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An EAACI position paper on the investigation of perioperative immediate hypersensitivity reactions

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Abstract

Perioperative immediate hypersensitivity reactions are rare. Subsequent allergy investigation is complicated by multiple simultaneous drug exposures, the use of drugs with potent effects and the many differential diagnoses to hypersensitivity in the perioperative setting. The approach to the investigation of these complex reactions is not standardized, and it is becoming increasingly apparent that collaboration between experts in the field of allergy/immunology/dermatology and anaesthesiology is needed to provide the best possible care for these patients. The EAACI task force behind this position paper has therefore combined the expertise of allergists, immunologists and anaesthesiologists. The aims of this position paper were to provide recommendations for the investigation of *immediate-type* perioperative hypersensitivity reactions and to provide practical information that can assist clinicians in planning and carrying out investigations.

Abbreviations: AAGBI, Association of Anaesthetists of Great Britain and Ireland; BAT, basophil activation test; BSACI, British Society of Allergy and Clinical Immunology; CHX, chlorhexidine; DPT, drug provocation test; EAACI, European Academy of Allergy and Clinical Immunology; EMA, European Medicines Agency; ENDA, European Network for Drug Allergy; EO, ethylene oxide; GERAP, Groupe d'Etude des Reactions Anaphylactoides Peranesthesiques; ICON, international consensus; IDT, intradermal test; LA, local anaesthetics; NMBAs, neuromuscular blocking agents; NRL, natural rubber latex; POH, perioperative immediate hypersensitivity reactions; SFAR, Société française d'Anesthésie-Réanimation; sIgE, specific IgE; SPT, skin prick test; SSAI, Scandinavian society of anaesthesia and intensive care; WAO, World Allergy Organization.

KEYWORDS
allergy, anaesthesia, anaphylaxis, investigation, perioperative hypersensitivity

1 | INTRODUCTION

Perioperative immediate hypersensitivity reactions (POH) are the most challenging clinical problems in drug allergy investigation. The combination of the effects of anaesthetic drugs, the surgical procedure, simultaneous administration of several drugs, hidden exposures and numerous differential diagnoses complicates the evaluation of perioperative events. The lack of international agreement on standardized investigations and the rare occurrence of POH make it difficult for individual centres to gather experience on the subject. The approach to investigating POH varies greatly across Europe, and the rest of the world, and is highly dependent on the availability of relevant expertise and resources.

This position paper was commissioned by the European Academy of Allergy and Clinical Immunology (EAACI) and is based on evidence from a thorough literature search in MEDLINE combined with expert opinion. The EAACI task force on POH has combined the expertise of allergists, immunologists and anaesthesiologists. Consensus on recommendations was obtained through two face-to-face focused meetings with participation of all members of the group. Grade of evidence throughout the manuscript is low, and at the level of case series, descriptive studies and expert opinion.

The aims of this position paper were to provide consensus on the investigation of *immediate-type* perioperative hypersensitivity reactions and to present a practical approach with suggestions of the minimum of testing recommended for centres with limited resources and more elaborate investigations for highly specialized centres.

2 | MECHANISMS

The nomenclature used in POH is the same that is used in drug hypersensitivity in general.[1] The overall term POH will be used in this paper and covers a wide variety of pathomechanisms. For life-threatening reactions, the term anaphylaxis will be used. Clinically, it is impossible to distinguish between different mechanisms and subsequent investigations are primarily aimed at identifying the *allergic* IgE-mediated reactions, for which there is an identifiable culprit and high risk of recurrence on re-exposure (Figure 1). The remainder of immediate perioperative reactions are either related to pharmacological effects of drugs, to anaesthetic or surgical management or fall in the category of nonallergic, nonspecific activation of mast cells and basophils or other pathways.[2,3] One such mast cell activation is via the recently discovered MRGPRX2 receptor.[4] The exact mechanisms and risk of recurrence on re-exposure are poorly described for these reactions. Patients with clonal or nonclonal mast cell disorders can have increased risk of severe reactions elicited either by specific triggers or via nonspecific activation.[5,6]

3 | EPIDEMIOLOGY AND IMPORTANT CAUSES

3.1 | Incidence

Estimates of the incidence of POH are influenced by the heterogeneity of studies (multicentre/ single centre, prospective/retrospective,

