perioperative bronchospasm. When it does occur, allergic POH results in bronchospasm triggered by the actions of degranulation products, including histamine and PAF, and may have some mediators in common with non-allergic POH (e.g. cysteinyl leukotrienes). It is likely that the severity of bronchospasm when anaphylaxis is triggered is determined by the underlying state of the airway and the presence, or not, of anticholinergic medication. In a recent report of a series of patients with intraoperative anaphylaxis, the incidence of bronchospasm in at-risk patients was not increased, but the severity of reactions, when they did occur, was more severe.[80]

Neural control of healthy airways

In normal lung, efferent parasympathetic nervous control via the vagus nerve is the predominant determinant of airway tone. In disease states such as asthma, the role of the nervous system has consistently been understated.[81] There is no sympathetic nerve supply to bronchiolar smooth muscle, but β-adrenergic receptors are widely expressed explaining the effectiveness of β2-agonist drugs as bronchodilators. Vagal preganglionic fibres enter the lung and terminate in ganglia within the bronchioles. The airways of healthy humans are tonically constricted, and maintained by efferent vagal activity acting via postganglionic fibres that release acetylcholine, the ligand for muscarinic receptors (M_3) on bronchiolar smooth muscle fibres (Fig. 4). This excitatory effect is balanced by a negative feedback loop via M_2 receptors on the postganglionic nerve.[82] Afferent sensory neurones respond to chemical stimulation and to bioactive molecules released during inflammation. Their cell bodies are in vagal and cervical dorsal root ganglia via which signals are transmitted to the brainstem and spinal cord.[83]

Neural control of diseased airways

Studies of the airway in asthma show that there are both sensory afferent and motor efferent vagal neural responses that are altered by the disease process. Acetylcholine and histamine are potent vasodilators of the tracheobronchial circulation, causing submucosal swelling and contributing to changes in airway resistance compounding that mediated by airway smooth muscle.[84] Mice sensitised to ovalbumin develop a marked immune reaction in the lung, with leucocyte infiltration and airway hyperreactivity. Ablation of a subset of sensory neurones completely abolishes the hyperresponsiveness, but has no effect on the inflammatory component. Indeed, in man, bronchial thermoplasty is successful in moderating severe asthma, in part, by interrupting central and local reflexes responsible for activating bronchospasm.[85] In asthma, inflammatory mediators sensitise vagal sensory neurones, resulting in an exaggerated response to bronchoconstricting stimuli, common during anaesthesia.[86]

Efferent neurones also contribute to the exaggerated response to airway stimulation. In asthma, the blockade of M_2 receptors by major basic protein from eosinophils that invade the bronchioles as part of the inflammatory process is one example. Viral neuraminidase has a similar effect and is recognised as a cause of airway hyperreactivity, particularly in children after respiratory tract infections. Gallamine, a neuromuscular blocking agent of historical interest, is a selective antagonist at the M_2 receptor that blocked autoinhibition, causing bronchospasm on vagal stimulation.[82] More recently, rapacuronium, a rapidly acting neuromuscular blocking agent, was developed speculatively to replace suxamethonium. After a number of deaths from bronchospasm in children, thought to have been allergic in origin, the drug was withdrawn. It was only proved later that the bronchospasm was because of rapacuronium having antagonist effects at the M_2 receptor and an indirect agonist effect at the M_3 receptor.[87] Administration of an anticholinergic drug such as atropine causes dilatation of the airways by blocking M_3 receptors. Since the advent of general anaesthesia, atropine has been universally used as a premedication, until relatively recently, because of its beneficial effects in blocking undesirable cholinergic effects such as excessive salivation, bradyarrhythmia, and reflex bronchoconstriction in response to non-antigenic stimuli.

The UK lifetime prevalence of patient-reported symptoms of asthma is 29.5%, and 15.6% for patient-reported clinician-diagnosed asthma. It is estimated that 1.2 million people (2% of the UK population) have chronic obstructive pulmonary disease (COPD).[88] If one includes smoking, it is clear that a large percentage of people presenting for surgery have hyperreactive airways and are at risk of developing bronchospasm. Many of those with COPD will be treated with selective short- or long-acting anticholinergic drugs such as ipratropium bromide and tiotropium bromide, respectively. Some asthmatics will also have had benefit from these drugs.

Studies in guinea pigs, that develop anaphylaxis characterised by lethal bronchospasm on exposure to an antigen to which they are sensitised, show that they are completely protected if pretreated with atropine. Similarly, asthmatics exposed to antigen aerosols of grass pollen or house dust mite develop bronchospasm, but are protected if pretreated with atropine, but not if it is administered after the allergen exposure.[89]

Pulmonary oedema

Pulmonary oedema is a rare, but described, complication of anaphylaxis. Pulmonary capillary hypertension, incompetence of the alveolocapillary membrane, or both, result in egress of fluid from the pulmonary circulation and cause alveolar oedema if it exceeds the capacity of pulmonary lymphatic drainage. In ovalbumin-sensitised rats, anaphylaxis is associated with an almost immediate decrease in pulmonary compliance as a result of massive tracheal, bronchial, and intrapulmonary microvascular leakage, causing bronchospasm.[90] In human patients, pulmonary artery and pulmonary capillary wedge pressures are reduced, although it is possible that pulmonary arteriolar dilatation, pulmonary venous constriction, or both could still result in raised pulmonary capillary hydrostatic pressures. In some instances of anaphylaxis, fulminant pulmonary oedema with a high fluid protein content (>70% fluid/serum protein concentration) has been described, and this membrane oedema may occur with normal or low pulmonary capillary hydrostatic pressures, and

in the presence of high mean positive airway pressures (with positive pressure invasive ventilation). Severe membrane oedema has been associated with the subsequent development of hypovolaemia and hypoxaemia.

Angioedema

Angioedema may be subclassified into cases with and without urticaria.[91] Urticaria is a manifestation of anaphylaxis in the skin, with red, raised, and itchy lesions as a consequence of vasodilatation, increased blood flow, and increased capillary permeability. Urticaria occurs in the superficial dermis, while angioedema is the same pathophysiological process occurring in the deeper tissues. Angioedema is defined as non-pitting, non-gravity-dependent, transient swelling of the skin or mucous membranes (as distinguished from oedema which is pitting and gravity-dependent). Angioedema can be distinguished mechanistically into histaminergic (including anaphylactic) and non-histaminergic (complement or bradykinin-mediated). Bradykinin-mediated angioedema[92] often involves the upper airways, and does not respond to antihistamines, corticosteroids, or adrenaline.

A feared complication of intraoperative anaphylaxis is angioedema and potential airway obstruction. Intraoperative presentations of anaphylaxis less commonly involve the respiratory system, with only 20% of fatal cases involving the respiratory system.[67] Respiratory presentations are more common in drug allergies in other hospital settings or in the community, and particularly with food allergies.

Although generalised oedema is common after IgE-mediated anaphylaxis, tongue and laryngeal swelling are more common after non-allergic reactions.[93] This is particularly the case when airway instrumentation is a trigger for localised tissue bradykinin activation. The syndrome of airway swelling in this situation can be prolonged (>48 h), and does not respond to the usual therapies for anaphylaxis-induced angioedema. In a series of 72 patients intubated and admitted to intensive care after idiopathic angioedema, the mean duration before extubation was 93.5 h.[94] In contrast, in a series of 205 patients with grade II–IV intraoperative (post-induction) anaphylaxis, only 97 patients were admitted to intensive care intubated (47%) and only 21 remained intubated 24 h after admission to the ICU (10%). No patient with grade II anaphylaxis was still intubated after 24 h.[72] The incidence of angioedema was not sought in this study, however only 10 remained intubated 48 h after admission (4.9%), and at least four of these had complications unrelated to airway swelling to account for prolonged intubation (Takatsubo's cardiomyopathy, ventilator-associated pneumonia, or hypoxic encephalopathy). Therefore, the incidence of airway swelling requiring ventilation for more than 48 h after intraoperative anaphylaxis is likely <3%.

ACE-inhibitor induced angioedema is more likely to affect the larynx than allergic angioedema or hereditary angioedema resulting from C1-inhibitor function deficiency.[95] The anaesthetist should be vigilant for cases of IgE-independent anaphylaxis, particular in patients on ACE-inhibitors, which may progress to life-threatening airway swelling.

Conclusions

The current definition of perioperative hypersensitivity reactions includes allergic and non-allergic phenomena. The non-allergic phenomena may involve both mast cell/basophil-dependent and independent syndromes such as COX-1 inhibition and generation of bradykinin. These distinct underlying pathomechanisms result in heterogenous clinical presentations that, as is the case for hypersensitivity reactions in the community, are modified by comorbid conditions. POH is further complicated by the interaction of these derangements with the surgical pathology and the effects of surgical and anaesthetic techniques, creating both a diagnostic challenge and newly-recognised treatment paradoxes. The suspicion of POH may be raised because of an unexpected diversion from the normal physiological or pharmacological response to the anaesthetic drugs used. Manifestations such as hypotension, mild increases of airway resistance, and even transitory patchy erythema are not uncommonly caused by anaesthetic drugs, but it is the magnitude, duration, combination of signs, and response to treatment that suggest POH. The most severe result of POH is anaphylaxis that in most patients rapidly responds to recommended treatment with epinephrine and fluids. Occasionally, protracted resuscitation is required, and in this setting a good understanding of the pathophysiology is critical in managing a severe multisystem disorder that is not stereotypical. Cardiovascular effects of POH may be mediated by a variable effect on various aspects of the circulation and heart, while the respiratory manifestations have to be distinguished from more common causes of bronchospasm under anaesthesia, or causes of angioedema that would not be expected to respond to the usual therapies for anaphylaxis. The pathophysiology of POH is a topic with incomplete knowledge and further investigation has the potential to improve patient outcomes.

Authors' contributions

Equally contributed to conception and design of the study, data collection, and interpretation; contributed to the drafting and reviewing of the manuscript; approved the final text: all authors

Declarations of interest

PMM: Scientific advisor for the ALPHO study (NCT02250729), the aim of which is to establish a possible link between pholcodine exposure and anaphylaxis to neuromuscular blocking agents, funded by a consortium of pharmaceutical companies (Zambon, Urgo, Pierre Fabre, Boots, Hepatoum, Biocodex, Sanofi, LBR, GSK, APL, Bells Healthcare, Pinewood, T and R, Ernest Jackson). The other authors have no conflicts to declare.

References

1. Johansson SG, Hourihane JO, Bousquet J, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001; **56**: 813–24
2. Castells M. Diagnosis and management of anaphylaxis in precision medicine. *J Allergy Clin Immunol* 2017; **140**: 321–33
3. Knol EF. Requirements for effective IgE cross-linking on mast cells and basophils. *Mol Nutr Food Res* 2006; **50**: 620–4
4. Ruso JM, Taboada P, Varela LM, Attwood D, Mosquera V. Adsorption of an amphiphilic penicillin onto human serum albumin: characterisation of the complex. *Biophys Chem* 2001; **92**: 141–53

5. Aubert N, Mertes PM, Janaszak M, et al. Dendritic cells present neuromuscular blocking agent-related epitopes to T cells from allergic patients. *Allergy* 2004; **59**: 1022–3
6. Ahmad B, Parveen S, Khan RH. Effect of albumin conformation on the binding of ciprofloxacin to human serum albumin: a novel approach directly assigning binding site. *Biomacromolecules* 2006; **7**: 1350–6
7. Bulfone-Paus S, Nilsson G, Draber P, Blank U, Levi-Schaffer F. Positive and negative signals in mast cell activation. *Trends Immunol* 2017; **38**: 657–67
8. Xu H, Bin NR, Sugita S. Diverse exocytic pathways for mast cell mediators. *Biochem Soc Trans* 2018; **46**: 235–47
9. Finkelman FD, Khodoun MV, Strait R. Human IgE-independent systemic anaphylaxis. *J Allergy Clin Immunol* 2016; **137**: 1674–80
10. Reber LL, Hernandez JD, Galli SJ. The pathophysiology of anaphylaxis. *J Allergy Clin Immunol* 2017; **140**: 335–48
11. Cheifetz A, Smedley M, Martin S, et al. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol* 2003; **98**: 1315–24
12. Steenholdt C, Svenson M, Bendtzen K, Thomsen OO, Brynskov J, Ainsworth MA. Severe infusion reactions to infliximab: aetiology, immunogenicity and risk factors in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; **34**: 51–8
13. Steenholdt C, Svenson M, Bendtzen K, Thomsen OO, Brynskov J, Ainsworth MA. Acute and delayed hypersensitivity reactions to infliximab and adalimumab in a patient with Crohn's disease. *J Crohns Colitis* 2012; **6**: 108–11
14. Hedin H, Richter W, Messmer K, Renck H, Ljungstrom KG, Laubenthal H. Incidence, pathomechanism and prevention of dextran-induced anaphylactoid/anaphylactic reactions in man. *Dev Biol Stand* 1980; **48**: 179–89
15. Novey HS, Pahl M, Haydik I, Vaziri ND. Immunologic studies of anaphylaxis to iron dextran in patients on renal dialysis. *Ann Allergy* 1994; **72**: 224–8
16. Umeda Y, Fukumoto Y, Miyauchi T, et al. [Anaphylactic shock related to aprotinin induced by anti-aprotinin immunoglobulin G antibody alone; report of a case]. *Kyobu Geka* 2007; **60**: 69–71 (in Japanese)
17. Kober BJ, Scheule AM, Voth V, Deschner N, Schmid E, Ziemer G. Anaphylactic reaction after systemic application of aprotinin triggered by aprotinin-containing fibrin sealant. *Anesth Analg* 2008; **107**: 406–9
18. Scheule AM, Beierlein W, Arnold S, Eckstein FS, Albes JM, Ziemer G. The significance of preformed aprotinin-specific antibodies in cardiosurgical patients. *Anesth Analg* 2000; **90**: 262–6
19. Arroyave CM, Tan EM. Mechanism of complement activation by radiographic contrast media. *Clin Exp Immunol* 1977; **29**: 89–94
20. Kishimoto TK, Viswanathan K, Ganguly T, et al. Contaminated heparin associated with adverse clinical events and activation of the contact system. *N Engl J Med* 2008; **358**: 2457–67
21. Szebeni J, Muggia F, Gabizon A, Barenholz Y. Activation of complement by therapeutic liposomes and other lipid excipient-based therapeutic products: prediction and prevention. *Adv Drug Deliv Rev* 2011; **63**: 1020–30
22. Zhang B, Li Q, Shi C, Zhang X. Drug-induced pseudoallergy: a review of the causes and mechanisms. *Pharmacology* 2018; **101**: 104–10
23. Merkel OM, Urbanics R, Bedocs P, et al. In vitro and in vivo complement activation and related anaphylactic effects associated with polyethylenimine and polyethylenimine-graft-poly(ethylene glycol) block copolymers. *Biomaterials* 2011; **32**: 4936–42
24. Tatemoto K, Nozaki Y, Tsuda R, et al. Immunoglobulin E-independent activation of mast cell is mediated by Mrg receptors. *Biochem Biophys Res Commun* 2006; **349**: 1322–8
25. McNeil BD, Pundir P, Meeker S, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature* 2015; **519**: 237–41
26. Ali H. Emerging roles for MAS-related G protein-coupled receptor-X2 in host defense peptide, opioid, and neuropeptide-mediated inflammatory reactions. *Adv Immunol* 2017; **136**: 123–62
27. Blunk JA, Schmelz M, Zeck S, Skov P, Likar R, Koppert W. Opioid-induced mast cell activation and vascular responses is not mediated by mu-opioid receptors: an in vivo microdialysis study in human skin. *Anesth Analg* 2004; **98**: 364–70
28. Gaudenzio N, Sibilano R, Marichal T, et al. Different activation signals induce distinct mast cell degranulation strategies. *J Clin Invest* 2016; **126**: 3981–98
29. Karhausen J, Abraham SN. How mast cells make decisions. *J Clin Invest* 2016; **126**: 3735–8
30. Dona I, Salas M, Perkins JR, et al. Hypersensitivity reactions to non-steroidal anti-inflammatory drugs. *Curr Pharm Des* 2016; **22**: 6784–802
31. Stojiljkovic L. Renin-angiotensin system inhibitors and angioedema: anesthetic implications. *Curr Opin Anaesthesiol* 2012; **25**: 356–62
32. Sarkar P, Nicholson G, Hall G. Brief review: angiotensin converting enzyme inhibitors and angioedema: anesthetic implications. *Can J Anaesth* 2006; **53**: 994–1003
33. Azimi E, Reddy VB, Shade KC, et al. Dual action of neurokinin-1 antagonists on Mas-related GPCRs. *JCI Insight* 2016; **1**: e89362
34. Che D, Rui L, Cao J, et al. Cisatracurium induces mast cell activation and pseudo-allergic reactions via MRGPRX2. *Int Immunopharmacol* 2018; **62**: 244–50
35. Navines-Ferrer A, Serrano-Candelas E, Lafuente A, Munoz-Cano R, Martin M, Gastaminza G. MRGPRX2-mediated mast cell response to drugs used in perioperative procedures and anaesthesia. *Sci Rep* 2018; **8**: 11628
36. Che D, Wang J, Ding Y, et al. Mivacurium induce mast cell activation and pseudo-allergic reactions via MAS-related G protein coupled receptor-X2. *Cell Immunol* 2018; **332**: 121–8
37. Lansu K, Karpiak J, Liu J, et al. In silico design of novel probes for the atypical opioid receptor MRGPRX2. *Nat Chem Biol* 2017; **13**: 529–36
38. Azimi E, Reddy VB, Lerner EA. Brief communication: MRGPRX2, atopic dermatitis and red man syndrome. *Itch (Phila)* 2017; **2**: e5
39. Spoerl D, Nigolian H, Czarnetzki C, Harr T. Reclassifying anaphylaxis to neuromuscular blocking agents based on the presumed patho-mechanism: IGE-mediated, pharmacological adverse reaction or "innate hypersensitivity"? *Int J Mol Sci* 2017; **18**: E1223
40. Yang S, Liu Y, Lin AA, Cavalli-Sforza LL, Zhao Z, Su B. Adaptive evolution of MRGX2, a human sensory neuron specific gene involved in nociception. *Gene* 2005; **352**: 30–5
41. Ebo DG, Bridts CH, Hagendorens MM, Mertens CH, De Clerck LS, Stevens WJ. Flow-assisted diagnostic management of anaphylaxis from rocuronium bromide. *Allergy* 2006; **61**: 935–9

42. Ebo DG, Venemalm L, Bridts CH, et al. Immunoglobulin E antibodies to rocuronium: a new diagnostic tool. *Anesthesiology* 2007; **107**: 253–9
43. Leysen J, Bridts CH, De Clerck LS, et al. Allergy to rocuronium: from clinical suspicion to correct diagnosis. *Allergy* 2011; **66**: 1014–9
44. Uyttebroek AP, Sabato V, Leysen J, Bridts CH, De Clerck LS, Ebo DG. Flowcytometric diagnosis of atracurium-induced anaphylaxis. *Allergy* 2014; **69**: 1324–32
45. Uyttebroek AP, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Immunoglobulin E antibodies to atracurium: a new diagnostic tool? *Clin Exp Allergy* 2015; **45**: 485–7
46. Baldo BA, Pham NH. Histamine-releasing and allergenic properties of opioid analgesic drugs: resolving the two. *Anaesth Intensive Care* 2012; **40**: 216–35
47. Leysen J, De Witte L, Sabato V, et al. IgE-mediated allergy to pholcodine and cross-reactivity to neuromuscular blocking agents: Lessons from flow cytometry. *Cytometry B Clin Cytom* 2013; **84**: 65–70
48. Nasser SM, Ewan PW. Opiate-sensitivity: clinical characteristics and the role of skin prick testing. *Clin Exp Allergy* 2001; **31**: 1014–20
49. Levy JH, Castells MC. Perioperative anaphylaxis and the United States perspective. *Anesth Analg* 2011; **113**: 979–81
50. Mertes PM, Tajima K, Regnier-Kimmoun MA, et al. Perioperative anaphylaxis. *Med Clin North Am* 2010; **94**: 761–89
51. Gibbs NM, Sadleir PH, Clarke RC, Platt PR. Survival from perioperative anaphylaxis in Western Australia 2000-2009. *Br J Anaesth* 2013; **111**: 589–93
52. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
53. Moss J, Fahmy NR, Sunder N, Beaven MA. Hormonal and hemodynamic profile of an anaphylactic reaction in man. *Circulation* 1981; **63**: 210–3
54. Beaupre PN, Roizen MF, Cahalan MK, Alpert RA, Cassorla L, Schiller NB. Hemodynamic and two-dimensional transesophageal echocardiographic analysis of an anaphylactic reaction in a human. *Anesthesiology* 1984; **60**: 482–4
55. Schellenberg RR, Ohtaka H, Paddon HB, Bramble SE, Rangno RE. Catecholamine responses to histamine infusion in man. *J Allergy Clin Immunol* 1991; **87**: 499–504
56. Kinsella SM, Tuckey JP. Perioperative bradycardia and asystole: relationship to vasovagal syncope and the Bezold-Jarisch reflex. *Br J Anaesth* 2001; **86**: 859–68
57. Zheng F, Collange O, Davidson J, et al. Epinephrine, compared with arginine vasopressin, is associated with similar haemodynamic effects but significantly improved brain oxygenation in the early phase of anaphylactic shock in rats: An experimental study. *Eur J Anaesthesiol* 2015; **32**: 563–70
58. Gouel-Cheron A, de Chaisemartin L, Jonsson F, Nicaise-Roland P, Granger V, Sabahov A, et al. Low end-tidal CO2 as a real-time severity marker of intra-anaesthetic acute hypersensitivity reactions. *Br J Anaesth* 2017; **119**: 908–17
59. Nakamura T, Murata T. Regulation of vascular permeability in anaphylaxis. *Br J Pharmacol* 2018; **175**: 2538–42
60. Fisher M. Blood volume replacement in acute anaphylactic cardiovascular collapse related to anaesthesia. *Br J Anaesth* 1977; **49**: 1023–6
61. Magder S. Volume and its relationship to cardiac output and venous return. *Crit Care* 2016; **20**: 271
62. Clarke R, Sadleir P, Van Niekerk AW, Platt P. Quantification of volume loss and haemodynamic changes of Gelofusine-induced anaphylaxis during cardiopulmonary bypass. *Anaesth Intensive Care* 2011; **39**: 492–5
63. Wagner EM, Mitzner WA, Bleecker ER. Peripheral circulatory alterations in canine anaphylactic shock. *Am J Physiol* 1986; **251**: H934–40
64. Cui S, Shibamoto T, Zhang W, Takano H, Kurata Y. Venous resistance increases during rat anaphylactic shock. *Shock* 2008; **29**: 733–9
65. Zhang W, Shibamoto T, Tanida M, Wang M, Sun L, Kurata Y. Rat hepatic and splanchnic vascular responses to anaphylactic shock, compared with hemorrhagic or vasodilator-induced shock. *In Vivo* 2013; **27**: 485–93
66. Pumphrey RS. Fatal posture in anaphylactic shock. *J Allergy Clin Immunol* 2003; **112**: 451–2
67. Mullins RJ, Wainstein BK, Barnes EH, Liew WK, Campbell DE. Increases in anaphylaxis fatalities in Australia from 1997 to 2013. *Clin Exp Allergy* 2016; **46**: 1099–110
68. Clarke RC, Sadleir PH, Platt PR. The role of sugammadex in the development and modification of an allergic response to rocuronium: evidence from a cutaneous model. *Anaesthesia* 2012; **67**: 266–73
69. Leysen J, Bridts CH, De Clerck LS, Ebo DG. Rocuronium-induced anaphylaxis is probably not mitigated by sugammadex: evidence from an in vitro experiment. *Anaesthesia* 2011; **66**: 526–7
70. Platt PR, Clarke RC, Johnson GH, Sadleir PH. Efficacy of sugammadex in rocuronium-induced or antibiotic-induced anaphylaxis. A case-control study. *Anaesthesia* 2015; **70**: 1264–7
71. Notarius CF, Magder S. Central venous pressure during exercise: role of muscle pump. *Can J Physiol Pharmacol* 1996; **74**: 647–51
72. Sadleir PHM, Clarke RC, Bozic B, Platt PR. Consequences of proceeding with surgery after resuscitation from intraoperative anaphylaxis. *Anaesthesia* 2018; **73**: 32–9
73. Lurie KG, Nemergut EC, Yannopoulos D, Sweeney M. The physiology of cardiopulmonary resuscitation. *Anesth Analg* 2016; **122**: 767–83
74. Wang M, Shibamoto T, Kuda Y, et al. The responses of pulmonary and systemic circulation and airway to anaphylactic mediators in anesthetized BALB/c mice. *Life Sci* 2016; **147**: 77–84
75. Miyahara T, Shibamoto T, Wang HG, Koyama S. Role of circulating blood components and thromboxane in anaphylactic vasoconstriction in isolated canine lungs. *J Appl Physiol (1985)* 1997; **83**: 1508–16
76. Memon S, Chhabra L, Masrur S, Parker MW. Allergic acute coronary syndrome (Kounis syndrome). *Proc (Bayl Univ Med Cent)* 2015; **28**: 358–62
77. Tahsili-Fahadan P, Geocadin RG. Heart-brain axis: effects of neurologic injury on cardiovascular function. *Circ Res* 2017; **120**: 559–72
78. Redfors B, Shao Y, Ali A, Omerovic E. Current hypotheses regarding the pathophysiology behind the takotsubo syndrome. *Int J Cardiol* 2014; **177**: 771–9
79. Sadleir P, Clarke R, Lim B, Platt P. Epinephrine preventing recovery from intraoperative anaphylactic shock complicated by systolic anterior motion of the mitral valve with left ventricular outflow tract obstruction on

transoesophageal echocardiography. *Anaesth Intensive Care* 2018; **46**: 566–71
80. Gouel-Cheron A, Neukirch C, Aubier B, Montravers P, Nicaise P, Chollet-Martin S, et al. Anaphylactic bronchospasm during general anesthesia is not related to asthma. *Allergy* 2015; **70**: 453–6
81. Canning BJ, Woo A, Mazzone SB. Neuronal modulation of airway and vascular tone and their influence on nonspecific airways responsiveness in asthma. *J Allergy (Cairo)* 2012; **2012**: 108149
82. Scott GD, Fryer AD. Role of parasympathetic nerves and muscarinic receptors in allergy and asthma. *Chem Immunol Allergy* 2012; **98**: 48–69
83. Mazzone SB, Undem BJ. Vagal afferent innervation of the airways in health and disease. *Physiol Rev* 2016; **96**: 975–1024
84. Lockhart A, Dinh-Xuan AT, Regnard J, Cabanes L, Matran R. Effect of airway blood flow on airflow. *Am Rev Respir Dis* 1992; **146**: S19–23
85. Menzella F, Lusuardi M, Galeone C, Facciolongo N. Bronchial thermoplasty and the role of airway smooth muscle: are we on the right direction? *Ther Clin Risk Manag* 2017; **13**: 1213–21
86. Trankner D, Hahne N, Sugino K, Hoon MA, Zuker C. Population of sensory neurons essential for asthmatic hyperreactivity of inflamed airways. *Proc Natl Acad Sci U S A* 2014; **111**: 11515–20
87. Jooste E, Klafter F, Hirshman CA, Emala CW. A mechanism for rapacuronium-induced bronchospasm: M2 muscarinic receptor antagonism. *Anesthesiology* 2003; **98**: 906–11
88. Mukherjee M, Stoddart A, Gupta RP, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC Med* 2016; **14**: 113
89. Yu DY, Galant SP, Gold WM. Inhibition of antigen-induced bronchoconstriction by atropine in asthmatic patients. *J Appl Physiol* 1972; **32**: 823–8
90. Zheng F, Copotoiu R, Tacquard C, et al. Epinephrine but not vasopressin attenuates the airway response to anaphylactic shock in rats. *Exp Lung Res* 2017; **43**: 158–66
91. Radonjic-Hoesli S, Hofmeier KS, Micaletto S, Schmid-Grendelmeier P, Bircher A, Simon D. Urticaria and Angioedema: an update on classification and pathogenesis. *Clin Rev Allergy Immunol* 2018; **54**: 88–101
92. Cicardi M, Zuraw BL. Angioedema due to bradykinin dysregulation. *J Allergy Clin Immunol Pract* 2018; **6**: 1132–41
93. Banerji A, Oren E, Hesterberg P, Hsu Y, Camargo Jr CA, Wong JT. Ten-year study of causes of moderate to severe angioedema seen by an inpatient allergy/immunology consult service. *Allergy Asthma Proc* 2008; **29**: 88–92
94. Saeb A, Hagglund KH, Cigolle CT. Using fresh frozen plasma for acute airway angioedema to prevent intubation in the emergency department: a retrospective cohort study. *Emerg Med Int* 2016; **2016**: 6091510
95. Schulkes KJG, Van den Elzen MT, Hack EC, Otten HG, Bruijnzeel-Koomen C, Knulst AC. Clinical similarities among bradykinin-mediated and mast cell-mediated subtypes of non-hereditary angioedema: a retrospective study. *Clin Transl Allergy* 2015; **5**: 5

Handling editor: H.C. Hemmings Jr

BJA

British Journal of Anaesthesia, 123 (1): e50–e64 (2019)

doi: 10.1016/j.bja.2019.04.044
Advance Access Publication Date: 24 May 2019
Special Article

MANAGEMENT

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

Lene H. Garvey[1,2,*,†,‡], Pascale Dewachter[3,4,†,‡], David L. Hepner[5,†,‡], Paul Michel Mertes[6,†,‡], Susanna Voltolini[7,†,‡], Russell Clarke[8,9,‡], Peter Cooke[10,‡], Tomaz Garcez[11,‡], Anne Berit Guttormsen[12,‡], Didier G. Ebo[13,‡], Philip M. Hopkins[14,‡], David A. Khan[15,‡], Peter Kopac[16,‡], Mogens Krøigaard[1,‡], Jose Julio Laguna[17,‡], Stuart Marshall[18,19,‡], Peter Platt[8,9,‡], Michael Rose[20,‡], Vito Sabato[13,‡], Paul Sadleir[8,9,21,‡], Louise Savic[22,‡], Sinisa Savic[23,‡], Kathrin Scherer[24,‡], Tomonori Takazawa[25,‡], Gerald W. Volcheck[26,‡] and Helen Kolawole[18,19,†,‡]

[1]Danish Anaesthesia Allergy Centre, Allergy Clinic, Department of Dermatology and Allergy, Copenhagen University Hospital, Gentofte, Denmark, [2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, [3]Service d'Anesthésie-Réanimation, Groupe Hospitalier de Paris-Seine-Saint-Denis, Assistance Publique-Hôpitaux de Paris, Paris, France, [4]Université Paris 13, Sorbonne-Paris-Cité, Paris, France, [5]Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, [6]Department of Anesthesia and Intensive Care, Hôpitaux Universitaires de Strasbourg, Nouvel Hôpital Civil, Strasbourg, France, [7]Allergy Unit, Policlinic Hospital San Martino, Genoa, Italy, [8]Department of Anaesthesia, Sir Charles Gairdner Hospital, Western Australia, Australia, [9]Anaesthetic Allergy Referral Centre of Western Australia, Australia, [10]Department of Anaesthesia and Perioperative Medicine, Auckland City Hospital, Auckland, New Zealand, [11]Department of Immunology, Manchester University NHS Foundation Trust, Manchester, UK, [12]Department of Anaesthesia and Intensive Care, Haukeland University Hospital and Department of Clinical Medicine, University of Bergen, Bergen, Norway, [13]Department of Immunology, Allergology and Rheumatology, University of Antwerp, Antwerp University Hospital, Belgium, [14]Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK, [15]Department of Internal Medicine, Division of Allergy & Immunology, University of Texas Southwestern Medical Center, Dallas, TX, USA, [16]University Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia, [17]Allergy Unit, Allergo-Anaesthesia Unit, Hospital Central de la Cruz Roja, Faculty of Medicine, Alfonso X El Sabio University, ARADyAL, Madrid, Spain, [18]Department of Anaesthesia and Perioperative Medicine, Monash University, Melbourne, Australia, [19]Department of Anaesthesia, Peninsula Health, Melbourne, Australia, [20]Department of Anaesthesia, Royal North Shore Hospital, University of Sydney, Sydney NSW, Australia, [21]Department of Pharmacology, University of Western Australia, Australia, [22]Anaesthetic Department, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [23]Department of Clinical Immunology and Allergy, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [24]Allergy Unit, Department of Dermatology, University Hospital Basel, Basel University, Basel, Switzerland, [25]Intensive Care Unit, Gunma University Hospital, Maebashi, Gunma, Japan and [26]Division of Allergic Diseases, Mayo Clinic College of Medicine, Rochester, MN, USA

*Corresponding author. E-mail: lene.heise.garvey@regionh.dk

[†]These authors contributed equally.
[‡]The authors are members of the ISPAR (International Suspected Perioperative Allergic Reaction) Group.

Editorial decision: 14 April 2019; **Accepted:** 14 April 2019

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 US[42] 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

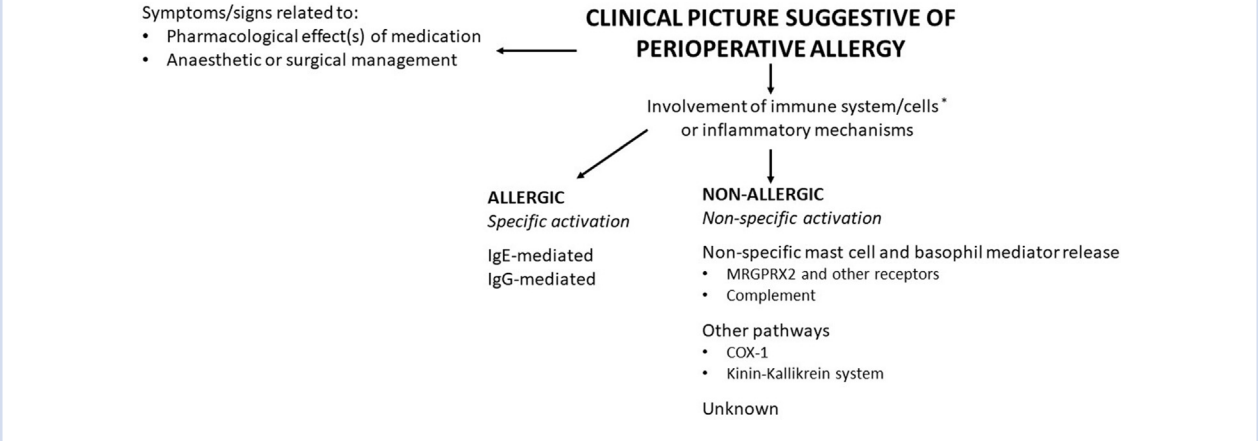


Fig. 1. Possible mechanisms for clinical presentation suggestive of immediate-type perioperative allergy.[8] *An underlying clonal mast cell disorder can be a risk factor for severe perioperative reactions and may present with or without a specific triggering allergen. COX-1, cyclooxygenase-1; Ig, immunoglobulin;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

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 antidepressants[58] 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 group[11]

Table 1 Grading of suspected perioperative allergic reactions according to the modified[1,2,48] Ring and Messmer[49] 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.

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 approach[64] 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 inital 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 Hg[40] and we *recommend* initiation of cardiac compression when the systolic arterial BP is <50 mm Hg. End-tidal CO_2 has been used as a measure of cardiac output during cardiac arrest.[67–69] Low end-tidal CO_2 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 CO_2 <3 kPa (20 mm Hg) provided other causes of a low end-tidal CO_2 (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 H_1-, H_2-, 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 parturients[93] 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 μg kg^{-1}	Bolus: 10 μg kg^{-1}	ND	• Titrate to response • If large doses are needed: use i.v. infusion (0.05–0.1 μg kg^{-1}min^{-1})
UK[5] (2009)	No	ND	Bolus: 1 μg 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 μg kg^{-1}
France[1] (2011)	No	Bolus 1 μg kg^{-1}	• Bolus: 1 μg kg^{-1} (up to 5–10 μg kg^{-1}) • Infusion: ND	• Bolus: 10 μg kg^{-1} (repeat 1–2 min) • Infusion starting at: 0.1 μg kg^{-1}min^{-1}	• Titrate to response
Australia[10] (2017)	No	Bolus 2 μg kg^{-1}	• Bolus: 4–10 μg kg^{-1} (repeat 1–2 min) • Infusion - starting at 0.1 μg kg^{-1}min^{-1} - up to 2 μg kg^{-1}min^{-1}	• Bolus: 10 μg kg^{-1} (repeat 1–4 min) • Infusion: starting at: 0.1 μg kg^{-1}min^{-1} up to 2 μg kg^{-1}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×baseline+2 μg 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 H_1-, H_2- 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

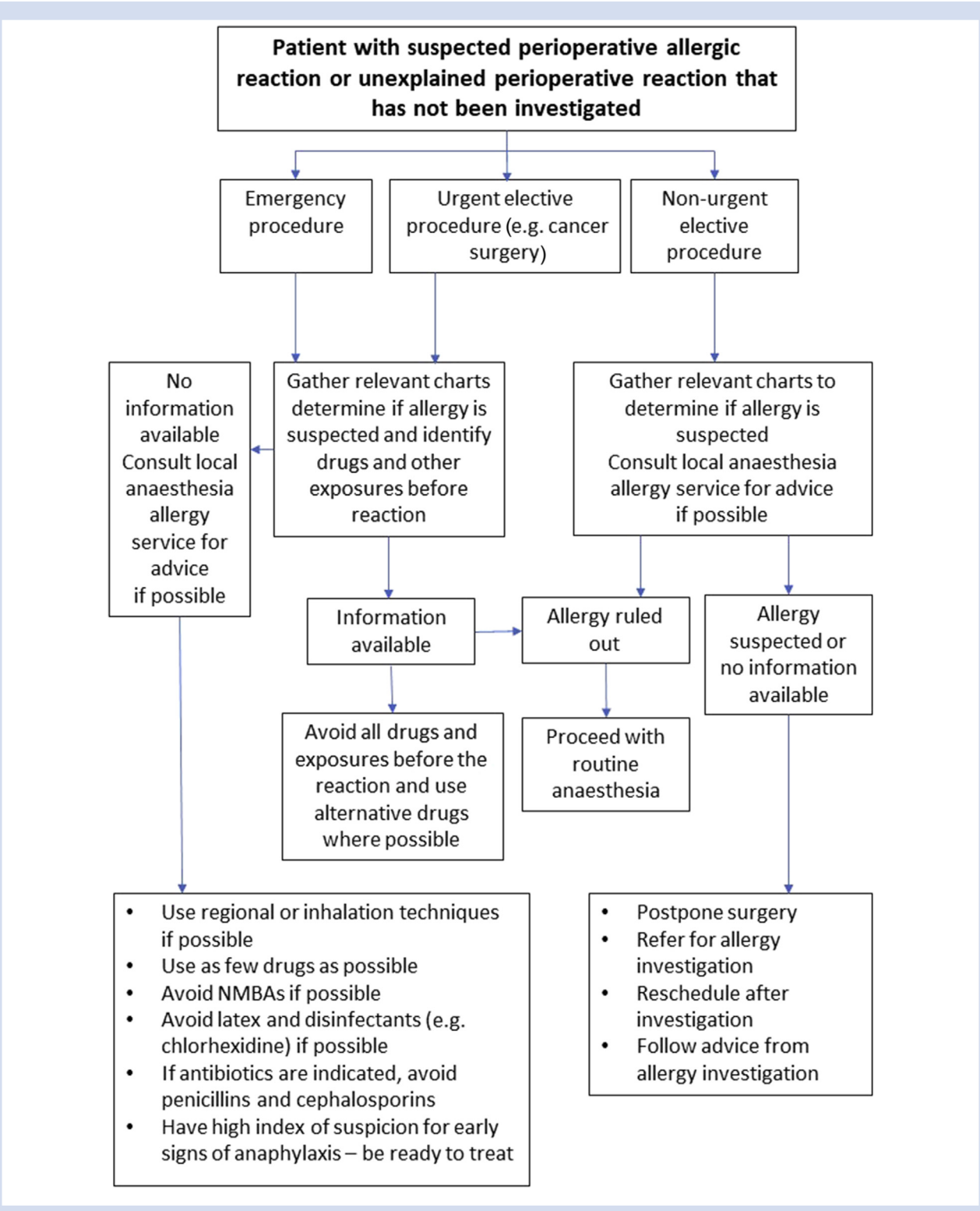


Fig. 2. Management of the patient with a suspected perioperative allergic reaction or unexplained perioperative reaction that has not been investigated. NMBA, neuromuscular blocking agent.

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.

PMH is an Editorial Board Member of BJA.

PMM: Scientific advisor for the ALPHO study (NCT02250729), funded by a consortium of pharmaceutical companies: Zambon, Urgo, Pierre Fabre, Boots, Hepatoum, Biocodex, Sanofi, LBR, GSK, APL, Bells Healthcare, Pinewood, T & R, Ernest Jackson.

PK has received lectures fees from Novartis Pharma Services Inc, Shire Pharmaceuticals Group Plc.

SM is in receipt of an Australian National Health and Medical Research Council (NHMRC) ECR Fellowship for the investigation of cognitive aids in emergencies.

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.

References

1. Mertes PM, Malinovsky JM, Jouffroy L, et al., Working Group of the SFAR and SFA, ENDA, EAACI Interest Group on Drug Allergy. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2011; **21**: 442–53
2. Kroigaard M, Garvey LH, Gillberg L, et al. Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Anaesthesiol Scand* 2007; **51**: 655–70
3. Guttormsen AB, Harboe T, Florvaag E. [Allergic reactions during anesthesia - a national network for registration, diagnosis and follow-up]. *Tidsskr Nor Laegeforen* 2000; **120**: 127
4. Garvey LH, Roed-Petersen J, Menne T, Husum B. Danish anaesthesia allergy centre - preliminary results. *Acta Anaesthesiol Scand* 2001; **45**: 1204–9
5. Harper NJ, Dixon T, Dugue P, et al. Suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia* 2009; **64**: 199–211
6. *Royal college of anaesthetists 6th national Audit project: perioperative anaphylaxis. NAP6 report anaesthesia, surgery and lifethreatening allergic reactions*. Harper NJ: Cook TM; 2018. ISBN 978-1-900936-18-7
7. Laguna JJ, Archilla J, Dona I, et al. Practical guidelines for perioperative hypersensitivity reactions. *J Investig Allergol Clin Immunol* 2018; **28**: 216–32
8. Garvey LH, Ebo D, Mertes PM, et al. An EAACI position paper on the investigation of perioperative immediate hypersensitivity reactions. *Allergy* 2019. https://doi.org/10.1111/all.13820. Adv Access published on April 9
9. Scolaro RJ, Crilly HM, Maycock EJ, et al. Australian and New Zealand Anaesthetic Allergy Group perioperative anaphylaxis investigation guidelines. *Anaesth Intensive Care* 2017; **45**: 543–55
10. Kolawole H, Marshall SD, Crilly H, Kerridge R, Roessler P. Australian and New Zealand anaesthetic allergy group/Australian and New Zealand college of anaesthetists perioperative anaphylaxis management guidelines. *Anaesth Intensive Care* 2017; **45**: 151–8

11. Hopkins PM, Garvey LH. Special issue on suspected perioperative allergic reactions. *Br J Anaesth* 2019; **11**. https://doi.org/10.1016/j.bja.2019.04.002
12. Harboe T, Guttormsen AB, Irgens A, Dybendal T, Florvaag E. Anaphylaxis during anesthesia in Norway: a 6-year single-center follow-up study. *Anesthesiology* 2005; **102**: 897–903
13. Sadleir PH, Clarke RC, Bunning DL, Platt PR. Anaphylaxis to neuromuscular blocking drugs: incidence and cross-reactivity in Western Australia from 2002 to 2011. *Br J Anaesth* 2013; **110**: 981–7
14. Fisher MM, Jones K, Rose M. Follow-up after anaesthetic anaphylaxis. *Acta Anaesthesiol Scand* 2011; **55**: 99–103
15. Reddy JI, Cooke PJ, van Schalkwyk JM, Hannam JA, Fitzharris P, Mitchell SJ. Anaphylaxis is more common with rocuronium and succinylcholine than with atracurium. *Anesthesiology* 2015; **122**: 39–45
16. Takazawa T, Mitsuhata H, Mertes PM. Sugammadex and rocuronium-induced anaphylaxis. *J Anesth* 2016; **30**: 290–7
17. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
18. Lobera T, Audicana MT, Pozo MD, et al. Study of hypersensitivity reactions and anaphylaxis during anesthesia in Spain. *J Investig Allergol Clin Immunol* 2008; **18**: 350–6
19. Ebo DG, Hagendorens MM, Bridts CH, De Clerck LS, Stevens WJ. Allergic reactions occurring during anaesthesia: diagnostic approach. *Acta Clin Belg* 2004; **59**: 34–43
20. Mota I, Gaspar A, Benito-Garcia F, Correia M, Chambel M, Morais-Almeida M. Drug-induced anaphylaxis: seven-year single-center survey. *Eur Ann Allergy Clin Immunol* 2018; **50**: 211–6
21. Lapisatepun W, Charuluxananan S, Kusumaphanyo C, Ittichaikulthol W, Suksompong S, Ratanachai P. The Thai anesthesia incident monitoring study of perioperative allergic reactions: an analysis of 1996 incidents reports. *J Med Assoc Thai* 2008; **91**: 1524–30
22. Galletly DC, Treuren BC. Anaphylactoid reactions during anaesthesia. Seven years' experience of intradermal testing. *Anaesthesia* 1985; **40**: 329–33
23. Savic LC, Kaura V, Yusaf M, et al. Incidence of suspected perioperative anaphylaxis: A multicenter snapshot study. *J Allergy Clin Immunol Pract* 2015; **3**. 454–5.e1
24. Gibbs NM, Sadleir PH, Clarke RC, Platt PR. Survival from perioperative anaphylaxis in Western Australia 2000-2009. *Br J Anaesth* 2013; **111**: 589–93
25. Charuluxananan S, Punjasawadwong Y, Suraseranivongse S, et al. The Thai Anesthesia Incidents Study (Thai Study) of anesthetic outcomes: II. Anesthetic profiles and adverse events. *J Med Assoc Thai* 2005; **88**: S14–29
26. Escolano F, Valero A, Huguet J, et al. [Prospective epidemiologic study of perioperative anaphylactoid reactions occurring in Catalonia (1996-7)]. *Rev Esp Anestesiol Reanim* 2002; **49**: 286–93
27. Mitsuhata H, Hasegawa J, Matsumoto S, Ogawa R. [The epidemiology and clinical features of anaphylactic and anaphylactoid reactions in the perioperative period in Japan: a survey with a questionnaire of 529 hospitals approved by Japan Society of Anesthesiology]. *Masui* 1992; **41**: 1825–31
28. Laxenaire MC, Moneret-Vautrin DA, Boileau S, Moeller R. Adverse reactions to intravenous agents in anaesthesia in France. *Klin Wochenschr* 1982; **60**: 1006–9
29. Watkins J. Adverse anaesthetic reactions. An update from a proposed national reporting and advisory service. *Anaesthesia* 1985; **40**: 797–800
30. Tacquard C, Collange O, Gomis P, et al. Anaesthetic hypersensitivity reactions in France between 2011 and 2012: the 10th GERAP epidemiologic survey. *Acta Anaesthesiol Scand* 2017; **61**: 290–9
31. Dong SW, Mertes PM, Petitpain N, Hasdenteufel F, Malinovsky JM. Hypersensitivity reactions during anesthesia. Results from the ninth French survey (2005-2007). *Minerva Anestesiol* 2012; **78**: 868–78
32. Volcheck GW, Mertes PM. Local and general anesthetics immediate hypersensitivity reactions. *Immunol Allergy Clin North Am* 2014; **34**: 525–46
33. Mertes PM, Volcheck GW, Garvey LH, et al. Epidemiology of perioperative anaphylaxis. *Presse Med* 2016; **45**: 758–67
34. Fisher MM, More DG. The epidemiology and clinical features of anaphylactic reactions in anaesthesia. *Anaesth Intensive Care* 1981; **9**: 226–34
35. Laxenaire MC. [Epidemiology of anesthetic anaphylactoid reactions. Fourth multicenter survey (July 1994-December 1996)]. *Ann Fr Anesth Reanim* 1999; **18**: 796–809
36. Mertes PM, Alla F, Trechot P, Auroy Y, Jougla E. Anaphylaxis during anesthesia in France: an 8-year national survey. *J Allergy Clin Immunol* 2011; **128**: 366–73
37. Mertes PM, Malinovsky JM, Mouton-Faivre C, et al. Anaphylaxis to dyes during the perioperative period: reports of 14 clinical cases. *J Allergy Clin Immunol* 2008; **122**: 348–52
38. Garvey LH, Kroigaard M, Poulsen LK, et al. IgE-mediated allergy to chlorhexidine. *J Allergy Clin Immunol* 2007; **120**: 409–15
39. Reitter M, Petitpain N, Latarche C, et al. Fatal anaphylaxis with neuromuscular blocking agents: a risk factor and management analysis. *Allergy* 2014; **69**: 954–9
40. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: management and outcomes in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 172–88
41. Garvey LH, Belhage B, Kroigaard M, Husum B, Malling HJ, Mosbech H. Treatment with epinephrine (adrenaline) in suspected anaphylaxis during anesthesia in Denmark. *Anesthesiology* 2011; **115**: 111–6
42. Hepner DL, Castells MC. Anaphylaxis during the perioperative period. *Anesth Analg* 2003; **97**: 1381–95
43. Garvey LH. Perioperative hypersensitivity reactions: diagnosis, treatment and evaluation. *Curr Treat Options Allergy* 2016; **3**: 113–28
44. Baldo BA, Pham NH. Histamine-releasing and allergenic properties of opioid analgesic drugs: resolving the two. *Anaesth Intensive Care* 2012; **40**: 216–35
45. McNeil BD, Pundir P, Meeker S, et al. Identification of a mast-cell-specific receptor crucial for pseudoallergic drug reactions. *Nature* 2015; **519**: 237–41
46. Takazawa T, Sabato V, Ebo DG. In vitro diagnostic tests for perioperative hypersensitivity: potential, limitations and perspectives. *Br J Anesth* 2019; **11**. https://doi.org/10.1016/j.bja.2019.01.002. Adv Access Published February
47. Bonadonna P, Pagani M, Aberer W, et al. Drug hypersensitivity in clonal mast cell disorders: ENDA/EAACI position paper. *Allergy* 2015; **70**: 755–63

48. Dewachter P, Mouton-Faivre C, Emala CW. Anaphylaxis and anesthesia: controversies and new insights. *Anesthesiology* 2009; **111**: 1141–50
49. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977; **1**: 466–9
50. Dewachter P, Mouton-Faivre C, Hepner DL. Perioperative anaphylaxis: what should be known? *Curr Allergy Asthma Rep* 2015; **15**: 21
51. Barriot P, Riou B. Hemorrhagic shock with paradoxical bradycardia. *Intensive Care Med* 1987; **13**: 203–7
52. Clarke R, Sadleir P, Van Niekerk AW, Platt P. Quantification of volume loss and haemodynamic changes of Gelofusine-induced anaphylaxis during cardiopulmonary bypass. *Anaesth Intensive Care* 2011; **39**: 492–5
53. Faye N, Fournier L, Balvay D, et al. Macromolecular capillary leakage is involved in the onset of anaphylactic hypotension. *Anesthesiology* 2012; **117**: 1072–9
54. Fisher MM, Ramakrishnan N, Doig G, Rose M, Baldo B. The investigation of bronchospasm during induction of anaesthesia. *Acta Anaesthesiol Scand* 2009; **53**: 1006–11
55. Dewachter P, Mouton-Faivre C, Emala CW, Beloucif S. Case scenario: bronchospasm during anesthetic induction. *Anesthesiology* 2011; **114**: 1200–10
56. Garvey LH. Practical aspects of perioperative anaphylaxis. *Trends Anaesth Crit Care* 2013; **3**: 320–6
57. Malinovsky JM, Decagny S, Wessel F, Guilloux L, Mertes PM. Systematic follow-up increases incidence of anaphylaxis during adverse reactions in anesthetized patients. *Acta Anaesthesiol Scand* 2008; **52**: 175–81
58. Takakura K, Nagaya M, Mori M, Koga H, Yoshitake S, Noguchi T. Refractory hypotension during combined general and epidural anaesthesia in a patient on tricyclic antidepressants. *Anaesth Intensive Care* 2006; **34**: 111–4
59. Ogbureke KU, Cruz C, Johnson JV, Helfrick JF. Perioperative angioedema in a patient on long-term angiotensin-converting enzyme (ACE)-inhibitor therapy. *J Oral Maxillofac Surg* 1996; **54**: 917–20
60. Ariño P, Aguado L, Cortada V, Baltasar M, Puig MM. Cold urticaria associated with intraoperative hypotension and facial edema. *Anesthesiology* 1999; **90**: 907–9
61. Dewachter P, Castells MC, Hepner DL, Mouton-Faivre C. Perioperative management of patients with mastocytosis. *Anesthesiology* 2014; **120**: 753–9
62. Dewachter P, Mouton-Faivre C. Concurrent immunoglobulin E-mediated neuromuscular blocking agent allergy in systemic mastocytosis. *Ann Allergy Asthma Immunol* 2018; **120**: 663–4
63. Campbell RL, Bellolio MF, Knutson BD, et al. Epinephrine in anaphylaxis: higher risk of cardiovascular complications and overdose after administration of intravenous bolus epinephrine compared with intramuscular epinephrine. *J Allergy Clin Immunol Pract* 2015; **3**: 76–80
64. Fitch K, Bernstein SJ, Aguilar MD, et al. *The RAND/UCLA appropriateness method user's manual*. Santa Monica: RAND Corporation; 2001
65. Gouel-Cheron A, Harpan A, Mertes PM, Longrois D. Management of anaphylactic shock in the operating room. *Presse Med* 2016; **45**: 774–83
66. Sadleir P, Clarke RC, Lim B, Platt PR. Epinephrine (adrenaline) preventing recovery from intraoperative anaphylactic shock complicated by systolic anterior motion of the mitral valve with left ventricular outflow tract obstruction on transoesophageal echocardiography. *Anaesth Intensive Care* 2018; **46**: 566–71
67. Sandroni C, De Santis P, D'Arrigo S. Capnography during cardiac arrest. *Resuscitation* 2018; **132**: 73–7
68. Paiva EF, Paxton JH, O'Neil BJ. Data supporting the use of end-tidal carbon dioxide (ETCO2) measurement to guide management of cardiac arrest: a systematic review. *Data Brief* 2018; **18**: 1497–508
69. Paiva EF, Paxton JH, O'Neil BJ. The use of end-tidal carbon dioxide (ETCO2) measurement to guide management of cardiac arrest: a systematic review. *Resuscitation* 2018; **123**: 1–7
70. Gouel-Cheron A, de Chaisemartin L, Jonsson F, et al. Low end-tidal CO2 as a real-time severity marker of intra-anaesthetic acute hypersensitivity reactions. *Br J Anaesth* 2017; **119**: 908–17
71. Chengot T, Goncalves J, Marzo K. Back from irreversibility: use of percutaneous cardiopulmonary bypass for treatment of shock from refractory anaphylaxis during coronary intervention. *J Invasive Cardiol* 2009; **21**: e97–100
72. Ford SA, Kam PC, Baldo BA, Fisher MM. Anaphylactic or anaphylactoid reactions in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 2001; **15**: 684–8
73. Egner W, Cook TM, Garcez T, et al. Specialist perioperative allergy clinic services in the UK 2018: results from the royal college of anaesthetists sixth national Audit project (NAP6) investigation of perioperative anaphylaxis. *Clin Exp Allergy* 2018; **48**: 846–61
74. Hepner DL, Castells M, Mouton-Faivre C, Dewachter P. Anaphylaxis in the clinical setting of obstetric anesthesia: a literature review. *Anesth Analg* 2013; **117**: 1357–67
75. McCall SJ, Bunch KJ, Brocklehurst P, et al. The incidence, characteristics, management and outcomes of anaphylaxis in pregnancy: a population-based descriptive study. *BJOG* 2018; **125**: 965–71
76. Mulla ZD, Ebrahim MS, Gonzalez JL. Anaphylaxis in the obstetric patient: analysis of a statewide hospital discharge database. *Ann Allergy Asthma Immunol* 2010; **104**: 55–9
77. Adriaensens I, Vercauteren M, Soetens F, Janssen L, Leysen J, Ebo D. Allergic reactions during labour analgesia and caesarean section anaesthesia. *Int J Obstet Anesth* 2013; **22**: 231–42
78. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006-2008. The eighth report of the confidential enquiries into maternal deaths in the United Kingdom. *BJOG* 2011; **118**: 1–203
79. Jeejeebhoy FM, Zelop CM, Lipman S, et al. Cardiac arrest in pregnancy: a scientific statement from the American Heart Association. *Circulation* 2015; **132**: 1747–73
80. Truhlar A, Deakin CD, Soar J, et al. European resuscitation council guidelines for resuscitation 2015: section 4. Cardiac arrest in special circumstances. *Resuscitation* 2015; **95**: 148–201
81. Murat I. Anaphylactic reactions during paediatric anaesthesia: results of the survey of the French society of paediatric anaesthetists (ADARPEF). 1991–1992. *Paediatr Anaesth* 1993; **3**: 339–43
82. Habre W, Disma N, Virag K, et al. Incidence of severe critical events in paediatric anaesthesia (APRICOT): a prospective multicentre observational study in 261 hospitals in Europe. *Lancet Respir Med* 2017; **5**: 412–25

83. Tadokoro F, Morita K, Michihata N, Fushimi K, Yasunaga H. Association between sugammadex and anaphylaxis in pediatric patients: a nested case-control study using a national inpatient database. *Paediatr Anaesth* 2018; **28**: 654–9
84. Karila C, Brunet-Langot D, Labbez F, et al. Anaphylaxis during anesthesia: results of a 12-year survey at a French pediatric center. *Allergy* 2005; **60**: 828–34
85. Baird MB, Futter M. Anaphylaxis to mivacurium. *Anaesth Intensive Care* 1996; **24**: 486–8
86. Prosser DP, Gompels M. Anaphylactic shock due to cefuroxime in a patient taking penicillin prophylaxis. *Paediatr Anaesth* 2002; **12**: 73–5
87. Pollock EM, MacLeod AD, McNicol LR. Anaphylactoid reaction complicating neonatal anaesthesia. *Anaesthesia* 1986; **41**: 178–80
88. Briassoulis G, Hatzis T, Mammi P, Alikatora A. Persistent anaphylactic reaction after induction with thiopentone and cisatracurium. *Paediatr Anaesth* 2000; **10**: 429–34
89. Borgeat A, Linder S, Schwander D. [An unusual anaphylactic reaction following succinylcholine chloride in a 21-month-old child]. *Can J Anaesth* 1990; **37**: 675–7
90. Legros CB, Orliaguet GA, Mayer MN, Labbez F, Carli PA. Severe anaphylactic reaction to cisatracurium in a child. *Anesth Analg* 2001; **92**: 648–9
91. Renauld V, Goudet V, Mouton-Faivre C, Debaene B, Dewachter P. Case Report: perioperative immediate hypersensitivity involves not only allergy but also mastocytosis. *Can J Anaesth* 2011; **58**: 456–9
92. Ishii K, Miyoshi H, Akiyama D, et al. Anesthetic management of patients with systemic mastocytosis. *J Clin Anesth* 2018; **50**: 61
93. Ciach K, Niedoszytko M, Abacjew-Chmylko A, et al. Pregnancy and delivery in patients with mastocytosis treated at the polish center of the european competence network on mastocytosis (ECNM). *PLoS One* 2016; **11**, e0146924
94. Matito A, Morgado JM, Sanchez-Lopez P, et al. Management of anesthesia in adult and pediatric mastocytosis: a study of the Spanish network on mastocytosis (REMA) based on 726 anesthetic procedures. *Int Arch Allergy Immunol* 2015; **167**: 47–56
95. Sadleir PHM, Clarke RC, Bozic B, Platt PR. Consequences of proceeding with surgery after resuscitation from intra-operative anaphylaxis. *Anaesthesia* 2018; **73**: 32–9
96. Garvey LH. Old, new and hidden causes of perioperative hypersensitivity. *Curr Pharm Des* 2016; **22**: 6814–24
97. Christiansen IS, Krøigaard M, Mosbech H, Garvey LH. Clinical and diagnostic features of perioperative hypersensitivity to cefuroxime. *Clin Exp Allergy* 2015; **45**: 807–14
98. Krøigaard M, Garvey LH, Menné T, Husum B. Allergic reactions in anaesthesia: are suspected causes confirmed on subsequent testing? *Br J Anaesth* 2005; **95**: 468–71
99. Low AE, McEwan JC, Karanam S, North J, Kong K-L. Anaesthesia-associated hypersensitivity reactions: seven years' data from a British bi-specialty clinic. *Anaesthesia* 2016; **71**: 76–84
100. Ebo DG, Faber M, Elst J, et al. In vitro diagnosis of immediate drug hypersensitivity during anesthesia: a review of the literature. *J Allergy Clin Immunol Pract* 2018; **6**: 1176–84
101. Laroche D, Gomis P, Gallimidi E, Malinovsky JM, Mertes PM. Diagnostic value of histamine and tryptase concentrations in severe anaphylaxis with shock or cardiac arrest during anesthesia. *Anesthesiology* 2014; **121**: 272–9
102. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002; **57**: 45–51
103. Ewan PW, Dugué P, Mirakian R, Dixon TA, Harper JN, Nasser SM, BSACI. BSACI guidelines for the investigation of suspected anaphylaxis during general anaesthesia. *Clin Exp Allergy* 2010; **40**: 15–31
104. Brockow K, Garvey LH. Aberer W; the ENDA/EAACI Drug Allergy Interest Group, *et al*. Skin test concentrations for systemically administered drugs - an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013; **68**: 702–12
105. Leysen J, Uyttebroek A, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Predictive value of allergy tests for neuromuscular blocking agents: tackling an unmet need. *Clin Exp Allergy* 2014; **44**: 1069–75
106. Chiriac AM, Tacquard C, Fadhel NB, et al. Safety of subsequent general anaesthesia in patients allergic to neuromuscular blocking agents: value of allergy skin testing. *Br J Anaesth* 2018; **120**: 1437–40
107. Mertes PM, Moneret-Vautrin DA, Leynadier F, Laxenaire MC. Skin reactions to intradermal neuromuscular blocking agent injections: a randomized multicenter trial in healthy volunteers. *Anesthesiology* 2007; **107**: 245–52
108. Li PH, Ue KL, Wagner A, Rutkowski R, Rutkowski K. Opioid hypersensitivity: predictors of allergy and role of drug provocation testing. *J Allergy Clin Immunol Pract* 2017; **5**: 1601–6
109. Brockow K. Dilemmas of allergy diagnosis in perioperative anaphylaxis. *Allergy* 2014; **69**: 1265–6
110. Garvey LH, Ebo DG, Krøigaard M, et al. The use of drug provocation testing in the investigation of suspected immediate perioperative allergic reactions. *Br J Anaesth Adv Access* 2019. https://doi.org/10.1016/j.bja.2019.03.018. published on April 23
111. Opstrup MS, Malling HJ, Krøigaard M. Standardized testing with chlorhexidine in perioperative allergy - a large single centre evaluation. *Allergy* 2014; **69**: 1390–6
112. Leysen J, Bridts CH, De Clerck LS, et al. Allergy to rocuronium: from clinical suspicion to correct diagnosis. *Allergy* 2011; **66**: 1014–9
113. Dewachter P, Mouton-Faivre C, Castells MC, Hepner DL. Anesthesia in the patient with multiple drug allergies: are all the allergies the same? *Curr Opin Anaesthesiol* 2011; **24**: 320–5
114. Choo KJ, Simons E, Sheikh A. Glucocorticoids for the treatment of anaphylaxis: cochrane systematic review. *Allergy* 2010; **65**: 1205–11
115. Opstrup MS, Poulsen LK, Malling HJ, Jensen BM, Garvey LH. Dynamics of specific IgE in chlorhexidine allergic patients with and without accidental re-exposure. *Clin Exp Allergy* 2016; **46**: 1090–8

Handling editor: H.C. Hemmings Jr

BJA

British Journal of Anaesthesia, 123 (1): e65–e81 (2019)

doi: 10.1016/j.bja.2019.01.020
Advance Access Publication Date: 13 March 2019
Special Article

Anaesthetic management of patients with pre-existing allergic conditions: a narrative review

Pascale Dewachter[1,2,*], Peter Kopac[3], Jose Julio Laguna[4,5], Paul Michel Mertes[6], Vito Sabato[7], Gerald W. Volcheck[8] and Peter J. Cooke[9]

[1]Department of Anesthesiology and Intensive Care Medicine, Groupe Hospitalier Paris-Seine-Saint-Denis, Assistance Publique-Hôpitaux de Paris, Paris, France, [2]University Paris 13, Sorbonne-Paris-Cité, Paris, France, [3]Division of Allergology, University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia, [4]Department of Allergy and Allergo-Anaesthesia, Hospital Central de la Cruz Roja, Madrid, Spain, [5]Faculty of Medicine, Alfonso X El Sabio University, ARADyAL, Madrid, Spain, [6]Department of Anaesthesia and Intensive Care, Hôpitaux Universitaires de Strasbourg, Nouvel Hôpital Civil, EA 3072, FMTS de Strasbourg, Strasbourg, France, [7]Department of Immunology, Allergology and Rheumatology, University Antwerp, Antwerp University Hospital, Antwerp, Belgium, [8]Division of Allergic Diseases, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN, USA and [9]Department of Anaesthesia and Peri-operative Medicine, Auckland City Hospital, Auckland, New Zealand

*Corresponding author. E-mail: pascale.dewachter@yahoo.fr

Summary

This narrative review seeks to distinguish the clinical patterns of pre-existing allergic conditions from other confounding non-allergic clinical entities, and to identify the potential related risks and facilitate their perioperative management. Follow-up investigation should be performed after a perioperative immediate hypersensitivity to establish a diagnosis and provide advice for subsequent anaesthetics, the main risk factor for perioperative immunoglobulin E (IgE)-mediated anaphylaxis being a previous uninvestigated perioperative immediate hypersensitivity reaction. The concept of cross-reactivity between drugs used in the perioperative setting and food is often quoted, but usually not supported by evidence. There is no reason to avoid propofol in egg, soy, or peanut allergy. The allergenic determinants have been characterised for fish, shellfish, and povidone iodine, but remain unknown for iodinated contrast agents. Iodinated drugs may be used in seafood allergy. Evidence supporting the risk for protamine allergy in fish allergy and in neutral protamine Hagedorn insulin use is lacking. Conversely, cross-reactivity to gelatin-based colloid may occur in α-gal syndrome. Atopy and allergic asthma along with other non-allergic conditions, such as NSAID-exacerbated respiratory disease, chronic urticaria, mastocytosis, and hereditary or acquired angioedema, are not risk factors for IgE-mediated drug allergy, but there is a perioperative risk associated with the potential for exacerbation of the various conditions.