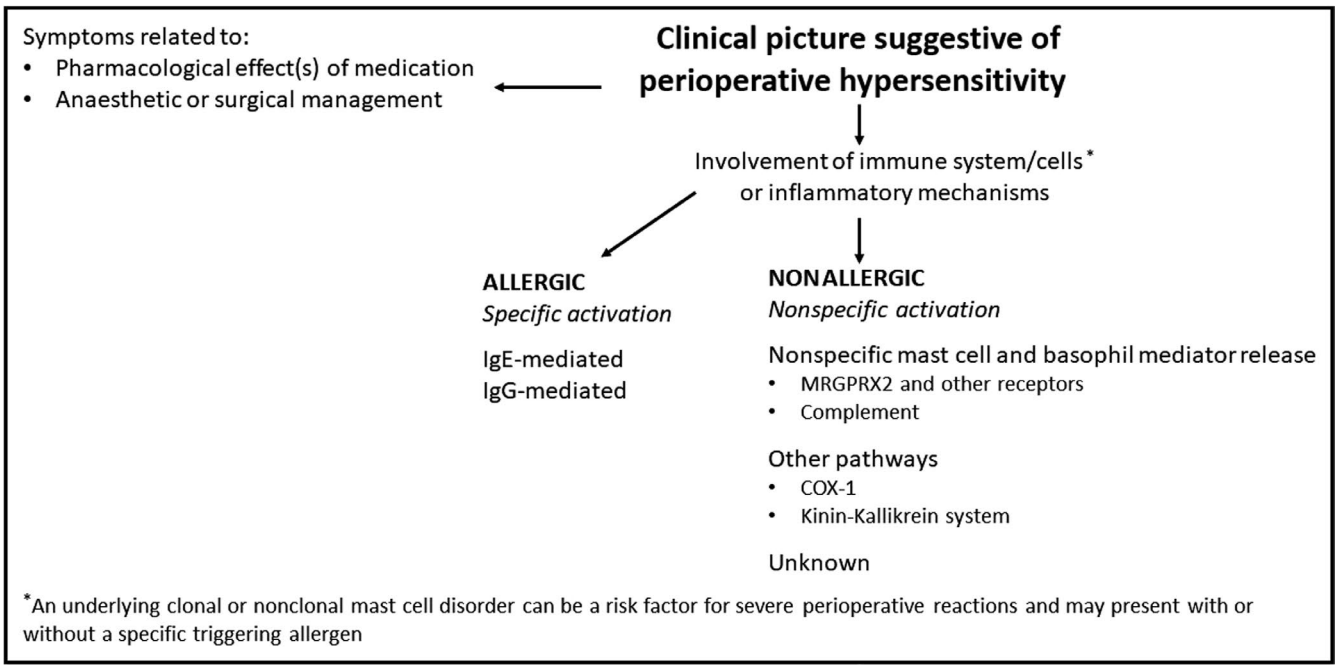

FIGURE 1 Possible pathomechanisms for clinical picture suggestive of perioperative hypersensitivity reactions[2,4]

etc) and by differences in terminology, local practice and drug use. Since 1985, in France, the Groupe d'Etude des Reactions Anaphylactoides Peranesthesiques (GERAP) network has regularly published surveys containing data collected throughout France. From these, and the data from a recent UK snapshot survey and the UK Sixth National Audit Project (NAP6) on perioperative anaphylaxis, the incidence of POH is estimated to be in the range of 1:353 to 1:18 600 procedures.[7-9] Prospective studies suggest incidences of 1:3180 from France[10] and 1:1480 from Spain.[11]

3.2 | Neuromuscular blocking agents (NMBAs)

Neuromuscular blocking agents (NMBAs) are the most common cause of POH in countries such as France, Norway and Belgium,[12-15] but are less common in the United States (USA),[16-18] Sweden[19] or Denmark.[20,21] In the UK, NMBAs were previously the most common cause,[22] but NAP6 recently reported them as the second most common cause.[23]

While the overall risk of POH to individual NMBAs remains very low, studies from countries with a high prevalence of NMBA allergy have suggested a slightly higher risk with use of succinylcholine and rocuronium than other NMBAs.[12,24,25] Recently, NAP6 reported a higher risk with succinylcholine, but equal risk for the nondepolarizing NMBAs (atracurium and rocuronium are most commonly used in UK).[26] Cross-sensitivity between NMBAs is widely reported especially from countries with high prevalence of NMBA reactions.[12,24]

The pholcodine hypothesis has contributed new knowledge.[27] Geographical variation in incidence and the observation that patients reacted on first exposure to NMBAs prompted a search for environmental factors, for example cosmetics containing quaternary substituted ammonium groups, that could cross-sensitize patients against NMBAs.[28,29] It is likely that the antitussive agent pholcodine is implicated, and pholcodine-consuming countries report more reactions to NMBAs than nonconsuming countries.[30] Following a ban of pholcodine in Norway, the incidence of NMBA reactions is reported to be decreasing.[31] Pholcodine is still available in several European countries as the European Medicines Agency (EMA) concluded, in 2011, that evidence for a link to NMBA anaphylaxis was weak and that benefits of pholcodine outweighed the risks.

3.3 | Antibiotics

Antibiotics are the leading cause of POH in several countries including Spain, United States and very recently UK, where they account for 44%-59% of IgE-mediated POH.[11,16,17,26] In France, antibiotics now take second place after NMBAs.[12] The most frequently involved antibiotics are β-lactams, especially amoxicillin or cefazolin due to widespread use. The recent increase in POH to teicoplanin in the UK is an example of how the increased use of a specific antibiotic can lead to an increase in POH reactions.[32] Antibiotics are often suspected to be the culprit drug, but a safe identification of the culprit is only possible through systematic investigation of all potential exposures.[33]

3.4 | Natural rubber latex

Natural rubber latex (NRL) was previously a leading cause of POH. Over the last decade, improvement of NRL quality, reduction in powdered glove use and NRL exposure generally have led to a marked decrease in new sensitizations. NRL is now only the fourth cause of POH in France[12] and only a minor cause in the UK[22,34] (no cases identified during the NAP6 project[26]) and in Germany.[35]

3.5 | Chlorhexidine

Chlorhexidine (CHX) is the most common disinfectant in many countries, but the incidence of POH caused by CHX varies. It accounts for 9% of reactions in the UK,[26] 9.6% in Denmark[21] and 9% in Belgium,[14] and in these countries, all patients with POH are routinely tested with CHX. In France, it is a rare cause, accounting for <1% of POH.[12] This variation may be related to under-recognition, differences in sensitization and disinfection practices, and lack of standardized testing. The most common exposures are through skin disinfection, CHX-coated central venous catheters and use of urethral or other lubricating gels containing CHX. Exposure to CHX is highly likely in most perioperative settings, but documentation of disinfectants is inconsistent. Therefore, several centres recommend routine testing with CHX, or other disinfectants according to local preference or availability, in all POH patients.[14,21,26]

3.6 | Blue dyes

The incidence of POH to blue dyes, especially patent blue, is increasing due to extensive use in sentinel lymph node mapping in cancer surgery. In the most recent French survey, dyes accounted for 5.4% of POH[12] and in NAP6 for 4.5% of reactions.[26] An incidence as high as 1:300 procedures has been reported,[36] but due to the potentially life-saving purpose of patent blue, the risk-benefit ratio is in favour of continued use. Preoperative screening for allergy to patent blue has been suggested but is not generally recommended.[37]

3.7 | Opioids and NSAIDs

IgE-mediated hypersensitivity to opiates and semisynthetic opioids is very rare, and most POH reactions to morphine, codeine phosphate or pethidine result from nonspecific skin mast cell activation.[3] There is little or no evidence of cross-reactivity between the different opioid subclasses: phenylpiperidines (alfentanil, fentanyl, remifentanil, sufentanil and meperidine) and diphenylheptanes (methadone and propoxyphene) and phenanthrenes (morphine, codeine),[38] but cross-reactivity between morphine and codeine is reported.[39]

Perioperative reactions to NSAIDs are rare.[40]

3.8 | Anaesthetic agents

Reactions to barbiturates are now rare, due to decreased use.[12,40]

Propofol is the most frequently used intravenous anaesthetic, but reactions are rare. Due to trace amounts of egg lecithin and

soybean oil in propofol, there have been concerns about the use in egg and soy allergic patients. However, such a connection has not been confirmed and avoidance is not recommended.[41,42]

Reactions to midazolam, etomidate, ketamine and inhalational agents appear to be extremely rare.[12,40]

3.9 | Local anaesthetics

Despite their widespread use, IgE-mediated hypersensitivity reactions to local anaesthetics are reported extremely rarely.[12,39,43,44] A recent study confirms this in the perioperative setting.[45]