Keywords: adverse effects; anaesthesia; anaphylaxis; drug hypersensitivity; food hypersensitivity; immediate hypersensitivity; perioperative period

Editorial decision date: 22 January 2019; **Accepted:** 22 January 2019

Editor's key points

- The main perioperative risk factor for anaphylaxis is a previous uninvestigated perioperative immediate hypersensitivity reaction.
- The main concerns are potential uncontrolled asthma in atopy, severe uncontrolled asthma and strict avoidance of all cyclooxygenase 1 (COX-1) inhibitors in NSAID-exacerbated respiratory disease, cross-reactivity to gelatin-based colloid in α-gal syndrome, non-specific mast-cell activation in mastocytosis, and upper airway and laryngeal angioedema in hereditary or acquired angioedema.
- There is no evidence to avoid the use of propofol in egg, soy, or peanut allergy; iodinated drugs in seafood allergy; or protamine in fish allergy and NPH insulin use.
- There is no reason to modify usual perioperative protocols in α-gal syndrome regarding the use of heparin, or in chronic urticaria, except the avoidance of COX-1 inhibitors.

Pre-existing allergic diseases and other confounding non-allergic but related clinical entities need to be carefully considered during the preoperative evaluation, as they may result in perioperative life-threatening conditions. The acquired knowledge during the past decades has helped us to better characterise the different conditions and identify their perioperative risks, which are displayed in this review.

The sole identified perioperative risk factor for anaphylaxis is a previous uninvestigated perioperative immediate hypersensitivity reaction. The concept of cross-reactivity between drugs used in the perioperative setting and food is often quoted, but usually not supported by evidence. Allergic asthma needs to be distinguished from aspirin-induced asthma, which may be characterised by potential severe uncontrolled asthma. Some other non-allergic conditions, such as mastocytosis or chronic urticaria, are not a risk factor for immunoglobulin E (IgE)-mediated drug allergy, but the potential perioperative risk is linked to the disease itself. Finally, the perioperative care management of hereditary and acquired angioedema is included because of the risk of laryngeal angioedema.

To provide guidance for practitioners, this narrative review seeks to (i) characterise and distinguish the clinical patterns of pre-existing allergic conditions from other confounding non-allergic clinical entities, (ii) identify the potential perioperative risks related to these conditions *per se* and facilitate their management, (iii) establish evidence or refute false beliefs of cross-reactivity for agents used in the perioperative setting, and (iv) discuss a rational approach to the identification of the culprit agent that allows for a safe subsequent management of patients experiencing perioperative allergy.

Methods

Search strategy

Both electronic and hand-searching techniques were used to identify all types of articles in English language only from PubMed database using the following Medical Subject Heading terms: Anaesthesia; Anaphylaxis; Acquired angioedema; Angioedemas, Hereditary; Asthma, Aspirin-Induced; Asthma; Rhinitis, Allergic; Cold Hypersensitivity; Contrast Media; Chronic urticaria; Egg Hypersensitivity; Fish Proteins; galactose alpha 1–3 galactose; Hypersensitivity, Immediate; Hypersensitivity, Delayed; Latex Hypersensitivity; Mastocytosis; Meat; Peanut Hypersensitivity; Perioperative Period; Povidone-Iodine; Propofol; Protamines; Shellfish Hypersensitivity; Soybeans; succinylated gelatin; surgery; and combinations of those. Conference abstracts were not considered. Searches were performed from January 1998 to August 2018. Key publications before 1998 reporting major findings or paradigm shifts that remain cornerstones of current understanding were also included.

Outcomes

Our searches failed to retrieve any randomised controlled trials or prospective studies on this subject. Guidelines, review articles, retrospective, cohort, or case studies were included. Bibliographies of retrieved articles were manually checked for additional references.

Data extraction

Two authors were assigned to each subsection. Relevant records, based on title and abstract, were provisionally selected. Identified citations were independently reviewed by the authors of the corresponding subsections. Full texts of the included titles and abstracts were then extensively reviewed by these authors to reach a final list.

Risk factors for perioperative IgE-mediated allergy

The risk factors of a perioperative allergic reaction include the propensity of certain drugs to elicit IgE-mediated allergy and patient factors. Perioperative IgE-mediated allergy mainly occurs after anaesthetic induction, and is most frequently linked to neuromuscular blocking agents (NMBAs) and β-lactam antibiotics. It may also arise during the maintenance phase of anaesthesia attributable to agents unrelated to anaesthetics (e.g. patent blue dye, succinylated gelatin, iodinated contrast agent, latex, sugammadex, and chlorhexidine).[1–3]

The main risk factor for perioperative IgE-mediated anaphylaxis is a previous uninvestigated perioperative immediate hypersensitivity reaction.[4–7] Uneventful previous exposure to a NMBA or an antibiotic does not exclude IgE-mediated allergy during a subsequent exposure, whilst IgE-mediated allergy to NMBAs or β-lactam drugs may occur without a prior exposure. One of the most important risk factors for drug allergy may be related to the chemical property and molecular weight of drugs,[8] whilst genetic modifiers and other host factors, and gene–environment interactions, may influence the development, clinical presentation, and severity of IgE-mediated allergy.[9] The onset of drug allergy may be modulated by cofactors that lower 'the allergen dose' necessary to elicit the clinical features. This has been clearly demonstrated in food allergy.[10] Furthermore, stress and infection might be cofactors involved in the perioperative setting. Finally, fatalities after perioperative anaphylaxis may be influenced by a higher ASA physical status, associated comorbidities (obesity and coronary artery disease), ongoing β-blockers, and angiotensin-converting-enzyme inhibitor (ACE-I) treatment.[11]

Pre-existing allergic conditions

Atopy, allergic asthma, and rhinitis

Atopy is a genetic predisposition for the development, mainly in childhood or adolescence, of an IgE-mediated response to common allergens and consequently rhinitis, allergic asthma, and food allergy.[12] Atopy is not a risk factor for IgE-mediated drug allergy. Asthma is an inflammatory chronic disease associated with airway hyperreactivity to various stimuli. Inhaled glucocorticoids are the most effective anti-inflammatory agents for persistent asthma, and an effective long-term treatment attenuating airway inflammation decreases the incidence of perioperative pulmonary complications.[13,14] The largest overall phenotype in children and adults is allergic asthma (see section 'Aspirin-induced asthma'). More than 80% of asthmatic individuals have rhinitis, and 10–40% of patients with rhinitis have asthma.[13] The main risk factor for perioperative bronchospasm is uncontrolled asthma.[15–17] In addition, coexisting obesity is associated with a poor asthma control in both children and adults. The preoperative assessment/treatment of asthma is thus crucial, and patients with persistent or severe rhinitis need to be evaluated for asthma.

A combined strategy including allergen avoidance whenever possible, inhaled and/or intranasal and/or i.v. corticosteroid along with inhaled β_2-agonist may be required to prevent the onset of perioperative bronchospasm. In case of emergency surgery, repeated aerosolised β_2-agonist/glucocorticoid along with i.v. corticosteroid may be required. Bronchodilators should be continued up to the time of surgery whenever possible.[18]

In summary, the main perioperative risk in atopy is related to potential underlying uncontrolled asthma.

Latex allergy

The risk factors for latex allergy include (i) atopy, (ii) previous history of immediate hypersensitivity after latex exposure, (iii) *spina bifida* patients, (iv) multiple surgeries especially in childhood, (v) occupational latex exposure, and (vi) allergy to exotic fruits (avocado, banana, kiwi, etc.). Clinical features suggestive of a previous latex-induced immediate hypersensitivity require subsequent investigation or latex avoidance if the delay is not compatible with the surgery. Latex avoidance is required in proven or highly suspected latex allergy. A list of latex-containing products and a supply of latex-free products should be available,[19,20] whilst a collaboration between physicians and pharmacists may be contributive to identify hidden latex-containing devices.[21] Finally, relevant staff (OR, recovery room, in-patient unit) must be alerted to the latex allergy status.

The goal of primary prevention is to reduce latex sensitisation. A latex-free environment prevents latex sensitisation/allergy, and the use of low-latex proteins and powder-free gloves has also reduced latex sensitisation.[22,23]

Food allergy and drugs

Food allergy and propofol

Warnings against the use of propofol in egg, soy, or peanut allergy are still a matter of concern.

Egg, soy, and peanut allergies

Egg, soy, and peanut allergies are amongst the most frequent IgE-mediated food allergies in childhood.[24,25] Food allergy patients, including those allergic to soy and egg, are allergic to proteins in the food, and not to the oils or fats.[26]

The prevalence of egg allergy is estimated to be 2% in children and 0.1% in adults. Most reactions are mild in childhood and likely to be severe in adulthood. The majority of egg-allergic patients are allergic to egg white with ovalbumin and ovomucoid being the main triggers. Egg-yolk allergy is related to chicken albumin. Propofol does not contain egg white proteins, but it does contain lecithin. Lecithin, from the Greek meaning 'egg yolk', is a phosphatide, a fatty substance in egg yolk that has no role in egg allergy.

The estimated prevalence of soy allergy is less than 1% in both adults and children.[27] Isolated soy allergy seems to be rare and soy anaphylaxis is very uncommon. Major soy allergens (i.e. glycinin [11S] and β-conglycinin [7S]) are proteins belonging to the cupin family.

The prevalence of peanut allergy is estimated to be less than 3% and 1% in children and adults, respectively.[27–29] Major peanut allergens have been identified and belong to the prolamin superfamily.

Whilst egg or soy allergy is more likely to be outgrown, peanut allergy is more persistent. Finally, food-induced fatalities are most commonly reported from exposure to peanuts.

Is there a link between food and propofol allergy?

Propofol is an alkylphenol derivative (2,6-di-isopropylphenol) formulated as an oil-in-water emulsion using 10% refined soybean oil, 1.2% highly purified egg lecithin, and 2.25% glycerol. A few cases of propofol allergy have been reported,[30–34] and none of these patients had egg or soy allergy. The isopropyl group or the phenol ring has been suggested as the allergenic determinant rather than the lipid vehicle.

Highly purified egg lecithin may contain residual proteins, but the amount of egg-yolk protein is very low (0.005%).[35] However, egg allergy is almost invariably the result of sensitisation to egg white proteins. Similarly, soybean oil is highly refined and is unlikely to contain significant quantities of allergenic particles.[36] In 10 egg-allergic children, skin tests to propofol and egg lecithin together with skin tests to propofol and soybean oil in three soy-allergic patients remained negative.[37] Finally, no propofol allergy has been demonstrated to be elicited by these components.[26]

Peanut allergy is still listed as a contraindication in the product information of propofol likely because of potential clinical cross-reactivity between peanut and soy, both belonging to the legume family. However, peanut-allergic patients are usually not soy allergic, and even if they were, would not be expected to react to soybean oil.[26]

Eosinophilic esophagitis (EoE) is a distinct phenotype of non-IgE-mediated food allergy, mainly triggered by cow's milk, soy, wheat, and egg. It is characterised by oesophageal dysfunction and eosinophil-predominant inflammation frequently associated to IgE-mediated food allergy.[38] A few retrospective mono- or bicentric studies evaluated the use of propofol in egg-, soy-, or peanut-sensitised or allergic patients with or without EoE (Table 1).[34,35,36,39] In one case, generalised urticaria was reported in a child with previous egg anaphylaxis.[35] Prick test to propofol was considered positive and an intradermal test was not performed. A false-positive result cannot be discounted.[40] The authors conclude that propofol is likely to be safe in egg-allergic children without prior egg anaphylaxis. Propofol use was safe in the remaining studies,[34,36,39] and some authors agree that propofol can be

Table 1 Retrospective studies evaluating the use of propofol in egg, soy, or peanut allergy with or without eosinophilic esophagitis (EoE). IDT, intradermal test; neg, negative; pos, positive; PT, prick test

Reference	Patient (*n*) age (range, yr)	Study design and propofol injection (n)	Clinical history	Perioperative event	Skin testing to propofol
Murphy and colleagues[35] (2011)	28 (1–15)	Monocentric (1999–2010) 43	(i) Egg sensitisation: 28 (a) Egg allergy: 19 (68%) (b) Previous egg anaphylaxis: 2/19	(i) Generalised urticaria 15 min after the second propofol dose in an EoE child with previous egg anaphylaxis (*n*=1)	(i) PT (neat): 3 mm (pos) (ii) IDT: not done
Molina-Infante and colleagues[36] (2014)	60 (14–56)	Bicentric (2009–2013) 404	(i) EoE: 60 (ii) Egg, soy, or peanut sensitisation: 52 (86%) (a) Egg, soy, or peanut allergy: 18/52 (35%) (b) Previous clinical reaction or anaphylaxis: egg (1), legume (4), and peanut (13)	(i) Intubation-induced bronchospasm in an adolescent with uncontrolled asthma (*n*=1)	PT (neat): neg
Asserhoj and colleagues[34] (2016)	99 (adults)	Monocentric (2004–2012) 171	(i) Egg, soy, or peanut sensitisation: 99 (ii) Egg, soy, or peanut allergy: 44 (44%)	None	
Mehta and colleagues[39] (2017)	144 (children)	Monocentric (2013–2014) 65	(i) Egg or soy allergy: 144 (ii) Previous egg anaphylaxis: 6 (4%) (iii) EoE: 76 (53%)	None	

administered regardless of food sensitisation or allergy and EoE.[34,36]

Interestingly, the US Food and Drug Administration does not contraindicate the use of parenteral fat emulsion (Intralipid®, Fresenius Kabi, Uppsala, Sweden) in egg or soy allergy,[41] whilst propofol 1% and Intralipid 10% share the same egg lecithin/soy oil content, and Intralipid 20% has double the amount of soy oil. Based on actual data, the American Academy of Allergy, Asthma and Immunology recently stated that egg- or soy-allergic patients can receive propofol without any special precautions.[26]

In summary, there is no evidence to avoid the use of propofol in egg, soy, or peanut allergy.

Seafood allergy and iodinated drugs

Seafood allergy

Fish or shellfish allergy seems to be more common in adults than in children.[27,29] The major fish allergen is the low-molecular-weight (10–13 kDa) heat-stable muscle protein, parvalbumin, a calcium-binding protein.[42] The high clinical cross-reactivity amongst fishes has been attributed to parvalbumin cross-reactive IgE from several species. Other fish allergens have been characterised (e.g. glycolytic enzymes [aldolase A and β-enolase] or collagen isolated from muscle tissues or skin). Tropomyosin is considered the major pan-allergen in all edible crustacean and mollusc species and arthropods (e.g. house dust mite).[42] This heat-stable protein (33–39 KDa) belongs to a family of actin-binding proteins. Clinical cross-reactivity is frequent between and amongst crustaceans and molluscs, as tropomyosins share a high degree of sequence identity. Other allergens have been identified (e.g. arginine kinase).

In summary, allergy to fish or shellfish is not related to iodine.

Iodinated drug allergy

Iodinated contrast media (ICM) and povidone iodine are the main iodinated drugs used in the perioperative setting. ICM are chemical modifications of a 2,4,6-tri-iodinated benzene ring. IgE-mediated[43–45] and delayed hypersensitivities[45–47] to ICM have been documented. ICM present a different degree of cross-reactivity in both immediate and delayed hypersensitivities. Negative skin-tested ICM have been safely administered during subsequent procedures despite previous ICM allergy.[43,46] The allergenic determinants remain unknown in both phenotypes. Iodine is not the epitope, as it is an essential element needed for life without potential to elicit allergy.

Povidone iodine is a stable chemical complex of molecular iodine and a polyvinylpyrrolidone, also called 'povidone', surfactant/iodine complex. Less than 10 cases of IgE-mediated allergy to povidone iodine, primarily after skin wound or mucosal application, have been published since 1998 (Table 2).[48–55] Povidone is the allergenic determinant involved. Delayed hypersensitivity to povidone iodine has also been reported. The allergenic determinant might be the surfactant (i.e. nonoxynol); the role of povidone remains unproved.[56]

In summary, there is no evidence to avoid iodinated drugs in seafood allergy.

Table 2 Clinical cases of immunoglobulin E-mediated allergy to povidone iodine (since 1998). Although most of the case reports did not use any grading system, the modified Ring and Messmer scale was used to classify their severity. AP, arterial pressure; F, female; ICM, iodinated contrast medium; IDT, intradermal test; M, male; ND, not done; neg, negative; pos, positive; PT, prick test; PVP, povidone; SAP, systolic arterial pressure.

Reference	F/M (age)	Site (onset delay)	Clinical features	Skin testing	Tryptase
Lopez Saez and colleagues[48] (1998)	M (27)	Skin wound (immediately)	Pruritus of the soles, generalised urticaria, facial angioedema (Grade I)	(i) PT (10^{-2}) PVP-iodine: pos (ii) PT (neat) PVP: pos (iii) PT (neat) Lugol's solution: neg (iv) PT (neat) 2 ICM: neg	ND
Adachi and colleagues[49] (2003)	F (59)	Mucosa (10 min)	Pruritus in the genital area, erythema, generalised urticaria, SAP: 40 mm Hg, dyspnoea (Grade III)	(i) PT (0.1%, 10%) PVP-iodine: pos (ii) PT (0.001%) PVP: pos (iii) PT (2%) iodine: neg	ND
Le Pabic and colleagues[50] (2003)	M (32)	Surgical wound (a few minutes)	Clinical features not detailed (Grade IV)	(i) PT (neat) PVP-iodine: pos (ii) IDT (10^{-4}) PVP-iodine: pos (iii) PT (neat) PVP: pos (iv) IDT (10^{-4}) PVP: pos	(i) T_0+? min: 39 (N<? µg L^{-1})
Pedrosa and colleagues[51] (2005)	M (9)	Skin (10 min)	Urticaria, facial angioedema, dyspnoea (Grade II); one previous clinical reaction after oral intake of flubendazole (containing povidone): (Grade IV)	(i) PT (neat) PVP-iodine: pos (ii) PT (neat) PVP: pos (iii) PT (neat) flubendazole: pos	ND
Caballero and colleagues[52] (2010)	M (42)	Surgical wound (15 min)	Skin preparation with PVP-iodine: no event; PVP-iodine on surgical wound: generalised urticaria, tongue swelling, SAP: 94 mm Hg, moderate bronchospasm (Grade II)	(i) PT (neat) PVP-iodine: pos (ii) PT (neat) iodine: neg	ND
Gray and colleagues[53] (2013)	F (12)	Skin wound (unknown)	Clinical features not detailed; one previous clinical reaction after PVP-iodine application on skin wound (Grade II)	(i) PT (neat) PVP-iodine: pos	ND
Castelain and colleagues[54] (2016)	M (56)	Knee wound (immediately)	Pruritus on the knee spreading to the whole body, generalised erythema, sweating, SAP: 70 mm Hg, HR ↑ (?) (Grade II)	(i) PT (neat) PVP-iodine: pos (ii) PT (10^{-1}) PVP: pos	(i) T_0+? min: 94 (ii) baseline: 3.7 (N<11 µg L^{-1})
Moreno-Escobosa[55] (2017)	M (4)	Skin wound (20 min)	Eyelids angioedema, generalised urticaria, AP: 80/40 mm Hg, HR: ? (Grade II); two subsequent clinical reactions after (i) facial application of a sun cream (Grade I) and (ii) prednisolone oral intake (Grade II); sun cream and prednisolone both contain PVP	(i) PT (10^{-1}) PVP-iodine: pos (ii) PT (neat) sun cream: pos (iii) PT (neat) prednisolone: pos	ND

HR: heart rate.

Fish allergy and protamine

Protamine is a highly basic polypeptide, initially isolated from salmon fish sperm, and currently produced by recombinant biotechnology. It is also used in insulin preparation to prolong the pharmacological effect (i.e. neutral protamine Hagedorn [NPH]). Protamine may induce various adverse effects, including acute pulmonary hypertension, whilst evidence for an actual IgE-mediated allergy to protamine is very limited.[57,58]

Two risk factors have been suggested for protamine allergy (i.e. fish allergy and NPH insulin exposure). Evidence supporting the increased risk for protamine allergy in fish allergy is lacking.[59] Some studies evaluated the incidence of severe adverse reactions to protamine in patients using NPH insulin.[59–61] Although the incidence of protamine reactions in NPH diabetics has been reported to be 0.6% compared with 0.06% in other cardiac surgical patients, no protamine allergy was evidenced. Recently, three cases of protamine allergy were reported.[62] A subsequent uneventful protamine exposure in two of these patients receiving NPH insulin suggests that other pathophysiological mechanisms may have been involved.[58]

In summary, there is no evidence to avoid the use of protamine in fish allergy and NPH insulin use.

Alpha-gal syndrome, gelatin-based colloid, and heparin

Over the past decade, α-gal syndrome has been recognised as an IgE-mediated red meat allergy and identified as a singular syndrome involving the carbohydrate (galactose-α-1,3-galactose, or α-gal) determinant, a sensitisation *via* tick bites and a delayed onset of the clinical features (i.e. 3–6 h after meat exposure).[29,63] The oligosaccharide is present in many mammalian foods, including meat and gelatin. IgE to α-gal was initially recognised in IgE-mediated allergy to cetuximab, a monoclonal antibody used in oncology.[64,65]

In addition, allergy to other drugs that contain or may contain the α-gal epitope has been suggested. It was shown that α-gal-allergic patients may cross-react to mammalian gelatin-based colloid, as some preparations contain α-gal.[66] This should be distinguished from gelatin allergy related to the protein backbone of the colloid.[67] As heparin is derived from bovine lung and porcine intestinal mucosa, it may contain the α-gal epitope as a result of a potential contamination during the manufacturing process. Some authors therefore suggested that heparin allergy might occur in α-gal syndrome, the likelihood of a reaction being related to the purity and the dose of heparin.[68,69] In the few reported case series, the timing between heparin administration and the symptom onset disproves its role; no IgE-mediated heparin allergy was evidenced, whilst uninvestigated drugs used in the perioperative setting may have been involved in the onset of immediate hypersensitivity.[68,70,71] Some authors therefore conclude that there is currently no evidence that 'heparin reactions' are related to IgE to α-gal.[68]

In summary, in α-gal syndrome, gelatin-based colloid should not be administered unless skin testing has proved negative, whilst evidence supporting the risk for heparin allergy is lacking.

Pre-existing non-allergic conditions

Aspirin-induced asthma

Aspirin-induced asthma is a non-allergic clinical syndrome consistent with asthma, nasal polyposis, and hypersensitivity to aspirin and other selective cyclooxygenase-1 (COX-1)-selective NSAIDs. This condition has been referred to as NSAID-exacerbated respiratory disease in Europe[72] and aspirin-exacerbated respiratory disease in the United States.[73] NSAID-exacerbated respiratory disease is a chronic eosinophilic inflammatory respiratory disorder affecting approximately 10% of patients with asthma or rhinosinusitis with nasal polyps. It appears from late childhood to adulthood. Two-thirds of these patients have a history of atopy. NSAID-exacerbated respiratory disease severity varies markedly, may involve only the upper airways, or causes severe asthma and rhinosinusitis. The risk of uncontrolled asthma is increased. The clinical symptoms exacerbated by NSAIDs result from COX-1 inhibition. Data regarding the perioperative management of NSAID-exacerbated respiratory disease are scarce.

Only one retrospective study evaluated the outcome of 45 patients with aspirin hypersensitivity or NSAID-exacerbated respiratory disease (80% with moderate or severe asthma) who underwent 51 general anaesthetics.[74] Optimal pulmonary function was achieved before surgery. The intra- and postoperative course remained uneventful. One patient exhibited urticaria and arrhythmia after being given metamizole (COX-1 and COX-2 inhibitor) in the postoperative period.

Before surgery, the preoperative assessment/treatment of uncontrolled asthma and rhinitis is paramount. Combined inhaled corticosteroid and long-acting β_2-agonist are usually sufficient. Additional drugs, such as leukotriene receptor antagonist (e.g. montelukast) or other agents (e.g. omalizumab) may be used as indicated for asthma. The upper airways are similarly treated.[72,73] In case of emergency surgery, repeated aerosolised β_2-agonist/steroid along with i.v. glucocorticoid may be required and continued up to the time of surgery whenever possible. Sevoflurane is likely to be preferred if volatile anaesthetics are used for the maintenance of anaesthesia. Neuromuscular block reversal with anticholinesterase does not precipitate bronchospasm in controlled asthma.[75] COX-1 inhibitors (e.g. ketoprofen) must be avoided in contrast to COX-2 inhibitors (e.g. celecoxib).[72,73,76] Weak inhibitor of COX-1, such as paracetamol (<1000 mg) is usually tolerated, but higher doses can induce symptoms.

In summary, the main concerns in NSAID-exacerbated respiratory disease include potential severe uncontrolled asthma and strict avoidance of all COX-1 inhibitors.

Non-allergic mast-cell-driven conditions

Chronic urticaria

Chronic urticaria has been defined as wheals (hives), angioedema, or both, lasting for more than 6 weeks.[77–80] Chronic urticaria is a non-allergic mast-cell-driven condition affecting 2–3% of individuals and involving two subtypes (i.e. chronic spontaneous and inducible urticaria). It may be intermittent or persistent, and often improves in pregnancy. No eliciting factor is involved in chronic spontaneous urticaria conversely to chronic inducible urticaria. Chronic spontaneous urticaria is characterised by spontaneous appearance and its idiopathic

nature in most cases. Angioedema is frequent in chronic spontaneous urticaria.[81] Chronic inducible urticaria is induced by physical triggers (e.g. cold, warm, exercise, vibration, pressure, etc.). In childhood, chronic spontaneous urticaria is rarely severe, whilst cold and pressure are the most common triggers of chronic inducible urticaria.

The management of chronic urticaria is based on the identification of underlying causes, avoidance of triggers, and use of second-generation H_1 antihistamines to prevent mast-cell-mediator release. Omalizumab, an anti-IgE monoclonal antibody, is effective in chronic urticaria unresponsive to H_1 antihistamines,[79] as it might contribute to the maintenance of mast-cell stability. A short course of corticosteroid is suggested in acute chronic urticaria exacerbation.[77,79]

Before surgery, chronic urticaria should be controlled whenever possible. Regular medications used to limit the effects of mast-cell mediators need to be continued until the day of surgery. Preoperative H_1 antihistamines may be useful, whilst H_2 antihistamines and leukotriene receptor antagonists (e.g. montelukast) seem to have little evidence.[79,80] The role of corticosteroids has not been evaluated.[78] There is no evidence to avoid histamine release agents. COX-1 inhibitors are not recommended, as they may aggravate chronic spontaneous urticaria,[79] unless it is clear that the patient is currently tolerating NSAIDs. Ten clinical cases regarding chronic inducible urticaria perioperative management have been reported since 1998 (Table 3). Particularly, no event related to cold-induced urticaria was reported during normothermic or hypothermic cardiopulmonary bypass in seven cases.[82–88] Preoperative H_1/H_2 antihistamines and steroids were mostly started a few days or hours before surgery, repeated before rewarming and after surgery. In the three remaining cases, pharmacological or physical factors triggered mild/moderate perioperative features.[89–91]

In summary, except avoidance of COX-1 inhibitors, there is no evidence to modify usual perioperative protocols in chronic urticaria.

Mastocytosis

Mastocytosis is the most important mast-cell clonal disorder characterised by an abnormal increase in tissue mast cells limited to the skin (i.e. cutaneous mastocytosis) or which infiltrates the bone marrow and other organs with/without skin involvement (i.e. systemic mastocytosis).[92,93] The estimated incidence is 1:10 000.[94] Mastocytosis is classified according to the age of onset (paediatric *vs* adult), the phenotype (cutaneous *vs* systemic), and the clinical characteristics (indolent *vs* aggressive) of the disease. Most patients have symptoms related to mast-cell-mediator release. Cutaneous mastocytosis is the most frequent phenotype characterised by its early appearance and spontaneous resolution by adolescence. Systemic mastocytosis primarily concerns adults and does not resolve spontaneously. Indolent systemic mastocytosis is the most common form. Aggressive systemic mastocytosis is more severe with a poorer prognosis.

Table 3 Clinical cases reporting the perioperative course of cold-induced urticaria during normothermic or hypothermic cardiopulmonary bypass (CPB) (since 1998). F, female; M, male.

Reference	F/M (age)	Surgery	Pretreatment regimen	CPB duration (min)	Core temperature (°C)	Perioperative event
Lancey and colleagues[82] (2004)	M (69)	Coronary bypass grafting	(i) Anti-H_1+anti-H_2 (ii) Methylprednisolone (a) 5 days before surgery (b) Before rewarming (c) Up to 6 h after surgery	?	32	None
Irani and colleagues[83] (2007)	F (34)	Mitral valve repair	(i) Anti-H_1+anti-H_2 (ii) Methylprednisolone (a) 6 h before surgery	109	37	None
Bakay and colleagues[84] (2010)	F (41)	Coronary bypass grafting	(i) Anti-H_1 (single dose) (ii) Methylprednisolone (a) 12 h before surgery (b) Up to 3 days after surgery	80	36	None
Booth and Parissis[85] (2011)	F (67)	Coronary bypass grafting	(i) Anti-H_1+anti-H_2 (ii) Hydrocortisone (a) Single dose	140	35.6–37.3	None
Ellis and colleagues[86] (2013)	M (70)	Aortic aneurysm repair	(i) Anti-H_1+anti-H_2 (ii) Methylprednisolone (iii) Montelukast (a) 7 days before surgery (b) Before rewarming (c) Up to 6 h after surgery	159	28	None
Fitzsimons and colleagues[87] (2015	M (57)	Pulmonary thrombo-endarterectomy	(i) Anti-H_1+anti-H_2 (ii) Hydrocortisone (a) 13 h before surgery (b) Anti-H_1 before rewarming	≈240	17–21.6	None
Maddy and colleagues[88] (2017)	F (66)	Aortic aneurysm repair	(i) Anti-H_1+anti-H_2 (ii) Hydrocortisone (a) Single dose	135	15.4–24.7	None

There is no evidence showing a higher prevalence of IgE- or non-IgE-mediated drug-induced immediate hypersensitivity in mastocytosis when compared with the general population.[95,96] Various triggers (i.e. histamine-releasing agents, mechanical [skin irritation and tourniquet], or physical [hypo- or hyperthermia] factors) and anxiety may elicit non-specific immediate hypersensitivity. Attention to the perioperative patient safety (homeothermy, positioning, and anxiolysis) makes these factors less likely to induce clinical features.[96] The Ring and Messmer scale is appropriate to characterise perioperative immediate hypersensitivity in mastocytosis.[95] Their incidence remains unknown. Care management is adapted to the clinical features. However, the role of drugs as elicitors appears to be overstated, as most uneventful procedures likely go unreported.[95–97]

A retrospective study included 501 cutaneous or systemic mastocytosis patients who underwent 726 anaesthetic procedures. The frequency of perioperative anaphylaxis was estimated to be 0.4% (n=3) and 2% (n=1) in adults and children, respectively.[98] Non-specific triggers were involved in two adults. The role of anaesthetics remains unproved in the two other cases. Uneventful procedures have been reported in four retrospective case series including parturients[99,100] and children.[101,102] Since 1998, the perioperative management of 21 cutaneous or systemic mastocytosis patients undergoing 25 procedures has been published (Table 4).[103–122] No perioperative event occurred in 52% (n=13) of the procedures. The pretreatment regimen was administered in most of the patients. Concurrent allergy (NMBA and gelatin) was proved or may have been involved in four cases, whilst non-specific triggers, including drugs (antibiotics and atracurium) or mechanical factors, were identified in five. The role of mastocytosis remained speculative in the three other cases.

Preoperative H_1 or H_2 antihistamine or corticosteroid is usually recommended, but has never been evaluated.[95–97] There is no evidence to the contrary, and most centres recommend pretreatment.[96] Medications used to maintain mast-cell stability should be continued until surgery and known triggers avoided, whenever possible. Although there is no general agreement in this issue, drugs that can be used in mastocytosis were compiled according to clinical reports (Table 5).[95,123] Caution has been recommended with benzylisoquinoline NMBAs because of their histamine-releasing potency.

In summary, the perioperative course is usually uneventful in mastocytosis.

Hereditary and acquired angioedema

Hereditary and acquired angioedema are rare conditions, primarily bradykinin mediated. Hereditary angioedema is an autosomal dominant disease with an estimated prevalence of 1:50 000. The main phenotypes include hereditary angioedema with deficient (Type 1) or dysfunctional (Type 2) C1 esterase inhibitor (C1–INH).[124,125] Acquired angioedema is less common and attributable to C1-inhibitor deficiency.[126] It might be associated with C1–INH autoantibodies with/without an underlying condition (e.g. lymphoma). Given the role of bradykinin, the latest guidelines classify angioedema related to the use of ACE-I or angiotensin receptor blocker as acquired, although C1–INH deficiency or dysfunction is absent.[125]

C1–INH deficiency/dysfunction results in inappropriate or excessive activation of the complement pathway allowing kallikrein activation. This leads to the production of bradykinin, increased capillary permeability, and angioedema. Recurrent angioedema may involve the face, oropharynx, larynx, extremities, abdomen, genitourinary tract, or a combination of these. Symptoms are similar in hereditary and acquired angioedema. In hereditary angioedema, swelling often begins during childhood and worsens around puberty. In acquired angioedema, the onset of symptoms is later, the family history of angioedema is absent, and facial angioedema is more frequent.[126] ACE-I-induced angioedema frequently occurs within the 1st month or after years of treatment. Angioedema may occur spontaneously or be precipitated by various stimuli (e.g. mechanical trauma, stress, and emotion). Upper airway manipulation, including dental surgery and tracheal intubation, is at particularly high risk as a result of upper airway and laryngeal angioedema.[124,125,127,128]

Only four retrospective case series regarding hereditary or acquired angioedema perioperative management were published since 1998 (Table 6). One study investigated 705 tooth extractions in 171 hereditary angioedema patients with/without C1–INH prophylaxis.[129] Short-term prophylaxis led to a 42% reduction in facial/laryngeal angioedema. Angioedema was recorded in less than 6% of the procedures in hereditary angioedema without short-term prophylaxis.[130] In most cases, angioedema was located at the site or region of surgery, although laryngeal angioedema was documented in three patients. A recent study included 24 hereditary or acquired angioedema patients who underwent 38 procedures.[131] Short-term prophylaxis was administered in all hereditary and in six acquired angioedema patients. Upon tracheal extubation, oral angioedema requiring re-intubation occurred in a hereditary angioedema patient on long-term androgen therapy who received fresh frozen plasma (FFP) before surgery. Finally, the course of vaginal delivery (n=110) or Caesarean section (n=15) was safe in 61 hereditary angioedema parturients with or without short-term prophylaxis.[132]

National, international, and society guidelines regarding the hereditary or acquired angioedema overall management, including the perioperative and obstetric settings, have been published. There is a general agreement that C1–INH concentrate is the short-term prophylaxis of choice in both children and adults.[124,125,127] If short-term prophylaxis should be considered prior to all medical, surgical, and dental procedures in Canada[127] and in the USA,[124] the latest international guidelines provide that C_1–INH concentrate should be used as close as possible to the start of surgery associated with mechanical impact to the upper aerodigestive tract.[125] Short-term prophylaxis can be achieved by FFP[124] as a second-line agent.[125] Attenuated androgens (e.g. danazol) may be used in light of their adverse effects.[124,125,127] Tranexamic acid is no longer recommended.[125] In the UK, no specific short-term prophylaxis regimen has been outlined.[128] Despite short-term prophylaxis, angioedema may occur even after minor procedures. A specific acute treatment should be available during and after any procedure, although short-term prophylaxis was administered.[124,125,127,128]

All attacks are considered for on-demand treatment, whilst any attack affecting or potentially affecting the upper airway is treated.[125] Hereditary and acquired angioedema fail to respond to corticosteroids, antihistamines, or epinephrine. Early treatments with a specific therapy (C1–INH concentrate, icatibant [selective bradykinin B2 receptor antagonist] or ecallantide [plasma kallikrein inhibitor]) are the acute treatments of choice. FFP could be used if the specific therapies are

Table 4 Clinical cases reporting the perioperative course in cutaneous (CM) or systemic (SM) mastocytosis (since 1998). AP, arterial pressure; CSE, combined spinal epidural anaesthesia; F, female; ISM, indolent systemic mastocytosis; M, male; MDZ, midazolam; MMAS, monoclonal mast-cell activation syndrome; MOF, multi-organ failure; MTK, montelukast; ND, not done; SA, spinal anaesthesia; SAP, systolic arterial pressure.

Reference	F/M (age)	Premedication	Agents and surgery	Perioperative event	Trigger	Tryptase
Borgeat and Ruetsch[103] (1998)	F (30) SM	MDZ, anti-H_2, steroid	Fentanyl, propofol, and vecuronium; splenectomy	None		During surgery: 10 (N<13 U L^{-1})
Vaughan and Jones[104] (1998)	M (43) SM	None	Fentanyl, propofol, isoflurane, morphine, and atracurium; olecranon fracture	Immediately after intubation: electromechanical dissociation followed by MOF and death	Atracurium allergy likely involved	T_0+?: 18 (N<1 ng ml^{-1})
Damodar and colleagues[105] (2006)	F (14) SM	Anti-H_1, anti-H_2, steroid	MDZ, fentanyl, and pancuronium; cardiac surgery	None		ND
Russell and Smith[106] (2006)	F (60) SM	None	SA (bupivacaine), midazolam, propofol, and tropisetron; knee arthroplasty (postponed)	After SA and propofol: extreme bradycardia then circulatory arrest	Role of SM?, likely attributable to the additive effects of SA and propofol	(i) T_0+90 min: 37 (ii) Baseline: 36 (N<15 μg L^{-1})
		None	Second surgery: MDZ, morphine, propofol, vecuronium, and desflurane; knee arthroplasty	None		ND
Villeneuve and colleagues[107] (2006)	F (37) CM	Anti-H_1, anti-H_2	CSE (lidocaine, fentanyl), nitrous oxide, oxytocin, naproxen, and paracetamol; Caesarean section	None		ND
Konrad and Schroeder[108] (2009)	F (52) SM	Anti-H_1, MDZ	Sufentanil, propofol, rocuronium, and sevoflurane; hysterectomy	None		ND
	M (45) SM	Anti-H_1, steroid	Sufentanil, remifentanil, and propofol; tonsillectomy	None		ND
Renauld and colleagues[109] (2011)	F (69) CM	Anti-H_1	Sufentanil, propofol, atracurium, desflurane, morphine, and nefopam; hysterectomy	2–3 min after atracurium: AP: 77/50 mm Hg, HR: 120 beats min^{-1}, generalised erythema	Atracurium (allergy excluded)	(i) T_0+90 min: 69 (ii) Baseline: 73 (N<10 μg L^{-1})
Bridgman and colleagues[110] (2013)	F (58) SM	None	MDZ, fentanyl, propofol, sevoflurane, cefazolin, paracetamol, ropivacaine, and dexamethasone; knee replacement	After tourniquet release: no erythema, SAP: 60 mm Hg, HR: ?	Tourniquet	(i) T_0+?>200 (ii) Baseline: 31 (N<14 ng ml^{-1})
Ulbrich and colleagues[111] (2013)	F (33) SM	MDZ	Propofol, piritramid, clonidine, oxytocin, and erythromycin; Caesarean section	None		ND
Duggal and colleagues[112] (2015)	M (53) SM	None	MDZ, fentanyl, propofol, vecuronium, and vancomycin; aortic aneurysm (postponed)	During vancomycin infusion: AP: 50 mm Hg, HR: 60 beats min^{-1}, erythema, urticaria	Non-allergic reaction to vancomycin likely involved	T_0+? min: 154 (N<11 ng ml^{-1})
		Anti-H_1, anti-H_2, steroid	Second surgery: fentanyl, propofol, lidocaine, succinylcholine, and linezolid; aortic aneurysm (postponed)	During linezolid infusion: AP<65 mm Hg, HR: ? erythema, urticaria	Non-allergic reaction to linezolid	T_0+? min: 56 (N<11 ng ml^{-1})

Continued

Table 4 Continued

Reference	F/M (age)	Premedication	Agents and surgery	Perioperative event	Trigger	Tryptase
		Anti-H_1, anti-H_2, steroid, MTK	Third surgery: fentanyl, lidocaine, propofol, succinylcholine, linezolid, cefuroxime, and protamine; aortic aneurysm	None		ND
Tew and Taicher[113] (2015)	F (6) CM	Anti-H_1	Fentanyl, propofol, sevoflurane, nafcillin, paracetamol, and oxycodone; lumbar laminectomy	None		ND
Aloysi and colleagues[114] (2016)	F (19) CM	Anti-H_1	Propofol and suxamethonium; electroconvulsive therapy	None		ND
Ten Hagen and colleagues[115] (2016)	M (70) ISM	None	SA (bupivacaine), propofol, ketamine, cefazolin, tranexamic acid, naproxen, ondansetron, and paracetamol; hip arthroplasty	After cement implantation: AP: 60/40 mm Hg, HR ?, SpO_2: 80%, no cutaneous signs	Bone cement (unrelated to ISM)	ND
Bryson and colleagues[116] (2017)	M (41) SM	Anti-H_1	MDZ, propofol, rocuronium, and neostigmine; electroconvulsive therapy	None		ND
de la Fuente Tornero and colleagues[117] (2017)	M (50) ISM	MDZ, anti-H_2	Fentanyl, lidocaine, propofol, rocuronium, sevoflurane, cefazolin, and succinylated gelatin; spinal surgery	Immediately after gelatin: AP: 60/30 mm Hg, HR: 40 beats min^{-1}, $EtCO_2$: 9 mm Hg and circulatory arrest	Gelatin allergy likely involved	(i) T_0+120 min: 410 (ii) Baseline: 50 (N<11 ng ml^{-1})
Richter and colleagues[118] (2017)	M (49) MMAS	Anti-H_1, anti-H_2, steroid	Fentanyl, lidocaine, propofol, rocuronium, heparin, and protamine; pulmonary embolectomy	6 h after ICU arrival: pruritus (chest and legs) and vasoplegia	Mast-cell activation may have contribute to vasoplegia	Immediately and every 6 h during 24 h<N (N<? ng ml^{-1})
Unterbuchner and colleagues[119] (2017)	M (45) ISM	Anti-H_1, anti-H_2, steroid	Sufentanil, propofol, rocuronium, ceftriaxone, metronidazole, and sugammadex; emergency laparotomy	None		(i) After induction: 18 (ii) After sugammadex: 20 (N<11 ng ml^{-1})
Chatterjee and colleagues[120] (2018)	F (57) ISM	None	Propofol and atracurium; thyroidectomy (postponed)	2 min after atracurium: AP: 50/32 mm Hg, HR: 153 beats min^{-1} $Sp0_2$: ↓, bronchospasm, erythema	Atracurium allergy likely involved	(i) T_0+45 min: >200 (i) Baseline: 161 (N<? ng ml^{-1})
Dewachter and Mouton-Faivre[121] (2018)	F (62) ISM	None	Sufentanil, propofol, rocuronium, desflurane, and sugammadex; appendectomy	2 min after rocuronium: AP: 55/28 mm Hg, HR: 130 beats min^{-1} $EtCO_2$: 23 mm Hg, SpO_2: 90% generalised erythema	Rocuronium allergy proved	(i) T_0+40 min: >200 (ii) Baseline: 86 (N<13 μg L^{-1})
Ishii and colleagues[122] (2018)	F (43) SM	Anti-H_2	Epidural (?), fentanyl, sevoflurane, vecuronium, flomoxef; colectomy (postponed)	Colon traction: ↑HR (?), severe hypotension, flushing (face and chest)	Colon traction	ND
		Anti-H_1, anti-H_2, steroid	Second surgery: same protocol, no antibiotic; colectomy	None		ND

HR: heart rate

Table 5 Drugs accepted and not recommended in mastocytosis. *Although there are no data concerning the use of these agents, there is no reason to avoid them. *This table is adapted with permission from: Dewachter P, Mouton-Faivre C, Cazalaà JB, Carli P, Lortholary O, Hermine O. Mastocytosis and anaesthesia. Ann Fr Anesth Reanim 2009; 28 (1):61–73. Copyright © 2008 Elsevier Masson SAS. All Rights Reserved.*[123] *Reproduced with permission from Wolters Kluwer: Dewachter P, Castells MC, Hepner DL, Mouton-Faivre C. Peri-operative management of patients with mastocytosis. Anesthesiology, 120 (3): 753–9 (http://anesthesiology.pubs.asahq.org/article.aspx?articleid=1917908)*[95]

Family of drugs	Accepted	Not recommended
I.V., inhalation, and local anaesthetics		
Benzodiazepine	Midazolam	
Hypnotics	Etomidate, ketamine, propofol, and thiopental	
Halogenated gases and nitrous oxide	Desflurane, isoflurane, sevoflurane, and nitrous oxide	
Local anaesthetics	Amide type and ester type*	
Neuromuscular blocking agents		
Depolarising agent	Suxamethonium	
Steroidal agents	Pancuronium, rocuronium, and vecuronium	
Benzylisoquinolines	Cisatracurium	Atracurium and mivacurium
Reversal of neuromuscular block		
Anti-cholinesterase agent	Neostigmine	
Cyclodextrin	Sugammadex*	
I.V. analgesics		
Opioids	Alfentanil, fentanyl, remifentanil, and sufentanil	
Morphine	Requires titration	
Analgesic	Paracetamol (acetaminophen)	Nefopam
Other agents		
Antiseptics*	Chlorhexidine and povidone iodine	
Plasma substitutes*	Albumin, gelatin, and hydroxyethyl starch	
Miscellaneous	Aprotinin* (topical glue), atropine, ondansetron, oxytocin, and protamine*	

not available, but may potentially worsen an attack by replacing depleted complement factors.

In pregnancy, short-term prophylaxis is not recommended before uncomplicated vaginal delivery, but C1–INH concentrate should be available.[124,125,127,133] Conversely, C1–INH concentrate is recommended (i) before labour and delivery when hereditary angioedema is severe, including frequent recurrence of symptoms during the last trimester or a history of mechanical-induced genital angioedema; (ii) if instrumental delivery or Caesarean section is performed; and (iii) as the first-line acute therapy in pregnancy or during breastfeeding.[125,133] Virus-inactivated FFP can be administered in case of attack if C1–INH concentrate is not available and FFP when virus-inactivated FFP is lacking. No data regarding the use of ecallantide or icatibant are available during pregnancy or breastfeeding. Close follow-up is recommended for at least 72 h after delivery.

In summary, the main concern in hereditary and acquired angioedema is the risk of laryngeal angioedema.

Anaesthesia for patients with previous perioperative immediate hypersensitivity

Follow-up allergological investigation should be performed after a perioperative immediate hypersensitivity or any perioperative context without an obvious explanation (i.e. unexplained prolonged hypotension or circulatory arrest). The perioperative management of the patient labelled as 'penicillin allergic' is reviewed in detail elsewhere in this issue of the *British Journal of Anaesthesia*.

Allergological investigation

Clinical history is crucial to establish the diagnosis of perioperative immediate hypersensitivity, and the Ring and Messmer scale is useful to describe the clinical features.[5,6,20] All the grades (I–IV) of this scale require a subsequent investigation. Combined acute plasma histamine and tryptase measurements are recommended in France[4] and in the USA,[134] whilst only tryptase measurement has been retained in Scandinavia,[5] the UK,[7] Australia and New Zealand,[135] and Spain.[136] Skin testing remains the 'gold standard' to identify the culprit agent and the pathophysiologic (allergic *vs* non-allergic) mechanism involved, and provides advice for subsequent anaesthetics.[5–7,20,134,135] Skin testing requires experience and time, and is best performed in dedicated clinics.[137]

Differential diagnoses after allergological investigation

The allergological assessment includes a review of the details of the reaction. A suggestive clinical history, usually a life-threatening reaction, associated with increased histamine or tryptase concentrations linked to skin-test positivity to the culprit agent proves the diagnosis of IgE-mediated allergy. The absence of tryptase increase does not preclude IgE-mediated allergy.[5,7,20,134] Conversely, a suggestive clinical history (usually mild/moderate reaction) associated with skin-test negativity, with or without increased histamine and tryptase (tryptase may be slightly elevated) concentrations, suggests a non-allergic reaction (e.g. histamine release induced by benzylisoquinoline NMBAs, suxamethonium, propofol, and vancomycin). Non-allergic reaction associated with vancomycin is also called 'red man syndrome', and is related to the strong histamine-releasing capacity along with rapid infusion of the first dose of the drug.[138] Discontinuation of the vancomycin infusion and H_1 antihistamines may reduce/prevent most of

Table 6 Retrospective case series regarding the perioperative and obstetric management in hereditary and acquired angioedema. AAE, acquired angioedema; C1−INH, C1-inhibitor concentrate; ENT, ear, nose, and throat; EPI, epidural anaesthesia; FFP, fresh frozen plasma; GA, general anaesthesia; HAE, hereditary angioedema; LA, local anaesthesia.