3.10 | Plasma expanders

Anaphylaxis to colloids may be difficult to diagnose since they are usually administered in hypotensive patients. Gelatins and dextrans are more commonly associated with reactions than albumin and hydroxyethyl starch.[39,40]

3.11 | Oxytocin

Oxytocin and analogues are used widely, but only few cases of POH are reported.[46] As rapid injection and high doses can induce hypotension, tachycardia, flushing and chest discomfort, a relative overdose can be misdiagnosed as anaphylaxis.[47]

3.12 | Ethylene oxide

Ethylene oxide (EO) is a gas used to sterilize most medical devices. Although reactions are rare in the perioperative setting in general,[48] there seems to be increased risk of sensitization in myelomeningocele patients and patients with ventriculoperitoneal shunts. It is rarely possible to completely avoid EO, but an EO minimized procedure is advised[49] and pretreatment with omalizumab has been tried successfully.[50]

3.13 | Excipients

In recent years, rare cases of POH to excipients have been reported. Excipients are often overlooked as they are rarely documented, but may be found in, for example, gels, sprays and haemostatic agents.[40] Hidden and undocumented excipients causing POH include methylcelluloses,[51] macrogols/polyethylene glycols (PEG) and polysorbates,[52] mannitol and others.[40]

3.14 | Sugammadex

Sugammadex is a reversal agent of the aminosteroid muscle relaxants, primarily rocuronium. Hypersensitivity reactions and IgE-mediated anaphylaxis have been reported.[53]

There is an ongoing debate on whether treatment of rocuronium-induced anaphylaxis should include sugammadex, due to the encapsulation of rocuronium, which potentially could prevent further mediator release from mast cells and basophils. Presently, studies show conflicting evidence.[54,55]

4 | CLINICAL PRESENTATION

In the clinical setting, POH is suspected based on a combination of symptoms, their severity and the timing of the reaction in relation to possible culprits. While it is impossible to identify a mechanism without subsequent testing, life-threatening reactions are more likely to be confirmed to be IgE-mediated.[56] The majority of POH reactions occur during anaesthetic induction, but may occur during any phase of the perioperative course.

4.1 | Signs and symptoms

Signs and symptoms of POH vary from mild skin symptoms to life-threatening anaphylaxis involving several organ systems. Isolated cardiovascular collapse or cardiac arrest may be the presenting feature.[57,58] When hypotension occurs unexpectedly, with or without tachycardia, or is unresponsive to vasopressors, POH should be considered.[59] Bradycardia or unchanged heart rate may be seen, especially in patients on β-blockers.[60] Paradoxical bradycardia occurring during extreme hypovolaemia has been reported in patients with perioperative anaphylaxis.[61,62] Marked capillary leakage leads to hypovolaemia and oedema formation.[63,64] Bronchospasm is usually a feature in patients with underlying airway hyperreactivity.

Cutaneous signs, such as urticaria and generalized erythema, are often present in anaphylaxis, but can be absent during severe hypotension and may reappear after restoration of adequate circulation.[59,61,65,66] Signs from the gastrointestinal tract are absent during general anaesthesia, but may be present during regional anaesthesia.

4.2 | Grading systems

Presently, the most widely used grading system is inspired by an early publication by Ring and Messmer for the description of reactions to colloid substitutes.[67] It was adapted for the perioperative setting in the 1980s in France and has been used there since.[66] It consists of four grades based on symptom severity (Table 1). Grade I and II reactions are mild to moderate, but grade III and IV reactions are typically life-threatening and fulfil the criteria for anaphylaxis.[62] This grading system grades severity only but is very operational in the clinical setting and therefore endorsed by the Scandinavian[65] and the Australian and New Zealand guidelines.[59]

An alternative 3-grade system, the *Perioperative Anaphylaxis Grading System*, has recently been suggested in Australia and New Zealand.[68] It has very clear definitions of each grade but may be seen to be too complex to apply in the clinical setting.

4.3 | Differential diagnoses

There are several differential diagnoses to POH, mainly related to anaesthetic and/or surgical management (Table 2). These reactions often involve a single organ in the absence of elevation in tryptase, for example bronchospasm caused by poorly controlled asthma[69] or isolated hypotension during uncontrolled bleeding.

TABLE 1 Classification of clinical severity of perioperative immediate hypersensitivity: modified Ring and Messmer four-step grading scale[66,67]

Grade I Skin or mucosal signs only • generalized erythema • extensive urticaria • with or without angio-oedema
Grade II Moderate signs from several organ systems • skin or mucosal signs • ± hypotension ± tachycardia • ± bronchospasm • ± gastrointestinal signs
Grade III Life-threatening signs from one or more organ systems • cardiovascular collapse (life-threatening hypotension) • tachycardia or bradycardia ± cardiac dysrhythmia • ± bronchospasm • ± skin or mucosal signs • ± gastrointestinal signs
Grade IV circulatory and/or respiratory arrest

Early involvement of an anaesthetist during investigation can be very helpful in identifying a differential diagnosis, potentially avoiding unnecessary investigation.[60]

5 | INVESTIGATION

5.1 | General principles

The aims of POH investigation are to identify a culprit drug, and safe alternatives, and to ensure safe future anaesthesia, even if no culprit is identified. Investigation of suspected POH requires a systematic approach and should ideally be a team effort combining the expertise of allergists/immunologists with experience in anaesthetic allergy testing, with the expertise of anaesthetists with experience in anaesthetic allergy investigation. The anaesthetist understands the perioperative setting and the many differential diagnoses, can interpret the chart and help identify possible culprits, even undocumented ones. The allergist/immunologist has the detailed knowledge of the tests and their limitations. As a minimum, collaborative efforts should be set up as multidisciplinary conferences, conjoint clinics or case-by-case discussions.[40,61,66,70]

To ensure that relevant expertise is maintained, investigation of >20 patients/y is considered the minimum for individual centres/collaborations. Centres with fewer patients should consider referral to larger centres. If for geographical, logistical or economic reasons this is not possible, it is imperative that international recommendations on selection of drugs for testing, preferred test methods and diagnostic criteria are followed, to aim for a universal standardized approach for the highest possible quality of care for patients.

Reactions grade 2-4 (see Table 1) should always be referred for investigation.[61,65,66,70] All reactions with generalized erythema or urticaria, even if grade 1, should also be referred. Transient self-limiting flushing or localized erythema is unlikely to represent significant hypersensitivity and does not need investigation.[60,65]

TABLE 2 Nonallergic differential diagnoses to perioperative hypersensitivity reactions[60,69]

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 and/or uncontrolled asthma/COPD • airway hyperreactivity (predisposing factors such as asthma, smoking or viral infection) • inadequate depth of anaesthesia • endotracheal tube malposition • aspiration
Isolated angio-oedema or pharyngeal/laryngeal angio-oedema without tryptase increase • soft tissue swelling/oedema due to manipulation of the airway during laryngeal mask insertion or handling of difficult intubation • ACE inhibitor–elicited angio-oedema (onset 1-8 h after surgery) • Inherited or acquired angio-oedema
Isolated skin symptoms or combined skin symptoms, hypotension and tachycardia without tryptase increase • nonspecific histamine release • exacerbation of existing chronic urticaria/angio-oedema • relative overdose of oxytocin • mesenteric traction syndrome
Others • Clonal or nonclonal mast cell disorders

Abbreviations: ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease.

All exposures prior to reaction onset may be relevant, and complete documentation including relevant timelines is essential. Documentation should include anaesthetic record, all drug charts (preoperative, theatre and recovery), anaesthetist's notes, details of any surgical or other perioperative exposures (disinfectants, local anaesthetic sprays/gels, dyes, cements) and details of all procedures (eg, arterial, venous and urinary catheters, stents). It is not recommended to plan investigations based on information in a referral letter only. Ideally, locally available referral documentation is completed by anaesthetic personnel (doctor or nurse) who was present and recalls the chronology of the event. Examples of referral forms can be found on www.nationalauditprojects.org.uk/NAP6-Resources (from NAP6), in recently published Spanish guidelines,[71] or in Appendix S1.

Exposure to NRL and skin disinfectants should be assumed and tested in all cases according to local usage. Other frequently used substances such as EO and lidocaine may also be considered for testing in all cases.

Investigation should include all exposures prior to the reaction, not just the cause(s) suspected by the referring doctor, as this is may be incorrect.[34,72] Drug groups/drugs the patient was *not* exposed to should *not* be tested, as preemptive testing is not considered cost-effective due to the rarity of POH.