Reference	Patient (*n*)/ phenotype	Study design/ study period	Type of procedure (*n*) / prophylaxis per procedure	Incidence of perioperative angioedema per procedure
Bork and colleagues[129] (2011)	171/HAE	Monocentric unknown	(i) Procedures: 705 (a) Tooth extraction (b) Local anaesthesia (ii) C1−INH: 128 (18%) (iii) No prophylaxis: 577 (82%)	(i) Without prophylaxis: 21.5% (*n*=124/577) (a) Isolated facial angioedema: 88 (b) Isolated laryngeal angioedema: 8 (c) Facial and laryngeal angioedema: 28 (ii) With prophylaxis: 12.5% (*n*=16/128) (a) Isolated facial angioedema: 9 (b) Isolated laryngeal angioedema: 4 (c) Facial and laryngeal angioedema: 3
Aygören-Pürsün and colleagues[130] (2013)	144/HAE	Monocentric unknown	(i) Procedures: 335 (a) Abdominal (113), ENT (71), gynaecologic (58), orthopaedic (45), other (48) (b) Type of anaesthesia: ? (ii) No prophylaxis	(i) Angioedema: 5.7% (*n*=19/335) (a) Site or region of surgery: 14 (b) Other site or region of surgery: 2 (c) Laryngeal: 3 (2 after ENT surgery, 1 after laparoscopy) (ii) No event: 69.6% (*n*=233) (iii) Missing data: 24.8% (*n*=83)
MacBeth and colleagues[131] (2016)	24/HAE: 13; AAE: 10; unknown: 1	Monocentric (2000−14)	(i) Procedures: 38 (a) General surgery (15), urology (6), endoscopy (4), orthopaedic (2), other (11) (b) GA with tracheal intubation (ii) Androgen: 24 (HAE: 14; AAE: 9; unknown: 1) (iii) C1−INH: 3 (HAE: 2; AAE: 1) (iv) Androgen+C1−INH: 5 (HAE) (v) Androgen+FFP: 2 (HAE) (vi) No prophylaxis: 4 (AAE)	(i) With prophylaxis (androgen+FFP) (a) Oral angioedema: 2.6% (*n*=1)
González-Quevedo and colleagues[132] (2016)	61/HAE	Five centres (2006−10)	(i) Procedures: 125 (a) Caesarean section: 15 (GA: 9; EPI: 6) (b) Vaginal delivery: 110 (GA: 8; EPI: 25; LA: 3; no anaesthesia: 74) (ii) C1−INH: 14 (11%) (a) Caesarean section: 5 (b) Vaginal delivery: 9 (iii) No prophylaxis: 111 (89%)	(i) Caesarean section: none (ii) Vaginal delivery: 5.4% (*n*=6/110) (a) Mild local symptoms

the reactions. Other antibiotics (e.g. fluoroquinolones and teicoplanin) may also cause red man syndrome.

Isolated bronchospasm is usually of non-allergic mechanism, and elicited by non-specific mechanical (i.e. intubation-induced bronchospasm) or pharmacological (e.g. histamine-releasing drugs) triggers in uncontrolled airway hyperreactivity.[15,17]

Systemic mastocytosis should be suspected in cases of severe cardiovascular disturbances associated with cutaneous signs and highly increased peak tryptase concentration compared with the grade of the clinical presentation. Baseline tryptase concentration and, when available, testing for KIT D816V mutation in peripheral blood may be useful followed by a subsequent investigation (e.g. bone marrow evaluation) if indicated, to prove or rule out the diagnosis of systemic mastocytosis.[95,96,121]

How to manage subsequent anaesthetics

The allergological assessment includes a medical report detailing the clinical history, phenotype of reaction, allergological work-up results, diagnosis, drugs involved, and advice for further anaesthetics.[136] Drug challenge test with negative skin-tested anaesthetic is not regularly performed. It is reviewed in this issue of the *British Journal of Anaesthesia*.

In case of a documented non-allergic reaction

Non-allergic reaction is usually mild/moderate, mainly elicited by histamine-release agents in young, atopic, or stressed patients. Severe clinical presentation is also reported. After mild/moderate non-allergic immediate hypersensitivity, the culprit drug is not contraindicated for further anaesthetics, as pretreatment with H_1 antihistamines and attention to slow injection and/or at a lesser dosage may reduce/prevent the clinical features induced by histamine release.[136,139]

In case of a documented IgE-mediated allergy (e.g. NMBA allergy)

The culprit and potential cross-reactive NMBA(s) must be avoided. Skin testing to NMBAs has been standardised in France,[4] the protocol has been adapted by others,[5,7,140] and endorsed by the European Academy of Allergy and Clinical Immunology.[141] The negative predictive value of skin tests to NMBAs is excellent. Despite previous NMBA allergy, NMBAs have been uneventfully used during subsequent anaesthetics on the sole basis of negative skin tests results, including intradermal tests only,[142] combined prick tests and intradermal tests,[143–146] or combined skin tests and basophil activation test.[147] The use of lower dilutions of NMBAs than those recommended and/or intradermal tests only,[142,148,149] inadequate communication,[146] or false negative skin tests[144] may explain second reactions to a negative-skin-test NMBA.

In summary, despite previous NMBA allergy, negative skin-tested NMBAs can be safely injected during subsequent anaesthesia with a low risk of further reaction.

Conclusions

The main identified risk factor of perioperative drug anaphylaxis is a previous uninvestigated perioperative immediate hypersensitivity reaction. However, perioperative IgE-mediated drug-induced allergy may occur during the first or subsequent anaesthetics. The concept of cross-reactivity between food and drugs is often quoted, but usually not supported by evidence. The nosological distinction in the different non-allergic conditions captures the risk linked to the condition itself and helps for rational decision-making in care management. Finally, the allergological investigation after perioperative immediate hypersensitivity highly contributes to the quality and safety in subsequent perioperative care.

Authors' contributions

Study conception: all authors.
Study design: all authors.
Data collection, analysis, and interpretation: all authors.
Drafting of manuscript: all authors.
All authors reviewed drafts of the manuscript and approved the final version.

Declarations of interest

PD has received lecture and travel fees from MSD France (Courbevoie, France); has received lecture and travel fees from Bracco Imaging France (Courcouronnes, France); expert for a task force group dedicated to neuromuscular blocking agents and anaphylactic reactions (until 2016) from the Agence Nationale de Sécurité du Médicament et des Produits de Santé, Saint-Denis, France; and belongs, until October 2019, to an MSD Expert Board on neuromuscular blocking agents and fast-tracking anaesthesia. PK has received lecture fees from Novartis Pharma Services Inc. and Shire Pharmaceuticals Group Plc. PMM is the scientific advisor for the Allergy to Neuromuscular Blocking Agents and Pholcodine Exposure study (NCT02250729) funded by a consortium of pharmaceutical companies: Zambon, Urgo, Pierre Fabre, Boots, Hepatoum, Biocodex, Sanofi, LBR, GSK, APL, Bell's Healthcare, Pinewood, T&R, and Ernest Jackson. All other authors confirm that they have no interests to disclose.

References

1. Wong A, Spillane A. Breast surgeons of Australia and New Zealand incorporated (BreastSurgANZ). Patent blue V dye anaphylaxis: experience of Australian and New Zealand surgeons. *ANZ J Surg* 2014; **84**: 37–41
2. Dewachter P, Mouton-Faivre C, Hepner DL. Peri-operative anaphylaxis: what should be known? *Curr Allergy Asthma Rep* 2015; **15**: 21
3. Royal College of Anaesthetists. *Peri-operative anaphylaxis. Anaesthesia, Surgery and life-threatening allergic reactions. Report and findings of the 6th national audit project, London* 2018. Available from, https://www.nationalauditprojects.org.uk/NAP6home. [Accessed 11 January 2019]
4. Société Française d'Anesthésie et de Réanimation. Reducing the risk of anaphylaxis during anaesthesia. Abbreviated text. *Ann Fr Anesth Reanim* 2002; **21**: 7–23
5. Kroigaard M, Garvey LH, Gillberg L, et al. Scandinavian clinical practice guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Anaesthesiol Scand* 2007; **51**: 655–70
6. Dewachter P, Mouton-Faivre C, Emala CW. Anaphylaxis and anesthesia: controversies and new insights. *Anesthesiology* 2009; **111**: 1141–50
7. Harper NJ, Dixon T, Dugue P, et al. Suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia* 2009; **64**: 199–211

8. Joint task force on practice parameters, American Academy of allergy, asthma and Immunology, American college of allergy, asthma and Immunology, joint council of allergy, asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010; **105**: 259–73
9. Reber LL, Hernandez JD, Galli SJ. The pathophysiology of anaphylaxis. *J Allergy Clin Immunol* 2017; **140**: 335–48
10. Wolbing F, Fischer J, Koberle M, Kaesler S, Biedermann T. About the role and underlying mechanisms of cofactors in anaphylaxis. *Allergy* 2013; **68**: 1085–92
11. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of peri-operative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
12. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the nomenclature review committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; **113**: 832–6
13. Brozek JL, Bousquet J, Agache I, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines—2016 revision. *J Allergy Clin Immunol* 2017; **140**: 950–8
14. Global Initiative for Asthma. *Global strategy for asthma management and prevention* 2018. https://www.ginasthma.org. [Accessed 11 January 2019]
15. Fisher MM, Ramakrishnan N, Doig G, Rose M, Baldo B. The investigation of bronchospasm during induction of anaesthesia. *Acta Anaesthesiol Scand* 2009; **53**: 1006–11
16. Liccardi G, Salzillo A, Piccolo A, De Napoli I, D'Amato G. The risk of bronchospasm in asthmatics undergoing general anaesthesia and/or intravascular administration of radiographic contrast media. Physiopatology and clinical/functional evaluation. *Eur Ann Allergy Clin Immunol* 2010; **42**: 167–73
17. Dewachter P, Mouton-Faivre C, Emala CW, Beloucif S. Case scenario: bronchospasm during anesthetic induction. *Anesthesiology* 2011; **114**: 1200–10
18. Woods BD, Sladen RN. Peri-operative considerations for the patient with asthma and bronchospasm. *Br J Anaesth* 2009; **103**: i57–65
19. Heitz JW, Bader SO. An evidence-based approach to medication preparation for the surgical patient at risk for latex allergy: is it time to stop being stopper poppers? *J Clin Anesth* 2010; **22**: 477–83
20. Mertes PM, Malinovsky JM, Jouffroy L, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2011; **21**: 442–53
21. De Queiroz M, Combet S, Berard J, et al. Latex allergy in children: modalities and prevention. *Paediatr Anaesth* 2009; **19**: 313–9
22. Kelly KJ, Wang ML, Klancnik M, Petsonk EL. Prevention of IgE sensitization to latex in health care workers after reduction of antigen exposures. *J Occup Environ Med* 2011; **53**: 934–40
23. Palosuo T, Antoniadou I, Gottrup F, Phillips P. Latex medical gloves: time for a reappraisal. *Int Arch Allergy Immunol* 2011; **156**: 234–46
24. Clark AT, Skypala I, Leech SC, et al. British Society for Allergy and Clinical Immunology guidelines for the management of egg allergy. *Clin Exp Allergy* 2010; **40**: 1116–29
25. Sicherer SH, Wood RA, Vickery BP, et al. The natural history of egg allergy in an observational cohort. *J Allergy Clin Immunol* 2014; **133**: 492–9
26. American Academy of Allergy Asthma and Immunology. Soy-allergic and egg-allergic patients can safely receive anesthesia. Available from https://www.aaaai.org/conditions-and-treatments/library/allergy-library/soy-egg-anesthesia (accessed 11 January 2019).
27. Burks AW, Tang M, Sicherer S, et al. ICON: food allergy. *J Allergy Clin Immunol* 2012; **129**: 906–20
28. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010; **126**: S1–58
29. Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. *J Allergy Clin Immunol* 2014; **133**: 291–307
30. Laxenaire MC, Gueant JL, Bermejo E, Mouton C, Navez MT. Anaphylactic shock due to propofol. *Lancet* 1988; **2**: 739–40
31. Laxenaire MC, Mata-Bermejo E, Moneret-Vautrin DA, Gueant JL. Life-threatening anaphylactoid reactions to propofol (Diprivan). *Anesthesiology* 1992; **77**: 275–80
32. de Leon-Casasola OA, Weiss A, Lema MJ. Anaphylaxis due to propofol. *Anesthesiology* 1992; **77**: 384–6
33. Koul A, Jain R, Sood J. A critical incident report: propofol triggered anaphylaxis. *Indian J Anaesth* 2011; **55**: 530–3
34. Asserhoj LL, Mosbech H, Kroigaard M, Garvey LH. No evidence for contraindications to the use of propofol in adults allergic to egg, soy or peanut. *Br J Anaesth* 2016; **116**: 77–82
35. Murphy A, Campbell DE, Baines D, Mehr S. Allergic reactions to propofol in egg-allergic children. *Anesth Analg* 2011; **113**: 140–4
36. Molina-Infante J, Arias A, Vara-Brenes D, et al. Propofol administration is safe in adult eosinophilic esophagitis patients sensitized to egg, soy, or peanut. *Allergy* 2014; **69**: 388–94
37. Dewachter P, Mouton-Faivre C, Castells MC, Hepner DL. Anesthesia in the patient with multiple drug allergies: are all allergies the same? *Curr Opin Anaesthesiol* 2011; **24**: 320–5
38. Lucendo AJ, Molina-Infante J, Arias A, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United Eur Gastroenterol J* 2017; **5**: 335–58
39. Mehta P, Sundaram SS, Furuta GT, Pan Z, Atkins D, Markowitz S. Propofol use in pediatric patients with food allergy and eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2017; **64**: 546–9
40. Harper NJ. Propofol and food allergy. *Br J Anaesth* 2016; **116**: 11–3
41. US Food and Drug Administration. Drugs@FDA: FDA approved drug products. Intralipid 20%. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020248 (accessed 11 January 2019).
42. Ruethers T, Taki AC, Johnston EB, et al. Seafood allergy: a comprehensive review of fish and shellfish allergens. *Mol Immunol* 2018; **100**: 28–57
43. Dewachter P, Laroche D, Mouton-Faivre C, et al. Immediate reactions following iodinated contrast media injection: a study of 38 cases. *Eur J Radiol* 2011; **77**: 495–501

44. Clément O, Dewachter P, Mouton-Faivre C, et al. Immediate hypersensitivity to contrast agents: the French 5-year CIRTACI study. *EClinicalMedicine* 2018; **1**: 51–61
45. Schrijvers R, Breynaert C, Ahmedali Y, Bourrain JL, Demoly P, Chiriac AM. Skin testing for suspected iodinated contrast media hypersensitivity. *J Allergy Clin Immunol Pract* 2018; **6**: 1246–54
46. Hasdenteufel F, Waton J, Cordebar V, et al. Delayed hypersensitivity reactions caused by iodixanol: an assessment of cross-reactivity in 22 patients. *J Allergy Clin Immunol* 2011; **128**: 1356–7
47. Torres MJ, Gomez F, Dona I, et al. Diagnostic evaluation of patients with nonimmediate cutaneous hypersensitivity reactions to iodinated contrast media. *Allergy* 2012; **67**: 929–35
48. Lopez Saez MP, de Barrio M, Zubeldia JM, Prieto A, Olalde S, Baeza ML. Acute IgE-mediated generalized urticaria-angioedema after topical application of povidone-iodine. *Allergol Immunopathol (Madr)* 1998; **26**: 23–6
49. Adachi A, Fukunaga A, Hayashi K, Kunisada M, Horikawa T. Anaphylaxis to polyvinylpyrrolidone after vaginal application of povidone-iodine. *Contact Dermat* 2003; **48**: 133–6
50. Le Pabic F, Sainte-Laudy J, Blanchard N, Moneret-Vautrin DA. First case of anaphylaxis to iodinated povidone. *Allergy* 2003; **58**: 826–7
51. Pedrosa C, Costa H, Oliveira G, Romariz J, Praca F. Anaphylaxis to povidone in a child. *Pediatr Allergy Immunol* 2005; **16**: 361–2
52. Caballero MR, Lukawska J, Dugue P. A hidden cause of peri-operative anaphylaxis. *J Investig Allergol Clin Immunol* 2010; **20**: 353–4
53. Gray PE, Katelaris CH, Lipson D. Recurrent anaphylaxis caused by topical povidone-iodine (Betadine). *J Paediatr Child Health* 2013; **49**: 506–7
54. Castelain F, Girardin P, Moumane L, Aubin F, Pelletier F. Anaphylactic reaction to povidone in a skin antiseptic. *Contact Dermat* 2016; **74**: 55–6
55. Moreno-Escobosa MC. Aanaphylactic shock due to povidone. *J Paediatr Child Health* 2017; **53**: 517
56. Dooms-Goossens A, Deveylder H, de Alam AG, Lachapelle JM, Tennstedt D, Degreef H. Contact sensitivity to nonoxynols as a cause of intolerance to antiseptic preparations. *J Am Acad Dermatol* 1989; **21**: 723–7
57. Levy JH, Adkinson Jr NF. Anaphylaxis during cardiac surgery: implications for clinicians. *Anesth Analg* 2008; **106**: 392–403
58. Levy JH, Bartz RR. Protamine, is something fishy about it? The spectre of anaphylaxis continues. *J Cardiothorac Vasc Anesth* 2019; **33**: 487–8
59. Levy JH, Schwieger IM, Zaidan JR, Faraj BA, Weintraub WS. Evaluation of patients at risk for protamine reactions. *J Thorac Cardiovasc Surg* 1989; **98**: 200–4
60. Vincent GM, Janowski M, Menlove R. Protamine allergy reactions during cardiac catheterization and cardiac surgery: risk in patients taking protamine-insulin preparations. *Cathet Cardiovasc Diagn* 1991; **23**: 164–8
61. Shokri H, Ali I, El Sayed HM. Protamine adverse reactions in NPH insulin treated diabetics undergoing coronary artery bypass grafting. *Egypt J Cardiothorac Anesth* 2016; **10**: 25–30
62. Valchanov K, Falter F, George S, et al. Three cases of anaphylaxis to protamine: management of anticoagulation reversal. *J Cardiothorac Vasc Anesth* 2019; **33**: 482–6
63. Wilson JM, Platts-Mills TAE. Meat allergy and allergens. *Mol Immunol* 2018; **100**: 107–12
64. O'Neil BH, Allen R, Spigel DR, et al. High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. *J Clin Oncol* 2007; **25**: 3644–8
65. Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med* 2008; **358**: 1109–17
66. Mullins RJ, James H, Platts-Mills TA, Commins S. Relationship between red meat allergy and sensitization to gelatin and galactose-alpha-1,3-galactose. *J Allergy Clin Immunol* 2012; **129**: 1334–42
67. Uyttebroek A, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Anaphylaxis to succinylated gelatin in a patient with a meat allergy: galactose-α(1,3)-galactose (α-gal) as antigenic determinant. *J Clin Anesth* 2014; **26**: 574–6
68. Mozzicato SM, Tripathi A, Posthumus JB, Platts-Mills TAE, Commins SP. Porcine or bovine valve replacement in 3 patients with IgE antibodies to the mammalian oligosaccharide galactose-α-1,3-galactose. *J Allergy Clin Immunol Pract* 2014; **2**: 637–8
69. Dunkman W, Rycek W, Manning MW. What does a red meat allergy have to do with anesthesia? Peri-operative management of alpha-gal syndrome. *Anesth Analg* May 25, 2018. https://doi.org/10.1213/ANE.0000000000003460. Access Published
70. Kleiman AM, Littlewood KE, Groves DS. Delayed anaphylaxis to mammalian meat following tick exposure and its impact on anesthetic management for cardiac surgery: a case report. *A A Case Rep* 2017; **8**: 175–7
71. Sell-Dottin KA, Sola M, Caranasos TG. Impact of newly emerging alpha-gal allergies on cardiac surgery: a case series. *Clin Surg* 2017; **2**: 1477
72. Kowalski ML, Agache I, Bavbek S, et al. Diagnosis and management of NSAID-exacerbated respiratory disease (N-ERD)—a EAACI position paper. *Allergy* 2019; **74**: 28–39
73. White AA, Stevenson DD. Aspirin-exacerbated respiratory disease. *N Engl J Med* 2018; **379**: 1060–70
74. Celiker V, Basgul E, Karakaya G, Oguzalp H, Bozkurt B, Kalyoncu AF. General anesthesia and postoperative pain management in analgesic intolerant patients with/without asthma: is it safe? *Allergol Immunopathol (Madr)* 2004; **32**: 64–8
75. Celiker V, Basgul E. Anaesthesia in aspirin-induced asthma. *Allergol Immunopathol (Madr)* 2003; **31**: 338–41
76. Ameratunga R, Randall N, Dalziel S, Anderson BJ. Samter's triad in childhood: a warning for those prescribing NSAIDs. *Paediatr Anaesth* 2013; **23**: 757–9
77. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol* 2014; **133**: 1270–7
78. Powell RJ, Leech SC, Till S, et al. BSACI guideline for the management of chronic urticaria and angioedema. *Clin Exp Allergy* 2015; **45**: 547–65
79. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy* 2018; **73**: 1393–414
80. Zuberbier T, Bernstein JA. A comparison of the United States and international perspective on chronic urticaria guidelines. *J Allergy Clin Immunol Pract* 2018; **6**: 1144–51
81. Sussman G, Abuzakouk M, Berard F, et al. Angioedema in chronic spontaneous urticaria is underdiagnosed and

has a substantial impact: analyses from ASSURE-CSU. *Allergy* 2018; **73**: 1724–34
82. Lancey RA, Schaefer OP, McCormick MJ. Coronary artery bypass grafting and aortic valve replacement with cold cardioplegia in a patient with cold-induced urticaria. *Ann Allergy Asthma Immunol* 2004; **92**: 273–5
83. Irani C, Gordon ND, Levinson AI. Normothermic cardioplegia in a patient with cold-induced urticaria. *J Allergy Clin Immunol* 2007; **120**: 722–3
84. Bakay C, Onan B, Onan IS, Ozkara A. Coronary artery bypass grafting in cold-induced urticaria. *Ann Thorac Surg* 2010; **89**: 949–51
85. Booth K, Parissis H. Management of cold-induced urticaria during cardiac surgery. *J Card Surg* 2011; **26**: 158–9
86. Ellis AK, Saha T, Arellano R, Zajac A, Payne DM. Successful management of cold-induced urticaria during hypothermic circulatory arrest. *Ann Thorac Surg* 2013; **96**: 1860–2
87. Fitzsimons MG, Vlahakes G, Makar R, et al. Deep hypothermic circulatory arrest in a patient with cold-induced urticaria. *Ann Thorac Surg* 2015; **100**: 722–3
88. Maddy EM, Schmoker JD, Tharp WG, Bender SP, Anderson EP, Martin JA. Deep hypothermic circulatory arrest in a patient with cold-induced urticaria. *J Cardiothorac Vasc Anesth* 2017; **31**: 1795–8
89. Arino P, Aguado L, Cortada V, Baltasar M, Puig MM. Cold urticaria associated with intraoperative hypotension and facial edema. *Anesthesiology* 1999; **90**: 907–9
90. Burbridge M. Dermographism: a rare cause of intraoperative hypotension and urticaria. *A A Case Rep* 2016; **7**: 41–3
91. Maciag MC, Nargozian C, Broyles AD. Intraoperative anaphylaxis secondary to systemic cooling in a pediatric patient with cold-induced urticaria. *J Allergy Clin Immunol Pract* 2018; **6**: 1394–5
92. Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001; **25**: 603–25
93. Onnes MC, Tanno LK, Elberink JN. Mast cell clonal disorders: classification, diagnosis and management. *Curr Treat Options Allergy* 2016; **3**: 453–64
94. Brockow K. Epidemiology, prognosis, and risk factors in mastocytosis. *Immunol Allergy Clin North Am* 2014; **34**: 283–95
95. Dewachter P, Castells MC, Hepner DL, Mouton-Faivre C. Peri-operative management of patients with mastocytosis. *Anesthesiology* 2014; **120**: 753–9
96. Bonadonna P, Pagani M, Aberer W, et al. Drug hypersensitivity in clonal mast cell disorders: ENDA/EAACI position paper. *Allergy* 2015; **70**: 755–63
97. Hermans MAW, Arends NJT, Gerth van Wijk R, et al. Management around invasive procedures in mastocytosis: an update. *Ann Allergy Asthma Immunol* 2017; **119**: 304–9
98. Matito A, Morgado JM, Sanchez-Lopez P, et al. Management of anesthesia in adult and pediatric mastocytosis: a study of the Spanish Network on Mastocytosis (REMA) based on 726 anesthetic procedures. *Int Arch Allergy Immunol* 2015; **167**: 47–56
99. Worobec AS, Akin C, Scott LM, Metcalfe DD. Mastocytosis complicating pregnancy. *Obstet Gynecol* 2000; **95**: 391–5
100. Ciach K, Niedoszytko M, Abacjew-Chmylko A, et al. Pregnancy and delivery in patients with mastocytosis treated at the Polish Center of the European Competence Network on Mastocytosis (ECNM). *PLoS One* 2016; **11**: e0146924
101. Carter MC, Uzzaman A, Scott LM, Metcalfe DD, Quezado Z. Pediatric mastocytosis: routine anesthetic management for a complex disease. *Anesth Analg* 2008; **107**: 422–7
102. Ahmad N, Evans P, Lloyd-Thomas AR. Anesthesia in children with mastocytosis—a case based review. *Paediatr Anaesth* 2009; **19**: 97–107
103. Borgeat A, Ruetsch YA. Anesthesia in a patient with malignant systemic mastocytosis using a total intravenous anesthetic technique. *Anesth Analg* 1998; **86**: 442–4
104. Vaughan ST, Jones GN. Systemic mastocytosis presenting as profound cardiovascular collapse during anaesthesia. *Anaesthesia* 1998; **53**: 804–7
105. Damodar S, John CN, Gopalakrishnan G, et al. Mast cell disease: surgical and anesthetic implications. *J Pediatr Hematol Oncol* 2006; **28**: 446–9
106. Russell WJ, Smith WB. Pseudoanaphylaxis. *Anaesth Intensive Care* 2006; **34**: 801–3
107. Villeneuve V, Kaufman I, Weeks S, Deschamps A. Anesthetic management of a labouring parturient with urticaria pigmentosa. *Can J Anaesth* 2006; **53**: 380–4
108. Konrad FM, Schroeder TH. Anaesthesia in patients with mastocytosis. *Acta Anaesthesiol Scand* 2009; **53**: 270–1
109. Renauld V, Goudet V, Mouton-Faivre C, Debaene B, Dewachter P. Case report: peri-operative immediate hypersensitivity involves not only allergy but also mastocytosis. *Can J Anaesth* 2011; **58**: 456–9
110. Bridgman DE, Clarke R, Sadleir PH, Stedmon JJ, Platt P. Systemic mastocytosis presenting as intraoperative anaphylaxis with atypical features: a report of two cases. *Anaesth Intensive Care* 2013; **41**: 116–21
111. Ulbrich F, Engelstadter H, Wittau N, Steinmann D. Anaesthetic management of emergency caesarean section in a parturient with systemic mastocytosis. *Int J Obstet Anesth* 2013; **22**: 243–6
112. Duggal N, Payne E, Engoren M. Aneurysm repair in a patient with systemic mastocytosis. *J Cardiothorac Vasc Anesth* 2015; **29**: 1025–8
113. Tew S, Taicher BM. Avoiding cardiovascular collapse: pediatric cutaneous mastocytosis and anesthetic challenges. *A A Case Rep* 2015; **5**: 179–81
114. Aloysi AS, Ahle GM, Geduldig E, Kellner CH, Bryson EO. General anesthesia in a patient with urticaria pigmentosa referred for electroconvulsive therapy. *J ECT* 2016; **32**: 204–6
115. Ten Hagen A, Doldersum P, van Raaij T. Anaphylactic shock during cement implantation of a total hip arthroplasty in a patient with underlying mastocytosis: case report of a rare intraoperative complication. *Patient Saf Surg* 2016; **10**: 25
116. Bryson EO, Aloysi AS, Farber KG, Kellner CH. General anesthesia for electroconvulsive therapy in a patient with systemic mastocytosis. *J ECT* 2017; **33**: e41–3
117. de la Fuente Tornero E, Vega Castro A, de Sierra Hernandez PA, et al. Kounis syndrome during anesthesia: presentation of indolent systemic mastocytosis: a case report. *A A Case Rep* 2017; **8**: 226–8
118. Richter EW, Hsu KL, Moll V. Successful management of a patient with possible mast cell activation syndrome undergoing pulmonary embolectomy: a case report. *A A Case Rep* 2017; **8**: 232–4
119. Unterbuchner C, Hierl M, Seyfried T, Metterlein T. Anaesthesia and orphan disease: rapid sequence induction in systemic mastocytosis. *Eur J Anaesthesiol* 2017; **34**: 176–8

120. Chatterjee M, Sengupta S, Chakravarty C, et al. Indolent systemic mastocytosis manifesting as protracted anaphylactic shock. *Indian J Crit Care Med* 2018; **22**: 311–3
121. Dewachter P, Mouton-Faivre C. Concurrent immunoglobulin E-mediated neuromuscular blocking agent allergy in systemic mastocytosis. *Ann Allergy Asthma Immunol* 2018; **120**: 663–4
122. Ishii K, Miyoshi H, Akiyama D, et al. Anesthetic management of patients with systemic mastocytosis. *J Clin Anesth* 2018; **50**: 61
123. Dewachter P, Mouton-Faivre C, Cazalaà JB, Carli P, Lortholary O, Hermine O. Mastocytosis and anaesthesia. *Ann Fr Anesth Reanim* 2009; **28**: 61–73
124. Zuraw BL, Bernstein JA, Lang DM, et al. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol* 2013; **131**: 1491–3
125. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—the 2017 revision and update. *Allergy* 2018; **73**: 1575–96
126. Zanichelli A, Azin GM, Wu MA, et al. Diagnosis, course, and management of angioedema in patients with acquired C1-inhibitor deficiency. *J Allergy Clin Immunol Pract* 2017; **5**: 1307–13
127. Betschel S, Badiou J, Binkley K, et al. Canadian hereditary angioedema guideline. *Allergy Asthma Clin Immunol* 2014; **10**: 50
128. Longhurst HJ, Tarzi MD, Ashworth F, et al. C1 inhibitor deficiency: 2014 United Kingdom consensus document. *Clin Exp Immunol* 2015; **180**: 475–83
129. Bork K, Hardt J, Staubach-Renz P, Witzke G. Risk of laryngeal edema and facial swellings after tooth extraction in patients with hereditary angioedema with and without prophylaxis with C1 inhibitor concentrate: a retrospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2011; **112**: 58–64
130. Aygören-Pürsün E, Martinez Saguer I, Kreuz W, Klingebiel T, Schwabe D. Risk of angioedema following invasive or surgical procedures in HAE type I and II—the natural history. *Allergy* 2013; **68**: 1034–9
131. MacBeth LS, Volcheck GW, Sprung J, Weingarten TN. Peri-operative course in patients with hereditary or acquired angioedema. *J Clin Anesth* 2016; **34**: 385–91
132. González-Quevedo T, Larco JI, Marcos C, et al. Management of pregnancy and delivery in patients with hereditary angioedema due to C1 inhibitor deficiency. *J Investig Allergol Clin Immunol* 2016; **26**: 161–7
133. Caballero T, Farkas H, Bouillet L, et al. International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. *J Allergy Clin Immunol* 2012; **129**: 308–20
134. Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis—a practice parameter update 2015. *Ann Allergy Asthma Immunol* 2015; **115**: 341–84
135. Kolawole H, Marshall SD, Crilly H, Kerridge R, Roessler P. Australian and New Zealand anaesthetic allergy group/Australian and New Zealand college of anaesthetists peri-operative anaphylaxis management guidelines. *Anaesth Intensive Care* 2017; **45**: 151–8
136. Laguna JJ, Archilla J, Dona I, et al. Practical guidelines for peri-operative hypersensitivity reactions. *J Investig Allergol Clin Immunol* 2018; **28**: 216–32
137. Scolaro RJ, Crilly HM, Maycock EJ, McAleer PT, Nicholls KA, Rose MA. Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) peri-operative anaphylaxis investigation guidelines. *Anaesth Intensive Care* 2017; **45**: 543–55
138. Sivagnanam S, Deleu D. Red man syndrome. *Crit Care* 2003; **7**: 119–20
139. Garvey LH. Peri-operative hypersensitivity reactions: diagnosis, treatment and evaluation. *Curr Treat Options Allergy* 2016; **3**: 113–28
140. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: diagnostic approach. *Allergy* 2007; **62**: 471–87
141. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs—an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013; **68**: 702–12
142. Thacker MA, Davis FM. Subsequent general anaesthesia in patients with a history of previous anaphylactoid/anaphylactic reaction to muscle relaxant. *Anaesth Intensive Care* 1999; **27**: 190–3
143. Ramirez LF, Pereira A, Chiriac AM, Bonnet-Boyer MC, Demoly P. Negative predictive value of skin tests to neuromuscular blocking agents. *Allergy* 2012; **67**: 439–41
144. Chiriac AM, Tacquard C, Fadhel NB, et al. Safety of subsequent general anaesthesia in patients allergic to neuromuscular blocking agents: value of allergy skin testing. *Br J Anaesth* 2018; **120**: 1437–40
145. Dewachter P, Chollet-Martin S, Mouton-Faivre C, de Chaisemartin L, Nicaise-Roland P. Comparison of basophil activation test and skin testing performances in NMBA allergy. *J Allergy Clin Immunol Pract* 2018; **6**: 1681–9
146. Miller J, Clough SB, Pollard RC, Misbah SA. Outcome of repeat anaesthesia after investigation for peri-operative anaphylaxis. *Br J Anaesth* 2018; **120**: 1195–201
147. Leysen J, Uyttebroek A, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Predictive value of allergy tests for neuromuscular blocking agents: tackling an unmet need. *Clin Exp Allergy* 2014; **44**: 1069–75
148. Fisher MM, Merefield D, Baldo B. Failure to prevent an anaphylactic reaction to a second neuromuscular blocking drug during anaesthesia. *Br J Anaesth* 1999; **82**: 770–3
149. Fraser BA, Smart JA. Anaphylaxis to cisatracurium following negative skin testing. *Anaesth Intensive Care* 2005; **33**: 816–9

Handling editor: J.G. Hardman

BJA

British Journal of Anaesthesia, 123 (1): e82–e94 (2019)

doi: 10.1016/j.bja.2019.01.026
Advance Access Publication Date: 11 March 2019
Special Article

Management of a surgical patient with a label of penicillin allergy: narrative review and consensus recommendations

L. C. Savic[1,*,#,†], D. A. Khan[2,#,†], P. Kopac[3,#,†], R. C. Clarke[4,5,†], P. J. Cooke[6,†], P. Dewachter[7,8,†], D. G. Ebo[9,†], T. Garcez[10,†], L. H. Garvey[11,12,†], A. B. Guttormsen[13,14,†], P. M. Hopkins[1,15,†], D. L. Hepner[16,†], H. Kolawole[17,18,†], M. Krøigaard[11,†], J. J. Laguna[19,†], S. D. Marshall[17,18,†], P. M. Mertes[20,†], P. R. Platt[4,5,†], M. A. Rose[21,†], V. Sabato[9,†], P. H. M. Sadleir[4,5,22,†], S. Savic[23,†], T. Takazawa[24,†], S. Voltolini[25,†] and G. W. Volcheck[26,#,†]

[1]Anaesthetic Department, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [2]Department of Internal Medicine, Division of Allergy & Immunology, University of Texas Southwestern Medical Center, Dallas, TX, USA, [3]University Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia, [4]Department of Anaesthesia, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia, [5]Anaesthetic Allergy Referral Centre of Western Australia, Nedlands, Western Australia, Australia, [6]Department of Anaesthesia and Perioperative Medicine, Auckland City Hospital, Auckland, New Zealand, [7]Service d'Anesthésie-Réanimation, Groupe Hospitalier de Paris-Seine-Saint-Denis, Assistance Publique-Hôpitaux de Paris, Paris, France, [8]Université Paris 13, Sorbonne-Paris-Cité, Paris, France, [9]Department of Immunology, Allergology and Rheumatology, University of Antwerp, Antwerp University Hospital, Belgium, [10]Department of Immunology, Manchester University NHS Foundation Trust, Manchester, United Kingdom, [11]Danish Anaesthesia Allergy Centre, Allergy Clinic, Department of Dermatology and Allergy, Copenhagen University Hospital, Gentofte, Denmark, [12]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, [13]Department of Anaesthesia and Intensive Care, Haukeland University Hospital, Bergen, Norway, [14]Department of Clinical Medicine, University of Bergen, Bergen, Norway, [15]Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK, [16]Department of Anesthesiology, Brigham and Women's Hospital, Boston, MA, USA, [17]Department of Anaesthesia and Perioperative Medicine, Monash University, Melbourne, Australia, [18]Department of Anaesthesia, Peninsula Health, Melbourne, Australia, [19]Allergy Unit, Allergo-Anaesthesia Unit, Hospital Central de la Cruz Roja, Faculty of Medicine, Alfonso X El Sabio University, ARADyAL, Madrid, Spain, [20]Department of Anesthesia and Intensive Care, Hôpitaux Universitaires de Strasbourg, Nouvel Hôpital Civil, Strasbourg, France, [21]Department of Anaesthesia, Royal North Shore Hospital, and University of Sydney, Sydney, NSW, Australia, [22]Department of Pharmacology, University of Western Australia, Crawley, Western Australia, Australia, [23]Department of

Editorial decision date: 09 January 2019; **Accepted:** 9 January 2019

Clinical Immunology and Allergy, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [24]Intensive Care Unit, Gunma University Hospital, Maebashi, Gunma, Japan, [25]Allergy Unit, Policlinic Hospital San Martino, Genoa, Italy and [26]Division of Allergic Diseases, Mayo Clinic College of Medicine, Rochester, MN, USA

*Corresponding author. E-mail: louise.savic@nhs.net

#These authors contributed equally.
†The authors are members of the ISPAR (International Suspected Perioperative Allergic Reaction) Group.

Summary

Unsubstantiated penicillin-allergy labels are common in surgical patients, and can lead to significant harm through avoidance of best first-line prophylaxis of surgical site infections and increased infection with resistant bacterial strains. Up to 98% of penicillin-allergy labels are incorrect when tested. Because of the scarcity of trained allergists in all healthcare systems, only a minority of surgical patients have the opportunity to undergo testing and de-labelling before surgery. Testing pathways can be modified and shortened in selected patients. A variety of healthcare professionals can, with appropriate training and in collaboration with allergists, provide testing for selected patients. We review how patients might be assessed, the appropriate testing strategies that can be used, and the minimum standards of safe testing.

Keywords: allergy; drug provocation testing; penicillin; prophylaxis; surgery; surgical site infection

The recommendations developed in this article concern the management of surgical patients with a label of penicillin allergy. We aimed to provide a practical guide for anaesthetists and other healthcare professionals in the perioperative setting.

To provide context, a literature search was performed to examine the existing evidence and current practices. The search was initially performed in June 2018 and repeated in September 2018, using the following criteria: English language only; humans; last 10 yrs; PubMed search engine; MESH key words: penicillin allergy (yields 904 articles), AND testing, de-labelling, AND health costs, implications, health benefits, AND pre-operative patients, surgical patients, surgery, AND testing strategies. A 10 yr limit was set on the basis that much of the work informing these guidelines has arisen in this period of time. A total of 301 articles were selected; 93 were deemed relevant after a review by the writing group. Additional articles were included on the basis of relevance, including some from more than 10 yr ago where these were judged to be of seminal importance.

Epidemiology of a penicillin-allergy label

Penicillin is the most common drug allergy recorded in medical records, with a prevalence ranging from 6 to 15% in recent large studies throughout the world.[1–4] Whilst frequently listed in the medical record, the incidence of confirmed penicillin allergy is much lower and appears to be decreasing. Longitudinal studies from a large health plan in the USA found the rate of positive penicillin skin tests to have decreased from 15% in 1995 to 3% in 2007.[5] In 2013, the same group reported that only 1.6% of penicillin-allergy histories from 500 patients could be confirmed.[6] A work in France has demonstrated a higher rate of immediate (immunoglobulin E [IgE]-mediated) penicillin allergy, although testing was only performed in those with a history already suggestive of an allergic reaction, rather than an unselected group of all patients with the label.[7]

Recent large studies from other countries have confirmed low rates (5–6%) of confirmed penicillin allergy in both children and adults.[8,9]

Nevertheless, penicillin remains a leading cause of drug-induced hypersensitivity and anaphylaxis. A recent US study of a large electronic health record database of more than 1.7 million patients determined that 1.1% reported drug-induced anaphylaxis, with the most common culprit being penicillin.[10] Cases collected by the French Allergy Vigilance Network between 2010 and 2012 determined that penicillins (especially amoxicillin) were the most commonly identified cause of severe drug-induced anaphylaxis.[11] Amongst fatal drug-induced anaphylaxis, penicillin was the most commonly identified culprit drug in a recent US study,[12] and a recent study of suspected perioperative anaphylaxis in the UK found that antibiotics were the commonest cause of life-threatening anaphylaxis, with amoxicillin clavulanate (co-amoxiclav) the most frequently causal agent.[13] Aside from anaphylaxis, penicillins may more rarely cause severe cutaneous adverse reactions, such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These severe blistering skin conditions can result in organ failure and be fatal.

Evidence of harm from the label

Over the past 10 yr, the clinical and economic ramifications of the 'penicillin allergy' label have been well defined. These include infection and antimicrobial resistance, hospital readmission rates, length of hospital stay, use of critical care beds, and healthcare costs. For surgical patients, postoperative surgical site infections (SSIs) are major contributors to patient morbidity and mortality, and therefore, costs. Antibiotic prophylaxis is a key strategy to prevent SSI, with beta-lactam antibiotics the preferred antibiotic for many procedures.[14] Several studies have assessed SSI in patients labelled as penicillin allergic. A retrospective cohort study of 8385 patients undergoing 9094 procedures showed that 11% reported

penicillin allergy, and those with the label had 50% increased odds of SSI attributable to the use of second-line antibiotics.[15] In approximately 250 patients undergoing head and neck surgery, clindamycin was substituted for a cephalosporin in those labelled penicillin allergic, and this was associated with a four-fold increase in SSI.[16] In a retrospective study of 18 830 elective primary arthroplasties, the use of vancomycin as a sole agent was associated with more SSIs than prophylaxis with cefazolin as a sole agent; penicillin-allergy labels accounted for 54% of the vancomycin group.[17] However, increased SSI was not demonstrated in another study, where arthroplasty patients received vancomycin alone attributable to the penicillin-allergy label, compared with those receiving cefazolin.[18]

Given the use of beta-lactam alternative antibiotics in those labelled penicillin allergic, the focus has turned to associated infection, particularly methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* infection. In a large population-based cohort study from the UK of more than 300 000 adults, those labelled with penicillin allergy were compared with matched controls[19]; penicillin allergy was associated with an increased risk of MRSA (hazard ratio: 1.69) and *C. difficile* (hazard ratio: 1.26). Increased use of beta-lactam alternatives accounted for 55% of the increased risk of MSRA and 35% of the increased risk of *C. difficile*. In a large cohort US study of more than 50 000 inpatients, those labelled penicillin allergic were treated with significantly more fluoroquinolones, clindamycin, and vancomycin compared with control subjects, and had 23.4% more *C. difficile*, 14.1% more MRSA, and 30.1% more vancomycin-resistant enterococcus infections.[4] In addition, penicillin-allergy-labelled patients averaged 0.59 more hospital days during an average of 20 months of follow-up compared with control patients.

The effect of a penicillin-allergy label on hospital readmissions has also been quantified. In a West Australian adult tertiary hospital, more than 600 patients were surveyed, with 18% labelled penicillin allergic. Those with the label had significantly more hospital readmissions within 4 weeks and 6 months of discharge compared with controls; the majority of readmitted patients had major infections.[20] In a large prospective matched cohort study from a Dutch university medical centre of more than 17 000 patients, of whom 5.6% were labelled penicillin allergic, the penicillin allergic group had a significantly higher risk of being re-hospitalised at 12 weeks (27% *vs* 22%), although there was no significant difference at 4 weeks between the groups.[3]

Current guidelines for penicillin-allergy testing and their limitations

In most countries, testing for penicillin allergy is performed predominantly under the supervision of allergy specialists and, typically, when there is a need for penicillin-based therapy. Given the morbidity associated with a spurious label of penicillin allergy and the low likelihood of a label of penicillin allergy being correct, it has now been recommended to perform such testing routinely in labelled patients, regardless of acute need.[21]

Standard testing guidelines

The gold standard test with which to establish tolerance to penicillin is a graded drug provocation test (DPT) using the index penicillin to which the patient reacted. Current guidelines from Europe and North America recommend that patients should first be skin tested using skin prick tests (SPTs) and intradermal tests (IDTs).[22–26] In the context of a patient who has had a clinical reaction, a positive skin test, with readings taken immediately, can identify the presence of IgE sensitisation. The skin test, therefore, provides a way of risk stratifying patients for a DPT. Skin tests for penicillin have a negative predictive value approaching 100%, and patients who do not react to SPT or IDT are therefore unlikely to have a severe immediate reaction on the DPT.[26,27] However, the interpretation of a positive skin test is less well defined, as these patients are not offered a DPT for obvious ethical reasons. The positive predictive value is generally accepted to be <50% based on limited numbers of prospective studies and outcomes from accidental re-exposure.[28–30] It is important to note that delayed readings are required for the diagnostic work-up of non-immediate type i.v. hypersensitivity reactions, although the predictive value of these readings is not well established and their utility may be lower.[22] Any subsequent DPT may also demonstrate delayed reactions such as these.

The panel of reagents used for skin testing varies geographically. In particular, the experience of using minor determinant mixtures (MDMs) and benzylpenicilloyl poly-L-lysine (PPL) is mixed, not least, because for many years in the USA, these reagents were not commercially available. The utility of PPL/MDM is best defined for immediate-type hypersensitivity reactions to penicillin, where the addition of each reagent increases the sensitivity of testing by 15% and 47%, respectively.[31,32] In Southern Europe, with its greater use of amoxicillin, the value of adding this drug to the skin-test panel has been well documented.[33] The British Society for Allergy and Clinical Immunology recommends that patients are tested against PPL, MDM, amoxicillin, and the index penicillin if known (and different), and penicillin G (benzylpenicillin) if this is not contained in the PPL/MDM reagent kits.[22]

There are some important limitations to the utility of skin tests. Many studies have commented on reduced sensitivity over time in the diagnosis of immediate reactions,[5,34,35] and low sensitivity and specificity in patients with non-severe, non-immediate, and vague reactions.[36–38] Reactions in childhood, typically delayed onset, and unspecified rashes can result in lifelong unnecessary avoidance of penicillin, and yet are only rarely associated with positive skin or DPT testing.[39]

Another testing modality that can be used is the serum-specific IgE assay. Although the sensitivity and specificity of this test are low, it is recommended by European guidelines. There have been cases where skin testing was negative but serum-specific IgE positive, and the patient went on to have anaphylaxis when exposed to the drug.[25] Its use as a sole test is not recommended.

The cost of performing a standard penicillin-allergy evaluation varies according to multiple local factors. A study in the USA examined the cost of testing using time-driven activity-based costing, which measures cost through calculation of time spent using a given resource and the per unit cost of the resource. They found that base-case penicillin-allergy evaluation costs $220 (2016), with a range of $40–537.[40] The skin testing component of testing is typically the most expensive, requiring highly trained personnel and relatively expensive consumables.

Direct penicillin challenge in low-risk patients

Where symptoms are mild and not suggestive of an IgE-mediated reaction, the utility of skin tests is low and a direct oral DPT may be appropriate. Although a recent work has shown that the risk of true allergy cannot be predicted with high sensitivity and specificity on the basis of clinical history alone,[41] a growing body of evidence suggests that the clinical history can nevertheless be used to risk stratify patients for a direct DPT. In a US study, 328 young military recruits with non-severe histories of penicillin allergy underwent a direct amoxicillin DPT with only 1.5% having objective reactions, none of which were life-threatening anaphylaxis.[42] An Israeli study of 642 patients (two-thirds were children and some had reactions not suggestive of true allergy) with delayed reactions (>1 h after the last dose) underwent skin testing and a 5 day amoxicillin DPT even if skin tests were positive, with only 6% displaying mild reactions and no cases of anaphylaxis.[43] Almost one-third of patients had equivocal skin tests and 5% had positive skin tests, yet the majority tolerated the DPT. It is worth noting that immediate readings of skin tests were used even though the index reactions were in keeping with delayed hypersensitivity. In a prospective study from Canada, 818 children underwent an amoxicillin DPT without skin testing, with 94% tolerating amoxicillin.[8] The immediate reactions were all mild, although a few developed serum-sickness-like reactions, as this was not an exclusion criterion. Of 17 children with immediate reactions to the DPT, only one (5.9%) had a positive penicillin skin test 2–3 months later. A prospective study from Spain evaluated 766 children with histories of penicillin allergy who underwent skin testing and DPT (regardless of skin-test results), and found around 5% to be allergic.[9] Penicillin-allergy skin tests had very low sensitivity (2.9% had positive immediate skin tests), but had good specificity. A study of 155 adults and children, with non-severe histories of penicillin allergy and who underwent placebo-controlled amoxicillin DPTs without skin testing in an allergy clinic, found 2.6% with true allergic reactions and 10% reacting to placebo.[44]

The primary advantage of this approach is that the lack of need for skin testing reduces time and cost. A direct DPT is also quick and non-invasive, which is more convenient for patients. There are disadvantages, however. Firstly, the data appear to be strongest in children; secondly, it is not yet known whether non-allergists will be able to adopt this approach with the safety and outcomes seen in studies to date. Finally, there is also no clear consensus on which patients can be considered low risk and forgo skin testing, although several groups have proposed criteria for this.[45]

Advice for de-labelled patients

Patients evaluated with skin tests, DPT, or both, and found not to be sensitised to penicillin should be advised that they have the same risk as the general population for developing new allergy to penicillin in the future. This statement acknowledges that any individual may become sensitised to penicillin during their lifetime and that negative testing is not a lifelong guarantee of tolerance. It must also be recognised, however, that a DPT for a single penicillin does not entirely preclude allergy to all other penicillins because of side-chain sensitivity, which might be missed with a single-drug DPT. For example, a patient whose index reaction was to flucloxacillin, but who does not remember this and has a negative DPT with amoxicillin remains at risk from re-exposure to flucloxacillin. However, this does not appear to be a significant problem given the lack of reports in the literature of this occurring, and current guidelines do not recommend multiple DPTs in cases where the index penicillin is not known.

Finally, the risk of re-sensitisation must be considered for any patient undergoing a DPT. This risk appears to be lower than initially reported in the USA, however, with the results of recent studies suggesting that repeating skin tests after an oral DPT in order to check for re-sensitisation is unnecessary.[46] Patients who have been tested and de-labelled should instead be monitored clinically for evidence of re-sensitisation. Repeating the skin tests may be of use in patients with confirmed severe reactions as a means of periodically reassessing whether the patient remains sensitised, but this is less the case in those with initial histories not suggestive of allergy.[24]

Novel testing strategies and pathways

As the impact of the 'penicillin allergic' label on antimicrobial stewardship and health costs becomes clearer, the need to find ways of reducing the burden of incorrect labels has become imperative. A key part of the problem is poor understanding of allergy amongst non-specialists (and patients) leading to incorrect labelling, and limited knowledge of the services available for allergy testing,[47,48] although there is evidence that knowledge can be improved through training.[49] These aspects are beyond the scope of this article.

Different strategies around the world have been used to address the expanding and unmet need for allergy testing; some of these are detailed next.

Inpatient-based penicillin skin testing programmes

Large numbers of hospitalised patients are treated with antibiotics, often requiring prolonged courses and including broad-spectrum antibiotics. The inpatient setting is therefore ideal for penicillin-allergy testing, and numerous studies have demonstrated the improved use of antibiotics after penicillin skin tests. Of ~1000 patients with self-reported penicillin allergy, same-day penicillin skin testing and consultation reduced the vancomycin use from 30% in historical controls to 16% in those judiciously evaluated.[50] In an ICU setting, a prospective study of 96 patients labelled as penicillin allergic were skin tested[51]; of the group receiving therapeutic antimicrobials, 82% were changed to a beta-lactam after a negative skin test with no adverse events. Long-term follow-up of 308 subjects evaluated with skin tests and matched with 1251 unique controls (labelled penicillin allergic; not evaluated) found that those tested received significantly more penicillins and first- and second-generation cephalosporins than controls, with less clindamycin and macrolides. Those evaluated also had fewer outpatient and emergency department visits, and 0.553 less hospital days per year than the controls. The authors estimated that testing 308 of the controls may have saved the health system more than $2 million over 3.6 yr.[52]

A recent systematic review described several studies, including six in the intensive care setting.[53] Penicillin skin tests were negative in 95% of patients overall, and increased use of penicillins and cephalosporins was noted, with rare reports of life-threatening anaphylaxis after amoxicillin challenge at an incidence of <1%. The largest reported inpatient experience is from the USA and utilises allergy-trained pharmacists to perform penicillin skin tests and amoxicillin

challenge.[54] To date, 98% of more than 700 penicillin allergic inpatients have been found to test negative (D. Khan, personal communication). Another large US study of inpatient penicillin-allergy skin testing (with 90% performed by a nurse) found a much higher rate (20%) of positive skin tests, but utilised minor determinant skin tests with different criteria for a positive skin test.[55] Another study utilised telemedicine to reduce the need for on-site allergy specialists, with skin testing performed by physician assistants.[56] Some studies have performed penicillin-allergy testing in the emergency department; however, higher than typical rates of positive skin tests (15.5%) might suggest that the 30 min training session for testers was inadequate.[57] The benefits of testing as an inpatient include a readily accessible high-risk population and immediate impact on antimicrobial stewardship outcomes. The main drawback to this approach is a lack of trained providers who can perform skin tests and allergists who can assist with setting up such programmes.

Clinical algorithms to guide the use of beta-lactams in penicillin allergy

An alternative approach to encourage a more appropriate use of antibiotics is through the use of clinical guidelines, which provide advice on the use of beta-lactams based on the history of the penicillin allergy. A recent study in the UK demonstrated proof of concept for guideline-based selection of patients suitable for a direct DPT using an algorithm suitable for use by non-specialists.[45] The use of guidelines such as these in an inpatient setting has demonstrated an increased use of beta-lactams (primarily cephalosporins) and a reduction in the use of vancomycin, aztreonam, and fluoroquinolones.[58,59] A study comparing usual care, penicillin skin tests, and a clinical guideline with additional web-based clinical decision support found that both penicillin skin testing and the guideline led to an increased use of penicillins or cephalosporins, although not penicillins alone.[60] The methodology for implementing this type of approach at a hospital level has been published.[61] The benefits are that guidelines can potentially be used to change antibiotic prescribing patterns in penicillin allergic patients without the need for additional personnel. Drawbacks to this approach are that a primary effect is to increase the use of cephalosporins in penicillin allergic patients,[62] a practice that may already be commonplace in some hospitals[63] and, which when used alone, typically does not allow de-labelling of the penicillin allergy.

Preoperative penicillin-allergy testing

Patients with a history of penicillin allergy often receive vancomycin for surgery. In the UK, the commonest alternative is now teicoplanin. Aside from the risks of increased SSI, longer hospital stay, and higher readmissions, there is also the risk of allergy to the alternative antibiotic used.[13] In order to reduce the use of alternatives in the perioperative setting, penicillin-allergy tests can be performed before surgery. The surgical population represents a large pool of accessible patients with an immediate need for good antibiotic stewardship. A recent UK study demonstrated that penicillin-allergy testing can be incorporated into the preoperative journey for a patient with a subsequent improved use of SSI prophylaxis.[64] The largest experience with preoperative testing comes from the Mayo Clinic in the USA, where a preoperative evaluation clinic was established in 2001.[50] To date, this programme has performed >29 000 penicillin-allergy tests with only 1% being positive (M. Park, personal communication). Recent studies have used electronic best practice alerts to identify patients with penicillin allergy who are scheduled for orthopaedic surgery and to facilitate referral to a specialised clinic for penicillin-allergy testing.[65] The benefit of a preoperative testing approach is that patients are de-labelled at the time of antibiotic need. Drawbacks are the requirement for personnel to perform the tests and the time pressures associated with surgery.

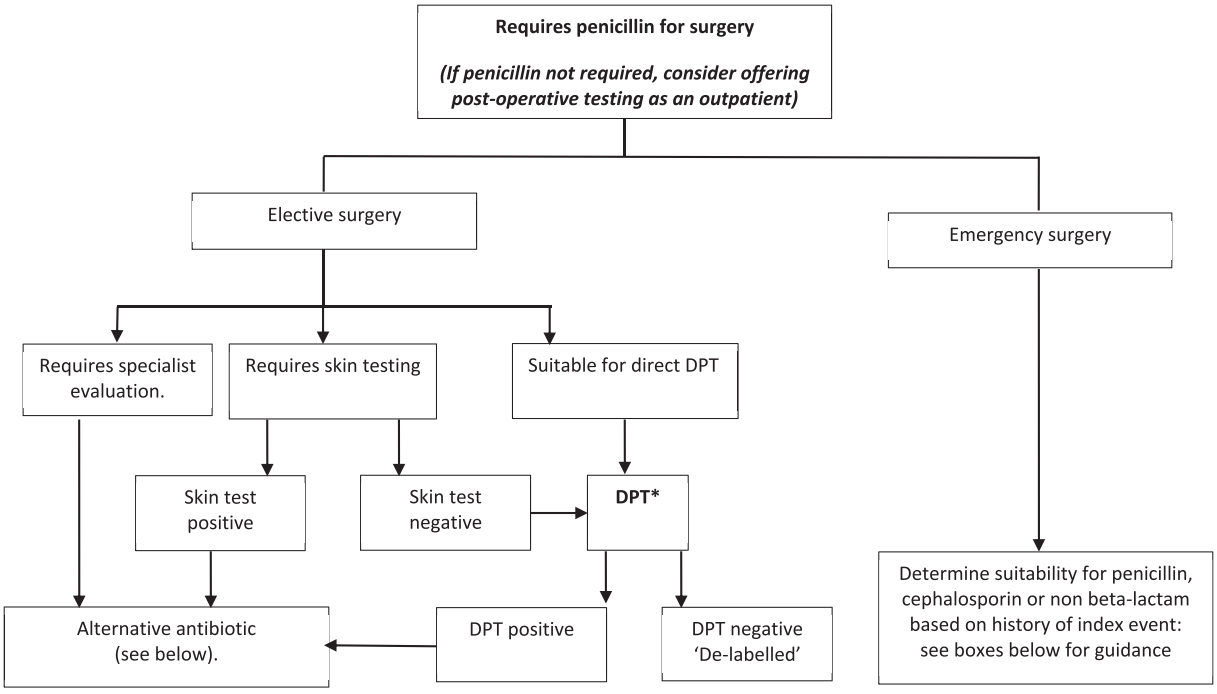
Use of alternative beta-lactam antibiotics in penicillin-allergic patients

Alternative beta-lactams include the cephalosporins, carbapenems, and monobactams, of which cephalosporins appear to be the most relevant. Carbapenem cross-reactivity with either penicillins or cephalosporins appears to be very low.[66–68] There is no apparent cross-reactivity between monobactams and penicillins,[68] although there may be between ceftazidime and aztreonam, partly because they share an R1 side chain.[69] The earliest studies of penicillin and cephalosporin cross-reactivity from the 1970s were tainted by the presence of trace amounts of benzylpenicillin in the cephalosporins, falsely increasing the apparent degree of cross-reactivity. The figure of 10% cross-reactivity stems from this work and is still quoted in the US Food and Drug Administration descriptions of the cephalosporins.