Often a large number of drugs have been administered prior to the reaction, and some centres apply timing as a criterion for selection of drugs for testing. In the Danish Anaesthesia Allergy Centre, all IV exposures given within 1 hour of reaction onset and all other exposures (intramuscular, subcutaneous, spinal, epidural, other local exposures) given within 2 hours of reaction onset are investigated.[21,33] A study on fatal anaphylaxis reported that median times to cardiac arrest varied with route of administration being 5 minutes after IV injection, 15 minutes after SC injection and 30 minutes after oral intake.[73] Therefore, the suggested timelines are thought to be sufficient. However, timing should not be used to guess the culprit, as this approach has been shown to be imprecise.[33,34,72]

In patients with a past history of POH, but where details of drug exposures are not available, it may be necessary to test with NRL, chlorhexidine, ethylene oxide and a simple battery of drugs, for example propofol, fentanyl, remifentanil and a NMBA, to ensure safe future anaesthesia.

Drugs that have been re-administered uneventfully at a later date do not need to be investigated. Drugs that have been continued or re-administered in the same anaesthetic after recovery of the reaction should still be considered for testing due to the risk of a possible refractory phase or antiallergic therapy masking symptoms. Drugs that have been continued for several days after the antiallergic therapy has been stopped, for example local anaesthetic infusion in an epidural, or continuous infusion of propofol for several days in intensive care, are less likely causes. However, the theoretical risk that desensitization could have taken place should be considered.

In cases of negative testing in patients with a strong clinical suspicion of POH and a significant elevation in serum tryptase, it is necessary to reassess the whole case. In addition, possible undocumented exposures, such as gels and sprays, should be identified for testing with the culprit product. Testing with a variety of excipients may also be warranted.[40] See Table 3 for an approach when all testing is negative.

When a culprit is identified, planned investigations should still be completed due to the risk that more than one culprit contributed to the reaction. In one study, 7% of patients tested positive to more than one culprit.[14] When a substance tests positive, cross-sensitivity should be investigated, if relevant. For NMBAs, all available NMBAs should be tested, and for, for example, antibiotics, NSAID, local anaesthetics at least one safe alternative should be identified.

Although test reactivity in both skin testing and in vitro testing may decrease over time, there is no upper limit for time passed between reaction and testing, as a positive test will still be relevant.[34,40,61,65,66,70]

The ideal timing of investigations is not known. It is recommended that testing takes place 1-4 months postevent[74] and at least 4-6 weeks postevent[75] to avoid false-negative results. British guidelines[61,70] have suggested that investigations can take place immediately after the event. However, negative skin test results before 4 weeks postevent may not exclude allergy and later re-testing may be needed.[75]

Antihistamines should be stopped 5 days prior to in vivo testing.[76] High-dose steroids and drugs with antihistaminergic effects such as antidepressants and antipsychotics should only be paused if deemed clinically safe by relevant specialists. Several guidelines on allergy investigations in general have suggested that β-blockers and ACE inhibitors should be paused prior to investigation. There is no evidence for this practice, which may put patients at risk of cardiovascular events.[77]

TABLE 3 Approach when initial investigations are negative. Modified from [40]

The reaction—should a nonallergic cause be considered?
• Go through all case notes and charts again
• Discuss alternative explanations with anaesthetist
The investigations—were they performed and interpreted correctly?
• Check skin test dilutions and diagnostic criteria comply with recommendations
• Consider additional tests, for example specific IgE, BAT, histamine release
• Consider drug provocation with suspected drugs
• Repeat skin testing/in vitro testing 2-3 mo later, if initial investigations are close to the reaction date
The exposures—are all exposures identified?
• Look again at all charts including surgeons notes and drug charts to identify overlooked or hidden culprits
• Discuss with anaesthetist/surgeon/surgical nurse to identify undocumented exposures
• Test latex, disinfectants and sterilizing agents if not part of standard investigations
• Test for excipients, for example polyethylene glycols, methylcelluloses, mannitol, lidocaine
Other considerations
• Consider if the patient could have clonal or nonclonal mast cell disorder

Abbreviation: BAT, basophil activation tests.

Children with POH are investigated using the same approach as for adults. There are no specific data about test sensitivity and specificity in this age group. In small children, IDT may be omitted or carried out after pretreatment with topical lidocaine, if lidocaine is not a suspected culprit.