The true incidence of cross-reactivity between penicillins and cephalosporins, and between different cephalosporins, is likely to be lower, but has been difficult to quantify or predict. Partly, this is because of differences in study methodology; this is compounded by the rarity of allergy to cephalosporins. The incidence of anaphylaxis to cephalosporins is estimated at 0.00002% and 0.00016% for oral and parenteral administration, respectively.[70] This is at least one order of magnitude less frequent than anaphylaxis to penicillin, which is about 0.005% and 0.002% with oral and parenteral administration, respectively.[71]

Variation in the degree of cross-reactivity between penicillin and cephalosporins is determined by structural differences amongst cephalosporins. All share with penicillin a four-membered beta-lactam ring, which is adjacent to a five-membered thiazolidine ring or a six-membered dihydrothiazine ring in cephalosporins. The penicillins and cephalosporins undergo different beta-lactam ring degradation patterns; breakdown of the penicillin beta-lactam ring results in the formation of haptens capable of allergenicity, whereas the cephalosporins undergo rapid breakdown that does not predictably produce haptens. Therefore, cross-reactivity between the penicillins and cephalosporins has focused on the R1 and R2 side-chain moieties that vary between the generations of cephalosporins, with side-chain similarity likely to contribute to cross-reactivity. Of note, cephazolin, used perioperatively in many parts of the world, does not have similar R1 or R2 side chains to either penicillins or other cephalosporins except for ceftezole. Cephazolin also offers superior Gram-positive antimicrobial activity compared with cephalosporins of later generations, and has been shown after testing not to cross-react with a number of other cephalosporins from all generations.[72,73] Thus, despite being a first-generation cephalosporin, it may be an option for a penicillin-allergic patient. It is worth noting that the R1 and R2 side chains are not always the antigenic determinant, and cross-reactivity may still exist.[74]

Studies on cephalosporin allergy can be broadly divided into two groups: large observational studies and smaller



*Drug provocation test (DPT), using index penicillin if known, otherwise the most commonly used penicillin in that country. Absolute contra-indications to DPT include history of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome Stevens-Johnson syndrome (SJS), or toxic epidermal necrolysis (TEN) and other severe cutaneous reactions, severe ischaemic heart disease, pregnancy

Patients suitable for direct DPT:
Initial reaction consisted of:

-GI disturbance only
- Thrush;
-Family history only;
-Minor, non-specific, non-allergic symptoms (e.g. headache)
-Benign rash >10 years ago (non-itchy, non-blistering, >1 hour after first dose;
-Uncertain history but has since taken penicillin with no reaction.

Patients requiring skin test prior to consideration for DPT:
Initial reaction consisted of:

-Rash, with no further details
-Urticarial rash
-Uncertain history but told reaction was severe requiring treatment.

Patients requiring specialist evalution:
Initial reaction consisted of:

-History of severe immediate systemic reaction with any of the following: wheeze, dyspnoea, collapse, angioedema, swelling, loss of consciousness.
-Patients with a history of severe and/or blistering rash or confirmed diagnosis DRESS, SJS, TENS

Advice on selection of alternative antibiotics
1. Confirmed penicillin allergy:
-Skin test (ST) to establish tolerance to other beta-lactams, followed by DPT
2. Unconfirmed penicillin allergy:
-History suitable for initial DPT: give penicillin (or any cephalosporin if patient refuses penicillin)
-History suitable for initial ST (+/- DPT): give cephalosporin with different R1 and R2 side chain if index penicillin not known, consider using cephazolin if available **and after advice from local allergist**; otherwise avoid all beta-lactams
-History not suitable for testing: avoid all beta-lactams

Fig 1. Flow chart for management of a surgical patient with a label of penicillin allergy.

studies with well-documented IgE-mediated hypersensitivity to penicillins undergoing evaluation with cephalosporins. A weakness of the large observational studies is the inclusion of self-labelled penicillin-allergic patients. As the vast majority of patients labelled penicillin allergic in medical charts and electronic medical records are not truly penicillin allergic, these studies automatically underestimate true penicillin cross-reactivity with cephalosporins. In addition, selection

bias would potentially exist in these studies, as clinicians would be unlikely to prescribe cephalosporins to a patient with a severe reaction to penicillin. In a compilation of eight observational studies, the range of cross-reactivity was 0–8%.[75–77] In a meta-analysis of cross-reactivity between penicillin and cephalosporin allergy that included nine studies of patients with reported history of penicillin allergy, the odds ratio of an allergic reaction to any cephalosporin was lower than that to first-generation cephalosporins,[74] emphasising the importance of cephalosporin structure, with higher cross-reactivity amongst the first-generation cephalosporins and minimal cross-reactivity with second and third generations.

The largest prospective study assessing penicillin and cephalosporin cross-reactivity included 252 subjects who experienced 319 immediate reactions to penicillins and had positive skin tests to at least one penicillin reagent.[78] Of the 39% with positive allergy tests to cephalosporins, 96% of these were to the amino-cephalosporins or cefamandole. This study demonstrated that skin testing, although helpful, does not always detect sensitivity to cephalosporins with similar side chains. However, DPT to cephalosporins with different side-chain determinants to penicillin (and negative skin tests) was tolerated. Further evidence that side-chain analysis alone without testing (both skin tests and DPT) is not 100% predictive in ruling out cross-reactivity was seen in a study with cefuroxime, where 2.9% cefuroxime sensitivity was seen in 69 patients with prior histories involving penicillin sensitivity only, despite dissimilar side chains.[79] It is worth noting that cross-reactivity was calculated only when the specific penicillin was known and patients with positive skin tests did not undergo a DPT; the rate of cross-reactivity may therefore be an overestimate.

In general, the risk of a reaction to a cephalosporin is higher in those with true penicillin allergy, and is estimated to be 2–5%.[77] When confronted with the rare patient with a genuine penicillin allergy who requires a cephalosporin, sensitivity to a cephalosporin with dissimilar R1 and R2 side chains should be explored with skin tests and a graded DPT if this is negative. The significance of positive skin testing in this context remains poorly understood. Two recent comprehensive overviews of side-chain cross-reactivity, including useful tables detailing this, are available.[62,80]

Consensus recommendations for management of surgical patients with a label of penicillin allergy

These recommendations are based on the results of a Delphi consensus process and were developed with reference to the Appraisal of Guidelines for Research & Evaluation 2 checklist.[81] All members of the writing group are experienced in this field and have published work in this area. A total of four rounds of questionnaires were completed, with 18–23 members participating in each round. Questions were amended or removed at each stage depending on the degree of consensus, and modified according to comments received from the group. Each statement was rated for appropriateness on a scale of 1 (completely inappropriate) to 9 (completely appropriate). The median score for each statement was calculated and used to rate each statement as appropriate (median score: 7–9), uncertain (3.5–6.9), or inappropriate (1–3.4). The disagreement index (DI) was used to determine the degree of consensus for each statement, with consensus defined as a DI<0.5; this approach is adapted from Fitch and colleagues.[82] For a full list of all statements where a consensus was reached and some of the key areas where it was not reached, see Supplementary Appendix 1.

For the purposes of these recommendations, the term *allergist* has been used to describe a medical professional whose primary specialisation is in allergy, or who trained in allergy as part of his/her specialty. It is accepted that the nomenclatures for the specialties of immunology and allergy vary across the world.

Defining the most appropriate testing strategy for an individual labelled as penicillin allergic

Risk stratification is a key aspect of investigating patients with a label of penicillin allergy. As discussed in earlier sections, there is no accepted consensus in the literature on how to define risk or group patients into different levels of risk. It is easiest to define those who lie at either end of the spectrum; for example, patients reporting thrush with penicillin use are easily defined as low (or indeed 'no') risk above the risk of penicillin allergy in the general population; patients who give a clear history of anaphylaxis or severe cutaneous reactions are easily categorised as being at high risk. Between these, however, fall myriad intermediate reactions that are harder to categorise, including the very common history of 'no recollection of the event'.

Initial rounds attempted to define risk groupings into no, low, medium, and high compared with risk in the general population. However, it proved difficult to reach a consensus on what constituted 'low risk' and how this group should be approached. Ultimately, it is probably more useful and practical to define instead the appropriate approach to testing for an individual based on the specific reaction reported. The algorithm in Figure 1 defines the pathway that patients may take, depending on whether they are suitable for a direct oral DPT, require skin testing before consideration for a DPT, do not require testing, or should not be tested. The terms *low*, *medium*, and *high risk*, which are open to different interpretations, have thus been avoided.

The definition of what constitutes an appropriate testing strategy for an individual was refined further to take into account the degree of urgency of the surgery, the time available, the level of expertise of the available personnel, and concomitant co-morbidities and medications. This provides a more practical approach to the management of patients in a variety of settings, and may help avoid the blanket avoidance of beta-lactams in both elective and emergency surgery.

In all statements that follow, it is assumed that the patient has no cognitive impairment that might impact recollection of the index event.

Group 1: Direct oral DPT

The following patients are suitable for a direct oral DPT, if lack of time or local expertise precludes prior skin testing (see Section Definition of the minimum standards required for penicillin-allergy testing below for details of who can perform this testing). Those with an asterisk (*) are patients who could be de-labelled without any formal testing based on their history. It is recognised that a significant proportion of these patients will be reluctant to have the label removed in

this way because of a longstanding belief in their allergic status, and for them a DPT is then the appropriate test.

(i) History only of thrush*
(ii) History only of minor gastrointestinal upset*
(iii) Family history of penicillin allergy, but no personal history*
(iv) Patient cannot remember why the label was given, but has had at least one course of penicillin antibiotic since then without adverse effects*
(v) History of only minor symptoms, which are not suggestive of any type of allergic reaction (e.g. headache and arthralgia), and did not require treatment*
(vi) History of benign rash (all of the following must apply: non-itchy, non-blistering, non-severe, and occurring >1 h after first dose) more than 10 yr ago, provided this did not require treatment

Group 2: Skin testing with or without DPT

The following patients require skin testing before consideration for a DPT (see Section D below for details on who is able to perform the skin testing):

(i) History of rash, but no details of this are remembered (including childhood rash)
(ii) History of itchy rash (urticaria) at any time during course of penicillin
(iii) Index reaction not remembered
(iv) Other symptoms, not detailed in Groups 1 or 3, and which required treatment

Group 3: Specialist evaluation

The following patients should not be tested or should be referred to an allergist for specialist investigation. This might include the need for desensitisation, an area that is beyond the scope of these guidelines.

(i) Clear history of immediate and severe reaction with any of the following problems: wheeze, shortness of breath, angioedema, tachycardia, swelling, low blood pressure, collapse, cardiac arrest, and loss of consciousness; these patients may be considered for penicillin desensitisation if there is an absolute indication for penicillin; this would not result in de-labelling of the patient
(ii) Patients with a history of severe or blistering rash appearing at any time during the course of penicillin or in the weeks afterwards, or a formal diagnosis of drug reaction with eosinophilia and systemic symptoms syndrome, SJS, or TEN are contraindicated from receiving penicillins in the future and should not be offered testing

Medical exclusion criteria for DPT (unrelated directly to symptoms of index reaction)

In addition to the patients in Group 3, the following were agreed as exclusion criteria:

(i) Severe or unstable ischaemic heart disease
(ii) Pregnancy (breastfeeding was not considered an exclusion criterion)

We were unable to reach a consensus on whether an airway disease, such as severe asthma or chronic obstructive pulmonary disease, should constitute an exclusion criterion. Ultimately, this decision must be at the discretion of the team performing the testing, and will be a balance between the need for penicillin and the likelihood of harm from a severe allergic reaction.

Patients undergoing cancer chemotherapy should not be excluded from testing, but the consensus view was that there is a greater chance of a false-negative DPT testing because of the immunosuppressive effects of the treatment.

One additional exclusion criterion, severe aortic stenosis, was suggested by a co-author during the editing phase. Although this was not formally agreed on during the consensus process, it is nevertheless a safe practice to avoid a DPT in such patients unless the risk–benefit analysis strongly favours proceeding.

Ideal timing of testing

There was a clear consensus within the group that testing of perioperative patients is ideally performed before the day of surgery, which may help mitigate both surgical flow issues and medico-legal concerns amongst anaesthetists. A recent work in the UK demonstrates that, when anaesthetists are confronted with a label of penicillin allergy that they consider highly unlikely to be correct, up to 60% will avoid giving penicillin where this is the first-line SSI prophylaxis. Concern about potential medico-legal issues was one of the predominant barriers (L. Savic, personal communication). By testing patients 'upstream' of surgery, the anaesthetist is presented with an already de-labelled patient, and subsequent antibiotic use in theatre is likely to be improved. There will be circumstances where testing cannot be performed in a timely manner and a decision needs to be made on the day of surgery. In these circumstances, the following recommendations were agreed:

(i) Patients who require penicillin for surgery
  (a) If surgery is elective, it may be appropriate to offer testing on the day, provided this does not delay surgery. This is most likely to apply to patients who are suitable for a direct oral DPT as a result of logistical problems around provision of skin testing.
  (b) If surgery is urgent or emergent, it should not be delayed in order to test the patient, and alternatives should be used.
(ii) Patients who do not require penicillin for surgery
  (a) Testing on the day of surgery is not recommended. However, if the patient wishes to be tested, this could be performed after operation as an outpatient.

Choice of reagents for skin-test panel and DPT

The choice of reagents for skin testing was not explored through a consensus process, as regional variations in standard practice and availability of reagents are likely to make recommendations redundant. This is also true of dosing regimens for a DPT, which should be decided based on locally existing practice.

In terms of drug choice for a DPT, a consensus was reached on the following:

(i) If the index penicillin is known, testing should be to this drug.
(ii) If the index penicillin is not known, testing should be with the penicillin most commonly used in that country (e.g. amoxicillin in the UK).

There was no agreement as to whether an i.v. DPT was more appropriate in patients due to receive i.v. penicillin during surgery, and therefore, this cannot be recommended.

Definition of the minimum standards required for penicillin-allergy testing

In this section, we explored how testing should proceed in practical terms. There was a clear consensus that any programme of testing and de-labelling should be set up and overseen by an allergist, but that the day-to-day running of the programme could be performed by a healthcare professional who had received training to a level deemed appropriate by the allergist. This leaves open the possibility that preoperative testing could be performed by a variety of appropriately trained healthcare professionals and that the allergist need not be physically present for all testing. Given the scarcity of these specialists in most healthcare systems around the world, testing is likely to take place at a site geographically separate from the allergist. However, it must be possible to contact the lead allergist for advice when required.

We have not defined in these guidelines what constitutes 'adequate training' for the healthcare professional providing the testing; this must be stipulated by the allergist and will vary between regions. The key area for training, aside from history taking, is in the use of skin tests. The healthcare professional performing these tests is likely to require extensive experience and be able to demonstrate proficiency on a regular basis. This requirement is likely to be a limiting factor for many healthcare settings and may in turn limit the provision of testing to only those patients who are suitable for a direct oral DPT.

The following provision was considered mandatory for the safe testing of patients:

(i) Basic life support training for the healthcare professional performing the testing
(ii) Immediate access to a resuscitation team, including an anaesthetist
(iii) Access to on-site critical care facilities
(iv) Equipment for i.v. and intra-osseous access
(v) Immediate access to epinephrine (for i.m. or i.v. use)
(vi) Immediate access to a defibrillator
(vii) Equipment for airway management, including oxygen, suction, and oral/supraglottic/tracheal airways

Use of prolonged DPT testing

There are geographical variations in the use of a prolonged DPT after an oral challenge. Broadly speaking, patients in the USA tend not to undergo a prolonged DPT, whilst practice in Europe is mixed.[83,84] There are also variations in the length of a DPT considered necessary. Ultimately, this is a decision for the allergist overseeing any programme of testing and de-labelling in the perioperative period. The following areas of agreement were reached:

(i) If used, a prolonged DPT should last for as many days as it took for the symptoms to appear in the index reaction, if this is known.
(ii) If it is not known how many days it took for the symptoms to appear in the index reaction, a prolonged DPT of 3–5 days is generally sufficient.
(iii) Patients suitable for de-labelling without any formal testing, but who choose to undergo a DPT (see definitions presented earlier) do not require prolonged challenge.

Advice on alternatives

There will be situations where testing either cannot be performed or is positive. For these situations, practical advice on the use of alternatives is offered in the algorithm in Figure 1. These recommendations are based on a consensus within the group and the evidence base described in earlier sections. The following are the key points:

(i) In patients who undergo testing and are found to be allergic to penicillin, tolerance to other beta-lactams should be explored with skin testing, followed by a DPT if negative.
(ii) In patients who require penicillin for SSI prophylaxis but cannot be tested for any reason, the choice of alternative is dictated by the degree of likelihood of true allergy. Please note that the use of cephazolin was not agreed via the formal Delphi consensus process, but arose after a discussion amongst the group when the first draft of the paper was disseminated. All members of the writing group had the opportunity to comment on this section of the guideline, which was highlighted in an e-mail correspondence for ease of review.
    (a) Patients from Group 1 (direct oral DPT): administer penicillin (or if patient declines penicillin, a cephalosporin of any generation).
    (b) Patients from Group 2 (skin test with or without DPT): if index penicillin is known, choose a cephalosporin with different R1 and R2 side chains. If not known, consider using cephazolin, if available, after a discussion with a local allergist. Otherwise, avoid all beta-lactams.
    (c) Patients from Group 3 (specialist evaluation): avoid all beta-lactams.

Dissemination of results after testing

A key component of penicillin-allergy testing is the effective dissemination of the results to the patient and their healthcare providers. Pharmacy-led counselling and provision of a wallet card detailing the results and implications of testing have been successfully used in some areas.[85] Whilst a consensus was not sought on this topic, the authors recommend that, as a minimum, written evidence of testing is provided to the patient and their primary care physician, and the electronic hospital record is updated accordingly. A wallet card that is standardised across geographical regions and becomes embedded in local practice might help prevent relabelling.

Summary

These guidelines provide a consensus-based outline of how to manage the surgical patient with a label of penicillin allergy across a wide spectrum of reported allergic reactions, urgency of surgery, and available facilities. Acknowledging the extremely limited resources available for allergy testing in most healthcare settings and increasing evidence that not all patients with the label require all elements of standard allergy testing, we have included strategies that reduce the need for

specialist input from allergists in selected circumstances. This allows the appropriately trained non-specialist to assess and test patients, working within agreed frameworks. Further work is needed to assess the utility and impact of such programmes.

Authors' contributions

Study conception: all authors.
Study design: LCS, GWV, DAK, PK.
Data collection: all authors.
Data analysis: all authors.
Data interpretation: all authors.
Drafting of manuscript: LCS, GWV, DAK, PK, SDM.
All authors reviewed the drafts of the manuscript and approved the final version.

Declarations of interest

PD has received lecture and travel fees from MSD France (Courbevoie, France), lecture and travel fees from Bracco Imaging France (Courcouronnes, France), and from Agence Nationale de Sécurité du Médicament et des Produits de Santé (Saint-Denis, France). He was an expert for a task force group dedicated to 'neuromuscular blocking agents and anaphylactic reactions' (until 2016) and is an MSD Expert Board on 'neuromuscular blocking agents and fast-tracking anesthesia' (until October 2019). LHG is a consultant and adjudication committee member for Merck (Kenilworth, NJ, USA) and Novo Nordisk (Gatwick, West Sussex, Denmark). PMH is an Editorial Board Member of the *British Journal of Anaesthesia*. PMM is a scientific advisor for the Allergy to Neuromuscular Blocking Agents and Pholcodine Exposure study (NCT02250729), funded by a consortium of pharmaceutical companies: Zambon, URGO, Pierre Fabre, Boots, Hepatoum, Biocodex, Sanofi, LBR, GSK, APL, Bell's Healthcare, Pinewood, T & R, and Ernest Jackson. PK has received lectures fees from Novartis Pharma Services Inc. and Shire Pharmaceuticals Group Plc. SDM is in receipt of an Australian National Health and Medical Research Council ECR Fellowship for the investigation of cognitive aids in emergencies. All other authors confirm that they have no interests to declare.

Disclaimer

The guidelines and recommendations included in this paper represent the views of the authors. They are based on careful consideration and interpretation of the available evidence 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 scheduled for surgery who give a history of penicillin allergy, and these clinicians are encouraged to take the guidelines and recommendations fully into account when exercising their clinical judgement. The guidelines and recommendations do not override the individual responsibility for clinicians to make appropriate decisions and give the best care according to the circumstances of individual patients. Where appropriate, decisions should be made in consultation with the patient and, where relevant, their guardian.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2019.01.026.

References

1. Zhou L, Dhopeshwarkar N, Blumenthal KG, et al. Drug allergies documented in electronic health records of a large healthcare system. *Allergy* 2016; **71**: 1305–13
2. Shah NS, Ridgway JP, Pettit N, Fahrenbach J, Robicsek A. Documenting penicillin allergy: the impact of inconsistency. *PLoS One* 2016; **11**: e0150514
3. van Dijk SM, Gardarsdottir H, Wassenberg MWM, Oosterheert JJ, de Groot MCH, Rockmann H. The high impact of penicillin allergy registration in hospitalised patients. *J Allergy Clin Immunol Pract* 2016; **4**: 926–31
4. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. *J Allergy Clin Immunol* 2014; **133**: 790–6
5. Macy E, Schatz M, Lin C, Poon KY. The falling rate of positive penicillin skin tests from 1995 to 2007. *Perm J* 2009; **13**: 12–8
6. Macy E, Ngor EW. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. *J Allergy Clin Immunol Pract* 2013; **1**: 258–63
7. Bousquet PJ, Pipet A, Bousquet-Rouanet L, Demoly P. Oral challenges are needed in the diagnosis of beta-lactam hypersensitivity. *Clin Exp Allergy* 2008; **38**: 185–90
8. Mill C, Primeau MN, Medoff E, et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and nonimmediate reactions to amoxicillin in children. *JAMA Pediatr* 2016; **170**: e160033
9. Ibanez MD, Rodriguez Del Rio P, Lasa EM, et al. Prospective assessment of diagnostic tests for pediatric penicillin allergy: from clinical history to challenge tests. *Ann Allergy Asthma Immunol* 2018; **121**: 235–44. e3
10. Dhopeshwarkar N, Sheikh A, Doan R, et al. Drug-induced anaphylaxis documented in electronic health records. *J Allergy Clin Immunol Pract* 2019; **7**: 103–11
11. Renaudin JM, Beaudouin E, Ponvert C, Demoly P, Moneret-Vautrin DA. Severe drug-induced anaphylaxis: analysis of 333 cases recorded by the Allergy Vigilance Network from 2002 to 2010. *Allergy* 2013; **68**: 929–37
12. Jerschow E, Lin RY, Scaperotti MM, McGinn AP. Fatal anaphylaxis in the United States, 1999-2010: temporal patterns and demographic associations. *J Allergy Clin Immunol* 2014; **134**: 1318–28. e7
13. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
14. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Surg Infect (Larchmt)* 2013; **14**: 73–156
15. Blumenthal KG, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES. The impact of a reported penicillin allergy on surgical site infection risk. *Clin Infect Dis* 2017; **66**: 329–36
16. Pool C, Kass J, Spivack J, et al. Increased surgical site infection rates following clindamycin use in head and neck free tissue transfer. *Otolaryngol Head Neck Surg* 2016; **154**: 272–8
17. Ponce B, Raines BT, Reed RD, Vick C, Richman J, Hawn M. Surgical site infection after arthroplasty: comparative effectiveness of prophylactic antibiotics: do surgical care

improvement project guidelines need to be updated? *J Bone Jt Surg Am* 2014; **96**: 970–7
18. Tan TL, Springer BD, Ruder JA, Ruffolo MR, Chen AF. Is vancomycin-only prophylaxis for patients with penicillin allergy associated with increased risk of infection after arthroplasty? *Clin Orthop Relat Res* 2016; **474**: 1601–6
19. Blumenthal KG, Lu N, Zhang Y, Li Y, Walensky RP, Choi HK. Risk of meticillin resistant *Staphylococcus aureus* and *Clostridium difficile* in patients with a documented penicillin allergy: population based matched cohort study. *BMJ* 2018; **361**, k2400
20. Knezevic B, Sprigg D, Seet J, et al. The revolving door: antibiotic allergy labelling in a tertiary care centre. *Intern Med J* 2016; **46**: 1276–83
21. Lang DM, Castells MC, Khan DA, Macy EM, Murphy AW. Penicillin allergy in antibiotic resistance w. penicillin allergy testing should be performed routinely in patients with self-reported penicillin allergy. *J Allergy Clin Immunol Pract* 2017; **5**: 333–4
22. Mirakian R, Leech SC, Krishna MT, et al. Management of allergy to penicillins and other beta-lactams. *Clin Exp Allergy* 2015; **45**: 300–27
23. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs—an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013; **68**: 702–12
24. Torres MJ, Blanca M, Fernandez J, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003; **58**: 961–72
25. Blanca M, Romano A, Torres MJ, et al. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy* 2009; **64**: 183–93
26. Joint task force on practice parameters, American academy of allergy, asthma and immunology, American college of allergy, asthma and immunology, joint Council of allergy, asthma and immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010; **105**: 259–73
27. del Real GA, Rose ME, Ramirez-Atamoros MT, et al. Penicillin skin testing in patients with a history of beta-lactam allergy. *Ann Allergy Asthma Immunol* 2007; **98**: 355–9
28. Park MA, Solensky R, Khan DA, Castells MC, Macy EM, Lang DM. Patients with positive skin test results to penicillin should not undergo penicillin or amoxicillin challenge. *J Allergy Clin Immunol* 2015; **135**: 816–7
29. Macy E, Burchette RJ. Oral antibiotic adverse reactions after penicillin skin testing: multi-year follow-up. *Allergy* 2002; **57**: 1151–8
30. Tannert LK, Mortz CG, Skov PS, Bindslev-Jensen C. Positive skin test or specific IgE to penicillin does not reliably predict penicillin allergy. *J Allergy Clin Immunol Pract* 2017; **5**: 676–83
31. Bousquet PJ, Co-Minh HB, Arnoux B, Daures JP, Demoly P. Importance of mixture of minor determinants and benzylpenicilloyl poly-L-lysine skin testing in the diagnosis of beta-lactam allergy. *J Allergy Clin Immunol* 2005; **115**: 1314–6
32. Matheu V, Perez-Rodriguez E, Sanchez-Machin I, de la Torre F, Garcia-Robaina JC. Major and minor determinants are high-performance skin tests in beta-lactam allergy diagnosis. *J Allergy Clin Immunol* 2005; **116**: 1167–8. author reply 8–9
33. Torres MJ, Romano A, Mayorga C, et al. Diagnostic evaluation of a large group of patients with immediate allergy to penicillins: the role of skin testing. *Allergy* 2001; **56**: 850–6
34. Mistry A, Corps C, Savic S, Savic L. Feasibility and utility of testing for penicillin allergy status in patients attending for elective surgery. *Clin Exp Allergy* 2016; **46**: 1625–74
35. Blanca M, Torres MJ, Garcia JJ, et al. Natural evolution of skin test sensitivity in patients allergic to beta-lactam antibiotics. *J Allergy Clin Immunol* 1999; **103**: 918–24
36. Salkind AR, Cuddy PG, Foxworth JW. The rational clinical examination. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. *JAMA* 2001; **285**: 2498–505
37. Goldberg A, Confino-Cohen R. Skin testing and oral penicillin challenge in patients with a history of remote penicillin allergy. *Ann Allergy Asthma Immunol* 2008; **100**: 37–43
38. Solensky R, Earl HS, Gruchalla RS. Penicillin allergy: prevalence of vague history in skin test-positive patients. *Ann Allergy Asthma Immunol* 2000; **85**: 195–9
39. Caubet JC, Kaiser L, Lemaitre B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol* 2011; **127**: 218–22
40. Blumenthal KG, Li Y, Banerji A, Yun BJ, Long AA, Walensky RP. The cost of penicillin allergy evaluation. *J Allergy Clin Immunol Pract* 2017; **6**: 1019–27
41. Chiriac AM, Wang Y, Schrijvers R, et al. Designing predictive models for beta-lactam allergy using the drug allergy and hypersensitivity database. *J Allergy Clin Immunol Pract* 2018; **6**: 139–48. e2
42. Tucker MH, Lomas CM, Ramchandar N, Waldram JD. Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits. *J Allergy Clin Immunol Pract* 2017; **5**: 813–5
43. Confino-Cohen R, Rosman Y, Meir-Shafrir K, et al. Oral challenge without skin testing safely excludes clinically significant delayed-onset penicillin hypersensitivity. *J Allergy Clin Immunol Pract* 2017; **5**: 669–75
44. Iammatteo M, Alvarez Arango S, Ferastraoaru D, et al. Safety and outcomes of oral graded challenges to amoxicillin without prior skin testing. *J Allergy Clin Immunol Pract* 2019; **7**: 236–43
45. Mohamed OE, Beck S, Huissoon A, et al. A retrospective critical analysis and risk stratification of penicillin allergy de-labelling in a UK specialist regional allergy service. *J Allergy Clin Immunol Pract Adv* 2019; **7**: 251–8
46. Solensky R, Earl HS, Gruchalla RS. Lack of penicillin resensitization in patients with a history of penicillin allergy after receiving repeated penicillin courses. *Arch Intern Med* 2002; **162**: 822–6
47. Staicu ML, Soni D, Conn KM, Ramsey A. A survey of inpatient practitioner knowledge of penicillin allergy at 2 community teaching hospitals. *Ann Allergy Asthma Immunol* 2017; **119**: 42–7
48. Jain V, Joshi N, Sidhu M, Kalicinsky C, Pun T. Penicillin allergies: referral and management practices of anesthesiologists. *Allergy Asthma Clin Immunol* 2014; **10**: A20
49. Blumenthal KG, Shenoy ES, Hurwitz S, Varughese CA, Hooper DC, Banerji A. Effect of a drug allergy educational program and antibiotic prescribing guideline on inpatient clinical providers' antibiotic prescribing knowledge. *J Allergy Clin Immunol Pract* 2014; **2**: 407–13

50. Park M, Markus P, Matesic D, Li JT. Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy. *Ann Allergy Asthma Immunol* 2006; **97**: 681–7
51. Arroliga ME, Radojicic C, Gordon SM, et al. A prospective observational study of the effect of penicillin skin testing on antibiotic use in the intensive care unit. *Infect Control Hosp Epidemiol* 2003; **24**: 347–50
52. Macy E, Shu YH. The effect of penicillin allergy testing on future health care utilization: a matched cohort study. *J Allergy Clin Immunol Pract* 2017; **5**: 705–10
53. Sacco KA, Bates A, Brigham TJ, Imam JS, Burton MC. Clinical outcomes following inpatient penicillin allergy testing: a systematic review and meta-analysis. *Allergy* 2017; **72**: 1288–96
54. Chen JR, Tarver SA, Alvarez KS, Tran T, Khan DA. A proactive approach to penicillin allergy testing in hospitalized patients. *J Allergy Clin Immunol Pract* 2017; **5**: 686–93
55. Geng B, Eastman JJ, Mori K, Braskett M, Riedl MA. Utility of minor determinants for skin testing in inpatient penicillin allergy evaluation. *Ann Allergy Asthma Immunol* 2017; **119**: 258–61
56. Staicu ML, Holly AM, Conn KM, Ramsey A. The use of telemedicine for penicillin allergy skin testing. *J Allergy Clin Immunol Pract* 2018; **6**: 2033–40
57. Marwood J, Aguirrebarrena G, Kerr S, Welch SA, Rimmer J. De-labelling self-reported penicillin allergy within the emergency department through the use of skin tests and oral drug provocation testing. *Emerg Med Australas* 2017; **29**: 509–15
58. Blumenthal KG, Shenoy ES, Varughese CA, Hurwitz S, Hooper DC, Banerji A. Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. *Ann Allergy Asthma Immunol* 2015; **115**: 294–300. e2
59. Ramsey A, Staicu M, Brundige ML. Use of a penicillin screening algorithm and penicillin skin testing for transitioning hospitalized patients to first line antibiotic therapy. *J Allergy Clin Immunol* 2017; **139**: AB182
60. Blumenthal KG, Wickner PG, Hurwitz S, et al. Tackling inpatient penicillin allergies: assessing tools for antimicrobial stewardship. *J Allergy Clin Immunol* 2017; **140**: 154–61. e6
61. Blumenthal KG, Shenoy ES, Wolfson AR, et al. Addressing inpatient beta-lactam allergies: a multihospital implementation. *J Allergy Clin Immunol Pract* 2017; **5**: 616–25. e7
62. Hermanides J, Lemkes BA, Prins JM, Hollmann MW, Terreehorst I. Presumed β-lactam allergy and cross-reactivity in the operating theater: a practical approach. *Anaesthesiology* 2018; **129**: 335–42
63. Daulat S, Solensky R, Earl HS, Casey W, Gruchalla RS. Safety of cephalosporin administration to patients with histories of penicillin allergy. *J Allergy Clin Immunol* 2004; **113**: 1220–2
64. Savic L, Gurr L, Kaura V, et al. Penicillin allergy de-labelling ahead of elective surgery—is it feasible and what are the barriers? *Br J Anaesth Adv Access* 2018. https://doi.org/10.1016/j.bja.2018.09.009. published on October 19
65. McDanel DL, Azar AE, Dowden AM, et al. Screening for beta-lactam allergy in joint arthroplasty patients to improve surgical prophylaxis practice. *J Arthroplasty* 2017; **32**: S101–8
66. Atanaskovic-Markovic M, Gaeta F, Medjo B, Viola M, Nestorovic B, Romano A. Tolerability of meropenem in children with IgE-mediated hypersensitivity to penicillins. *Allergy* 2008; **63**: 237–40
67. Kula B, Djordjevic G, Robinson JL. A systematic review: can one prescribe carbapenems to patients with IgE-mediated allergy to penicillins or cephalosporins? *Clin Infect Dis* 2014; **59**: 1113–22
68. Terico AT, Gallagher JC. Beta-lactam hypersensitivity and cross-reactivity. *J Pharm Pract* 2014; **27**: 530–44
69. Frumin J, Gallagher JC. Allergic cross-sensitivity between penicillin, carbapenem, and monobactam antibiotics: what are the chances? *Ann Pharmacother* 2009; **43**: 304–15
70. Macy E, Contreras R. Adverse reactions associated with oral and parenteral use of cephalosporins: a retrospective population-based analysis. *J Allergy Clin Immunol* 2015; **135**: 745–52. e5
71. Macy EM, Chen LH. The incidence of anaphylaxis associated with oral and parenteral penicillin-class antibiotic exposures. *J Allergy Clin Immunol* 2017; **139**: AB33
72. Sadleir PH, Clarke RC, Platt PR. Cefalotin as antimicrobial prophylaxis in patients with known intraoperative anaphylaxis to cefazolin. *Br J Anaesth* 2016; **117**: 464–9
73. Uyttebroek AP, Decuyper II , Bridts CH, et al. Cefazolin hypersensitivity: toward optimized diagnosis. *J Allergy Clin Immunol Pract* 2016; **4**: 1232–6
74. Pichichero ME, Casey JR. Safe use of selected cephalosporins in penicillin-allergic patients: a meta-analysis. *Otolaryngol Head Neck Surg* 2007; **136**: 340–7
75. MacPherson RD, Willcox C, Chow C, Wang A. Anaesthetist's responses to patients' self-reported drug allergies. *Br J Anaesth* 2006; **97**: 634–9
76. Fonacier L, Hirschberg R, Gerson S. Adverse drug reactions to a cephalosporins in hospitalized patients with a history of penicillin allergy. *Allergy Asthma Proc* 2005; **26**: 135–41
77. Macy E, Blumenthal KG. Are cephalosporins safe for use in penicillin allergy without prior allergy evaluation? *J Allergy Clin Immunol Pract* 2018; **6**: 82–9
78. Romano A, Valluzzi RL, Caruso C, Maggioletti M, Quaratino D, Gaeta F. Cross-reactivity and tolerability of cephalosporins in patients with IgE-mediated hypersensitivity to penicillins. *J Allergy Clin Immunol Pract* 2018; **6**: 1662–72
79. Caimmi S, Galera C, Bousquet-Rouanet L, Arnoux B, Demoly P, Bousquet PJ. Safety of cefuroxime as an alternative in patients with a proven hypersensitivity to penicillins: a DAHD cohort survey. *Int Arch Allergy Immunol* 2010; **153**: 53–60
80. Zagursky RJ, Pichichero ME. Cross-reactivity in beta-lactam allergy. *J Allergy Clin Immunol Pract* 2018; **6**: 72–81. e1
81. Brouwers MC, Kerkvliet K, Spithoff K, AGREE Next Steps Consortium. The AGREE reporting checklist: a tool to improve reporting of clinical practice guidelines. *BMJ* 2016; **352**: i1152
82. Fitch K, Bernstein SJ, Aguilar MD, et al. *The RAND/UCLA appropriateness method user's manual*. Santa Monica, CA: RAND; 2001
83. Fransson S, Mosbech H, Kappel M, et al. The importance of prolonged provocation in drug allergy—results from a Danish allergy clinic. *J Allergy Clin Immunol Pract* 2017; **5**: 1394–401

84. Soria A, Autegarden E, Amsler E, et al. A clinical decision-making algorithm for penicillin allergy. *Ann Med* 2017; **49**: 710–7
85. Patel SV, Tarver SA, Alvarez KS, Lutek KE, Schlebus J, Khan DA. Effectiveness of interventions to maintain penicillin allergy label removal as part of an inpatient penicillin allergy testing protocol. *J Allergy Clin Immunol* 2017; **139**: AB183

Handling editor: H.C. Hemmings Jr

BJA

British Journal of Anaesthesia, 123 (1): e95–e103 (2019)

doi: 10.1016/j.bja.2019.01.033
Advance Access Publication Date: 5 April 2019
Special Article

Chlorhexidine allergy in the perioperative setting: a narrative review

Michael A. Rose[1,*], Tomaz Garcez[2], Sinisa Savic[3] and Lene Heise Garvey[4,5]

[1]Department of Anaesthesia, Royal North Shore Hospital, University of Sydney, Sydney, Australia, [2]Department of Immunology, Manchester University NHS Foundation Trust, Manchester, UK, [3]Department of Clinical Immunology and Allergy, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [4]Danish Anaesthesia Allergy Centre, Allergy Clinic, Department of Dermatology and Allergy, Copenhagen University Hospital, Gentofte, Denmark and [5]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

*Corresponding author. E-mail: m.rose@sydney.edu.au

Summary

Chlorhexidine is an antiseptic with a broad spectrum of activity and a persistent effect on skin. Consequently, it has become an ubiquitous antiseptic in healthcare and the community. As use has become widespread, increasing numbers of cases of allergy have been reported in the literature, including cases of anaphylaxis to chlorhexidine gels used on mucous membranes, chlorhexidine-impregnated devices such as central venous catheters, chlorhexidine preparations used on wounds and broken skin, and cases after dental procedures. Numerous governmental warnings have been issued over recent decades to warn of the risk of allergy to chlorhexidine on mucosal surfaces or in medical devices. Whilst the number of published cases likely underestimates the true prevalence of reactions, we retrospectively surveyed clinics with experience in investigating perioperative chlorhexidine allergy. Despite differences in investigation practice before the survey took place, 13 clinics responded which together had diagnosed 252 cases of anaphylaxis to chlorhexidine, and cases of delayed allergy. In eight of 13 clinics, chlorhexidine was within the top four most commonly diagnosed causes of perioperative anaphylaxis. Despite this, the incidence of anaphylaxis to chlorhexidine is low given that patients are very commonly exposed. Sensitisation of healthcare workers can occur, but is uncommon. Before exposing patients to this antiseptic, consideration of the potential risk *vs* benefit should be undertaken, particularly for higher risk exposures, such as mucosal exposure or i.v. exposure via impregnated lines. Difficulties exist in protecting patients with known allergies from re-exposure to chlorhexidine, which would be improved with uniform labelling and chlorhexidine product registers.

Keywords: adverse effects; allergens; anaphylaxis; chlorhexidene; perioperative; drug hypersensitivity; survey

Chlorhexidine (1:6-di-4'-chlorophenyldiguanidohexane) is a synthetic biguanide, broad-spectrum antiseptic and disinfectant used widely in the healthcare sector in many countries (Fig. 1). This narrative review summarises the current published knowledge on chlorhexidine allergy in the perioperative setting, as it has become one of the most important causes of

Editorial decision: 26 January 2019; **Accepted:** 26 January 2019

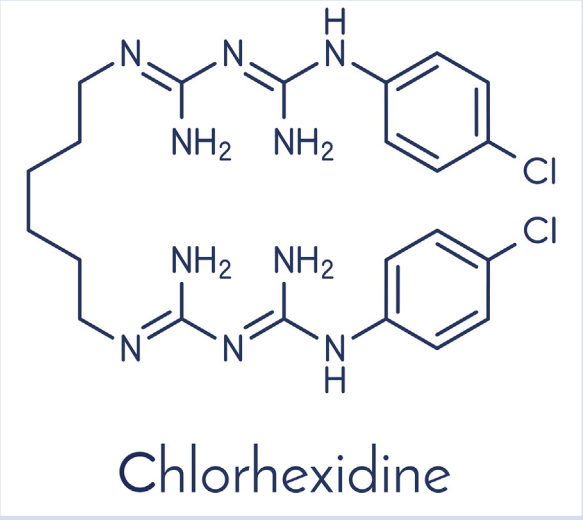


Fig 1. Chemical structure of chlorhexidine. Reproduced with permission from 123rf.com.

perioperative allergy. Results of a retrospective survey of chlorhexidine allergy in 13 worldwide perioperative allergy clinics are presented.

The appreciation of chlorhexidine's attractive spectrum of activity and persistent effect has seen the use of chlorhexidine increase in recent years.[1] At lower concentrations it is bacteriostatic and at higher concentrations rapidly bacteriocidal.[2,3] It is active against Gram-negative and -positive bacteria, fungi, and some viruses, but is not sporocidal.[4] As proteins in the skin are anionic, the positive ammonium charges in chlorhexidine bind well to these, which gives it a persistent effect in the superficial skin layers.[5]

Chlorhexidene has found use in diverse forms both in and outside the perioperative setting including, but not limited to, alcoholic and aqueous surgical skin preps, skin wipes, and lubricant gels for urethral catheterisation and vaginal and rectal examination. It has been impregnated into central venous catheters (CVCs) and other medical devices, and may be found in wound dressings, throat gargles/mouthwashes, toothpastes, contact lens solutions, and cosmetics. In many of these forms, the presence of chlorhexidine is obvious, however the presence of chlorhexidine is not always obvious (such as in gels, devices, toothpastes, and dressings) leading to its reputation of being an 'occult' or 'hidden' allergen in the healthcare environment.

Initial descriptions of hypersensitivity began in the early 1960s in the UK.[6,7] In Japan between 1967 and 1984, 50 adverse reactions, many of which were consistent with hypersensitivity, were reported, and in 1984 the Japanese Ministry of Welfare recommended prohibition of the use of chlorhexidine on mucous membranes.[8] In 1985, the manufacturers of chlorhexidine in Japan recommended that only the lowest bactericidal concentration (0.05%) of chlorhexidine gluconate should be used on wound surfaces.[8] In 1988, reports of hypersensitivity reactions to chlorhexidine impregnated CVCs led the US Food and Drug administration (FDA) to issue an alert about the risk of anaphylactic reactions.[9] A similar alert was issued by the Therapeutic Goods Administration in Australia in 2012,[10] and an Australian Adverse Drug Reactions Bulletin warned of reports of anaphylaxis to gels containing lignocaine and chlorhexidine.[11] The Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK issued an alert in 2012[12] warning about reports of allergic reactions to devices and products containing chlorhexidine. In 2013, New Zealand's regulator reported 69 reports of anaphylaxis over 13 yr.[13] In 2016, increased reports of allergy (53 to topical non-prescription products) led Canadian authorities to a safety review and updating of product information with allergy concerns.[14] In addition, in 2017, the FDA issued another alert as a result of a recent increase in allergic reactions to chlorhexidine skin antiseptics and a request that manufacturers of over-the-counter antiseptic products containing chlorhexidine gluconate add an allergy warning to their products' Drug Facts labels.[15] These warnings, though important, must be seen in context. The individual patient risk for chlorhexidine allergy is very low (for patients without a history suggestive of chlorhexidine allergy), and its spectrum makes chlorhexidine the antiseptic of choice for many procedures.

Methods

A literature search was conducted using Medline (1946–2018), Embase (1980–2018), Cochrane, CINAHL Complete, and Web of

Table 1 Clinical features of chlorhexidine allergy

		Onset of symptoms after exposure*		Severity of reaction		
Route of exposure	Example	Immediate	Delayed	Localised (urticaria)	Generalised (urticaria)	Systemic anaphylaxis
Topical cutaneous	Preoperative whole body wash	Yes	Yes	Yes	Yes	Rare
	Preoperative skin preparation	Yes	Rare	Yes	Yes	Rare
Mucous membrane	Transurethral	Yes	Yes	Rare	Rare	Yes
	Rectal	Yes	Yes	Rare	Rare	Yes
	Vaginal	Yes	Yes	Rare	Rare	Yes
	Oral (mouthwash)	Yes	Rare	Yes	Rare	Rare
	Ophthalmic	Yes	Rare	Yes	Rare	Rare
Parenteral	I.V. cannula preparation	Rare	Yes	Yes	Rare	Rare
	CVC, arterial and epidural catheter insertion	Yes	Yes	Yes	Yes	Yes

* Immediate reactions occur within minutes to 1 hour after exposure, delayed reactions may present hours to days after exposure. CVC, central venous catheter

Science for relevant articles (details of search in Supplementary Appendix S1). The 238 articles identified were screened for relevance. Articles from exploration of references from key articles were also included.

In order to survey experiences and differences in investigation practices of the experts involved in the International Suspected Perioperative Allergic Reaction (ISPAR) group[3] (formed in 2018), a questionnaire was circulated to the 26 members. Information was sought from those with active experience investigating perioperative allergy (maximum of one response per testing location). The survey questions (Supplementary Appendix S2) and a summary of results is attached (Supplementary Appendix S3).

Clinical features

The spectrum of symptoms and signs of perioperative chlorhexidine allergy is varied in onset time and severity, and ranges from mild reactions confined to the skin, to life-threatening anaphylaxis. Table 1 summarises common presentations of allergy seen after different routes of chlorhexidine exposure. In the context of chlorhexidine-coated CVC insertion, exposure to the drug is i.v., and can therefore result in immediate anaphylaxis that can be life-threatening.[57] If the catheter is not recognised as the source of the problem and removed, this can lead to prolonged and intractable anaphylaxis.[17] A slower onset of symptoms occurs when chlorhexidine is administered topically to skin or mucous membranes, and time is required for the drug to reach the vascular system. Allergic reactions to chlorhexidine can thus occur with delayed onset, appearing not to be temporally related to administration of the drug. These atypical presentations can result in diagnostic confusion, with chlorhexidine being overlooked as a potential causal agent, and other drugs incorrectly blamed.

Topical chlorhexidine exposure in the perioperative setting frequently begins with skin cleaning before insertion of a peripheral venous cannula. This may result in only localised reactions, with insufficient exposure, to result in widespread systemic symptoms. These reactions are nevertheless IgE-mediated.[18] typically involving localised urticaria. In a study of 33 patients with positive skin tests to chlorhexidine, 11 had localised urticarial reactions when tested with open application of a chlorhexidine-containing solution.[19] A history of localised reactions such as this can often be found in patients who present later with more severe, systemic reactions[20,21] and should be actively sought when assessing preoperative allergy status,[22] as further exposure to chlorhexidine may result in more severe reactions.

In the UK and many other countries, chlorhexidine is the most frequently used skin disinfectant before regional anaesthesia. For neuraxial techniques this typically involves spraying the whole back, thus exposing the patient to a large mass of drug. Broken or damaged skin allows relatively rapid absorption of chlorhexidine. In addition, there is some evidence that the alcohol contained in cleaning solutions may enhance chlorhexidine absorption through its damaging, drying effect.[23] Further exposure occurs if chlorhexidine-containing skin cleaning preparations are used before surgery where a large area of skin is covered, and surgical incision through the disinfected area may result in a more rapid onset of symptoms.[24]

Probably the most common cause of perioperative anaphylaxis to chlorhexidine is secondary to its use on mucosal surfaces. Typically, this is associated with insertion of chlorhexidine-impregnated urethral catheters, or more commonly with the use of chlorhexidine-containing lubricants such as Instillagel® and KY Jelly®. Allergic manifestations are usually delayed compared with reactions caused by i.v. exposure to allergen. Rapid development of allergic manifestations can occur in cases of urethral chlorhexidine exposure,[25] which possibly results from traumatic injury to the urethra during catheterisation facilitating venous uptake of allergen. This is frequently misattributed to other causes, unless the anaesthetist is aware that such lubricants contain chlorhexidine. Other mucosal surfaces that may be exposed to chlorhexidine include rectal (examination or colonoscopy lubricants), vaginal (examination lubricants), ophthalmic (cleaning solutions), and oral (mouthwash). Anaphylaxis after chlorhexidine exposure via mouthwash and oral gels has been reported,[26,27] though possibly less than would be expected compared with those from other mucosal routes of exposure. Two perioperative fatalities have been reported from anaphylaxis as a result of chlorhexidine use in open dental sockets after surgery,[28] though this may be attributable to direct vascular access of allergen through the socket rather than transmucosal absorption.

Chlorhexidine may also cause contact dermatitis through delayed type IV allergic reactions, and there is evidence that some patients simultaneously have both immediate and contact allergy.[29] Patients with delayed-type hypersensitivity to chlorhexidine may develop unpleasant reactions on mucosal exposure and be predisposed to develop IgE-mediated allergy; these patients should be advised to avoid chlorhexidine-containing products.[30]

Epidemiology

Chlorhexidine-induced perioperative hypersensitivity reactions are reported to account for between 7.7%[31] and 9% of cases in the UK,[32] 9% in Belgium,[33] and 9.6% in Denmark.[34] Chlorhexidine appears to be a rare culprit in France.[35] It is possible that under-recognition or differences in practice account for the discrepancy. Testing for chlorhexidine allergy in all patients referred with perioperative hypersensitivity reactions increases recognition, particularly in countries where chlorhexidine exposure is highly likely in the operating room.[22,31,33,34] The true prevalence of chlorhexidine allergy remains unknown, but is likely to be increasing. In the 10-yr period up to 2004, only 50 cases of IgE-mediated reactions were reported.[36] Between 2009 and 2013, 104 cases were reported from four UK specialist centres.[37]

The largest UK study of anaesthetic hypersensitivity reactions to date, the Royal College of Anaesthetists' 6th National Audit Project (NAP6),[22] identified 18 cases of chlorhexidine anaphylaxis (overall 9%), the third most common trigger. Most cases were in males (16/18) and urological. Interestingly, in the NAP6 study the anaesthetist only considered chlorhexidine as the cause in five (28%) of the cases. There were 2 298 567 annual exposures to chlorhexidine estimated in the same time period by at least one route, with 74% of all patients being exposed. The NAP6 study estimated the incidence of anaphylaxis to chlorhexidine to be 0.78 per 100 000 exposures, but this may be an overestimate as the denominator is unlikely to reflect all exposures.[32]

Multiple reactions and misdiagnoses are common and were confirmed in the NAP6 study.[32] One patient with a reported chlorhexidine allergy was re-exposed to chlorhexidine and developed anaphylaxis. In another case, after the

Table 2 Questions to ask for a chlorhexidine allergy history

- Have you ever been told you might be allergic to chlorhexidine or disinfectant/cleaning solutions or lubricant gels?
- Have you ever had swelling in the mouth or developed an itchy rash when you have used mouthwashes?
- Have you ever had swelling or an itchy rash develop when your skin is cleaned before taking blood/putting a drip in?
- Have you ever had swelling or an itchy rash develop after using disinfectant/cleaning solution for minor scratches in the home or when asked to wash in it before surgery?
- Have you ever had a rash or swelling after a procedure in hospital or been told that you have had an allergic reaction during surgery, which was not investigated?

anaphylactic event reported to NAP6 was confirmed to be attributable to chlorhexidine, the patient had a further procedure, was exposed to chlorhexidine, and had another hypersensitivity reaction. A Danish study of 23 patients with confirmed chlorhexidine hypersensitivity showed that one-third were accidentally re-exposed in the healthcare setting.[38]

Our retrospective survey (Supplementary Appendix S2) of the current investigation practice in centres in the ISPAR group[3] returned responses (Supplementary Appendix S3) from 13 clinics involved in the investigation of perioperative anaphylaxis from the UK (2), Europe (7), Australia (2), New Zealand (1), and the USA (1). The total number of cases of perioperative chlorhexidine anaphylaxis diagnosed by these clinics was 252, which is much larger than any previous published series (although some cases may have been reported previously). The clinics with the three largest numbers of cases reported 64 over 19 yr (Denmark), 45 over 17 yr (Belgium), and 42 over 9 yr (Australia), respectively, and all tested for chlorhexidine routinely. Not all centres were able to break down their cases by method of exposure, but mucosal exposure, skin/wound and i.v. catheter site/CVC routes were common. It was interesting to note that as a perioperative allergen, chlorhexidine is now relatively prominent, featuring as the second most commonly diagnosed in two clinics. It ranked third in three clinics and within the top four in eight of 13 clinics. Three centres diagnosed chlorhexidine allergy rarely, however two of these three reported they test for chlorhexidine allergy selectively (rather than routinely), reflecting the lack of standardisation of testing even in specialised centres. Given that exposure to chlorhexidine in the perioperative environment often goes unnoticed, not testing routinely for chlorhexidine may have contributed to under-reporting of chlorhexidine anaphylaxis from those centres.

Main exposure routes

Lubricating gels used for urological and gynaecological procedures often contain chlorhexidine and local anaesthetic, but there are aqueous gels without one or both. The predominant surgical specialty associated with chlorhexidine anaphylaxis in the NAP6 study was urology (six cases), and there were cases from cardiac and orthopaedics (three cases each).[32] Overall, this is consistent with previous studies reporting the highest prevalence of reactions during urological procedures.[18,37–39]

Chlorhexidine-coated or -impregnated CVCs are intended to reduce the risk of catheter-associated infection, and clinicians may not be aware of the chlorhexidine coating on these catheters. Reactions to chlorhexidine-impregnated CVCs are often rapid in onset and severe[40] requiring prompt treatment and removal of the catheter. The line was not removed during resuscitation in two of five cases related to chlorhexidine-coated central venous lines in the NAP6 study.[22] Chlorhexidine-free CVCs should be considered where possible. A recent Cochrane review questioned the efficacy of chlorhexidine-coated venous catheters in preventing clinically important morbidity.[41]

Chlorhexidine is used widely for skin preparation before surgery or venipuncture. Povidone-iodine and alcohol-based swabs can be used as alternatives. In the NAP6 study, the reported routes of chlorhexidine exposure included skin preparation for cannulation or surgery, coated CVCs, and urethral or similar medical gels. Seven cases had a single route of exposure, while five cases had two, five had three, and one had four, reflecting that exposure is commonly from multiple sites.

Chlorhexidine-containing products are widely used and regarded as the 'gold standard' in dentistry because of their wide antimicrobial spectrum and efficacy. There are multiple preparations including mouthwash or spray solutions, gels, and impregnated chips for use in periodontal pockets. There have been a number of reports of allergies including fatalities linked to dental chair chlorhexidine reactions,[28] though possibly less than would be expected compared with those from other mucosal routes of exposure. The main alternative product, hexetidine, has a much weaker evidence base and is considered a poor alternative to chlorhexidine.[42] Other alternatives for dental use include sodium hypochlorite solution and normal saline.

Challenges in diagnosis of chlorhexidine allergy

The mechanism of immediate-type chlorhexidine allergy has been shown to be IgE-mediated,[18] and methods for diagnosing chlorhexidine allergy are the same as used in other allergy testing: *in vitro* tests [specific IgE test, basophil activation tests (BAT) and histamine release (HR) test] and *in vivo* tests [skin prick test (SPT) and intradermal test (IDT)].[34] As no single test has 100% sensitivity or specificity, the results should always be interpreted in the context of a clinical reaction on exposure to chlorhexidine. Sensitivity can be increased by combining several test modalities, and some centres suggest that allergy can be confirmed if two or more test modalities are positive in the light of a relevant clinical reaction.[34,43] In many countries, chlorhexidine is used routinely in the perioperative setting, and testing for chlorhexidine should always be included in the investigation of suspected perioperative allergic reactions.[40,44]

A relevant clinical history includes symptoms elicited in a setting of exposure to chlorhexidine. Many patients retrospectively report a minor reaction on previous chlorhexidine exposure, or repeated severe reactions,[39] as a result of chlorhexidine being missed as an allergen on initial evaluation. Identifying minor reactions before future exposure is important; Table 2 lists some relevant questions that may help elicit a history of chlorhexidine allergy. On suspicion of allergy to

chlorhexidine, patients should be referred for allergy investigation, preferably in a centre with experience in perioperative allergy investigation, and chlorhexidine should be avoided until investigations are completed.

The commercially available specific IgE analysis for chlorhexidine (ImmunoCAP Allergen C8, Phadia, Uppsala, Sweden) has a recommended cutoff of 0.35 $kU_A\ L^{-1}$. In patients with high total IgE concentrations, chlorhexidine-specific IgE may be falsely elevated above 0.35 $kU_A\ L^{-1}$.[43] In Denmark, the false positive rate of specific IgE for chlorhexidine is quite low,[29,38] and the sensitivity and specificity of specific IgE to chlorhexidine has been reported to be very high when sampled in the months after the reaction. Concentrations of IgE are dynamic, showing an increase after exposure followed by a decline over time to concentrations <0.1 $kU_A\ L^{-1}$ if exposure is avoided. This means that allergy cannot be ruled out if specific IgE is <0.1 $kU_A\ L^{-1}$.[38,45] For this reason, one study has recommended that the optimal sampling time for specific IgE is 1–4 months after the reaction.[38]

The BAT and HR test are additional *in vitro* tests that can be carried out in highly specialised centres and require freshly sampled blood for analysis. They are generally used to aid diagnosis in patients where other tests are equivocal or not available. Sensitivities of the BAT and HR test are generally lower than those of other test modalities, but specificity is usually high.[18,46]

Skin testing is the most common modality in allergy testing. The SPT and IDT are supplementary to each other, as the sensitivity of testing is increased when both tests are performed. As chlorhexidine is a skin irritant, it is important that skin testing is performed with a non-irritant concentration. The recommended maximum skin test concentrations for chlorhexidine are 0.5% (5 mg ml^{-1}) for SPT and 0.0002% (0.002 mg ml^{-1}) for IDT.[18,47] The skin test response declines over time with lack of exposure, but it is not known how long skin tests stay positive.

No reliable challenge test has been identified at the present time. The majority of severe reactions have been triggered by intraurethral or i.v. exposure, and a challenge protocol using these exposures presents difficulties in terms of safe dosing and acceptability to the patient. Other exposure routes, such as intact skin and the mucous membrane in the mouth, are likely to present strong barriers to absorption of allergen and thus are likely to produce false negative challenge responses. The current recommendation is to combine several tests with a relevant clinical history. For patients tested within a few months of the reaction, a combination of a positive SPT and positive specific IgE test has very high sensitivity and specificity.[34] When investigations are delayed many months, the IDT may prove more sensitive.[37] If clinical suspicion is high and all tests are negative, testing can be repeated some months later, and may then have become positive (LH Garvey, personal communication).

Risk *vs* benefit in chlorhexidine use

The utility of chlorhexidine as an antiseptic is well established. It is also clear that through the incredibly widespread use of chlorhexidine in many products throughout modern healthcare environments, exposure to chlorhexidine is very common. Whilst the actual denominator is not known, even if the prevalence of chlorhexidine anaphylaxis has increased in recent years, the incidence of hypersensitivity reactions to chlorhexidine is very low. As with all interventions in healthcare, the aim is to make sure that there is a positive benefit/risk ratio. Given that there is a risk of anaphylaxis with exposure to chlorhexidine, its use should be reserved for situations where benefit is likely to exist. Currently, some exposures to chlorhexidine in the perioperative environment, such as use of chlorhexidine-containing urethral gels, are potentially unnecessary, and if so may carry risk without benefit.

The reduction in catheter-related bloodstream infections (CRBSI), clinically diagnosed sepsis, and associated mortality caused by i.v. access devices such as CVCs and peripheral IV catheters (PIVCs), is a common goal globally. The risk *vs* benefit of using chlorhexidine skin preparations, chlorhexidine-impregnated CVCs, and chlorhexidine-impregnated dressings has long been debated. The most recent Cochrane reviews suggest that chlorhexidine skin prep may be more effective than povidone-iodine at preventing CRBSI, however the quality of evidence was very low.[48] Assessment of the value of antimicrobial impregnated CVCs suggested they may decrease CRBSI in adults, but with a number needed to treat for benefit of 50.[49] The evidence does not suggest a significant decrease in clinically diagnosed sepsis events or mortality.[41,49] There was moderate quality evidence that impregnated dressings with chlorhexidine or silver may reduce CRBSI.[50] Given that reported cases of anaphylaxis to chlorhexidine products are increasing and that governmental warnings exist[10–15] about hypersensitivity reactions, decisions about the use of these products should be made after consideration of allergy history and route of exposure (topical with access to broken skin *vs* i.v.). Chlorhexidine should be used when the benefit to the patient is likely to be tangible and outweighs the potential risk. It is not recommended to use impregnated CVCs routinely in all settings.[49]

The rate of CRBSI from PIVCs is highly dependent on line duration. For this reason, it may be prudent to reserve the use of chlorhexidine as an antiseptic for PIVCs that are intended to stay *in situ* for several days, and in particular to use 70% alcohol skin swabs as skin prep for day cases or overnight PIVCs. Such a strategy is likely to greatly reduce exposure of patients to a potential allergen where benefit is unlikely to be derived.

Many of the cases of perioperative anaphylaxis resulting from chlorhexidine have originated from lubricant gels, particularly in urology procedures.[18,37,39] The US Centers for Disease Control and Prevention considers the routine use of antiseptic urethral lubricants 'unnecessary',[53] suggesting that many of these anaphylactic reactions have occurred unnecessarily. The ISPAR group[3] survey (Supplementary Appendices S2 and S3) found that rates of chlorhexidine anaphylaxis have decreased in two large perioperative allergy clinics in Australia in recent years, after local decisions to discontinue the use of chlorhexidine-containing urethral lubrication gels.

Prevention of re-exposure to chlorhexidine in patients with a history of hypersensitivity

The widespread use of chlorhexidine in the healthcare and pharmacy environments brings with it a great challenge when trying to avoid re-exposure in allergic patients. Repeated episodes of allergy have been described before or after diagnosis of chlorhexidine hypersensitivity.[18,38,54–57] Challenges include the easy identification of these products in the absence of standards for clear labelling of the presence of chlorhexidine and the need to remove these products from the environment of allergic patients without affecting access for the vast

Table 3 Important considerations in the management of chlorhexidine allergic patients (adapted from Australian and New Zealand College of Anaesthetists [ANZCA] Guidelines PS60[58])

- Adequate history taking for all hypersensitivity including to chlorhexidine before exposure
- Single room, removal of all chlorhexidine-containing products from the room
- Development of a chlorhexidine product register for each site. Access to this register in the patient's room
- All products must be checked for absence of chlorhexidine before use
- Clear 'Allergy to Chlorhexidine' signs on the room door, patient notes, and patient's bed
- Medic-Alert®/Patient allergy band in place
- Handover need of chlorhexidine avoidance when patient transferred to other locations in the healthcare facility
- Inform patient to be vigilant towards potential chlorhexidine exposures

majority of patients without a history of hypersensitivity. The Australian and New Zealand College of Anaesthetists has released professional guidelines on the management of patients with suspected or proved hypersensitivity to chlorhexidine;[58] the key recommendations are summarised in Table 3.

In addition to these recommendations, uniform international regulations requiring clear labelling of the presence of chlorhexidine would provide some additional protection to allergic patients, but would be difficult to achieve. Practically, the maintenance of a high index of suspicion for chlorhexidine as an allergen is important in cases where milder allergic features are noted in patients known to, or suspected to, have recently been exposed to chlorhexidine. If these patients are diagnosed appropriately with chlorhexidine allergy at this time, further more severe reactions may be avoided.

Empowering patients diagnosed with chlorhexidine allergy to be vigilant for products in medical and pharmacy environments and to actively ask healthcare staff to check all products to be used on them is extremely important, as healthcare staff are often unaware of chlorhexidine content in products. In a perioperative environment, the same principles apply as to all healthcare environments, such as the handover of allergy status, and the identification and avoidance of products containing chlorhexidine in the environment. The key differences are that the number of products containing chlorhexidine is many and varied, and the patient is often not conscious and able to be their own advocate. As a result of this, the responsibility for avoiding re-exposure in chlorhexidine allergic patients falls more directly on perioperative staff.

Occupational exposure in healthcare

As the number of patients with allergy to chlorhexidine has increased with increasing utilisation, the question of potential sensitisation and allergy to chlorhexidine in healthcare workers has arisen. Occupational exposure to chlorhexidine may occur directly on the skin through hand disinfectants, soaps, and scrubs used repeatedly throughout the working day. Indirect exposure can occur on skin when handling chlorhexidine-containing dressings, gels, creams, and lotions to be applied to patients.[59] Lastly, exposure can occur in the respiratory tract via solutions and sprays used for disinfection of equipment.[60]

Chlorhexidine is a known irritant in high concentrations, and irritant contact dermatitis causing localised transient irritation, which disappears spontaneously on avoidance, has been reported in doctors and other healthcare workers.[61,62] Allergic contact dermatitis with more chronic eczematous reactions and recurrence on repeated exposure has been described in 2% of 549 healthcare workers presenting with skin symptoms to an Australian occupational dermatology clinic. The rate of sensitisation to chlorhexidine in the general dermatology clinic in the same hospital was 0.24% for comparison.[59] A Danish study investigating potential allergic sensitisation in 104 healthcare workers who were asymptomatic failed to identify any cases,[63] and a more recent study of healthcare workers with self-reported hand eczema identified one case in 120 with concomitant contact dermatitis and immediate-type allergy to chlorhexidine.[64]

In recent years, cases of immediate-type IgE-mediated allergy to chlorhexidine have been reported in healthcare workers with very low frequency when considering the widespread exposure to chlorhexidine. Symptoms in healthcare workers in the workplace range from itching and urticaria on skin exposure[64,65] to respiratory symptoms such as rhinitis, sneezing, and asthma symptoms.[66,67] The relative rarity of severe reactions in healthcare workers is probably related to the route of exposure which is mainly via the skin or respiratory tract. In patients, where exposure may occur on mucous membranes in the urinary tract during catheterisation or directly in the bloodstream when inserting chlorhexidine-coated central lines, anaphylaxis with severe circulatory compromise is relatively more common.[39] Once sensitised to chlorhexidine, healthcare workers are at risk of severe reactions if they themselves become patients and are accidentally exposed to chlorhexidine. One very rare case of full-blown anaphylaxis occurring in a dentist in the workplace has been reported recently.[68]

There is no evidence for the mechanisms behind allergic sensitisation to chlorhexidine in healthcare workers. Co-sensitisation of healthcare workers can occur,[45] and it could be speculated that one allergy caused the skin barrier to be impaired leading to the other allergy. High concentrations of chlorhexidine of 2–4% have irritant effects on the skin, again leading to an impaired skin barrier and potentially increasing the risk of allergic sensitisation.[70] In some countries, 0.5% chlorhexidine is recommended and in others much higher concentrations of 2–4% are used. The issue of potentially increased risk of allergic sensitisation with higher concentrations of chlorhexidine has been raised,[24] and the recommendation should be to use the minimum effective concentration of chlorhexidine. Because of the widespread use of chlorhexidine in the health sector, healthcare workers presenting with occupational allergy should always be investigated for chlorhexidine allergy.

Conclusions

Chlorhexidine is widespread in the perioperative environment, an excellent antiseptic, and generally well-tolerated. True

allergy is rare, however increases in numbers of diagnosed cases have seen it elevated from an obscure cause of perioperative allergy to the second to fourth most commonly diagnosed cause of perioperative allergy in clinics around the world (Supplementary Appendix S3). Delays between exposure and allergic features and the lack of recognition of chlorhexidine as an allergen remain barriers to successful diagnosis of chlorhexidine allergy, and multiple reactions can occur before diagnosis. Difficulty in identifying the wide range of healthcare products containing chlorhexidine is an obstacle to successfully avoiding inadvertent exposure to chlorhexidine in those patients with a diagnosed allergy. Healthcare workers frequently exposed to chlorhexidine occupationally may also be sensitised. Progress towards standardisation of the labelling of chlorhexidine-containing products is needed. Evaluation of the risk *vs* benefit of using chlorhexidine as an antiseptic in common procedures should be investigated to minimise both infection and unnecessary chlorhexidine exposure.

Authors' contributions

Contributed to the conception and design of the study, data collection, analysis, and interpretation, and drafting of the manuscript, and approved the final version of the manuscript:: all authors

Declarations of interest

LHG: Consultant and adjudication committee member for Merck, Kenilworth, NJ, USA and Novo Nordisk, Bagsvaerd, Denmark. Other authors have no conflicts to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2019.01.033.

References

1. Kampf G. Acquired resistance to chlorhexidine - is it time to establish an 'antiseptic stewardship' initiative? *J Hosp Infect* 2016; **94**: 213–27
2. Gilbert P, Moore LE. Cationic antiseptics: diversity of action under a common epithet. *J Appl Microbiol* 2005; **99**: 703–15
3. Garvey LH, Hopkins P. Special issue on suspected perioperative allergic reactions. *Br J Anaesth* 2019; **123**: 1–3
4. McDonnell G, Russell AD. Antiseptics and disinfectants: activity, action, and resistance. *Clin Microbiol Rev* 1999; **12**: 147–79
5. Casey AL, Karpanen TJ, Conway BR, et al. Enhanced chlorhexidine skin penetration with 1,8-cineole. *BMC Infect Dis* 2017; **17**: 350
6. Birdwood B. Reaction to chlorhexidine and cetrimide. *Lancet* 1965; **1**: 651–2
7. Calnan CD. Contact Dermatitis from Drugs. *Proc R Soc Med* 1962; **55**: 39–42
8. Okano M, Nomura M, Hata S, et al. Anaphylactic symptoms due to chlorhexidine gluconate. *Arch Dermatol* 1989; **125**: 50–2
9. Nightingale SL. Hypersensitivity to chlorhexidine-impregnated medical devices. *J Am Med Assoc* 1998; **279**: 1684
10. Therapeutic Goods Administration. Anaphylaxis with chlorhexidine-impregnated central venous catheters. *Australian Prescriber* 2012; **3**
11. Therapeutic Goods Administration. *Australian adverse drug reactions bulletin April 2009*. Available from, https://www.tga.gov.au/publication-issue/australian-adverse-drug-reactions-bulletin-vol-28-no-2#a3; 2009 (accessed 21 September 2018)
12. *Medicines & Healthcare Products Regulatory Agency Medical Device Alert* 2012. Available from, https://assets.publishing.service.gov.uk/media/5485abd7e5274a4290000281/con197920.pdf (accessed 25 September 2018)
13. Medsafe. Chlorhexidine - risk of anaphylaxis. *Prescriber* 2013; **34**: 22
14. MedEffect. *Summary safety review - topical antiseptic non-prescription chlorhexidine products - assessing the potential risk of serious allergic reactions (hypersensitivity reactions)* 2016. Available from, https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-topical-antiseptic-non-prescription-chlorhexidine-products-potential-risk.html (accessed 25 September 2018)
15. FDA US. *FDA warns about rare but serious allergic reactions with the skin antiseptic chlorhexidine gluconate* 2017. Available from, https://www.fda.gov/Drugs/DrugSafety/ucm530975.htm. accessed 18/09/2017)
17. Stephens R, Mythen M, Kallis P, Davies DWL, Egner W, Rickards A. Two episodes of life-threatening anaphylaxis in the same patient to a chlorhexidine–sulphadiazine-coated central venous catheter. *Br J Anaesth* 2001; **87**: 306–8
18. Garvey LH, Kroigaard M, Poulsen LK, et al. IgE-mediated allergy to chlorhexidine. *J Allergy Clin Immunol* 2007; **120**: 409–15
19. Aalto-Korte K, Makinen-Kiljunen S. Symptoms of immediate chlorhexidine hypersensitivity in patients with a positive prick test. *Contact Dermatitis* 2006; **55**: 173–7
20. Knight BA, Puy R, Douglass J, O'Hehir RE, Thien F. Chlorhexidine anaphylaxis: a case report and review of the literature. *Intern Med J* 2001; **31**: 436–7
21. Krautheim AB, Jermann TH, Bircher AJ. Chlorhexidine anaphylaxis: case report and review of the literature. *Contact Dermatitis* 2004; **50**: 113–6
22. Cook T, Harper N. *Anaesthesia, Surgery and Life-Threatening Allergic Reactions. Report and findings of the Royal College of Anaesthetists' 6th National Audit Project*. Available from, https://www.nationalauditprojects.org.uk/NAP6Report#pt; 2018 (accessed 30 September 2018)
23. Calogiuri GFDLE, Trautmann A, Nettis E, Ferrannini A, Vacca A. Chlorhexidine hypersensitivity: a critical and updated review. *J Allergy Ther* 2013; **4**: 141
24. Bahal S, Sharma S, Garvey LH, Nagendran V. Anaphylaxis after disinfection with 2% chlorhexidine wand applicator. *BMJ Case Rep* 2017. bcr-2017-219794
25. Parkes AW, Harper N, Herwadkar A, Pumphrey R. Anaphylaxis to the chlorhexidine component of Instillagel: a case series. *Br J Anaesth* 2009; **102**: 65–8
26. Lloyd-Lavery A, Reed J. A case of chlorhexidine-induced anaphylaxis to mouthwash. *Br J Dermatol* 2012; **1**: 143
27. Thune P. Two patients with chlorhexidine allergy–anaphylactic reactions and eczema. *Tidsskr Nor Laegeforen* 1998; **118**: 3295–6
28. Pemberton MN, Gibson J. Chlorhexidine and hypersensitivity reactions in dentistry. *Br Dent J* 2012; **213**: 547–50
29. Opstrup MS, Johansen JD, Zachariae C, Garvey LH. Contact allergy to chlorhexidine in a tertiary dermatology clinic in Denmark. *Contact Dermatitis* 2016; **74**: 29–36

30. Ebo DG, Stevens WJ, Bridts CH, Matthieu L. Contact allergic dermatitis and life-threatening anaphylaxis to chlorhexidine. *J Allergy Clin Immunol* 1998; **101**: 128–9–
31. Krishna MT, York M, Chin T, et al. Multi-centre retrospective analysis of anaphylaxis during general anaesthesia in the United Kingdom: aetiology and diagnostic performance of acute serum tryptase. *Clin Exp Immunol* 2014; **178**: 399–404
32. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
33. Leysen J, De Witte L, Bridts CH, Ebo DG. Anaphylaxis during general anaesthesia: a 10-year survey 1 at the University Hospital of Antwerp. *P Belg Royal Acad Med* 2013; **2**: 88–100
34. Opstrup MS, Malling HJ, Kroigaard M, et al. Standardized testing with chlorhexidine in perioperative allergy–a large single-centre evaluation. *Allergy* 2014; **69**: 1390–6
35. Mertes PM, Volcheck GW, Garvey LH, et al. Epidemiology of perioperative anaphylaxis. *Presse Med* 2016; **45**: 758–67
36. Beaudouin E, Kanny G, Morisset M, et al. Immediate hypersensitivity to chlorhexidine: literature review. *Eur Ann Allergy Clin Immunol* 2004; **36**: 123–6
37. Egner W, Helbert M, Sargur R, et al. Chlorhexidine allergy in four specialist allergy centres in the United Kingdom, 2009-13: clinical features and diagnostic tests. *Clin Exp Immunol* 2017; **188**: 380–6
38. Opstrup MS, Poulsen LK, Malling HJ, Jensen BM, Garvey LH. Dynamics of plasma levels of specific IgE in chlorhexidine allergic patients with and without accidental re-exposure. *Clin Exp Allergy* 2016; **46**: 1090–8
39. Sharp G, Green S, Rose M. Chlorhexidine-induced anaphylaxis in surgical patients: a review of the literature. *ANZ J Surg* 2016; **86**: 237–43
40. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: management and outcomes in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 172–88
41. Chong HY, Lai NM, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy of antimicrobial central venous catheters in reducing catheter-related bloodstream infections in adults: abridged Cochrane systematic review and network meta-analysis. *Clin Infect Dis* 2017; **64**: S131–40
42. Afennich F, Slot D, Hossainian N, Van der Weijden G. The effect of hexetidine mouthwash on the prevention of plaque and gingival inflammation: a systematic review. *Int J Dent Hyg* 2011; **9**: 182–90
43. Anderson J, Rose M, Green S, Fernando SL. The utility of specific IgE testing to chlorhexidine in the investigation of perioperative adverse reactions. *Ann Allergy Asthma Immunol* 2015; **114**: 425–426.e1
44. Garvey LH, Ebo D, Mertes PM, et al. Position Paper on the investigation of perioperative immediate hypersensitivity reactions – an expert consensus from the EAACI task force on perioperative hypersensitivity. *Allergy* March 2019
45. Nagendran V, Wicking J, Ekbote A, Onyekwe T, Garvey LH. IgE-mediated chlorhexidine allergy: a new occupational hazard? *Occup Med (Lond)* 2009; **59**: 270–2
46. Ebo DG, Faber M, Elst J, et al. In vitro diagnosis of immediate drug hypersensitivity during anesthesia: a review of the literature. *J Allergy Clin Immunol Pract* 2018; **6**: 1176–84
47. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs – an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013; **68**: 702–12
48. Lai NM, Lai NA, O'Riordan E, Chaiyakunapruk N, Taylor JE, Tan K. Skin antisepsis for reducing central venous catheter-related infections. *Cochrane Database Syst Rev* 2016; **7**: CD010140
49. Lai NM, Chaiyakunapruk N, Lai NA, et al. Catheter impregnation, coating or bonding for reducing central venous catheter-related infections in adults. *Cochrane Database Syst Rev* 2016; **3**: CD007878
50. Ullman AJ, Cooke ML, Mitchell M, et al. Dressing and securement for central venous access devices (CVADs): a Cochrane systematic review. *Int J Nurs Stud* 2016; **59**: 177–96
53. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/infectioncontrol/guidelines/CAUTI/index.html; 2017 (accessed 25 September 2018)
54. Noel J, Temple A, Laycock GJ. A case report of anaphylaxis to chlorhexidine during urinary catheterisation. *Ann R Coll Surg Engl* 2012; **94**: e159–60
55. Oda T, Hamasaki J, Kanda N, Mikami K. Anaphylactic shock induced by an antiseptic-coated central venous [correction of nervous] catheter. *Anesthesiology* 1997; **87**: 1242–4 [Erratum appears in Anesthesiology 1998; 88: 560]
56. Stephens R, Mythen M, Kallis P, Davies DW, Egner W, Rickards A. Two episodes of life-threatening anaphylaxis in the same patient to a chlorhexidine-sulphadiazine-coated central venous catheter. *Br J Anaesth* 2001; **87**: 306–8
57. Guleri A, Kumar A, Morgan RJ, Hartley M, Roberts DH. Anaphylaxis to chlorhexidine-coated central venous catheters: a case series and review of the literature. *Surg Infect* 2012; **13**: 171–4
58. Australian and New Zealand College of Anaesthetists (ANZCA). *PS60 - Gulidelines on the perioperative management of patients with suspected or proven hypersensitivity to chlorhexidine* 2016. Available from, www.anzca.edu.au/.../ps60-2015-guidelines-on-the-perioperative-manageme.pdf (accessed 12 October 2018)
59. Toholka R, Nixon R. Allergic contact dermatitis to chlorhexidine. *Australas J Dermatol* 2013; **54**: 303–6
60. Waclawski ER, McAlpine LG, Thomson NC. Occupational asthma in nurses caused by chlorhexidine and alcohol aerosols. *BMJ* 1989; **298**: 929–30
61. Sato K, Kusaka Y, Suganuma N, Nagasawa S, Deguchi Y. Occupational allergy in medical doctors. *J Occup Health* 2004; **46**: 165–70
62. Apisarnthanarak A, Mundy LM. High incidence of chlorhexidine-induced rash among thai health care workers. *Clin Infect Dis* 2011; **53**: 848–9
63. Garvey LH, Roed-Petersen J, Husum B. Is there a risk of sensitization and allergy to chlorhexidine in health care workers? *Acta Anaesthesiol Scand* 2003; **47**: 720–4
64. Ibler KS, Jemec GBE, Garvey LH, Agner T. Prevalence of delayed-type and immediate-type hypersensitivity in healthcare workers with hand eczema. *Contact Dermatitis* 2016; **75**: 223–9
65. Alam S, Thayalan S, Nagendran V. Prevalence of chlorhexidine specific IgE sensitisation in healthcare workers attending an occupational health department. *Allergy: Eur J Allergy Clin Immunol* 2011; **94**: 591

66. Vu M, Rajgopal Bala H, Cahill J, Toholka R, Nixon R. Immediate hypersensitivity to chlorhexidine. *Australas J Dermatol* 2018; **59**: 55–6
67. Wittczak T, Dudek W, Walusiak-Skorupa J, Swierczynska-Machura D, Palczynski C. Chlorhexidine - still an underestimated allergic hazard for health care professionals. *Occup Med* 2013; **63**: 301–5
68. Toletone A, Dini G, Massa E, et al. Chlorhexidine-induced anaphylaxis occurring in the workplace in a health-care worker: case report and review of the literature. *Med Lav* 2018; **109**: 68–76
70. Antunes J, Van Vuchelen R, Kochuyt A, Ceuppens J. Causes of perioperative anaphylaxis: A Flemish referral center experience. *Allergy: Eur J Allergy Clin Immunol* 2012; **96**: 21

Handling editor: H.C. Hemmings Jr

BJA

British Journal of Anaesthesia, 123 (1): e110–e116 (2019)

doi: 10.1016/j.bja.2018.09.009
Advance Access Publication Date: 19 October 2018
Management

Penicillin allergy de-labelling ahead of elective surgery: feasibility and barriers

L. Savic[1,*], L. Gurr[2], V. Kaura[3], J. Toolan[4], J. A. T. Sandoe[2,5], P. M. Hopkins[1,3] and S. Savic[2,4]

[1]Anaesthetic Department, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [2]University of Leeds School of Medicine, Leeds, UK, [3]Leeds Institute of Biomedical and Clinical Sciences, Leeds, UK, [4]Department of Clinical Immunology and Allergy, Leeds Teaching Hospitals NHS Trust, Leeds, UK and [5]Microbiology Department, Leeds Teaching Hospitals NHS Trust, Leeds, UK

*Corresponding author. E-mail: louise.savic@nhs.net

Abstract

Background: Around 10–15% of the in-patient population carry unsubstantiated 'penicillin allergy' labels, the majority incorrect when tested. These labels are associated with harm from use of broad-spectrum non-penicillin antibiotics. Current testing guidelines incorporate both skin and challenge tests; this is prohibitively expensive and time-consuming to deliver on a large scale. We aimed to establish the feasibility of a rapid access de-labelling pathway for surgical patients, using direct oral challenge.

Methods: 'Penicillin allergic' patients, recruited from a surgical pre-assessment clinic, were risk-stratified using a screening questionnaire. Patients at low risk of true, immunoglobulin E (IgE)-mediated allergy were offered direct oral challenge using incremental amoxicillin to a total dose of 500 mg. A 3-day course was completed at home. De-labelled patients were followed up to determine antibiotic use in surgery, and attitudes towards de-labelling were explored.

Results: Of 219 patients screened, 74 were eligible for inclusion and offered testing. We subsequently tested 56 patients; 55 were de-labelled. None had a serious reaction to the supervised challenge, or thereafter. On follow-up, 17 of 19 patients received appropriate antimicrobial prophylaxis during surgery. Only three of 33 de-labelled patients would have been happy for the label to be removed without prior specialist testing.

Conclusion: Rapid access de-labelling, using direct oral challenge in appropriately risk-stratified patients, can be incorporated into the existing surgical care pathway. This provides immediate and potential long-term benefit for patients. Interest in testing is high among patients, and clinicians appear to follow clinic recommendations. Patients are unlikely to accept removal of their allergy label on the basis of history alone.

Clinical trial registration: ClinicalTrials.gov: AN17/92982.

Keywords: allergy; anaphylaxis; antibiotics; de-labelling; perioperative; preoperative assessment

Editorial decision: 3 Sep 2018; **Accepted:** 3 September 2018

Editor's key points

- Direct oral challenge appeared to be safe and effective in patients at low risk of true penicillin allergy.
- Removal of the allergy label resulted in appropriate use of penicillin during surgery.
- Widespread adoption of this model has the potential to reduce the burden of incorrect penicillin allergy labels in this population.

An estimated 5–10% of people carry a label of penicillin allergy,[1,2] with a higher incidence of around 15% observed in the inpatient population.[2,3] At least 92–95% of unsubstantiated penicillin allergy labels are incorrect when tested[4,5] with side-effects and other non-allergic phenomena misattributed to allergy by patients, clinicians, or both. It is now widely recognised that the 'penicillin allergic' label is associated with increased morbidity, greater healthcare costs, increased rates of methicillin resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile*, and vancomycin-resistant *Enterococcus* (VRE) infection, longer hospital stays, increased readmission rates, and more critical care admissions.[2,6–8] This is most likely through the avoidance of 'best first-line' antimicrobial therapy with penicillins, and use of broad-spectrum alternatives. In surgical patients, there is evidence of increased risk of wound infections when penicillins are replaced with non-beta lactam alternatives[9,10] and of perioperative anaphylaxis from the alternatives used.[11,12]

Testing patients for penicillin allergy, according to current guidelines, is a relatively time-consuming and expensive process.[13] As a result, it is generally only accessible to a minority of patients. In the UK, this is typically those in whom penicillin is the only therapeutic option or those likely to require multiple courses of antibiotics.[14]

In this study, we tested the feasibility of incorporating a rapid access, and abbreviated, de-labelling programme into the existing surgical care pathway. This involved a direct oral challenge, in patients identified as being at low risk of a true penicillin allergy. We assessed the acceptability of this intervention among patients and clinicians, and the impact on prescribing during their surgery.

Methods

The study was approved by the Leeds East Research Ethics Committee (ref: 17/YH/0096), and registered with ClinicalTrials.gov (protocol ID: AN17/92982). It took place in a single-centre, tertiary care setting in the UK, between May 2017 and June 2018.

Patients were recruited by the surgical pre-assessment clinic nurses, who identified 'penicillin allergic' patients and administered a screening questionnaire. The questionnaire risk stratified them for likelihood of immunoglobulin E (IgE)-mediated penicillin allergy (see Appendix 1), and also identified suitability for inclusion into the study. See Tables 1 and 2 for details of risk stratification and eligibility criteria. Only a small proportion of pre-assessment nurses were trained to undertake this screening, so recruitment was undertaken on an *ad hoc* basis, dependent on their availability.

Eligible patients attended a dedicated de-labelling clinic, where a direct oral challenge was performed using oral amoxicillin, after written consent was obtained. The clinic had the facility to test for alternatives, should the index penicillin be different. An incremental dosing regimen of 10%, 50%, and 100% full dose (500 mg) was used, with 20 min intervals between doses. This is the protocol used for low risk patients who undergo challenge testing in the Immunology Department in Leeds Teaching Hospitals, Leeds, UK. Patients were observed for a further 1 h after the full dose, before being allowed home. Baseline blood pressure, heart rate, and oxygen saturations were measured, but only repeated if the patient became unwell during testing. Full resuscitation equipment and personnel were immediately available.

Challenge negative patients were given a 3-day course of antibiotics to complete at home, with an information sheet containing advice and contact details in the event of problems. The team contacted patients by telephone at the end of the course, and checked for delayed symptoms. This was generally at a minimum of 5–7 days after the patient had left the hospital. The results of testing were confirmed in writing to the patient, general practitioner (GP), and surgeon, and the hospital electronic record updated accordingly. Feedback was sought during the phone consultation, on several aspects of the testing process.

Where appropriate, notes were reviewed to determine which antibiotics had been administered for surgical prophylaxis. Three months after testing, the GP was contacted by telephone to check the patient's allergy status on their primary care record.

Table 1 Definition of 'high risk' and 'low risk' symptoms

'Low risk' symptoms	'High risk' symptoms
Nausea, vomiting, diarrhoea	Anaphylaxis
Non-itchy rash	Angioedema
Thrush	Swelling of face/body
Not admitted to hospital	Severe blistering skin rash
Do not know/cannot remember	Wheeze, shortness of breath
	Collapse or dizziness
	Itchy rash
	Symptoms required hospital admission and treatment

Table 2 Eligibility criteria. *These three criteria were amended after high demand for testing amongst otherwise eligible patients

Eligible	Ineligible
Low risk symptoms	High risk symptoms
Reaction occurred >15 yr ago*	Reaction <15 yr ago
Sufficient time for testing before operation*	No time for testing
Wants to be tested	Declines testing
Requires penicillin for surgery*	Doesn't require penicillin for surgery
Aged >18 yr	Pregnant, breastfeeding
	Unstable asthma (oral steroids required in the past 6 months)

Midway through the study, the eligibility criteria were amended in response to high patient demand for testing (substantive amendment October 31, 2017). From this point, all patients with low risk symptoms were offered testing, including those with recent reactions (if symptoms were clearly remembered by the patient), those not requiring penicillin for surgery, and those who could only be tested after operation.

Results

During the study period, a total of 219 patients with the 'penicillin allergic' label were screened. Of these, 74 patients were eligible for testing, and 145 were ineligible. See Figure 1 for outcome of screening for all patients.

A total of 56 patients underwent a direct oral challenge. No patient suffered any immediate adverse reactions, and none suffered any serious delayed reactions subsequent to leaving hospital. One patient developed urticaria in her hands after the second dose and stopped taking the amoxicillin. On questioning, it was discovered that her index reaction had been of widespread urticaria, but she had chosen not to disclose this to the study team previously as she was keen to be tested. Four patients experienced mild non-allergic symptoms during the prolonged antibiotic course. Two patients were considered to be unrelated to the amoxicillin (sore throat and a cough in one patient, and a worsening of existing arthralgia in the other); another two experienced mild nausea. All four patients completed the course of antibiotic therapy.

Among the patients who did not attend clinic (N=18), five were unable to attend because of ongoing illness and treatment, or a change of surgical date. The remainder simply did not turn up for their appointments. This was despite the study team attempting to contact all patients a few days ahead of the appointments to confirm attendance.

A total of 119 patients had 'low risk' symptoms, described in Table 3. Not all of these were eligible for testing, however, as they did not meet other eligibility criteria. In around half of patients, the reason for ineligibility was refusal to undergo testing; the remainder were ineligible because penicillin was not required, or the operation was too soon to have time to be tested. These eligibility criteria were removed midway through the study in response to high patient demand. One patient was ineligible because of high risk co-morbidities.

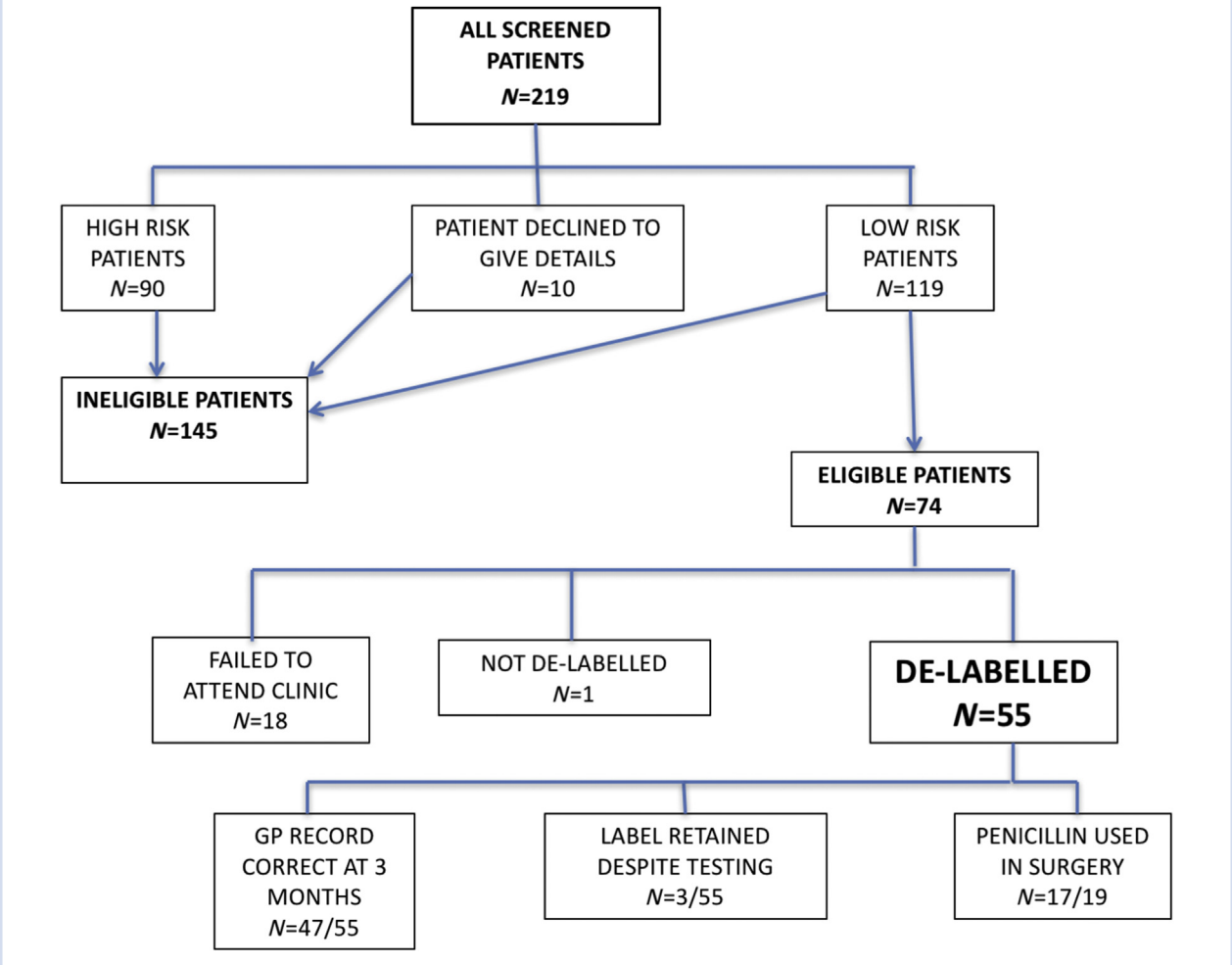


Fig 1. Outcomes of all screened patients.

Table 3 Symptoms of index reaction in 119 patients in the low risk group. GI, gastrointestinal. The total number of symptoms exceeds 119 as some patients had more than one symptom

Symptom	GI upset	Red rash Flushing	Rash (unspecified)	Don't know Can't remember	Thrush	Miscellaneous (e.g. 'convulsions')
n	32	41	25	41	1	2

All screened patients were asked if they would like to undergo testing. Overall, 74% (163/219) stated they would like to be tested. Within the 'low risk' population 82% (98/119) requested testing; in the 'high risk' group 66% (59/90) requested it. In patients who declined testing (56 patients), the reasons for this were explored (Fig. 2). There were 10 patients for whom no information was available except whether they would like to be tested; six of them wished to be tested.

Among the patients who were successfully de-labelled, feedback was sought on levels of satisfaction with the process. Although a majority stated they would have preferred testing to be performed on the same day as pre-assessment (70%, 30/47), it was broadly considered to be a 'smooth process' (85%, 40/47). Low levels of anxiety about the testing were noted, with 81% (35/43) of patients stating they had little or no anxiety on the day. Patients were asked if they would have been happy for their label to be removed without any testing at all, on the basis that their index reaction did not indicate allergy. The majority (70%, 30/43) would not have been happy to have their allergy label removed in this way. Comments included: 'The security of supervision takes away the anxiety'; 'In case I had a bad reaction'; 'I would worry about having a bad reaction without support, in case help was needed'; and 'You can't undo 30 years of being allergic to penicillin with a quick conversation'.

In the follow-up of patients subsequently undergoing surgery, 17/19 were given appropriate penicillin-based surgical prophylaxis uneventfully; penicillin was avoided in two patients despite negative testing. In patients successfully de-labelled, the GP confirmed that the correct allergy status was present on the primary care record in 47/55 patients. The reason for re-labelling in our current cohort is only known in one patient; this patient was discovered to have re-labelled himself, when he was incidentally anaesthetised for an emergency operation by a member of the study team. This patient's recollection of the testing was that he had been told he had 'suffered a severe allergic reaction and must continue to avoid penicillin at all costs'. Despite the reassurance, he was adamant he would not wish to receive penicillin for surgery, and instead received teicoplanin.

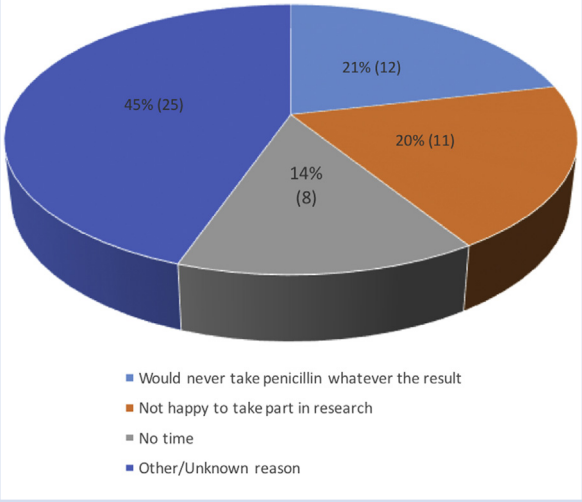


Fig 2. Reasons why patients with a label of 'penicillin allergy' declined testing.

Discussion

In this study, a rapid access and abbreviated de-labelling test was integrated into the existing preoperative care pathway. Patients were risk stratified on the basis of history alone, and those at low-risk of IgE-mediated hypersensitivity, in whom skin testing was unlikely to offer additional diagnostic value, underwent a direct oral challenge test. Recall of exact timing of the index reaction by patients is accepted to be poor, especially when from many years ago.[15] Instead, we focused on the symptoms of the reaction, and their severity. In particular, we asked about the requirement for hospitalisation and treatment of the index event, as a marker of severity. None of the patients tested suffered serious adverse events during testing. This is consistent with the findings of similar studies, which demonstrate the safety of this approach when patients are appropriately risk stratified.[16–18]

The incidence of unsubstantiated penicillin allergy labels in hospital inpatients is around 10–15%. In addition to potential harm for individuals, there exists the wider problem of multi-resistant bacterial strains that are promoted by the use of broad-spectrum antibiotics, and an ever-decreasing pool of antimicrobial options to treat these. Improving stewardship through more rational antibiotic use is a key strategy for healthcare systems.[19] Reducing the number of people inappropriately denied penicillin contributes to this, and novel strategies should be developed to allow wider access to de-labelling and promote effective use of penicillins where possible.[20]

Current guidelines advise that patients are referred to specialist services for testing. The gold standard test with which to establish tolerance to penicillin is a challenge, using the index penicillin to which the patient reacted. According to current UK and European guidelines, patients should first be skin tested, using prick test, intradermal test, or both.[1,21,22] This identifies patients who are IgE-sensitised and provides risk stratification for progression to the next step in the diagnostic pathway, a challenge test.[1,21] Skin tests have a negative predictive value (NPV) approaching 100%, and patients who do not react to prick or intradermal tests are therefore unlikely to have a severe reaction on challenge.[5,23] However, the interpretation of positive skin tests is less clear; these patients are generally

not offered a challenge test and so the positive predictive value (PPV) is difficult to determine. The PPV is generally accepted to be less than 50% based on a limited number of prospective studies and on outcomes from accidental re-exposure.[24–26]

There are significant limitations to skin testing. Many studies have commented on reduced sensitivity over time,[3,27,28] and low sensitivity and specificity in patients with non-severe, non-immediate, and vague reactions.[29–32] Reactions in childhood, typically delayed onset and unspecified rashes which can result in life long allergy labels, are only rarely associated with positive skin or challenge testing.[33]

Increasingly, the evidence demonstrates that patients can be risk stratified for a challenge test on the basis of history alone. Where symptoms are not severe, not suggestive of an IgE-mediated reaction, are vague, or historic, the utility of skin testing is low and a direct oral challenge may be safe and appropriate. This approach is already used routinely for children in the UK,[34,35] and several studies have demonstrated safety and efficacy in adults.[16–18]

A number of antimicrobial stewardship programmes have been successful at reducing the burden of unsubstantiated penicillin allergy labels and have demonstrated benefits from doing so.[10,36–40] Some programmes have been used specifically in the preoperative setting, with subsequent reduced use of intraoperative vancomycin and other beta-lactam alternatives.[41,42] The majority of these programmes administer skin tests initially and only proceed to challenge testing if these are negative. Although this is an accepted and valid strategy, the skin-testing component has implications for the overall cost and convenience of the pathway. Skin testing kits are relatively expensive and require trained personnel for their use and interpretation. There is also the potential for overdiagnosis because of false positive skin tests and continued unnecessary avoidance of penicillin in such patients. The use of direct oral challenge in low risk patients is recent in Europe but has been successfully used in several centres in the USA; this gap in practice has recently been commented.[43]

Although not all labels can be removed using this pathway, we estimate from this study that at least one-third of 'penicillin allergic' patients would be suitable for direct oral challenge. Patients with labels more suggestive of IgE-mediated allergy continue to require skin testing as part of their diagnostic work-up, or should be advised to continue avoiding penicillins. Patients with histories of severe, widespread skin reactions, including delayed and blistering eruptions such as DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) and TENS (Toxic Epidermal Necrolysis), are also high risk and must avoid penicillin.

The barriers to implementing this on a large scale are twofold: human factors leading to anxiety around allergy labels and financial implications. We were able to explore some of the human factors in this study.

The first perceived barrier was a lack of interest in testing. However, patients appeared keen to be tested, irrespective of the severity of their presenting symptoms. The change to our eligibility criteria was indeed made in direct response to demand among patients with low risk labels, but who were ineligible for other reasons—most commonly lack of time, or lack of immediate need for penicillin.

A second potential barrier was lack of acceptance among clinicians (primarily anaesthetists) that the abbreviated pathway provided conclusive evidence of tolerance to penicillin. However, clinic advice was generally accepted by anaesthetists on the day of surgery. In the two patients denied penicillin during the course of the operation, it is not known whether the anaesthetist actively disregarded the test result or was simply unaware of it.

Lastly, it has been demonstrated previously that a high proportion of patients re-label themselves after negative testing for penicillin allergy, or are re-labelled by healthcare providers.[44] However, the rate of 're-labelling' in our population appeared to be very low. Only the longer-term follow-up of this cohort will determine whether this is indeed true. It is likely that behavioural change interventions will be required in addition to the de-labelling itself, in order to address this issue. There is little literature in this field to date, although one centre in the USA has used pharmacist counselling and wallet cards with confirmation of test results, to good effect.[45]

The financial barrier to widespread testing is likely to be significant. Although long-term cost benefits are likely to be realised through de-labelling patients, there is an 'upfront' cost to perform the testing. Omitting skin tests helps with this, but even abbreviated pathways using direct oral challenge have a cost attached, which is not immediately offset by the avoidance of a single intraoperative dose of a more expensive alternative antibiotic.

Finally, this study addressed the question of acceptability of de-labelling without formal testing—that is, on the basis of history alone. In those with histories clearly consistent with side-effects (e.g. nausea or thrush), those who have received penicillin uneventfully since their index reaction, and those with only a family history of allergy, there is no requirement for allergy testing. In the authors' institution, guidelines recommend that penicillin can be administered without prior testing in such patients, although these are rarely followed. Our results indicate that patients may be reluctant to receive penicillin without formal testing under supervision.

The limitation of this study is primarily its small size, and further work is needed to corroborate our findings. In addition, we only have follow-up data from 3 months after testing. It would be informative to identify the rate of re-labelling several years after testing, and explore the reasons for this. Nevertheless, our results are encouraging in terms of potential uptake in future studies. Based on our work, uptake could be maximised by offering 'opportunistic' testing of all patients attending for surgical pre-assessment irrespective of the need for penicillin during surgery, offering testing as part of the initial pre-assessment visit rather than a separate clinic appointment, and reducing the time required for testing. The last of these could be achieved by moving from an incremental, to single dose challenge, using 250 or 500 mg amoxicillin. The utility of this has been confirmed in a study of 500 sequential patients in the USA,[4] and a cohort of Marine recruits also in the USA,[18] where low risk patients received a single dose oral challenge with none having a severe life-threatening reaction. Using this protocol, the time for testing would be reduced from 1 h and 45 min, to about 1 h, increasing both the likelihood of uptake among patients and the turnover in clinic. In the last few months of this study, the protocol was altered to allow single dose challenge (substantial amendment January 5, 2018), although none received this before the end of the study period. A single dose approach will be taken in future de-labelling programs at the host site.

It is increasingly clear that the burden of 'en masse' de-labelling cannot be shouldered by specialist services in isolation, as these are relatively small groups with already scarce resources. Our protocol is one example of how testing might be integrated into an existing patient pathway, and delivered

by non-specialists working in close collaboration with allergy/immunology specialists.

Authors' contributions

Study design: LS, SS, PH, JS.
Writing of the manuscript: LS, SS, PH, JS.
Patient recruitment: LS, LG, VK, JT.
Conduct of challenge testing: LS, LG, VK, JT.

Declaration of interest

The authors declare that they have no conflicts of interest.

Funding

Leeds Teaching Hospital NHS Trust.

Acknowledgements

The authors are grateful to N. Glover, A. Rose, and A.-M. Jones for invaluable help in screening patients in pre-assessment; to S. Farooque, who provided critical review of the protocol; and to the Immunology and Anaesthetic departments of Leeds Teaching Hospitals for their support for this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2018.09.009.

References

1. Mirakian R, Leech SC, Krishna MT, et al. Management of allergy to penicillins and other beta-lactams. *Clin Exp Allergy* 2015; **45**: 300–27
2. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. *J Allergy Clin Immunol* 2014; **133**: 790–6
3. Mistry AMD, Corps C, Savic S, Savic L. Feasibility and utility of testing for penicillin allergy status in patients attending for elective surgery. *Clin Exp Allergy* 2016; **46**: 1625–74
4. Macy E, Ngor EW. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. *J Allergy Clin Immunol Pract* 2013; **1**: 258–63
5. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and, Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010; **105**: 259–73
6. Knezevic B, Sprigg D, Seet J, et al. The revolving door: antibiotic allergy labelling in a tertiary care centre. *Intern Med J* 2016; **46**: 1276–83
7. Charneski L, Deshpande G, Smith SW. Impact of an antimicrobial allergy label in the medical record on clinical outcomes in hospitalized patients. *Pharmacotherapy* 2011; **31**: 742–7
8. van Dijk SM, Gardarsdottir H, Wassenberg MW, Oosterheert JJ, de Groot MC, Rockmenn H. The high impact of penicillin allergy registration in hospitalised patients. *J Allergy Clin Immunol Pract* 2016; **4**: 926–31
9. Blumenthal K, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES. The impact of a reported penicillin allergy on surgical site infection risk. *Clin Infect Dis* 2017; **66**: 329–36
10. McDanel DL, Azar AE, Dowden AM, et al. Screening for beta-lactam allergy in joint arthroplasty patients to improve surgical prophylaxis practice. *J Arthroplasty* 2017; **32**: S101–8
11. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
12. Savic LC, Garcez T, Hopkins PM, Harper NJ, Savic S. Teicoplanin allergy — an emerging problem in the anaesthetic allergy clinic. *Br J Anaesth* 2015; **115**: 595–600
13. Blumenthal KG, Li Y, Banerji A, Yun BJ, Long AA, Walensky RP. The cost of penicillin allergy evaluation. *J Allergy Clin Immunol Pract* 2017; **6**: 1019–27
14. National Clinical Guideline Centre (UK). *Drug allergy: diagnosis and management of drug allergy in adults, children and young people*. London: National Institute for Health and Care Excellence (UK); 2014 Sep (NICE Clinical Guidelines, No. 183.) 5, Guideline summary
15. Borch JE, Andersen KE, Bindslev-Jensen C. The prevalence of suspected and challenge-verified penicillin allergy in a university hospital population. *Basic Clin Pharmacol Toxicol* 2006; **98**: 357–62
16. Confino-Cohen R, Rosman Y, Meir-Shafrir K, et al. Oral challenge without skin testing safely excludes clinically significant delayed-onset penicillin hypersensitivity. *J Allergy Clin Immunol Pract* 2017; **5**: 669–75
17. Iammatteo M, Alvarez Arango S, Ferastraoaru D, et al. Safety and outcomes of oral graded challenges to amoxicillin without prior skin testing. *J Allergy Clin Immunol Pract* 2018. https://doi.org/10.1016/j.jaip.2018.05.008. Advance Access published on May 23
18. Tucker MH, Lomas CM, Ramchandar N, Waldram JD. Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits. *J Allergy Clin Immunol Pract* 2017; **5**: 813–5
19. UK 5 Yeat Antimicrobial Resistance Strategy 2013 to 2018. Available from: https://www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018. [Accessed 4 October 2018].
20. Krishna MT, Huissoon AP, Li M, et al. Enhancing antibiotic stewardship by tackling "spurious" penicillin allergy. *Clin Exp Allergy* 2017; **47**: 1362–73
21. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs — an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013; **68**: 702–12
22. Torres MJ, Blanca M, Fernandez J, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003; **58**: 961–72
23. del Real GA, Rose ME, Ramirez-Atamoros MT, et al. Penicillin skin testing in patients with a history of beta-lactam allergy. *Ann Allergy Asthma Immunol* 2007; **98**: 355–9
24. Park MA, Solensky R, Khan DA, Castells MC, Macy EM, Lang DM. Patients with positive skin test results to penicillin should not undergo penicillin or amoxicillin challenge. *J Allergy Clin Immunol* 2015; **135**: 816–7
25. Macy E, Burchette RJ. Oral antibiotic adverse reactions after penicillin skin testing: multi-year follow-up. *Allergy* 2002; **57**: 1151–8

26. Tannert LK, Mortz CG, Skov PS, Bindslev-Jensen C. Positive skin test or specific IgE to penicillin does not reliably predict penicillin allergy. *J Allergy Clin Immunol Pract* 2017; **5**: 676–83
27. Macy E, Schatz M, Lin C, Poon KY. The falling rate of positive penicillin skin tests from 1995 to 2007. *Perm J* 2009; **13**: 12–8
28. Blanca M, Torres MJ, Garcia JJ, et al. Natural evolution of skin test sensitivity in patients allergic to beta-lactam antibiotics. *J Allergy Clin Immunol* 1999; **103**: 918–24
29. Salkind AR, Cuddy PG, Foxworth JW. The rational clinical examination. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. *JAMA* 2001; **285**: 2498–505
30. Goldberg A, Confino-Cohen R. Skin testing and oral penicillin challenge in patients with a history of remote penicillin allergy. *Ann Allergy Asthma Immunol* 2008; **100**: 37–43
31. Solensky R, Earl HS, Gruchalla RS. Penicillin allergy: prevalence of vague history in skin test-positive patients. *Ann Allergy Asthma Immunol* 2000; **85**: 195–9
32. Padial A, Antunez C, Blanca-Lopez N, et al. Non-immediate reactions to beta-lactams: diagnostic value of skin testing and drug provocation test. *Clin Exp Allergy* 2008; **38**: 822–8
33. Caubet JC, Kaiser L, Lemaitre B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol* 2011; **127**: 218–22
34. Mill C, Primeau MN, Medoff E, et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and nonimmediate reactions to amoxicillin in children. *JAMA Pediatr* 2016; **170**: e160033
35. Ibanez MD, Del Rio PR, Lasa EM, et al. Prospective assessment of diagnostic tests for pediatric penicillin allergy, from clinical history to challenge tests. *Ann Allergy Asthma Immunol* 2018; **121**. 235–44.e3
36. Moussa Y, Shuster J, Matte G, et al. De-labeling of B-lactam allergy reduces intraoperative time and optimises choice in antibiotic prophylaxis. *Surgery* 2018; **164**: 117–23
37. Sacco KA, Bates A, Brigham TJ, Imam JS, Burton MC. Clinical outcomes following inpatient penicillin allergy testing: a systematic review and meta-analysis. *Allergy* 2017; **72**: 1288–96
38. Trubiano JA, Thursky KA, Stewardson AJ, et al. Impact of an integrated antibiotic allergy testing program on antimicrobial stewardship: a multicenter evaluation. *Clin Infect Dis* 2017; **65**: 166–74
39. Trubiano J, Phillips E. Antimicrobial stewardship's new weapon? A review of antibiotic allergy and pathways to 'de-labeling'. *Curr Opin Infect Dis* 2013; **26**: 526–37
40. Leis JA, Palmay L, Ho G, et al. Point-of-care beta-lactam allergy skin testing by antimicrobial stewardship programs: a pragmatic multicenter prospective evaluation. *Clin Infect Dis* 2017; **65**: 1059–65
41. Frigas E, Park MA, Narr BJ, et al. Preoperative evaluation of patients with history of allergy to penicillin: comparison of 2 models of practice. *Mayo Clin Proc* 2008; **83**: 651–62
42. Park M, Markus P, Matesic D, Li JT. Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy. *Ann Allergy Asthma Immunol* 2006; **9**: 681–7
43. Aberer W, Macy E. Moving toward optimizing testing for penicillin allergy. *J Allergy Clin Immunol Pract* 2017; **5**: 684–5
44. Rimawi RH, Shah KB, Cook PP. Risk of redocumenting penicillin allergy in a cohort of patients with negative penicillin skin tests. *J Hosp Med* 2013; **8**: 615–8
45. Patel SV, Tarver SA, Alvarez KS, Lutek KE, Schlebus J, Khan DA. Effectiveness of interventions to maintain penicillin allergy label removal as part of an inpatient penicillin allergy testing protocol. *J Allergy Clin Immunol* 2017; **139**: AB183

Handling editor: J.G. Hardman

BJA

British Journal of Anaesthesia, 123 (1): e117–e125 (2019)

doi: 10.1016/j.bja.2019.01.002
Advance Access Publication Date: 12 February 2019
Review Article

TESTING

In vitro diagnostic tests for perioperative hypersensitivity, a narrative review: potential, limitations, and perspectives

Tomonori Takazawa[1,*], Vito Sabato[2] and Didier G. Ebo[2]

[1]Intensive Care Unit, Gunma University Hospital, Maebashi, Japan and [2]Department of Immunology, Allergology, and Rheumatology, University Antwerp, Antwerp University Hospital, Antwerp, Belgium

*Corresponding author. E-mail: takazawt@gunma-u.ac.jp

This article is accompanied by an editorial: Optimising diagnostics in perioperative allergy by Opstrup & Garvey, *Br J Anaesth* 2019:123:e11–e13, doi: 10.1016/j.bja.2019.03.010

Summary

Correct diagnostic management of perioperative hypersensitivity aims to identify the underlying mechanism(s), responsible culprit(s), and safe alternative drugs or techniques. Although drug provocation tests are considered the gold standard, diagnosis of perioperative hypersensitivity mainly relies on skin testing. Use of *in vitro* tests, such as quantification of specific immunoglobulin E antibodies, serum tryptase, and plasma histamine, as well as basophil activation tests is becoming widespread. These latter tests have the advantage of having no risk of recurrence of immediate hypersensitivity reactions. In this narrative review, we summarise the principles of these *in vitro* tests, and the possibilities and limitations when these tests are used for testing sensitivity to substances with a high risk of causing perioperative hypersensitivity. Hence, we focus on neuromuscular blocking agents, antibiotics, natural rubber latex, and opiates/opioids. The combination of multiple tests would allow diagnosis of perioperative hypersensitivity with the right balance of safety and accuracy.