5.2 | Skin testing

Skin testing comprising skin prick tests (SPT) and intradermal tests (IDT) is universally used in POH investigation. To minimize variations in performance and interpretation of tests, it is recommended that tests are performed by experienced testers.

Despite efforts to standardize concentrations used for skin testing, the nonirritant concentrations for some drugs, for example NMBAs,[78] are still a matter of debate. Some Australian anaesthetists advise hundredfold lower concentrations than in Europe.[24,40,76] However, a recent guideline published by the Australian and New Zealand Anaesthesia Allergy Group (ANZAAG) recommend concentrations for NMBA testing similar to those used in Europe.[79] Appendix S2 is an overview of recommendations from different current guidelines, and Table 4 provides an overview of the concentrations recommended by this task force.

Skin prick tests should always be performed first, usually on the forearm with relevant negative and positive controls. Results are read after 15-20 minutes, and a wheal ≥3 mm is considered positive.

When SPT is negative or inconclusive IDT is performed either on the volar side of the forearm or on the back. In the ENDA working group, a standardized method for IDT has been developed: A fixed volume of 0.02 mL is injected achieving a bleb of 3-5 mm, and the initial bleb is drawn up with a broken line. Results are read after 20 minutes, and a wheal with an increase in diameter of ≥3 mm compared to the original bleb, together with a flare, is considered positive. If SPT is performed the same day, a second positive and negative control is not considered necessary.

In some centres, all skin tests are performed in duplicate to minimize the risk of false-positive and false-negative tests.[21] If this is not possible, inconclusive SPT or IDT should always be repeated.

As patients with POH are considered high risk, most guidelines recommend titrated skin testing for both SPT and IDT using 2-3 dilutions with 20-minutes intervals, starting with the lowest concentrations and not exceeding the maximum nonirritant concentration.[65,66,79,80] In UK, recommended practice differs from other

TABLE 4 Recommended concentrations for perioperative drugs and other substances. See Appendix S2 for details of recommendations from other guidelines

Drug	Maximum nonirritative concentration Skin prick test	Maximum nonirritative concentration Intradermal test	Drug	Maximum nonirritative concentration Skin prick test	Maximum nonirritative concentration Intradermal test
Neuromuscular blocking agents			IV anaesthetic agents		
Atracurium	SPT 1 mg/mL	IDT 0.01 mg/mL	Propofol	SPT 10mg/mL	IDT 1 mg/mL
Cisatracurium	SPT 2 mg/mL	IDT 0.02 mg/mL	Etomidate	SPT 2 mg/mL	IDT 0.2 mg/mL
Mivacurium	SPT 0.2 mg/mL	IDT 0.002 mg/mL	Ketamine	SPT 100 mg/mL	IDT 0.1 mg/mL
Rocuronium	SPT 10 mg/mL	IDT 0.05 mg/mL	S-ketamine[b]	SPT 25 mg/mL	IDT 0.25 mg/mL
Vecuronium	SPT 4 mg/mL	IDT 0.04 mg/mL	Thiopental	SPT 25 mg/mL	IDT 2.5 mg/mL
Pancuronium	SPT 2 mg/mL	IDT 0.02 mg/mL	Midazolam	SPT 5 mg/mL	IDT 0.05 mg/mL
Suxamethonium	SPT 10 mg/mL	IDT 0.1 mg/mL			
Reversal agents			Local anaesthetics		
Sugammadex	SPT 100mg/mL	IDT 10 mg/mL	Lidocaine	SPT 10 mg/mL	IDT 1 mg/mL
Opiates			Articaine	SPT 20 mg/mL	IDT 2 mg/mL
Fentanyl	SPT 0.05 mg/mL	IDT 0.005 mg/mL	Prilocaine	SPT 20 mg/mL	IDT 2 mg/mL
Alfentanil	SPT 0.5 mg/mL	IDT 0.05 mg/mL	Bupivacaine	SPT 2.5 mg/mL	IDT 0.25 mg/mL
Sufentanil	SPT 0.005 mg/mL	IDT 0.0005 mg/mL	Levobupivacaine	SPT 7.5 mg/mL	IDT 0.75 mg/mL
Remifentanil	SPT 0.05 mg/mL	IDT 0.005 mg/mL	Mepivacaine	SPT 20 mg/mL	IDT 2 mg/mL
Morphine[a]	SPT 1.0 mg/mL	IDT 0.005 mg/mL	Ropivacaine	SPT 10 mg/mL	IDT 1 mg/mL
Antiseptics			Ester derivative		
Povidone iodine	SPT 100 mg/mL	No IDT	Chloroprocaine[b]	SPT 10 mg/mL	IDT 1 mg/mL
Chlorhexidine	SPT 5 mg/mL	IDT 0.002 mg/mL (sterile uncoloured alcohol-free solution)			
Plasma expanders			Additives		
Dextran	no skin tests, IgG-mediated mechanism		PEG/macrogol 300 3000 6000	 SPT undiluted SPT 50% w/v SPT 50% w/v	High risk of systemic reactions on IDT
Hydroxyethyl starch	SPT 60 mg/mL	IDT 6 mg/mL	Polysorbate 80 Poloxamer 407	SPT 20% w/v SPT 10% w/v	
Sentinel node dyes			Carboxymethyl cellulose	SPT 1% w/v	
Methylene blue	SPT 10 mg/mL	IDT 0.1 mg/mL			
Patent blue	SPT 25 mg/mL	IDT 0.25 mg/mL			