Keywords: allergy; anaphylaxis; anaesthesia; basophil activation test; hypersensitivity; perioperative; skin test; specific IgE

Perioperative hypersensitivity (POH) reactions, although rare, can have potentially life-threatening consequences because of the potential for diagnostic error. Hypersensitivity reactions in the perioperative period can be provoked by a variety of triggers, although, in most cases, POH reactions are triggered by drugs such as neuromuscular blocking agents (NMBAs) and antibiotics, natural rubber latex from *Hevea brasiliensis*, or related products such as chlorhexidine and dyes.[1–4] The standard reference test for accurate diagnosis of immediate hypersensitivity reactions to these substances is a controlled drug provocation test. However, drug provocation tests are not always possible for obvious ethical and practical reasons, and they might not always be predictive of the clinical outcome.[5] Therefore, in clinical practice, diagnostic workup of POH reactions generally starts with judicious skin testing.[6,7]

Editorial decision date: 03 January 2019; **Accepted:** 3 January 2019

Although skin tests still merit the status of the primary diagnostic test in the evaluation of POH reactions, we believe that there is room for additional *in vitro* tests. First, skin test procedures have not been thoroughly validated for many compounds, as studies have mainly focused on determination of non-irritating concentrations in (exposed) control individuals.[8] Second, skin tests do not have absolute predictive value. For example, uncertainties remain for skin tests with potent non-specific histamine releasers, such as opiates[9] and fluoroquinolones,[10] or with NMBAs that can elicit positive intradermal test responses independent of mast cell degranulation.[11] Alternatively, negative skin tests might not always guarantee safe re-exposure to the substance being evaluated.[12] Third, a positive skin test is not necessarily indicative of a specific immune-mediated pathomechanistic process, but could mirror off-target occupation of the MRGPRX2 receptor that is constitutively expressed on cutaneous mast cells.[13] Collectively, these observations indicate that *in vitro* tests would not only facilitate diagnosis of POH, but might also deepen our knowledge and cause paradigm shifts in our understanding about the pathomechanisms of potentially life-threatening POH reactions.[14] Here, we stress the need for acute serum effector cell mediator measurement, and summarise the main principles, possibilities, and limitations of quantification of specific immunoglobulin E (IgE) antibody assays and basophil activation tests.

Quantification of serum tryptase and plasma histamine

The diagnosis of POH relies on the presence of clinical, biological, and allergological evidence.[15] Clinical evidence, including the features and severity of clinical signs, and the interval between introduction of a suspected allergen and the onset of symptoms should be the first line of evidence for initial diagnosis. These are beyond the focus of this review, which will describe the second-most important evidence, *in vitro* primary testing.

Immediate hypersensitivity reactions, such as POH, result from activation of mast cells and basophils by the allergen, recognised through specific IgEs attached to the surface of these cells, resulting in the release of inflammatory mediators.[7] Measurement of these inflammatory mediators is the basis of biochemical confirmation of the occurrence of such reactions. Of the several inflammatory mediators that are released in anaphylaxis, including tryptase, histamine, platelet-activating factor, prostaglandin D2, and leukotriene E4, tryptase is most widely assessed in blood tests used to confirm the occurrence of anaphylaxis. This is because of its longer half-life compared with the other mediators: tryptase levels peak 1–2 h after onset of the reaction and return to baseline values within several hours. As tryptase levels in basophils are <1% of those found in tissue mast cells,[17] increases in tryptase concentrations are considered to be indicative of mast cell activation.[18] Several tryptase cut-off values, such as >25[16] or >15.7 μg L^{-1},[19] have been proposed to identify mast cell activation. Alternatively, use of the ratio of peak to basal tryptase has been recommended to improve accuracy for diagnosis of anaphylaxis.[19,20] Comparison between peak and baseline serum tryptase values is reported to provide more valuable information about mast cell activation than do absolute cut-off values, and a consensus equation has been formulated.[21] According to this formula, mast cell activation is defined as peak tryptase levels > 2+1.2(baseline tryptase). This formula has recently been validated for POH with sensitivity, specificity, positive predictive value, and negative predictive value of 78%, 91%, 98%, and 44%, respectively.[22] However, the sensitivity is not absolute, and patients who present clinically with anaphylaxis but in whom serum tryptase concentrations are not increased still require investigation, as false negatives do occur.[23]

Histamine is one of the important mediators in the early onset of anaphylaxis. It is produced by decarboxylation of histidine present in the Golgi apparatus of mast cells and basophils, and is rapidly metabolised by histamine transferase once it is released into the blood.[24] Therefore, plasma histamine begins to rise within 5 min after onset of anaphylaxis, although its increase lasts for only 30–60 min. Hence, it is difficult to prove its presence more than 1 h after onset of hypersensitivity reactions. The short half-life of histamine prevents its use as a reliable marker of anaphylaxis. Other disadvantages include the following: (a) because histamine is also produced by neurons and bacteria, increased histamine does not necessarily indicate mast cell/basophil activation; (b) histamine levels can be influenced by food intake, drug intake, or both; and (c) measurement methods have specific requirements and are expensive. However, histamine assay at 30 min after a suspected hypersensitivity reaction is recommended by French guidelines.[7] This recommendation seems to be based on the evidence that the diagnostic accuracy of POH is increased when histamine and tryptase assays are combined. Although the significance of histamine assay in the diagnosis of POH is controversial, there is no reason not to measure histamine levels if facilities for the measurement are available.

Quantification of serum specific IgE

Principles

Quantification of drug-specific IgE with IgE immunoassays relies upon detection of a drug (hapten)–carrier–antibody complex (Fig. 1). The drug (hapten)–carrier conjugate is coupled with a solid phase, which is incubated with patient serum. The amount of specific IgE bound is subsequently detected with a secondary antihuman IgE antibody, labelled with a radioisotope in the older, largely abandoned, radioimmunoassays, or with an enzyme with colorimetric reading in more recent enzyme-linked immunosorbent assays, or with fluorescence reading in fluorescent enzyme immunoassays. Results of most commercially available assays are expressed as arbitrary units of allergen (UA) per volume (e.g. kUA L^{-1}). For years, the technical detection limit was 0.35 kUA L^{-1}. However, recently a new heterologous calibration scheme has been introduced where quantification is based on of IgE antibody curves with a range of 0.00–100 kUA L^{-1}, with a detection limit of 0.10 kUA L^{-1} and a cut-off of 0.10 or 0.35 kUA L^{-1} for positive results. However, these decision thresholds have been set arbitrarily and the tests might benefit from allergen-specific cut-offs.[25]

Clinical applications

Neuromuscular blocking agents

Sensitisation to NMBAs is generally assessed serologically using various methods that measure drug-specific IgE antibodies, such as to suxamethonium, rocuronium, and atracurium, or indirectly by measuring IgE reactivity to tertiary and quaternary substituted ammonium structures (NH_3^+) that are considered to be the major epitopes of NMBAs. Most frequently used is the

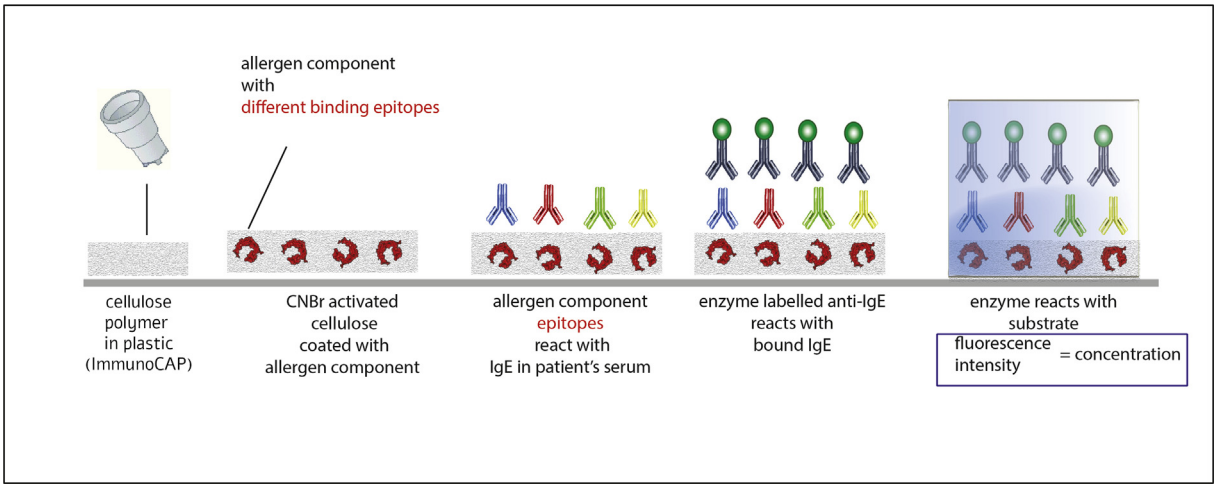


Fig 1. Quantification of drug-specific immunoglobulin E (IgE) with IgE immunoassays relies upon detection of a drug (hapten)–carrier–antibody complex. Cyanogen bromide (CNBr)-activated cellulose is a carrier used for binding the drug (hapten)–carrier conjugate (allergen component). The binding of specific IgE in serum to epitopes of the allergen component is evaluated with enzyme-linked immunosorbent assay. The amount of specific IgE bound is detected with a secondary antihuman IgE antibody labelled with a fluorophore generating enzyme, and fluorescence intensity generated by adding enzyme substrate is quantified.

morphine-based assay[25–27] or, in France, methods using choline chloride or a *p*-aminophenyl phosphorylcholine.[28–30] The specific IgE assays for suxamethonium, rocuronium, atracurium, and morphine from Phadia Thermo Fisher (Uppsala, Sweden) display a specificity generally exceeding 85% and a sensitivity varying between 40% and 90%.[31] The morphine-based assay, although valuable for depiction of sensitisation to suxamethonium and rocuronium, is unreliable for detection of antibodies to benzylisoquinolines.[32,33] In addition, as IgE reactivity to tertiary and quaternary substituted ammonium structures are frequent in the general population, the morphine-based test should not be used in isolation to diagnose NMBA hypersensitivity, nor should it be used to absolutely preclude use of an NMBA that tests negative in skin tests and basophil activation tests.[34]

Antibiotics

The most studied antibiotic-specific IgE assays and the only ones commercially available, are those for β-lactams. Although several cases of positive specific IgE results in cases of immediate hypersensitivity reactions with negative skin tests have been described,[35,36] specific IgE for β-lactam assays generally exhibit a variably poor sensitivity (0–70%) that decreases over time.[37] There is also increasing evidence supporting the low specificity of the tests because of the non-specific binding of these antibodies in solid phase assay as a result of elevated total IgE titres or specific IgE antibodies to phenylethylamine.[38] Therefore, specific IgE antibodies to β-lactams seem of restricted utility and should not be used in isolation to exclude or confirm immediate hypersensitivity reactions to these antibiotics.

Natural rubber latex

Although its use is apparently decreasing because of the application of other elastomers, natural rubber latex remains another significant cause of POH.[1–4] Diagnosis of natural rubber latex hypersensitivity is best documented by a positive result with both skin tests and measurement of specific IgEs,[39] because an isolated positive specific IgE to latex—as seen in up to 25% of patients with a grass/weed pollen allergy and 20% of patients with an allergy to wasps/honeybees[40]—can easily be misleading and hide an alternative culprit. In cases with incongruent skin tests and specific IgEs to latex, molecular diagnostics (reviewed by Van Gasse and colleagues[41]), basophil activation tests, or both[42] might be required for correct diagnosis, as these techniques frequently enable identification of clinically irrelevant specific IgE results caused by sensitisation to cross-reactive carbohydrate determinants and profilins.

Opioids and opiates

Despite their ubiquitous use, genuine IgE-mediated reactions to opiates and (semi)synthetic opioids are exceedingly rare.[43] Moreover, hypersensitivity reactions to these substances often result from alternative mechanisms, such as off-target occupation of the MRGPRX2 receptor[44] that is constitutively expressed on some mast cell subpopulations. Correct diagnosis of hypersensitivity reactions to opiates and certain opioids is challenging mainly because of uncertainties associated with skin tests[9] and the absolute inadequacy of specific IgEs to poppy seed (*Papaver somniferum*) and morphine.[45]

Miscellaneous

A commercial assay of specific IgE to chlorhexidine is available, although studies evaluating this assay in a large patient group are limited.[46,47] For a traditional, arbitrarily chosen threshold of 0.35 kUA L^{-1}, the sensitivity and specificity of specific IgE to chlorhexidine was 84% and 94%, respectively.[47] For a receiver operating characteristic (ROC)-generated threshold of 0.20 kUA L^{-1}, the sensitivity was 94% and the specificity was 91%.[47]

Gelatine-containing products include certain plasma substitutes, haemostatic sponges, and vaccines. To date, two

distinct types of IgE-mediated bovine gelatine allergies have been recognised: genuine gelatine allergy that results from sensitisation to the protein part of the molecule, and gelatine allergy resulting from sensitisation to the glycan moiety of the molecule, that is galactose-α-1,3-galactose (α-Gal).[48–50]

Ethylene oxide is used for sterilisation of many medical devices because it exerts sterilising effects even at low temperatures and has minimal effects on materials, despite the fact that it is toxic and suspected to be carcinogenic. Patients who frequently undergo surgery, such as those with spina bifida, reportedly have a high positivity rate for specific IgE to ethylene oxide.[51] One-third of spina bifida patients with specific IgE antibodies against latex also have specific IgE against ethylene oxide.[51] As there are only a few reports of immediate hypersensitivity reactions to ethylene oxide, patients with specific IgE to ethylene oxide rarely show symptoms of an immediate hypersensitivity reaction despite being positive for the antibodies. However, ethylene oxide should always be kept in mind when determining the cause of POH in patients who frequently undergo surgery.[52]

Basophil activation tests

Principles

The foundations of current flow-assisted basophil activation tests were laid 25 yr ago[53]; the technique has largely supplanted older mediator release assays that rely upon difficult quantification of mediators released in the supernatant.[54] The technical principles and requirements of basophil activation tests have been detailed elsewhere (Fig. 2).[55,56] Traditional basophil activation tests rely upon flow cytometric analysis of various activation and degranulation markers on the surface membrane of basophils. These changes can be detected and quantified on a single-cell level using specific monoclonal antibodies conjugated with different laser-excitable fluorochromes. Although there are different ways to phenotype basophils, typically they are characterized according to scatters, presence of membrane-specific IgE, and CD203c. Activation is measured through appearance of CD63, upregulation of CD203c, and decrease of intracellular histamine content.

Clinical applications

Neuromuscular blocking agents

As it is impossible to perform full-dose drug provocation tests with NMBAs for obvious ethical and practical reasons, anaesthetists and immunologists/allergists mainly rely upon skin tests to confirm clinical suspicions of NMBA hypersensitivity. The predictive value of skin testing is not absolute, which leaves room for additional *in vitro* tests. Basophil activation tests constituted the principal *in vitro* test to document hypersensitivity to NMBAs for a long time because of the absence of specific IgE assays for many types of NMBAs. The sensitivity of basophil activation tests for NMBAs varies between 36% and 92%, and the specificity between 81% and 100%.[31] Basophil activation tests not only complement skin tests in the diagnostic workup of patients with drug hypersensitivity, but also enable assessment of cross–reactivity between NMBAs.[57]

Antibiotics

Most data about the usefulness of basophil activation tests to assess antibiotic hypersensitivity have been provided in the context of IHRs to β-lactams and quinolones.[31] Studies that have investigated the basophil activation test as a diagnostic tool in immediate hypersensitivity reactions to β-lactams have mainly focused on amoxicillin. Compared with the quantification of specific IgE antibodies, basophil activation tests show a higher sensitivity (~50%) and specificity (~90%). As with specific IgE assessments, the sensitivity of basophil activation tests to β-lactams is rather low and decreases over time, although both specific IgE antibody tests and basophil activation tests can remain positive for years. Regarding cefazolin-induced immediate hypersensitivity reactions, a recent study demonstrated that the CD63–basophil activation test attained a sensitivity of 38% and a specificity of 94%, whereas the CD203c read-out yielded a sensitivity of 67% and a specificity of 94%.[58] It has also been suggested that higher concentrations of cefazolin might increase the performance of basophil activation tests.[59] Studies on basophil activation tests with quinolones revealed divergent, but highly interesting, findings.[60] Most CD63-based assays yielded poor or negative results, expect for the study by Aranda and colleagues.[61] Alternatively, the more consistent results with CD203c upregulation could indicate that mediator release in response to quinolones results from alternative degranulation pathways. The basophil activation test could be useful for individual cases where other *in vitro* tests are not available and skin tests are not well validated.[31]

Natural rubber latex

Accurate diagnosis of natural rubber latex hypersensitivity has mainly been hindered by clinically irrelevant specific IgE results. The basophil activation test proved highly accurate in discriminating between relevant and irrelevant results,[42] especially for irrelevant IgE results caused by sensitisation to cross-reactive carbohydrate determinants ubiquitously present in the plant kingdom. Since 2018, the basophil activation test has largely been supplanted by component-resolved diagnosis using *Hevea* proteins (purified, recombinant, or both) that are available in single and multiplexed tests.[41,62]

Opioids and opiates

Accurate diagnosis of IgE-mediated opiate and (semi)synthetic opioid hypersensitivity is not always straightforward, mainly because of uncertainties associated with skin tests[9] and unavailability of reliable drug-specific IgE assays.[45] Accumulated evidence has shown that the basophil activation test is useful in the correct diagnosis of genuine IgE-mediated opiate hypersensitivity, because unlike cutaneous mast cells, basophils do not respond non-specifically to these substances. Moreover, we have demonstrated basophil activation experiments not only to differentiate between IgE-dependent and IgE-independent mast cell activation,[43] but also to identify safe alternative drugs.[63]

Miscellaneous

Since application of the basophil activation test for chlorhexidine has not been studied extensively, its diagnostic accuracy is not known. However, a small-scale study reported a sensitivity of 50%.[64] Gelofusine®, a 4% w/v solution of succinylated gelatine used as an i.v. colloid, was also targeted for studies on the outcomes of basophil activation

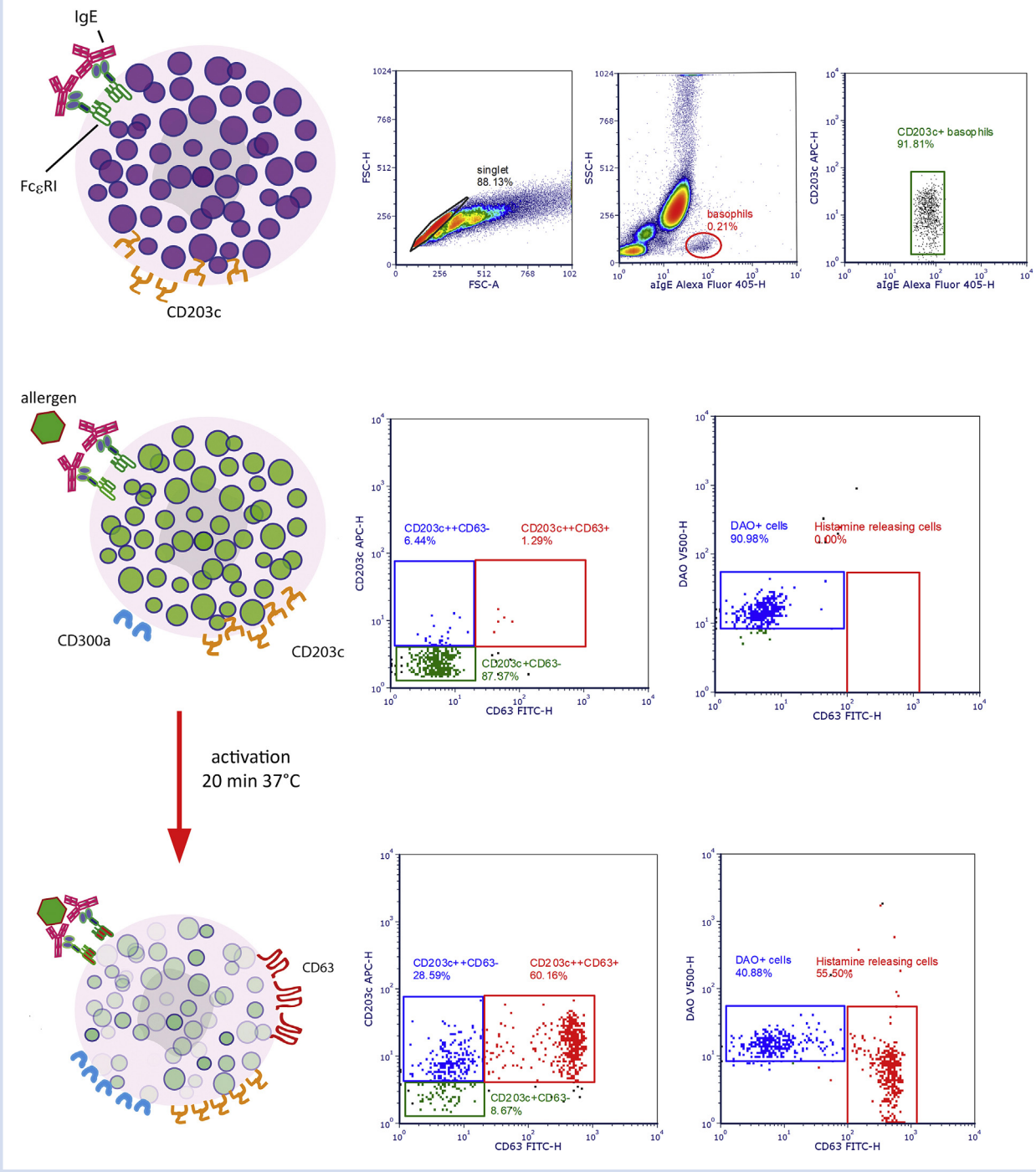


Fig 2. Basophil activation tests rely upon a flow cytometric analysis of activation and degranulation markers on the surface membrane of basophils. (a) Schematic diagram of a basophil with immunoglobulin E (IgE)-crosslinked FcεRI. (b) Basophils are characterised by flow cytometry using forward scatter (FSC)/side scatter (SSC) (left), SSC/anti-IgE (middle), and anti-IgE/CD203c (right). Basophils are defined as anti-IgE and CD203c positive cells. (c) Schematic diagram of a basophil before stimulation with allergen. (d) Most basophils express CD203c but not CD63 on the cell surface (left). Most basophils have diamine oxidase (DAO), which is an enzyme involved in histamine metabolism (right). (e) Schematic diagram of a basophil after stimulation by an allergen. Activation of basophils results in increased expression of CD203c/CD300a and novel expression of CD63 on the cell surface. (f) These changes can be detected by flow cytometry. The number of cells positive for both CD203c and CD63 are increased (left). Because activated basophils release histamine by degranulation, histamine-releasing basophils are defined as DAO negative and CD63 positive cells (right).

tests. The sensitivity and specificity levels were observed as 100% and 88%, respectively.[65] Sugammadex, an agent for antagonism of neuromuscular block, is not a common cause of POH in all countries. In the UK, it is only used in <10% of antagonised cases, and there has been only one case of sugammadex-induced anaphylaxis reported in the UK.[66] But in Japan, it is now the leading cause of POH, probably because of its high usage—an estimated 10% of the population received sugammadex during an 8-yr period from 2010 to 2018.[67] Usefulness of the basophil activation test for sugammadex-induced anaphylaxis has been shown.[68,69] When CD203c was used as the marker, the sensitivity of the test for sugammadex was 88% and specificity was 100%, whereas sensitivity and specificity for CD63 were 75% and 100%, respectively.[69]

Discussion

When conducting *in vitro* tests for POH, the order in which tests for hypersensitivity are conducted is extremely important. Although the test with higher diagnostic accuracy is obviously better, it is necessary to consider the risks and burden on the patient.

Quantification of serum tryptase

Diagnosis of POH requires distinguishing it from other conditions that exhibit similar symptoms. Measurement of serum tryptase is useful for establishing a differential diagnosis. Although the possibility of an immediate hypersensitivity reaction increases if serum tryptase levels are elevated, an elevated tryptase measurement does not necessarily indicate mast cell activation.[70,71] Elevated 'peak' serum tryptase levels can result from mast cell hyperplasia because of the slow elimination of stem cell factors. Tryptase can also be elevated in critically ill patients without anaphylaxis and in victims of trauma. Therefore, it is critical to measure both peak and baseline serum tryptase levels. Conversely, immediate hypersensitivity reactions cannot be excluded even if serum tryptase levels are not elevated.

Quantification of serum specific IgE

Since the commercial availability of specific IgE determination kits, they can now be carried out easily. However, these tests generally have a low sensitivity and specificity and are only available for a limited number of drugs.

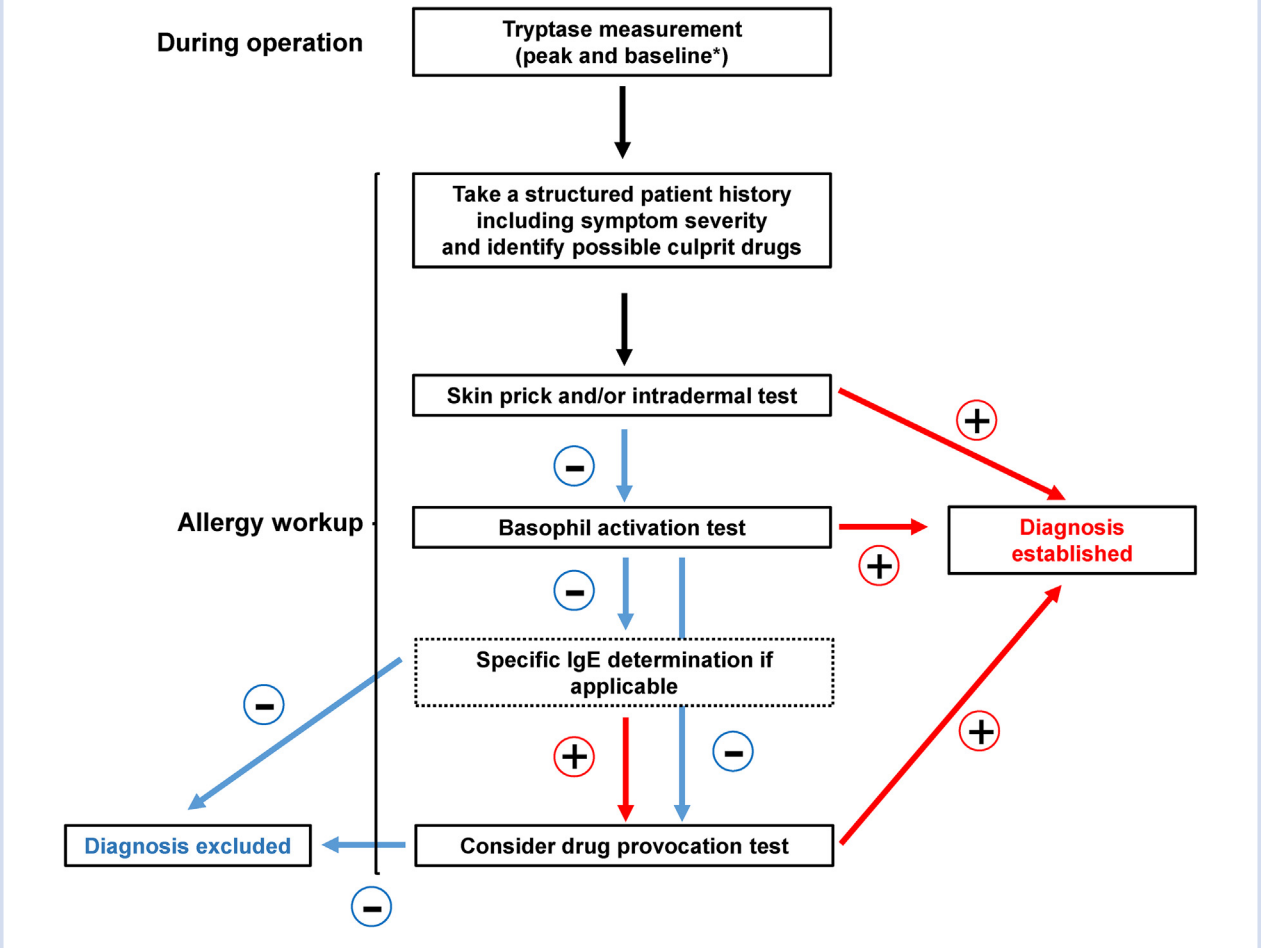


Fig 3. Diagnostic algorithm for perioperative hypersensitivity (POH). Adapted from Ebo and colleagues[31] with permission. As this algorithm is mainly designed for neuromuscular blocking agents (NMBAs), it is not necessarily applicable to all drugs. *, Blood samples for baseline tryptase measurements should be obtained within 24 h of the reaction; +, positive results; −, showing results.

When an early surgical re-intervention (<4 weeks) is necessary after POH, skin tests can have insufficient sensitivity to identify the culprit drug(s) and to rule out potential allergy to other drugs.[72] In such cases, specific IgE determination can help to identify the culprit drug(s) and guide choices for alternatives soon after the event. Although it is known that the specific IgE titre decreases over time, the attenuation over time of specific IgE titres might be different depending on the causative agent and may vary between individuals. Although determination of specific IgEs can be performed soon after the reaction, the test might need to be repeated after 1–2 months if the test result is negative in samples obtained at the time of the suspected hypersensitivity event.

Basophil activation tests

In vitro testing is often compared with *in vivo* testing. Basophil activation tests generally have high diagnostic accuracy in identifying causative agents of POH with sensitivities of 50–90% and specificities >90%.[31,73,74] A recent study showed that a basophil activation test allowed identification of the culprit antigen in only 80% of NMBA-allergic patients. Because negative skin tests do not always guarantee subsequent safe use of the NMBA,[75] diagnosis of rocuronium-induced mast cell activation in patients with negative skin tests can be substantiated by the basophil activation test.[14] In a recent study of patients who had anaphylaxis to amoxicillin-clavulanic acid, 30% needed the drug provocation test because they showed negative skin test results. Even in these patients, ~50% (15 out of 29) had positive basophil activation test results. The authors argue that basophil activation tests are particularly useful in patients with negative skin test results.[76] This suggests that the vast majority of patients show the same results in skin tests and basophil activation tests, although a few patients show different results. In summary, as the positive predictive value of skin tests is not 100%, there seems to be room for other tests, including basophil activation tests, in the diagnosis of POH. Moreover, basophil activation tests have been shown to complement skin tests in the identification of safe alternatives.[57,74]

Basophil activation tests require different considerations, including selection of the activation marker and determination of the threshold of positivity. The most commonly used markers in basophil activation experiments are CD63 and CD203c. Comparative studies show that CD63 and CD203c are clearly different in their upregulation profile. The appearance of CD63 is generally bimodal, with a subpopulation of cells that express CD63 with high intensity *vs* a population with lower CD63 expression. Upregulation of CD203c expression is generally less prominent, but often occurs in almost all cells.[77] Because the marker with higher diagnostic accuracy varies depending on the drug of interest, future research to determine the ideal activation/degranulation marker will be necessary. The threshold for positivity is determined using two-graph ROC analysis corresponding to the best sensitivity and specificity.[78]

Diagnostic procedure in clinical settings

When POH is suspected, we propose the diagnostic algorithm shown in Fig. 3. As this algorithm is designed for NMBAs, it is not necessarily applicable for all drugs. For β-lactam antibiotics, for example, *in vitro* diagnostics should be carried out in the order of skin testing, specific IgE determination, and basophil activation test.[79,80]

Conclusions

In vitro diagnostic procedures, including quantification of specific IgE and basophil activation tests, have several advantages over skin tests and drug provocation tests. They are less cumbersome for patients and do not carry the risk of precipitating immediate hypersensitivity reactions. *In vitro* tests, besides being complementary diagnostic instruments to skin tests and drug provocation tests, can aid elucidation of mechanistic processes. The combination of these tests allows diagnosis of POH with the right balance of safety and accuracy.

Authors' contributions

Study concept/design: all authors.
Data collection, analysis, and interpretation: all authors.
Writing/revising paper and responsibility for contents: all authors.

Declaration of Interest

The authors declare that they have no conflicts of interest.

References

1. Leysen J, De Witte L, Bridts CH, Ebo DG. Anaphylaxis during general anaesthesia: a 10-year survey at the University Hospital Antwerp. *Proc Belg Roy Acad Med* 2013; **2**: 88–100
2. Mertes PM, Volcheck GW, Garvey LH, et al. Epidemiology of perioperative anaphylaxis. *Presse Medicale (Paris, France: 1983)* 2016; **45**: 758–67
3. Garvey LH. Old, New and hidden causes of perioperative hypersensitivity. *Curr Pharm Des* 2016; **22**: 6814–24
4. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
5. Demoly P, Romano A, Botelho C, et al. Determining the negative predictive value of provocation tests with beta-lactams. *Allergy* 2010; **65**: 327–32
6. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: diagnostic approach. *Allergy* 2007; **62**: 471–87
7. Mertes PM, Malinovsky JM, Jouffroy L, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2011; **21**: 442–53
8. Mertes PM, Moneret-Vautrin DA, Leynadier F, Laxenaire MC. Skin reactions to intradermal neuromuscular blocking agent injections: a randomized multicenter trial in healthy volunteers. *Anesthesiology* 2007; **107**: 245–52
9. Nasser SM, Ewan PW. Opiate-sensitivity: clinical characteristics and the role of skin prick testing. *Clin Exp Allergy* 2001; **31**: 1014–20
10. Uyttebroek AP, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Moxifloxacin hypersensitivity: uselessness of skin testing. *J Allergy Clin Immunol Pract* 2015; **3**: 443–5

11. Berg CM, Heier T, Wilhelmsen V, Florvaag E. Rocuronium and cisatracurium-positive skin tests in non-allergic volunteers: determination of drug concentration thresholds using a dilution titration technique. *Acta Anaesthesiol Scand* 2003; **47**: 576–82
12. Fisher MM, Merefield D, Baldo B. Failure to prevent an anaphylactic reaction to a second neuromuscular blocking drug during anaesthesia. *Br J Anaesth* 1999; **82**: 770–3
13. Spoerl D, Nigolian H, Czarnetzki C, Harr T. Reclassifying anaphylaxis to neuromuscular blocking agents based on the presumed patho-mechanism: IgE-mediated, pharmacological adverse reaction or "innate hypersensitivity"? *Int J Mol Sci* 2017; **18**: 1223
14. Van Gasse AL, Elst J, Bridts CH, et al. Rocuronium hypersensitivity: does off-target occupation of the MRGPRX2 receptor play a role? *J Allergy Clin Immunol Pract* 2018. https://doi.org/10.1016/j.jaip.2018.09.034. Advance access published on October 10
15. Dewachter P, Mouton-Faivre C, Emala CW. Anaphylaxis and anesthesia: controversies and new insights. *Anesthesiology* 2009; **111**: 1141–50
16. Ebo DG, Clarke RC, Mertes P-M, et al. Molecular mechanisms and pathophysiology of perioperative hypersensitivity and anaphylaxis. *Br J Anaesth* 2019; **123**: e38–49
17. Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. *Immunol Allergy Clin North Am* 2006; **26**: 451–63
18. Castells MC, Irani AM, Schwartz LB. Evaluation of human peripheral blood leukocytes for mast cell tryptase. *J Immunol* 1987; **138**: 2184–9
19. Krishna MT, York M, Chin T, et al. Multi-centre retrospective analysis of anaphylaxis during general anaesthesia in the United Kingdom: aetiology and diagnostic performance of acute serum tryptase. *Clin Exp Immunol* 2014; **178**: 399–404
20. Gastaminza G, Lafuente A, Goikoetxea MJ, et al. Improvement of the elevated tryptase criterion to discriminate IgE- from non-IgE-mediated allergic reactions. *Anesth Analg* 2018; **127**: 414–9
21. Valent P, Akin C, Arock M, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol* 2012; **157**: 215–25
22. Baretto RL, Beck S, Heslegrave J, et al. Validation of international consensus equation for acute serum total tryptase in mast cell activation: a perioperative perspective. *Allergy* 2017; **72**: 2031–4
23. Fisher MM, Baldo BA. Mast cell tryptase in anaesthetic anaphylactoid reactions. *Br J Anaesth* 1998; **80**: 26–9
24. Friedman BS, Steinberg SC, Meggs WJ, Kaliner MA, Frieri M, Metcalfe DD. Analysis of plasma histamine levels in patients with mast cell disorders. *Am J Med* 1989; **87**: 649–54
25. Ebo DG, Venemalm L, Bridts CH, et al. Immunoglobulin E antibodies to rocuronium: a new diagnostic tool. *Anesthesiology* 2007; **107**: 253–9
26. Fisher MM, Baldo BA. Immunoassays in the diagnosis of anaphylaxis to neuromuscular blocking drugs: the value of morphine for the detection of IgE antibodies in allergic subjects. *Anaesth Intensive Care* 2000; **28**: 167–70
27. Laroche D, Gomis P, Gallimidi E, Malinovsky JM, Mertes PM. Diagnostic value of histamine and tryptase concentrations in severe anaphylaxis with shock or cardiac arrest during anesthesia. *Anesthesiology* 2014; **121**: 272–9
28. Gueant JL, Mata E, Monin B, et al. Evaluation of a new reactive solid phase for radioimmunoassay of serum specific IgE against muscle relaxant drugs. *Allergy* 1991; **46**: 452–8
29. Guilloux L, Ricard-Blum S, Ville G, Motin J. A new radioimmunoassay using a commercially available solid support for the detection of IgE antibodies against muscle relaxants. *J Allergy Clin Immunol* 1992; **90**: 153–9
30. Johansson SG, Florvaag E, Oman H, et al. National pholcodine consumption and prevalence of IgE-sensitization: a multicentre study. *Allergy* 2010; **65**: 498–502
31. Ebo DG, Faber M, Elst J, et al. In vitro diagnosis of immediate drug hypersensitivity during anesthesia: a review of the literature. *J Allergy Clin Immunol Pract* 2018; **6**: 1176–84
32. Uyttebroek AP, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Immunoglobulin E antibodies to atracurium: a new diagnostic tool? *Clin Exp Allergy* 2015; **45**: 485–7
33. Rose MA, Anderson J, Green SL, Yun J, Fernando SL. Morphine and pholcodine-specific IgE have limited utility in the diagnosis of anaphylaxis to benzylisoquinolines. *Acta Anaesthesiol Scand* 2018; **62**: 628–34
34. Leysen J, Uyttebroek A, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Predictive value of allergy tests for neuromuscular blocking agents: tackling an unmet need. *Clin Exp Allergy* 2014; **44**: 1069–75
35. Fontaine C, Mayorga C, Bousquet PJ, et al. Relevance of the determination of serum-specific IgE antibodies in the diagnosis of immediate beta-lactam allergy. *Allergy* 2007; **62**: 47–52
36. Qiao HL, Li Z, Yang J, Tian X, Gao N, Jia LJ. Hypersensitivity reactions to penicillins: studies in a group of patients with negative benzylpenicillin G skin test. *J Clin Pharm Ther* 2009; **34**: 249–54
37. Fernandez TD, Torres MJ, Blanca-Lopez N, et al. Negativization rates of IgE radioimmunoassay and basophil activation test in immediate reactions to penicillins. *Allergy* 2009; **64**: 242–8
38. Johansson SG, Adedoyin J, van Hage M, Gronneberg R, Nopp A. False-positive penicillin immunoassay: an unnoticed common problem. *J Allergy Clin Immunol* 2013; **132**: 235–7
39. Ebo DG, Stevens WJ, Bridts CH, De Clerck LS. Latex-specific IgE, skin testing, and lymphocyte transformation to latex in latex allergy. *J Allergy Clin Immunol* 1997; **100**: 618–23
40. Ebo DG, Hagendorens MM, Bridts CH, De Clerck LS, Stevens WJ. Sensitization to cross-reactive carbohydrate determinants and the ubiquitous protein profilin: mimickers of allergy. *Clin Exp Allergy* 2004; **34**: 137–44
41. Van Gasse AL, Mangodt EA, Faber M, Sabato V, Bridts CH, Ebo DG. Molecular allergy diagnosis: status anno 2015. *Clin Chim Acta* 2015; **444**: 54–61
42. Ebo DG, Lechkar B, Schuerwegh AJ, Bridts CH, De Clerck LS, Stevens WJ. Validation of a two-color flow cytometric assay detecting in vitro basophil activation for the diagnosis of IgE-mediated natural rubber latex allergy. *Allergy* 2002; **57**: 706–12
43. Baldo BA, Pham NH. Histamine-releasing and allergenic properties of opioid analgesic drugs: resolving the two. *Anaesth Intensive Care* 2012; **40**: 216–35
44. Lansu K, Karpiak J, Liu J, et al. In silico design of novel probes for the atypical opioid receptor MRGPRX2. *Nat Chem Biol* 2017; **13**: 529–36
45. Van Gasse AL, Hagendorens MM, Sabato V, Bridts CH, De Clerck LS, Ebo DG. IgE to poppy seed and morphine are not

useful tools to diagnose opiate allergy. *J Allergy Clin Immunol Pract* 2015; **3**: 396–9
46. Opstrup MS, Malling HJ, Kroigaard M, et al. Standardized testing with chlorhexidine in perioperative allergy—a large single-centre evaluation. *Allergy* 2014; **69**: 1390–6
47. Anderson J, Rose M, Green S, Fernando SL. The utility of specific IgE testing to chlorhexidine in the investigation of perioperative adverse reactions. *Ann Allergy Asthma Immunol* 2015; **114**: 425–426 e1
48. Mullins RJ, James H, Platts-Mills TA, Commins S. Relationship between red meat allergy and sensitization to gelatin and galactose-alpha-1,3-galactose. *J Allergy Clin Immunol* 2012; **129**: 1334–13342 e1
49. Ebo DG, Faber M, Sabato V, et al. Sensitization to the mammalian oligosaccharide galactose-alpha-1,3-galactose (alpha-gal): experience in a Flemish case series. *Acta Clin Belg* 2013; **68**: 206–9
50. Uyttebroek A, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Anaphylaxis to succinylated gelatin in a patient with a meat allergy: galactose-alpha(1, 3)-galactose (alpha-gal) as antigenic determinant. *J Clin Anesth* 2014; **26**: 574–6
51. Pittman T, Kiburz J, Steinhardt G, Krock J, Gabriel K. Ethylene oxide allergy in children with spina bifida. *J Allergy Clin Immunol* 1995; **96**: 486–8
52. Bache S, Petersen JT, Garvey LH. Anaphylaxis to ethylene oxide — a rare and overlooked phenomenon? *Acta Anaesthesiol Scand* 2011; **55**: 1279–82
53. Knol EF, Koenderman L, Mul FP, Verhoeven AJ, Roos D. Differential activation of human basophils by anti-IgE and formyl-methionyl-leucyl-phenylalanine. Indications for protein kinase C-dependent and -independent activation pathways. *Eur J Immunol* 1991; **21**: 881–5
54. Demoly P, Lebel B, Arnoux B. Allergen-induced mediator release tests. *Allergy* 2003; **58**: 553–8
55. Ebo DG, Sainte-Laudy J, Bridts CH, et al. Flow-assisted allergy diagnosis: current applications and future perspectives. *Allergy* 2006; **61**: 1028–39
56. Bridts CH, Sabato V, Mertens C, Hagendorens MM, De Clerck LS, Ebo DG. Flow cytometric allergy diagnosis: basophil activation techniques. *Methods Mol Biol* 2014; **1192**: 147–59
57. Ebo DG, Bridts CH, Hagendorens MM, Mertens CH, De Clerck LS, Stevens WJ. Flow-assisted diagnostic management of anaphylaxis from rocuronium bromide. *Allergy* 2006; **61**: 935–9
58. Uyttebroek AP, Decuyper II, Bridts CH, et al. Cefazolin hypersensitivity: toward optimized diagnosis. *J Allergy Clin Immunol Pract* 2016; **4**: 1232–6
59. Horiuchi T, Takazawa T, Orihara M, et al. Required cefazolin concentration to maximize diagnostic accuracy of the basophil activation test for cefazolin-induced anaphylaxis. *J Anesth* 2018; **32**: 797–805
60. Decuyper II, Mangodt EA, Van Gasse AL, et al. In vitro diagnosis of immediate drug hypersensitivity anno 2017: potentials and limitations. *Drugs R D* 2017; **17**: 265–78
61. Aranda A, Mayorga C, Ariza A, et al. In vitro evaluation of IgE-mediated hypersensitivity reactions to quinolones. *Allergy* 2011; **66**: 247–54
62. Ebo DG, Hagendorens MM, De Knop KJ, et al. Component-resolved diagnosis from latex allergy by microarray. *Clin Exp Allergy* 2010; **40**: 348–58
63. Leysen J, De Witte L, Sabato V, et al. IgE-mediated allergy to pholcodine and cross-reactivity to neuromuscular blocking agents: lessons from flow cytometry. *Cytometry B Clin Cytom* 2013; **84**: 65–70
64. Egner W, Helbert M, Sargur R, et al. Chlorhexidine allergy in four specialist allergy centres in the United Kingdom, 2009–13: clinical features and diagnostic tests. *Clin Exp Immunol* 2017; **188**: 380–6
65. Apostolou E, Deckert K, Puy R, et al. Anaphylaxis to Gelofusine confirmed by in vitro basophil activation test: a case series. *Anaesthesia* 2006; **61**: 264–8
66. Marinho S, Kemp H, Cook TM, et al. Cross-sectional study of perioperative drug and allergen exposure in UK practice in 2016: the 6th National Audit Project (NAP6) Allergen Survey. *Br J Anaesth* 2018; **121**: 146–58
67. Takazawa T, Miyasaka K, Sawa T, Iida H. Current status of sugammadex usage and the occurrence of sugammadex-induced anaphylaxis in Japan. *APSF Newsl* 2018; **33**: 1
68. Takazawa T, Horiuchi T, Yoshida N, Yokohama A, Saito S. Flow cytometric investigation of sugammadex-induced anaphylaxis. *Br J Anaesth* 2015; **114**: 858–9
69. Horiuchi T, Yokohama A, Orihara M, et al. Usefulness of basophil activation tests for diagnosis of sugammadex-induced anaphylaxis. *Anesth Analg* 2018; **126**: 1509–16
70. Sprung J, Weingarten TN, Schwartz LB. Presence or absence of elevated acute total serum tryptase by itself is not a definitive marker for an allergic reaction. *Anesthesiology* 2015; **122**: 713–4
71. Sprung J, Larson KJ, Divekar RD, Butterfield JH, Schwartz LB, Weingarten TN. Refractory intraoperative hypotension with elevated serum tryptase. *Asia Pac Allergy* 2015; **5**: 47–50
72. Goldberg A, Confino-Cohen R. Timing of venom skin tests and IgE determinations after insect sting anaphylaxis. *J Allergy Clin Immunol* 1997; **100**: 182–4
73. Uyttebroek AP, Sabato V, Faber MA, et al. Basophil activation tests: time for a reconsideration. *Expert Rev Clin Immunol* 2014; **10**: 1325–35
74. Dewachter P, Chollet-Martin S, Mouton-Faivre C, de Chaisemartin L, Nicaise-Roland P. Comparison of basophil activation test and skin testing performances in NMBA allergy. *J Allergy Clin Immunol Pract* 2018; **6**: 1681–9
75. Sabato V, Ebo DG. Hypersensitivity to neuromuscular blocking agents: can skin tests give the green light for re-exposure? *J Allergy Clin Immunol Pract* 2018; **6**: 1690–1
76. Salas M, Fernandez-Santamaria R, Mayorga C, et al. Use of the basophil activation test may reduce the need for drug provocation in amoxicillin–clavulanic allergy. *J Allergy Clin Immunol Pract* 2018; **6**: 1010–1018 e2
77. Ebo DG, Bridts CH, Hagendorens MM, Aerts NE, De Clerck LS, Stevens WJ. Basophil activation test by flow cytometry: present and future applications in allergology. *Cytometry B Clin Cytom* 2008; **74**: 201–10
78. Greiner M, Pfeiffer D, Smith RD. Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. *Prev Vet Med* 2000; **45**: 23–41
79. Ebo DG, Leysen J, Mayorga C, Rozieres A, Knol EF, Terreehorst I. The in vitro diagnosis of drug allergy: status and perspectives. *Allergy* 2011; **66**: 1275–86
80. Blanca M, Romano A, Torres MJ, et al. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy* 2009; **64**: 183–93

Handling editor: H.C. Hemmings Jr

BJA

British Journal of Anaesthesia, 123 (1): e126–e134 (2019)

doi: 10.1016/j.bja.2019.03.018
Advance Access Publication Date: 23 April 2019
Special Article

The use of drug provocation testing in the investigation of suspected immediate perioperative allergic reactions: current status

Lene H. Garvey[1,2,*,#,†], Didier G. Ebo[3,#,†], Mogens Krøigaard[1,#,†], Sinisa Savic[4,#,†], Russell Clarke[5,6,†], Peter Cooke[7,†], Pascale Dewachter[8,9,†], Tomaz Garcez[10,†], Anne B. Guttormsen[11,12,†], Philip M. Hopkins[13,†], David L. Hepner[14,†], David A. Khan[15,†], Helen Kolawole[16,17,†], Peter Kopac[18,†], Stuart Marshall[16,17,†], Paul-Michel Mertes[19,†], Peter Platt[5,6,†], Michael Rose[20,†], Vito Sabato[3,†], Paul Sadleir[5,6,21,†], Louise Savic[22,†], Kathrin Scherer[23,†], Tomonori Takazawa[24,†], Gerald W. Volcheck[25,†], Susanna Voltolini[26,†] and Jose J. Laguna[27,#,†]

[1]Danish Anaesthesia Allergy Centre, Allergy Clinic, Department of Dermatology and Allergy, Copenhagen University Hospital, Gentofte, Denmark, [2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, [3]Department of Immunology, Allergology and Rheumatology, University of Antwerp, Antwerp University Hospital, Belgium, [4]Department of Clinical Immunology and Allergy, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [5]Department of Anaesthesia, Sir Charles Gairdner Hospital, Western Australia, Australia, [6]Anaesthetic Allergy Referral Centre of Western Australia, Australia, [7]Department of Anaesthesia and Perioperative Medicine, Auckland City Hospital, Auckland, New Zealand, [8]Service d'Anesthésie-Réanimation, Groupe Hospitalier de Paris-Seine-Saint-Denis, Assistance Publique-Hôpitaux de Paris, Paris, France, [9]Université Paris 13, Sorbonne-Paris-Cité, Paris, France, [10]Department of Immunology, Manchester University NHS Foundation Trust, Manchester, UK, [11]Department of Anaesthesia and Intensive Care, Haukeland University Hospital, Bergen, Norway, [12]Department of Clinical Medicine, University of Bergen, Bergen, Norway, [13]Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK, [14]Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, [15]Department of Internal Medicine, Division of Allergy & Immunology, University of Texas Southwestern Medical Center, Dallas, TX, USA, [16]Department of Anaesthesia and Perioperative Medicine, Monash University, Melbourne, Australia, [17]Department of Anaesthesia, Peninsula Health, Melbourne, Australia, [18]University Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia, [19]Department of Anesthesia and Intensive Care, Hôpitaux Universitaires de Strasbourg, Nouvel Hôpital Civil, FMTS Strasbourg, EA 3072, Strasbourg, France, [20]Department of Anaesthesia, Royal North Shore Hospital, and University of Sydney, Sydney, NSW, Australia, [21]Department of Pharmacology, University of Western

Editorial decision: 12 March 2019; **Accepted:** 12 March 2019

Australia, Australia, [22]Anaesthetic Department, Leeds Teaching Hospitals NHS Trust, Leeds, UK, [23]Allergy Unit, Department of Dermatology, University Hospital Basel, Basel University, Basel, Switzerland, [24]Intensive Care Unit, Gunma University Hospital, Maebashi, Gunma, Japan, [25]Division of Allergic Diseases, Mayo Clinic College of Medicine, Rochester, MN, USA, [26]Allergy Unit, Policlinic Hospital San Martino, Genoa, Italy and [27]Allergy Unit, Allergo-Anaesthesia Unit, Hospital Central de la Cruz Roja, Faculty of Medicine, Alfonso X El Sabio University, ARADyAL, Madrid, Spain

*Corresponding author. E-mail: lene.heise.garvey@regionh.dk

[#]These authors contributed equally.
[†]All authors are members of the ISPAR (International Suspected Perioperative Allergic Reaction) Group.

Summary

Suspected perioperative allergic reactions are often severe. To avoid potentially life-threatening re-exposure to the culprit drug, establishing a firm diagnosis and identifying the culprit is crucial. Drug provocation tests are considered the gold standard in drug allergy investigation but have not been recommended in the investigation of perioperative allergy, mainly because of the pharmacological effects of drugs such as induction agents and neuromuscular blocking agents. Some specialised centres have reported benefits of provocation testing in perioperative allergy investigation, but the literature on the subject is limited. Here we provide a status update on the use of drug provocation testing in perioperative allergy, including its use in specific drug groups. This review is based on a literature search and experiences of the authors comprising anaesthesiologists and allergists with experience in perioperative allergy investigation. In addition, 19 participating centres in the International Suspected Perioperative Allergic Reaction Group were surveyed on the use of provocation testing in perioperative allergy investigation. A response was received from 13 centres in eight European countries, New Zealand, and the USA. Also, 21 centres from the Australian and New Zealand Anaesthetic Allergy Group were surveyed. Two centres performed provocation routinely and seven centres performed no provocations at all. Nearly half of the centres reported performing provocations with induction agents and neuromuscular blocking agents. Drug provocation testing is being used in perioperative allergy investigation in specialised centres, but collaborations between relevant specialties and multicentre studies are necessary to determine indications and establish common testing protocols.

Keywords: allergy; anaphylaxis; challenge testing; drug hypersensitivity; drug provocation test; perioperative period

Editor's key points

- Drug provocation tests (DPTs) are the gold standard in drug allergy investigation but are not commonly used in the investigation of perioperative allergy.
- Specialised centres have reported benefits of provocation testing in perioperative allergy investigation.
- In a literature review and survey of specialised allergy clinics, drug provocation was used widely but not uniformly in testing of suspected perioperative allergens.
- There is a place for DPT in perioperative allergy investigation to identify safe alternatives after perioperative allergic reactions, as a false negative result on conventional testing can have fatal consequences.

Investigation of patients with suspected allergic reactions in the perioperative setting is challenging and requires collaboration between anaesthesiologists and allergists. Investigations recommended in current international guidelines comprise skin testing and *in vitro* testing,[1–5] but these have limitations in both sensitivity and specificity. To avoid potentially life-threatening re-exposure to the culprit drug, establishing a firm diagnosis and identifying the culprit is crucial. Drug provocation testing (DPT) has not been recommended in the investigation of suspected perioperative allergy, even though it is considered the gold standard test in drug allergy in general, and is used to establish a diagnosis when other tests are negative.[6] Recent publications have shown the benefit of DPT in identifying the culprit drug in perioperative allergy cases where conventional tests were negative, and the clinical suspicion of allergy was high.[7,8] It has been suggested in recent guidelines that DPT can be used in highly specialised centres to confirm or disprove allergy to specific drugs in the perioperative setting.[5,9]

Although use of DPT in perioperative allergy investigation is in its infancy, it is appropriate to outline its current status. This report is based on a literature search; expert opinion from the authors comprising anaesthesiologists and allergists with experience in perioperative allergy investigation; and a survey on the use of DPT in the participating centres in the International Suspected Perioperative Allergic Reaction (ISPAR) Group and the Australian and New Zealand Anaesthetic Allergy Group (ANZAAG). Because of the limited literature on this subject and the lack of consensus in the field of drug provocation in general, it is premature to attempt to achieve formal consensus on recommendations for drug provocation in perioperative allergy investigation. As a result, the level of evidence throughout this manuscript

is low at level 2C (weak recommendations based on low quality evidence) according to the GRADE Working Group definition (www.gradeworkinggroup.org).

Principles of drug provocation testing in general drug allergy

Although considered to be the gold standard for confirming or excluding a diagnosis of drug allergy, DPT is time-consuming, expensive, and carries inherent risk. Existing guidelines state that DPT should only be performed after a thorough evaluation of the clinical history and after appropriate investigation with skin and *in vitro* tests. In addition, an individual risk benefit analysis should always be carried out before DPT, which should be performed by trained personnel, in an appropriate clinical setting, with access to resuscitation facilities.[6,10,11]

The utility of DPT in drug allergy investigation, outside the perioperative setting, has been demonstrated by large case series. In 898 patients with a history of immediate drug hypersensitivity, 17.6% were diagnosed using DPT with a variety of drugs, including antibiotics (primarily β-lactams and NSAIDs).[12] In another study of 4460 patients, drug allergy was confirmed by clinical history alone in 44%, with help of skin testing (14.6%), *in vitro* testing (10.4%), and by DPT in 30.8% of patients.[13]

There is no international consensus on indications for DPT. The European Academy for Allergy and Clinical Immunology (EAACI) Drug Allergy Interest Group guideline from 2003 suggested using DPT only to determine safe alternatives, thereby avoiding exposure to the suspected culprit drug and minimising the risk of an adverse reaction.[10] The 2010 US Practice Parameters only recommend DPT in patients at low risk of adverse reaction, as a means to rule out allergy.[14] The 2009 British Society of Allergology and Clinical Immunology guideline advocates DPT for identifying safe alternatives, but also to confirm the culprit drug in selected cases.[15] More recently, an international consensus and an EAACI Position Paper suggests DPT with culprit drug when possible.[6,11]

There is consensus on contraindications to DPT in drug allergy investigation. Absolute contraindications are primarily severe life-threatening delayed hypersensitivity reactions, such as Stevens–Johnson syndrome and toxic epidermal necrolysis. Relative contraindications include pregnancy and anaphylaxis, although DPT may sometimes be used when the risk–benefit analysis is favourable.[2,6]

There is no international consensus on the procedure for DPT in general drug allergy. Where possible, it is important to replicate the initial route of administration.[11] The oral route has been suggested to be preferable, because of slower absorption of the drug allowing for earlier recognition and treatment of any adverse reaction. However, oral absorption can be unpredictable. The i.v. route is advocated where possible by some of the authors (LHG, DGE, JJL, MK) based on personal experience in that it allows smaller and more precise dosing, and almost immediate recognition of adverse reactions at smaller doses. In patients with a history of an immediate reaction it is recommended that the drug is given in divided doses, starting with a low dose, and increasing gradually, until either the therapeutic dose is reached, or the patient develops allergic symptoms/signs. However, it is important to make a distinction between dosing for the purposes of DPT compared with that for desensitisation. The latter is a procedure resulting in temporary modification of the immune system so that the drug can be administered safely, even to an allergic patient. Typically, desensitisation protocols start with minute amounts of the drug and have many more dosing steps with small increases in drug dose between steps.[16]

There is no international consensus on dosing or number of steps needed in a DPT protocol. Dosing intervals vary with route of administration. Usually, the interval in i.v. provocation is 30 min with intervals of 45–60 min for oral, subcutaneous, or intramuscular administration, as drug absorption is slower and less predictable. The starting dose, the interval between dosing, and the incremental dose increases can all be individually tailored, depending on the drug, the nature and severity of the previous reaction, and comorbidities of the patient. Patients with immediate reactions will be at higher risk of a reaction during DPT and will need more cautious dosing than patients with milder delayed reactions.[17,18] Patients with very mild delayed reactions are considered at low risk of a reaction, and it is possible to use a single oral therapeutic dose without preceding skin testing.[19,20] Although this strategy is not directly relevant for patients with suspected perioperative allergic reactions, it has been used in surgical patients with labels of penicillin allergy, which are likely to be incorrect.[21] The initial DPT may be followed up with a prolonged course over 1–10 days to exclude or confirm delayed reactions.[18]

It is recommended that the interval between the index reaction and DPT is at least 4 weeks, and after the symptoms of the previous reaction have fully resolved.[10] Medications such as antihistamines and steroids might interfere with recognition of early symptoms during DPT, and a sufficient washout period should be allowed for these medications before performing DPT. Even though regular treatment with β-blocking agents and angiotensin-converting enzyme (ACE) inhibitors has been thought to be detrimental if emergency treatment of anaphylaxis with epinephrine should be needed during the DPT, a recent study does not support stopping such medications before DPT.[22] However, consensus has not been reached on this issue.

Shortfalls of current test methods used in general drug allergy investigation

In daily clinical practice the diagnosis of drug allergy is based on detailed history taking complemented with skin testing and *in vitro tests* (e.g. specific immunoglobulin E [IgE] antibodies and basophil activation tests).[6,23–25] Unfortunately, in both general drug allergy and in suspected perioperative allergy the correct diagnosis may be difficult to make. Limitations include a lack of reliable specific IgE antibody tests for anaesthetic drugs, analgesics, and most neuromuscular blocking agents (NMBAs); and low sensitivity and especially low specificity of skin testing, which often shows false positive tests in the diagnosis of suspected NMBA and opioid hypersensitivity.[23,26–28] A specific IgE test is only readily available for suxamethonium, as tests for rocuronium and atracurium are available for research purposes only.[29–31] Basophil histamine release and activation tests have still not entered mainstream use, mainly because of the need for specific expertise and analysis within a maximum of 24 h of sampling.[31] In addition, suspected perioperative hypersensitivity can result from various non-allergic processes without specific immune

responses such as direct activation of the mast cell via specific receptors or enzymatic interference.[32] These will go undetected by traditional tests, as skin testing and *in vitro tests* primarily diagnose IgE-mediated reactions.

Barriers against provocation in suspected perioperative allergy

The most important barrier against performing DPT in the investigation of suspected perioperative allergic reactions is the pharmacological effects of anaesthetic drugs.[2,33] As with general drug allergy, there are no consensus protocols for performing DPT in perioperative allergy investigation.[1,2,34]

A large proportion of perioperative reactions are very severe. In one study, 45% of patients presented with grade III reactions (anaphylactic shock with circulatory instability) or grade IV reactions (cardiac arrest).[35] As life-threatening allergic reactions are seen as a relative contraindication to DPT by many allergists, this also presents an important barrier against performing DPT in perioperative allergy investigation.

Many allergists/immunologists, outside specialised clinics, have limited knowledge of the nature and effects of drugs used in the perioperative setting, and most anaesthetists have little experience with provocation testing. Therefore, the collaboration between both specialties is essential. The procedure of provocation testing is complex, demanding on resources and requires specially trained personnel. As a result, only highly specialised units will be able to undertake provocation testing in perioperative allergy on a regular basis.[2,5,9,15,36] As DPT is not generally recommended for investigation of perioperative allergy, approval of protocols by an ethics committee may be necessary in some countries, especially if it involves DPT with NMBAs, anaesthetising the patient, or both.

Potential advantages of provocation in suspected perioperative allergy

One of the main advantages of DPT is that it can confirm or exclude the culprit drug regardless of the underlying mechanism.[15,37] Only 50–60% of immediate allergic reactions to anaesthetics can be expected to be diagnosed by the conventional skin tests and *in vitro* tests.[38]

A correct diagnosis is very important in suspected perioperative allergy. However, sometimes a culprit is not identified in cases of clinical anaphylaxis with elevated tryptase suggesting an allergic mechanism. In such cases, the culprit may have been overlooked or the tests may have proved insufficient to make the diagnosis. The latter has been shown for propofol and cefuroxime, where some patients testing negative on skin testing and *in vitro* tests had positive provocation tests. In these cases, without DPT, the true diagnosis would have been missed, putting the patient at risk of re-exposure and further reactions.[7,8]

Owing to the limitations of conventional tests it has been suggested that without provocation tests, the causal relationship and sensitivity and specificity for skin tests, specific IgE and cellular tests cannot be reliably determined.[39] In practice clarification of this issue would require DPT in patients where other tests have been positive, and this is not accepted practice in most countries. However, for drugs such as opioids and NMBAs carrying a high risk of false positive results, especially on intradermal testing, provocation could prove useful.[28] Skin test and *in vitro* test sensitivity may also decline over time making it difficult to confirm a diagnosis.[40] Provided clinical reactivity remains high, drug provocation may also be useful in this setting.

In some cases, effects of other drugs or the surgical procedure may mimic symptoms of anaphylaxis. Allergy investigation including DPT can be useful in disproving allergy to drugs used in the perioperative setting, and convincing patients that they can undergo future anaesthetics safely.[36]

Indications and contraindications

Despite the limitations of skin tests and *in vitro* tests, a reliable diagnosis can be made in most perioperative allergy patients from the clinical history combined with these traditional tests. The most important indication for DPT in perioperative allergy investigation is therefore in patients where the clinical suspicion of allergy is high, but where traditional skin tests, *in vitro* tests, or both, yield equivocal or negative results. Secondly, DPT may be used to establish the correct diagnosis in situations where false positive skin test results are suspected. Lastly, DPT should be offered when no other reliable diagnostic tests are available.

In addition, DPT may be used to diagnose or rule out immunological cross-reactivity between structurally related compounds, for example, by identifying a safe alternative NMBA in cases of proven allergy to another NMBA.[41]

However, it should always be kept in mind that DPT is a high-risk procedure. When deciding to perform DPT in the investigation of suspected perioperative allergy, the benefit should always clearly outweigh the risk. In the context of anaesthetic drugs, full dose provocation is relatively contraindicated because of the potent pharmacological effects of several drug groups, unless performed in a highly specialised setting with anaesthetic expertise. Other contraindications include severe co-morbidity and pregnancy. One exception to this is the parturient suspected of allergy to local anaesthetics, where a subcutaneous provocation with a local anaesthetic may be performed if skin tests are negative. Because of the extremely low risk of allergy to local anaesthetics, this is done to ensure that local anaesthesia can be safely used for infiltration, epidural, or spinal anaesthesia if a Caesarean section is indicated.[2,6]

Provocation testing in suspected perioperative allergy

Planning the procedure including safety considerations

Ideally, the planning of investigations and decisions on which drugs to test with DPT should be made in close collaboration between allergist and anaesthesiologist. The final goal is to rule out allergy to specific drugs used in the perioperative setting to avoid unnecessary limitations for future anaesthetics. Decision on provocation should be made after a careful risk–benefit analysis considering patient comorbidity, factors related to the reaction, the availability of a suitable setting for performing provocation, and the future indication for individual drugs or classes of drugs.

Assessment of patient comorbidity includes age, medical history especially cardiac or pulmonary, systemic mastocytosis or elevated baseline serum tryptase, current

medications, and the physical status of the patient usually classified using the ASA system.[42]

Factors related to the reaction include grade of severity of index reaction[2] and suspected drugs. Drugs such as NMBAs, opioids, and intravenous induction agents (e.g. thiopental and propofol), demand special care to be taken in planning the provocations.

The availability of personnel with adequate experience, access to emergency assistance, and continued high level observation/care are all prerequisites for performing provocation. If full dose provocation is considered, the added risk of an anaesthetic, including the need for ventilatory assistance or tracheal intubation, must be included in the planning.

Patient safety must be given high priority as two high-risk procedures are combined. Provocation testing will always involve the risk of eliciting anaphylaxis; thus, allergist experience in recognising the early signs and skills in treating anaphylaxis is essential. Even with small doses of anaesthetic drugs it is possible to observe the therapeutic effects (e.g. impaired consciousness or respiration and hypotension, or a combination of all three). The combination of skills and experience of the allergist and anaesthesiologist is thus essential, both in planning, performing and interpreting provocation testing in perioperative allergy investigation.

Consent and informing the patient

Informed consent should be obtained before DPT. In rare cases where anaesthetic drugs are tested in full dose, an additional consent for anaesthesia is required, and the risks of the anaesthetic and of anaphylaxis should be explained. Patients with suspected perioperative allergy are often extremely anxious about what happened during the perioperative reaction. They were usually anaesthetised during the reaction and rely on information from anaesthetic personnel or relatives, neither of whom have any detailed knowledge about perioperative allergy and often recall a dramatic course of events. It is therefore essential that patients feel safe and are well informed at all stages of the investigation.

Level of monitoring and location for provocation testing

A baseline value for blood pressure, heart rate and peak flow should be measured before DPT. Facilities for DPT with anaesthetic drugs should include continuous monitoring system (ECG, non-invasive blood pressure, pulse oximetry, and ventilatory frequency), oxygen, suction, equipment necessary to provide intermittent positive pressure ventilation, oropharyngeal and laryngeal mask airways, equipment for intubation, and the possibility for connecting an anaesthetic machine if necessary. All medications and fluids for anaphylaxis treatment should be immediately available, and in addition, rapid access to the emergency team or cardiac arrest team, should be possible.

In some specialised centres DPT are performed in a high dependency unit, recovery unit, or in a room dedicated to perioperative allergy investigation. In smaller centres where such facilities are not available, DPT may be arranged on a case-by-case basis in collaboration between allergist and anaesthesiologist. The procedure may then be undertaken in the local anaesthetic department in an operating room, recovery unit, or high dependency unit/ICU.

In some cases, DPT may be performed on the day of surgery. In cases where an NMBA needs to be administered as part of an anaesthetic, a safe alternative (skin test negative drug) can be administered by DPT on the day of surgery.

General principles for provocation testing in perioperative allergy investigation

Many of the principles of DPT in general drug allergy can be applied in suspected perioperative allergy. Provocation should only be performed if other tests are negative or equivocal and do not allow firm conclusions (e.g. when there is a suspicion of false positive skin tests).[10,37]

For DPT for non-anaesthetic drugs administered in the perioperative period (e.g. antibiotics and NSAIDs), protocols used in general drug allergy can be used. For anaesthetic drugs, however, evidence is scarce and a few specialised centres use protocols based on principles derived from general drug allergy protocols, and modified by experience.

As a rule, the route of administration for the DPT should be the same as in the index reaction. For local anaesthetics, subcutaneous administration is used as the epidural/spinal route is not suitable for provocation.

In the perioperative setting DPT it is always considered a high-risk procedure and should be performed as a titrated approach of increasing doses until therapeutic dose is reached, or symptoms occur.[9,10,37] The patient should be observed for at least 2 h after the final dose or from the last symptom in case of a reaction. Longer observation times may be necessary after full dose anaesthetic provocation or after anaphylaxis.

Examples of procedures used in specialised centres

In the Danish Anaesthesia Allergy Centre, the Danish national reference centre for investigation of suspected perioperative allergic reactions, DPT has been carried out with all drugs including anaesthetic drugs since 2004. A maximum dose of 1/10 of a therapeutic dose is used for drugs with potent actions such as anaesthetic drugs, opioids, and vasopressors. All other drugs including antibiotics, local anaesthetics, NSAIDs, and anti-emetics are tested up to a full therapeutic dose. The protocol consists of three steps with 10-fold increase with 30–45 min intervals (30 min for i.v. and 45 min for oral and other routes of administration)[7,8] like protocols used in general drug allergy investigation. This protocol gives minimal risk of desensitisation (M. Castells, personal communication).

Some centres take the approach that hypersensitivity can only be excluded with confidence if the total dose of drug needed for an anaesthetic is reached during DPT. This dose is individualised based on age, gender, weight, and underlying diseases. Recent Spanish guidelines recommend performing DPT with anaesthetic drugs up to a full dose, in highly specialised centres with full monitoring and resuscitation facilities, at the level of a recovery unit/operating room.[5] In the Allergy Anaesthesia Unit of Hospital Central de la Cruz Roja in Madrid, Spain, DPT is performed in such a setting reaching full therapeutic doses with opioids, propofol, and other induction agents. The protocol is a four-step continuous i.v. protocol with increases in doses and infusion rate every 15 min.

There are no studies examining whether 1/10 of a full dose is sufficient to rule out IgE-mediated allergy. It is generally accepted that too low a dose might give false negative results.[10]

Table 1 Results of survey on provocation testing in perioperative allergy investigation. ISPAR Group, International Suspected Perioperative Allergic Reaction group; ANZAAG, Australian and New Zealand Anaesthetic Allergy Group; NMBAs, neuromuscular blocking agents; LA, local anaesthetics.

Do you perform provocation testing in the investigation of suspected perioperative allergic reactions in your centre?					
Centres	Routinely in all patients	When no conclusion from testing	With culprit drugs	To find alternative	Not done
ISPAR group, *n*=13	2	8	8	6	1
ANZAAG, *n*=21	0	11	6	10	6
In what proportion of your patients with suspected perioperative allergic reactions do you use provocation?					
Centres	0%	<20%	21–50%	51–80%	>80%
ISPAR group, *n*=13	1	3	5	2	2
ANZAAG, *n*=21	6	15	0	0	0
Do you carry out provocation with non-anaesthetic drugs in patients with suspected perioperative allergic reactions?					
Centres	NSAIDs	Antibiotics	Antiemetics	Latex/disinfectants	Others
ISPAR group, *n*=13	10	13	8	5	6
ANZAAG, *n*=21	0	8	0	0	0
Do you carry out provocation with anaesthetic drugs?					
Centres	Induction agents	Opioids	NMBAs	LA	Not done
ISPAR group, *n*=13	5	8	6	10	2
ANZAAG, *n*=21	10	11	9	15	6
Which setting are provocations performed in?					
Centres	Allergy clinic setting	Operating room	Recovery unit/ICU	Other	
ISPAR group, *n*=13	12 (low risk)	0	3 (high risk)	Day hospital, near ICU	
ANZAAG, *n*=21	14 (LA)	8	7		
Who is involved (or immediately available) during provocation testing?					
Centres	Allergist	Specialist allergy nurse	Anaesthetist	Anaesthetic nurse	Other
ISPAR group, *n*=13	12	10	9 (high risk)	1	1 (Day hospital staff)
ANZAAG, *n*=21	2	2	14	8	1 (Code teams)

It could be that the most severe reactions with an IgE-mediated mechanism would be identified on a 1/10 dose, but that reactions caused by other mechanisms might be overlooked. This, and the added risk of a full dose provocation, needs to be taken into consideration in the risk–benefit analysis.

Criteria for a positive provocation test

A provocation test is considered positive when symptoms from the initial reaction are reproduced or other clear signs of allergy appear during provocation. For example, in a case where the index reaction included respiratory or cardiovascular compromise, or both, without skin symptoms, the appearance of urticaria on a low dose will be interpreted as a positive test. Only objective signs should be considered. As patients were unconscious or sedated during the index reaction in most cases, they do not have a preconceived idea about which symptoms they might experience during provocation. For this reason, placebo-controlled provocation is rarely needed in perioperative allergy investigation.

Specific drug groups and survey results

A questionnaire survey on the use of DPT in perioperative allergy investigation was circulated to the 26 members of the International Suspected Perioperative Allergy Group (ISPAR) representing 19 centres, in September 2018. A response was received from 13 centres (from eight European countries, New Zealand and three US States) primarily led by allergists/immunologists. In addition, the survey was circulated at the 2018 annual meeting of the ANZAAG and 21 centres from Australia and New Zealand, primarily led by anaesthesiologists, responded. A summary of survey results can be seen in Table 1.

Overall, two centres performed DPT routinely and seven centres did not perform DPT in perioperative allergy investigation at all. Most centres performed provocation testing in <50% of patients. In the ISPAR centres, most provocations were performed in an allergy clinic setting with anaesthetic back-up immediately available for high-risk provocations. In the ANZAAG centres most provocations were performed in the operating room or recovery unit, and only few centres reported an allergist involved.

Anaesthetic agents

The Danish Anaesthesia Allergy Centre reported results of titrated DPT with propofol up to a maximum of 1/10 of a small induction dose (10 mg). A total of 133 patients had i.v. provocations with propofol and four tested positive. Of these, three had negative skin tests, and the diagnosis would have been missed if DPT had not been performed.[7] There are no publications on DPT with other induction agents, but the survey showed that 5/13 ISPAR centres and 10/21 ANZAAG centres reported performing DPT with induction agents. Provocation with opioids can prove useful to identify patients who are very sensitive to the propensity for these drugs to cause non-specific histamine release from mast cells, leading to skin symptoms even at quite small doses. The mechanism is not

likely to be IgE-mediated and can probably be blocked by antihistamine pretreatment. Eight of 13 ISPAR and 11/21 ANZAAG centres reported performing DPT with opioids.

Neuromuscular blocking agents

The paralysing effects of NMBAs present an obvious challenge and a full dose DPT requires simultaneous administration of a hypnotic drug. This may lead to doubts about causation if a reaction occurs. However, NMBAs carry a high risk of false positive skin testing because of a marked irritant effect. Consequently, some highly specialised centres, such as the Danish Anaesthesia Allergy Centre, have introduced DPT with NMBAs to a maximum dose of 1/10 of the intubation dose, administered over 5–10 min, when skin test results are negative or equivocal. In Denmark the prevalence of reactions to NMBAs is low, and in this setting the approach has proved safe and acceptable to patients who experience transient double vision in most cases, but no respiratory effects of the drug.[43] The negative predictive value of skin testing to NMBAs is generally reported to be high.[44,45] However, this has never been validated systematically by DPT, except when patients tolerate an NMBA during subsequent anaesthesia.

A recent case report describes successful NMBA provocation in a sedated and ventilated patient. The patient had developed anaphylaxis to rocuronium, which tested positive on skin testing. A skin test negative drug from another chemical group, cisatracurium, was administered i.v. in incremental doses up to 2 mg without reaction.[46] The survey revealed that 6/13 ISPAR and 9/21 ANZAAG centres report performing DPT with NMBAs.

Local anaesthetics

Allergy to local anaesthetics is extremely rare. Because of a small risk of false-positive intradermal testing, it is recommended to always consider subcutaneous DPT, even if intradermal skin testing is positive. This is especially important when the local anaesthetic is not the most suspected drug.[17,47] The survey showed that 10/13 ISPAR centres and 15/21 ANZAAG centres perform DPT with local anaesthetics.

Patent blue dye

The dye Patent blue used for sentinel node detection in certain types of cancer surgery is a relatively common cause of perioperative allergy.[48] For this drug DPT can be used to confirm oral tolerance despite a perioperative reaction on subcutaneous exposure. In the Danish Anaesthesia Allergy Centre, patients testing positive on skin testing with Patent blue have all been shown to tolerate sublingual and oral DPT with Patent blue (M. Krøigaard, personal communication). This has important implications for patients, as Patent blue is used as a food colouring in some countries. Patients can be reassured that, whereas further subcutaneous exposure should be avoided, foods with blue colouring are well tolerated.

Non-anaesthetic drugs

For drugs that are not exclusive to the perioperative setting (e.g. antibiotics, antiemetics, and NSAIDs), DPT protocols developed for use in general drug allergy can be used. Incremental dose increases are administered to reach a full maximum single unit dose. Eight of 13 ISPAR centres perform DPT for antibiotics, NSAIDs, and antiemetics, whereas only 8/21 ANZAAG centres tested antibiotics and none tested NSAIDS or antiemetics.

Chlorhexidine

Chlorhexidine exposure usually occurs on mucous membranes in the urethra or the mouth, or on broken skin. There is no ideal DPT protocol for chlorhexidine. For this and other drugs where the gold standard of DPT is not available, sensitivity and specificity can be estimated against a 'silver' standard. One such approach is to combine test results from different test modalities (e.g. skin prick test, intradermal test, specific IgE test, and basophil activation test), and make the diagnosis based on two or more positive test results.[49,50]

Limitations and future challenges

Although titrated DPT is considered the gold standard to correctly establish a diagnosis in general drug allergy, it has some limitations. Firstly, DPT cannot reproduce co-factors such as concurrent illness or inflammation or psychological stress that might have contributed to the reaction. In addition, DPT does not display 100% sensitivity as false negative DPT has been reported.[51]

Specific to the perioperative setting, the combination of effects of drugs administered simultaneously cannot be reproduced, and there are major challenges for specific drug groups. For drugs such as NMBAs, full-dose DPT is not possible without administering additional drugs, and DPT with a maximum of 1/10 of the therapeutic dose might not be sufficient to produce a reaction. Future challenges in perioperative allergy investigation include the continued optimisation of skin and *in vitro* tests to minimise the need for DPT. At the same time studies should be undertaken to investigate the sensitivity of DPT protocols with 1/10 maximum dose and to develop standardised indications and protocols for DPT with drugs specific to the perioperative setting.

Conclusions

There is a place for DPT in perioperative allergy investigation, as a false negative result on conventional testing can have fatal consequences. Recently, European[9] and Spanish guidelines[5] mention the use of DPT in perioperative allergy investigation, but strongly emphasise that it should be undertaken in close collaboration between anaesthesiologists and allergists in highly specialised centres. However, the use of DPT in this field is still in the very early stages and the literature on the subject is limited. Our questionnaire survey of expert centres participating in the ISPAR group and centres from the primarily anaesthesiologist-led ANZAAG group showed that many centres carry out DPT on a regular basis even with induction agents and NMBAs. As data on DPT from these practices are all unpublished, it highlights the importance of collaborations between centres worldwide to enable the exchange of knowledge and expertise. This could lead to more formalised alliances and multicentre studies aimed at establishing common protocols improving diagnosis and optimising patient safety.

Authors' contributions

Design of the study: LHG, MK, DGE, JJL, SS.
Drafting of manuscript: LHG, MK, DGE, JJL, SS.

All authors were involved in the conception of the study, and in the collection, analysis, and interpretation of data. All authors reviewed drafts of the manuscript and approved the final version.

Declarations 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. PMH: is an Editorial Board Member of BJA. PMM: Scientific advisor for the ALPHO study (NCT02250729), funded by a consortium of pharmaceutical companies: Zambon, Urgo, Pierre Fabre, Boots, Hepatoum, Biocodex, Sanofi, LBR, GSK, APL, Bells Healthcare, Pinewood, T & R, Ernest Jackson. PK has received lectures fees from Novartis Pharma Services Inc, Shire Pharmaceuticals Group Plc.SM is in receipt of an Australian National Health and Medical Research Council (NHMRC) ECR Fellowship for the investigation of cognitive aids in emergencies. All other authors confirm that they have no interests to declare.

References

1. Krøigaard M, Garvey LH, Gillberg L, et al. Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Anaesthesiol Scand* 2007; **51**: 655–70
2. Mertes PM, Malinovsky JM, Jouffroy L, et al., Working Group of the SFAR and SFA, ENDA, EAACI Interest Group on Drug Allergy. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2011; **21**: 442–53
3. Scolaro RJ, Crilly HM, Maycock EJ, et al. Australian and New Zealand Anaesthetic Allergy Group perioperative anaphylaxis investigation guidelines. *Anaesth Intensive Care* 2017; **45**: 543–55
4. Harper NJ, Dixon T, Dugue P, et al. Suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia* 2009; **64**: 199–211
5. Laguna JJ, Archilla J, Doña I, et al. Practical guidelines for perioperative hypersensitivity reactions. *J Investig Allergol Clin Immunol* 2018; **28**: 216–32
6. Demoly P, Adkinson NF, Brockow K, et al. International Consensus on drug allergy. *Allergy* 2014; **69**: 420–37
7. Asserhøj LL, Mosbech H, Krøigaard M, Garvey LH. No evidence for contraindications to the use of propofol in adults allergic to egg, soy or peanut. *Br J Anaesth* 2016; **116**: 77–82
8. Christiansen IS, Krøigaard M, Mosbech H, Garvey LH. Clinical and diagnostic features of perioperative hypersensitivity to cefuroxime. *Clin Exp Allergy* 2015; **45**: 807–14
9. Garvey LH, Ebo D, Mertes PM, *et al*. Position Paper on the investigation of perioperative immediate hypersensitivity reactions—an expert consensus from the EAACI task force on perioperative hypersensitivity. Accepted for publication in Allergy March 2019.
10. Aberer W, Bircher A, Romano A, et al. European Network for Drug Allergy (ENDA); EAACI interest group on drug hypersensitivity. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003; **58**: 854–63
11. Agache I, Bilò M, Braunstahl GJ, et al. In vivo diagnosis of allergic diseases—allergen provocation tests. *Allergy* 2015; **70**: 355–65
12. Messaad D, Sahla H, Benahmed S, et al. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Intern Med* 2004; **140**: 1001–6
13. Dona I, Blanca-Lopez N, Torres MJ, et al. Drug hypersensitivity reactions: response patterns, drug involved, and temporal variations in a large series of patients. *J Investig Allergol Clin Immunol* 2012; **22**: 363–71
14. Joint task force on practice Parameters; American Academy of allergy, asthma and Immunology; American college of allergy, asthma and Immunology; joint council of allergy, asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010; **105**: 259–73
15. Mirakian R, Ewan PW, Durham SR, et al. BSACI guidelines for the management of drug allergy. *Clin Exp Allergy* 2009; **39**: 43–61
16. de Las Vecillas Sánchez L, Alenazy LA, Garcia-Neuer M, Castells MC. Drug hypersensitivity and desensitizations: mechanisms and new approaches. *Int J Mol Sci* 2017; **18**: E1316. 20
17. Kvisselgaard A, Mosbech H, Fransson S, Garvey LH. Risk of immediate type allergy to local anaesthetics is over-estimated—results from 5 years of provocation testing in a Danish Allergy Clinic. *J Allergy Clin Immunol Pract* 2018; **6**: 1217–23
18. Fransson S, Mosbech H, Kappel M, et al. The importance of prolonged provocation in drug allergy—results from a Danish allergy clinic. *J Allergy Clin Immunol Pract* 2017; **5**: 1394–401
19. Caubet JC, Kaiser L, Lemaitre B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol* 2011; **127**: 218–22
20. Confino-Cohen R, Rosman Y, Meir-Shafrir K, et al. Oral challenge without skin testing safely excludes clinically significant delayed-onset penicillin hypersensitivity. *J Allergy Clin Immunol Pract* 2017; **5**: 669–75
21. Savic L, Gurr L, Kaura V, et al. Penicillin allergy de-labelling ahead of elective surgery—is it feasible and what are the barriers? *Br J Anaesth* 2019 Mar 11. https://doi.org/10.1016/j.bja.2019.01.026. pii: S0007-0912(19)30068-6
22. Coop CA, Schapira RS, Freeman TM. Are ACE inhibitors and beta-blockers dangerous in patients at risk for anaphylaxis? *J Allergy Clin Immunol Pract* 2017; **5**: 1207–11
23. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs—an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2013; **68**: 702–12
24. Mayorga C, Celik G, Rouzaire P, et al. In vitro tests for drug hypersensitivity reactions: an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy* 2016; **71**: 1103–34
25. Ebo DG, Faber M, Elst J, et al. In vitro diagnosis of immediate drug hypersensitivity during anesthesia: a

review of the literature. *J Allergy Clin Immunol Pract* 2018; **6**: 1176–84
26. Nasser SM, Ewan PW. Opiate-sensitivity: clinical characteristics and the role of skin prick testing. *Clin Exp Allergy* 2001; **31**: 1014–20
27. Leysen J, De Witte L, Sabato V, et al. IgE-mediated allergy to pholcodine and cross-reactivity to neuromuscular blocking agents: lessons from flow cytometry. *Cytometry B Clin Cytom* 2013; **84**: 65–70
28. Li PH, Ue KL, Wagner A, Rutkowski R, Rutkowski K. Opioid hypersensitivity: predictors of allergy and role of drug provocation testing. *J Allergy Clin Immunol Pract* 2017; **5**: 1601–6
29. Ebo DG, Venemalm L, Bridts CH, et al. Immunoglobulin E antibodies to rocuronium: a new diagnostic tool. *Anesthesiology* 2007; **107**: 253–9
30. Uyttebroek AP, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Immunoglobulin E antibodies to atracurium: a new diagnostic tool? *Clin Exp Allergy* 2015; **45**: 485–7
31. Decuyper II, Mangodt EA, Van Gasse AL, et al. In vitro diagnosis of immediate drug hypersensitivity anno 2017: potentials and limitations. *Drugs R D* 2017; **17**: 265–78
32. Ebo DG, Clarke RC, Mertes PM, Platt PR, Sabato V, Sadleir PH. Molecular mechanisms and pathophysiology of perioperative hypersensitivity and anaphylaxis: a narrative review. *Br J Anaesth* 2019; **123**: e38–49
33. Volcheck GW, Mertes PM. Local and general anesthetics immediate hypersensitivity reactions. *Immunol Allergy Clin North Am* 2014; **34**: 525–46
34. Sanchez Palacios A, Ortiz Ponce M, Rodriguez Perez A. Allergic reactions and pseudoallergies in surgical interventions with general anesthesia. *Allergolog Immunopathol* 2000; **28**: 24–36
35. Garvey LH, Belhage B, Krøigaard M, Husum B, Malling HJ, Mosbech H. Treatment with epinephrine (adrenaline) in suspected anaphylaxis during anesthesia in Denmark. *Anesthesiology* 2011; **115**: 111–6
36. Garvey LH. Perioperative hypersensitivity reactions: diagnosis, treatment and evaluation. *Curr Treat Options Allergy* 2016; **3**: 113–28
37. Bousquet PJ, Pipet A, Bousquet-Rouanet L, Demoly P. Oral challenges are needed in the diagnosis of beta-lactam hypersensitivity. *Clin Exp Allergy* 2008; **38**: 185–90
38. Mertes PM, Volcheck GW, Garvey LH, et al. Epidemiology of perioperative anaphylaxis. *Presse Med* 2016; **45**: 758–67
39. Brockow K. Dilemmas of allergy diagnosis in perioperative anaphylaxis. *Allergy* 2014; **69**: 1265–6
40. Opstrup MS, Poulsen LK, Malling HJ, Jensen BM, Garvey LH. Dynamics of plasma levels of specific IgE in chlorhexidine allergic patients with and without accidental re-exposure. *Clin Exp Allergy* 2016; **46**: 1090–8
41. Li, et al. Assessing cross-reactivity to muscle relaxants by skin and basophil activation tests in patients with neuromuscular blocking agent anaphylaxis. *Br J Anaesth* 2019. https://doi.org/10.1016/j.bja.2019.03.001
42. ASA Physical Status Classification System—American Society of Anesthesiologists (ASA). https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system (accessed October 15, 2018).
43. Melchiors BLB, Kroigaard M, Garvey LH. Intravenous provocation with Neuromuscular Blocking Agents in the investigation of perioperative anaphylaxis – preliminary findings from the Danish Anaesthesia Allergy Centre (DAAC). *Eur J Anaesthesiol.* 2018; **35**. e suppl 56 p 318
44. Leysen J, Uyttebroek A, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Predictive value of allergy tests for neuromuscular blocking agents: tackling an unmet need. *Clin Exp Allergy* 2014; **44**: 1069–75
45. Ramirez LF, Pereira A, Chiriac AM, Bonnet-Boyer MC, Demoly P. Negative predictive value of skin tests to neuromuscular blocking agents. *Allergy* 2012; **67**: 439–41
46. Schulberg EM, Webb AR, Kolawole H. Early skin and challenge testing after rocuronium anaphylaxis. *Anaesth Intensive Care* 2016; **44**: 425–7
47. Kvisselgaard AD, Krøigaard M, Mosbech H, Garvey LH. No cases of perioperative allergy to local anaesthetics in the Danish Anaesthesia Allergy Centre. *Acta Anaesthesiol Scand* 2017; **61**: 149–55
48. Brenet O, Lalourcey L, Queinnec M, et al. Hypersensitivity reactions to Patent Blue V in breast cancer surgery: a prospective multicentre study. *Acta Anaesthesiol Scand* 2013; **57**: 106–11
49. Leysen J, Bridts CH, De Clerck LS, et al. Allergy to rocuronium: from clinical suspicion to correct diagnosis. *Allergy* 2011; **66**: 1014–9
50. Opstrup MS, Malling HJ, Krøigaard M, et al. Standardized testing with chlorhexidine in perioperative allergy—a large single centre evaluation. *Allergy* 2014; **69**: 1390–6
51. Demoly P, Romano A, Botelho C, et al. Determining the negative predictive value of provocation tests with beta-lactams. *Allergy* 2010; **65**: 327–32

Handling editor: H.C. Hemmings Jr

BJA

British Journal of Anaesthesia, 123 (1): e135–e143 (2019)

doi: 10.1016/j.bja.2019.02.024
Advance Access Publication Date: 4 April 2019
Testing

Integrating basophil activation tests into evaluation of perioperative anaphylaxis to neuromuscular blocking agents

Jamma Li[1,2,3,*], Oliver G. Best[2], Michael A. Rose[4], Sarah L. Green[4], Richard B. Fulton[3] and Suran L. Fernando[1,2,3]

[1]Department of Clinical Immunology and Allergy, Royal North Shore Hospital, Sydney, Australia, [2]Medicine (Immunology & Infectious Diseases), University of Sydney, Sydney, Australia, [3]Medicine (Immunology & Infectious Diseases), NSW Health Pathology, Sydney, Australia and [4]Department of Anaesthesia, Royal North Shore Hospital, Sydney, Australia

*Corresponding author. E-mail: jamma.li@health.nsw.gov.au

Abstract

Background: Neuromuscular blocking agents (NMBAs) remain the leading cause of perioperative anaphylaxis in Australia. Standard evaluation comprises history, skin tests, and *in vitro* specific immunoglobulin E tests. Drug provocation tests to suspected NMBA culprits are associated with a significant risk. Basophil activation testing (BAT) is a potentially useful *in vitro* test that is not commercially available in Australia or as part of standard evaluation.

Methods: All patients attending the Anaesthetic Allergy Clinic in Sydney, Australia between May 2017 and July 2018 exposed to an NMBA before the onset of anaphylaxis during their anaesthetic qualified for the study. We recruited 120 patients sequentially who received standard evaluation plus BAT using CD63, CD203c, and CD300a as surface activation markers.

Results: BAT results were expressed as % upregulation above the negative control and stimulation index (mean fluorescence index of stimulated sample divided by the negative control). We calculated cut-offs of 4.45% and 1.44 for CD63, and 8.80% and 1.49 for CD203c, respectively. Sensitivity was 77% with specificity of 76%. A subgroup of 10 patients with NMBA anaphylaxis had no sensitisation on skin tests. BAT using CD63 and CD203c showed sensitisation in six of these 10, and adding CD300a identified sensitisation in nine patients. BAT was positive in seven of nine patients with anaphylaxis of unknown aetiology.

Conclusions: BAT may be a useful supplement to the standard evaluation in diagnosing NMBA anaphylaxis in patients with suggestive histories, but no sensitisation on skin tests. Ongoing study of this specific group of patients is required to clarify its utility in clinical practice.

Keywords: anaestehsia; anaphylaxis; basophil degranulation test; drug hypersensitivity; neuromuscular blocking agents; skin tests

Editorial decision: 24 February 2019; **Accepted:** 24 February 2019

Editor's key points

- Neuromuscular blocking agents (NMBAs) remain the leading cause of perioperative anaphylaxis in Australia.
- Drug provocation tests to suspected NMBA culprits are associated with a significant risk.
- In a prospective study of 120 patients at an Australian allergy clinic, basophil activation testing showed good sensitivity and specificity, and identified sensitisation in a subset of patients with negative standard testing results.
- Basophil activation testing is a potentially useful *in vitro* test to supplement standard evaluation in diagnosing NMBA anaphylaxis.

Perioperative anaphylaxis is potentially a life-threatening event,[1] with an estimated worldwide incidence of one in 1250 to one in 20 000 operations.[2,3] Neuromuscular blocking agents (NMBAs) remain the leading cause of perioperative anaphylaxis in Australia.[4,5] Routine evaluation comprises clinical history, in vivo skin tests, and in vitro specific immunoglobulin E (sIgE) assays. Whilst the gold standard to confirm allergy is drug provocation testing to a suspected NMBA culprit, this is associated with a significant risk of anaphylaxis.

Allergens engage with the surface receptors of mast cells and basophils, and trigger degranulation, releasing mediators that create the clinical manifestations of anaphylaxis.[6] Basophils, unlike mast cells, can be isolated from peripheral blood, and are a model for mast cells. The activation of basophils triggers the upregulation of surface markers, including CD63, CD203c, and CD300a,[7] which can be measured by an *in vitro* method known as basophil activation testing (BAT). BAT is available in a few specialised centres for investigation of drug allergy, including NMBA allergy. As BAT is not available in Australia for routine use, we assessed its utility for the investigation of NMBA anaphylaxis, and how it should be introduced into our testing strategy.

Methods

We recruited patients sequentially from the Anaesthetic Allergy Clinic, Royal North Shore Hospital, Sydney, New South Wales (NSW), Australia, between May 2017 and July 2018. This service receives referrals for evaluation of perioperative anaphylaxis from across NSW and is the largest test centre in the state. Approximately 24 patients are reviewed monthly.

We recruited all patients exposed to an NMBA before the onset of anaphylaxis during their anaesthetic. All patients received BAT in addition to the standard assessment comprising clinical history, review of anaesthetic records, tryptase results, skin tests to all drugs and substances administered before the onset of anaphylaxis (including NMBAs, chlorhexidine, and povidone iodine), and sIgE tests. Specific IgE to morphine, pholcodine, latex, and chlorhexidine are routinely performed, and sIgE to penicillins where a patient has received a beta-lactam. The following data were collected: age, sex, interval between reaction and evaluation, preoperative anaesthetic review, clinical history of anaphylaxis, and full anaesthetic records. Relevant patient medical history was also obtained, including history of atopy.

Skin testing

Concentrations used for skin tests (Table 1) were as recommended by the Australian and New Zealand Anaesthetic Allergy Group (ANZAAG).[5] We performed intradermal skin tests to all agents administered in the perioperative period before anaphylaxis, and a standard panel of NMBAs (rocuronium, vecuronium, pancuronium, suxamethonium, and cisatracurium).[5] Atracurium and mivacurium are sold, but not commonly used in NSW. Skin prick tests to NMBAs were performed if intradermal tests were positive only at strong concentrations. All patients with positive intradermal tests at strong concentrations also had positive skin prick tests.

Specific IgE to morphine and pholcodine

These assays were performed at NSW Health Pathology, Sydney, Australia, using ImmunoCAP® (Phadia, Uppsala, Sweden), and have superior performance characteristics to sIgE to rocuronium and suxamethonium.[8,9] IgE antibodies directed against morphine and pholcodine moieties, which contain substituted ammonium groups similar to those present on NMBAs, were measured.[10] The detection limit of both assays is 0.1 kUA L^{-1}. We applied the manufacturer-recommended cut-off of 0.35 kUA L^{-1},[10–12] plus 0.23 kUA L^{-1} as calculated by our group for our patient population.[10]

Diagnosing NMBA anaphylaxis

A suggestive clinical history of NMBA anaphylaxis is where anaphylaxis occurs within 15 min of administration of the NMBA.[13] All patients diagnosed with NMBA anaphylaxis have a suggestive clinical history supported by positive skin and sIgE tests. If there was isolated sIgE sensitisation, other

Table 1 Standard and strong concentrations of neuromuscular blocking agents used in the evaluation of perioperative anaphylaxis. Adapted from Scolaro and colleagues[5]

	Standard concentration for intradermal testing (μg ml^{-1})	Strong concentration for intradermal testing (μg ml^{-1})	Skin prick test concentration (mg ml^{-1})
Rocuronium	10	100	10
Vecuronium	4	40	4
Pancuronium	2	20	2
Suxamethonium	50	100	10
Cisatracurium	2	20	2

potential culprits need to be excluded by skin and serum tests, and occasionally challenges on at least two separate occasions.

Basophil activation test

We used a standard BAT protocol. Whole blood was collected in lithium heparin vacutainers (Becton Dickinson, Franklin Lakes, NJ, USA). Basophil surface activation markers were measured within 3 h of collection. For each subject, whole blood was incubated for 20 min at 37°C with:

(i) Negative control, comprising basophil stimulation buffer (BSB) in RPMI-1640 Medium (Life Technologies, Carlsbad, CA, USA)
(ii) Positive control, comprising BSB and 1 μM N-formyl-methionyl-leucyl-phenylalanine (fMLP) chemotactic peptide (Sigma-Aldrich, St Louis, MO, USA)
(iii) Three serial dilutions of each NMBA: rocuronium (0.5, 2.75, and 5×10^3 μg ml^{-1}), vecuronium (0.5, 1.25, and 2×10^3 μg ml^{-1}), pancuronium (0.5, 0.75, and 1 μg ml^{-1}), suxamethonium (0.5, 2.75, and 5×10^3 μg ml^{-1}), and cisatracurium (0.5, 0.75, and 1×10^3 μg ml^{-1})

Reactions were stopped by adding 20 mM ethylenediamine tetra-acetic acid 20 μl (Sigma-Aldrich). Cells were stained with premixed, fluorochrome-conjugated monoclonal antibodies to CD63-FITC, CD123-PE, HLA-DR-PerCP (FastImmune™; BD Biosciences, Franklin Lakes, NJ, USA), CD203c Alexa Fluor® 405 (R&D Systems, Minneapolis, MN, USA), and CD300a-APC (R&D Systems), according to the manufacturer's recommendations. Red cells were lysed with FACS™ lysing solution 2 ml (BD Biosciences), and centrifuged. The cells were washed with phosphate-buffered saline 2 ml, and fixed in paraformaldehyde 0.5% (300 μl) (Sigma-Aldrich). Flow cytometric analysis was performed using an LSRFortessa™ instrument (Becton Dickinson) by acquiring at least 500 basophils per sample. Basophils were gated as CD123 positive and HLA-DR negative.

The results of BAT were expressed as (i) net percentage upregulation in stimulated basophils compared with the negative control (% upregulation). Gates were placed assuming baseline expression levels of 0% for CD63 and 10% for CD203c in the negative control.[14] For each patient, % upregulation for both antigens was recorded for the positive control, and NMBA-stimulated basophils. Two results are recorded for each NMBA: (i) %(max), the highest % upregulation out of the three dilutions for each NMBA, and %(mean), the mean % upregulation of the three dilutions for each NMBA, and (ii) Stimulation index (SI) is calculated as the ratio of the mean fluorescence intensity (MFI) of antigen expression in the positive control or NMBA-stimulated samples to MFI of the negative control. Two results are recorded for each NMBA. SI(max) is the highest SI of the three dilutions; SI(mean) is the mean SI of the three dilutions.

Receiver operating characteristic curve analysis

We included all 111 patients in the NMBA anaphylaxis and control groups in receiver operating characteristic (ROC) curve analysis for CD63 and CD203c, except for one non-responder to fMLP. In one construct, we included only rocuronium-exposed patients, as 78.3% of our cohort received rocuronium. In a second construct, we included all patients. We obtained cut-offs for a positive test using Youden's statistic for BAT by both CD63 and CD203c calculated as %(max), %(mean), SI(max), and SI(mean). For the analysis of CD300a, we included only patients with significant CD300a upregulation by fMLP. In one construct, we included only rocuronium-exposed patients (25 NMBA allergic and 11 control patients); in a second construct, all 50 patients. We calculated cut-offs using SI only, as there are no published data on constitutive expression of CD300a by unstimulated basophils.

Serum tryptase

Tryptase is a preformed mediator contained within mast cells released upon mast-cell degranulation. The assay was performed at NSW Health Pathology, using ImmunoCAP (Phadia) with a detection limit of 1 μg L^{-1}. We used the ANZAAG definition of a significant rise and fall: elevation of baseline tryptase by 120% plus 2 μg L^{-1}, and return to baseline.[15] All peak tryptase concentrations were collected within 1–4 h of the reaction. Baseline tryptase concentrations were collected at least 24 h after the reaction. Results were classified 'yes' for a significant tryptase rise and fall, or 'no'. If the peak tryptase concentration was not collected within the required time frame, the tryptase result is 'not available'.

Statistical analysis

SPSS version 24 (IBM, Armonk, NY, USA) was used to conduct the statistical analysis. Calculation of the ROC curves was performed on continuous variables. Sensitivity and specificity, and χ^2 values were calculated on categorical variables. A result was considered significant if $P<0.05$.

Results

A total of 120 patients were recruited (Table 2). No patients declined participation. Patients were classified into three groups: (i) patients with NMBA anaphylaxis ($n=61$); (ii) control patients, who did not have NMBA anaphylaxis ($n=50$); and (iii) patients with anaphylaxis to an unknown culprit and NMBA was administered within 15 min of anaphylaxis ($n=9$).

Control patients had anaphylaxis to cephazolin ($n=23$), sugammadex ($n=2$), blood products ($n=2$), latex ($n=1$), or vancomycin ($n=1$). Others had non-immunological reactions ($n=13$), hypotension with no evidence of IgE sensitisation or significant tryptase change ($n=8$), bronchospasm and a significant smoking history or asthma with no evidence of IgE sensitisation or significant tryptase change ($n=3$), or angioedema with an alternate aetiology ($n=2$). Also included were patients with reactions after uneventful induction and maintenance anaesthesia ($n=4$), and incomplete documentation of a historical reaction with negative skin and serum tests ($n=4$).

Receiver operating characteristic curve analysis

The following cut-offs were obtained using %(max), SI(max), %(mean), and SI(mean) for both CD63 and CD203c (Table 3). Superior performance characteristics were noted when ROC curves were constructed using only rocuronium-exposed patients. Using these cut-offs, we classified BAT as positive or negative for the NMBA administered. One patient in

Table 2 Patient characteristics of a cohort of 120 patients exposed to a neuromuscular blocking agent (NMBA) before perioperative anaphylaxis. IgE, immunoglobulin E. *Tryptase concentrations were not available for all patients, as a peak mast-cell tryptase concentration was not collected within the correct time frame and number of patients for each study group where tryptase is not available (indicated in brackets): NMBA anaphylaxis group (five), control patients (four), and anaphylaxis to unknown culprit (three). †Includes six patients reviewed beyond 1 yr of reaction. ‡Includes three patients reviewed beyond 1 yr of reaction

	NMBA anaphylaxis	Control	Anaphylaxis to unknown culprit
Total subjects	61	50	9
Age (yr), average (range)	52 (16–75)	47 (20–79)	49 (28–72)
Female, *n* (%)	41 (67)	24 (48)	5 (56)
Interval between reaction and assessment (days)	102	472†	380‡
Atopy, *n* (%)	26 (43)	13 (27)	2 (23)
Significant rise and fall in tryptase *n* (%)*	47 (77)	30 (60)	3 (33)
Skin test positive to NMBA administered	51	0	0
Specific IgE to morphine or pholcodine positive*	53	0	0
System involved			
Cardiovascular only	17	19	3
Respiratory	3	5	2
Cardiovascular and respiratory	38	17	6
Skin involvement	22	15	3
NMBA exposed to			
Rocuronium	48	40	7
Vecuronium	4	7	1
Cisatracurium	0	1	1
Suxamethonium	9	2	0
Pancuronium	0	0	0
Category of anaphylaxis			
Non-life threatening	2	8	4
Life threatening	48	37	3
Cardiac or respiratory arrest	11	5	2

the NMBA anaphylaxis group was a non-responder and recorded as BAT negative in the analysis.

We noted optimal sensitivity where CD63 and CD203c were combined, and a positive BAT was defined as above the cut-off by either %(max) or SI(max). BAT achieved a sensitivity of 77% and a specificity of 76% compared against standard evaluation. Using %(mean) or SI(mean), sensitivity was 73% with a specificity of 78%. Full performance characteristics are shown in Table 4. Combining surface activation markers increased the number of false positives and lowered the specificity.

Does BAT using CD63 and CD203c enhance the evaluation of perioperative anaphylaxis?

Within our cohort of 120 patients, 61 had NMBA anaphylaxis, of which 51 had sensitisation on skin tests, 53 had positive sIgE, and 43 also had a positive BAT. Ten of 61 patients with NMBA anaphylaxis had sensitisation on sIgE only (Table 5). Nine patients had positive sIgE to both morphine and pholcodine using a cut-off of 0.23 kUA L^{-1}. One patient had only a positive sIgE to pholcodine (sIgE to morphine 0.21 kUA L^{-1}). Using a cut-off of 0.35 kUA L^{-1}, eight patients had positive sIgE

Table 3 Cut-off values for basophil activation testing using CD63 and CD203c. NMBA, neuromuscular blocking agent

Basophil activation marker	Calculation method	Cut-off (including patients exposed to rocuronium only)	Cut-off (including patients exposed to rocuronium and any NMBA)
CD63	%(max)	4.45%	4.20%
CD63	%(mean)	1.65%	1.25%
CD63	SI(max)	1.4386	1.5642
CD63	SI(mean)	1.2836	1.2544
CD203c	%(max)	8.8%	8.85%
CD203c	%(mean)	5.85%	5.05%
CD203c	SI(max)	1.4875	1.4453
CD203c	SI(mean)	1.2793	1.2540

Table 4 Performance characteristics of basophil activation testing using CD63 and CD203c. SI, stimulation index

	Maximal values			Mean values		
	Sensitivity	Specificity	False positives (*n*)	Sensitivity	Specificity	False positives (*n*)
Combining all strategies (using maximal values)	0.767	0.756	11	0.733	0.778	10
CD63 only (% upregulation and SI)	0.633	0.822	8	0.583	0.844	7
CD203c only (% upregulation and SI)	0.633	0.889	5	0.633	0.889	5
% upregulation only (CD63 and CD203c)	0.667	0.778	10	0.667	0.844	7
SI only (CD63 and CD203c)	0.617	0.778	10	0.533	0.867	6
CD63 (% upregulation)	0.483	0.867	6	0.567	0.911	4
CD63 (SI)	0.533	0.822	8	0.424	0.913	4
CD203c (% upregulation)	0.583	0.889	5	0.667	0.911	4
CD203c (SI)	0.4	0.933	3	0.433	0.933	3

to both assays, and two to pholcodine only (sIgE to morphine was 0.21, and 0.29 kUA L^{-1}). Six of 10 patients had a positive BAT. We also applied BAT to our third group of nine patients who had anaphylaxis to an unknown culprit (Table 6). Seven of nine patients (78%) had a positive BAT.

Utility of CD300a in diagnosing NMBA anaphylaxis

Upregulation of CD300a by fMLP in the positive control above 10% of the negative control occurred in only 34 patients (56%) in the NMBA anaphylaxis and 16 (35%) in the control group. The MFI for CD300a in the positive control was equal or lower than in the negative control for 42 patients (39%). We constructed an ROC curve for CD300a using SI(max), as our data for CD63 and CD203c showed that performance characteristics were superior using maximal rather than mean values. A cut-off of 1.70 was obtained when including rocuronium-exposed patients only; a cut-off of 1.43 was obtained when all patients were included. Specificity of BAT for CD300a was 93.8% at either cut-off. Sensitivity was superior using the lower cut-off of 1.43 at 55.9% against 41.2% with the higher cut-off. Ten of 61 patients with NMBA anaphylaxis had no sensitisation on skin tests. Of these 10 patients, only six had significant CD300a upregulation with fMLP. CD300a indicated sensitisation in four of six patients, three of which showed sensitisation to CD300a only with no positive BAT using CD63 or CD203c (Table 5).

Discussion

NMBAs continue to be the leading cause of perioperative anaphylaxis in Australia.[4,5] Whilst NMBAs have been surpassed in the UK as the leading cause by antibiotics,[13] surgical prophylaxis in Australia usually comprises cephazolin and vancomycin in penicillin-allergic patients,[16] which combined has a lower incidence of anaphylaxis than amoxycillin–clavulanate and teicoplanin.[13]

We present a prospective study where we incorporated BAT into clinical evaluation with a sizeable cohort of 120 patients who were exposed to NMBAs. BAT had a sensitivity of 77% and a specificity of 76%, which is comparable with published performance characteristics.[17–21] We build on the current literature by presenting performance characteristics of BAT using different combinations of surface markers and methods of calculation. We found that, combining CD63 and CD203c, and expressing basophil activation by both % upregulation and SI were most effective.

CD203c has not been well studied as a marker for basophil activation in NMBA anaphylaxis. An early study, comprising 12 patients with suxamethonium, vecuronium, and atracurium anaphylaxis, found CD63 had superior performance characteristics.[22] A recent French retrospective study,[23] comprising 31 patients, 21 with suxamethonium anaphylaxis, found that combining CD63 and CD203c did not increase sensitivity. This is discordant with our study, which is prospective, and comprises a larger cohort biased towards rocuronium anaphylaxis.

The cut-offs obtained in our study are comparable with those reported previously, which include upregulation above 4% for rocuronium with CD63,[19] above 4%[17,24] and above 5.01% for all NMBAs with CD63,[25] and above 10% for CD203c.[22] The SI has been proposed as an alternate calculation, with 1.76 suggested as the optimal threshold for BAT in NMBA allergy,[25] but 2.00 has also been applied in line with BAT for non-NMBA drug allergy.[23] We applied published cut-offs of 5% for CD63, 10% for CD203c, and SI of 1.76 to our data, and obtained a comparable sensitivity of 73% and specificity of 88%.

BAT, using CD63 and CD203c, demonstrated sensitisation in six of 10 patients who did not have sensitisation on skin tests. By including CD300a into the testing algorithm, this increased to nine of 10 patients. Although the diagnosis of NMBA anaphylaxis can be made from suggestive clinical history and isolated sIgE sensitisation, positive BAT to the culprit drug increases the confidence of the diagnosis. At this stage, we perform drug provocation testing only to alternate NMBA(s) that are not likely to cause anaphylaxis, but will provide a safe alternative for future anaesthesia.[5,26] Questions have been raised about the reliability of an isolated positive sIgE as a marker of NMBA allergy.[24] In Australia, a country with high consumption of pholcodine,[27] sensitisation in atopic subjects is ~10% to pholcodine, 8.6% to morphine, and 4.3% to suxamethonium.[28] Our rate of sensitisation is comparable with other high-consumption countries.[29]

In our cohort, there were nine patients where a diagnosis could not be confidently reached at the time of original

Table 5 Characteristics of perioperative anaphylaxis in patients with neuromuscular blocking agent (NMBA) anaphylaxis, but negative skin testing. BAT, basophil activation testing; IgE, immunoglobulin E

Patient	Age at reaction (yr)	Onset of anaphylaxis	Clinical feature	NMBA administered	Peak serummast-cell tryptase (μg L^{-1})	Baseline serummast-cell tryptase (μg L^{-1})	Significant rise and fall in tryptase	Specific IgE (kUA L^{-1})		Total IgE (kU L^{-1})	Atopy	BAT result		
								Morphine	Pholcodine			CD63	CD203c	CD300a
JG	54	Shortly after induction, within 15 min of NMBA administration	Tachycardia, generalised rash, high airway pressures, transient desaturation	Rocuronium	3.8	4.2	No	0.29	0.47	126	No	Positive	Positive	Negative
JH	48	Shortly after induction, within 15 min of NMBA administration	Hypotension, tachycardia, desaturation	Rocuronium	12.3	4.1	Yes	0.42	0.18	43	No	Positive	Negative	Negative
LH	46	Shortly after induction, within 15 min of NMBA administration	Bronchospasm, hypotension <60 mm Hg, desaturation <90%	Rocuronium	26.2	2.6	Yes	11.7	17.2	344	Yes	Negative	Negative	Positive
DS	62	Shortly after induction, within 15 min of NMBA administration	Hypotension <60 mm Hg, bronchospasm, desaturation <80%	Rocuronium	41.3	3.9	Yes	8.03	2.64	18	Yes	Positive	Positive	Positive
JH	25	Shortly after induction, within 15 min of NMBA administration	Bronchospasm, rash	Rocuronium	2.9	3.2	No	1.88	1.58	637	No	Negative	Negative	Negative
NF	44	Shortly after induction, within 15 min of NMBA administration	Bronchospasm, very difficult to ventilate	Vecuronium	1.2	0.7	No	82.8	37.7	1517	Yes	Negative	Negative	Positive
MP	68	Shortly after induction, within 15 min of NMBA administration	Cardiac arrest	Rocuronium	6.3	3.6	Yes	0.94	0.82	36	No	Negative	Negative	Positive
RM	38	Shortly after induction, within 15 min of NMBA administration	Tachycardia, rash	Rocuronium	4.7	2.9	No	0.21	0.40	57	Yes	Positive	Negative	Negative
BE	71	Shortly after induction, within 15 min of NMBA administration	Hypotension <60 mm Hg, desaturation <80%, rash	Rocuronium	Not available	3.9	Not available	1.07	1.26	124	No	Negative	Positive	Negative
MK	67	Shortly after induction, within 15 min of NMBA administration	Hypotension <60 mm Hg, tachycardia, bronchospasm, rash	Rocuronium	13.9	4.8	Yes	0.55	1.07	68	No	Positive	Positive	Negative

Table 6 Characteristics of perioperative anaphylaxis in patients with suspected anaphylaxis and no identified culprit (n=13). BAT, basophil activation testing; NMBA, neuromuscular blocking agent

Patient	Age at reaction (yr)	Onset of anaphylaxis	Clinical features	NMBA administered	Peak serum mast-cell tryptase (μg L^{-1})	Baseline serum mast-cell tryptase (μg L^{-1})	Significant rise and fall in tryptase	Culprit agent	BAT result
MM	59	Shortly after induction, within 15 min of NMBA administration	Cardiac arrest	Rocuronium	16.5	11.3	No	Unknown	Positive
RD	40	Shortly after induction, within 15 min of NMBA administration	Desaturation below 90%, high airway pressures, tachycardia	Rocuronium	Not available	2.7	Not available	Unknown	Positive
LR	28	Within 15 min after induction, shortly after administration of blood products	Hypotension <60 mm Hg, high airway pressures, generalised rash, perioral angioedema	Rocuronium	5.7	1.9	Yes	Unknown, caution with blood products	Positive
AK	56	Within 15 min of NMBA administration, and commencement of teicoplanin infusion	Hypotension <60 mm Hg, generalised rash	Cisatracurium	20.7	2.8	Yes	Unknown	Positive
KR	39	Shortly after induction, within 15 min of NMBA administration	Generalised rash and bronchospasm	Rocuronium	7.8	7.9	No	Unknown	Positive
FT	72	Shortly after induction, within 15 min of NMBA administration	Higher airway pressures, hypotension	Rocuronium	Not available	7.9	Not available	Unknown	Positive
SM	42	Shortly after induction, within 15 min of NMBA administration	Cardiac arrest	Vecuronium	Not available	3.5	Not available	Unknown	Negative
GE	56	Shortly after induction, within 15 min of NMBA administration	Hypotension, desaturation	Rocuronium	Not available	5.4	Not available	Unknown at initial evaluation, rocuronium skin test positive 6 weeks after initial evaluation	Positive
PM	51	Shortly after induction, within 15 min of NMBA administration	Hypotension <60 mm Hg	Rocuronium	16.9	3.1	Yes	Unknown, presumed rocuronium attributable to non-diagnostic wheal and flare	Negative

evaluation. All patients received an NMBA within 15 min of anaphylaxis, and there was no sensitisation to all drugs or substances administered at least on two separate occasions. Seven patients (78%) had a positive BAT to the NMBA administered using CD63 and CD203c. Adding CD300a to the algorithm did not increase sensitivity in this group. The clinical significance of this BAT sensitisation needs further study.

CD300a is accepted as a marker of basophil activation, although there is only one report in the literature.[30,31] Our study suggests a benefit of assessing CD300a expression, in addition to CD63 and CD203c, in patients who have a clinical history suggestive of NMBA anaphylaxis, but isolated sIgE sensitisation. Six out of 10 patients in the preceding scenario had a positive BAT with CD63 and CD203c, which increased to nine out of the 10 patients by including CD300a expression. However, our study identified no benefit of using CD300a alone as an activation marker, as sensitivity was inferior to combining CD63 and CD203c.

The literature suggests that fMLP induces upregulation of CD300a in basophils in all patients, although its expression is significantly weaker than for cells stimulated with anti-IgE.[1] Our data were not consistent, as only 47% of patients in our cohort showed upregulation of CD300a in response to fMLP. In a subset of our cohort of 10 patients who showed CD300a upregulation in response to anti-IgE, only five had significant upregulation in expression after stimulation with fMLP. More studies are required to determine whether it is a useful marker of basophil surface activation.

The main limitation of our study is that our cohort mainly comprises rocuronium-exposed patients, which is consistent with statewide patterns of use. There were no patients with pancuronium and cisatracurium anaphylaxis, and this affects the generalisability of our study. The technique of BAT has multiple limitations. The cost of monoclonal antibodies used in this study was estimated at $US230 per patient. Expertise is required to perform and interpret results. Fresh basophils are required for BAT, usually processed within 4 h of collection, and care must be taken in collection, transport, and handling to prevent spontaneous basophil degranulation.[32] BAT cannot be used for patients with basophils that do not respond to the positive control.[32]

Conclusions

Our prospective study suggests that BAT may be useful in the diagnosis of perioperative anaphylaxis to NMBAs. We are unable to offer BAT to all patients, as cost is high. BAT is not required to confirm NMBA diagnosis in patients with positive skin tests. In patients with isolated sIgE, BAT using CD63 and CD203c showed sensitisation in six of 10 patients, improving to nine of 10 with the addition of CD300a. Further, we observed that seven of nine patients with anaphylaxis of unknown aetiology, but a history compatible with NMBA anaphylaxis, had a positive BAT. The clinical significance of this is unclear at this stage. Therefore, BAT may be useful in patients with suggestive histories and negative skin tests, but an ongoing study of BAT in this specific group of patients is required before we can determine its utility.

Authors' contributions

Research design: JL, OGB, SLG, MAR, SLF
Experimentation: JL, OGB
Result analysis: all authors
Table construction: all authors
Writing paper: JL
Read and approved final manuscript: all authors

Declaration of interest

The authors declare that they have no conflicts of interest.

Funding

NSW Health Pathology; Marianne Lesnie and Warren Lesnie.

References

1. Rose M, Green S, Crilly H, Kolawole H. Perioperative anaphylaxis grading system: 'making the grade'. *Br J Anaesth* 2016; **117**: 551–3
2. Galvão V, Giavina-Bianchi P, Castells M. Perioperative anaphylaxis. *Curr Allergy Asthma Rep* 2014; **14**: 452
3. Mertes P, Volcheck G, Garvey L, et al. Epidemiology of perioperative anaphylaxis. *Presse Med* 2016; **45**: 758–67
4. Sadleir P, Clarke R, Bunning D, Platt P. Anaphylaxis to neuromuscular blocking drugs: incidence and cross-reactivity in Western Australia from 2002 to 2011. *Br J Anaesth* 2013; **110**: 981–7
5. Scolaro R, Crilly H, Maycock E, et al. Australian and New Zealand Anaesthetic Allergy Group perioperative anaphylaxis investigation guidelines. *Anaesth Intensive Care* 2017; **45**: 543–55
6. Metcalfe D, Peavy R, Gilfillan A. Mechanisms of mast cell signalling in anaphylaxis. *J Allergy Clin Immunol* 2009; **124**: 639–48
7. Hoffmann H, Santos A, Mayorga C, et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. *Allergy* 2015; **70**: 1393–405
8. Fisher M, Baldo B. Immunoassays for the diagnosis of anaphylaxis to neuromuscular blocking drugs: the value of morphine for the detection of IgE antibodies in allergic subjects. *Anaesth Intensive Care* 2000; **28**: 167–70
9. Ebo D, Venemalm L, Bridts C, et al. Immunoglobulin E antibodies to rocuronium. *Anesthesiology* 2007; **107**: 253–9
10. Rose M, Anderson J, Green S, Yun J, Fernando S. Morphine and pholcodine-specific IgE have limited utility in the diagnosis of anaphylaxis to benzylisoquinolines. *Acta Anaesthesiol Scand* 2018; **62**: 628–34
11. Phadia ImmunoCAP. *Allergen c260 morphine* 2009. Uppsala, Sweden
12. ImmunoCAP Phadia. *Allergen c261 pholcodine* 2009. Uppsala, Sweden
13. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
14. Sturm E, Kranzelbinder B, Heinemann A, Groselj-Strele A, Aberer W, Sturm G. CD203c-based basophil activation test in allergy diagnosis: characteristics and differences to CD63 upregulation. *Cytom B Clin Cytom* 2010; **78**: 308–18
15. Valent P, Akin C, Arock M, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol* 2012; **157**: 215–25

16. Therapeutic Guidelines. In: Spicer J, editor. *Antibiotic, Version 15*. Melbourne: Therapeutic Guidelines Limited; 2014
17. Ebo D, Bridts C, Hagendorens M, Mertens C, De Clerck L, Stevens W. Flow-assisted diagnostic management of anaphylaxis from rocuronium bromide. *Allergy* 2006; **61**: 935–9
18. Kvedariene V, Kamey S, Ryckwaert Y, et al. Diagnosis of neuromuscular blocking agent hypersensitivity reactions using cytofluorimetric analysis of basophils. *Allergy* 2006; **61**: 311–5
19. Leysen J, Bridts C, De Clerck L, et al. Allergy to rocuronium: from clinical suspicion to correct diagnosis. *Allergy* 2011; **66**: 1014–9
20. Uyttebroek V, Sabato V, Leysen J, Bridts CH, De Clerck LS, Ebo DG. Flowcytometric diagnosis of atracurium-induced anaphylaxis. *Allergy* 2014; **69**: 1324–32
21. Mangodt E, Van Gasse A, Bastiaensen A, et al. Flow-assisted basophil activation tests in immediate drug hypersensitivity: two decades of Antwerp experience. *Acta Clin Belgica* 2016; **71**: 19–25
22. Sudheer P, Hall J, Read G, Rowbottom A, Williams P. Flow cytometric investigation of peri-anaesthetic anaphylaxis using CD63 and CD203c. *Anaesthesia* 2005; **60**: 251–6
23. Dewachter P, Chollet-Martin S, Mouton-Faivre C, de Chaisemartin L, Nicaise-Roland P. Comparison of basophil activation test and skin testing performances in NMBA allergy. *J Allergy Clin Immunol Pract* 2018; **6**: 1681–9
24. Leysen J, Uyttebroek V, Sabato V, Bridts C, De Clerck L, Ebo D. Predictive value of allergy tests for neuromuscular blocking agents: tackling an unmet need. *Clin Exp Allergy* 2014; **44**: 1069–75
25. Hagau N, Gherman-Ionica N, Sfichi M, Petrisor C. Threshold for basophil activation test positivity in neuromuscular blocking agents hypersensitivity reactions. *Allergy Asthma Clin Immunol* 2013; **9**: 42
26. Schulberg E, Webb A, Kolawole H. Early skin and challenge testing after rocuronium anaphylaxis. *Anaesth Intensive Care* 2016; **44**: 425–7
27. International Narcotics Control Board. *Narcotic drugs 2015*. New York: United Nations; 2016
28. Katelaris C, Kurosawa M, Moon H, Borres M, Florvaag E, Johansson S. Pholcodine consumption and immunoglobulin E-sensitization in atopics from Australia, Korea, and Japan. *Asia Pac Allergy* 2014; **4**: 86–90
29. Johansson S, Florvaag E, Oman H, et al. National pholcodine consumption and prevalence of IgE-sensitization: a multicentre study. *Allergy* 2010; **65**: 498–502
30. Sabato V, Verweij M, Bridts C, et al. CD300a is expressed on human basophils and seems to inhibit IgE/FcεRI-dependent anaphylactic degranulation. *Cytom B Clin Cytom* 2012; **82**: 132–8
31. Zenarruzabeitia O, Vitallé J, Eguizabal C, Simhadri V, Borrego F. The biology and disease relevance of CD300a, an inhibitory receptor for phosphatidylserine and phosphatidylethanolamine. *J Immunol* 2015; **194**: 5053–60
32. Depince-Berger A, Sidi-Yahya K, Jeraiby M, Lambert C. Basophil activation test: implementation and standardization between systems and between instruments. *Cytometry A* 2017; **91**: 261–9

Handling editor: H.C. Hemmings Jr

BJA

British Journal of Anaesthesia, 123 (1): e144–e150 (2019)

doi: 10.1016/j.bja.2019.03.001
Advance Access Publication Date: 5 April 2019
Testing

Assessing cross-reactivity to neuromuscular blocking agents by skin and basophil activation tests in patients with neuromuscular blocking agent anaphylaxis

Jamma Li[1,2,3,*], Oliver G. Best[2], Michael A. Rose[4], Sarah L. Green[4], Richard B. Fulton[3], Marc J. Capon[4], Benedict A. Krupowicz[4] and Suran L. Fernando[1,2,3]

[1]Department of Clinical Immunology and Allergy, Australia, [2]Medicine (Immunology & Infectious Diseases), University of Sydney, Sydney, Australia, [3]NSW Health Pathology, Sydney, Australia and [4]Department of Anaesthesia, Royal North Shore Hospital, Sydney, Australia

*Corresponding author. E-mail: jamma.li@health.nsw.gov.au

Abstract

Background: Following diagnosis of neuromuscular blocking agent (NMBA) anaphylaxis, identifying safe alternatives for subsequent anaesthesia is critical. A patient with anaphylaxis to one NMBA can also have an allergic reaction to other NMBAs (cross-reactivity). Whilst drug provocation testing is standard for identifying or excluding allergy, there is significant risk. *In vitro*, after an allergen activates basophils, basophils express surface activation markers that can be measured by basophil activation testing (BAT). We compared cross-reactivity between NMBAs assessed by BAT against that by skin testing.

Methods: All patients attending an anaesthetic allergy clinic in Sydney, Australia between May 2017 and July 2018 diagnosed with NMBA anaphylaxis qualified for this study comparing intradermal skin tests and BAT with a panel of NMBAs (rocuronium, vecuronium, pancuronium, suxamethonium, cisatracurium).

Results: Of the 61 patients participating, sensitisation on skin testing and on BAT completely matched in only nine patients (15%). Sensitisation was not in agreement for pancuronium, cisatracurium and rocuronium, but was in agreement for vecuronium and suxamethonium. Nine patients with negative skin tests subsequently tolerated cisatracurium, and one false positive on BAT to cisatracurium was detected.

Conclusions: The utility of BAT in identifying safe NMBAs for subsequent anaesthesia needs further evaluation. BAT detects a different cross-reactivity profile to skin tests. Negative skin testing and BAT might increase confidence in performing drug provocation testing, but this and follow-up of subsequent anaesthesia in our cohort is necessary to determine the clinical significance of BAT sensitisation.

Keywords: anaphylaxis; drug hypersensitivity; neuromuscular blocking agents; skin tests; basophil degranulation test

Editorial decision: 01 March 2019; **Accepted:** 1 March 2019

Editor's key points

- Identifying safe anaesthetic drugs for use after perioperative anaphylaxis is critical, particularly for neuromuscular blocking agents (NMBAs) that exhibit cross-reactivity.
- Cross-reactivity between NMBAs was assessed by basophil activation testing (BAT) and by skin testing in 61 patients presenting to an Australian anaesthetic allergy clinic.
- Sensitisation on skin testing and on BAT completely matched in only nine patients (15%).
- Further study using drug provocation testing and follow-up of subsequent anaesthesia is needed to determine the clinical significance of sensitisation detected on skin testing and BAT.

Anaphylaxis to neuromuscular blocking agents (NMBAs) remains the leading cause of perioperative anaphylaxis in Australia.[1] Following diagnosis of NMBA anaphylaxis, identification of safe agents for subsequent anaesthesia is necessary. A patient with anaphylaxis to one NMBA can also have an allergic reaction to one or more other NMBAs (cross-reactivity).[2–6] Whilst drug provocation testing is the standard for identifying or excluding allergy, there are no standardised algorithms for its use in identifying safe NMBAs,[7] and there is a significant risk profile that needs to be carefully considered before use in this context.[1] Therefore, current standard practice in Australia and New Zealand to assess for cross-reactivity initially involves *in vivo* skin tests to a panel of other available NMBAs.[1] However, the clinical significance of sensitisation to these other NMBAs is not clear. This position is supported internationally.[8]

Basophil activation testing (BAT) is an *in vitro* test that has been used in investigation of drug allergy, including NMBA allergy.[9] Following activation by allergen, mast cells and basophils degranulate, triggering release of mediators that create the clinical manifestations of allergy and anaphylaxis. Basophils, unlike mast cells, are found in sufficient numbers in peripheral blood. Activated basophils express surface markers, including CD63 and CD203c, that can be measured by flow cytometry. We examined the use of BAT for assessing cross-reactivity, its agreement with skin testing, and its role in identifying safe NMBAs for subsequent anaesthesia.

Methods

We recruited patients sequentially from the anaesthetic allergy clinic, Royal North Shore Hospital, New South Wales (NSW), Australia, between May 2017 and July 2018, who were diagnosed with NMBA anaphylaxis. No patient declined participation. Patients received standard assessment comprising a review of clinical history, skin tests to all drugs and substances administered before the onset of anaphylaxis, skin tests to a standard panel of NMBAs (rocuronium, vecuronium, pancuronium, suxamethonium, cisatracurium), serum tryptase concentrations (ImmunoCAP, Phadia, Uppsala, Sweden), and specific IgE assays (sIgE) to morphine, pholcodine, latex, and chlorhexidine (ImmunoCAP). sIgE to morphine and pholcodine measure IgE antibodies directed against morphine and pholcodine moieties, respectively, which contain substituted ammonium groups, considered to be the antigenic determinant of NMBAs.[3,10] Additionally, BAT was performed in our research laboratory, using CD63 and CD203c as surface activation markers.[11]

A patient was diagnosed with NMBA anaphylaxis in one of two scenarios: (1) There was a suggestive clinical history, that is anaphylaxis occurs within 15 min of administration of the NMBA,[12] supported by positive skin tests and (2) there was a suggestive clinical history but only positive sIgE to morphine or pholcodine, and all other potential culprits had been excluded by skin and serum tests, and occasionally challenges on at least two separate occasions.

Skin tests

All patients had intradermal tests (IDT) to the suspected NMBA culprit and a panel of other available NMBAs (rocuronium, vecuronium, pancuronium, suxamethonium and cisatracurium) that reflects local patterns of use. IDT was performed at both standard and strong concentrations (see Table 1 in a recent study by Li and colleagues[11]), as recommended in the Australian and New Zealand Anaesthetic Allergy Group Perioperative Anaphylaxis Investigation Guidelines.[1] IDT for each NMBA was classified as positive or negative for both standard and strong concentrations; a test was positive if the wheal doubled in size or increased by 3 mm.[1]

BAT

Our method has been described in detail elsewhere.[11] To summarise, basophils were incubated with a negative control, positive control, and the standard NMBA panel above. Basophils were incubated with each NMBA at three serial dilutions.[13] We measured the upregulation of CD63 and CD203c on basophils and calculated individual results for all NMBA-stimulated samples using both % upregulation above the negative control and stimulation index (SI), the ratio of the mean fluorescence intensity (MFI) of antigen expression on basophils in NMBA-stimulated samples to MFI of the negative

Table 1 Standard and strong concentrations of NMBAs used in the evaluation of perioperative anaphylaxis. NMBA, neuromuscular blocking agent. Adapted from Scolaro and colleagues.[1]

	Standard concentration for intradermal testing (μg ml^{-1})	Strong concentration for intradermal testing (μg ml^{-1})	Skin prick test concentration (mg ml^{-1})
Rocuronium	10	100	10
Vecuronium	4	40	4
Pancuronium	2	20	2
Suxamethonium	50	100	10
Cisatracurium	2	20	2

control. We selected the maximum value obtained across the three serial dilutions for each NMBA. BAT results were then classified as positive or negative based on previously calculated cut-offs for a positive test in our cohort using receiver operating characteristic curve analysis.[11] For CD63, we applied a cut-off of 4.45% and SI=1.44, and for CD203c, 8.80% and SI=1.49.[11]

Comparing skin test and BAT results

For each patient, the results of IDT at standard and strong concentrations, and BAT using CD63 and CD203c for rocuronium, vecuronium, pancuronium, suxamethonium and cisatracurium were recorded. Each result was then placed into one of four categories: BAT+Skin+, BAT+Skin−, BAT−Skin+, and BAT−Skin−.

Statistical analysis

SPSS version 24 (IBM, Armonk, NY, USA) was used to conduct the statistical analysis of the categorical variables. We used McNemar's test to compare the performance of skin testing and BAT in assessing cross-reactivity; this statistical test is used to determine if there are differences in dichotomous dependent variable data. A result with $P<0.05$ was considered significant.

Results

Of 61 patients diagnosed with NMBA anaphylaxis, anaphylaxis was to rocuronium ($n=48$), vecuronium ($n=4$), or suxamethonium ($n=9$). No patients had pancuronium or cisatracurium anaphylaxis. Of the 61 patients, 51 had positive skin testing to the culprit NMBA, and 53 had positive sIgE, 51 to both morphine and pholcodine, one to morphine only, and one to pholcodine only (Table 1).

Of the 51 patients with positive skin testing to the culprit NMBA, 20 showed no cross-reactivity on skin testing, that is skin testing was positive to the culprit NMBA only, and 31 showed cross-reactivity on skin testing, that is skin testing was positive to at least one other NMBA. Of these 31 patients, 12 had sensitisation to one or more aminosteroids (rocuronium, vecuronium, pancuronium), 15 had sensitisation to aminosteroids and suxamethonium, and four had sensitisation to aminosteroids, suxamethonium and cisatracurium. Of the 61 patients, 10 had isolated sensitisation on sIgE to morphine and pholcodine, and none of these had skin sensitisation to any NMBAs (Table 2).

Table 2 Patient characteristics of 61 patients diagnosed with NMBA anaphylaxis.

Patient characteristics	
Total subjects	61
Age in years, average (range)	52 (16–75)
Female, n(%)	41 (67%)
Interval between reaction and assessment (days)	102
Atopy, n(%)	26 (43%)
Significant rise and fall in tryptase, n(%)	47 (77%)
Number of patients skin test (IDT) positive to NMBA administered	51
Positive at standard concentrations	33
Positive at strong concentrations only	18
Number of patients skin test negative to NMBA administered	10
NMBA exposed to	
Rocuronium	48
Vecuronium	4
Cisatracurium	0
Suxamethonium	9
Pancuronium	0
Sensitisation to standard NMBA panel on skin testing	
To culprit NMBA only	20
Amongst aminosteroids only	12
Across aminosteroids and succinylcholine	15
Across aminosteroids, succinylcholine and cisatracurium	4
No sensitisation to any NMBA	10

IDT, intradermal tests; NMBA, neuromuscular blocking agent.

Skin testing compared with BAT

Skin test and BAT results were categorised as positive or negative (Table 3). Of 61 patients, sensitisation on skin testing and BAT only completely matched in nine patients. There was a significant lack of agreement between skin testing and BAT for pancuronium and cisatracurium ($P<0.05$) using McNemar's test (Table 4), with more sensitisation to pancuronium and cisatracurium on BAT compared with skin testing (Table 3). There were only three positive skin tests to cisatracurium, but 20 positive on BAT when we combined surface markers. There were 12 positive skin tests to pancuronium at standard or strong concentrations, but 23 positive on BAT. Of the 18 patients with a positive BAT for pancuronium and a negative skin test for pancuronium, nine had a positive skin test to rocuronium and vecuronium. However, the remaining nine patients did not have any sensitisation to aminosteroids on skin tests, but eight had sensitisation to two or more aminosteroids on BAT.

There was a significant lack of agreement between skin testing and BAT for rocuronium ($P<0.05$) using McNemar's test (Table 4), with more sensitisation to rocuronium on skin testing compared with BAT (Table 3). There were 45 positive skin tests compared with 30 by BAT. However, if we analysed the results of skin testing using standard concentrations only, there was agreement between skin testing and BAT ($P>0.05$).

There was agreement in sensitisation to vecuronium and suxamethonium using skin testing and BAT ($P>0.05$) using McNemar's test (Table 4). There were 24 positive skin tests to vecuronium against 23 by BAT, and 21 positive skin tests to suxamethonium against 24 by BAT (Table 3).

Outcomes

We have limited follow-up from nine patients in the study (Table 5). All patients had a negative skin test to cisatracurium. Five patients received cisatracurium as part of their subsequent anaesthetic based on our recommendations. We performed cisatracurium drug provocation testing for four patients to identify it as a safe agent for subsequent anaesthesia. Of these nine patients, seven had negative BAT and no reaction to cisatracurium, one had positive BAT but uneventful cisatracurium drug provocation testing, and one with negative skin testing but positive BAT had cisatracurium anaphylaxis at the next anaesthetic (Table 6).

Table 3 Cross-reactivity of patients with NMBA anaphylaxis on skin tests. *Nine patients (15%) with rocuronium anaphylaxis had a suggestive clinical history and isolated sIgE to morphine and pholcodine that was negative on skin testing to rocuronium. No sensitisation was demonstrated to all NMBAs. †One patient (25%) with vecuronium anaphylaxis had a suggestive clinical history and isolated sIgE to morphine and pholcodine that was negative on skin testing to vecuronium. No sensitisation was demonstrated to all NMBAs. n/a, not applicable; NMBA, neuromuscular blocking agent.

NMBA anaphylaxis	Cross-reactivity (No. of patients), *n* (%)					
	No cross-reactivity	Rocuronium (%)	Vecuronium (%)	Pancuronium (%)	Suxamethonium (%)	Cisatracurium (%)
Rocuronium (*n*=48)*	13 (27)	n/a	20 (42)	9 (19)	13 (27)	3 (6)
Vecuronium (*n*=4)†	1 (25)	3 (75)	n/a	2 (50)	1 (25)	1 (25)
Suxamethonium (*n*=9)	6 (67)	3 (33)	2 (22)	1 (11)	n/a	0 (0)

Table 4 Results of skin tests and BAT basophil activation testing to NMBAs. BAT+Skin+, sensitisation demonstrated on both BAT and skin testing; BAT+Skin−, sensitisation demonstrated on BAT but not on skin testing; BAT−Skin+, sensitisation demonstrated on skin testing but not on BAT; BAT−Skin−, sensitisation not demonstrated on BAT or skin testing. BAT, basophil activation testing; NMBA, neuromuscular blocking agent.

Results of skin testing (by standard or strong concentrations) and BAT (by CD63 or CD203c)				
	BAT+Skin+ (*n*)	BAT+Skin- (*n*)	BAT−Skin+ (*n*)	BAT−Skin− (*n*)
Rocuronium	23	7	17	10
Vecuronium	14	9	10	24
Cisatracurium	2	18	1	36
Suxamethonium	13	11	8	25
Pancuronium	5	18	7	27
Results of skin testing (by standard concentrations) and BAT (by CD63 only)				
NMBA				
Rocuronium	11	11	10	25
Vecuronium	8	10	5	34
Cisatracurium	0	14	2	41
Suxamethonium	9	7	10	31
Pancuronium	2	12	5	38
Results of skin testing (by strong concentrations) and BAT (by CD63 only)				
Rocuronium	17	5	23	12
Vecuronium	11	7	13	26
Cisatracurium	1	13	2	41
Suxamethonium	10	6	11	30
Pancuronium	4	10	8	35
Results of skin testing (by standard concentrations) and BAT (by CD203c only)				
Rocuronium	11	14	9	23
Vecuronium	7	12	6	32
Cisatracurium	1	13	1	42
Suxamethonium	10	12	10	25
Pancuronium	3	14	4	36
Results of skin testing (by strong concentrations) and BAT (by CD203c only)				
Rocuronium	20	5	20	12
Vecuronium	10	9	14	24
Cisatracurium	1	13	2	41
Suxamethonium	11	11	10	25
Pancuronium	5	12	7	33

Discussion

Modern-day NMBAs commonly used in NSW, Australia comprise aminosteroids (rocuronium, vecuronium, and pancuronium), benzylisoquinolines (cisatracurium), and suxamethonium. A patient with NMBA anaphylaxis can potentially have allergic reactions to other NMBAs (cross-reactivity), as the major antigenic determinant, the substituted ammonium moiety,[2,3] is present in all of these. In our cohort, 20 patients (31%) had no cross-reactivity on skin testing, and they were sensitised only to the culprit NMBA. However, 31 (51%) had cross-reactivity on skin testing with sensitisation to at least one other NMBA. The majority of cross-reactivity occurred across aminosteroids and

Table 5 P-values for McNemar's test for agreement of proportion of positive skin tests and BAT. BAT, basophil activation testing.

		NMBA				
Skin test concentration	BAT	Rocuronium	Vecuronium	Cisatracurium	Suxamethonium	Pancuronium
Standard	CD63	1.000	0.302	0.004	0.629	0.143
Strong	CD63	0.001	0.263	0.007	0.332	0.815
Standard	CD203c	0.405	0.238	0.002	0.832	0.301
Strong	CD203c	0.004	0.405	0.007	1.000	0.359
Standard or strong	CD63 or CD203c	0.064	1.000	<0.001	0.648	0.043

suxamethonium, consistent with the literature[6]: 12 (20%) had cross-reactivity with the aminosteroid group only, and 15 (25%) across aminosteroids and suxamethonium. Only four cases (7%) involved cross-reactivity across aminosteroids, suxamethonium and benzylisoquinolines.

A few hypotheses have been suggested to explain the variation in cross-reactivity. The flexibility of the chain and distance between the substituted ammonium can affect immunogenicity.[5,14,15] Suxamethonium, with a more flexible chain, is considered more potent in initiating mast cell mediator release than NMBAs with a rigid chain,[14] for example vecuronium, pancuronium, and rocuronium. It is also possible that the antigenic determinant of NMBAs extends to structures adjacent to the substituted ammonium, or IgE antibodies recognise structures other than the ammonium group.[3] There may be variation of these structures across different NMBAs.

The most critical part in the evaluation of perioperative anaphylaxis is advice on subsequent anaesthesia. We formulate advice in our service based on standard assessment comprising a review of clinical history, skin testing, and sIgE tests. BAT is not routine. We advise avoidance of all three aminosteroids (rocuronium, vecuronium, pancuronium) in patients who have sensitisation on skin tests to two or more aminosteroids. If sensitisation is to only one aminosteroid, we advise avoidance of that aminosteroid only. We advise avoidance of suxamethonium and cisatracurium only if sensitisation to these is present.

A model incorporating a review of clinical history and skin and sIgE tests has been reasonably effective in successfully advising on subsequent anaesthesia.[16–18] However, even in these case series, there are patients who have anaphylaxis at subsequent anaesthesia.[17–19] This is concordant with our experience. Therefore, ongoing research into new potentially useful investigations for perioperative anaphylaxis is necessary. A prominent Belgian group currently dissuades administration of an NMBA where BAT is positive, despite negative skin testing, on the basis that neither has a significant positive predictive value for allergy.[8]

We found good agreement between BAT and skin testing for vecuronium and suxamethonium. There is a lack of agreement in relation to rocuronium, pancuronium, and cisatracurium, so if we incorporated BAT results for these drugs into our advice, we might offer different advice on safe subsequent anaesthesia than when considering skin testing and

Table 6 Follow up of nine patients with NMBA anaphylaxis. Allergic, patient had anaphylaxis to cisatracurium; not allergic, patient tolerated cisatracurium with no adverse reaction. BAT, basophil activation testing; DPT, drug provocation testing; NMBA, neuromuscular blocking agent; sIgE, specific IgE.

Patient	Cross-reactivity (number of patients)									
	Culprit NMBA	Skin test results					sIgE to morphine/ pholcodine	BAT to cisatracurium		Cisatracurium at next anaesthetic or DPT
		Rocuronium	Vecuronium	Pancuronium	Suxamethonium	Cisatracurium		CD63	CD203c	
DT	Rocuronium	+	+	−	+	−	+	+	+	Allergic (at next anaesthetic)
MP	Rocuronium	−	−	−	−	−	+	−	−	Not allergic (at next anaesthetic)
JT	Rocuronium	+	−	−	−	−	+	−	−	Not allergic (at next anaesthetic)
NR	Vecuronium	−	+	−	−	−	+	−	−	Not allergic (at next anaesthetic)
JS	Rocuronium	+	+	−	+	−	+	−	−	Not allergic (at next anaesthetic)
LH	Rocuronium	−	−	−	−	−	+	−	−	Not allergic (DPT)
ME	Rocuronium	+	+	+	+	−	+	−	−	Not allergic (DPT)
KD	Rocuronium	+	+	+	−	−	+	−	−	Not allergic (DPT)
MK	Rocuronium	−	−	−	−	−	+	+	+	Not allergic (DPT)

sIgE results only. The number of positive tests is biased toward skin testing for rocuronium, and therefore would not change our clinical practice. However, the number of positive tests is biased toward BAT for cisatracurium and pancuronium.

We report 18 patients who were skin test-negative but BAT-positive for pancuronium. Nine of these 18 patients were positive on skin testing to rocuronium and vecuronium, so we already advised avoidance of pancuronium, and the BAT result does not change this advice. However, the remaining nine patients were skin test-negative to all aminosteroids, and eight of these nine patients were BAT-positive to pancuronium plus another aminosteroid. If we adopted the approach of Sabato and Ebo,[8] we would need to change our advice on subsequent anaesthesia.

There were 20 patients sensitised to cisatracurium by BAT compared with three by skin testing. We have limited follow-up data from nine patients who received cisatracurium at subsequent anaesthesia or drug provocation testing, and only have information on the clinical significance of cisatracurium sensitisation for these patients (Table 5). The seven patients with negative skin testing and BAT tolerated cisatracurium, but the dataset is small, and the clinical significance of sensitisation to cisatracurium on skin testing and BAT requires further study.

In patients with NMBA anaphylaxis, we assess cross-reactivity initially by performing skin testing to other NMBAs.[1] Recent studies have confounded our understanding of skin sensitisation, suggesting that it may not only reflect IgE-mediated anaphylaxis, but perhaps activation of other mast cell receptors such as MAS-related G protein coupled receptor-X2, where clinical manifestations may be less severe and dose-dependent.[20–22]

Drug provocation testing (DPT) is the standard for diagnosing or negating drug allergy, but this is a challenging area of anaesthetic practice as there are no standard recommendations,[7] and higher concentrations of the drugs can have pharmacologic effects. We use DPT when we believe that the reaction is consistent with anaphylaxis to NMBAs and that no conclusion can be made from skin testing that provides a high likelihood of safe future anaesthesia with an NMBA. DPT is performed only after consideration of risks and benefits.[7] Our local health service does not support using DPT of an NMBA where patients have a positive skin test to the NMBA because of a perceived risk of a significant reaction.

We perform DPT to identify safe anaesthesia[1,23] for a NMBA group (benzylisoquinolines, suxamethonium, or aminosteroids) where there is no sensitisation on skin testing, and that is unlikely to cause anaphylaxis. We currently have most experience with cisatracurium DPT, although we have performed suxamethonium and rocuronium DPT on occasion. Perhaps a negative BAT together with negative skin testing gives more reassurance that there is no excessive risk. A Belgian study in 2014 reported 19 patients with NMBA allergy who tolerated subsequent anaesthesia with negative skin testing and BAT for an NMBA.[24] Further study is needed, and at this stage BAT does not appear to be indicated to replace DPT in skin test-negative patients with suspected NMBA anaphylaxis.

Limitations

We have insufficient knowledge of the clinical significance of sensitisation on BAT or skin testing. Our study included only a small cohort of 61 patients, with follow-up data available for only nine at the time of publication. Limited resources restricted the number of DPTs we were able to perform.

Conclusions

In 61 sequential patients diagnosed with NMBA anaphylaxis, BAT detected a different cross-reactivity profile than skin testing, in particular, increased sensitisation to pancuronium and cisatracurium detected using BAT. We are currently unsure of the significance of this increased sensitisation. The ultimate aim is to develop an algorithm for identifying safe anaesthetic approaches following NMBA anaphylaxis, integrating the use of DPT, skin testing, BAT, or all three, but we need further study using DPT and follow-up of subsequent anaesthesia to determine the clinical significance of sensitisation detected on skin testing and BAT.

Authors' contributions

Performed the experiments: JL, OGB.
Analysed the results and constructed the tables: all authors.
Designed the research: JL, OGB, MAR, SLF.
Wrote the paper: JL.
Read and approved the final manuscript: all authors.

Declaration of interests

The authors declare that they have no conflicts of interest.

Funding

NSW Health Pathology contributed to reagents and the salary for JL, Marianne Lesnie, and Warren Lesnie contributed to the salary for OGB.

References

1. Scolaro R, Crilly H, Maycock E, et al. Australian and New Zealand anaesthetic allergy group perioperative anaphylaxis investigation Guidelines. *Anaesth Intensive Care* 2017; **45**: 543–55
2. Baldo B, Fisher M. Substituted ammonium ions as allergenic determinants in drug allergy. *Nature* 1983; **306**: 262–4
3. Baldo B, Fisher M, Pham N. On the origin and specificity of antibodies to neuromuscular blocking (muscle relaxant) drugs: an immunochemical perspective. *Clin Exp Allergy* 2009; **39**: 325–44
4. Lee C. Structure, conformation, and action of neuromuscular blocking drugs. *Br J Anaesth* 2001; **87**: 755–69
5. Mertes P, Aimone-Gastin I, Gueant-Rodriguez R, et al. Hypersensitivity reactions to neuromuscular blocking agents. *Curr Pharm Des* 2008; **14**: 2809–25
6. Sadleir P, Clarke R, Bunning D, Platt P. Anaphylaxis to neuromuscular blocking drugs: incidence and cross-reactivity in Western Australia from 2002 to 2011. *Br J Anaesth* 2013; **110**: 981–7
7. Aberer W, Kranke B. Provocation tests in drug hypersensitivity. *Immunol Allergy Clin North Am* 2009; **29**: 567–84
8. Sabato V, Ebo D. Hypersensitivity to neuromuscular blocking agents: can skin tests give the green light for re-exposure? *J Allergy Clin Immunol Pract* 2018; **6**: 1690–1
9. MacGlashan D. Basophil activation testing. *J Allergy Clin Immunol* 2013; **132**: 777–87

10. Rose M, Anderson J, Green S, Yun J, Fernando S. Morphine and pholcodine-specific IgE have limited utility in the diagnosis of anaphylaxis to benzylisoquinolines. *Acta Anaesthesiol Scand* 2018; **62**: 628–34
11. Li J, Best O, Green S, Rose M, Fulton R, Fernando S. Integrating basophil activation tests into the routine evaluation of perioperative anaphylaxis to neuromuscular blocking agents at a dedicated Anaesthetics Allergy Clinic in Sydney, Australia. Br J Anaesth [update BJA-2018-01876-HH846].
12. Harper N, Cook T, Garcez T, et al. Anaesthesia, surgery and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
13. Ebo D, Bridts C, Hagendorens M, Mertens C, De Clerck L, Stevens W. Flow-assisted diagnostic management of anaphylaxis from rocuronium bromide. *Allergy* 2006; **61**: 935–9
14. Didier A, Cador D, Bongrand P, et al. Role of the quaternary ammonium ion determinants in allergy to muscle relaxants. *J Allergy Clin Immunol* 1987; **79**: 578–84
15. Birnbaum J, Vervloet D. Allergy to muscle relaxants. *Clin Rev Allergy* 1991; **9**: 281–93
16. Ramirez L, Pereira A, Chiriac A, Bonnet-Boyer M, Demoly P. Negative predictive value of skin tests to neuromuscular blocking agents. *Allergy* 2012; **67**: 439–41
17. Trautmann A, Seidl C, Stoevesandt J, Seitz C. General anesthesia-induced anaphylaxis: impact of allergy testing on subsequent anesthesia. *Clin Exp Allergy* 2015; **46**: 125–32
18. Chiriac A, Tacquard C, Fadhel N, et al. Safety of subsequent general anaesthesia in patients allergic to neuromuscular blocking agents: value of allergy skin testing. *Br J Anaesth* 2018; **120**: 1437–40
19. Fraser B, Smart J. Anaphylaxis to cisatracurium following negative skin testing. *Anaesth Intensive Care* 2005; **33**: 816–9
20. McNeil B, Pundir P, Meeker S. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature* 2015; **519**: 237–41
21. Subramanian HGK, Ali H. Roles of Mas-related G protein-coupled receptor X2 on mast cell-mediated host defense, pseudoallergic drug reactions, and chronic inflammatory diseases. *J Allergy Clin Immunol* 2016; **138**: 700–10
22. Navines-Ferrer A, Serrano-Candelas E, Lafuente A. MRGPRX2-mediated mast cell response to drugs used in perioperative procedures and anaesthesia. *Sci Rep* 2018; **8**: 11628
23. Schulberg E, Webb A, Kolawole H. Early skin and challenge testing after rocuronium anaphylaxis. *Anaesth Intensive Care* 2016; **44**: 425–7
24. Leysen J, Uyttebroek V, Sabato V, Bridts C, De Clerck L, Ebo D. Predictive value of allergy tests for neuromuscular blocking agents: tackling an unmet need. *Clin Exp Allergy* 2014; **44**: 1069–75

Handling editor: H.C. Hemmings Jr

BJA

British Journal of Anaesthesia, 123 (1): e151–e156 (2019)

CORRESPONDENCE

Anaphylaxis-related mortality in the obstetrical setting: analysis of the French National Confidential Enquiry into Maternal Deaths from 2001 to 2012

Charles Tacquard[1], Dominique Chassard[2], Jean-Marc Malinovsky[3], Monica Saucedo[4], Catherine Deneux-Tharaux[4], Paul Michel Mertes[1,*] for the National Expert Committee on Maternal Mortality (CNEMM)

[1]Strasbourg, France, [2]Lyon, France, [3]Reims, France and [4]Paris, France

*Corresponding author. E-mail: paul-michel.mertes@chru-strasbourg.fr

Editor—Anaphylaxis is an unpredictable and severe systemic immediate hypersensitivity reaction after exposure to an antigen. During pregnancy, this complication is rare, with an estimated incidence of 1.6–2.7 per 100 000 deliveries, but it is associated with significant morbidity for mother and the fetus.[1–3] Few data are available on anaphylaxis-related maternal death. The specific anaphylaxis-related maternal mortality ratio (MMR) was recently estimated to be 0.09 per 100 000 live births (95% confidence interval [CI], 0.01–0.30) over the period 2012–14 in the UK, but the specific epidemiology of anaphylaxis-related maternal death was not analysed.[3]

The study of maternal mortality in France benefits from an enhanced national surveillance system with a dual epidemiological and clinical audit objective, the National Confidential Enquiry into Maternal Deaths (ENCMM).[4] For each pregnancy-associated death identified, a team of assessors (an obstetrician or midwife, and an anaesthetist) conducts a confidential enquiry. Deaths are then anonymously reviewed by the national expert committee of the ENCMM, which reaches a unanimous determination of the underlying cause of death.

We retrospectively assessed this permanent nationwide database from 2001 to 2012 to identify maternal deaths related to anaphylaxis in order to estimate their frequency and identify the incriminated agent. Each case of possible anaphylaxis-related maternal death was reviewed by experts in anaphylaxis in order to confirm the diagnosis of anaphylaxis according to the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) and the French Society of Anaesthesia and Intensive Care.[5] MMR and 95% CI were calculated overall and specifically for anaphylaxis-related deaths using the number of live births as denominator and the number of corresponding maternal deaths as numerator.

Between 2001 and 2012, 973 maternal deaths and 9 779 756 live births were recorded in France for a total MMR of 9.95 per 100 000 live births (95% CI, 9.33–10.59). Five maternal deaths (0.5%) were attributed to anaphylaxis during this 12 yr period (Table 1). The ratio of anaphylaxis-related maternal mortality was estimated at 0.05 per 100 000 live births (95% CI, 0.02–0.19). In all patients, anaphylaxis occurred just after anaesthesia induction. In three patients (patients 1, 4, and 5), suxamethonium was highly suspected to be responsible for the reaction. Atracurium could also be involved in patient 1 as shown by the level of inhibition. In the two remaining patients (patients 3 and 4), the absence of specific IgE measurement did not allow certainty in identifying the culprit agent, but the assessors judged that suxamethonium was the most likely agent.

Data on anaphylaxis-related mortality during pregnancy are lacking, and only a few studies have tried to estimate its frequency. Although latex and antibiotics (penicillins or cephalosporins used for *Streptococcus* B infection prevention) are the most frequent allergens involved in peripartum anaphylaxis,[3,6,7] our results clearly suggest that in France, fatal reactions are attributable to neuromuscular blocking agents (NMBAs). In this series of patients, because skin tests were impossible to perform, the diagnosis of anaphylaxis and identification of the triggering agent were based on a combination of a typical clinical history, increased tryptase values (4/4), and the presence of specific IgE against quaternary ammonium ions (3/3), when measured.

Epidemiological studies have shown that, at the time of anaesthesia induction, clinical identification of an NMBA as the triggering agent was usually correct when a combination of a hypnotic and an NMBA were the only drugs administered.[8] Although all injected drugs can be involved, NMBAs are by far the leading culprit in perioperative IgE-mediated

Table 1 Main characteristics of maternal anaphylaxis-related death. *Meningitis due to *Streptococcus pneumoniae*. †The hypnotic used for anaesthetic induction was not available. STP, sodium thiopental; SUX, suxamethonium; ATRA, atracurium; PRO, propofol; SUF, sufentanil; sIgE, anti-quaternary ammonium-specific IgE (positive threshold 2.3%); INH, specific inhibition (positive threshold 20%); NA, not available

Patient no.	Age (yr)	Weeks of gestation	Allergy history	Circumstances	Substances injected before anaphylaxis	Tryptase (μmol L^{-1})	sIgE (%)	INH (%)	Suspected causal agent	Fetus survival
1	48	39	No	Elective Caesarean section	STP, SUX, ATR	12	2.4	SUX 76 ATR 77	SUX/ATR	No
2	33	39	No	Postpartum haemorrhage	PRO, SUX	49.4	NA	NA	SUX/PRO	Yes
3	30	33	No	Coma*	STP, SUX	NA	NA	NA	SUX/STP	Yes
4	39	39	No	Elective Caesarean section	STP, SUX, ATR, SUF	12	7.61	SUX 79	SUX	Yes
5	41	7	Atopic status	Ectopic pregnancy	SUX†	>200	9.32	SUX 42.9	SUX	No

hypersensitivity reactions,[9] whereas reactions to hypnotics appear to be quite rare.[10] Among NMBAs, suxamethonium, used for rapid sequence induction in all our patients, is associated with the highest risk of perioperative allergic reactions in many countries.[9,11] NMBA-related anaphylactic reactions usually have symptoms occurring minutes after intravenous injection, which facilitates identification. In addition, increased tryptase levels have been demonstrated to be strong indicators of the allergic mechanism of the reaction[8] especially in cases of fatal anaphylaxis, in the absence of another plausible cause.[12] Moreover, specific IgE measurements at the time of the reaction possess a high positive diagnostic value, making them helpful in identifying the culprit agent.[13]

Previous studies have focused mainly on non-fatal reactions. Anaphylaxis-related maternal deaths are rare, which probably explains why our incriminated drugs had not been reported earlier. NMBA-related anaphylactic shock is more severe and is associated with a higher risk of fatal reactions whereas latex-related reactions are generally delayed, occurring in the middle of the surgery, and are less severe.[14]

In conclusion, NMBAs appear to be the leading culprits in anaphylaxis-related maternal death. Fortunately, these reactions are rare and NMBAs should not be avoided when required. However, anaesthetists must be aware of this particular risk in order to ensure prompt recognition of these reactions and early intervention with the appropriate treatment. In case of a fatal reaction, tryptase measurement and specific IgE assays are helpful to identify the mechanism of the reaction.

Authors' contributions

Study conception and design: DC, CDT.
Acquisition of data: DC, CDT, MS, JMM.
Analysis and interpretation of data: CT, PMM.
Drafting of the article: CT, PMM.
Final approval of the version to be published: CT, PMM, DC, CDT, MS, JMM.
Agreement to be accountable for all aspects of the work: CT, PMM, DC, CDT, MS, JMM.
Critical revision of the article for important intellectual content: DC, CDT, MS, JMM.

Acknowledgements

The authors thank the obstetricians, midwives, and anaesthetists of the French Confidential Enquiry into Maternal Deaths who collected information for the case reviews and the national centre for cause-of-death statistics and epidemiology (CépiDc) for assistance in case identification.

Declaration of interest

The authors declare that they have no conflicts of interest.

Funding

The French Confidential Enquiry into Maternal Deaths was funded by the French National Public Health agency (Santé Publique France) and the French National Institute of Health and Medical Research (Inserm).

References

1. Chaudhuri K, Gonzales J, Jesurun CA, Ambat MT, Mandal-Chaudhuri S. Anaphylactic shock in pregnancy: a case study and review of the literature. *Int J Obstet Anesth* 2008; **17**: 350–7
2. Mulla ZD, Ebrahim MS, Gonzalez JL. Anaphylaxis in the obstetric patient: analysis of a statewide hospital discharge database. *Ann Allergy Asthma Immunol* 2010; **104**: 55–9
3. McCall SJ, Bunch KJ, Brocklehurst P, et al. The incidence, characteristics, management and outcomes of anaphylaxis in pregnancy: a population-based descriptive study. *BJOG* 2018; **125**: 965–71
4. Deneux-Tharaux C, Saucedo M. Enhanced system for maternal mortality surveillance in France, context and methods. *Gynecol Obstet Fertil Senol* 2017; **45**: S3–7
5. Mertes PM, Malinovsky JM, Jouffroy L, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2011; **21**: 442–53
6. Simons FE, Schatz M. Anaphylaxis during pregnancy. *J Allergy Clin Immunol* 2012; **130**: 597–606

7. Hepner DL, Castells M, Mouton-Faivre C, Dewachter P. Anaphylaxis in the clinical setting of obstetric anesthesia: a literature review. *Anesth Analg* 2013; **117**: 1357–67
8. Laroche D, Gomis P, Gallimidi E, Malinovsky JM, Mertes PM. Diagnostic value of histamine and tryptase concentrations in severe anaphylaxis with shock or cardiac arrest during anesthesia. *Anesthesiology* 2014; **121**: 272–9
9. Tacquard C, Collange O, Gomis P, et al. Anaesthetic hypersensitivity reactions in France between 2011 and 2012: the 10th GERAP epidemiologic survey. *Acta Anaesthesiol Scand* 2017; **61**: 290–9
10. Mertes PM, Volcheck GW, Garvey LH, et al. Epidemiology of perioperative anaphylaxis. *Presse Med* 2016; **45**: 758–67
11. Volcheck GW, Mertes PM. Local and general anesthetics immediate hypersensitivity reactions. *Immunol Allergy Clin North Am* 2014; **34**: 525–46. viii
12. Reitter M, Petitpain N, Latarche C, et al. Fatal anaphylaxis with neuromuscular blocking agents: a risk factor and management analysis. *Allergy* 2014; **69**: 954–9
13. Guttormsen AB, Johansson SG, Oman H, Wilhelmsen V, Nopp A. No consumption of IgE antibody in serum during allergic drug anaphylaxis. *Allergy* 2007; **62**: 1326–30
14. Laxenaire MC, Mertes PM. Anaphylaxis during anaesthesia. Results of a two-year survey in France. *Br J Anaesth* 2001; **87**: 549–58

doi: 10.1016/j.bja.2018.12.009
Advance Access Publication Date: 23 January 2019

Awake intravenous provocation with small doses of neuromuscular blocking agent in patients with suspected allergy: experiences from the Dutch Perioperative Allergy Centre

Vincent R. van Cuilenborg*, Jeroen Hermanides, Elke M. E. Bos, Markus W. Hollmann, Fabian O. Kooij and Ingrid Terreehorst

Amsterdam, the Netherlands

*Corresponding author. E-mail: v.r.vancuilenborg@amc.uva.nl

Editor—Neuromuscular blocking agents (NMBAs) are considered to cause 40–60% of perioperative drug reactions.[1,2] Although recognised to be the first step in NMBA allergy testing, skin tests can be insufficient to fully evaluate allergic reactions to NMBAs as they can lead to false positive or false negative results.[3–5] Hence, as in conventional allergy diagnostics, direct provocation tests deserve to be more frequently considered in the diagnosis of a suspected NMBA allergy. However, contrary to conventional provocation testing, using the normal clinical dose of these drugs is impossible in awake patients because of the unacceptable risks of respiratory compromise, and unpleasant sequelae for the patients.[4] Yet, a subclinical dose could lead to false negative results.

We describe a protocol for intravenous provocation testing with NMBAs as part of a structured programme for evaluation of perioperative allergic reactions. We focus on the optimum dose of NMBA for awake intravenous provocation testing, and we propose a relevant test protocol, considering the side-effects of the NMBA dose required to confirm or rule out an allergy.

We have tested 11 patients between 2015 and 2018 in the Amsterdam University Medical Centre (The Netherlands); nine patients were to receive an i.v. rocuronium provocation test, one patient was to be given an i.v. cisatracurium provocation test, and one patient an i.v. succinylcholine provocation test (Table 1). All of these patients had either had a suspected anaphylactic reaction or a generalised rash within 2 h of administration of NMBA. During the provocation tests, patients were monitored using electrocardiography, pulse oximetry, and blood pressure monitoring, and were under direct supervision of an anaesthesiologist and allergist. All tests were performed in the PACU. For provocation with rocuronium, increasing doses of 0.5, 2.5, and 5 mg were used, which correspond to 1%, 5%, and 10% of the average dosage (50 mg), respectively. Cisatracurium was tested with doses of 0.1, 0.5, and 1 mg and succinylcholine with doses of 1, 2.5, and 10 mg. As rescue measures, clemastine (an antihistamine), epinephrine, sugammadex, prednisolone, and resuscitation equipment were available during the provocation tests.

Table 1 shows the medication used for the provocation tests, the test dosages, the occurrence of any effects caused by the medication used, the result of the previously performed skin test, and the result of the provocation test. One of the patients had a positive reaction to the rocuronium skin test and was planned for a provocation test because of the possibility of the skin test being false positive; however, the patient cancelled the appointment because of undue anxiety. One other patient cancelled his planned provocation test because of an intercurrent illness and was lost to follow-up. One patient had a reaction during the provocation test with rocuronium: the patient had had a negative skin test for rocuronium. This patient developed inspiratory stridor within seconds of the lowest provocative dose (0.5 mg). However, there were no skin symptoms or haemodynamic changes. She was immediately treated with epinephrine, dexamethasone, clemastine, sugammadex, and ranitidine. Despite this treatment, the stridor persisted and the patient was intubated using S-ketamine and succinylcholine. (Although an incidence of cross-reactivity between rocuronium and succinylcholine may exist, this was the only

small doses of NMBAs is acceptable in conscious patients, the diagnostic value of these provocation tests is still unclear. In our small population of 11 patients, only one patient possibly reacted positive to the doses we used for provocation testing, and for some patients the culprit for the perioperative allergic reaction could not be found (Table 1). This could suggest that i.v. provocation testing in the dosages we used is of limited value. Therefore, we also recommend to take the possibility of the provocation test being a false negative into account when the culprit for the perioperative allergy cannot be found.

Future prospective studies in a larger population are required to further assess the diagnostic value of intravenous NMBA provocation tests. For clinical practice, because i.v. NMBA provocation tests are a high-risk procedure, consideration has to be made of whether the benefits of the tests outweigh the risks. This is especially the case in patients with comorbidities and patients at increased risk during emergency treatment (e.g. patients with a history of difficult intubation). Our final recommendation is that these provocations should only be performed in specialised centres under supervision, with a disciplinary team including an allergist, anaesthesiologist, and specialised nurses able to perform emergency rescue procedures if necessary.

Authors' contributions

Data collection: VRC
Writing of the initial draft of the paper: VRC
Conduct of the research process: JH, EB, FK, IT
Supervision: MWH
Critical review of the paper: JH, EB, MWH, FK, IT

Declaration of interest

The authors declare that they have no conflict of interest.

References

1. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth* 2018; **121**: 159–71
2. Petitpain N, Argoullon L, Masmoudi LAK, et al. Neuromuscular blocking agents induced anaphylaxis: results and trends of a French pharmacovigilance survey from 2000 to 2012. *Allergy* 2018; **73**: 2224–33
3. Pfützner W, Brockow K. Perioperative drug reactions—practical recommendations for allergy testing and patient management. *Allergo J Int* 2018; **27**: 126–9
4. Melchiors BLB, Kroiegaard M, Garvey LH. Intravenous provocation with Neuromuscular Blocking Agents in the investigation of perioperative anaphylaxis – preliminary findings from the Danish Anaesthesia Allergy Centre (DAAC). Available from: https://www.morressier.com/article/12_intravenous_provocation_neuromuscular_blocking_agents_investigation_perioperative_anaphylaxis_preliminary_findings_danish_anaesthesia_allergy_centredaac/5aeb0acd07b0d6001a79acef (May 21, 2018)
5. Aberer W, Bircher A, Romano A, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003; **58**: 854–63

doi: 10.1016/j.bja.2019.04.001
Advance Access Publication Date: 24 April 2019

Sugammadex-induced bronchospasm during desflurane anaesthesia

S. Baronos*, B. J. Selvaraj, M. Liang, K. Ahmed and J. Yarmush

Brooklyn, NY, USA

*Corresponding author. E-mail: sbaronos@gmail.com

Editor—We read the article by McDonnell and colleagues[1] with great interest; although sugammadex has been reported as a treatment of rocuronium-induced anaphylaxis, we believe that further research is needed to demonstrate the safety profile of sugammadex. Here, we report a rare but potentially life-threatening adverse effect that can occur after administration of sugammadex for antagonism of neuromuscular block with rocuronium during general anaesthesia with desflurane maintenance.

A previously healthy 31-yr-old female with no history of pulmonary disease underwent laparoscopic cholecystectomy. She was premedicated with midazolam and anaesthesia was induced with i.v. fentanyl, lidocaine, and propofol. Paralysis was facilitated with a single dose of rocuronium 40 mg i.v. at induction, and anaesthesia was maintained with inhaled desflurane. Sugammadex 4 mg kg^{-1} i.v. was used to antagonise neuromuscular block 35 min after rocuronium administration (0 train-of-four twitches at ulnar nerve, SunStim™ peripheral nerve stimulator, SunMed, 2710 Northridge Dr. NW, Suite A Grand Rapids, MI, 49544, USA). Shortly after administration of sugammadex, peak inspiratory pressures increased from 21 to 40 cm H_2O, with associated elevation of end-tidal CO_2 ($EtCO_2$), reduced tidal volumes, prolonged phase II capnogram segment, and bilateral wheezes on auscultation. Treatment for bronchospasm was initiated with deepening of desflurane anaesthesia, albuterol administered with a metered-dose inhaler, and dexamethasone 10 mg i.v., with resolution of wheezing, improvement in tidal volume, and

normalisation of peak inspiratory pressures and $EtCO_2$. The patient was extubated successfully, and had an uneventful course in the PACU with no need for further treatment. The patient recovered completely and was discharged home after being observed at the hospital for 1 day.

There are limited published data on the incidence of bronchospasm in patients receiving sugammadex. Eskander and colleagues[2] reported three cases of bronchospasm after sugammadex administration in patients with no pre-existing pulmonary disease who received general anaesthesia with desflurane and rocuronium. These authors hypothesised that the irritant properties of desflurane, and the interaction of sugammadex with circulating rocuronium molecules, is the probable aetiology for an increased incidence of bronchospasm in patients in whom all these agents are administered together. In a recent case report,[3] the sugammadex–rocuronium complex, rather than sugammadex or rocuronium alone, was confirmed by intradermal allergy testing as the causative agent for anaphylaxis during a Caesarean section. Amao and colleagues[4] reported two patients with pre-existing pulmonary disease receiving sugammadex, rocuronium, and desflurane who developed bronchospasm. Based on these reports and our clinical experience, we advise caution when using sugammadex in patients receiving both desflurane and rocuronium, irrespective of pre-existing pulmonary disease. Of note, there have been no reports of bronchospasm with sugammadex during isoflurane or sevoflurane anaesthesia.

Declaration of interest

The authors declare that they have no conflicts of interest.

References

1. McDonnell NJ, Pavy TJG, Green LK, Platt PR. Sugammadex in the management of rocuronium-induced anaphylaxis. *Br J Anaesth* 2011; **106**: 199–201
2. Eskander JP, Cornett EM, Stuker W, Fox CJ, Breehl M. The combination of sugammadex and desflurane may increase the risk of bronchospasm during general anesthesia. *J Clin Anesth* 2017; **41**: 73
3. Yamaoka M, Deguchi M, Ninomiya K, Kurasako T, Matsumoto M. A suspected case of rocuronium-sugammadex complex-induced anaphylactic shock after cesarean section. *J Anesth* 2017; **31**: 148–51
4. Amao R, Zornow MH, Cowan RM, Cheng DC, Morte JB, Allard MW. Use of sugammadex in patients with a history of pulmonary disease. *J Clin Anesth* 2012; **24**: 289–97

doi: 10.1016/j.bja.2019.04.001
Advance Access Publication Date: 24 April 2019