Abbreviations: IDT, intradermal test; PEG, polyethylene glycol; SPT, skin prick test.

[a]Great variation in recommended concentrations. False-positive tests may occur, consider provocation in skin test–positive patients.

[b]Insufficient evidence.

guidelines by suggesting starting with the maximum nonirritant concentration on IDT.[70]

If SPT is clearly positive, IDT should be avoided, especially in high-risk patients (severe comorbidity, anaphylaxis) with a clear history. However, if SPTs are inconclusive or confirmation of a positive result is needed, IDT can be performed starting at a very low concentration, for example 1:10.000 or 1:1000.

Although much feared, the risk of anaphylaxis during IDT is very low; however, the risk of milder systemic reactions elicited by IDT increases with higher concentrations, large volumes or multiple tests.

Fresh extracts should be used; the use of preservatives is discouraged due to unknown effects on the test drug. There are neither data on stability of individual drugs after dilution nor on storage temperature. The recommendation is to get advice from the hospital pharmacy on preparation and storage. See table in Appendix S3 for stability for different drugs used in the perioperative setting.

6 | IN VITRO TESTING

The diagnosis in POH is based on a relevant clinical history and a combination of available tests, that is skin testing supplemented with in vitro tests such as serum tryptase, histamine, specific IgE, basophil activation test (BAT) or histamine release (HR) tests. A comprehensive review on in vitro *testing* for POH was published recently.[81] Serum tryptase taken at the time of reaction is recommended in most guidelines, while plasma histamine is used rarely. Specific IgE, BAT and HR generally show high specificity. However, sensitivity varies with test and drugs and may be quite low. Tests should therefore be performed and interpreted by specialist services, and results should always be interpreted in the context of other test results and clinical information. Both BAT and HR rely on fresh blood for analysis.

Timing of sampling in close relation to the reaction is important as responses decrease over time without exposure.[74,82,83] There is no maximal upper time limit that discloses testing, and positive results are usually relevant.

6.1 | Serum tryptase

Total tryptase is the sum of continuously secreted baseline α-tryptase and β-tryptase released from degranulating mast cells (ImmunoCAP Thermo Fisher Scientific). It is recommended to measure tryptase within 1-3 hours after a suspected POH.[65,66] It has been suggested that two consecutive acute samples are needed to demonstrate an increase,[70] but this is difficult to achieve in clinical practice.[22] Recently, the decision threshold of 11.4 μg/L has been abandoned[84-86] and the recommendation is to use an algorithm suggesting a clinically relevant increase when tryptase at time of reaction >2 + 1.2 × baseline tryptase.[60,71,87] Measuring baseline tryptase has an additional purpose, as elevated baseline levels might be indicative of underlying clonal mast cell disorders, especially in severe POH.[5,6] The baseline sample should be taken a minimum of 24 hours after the reaction and later for very severe reactions, for example at time of investigation. Due to high stability, postmortem sampling can be carried out if necessary.[88]

6.2 | Plasma histamine

Quantification of plasma histamine, although highly sensitive, has low specificity.[89] Important preanalytic laboratory handling is needed, and only very few highly specialized centres measure plasma histamine.

6.3 | Specific IgE testing (sIgE)

The presence of sIgE antibodies to a specific trigger is considered proof of IgE sensitization, but this does not always give rise to clinical allergy. Measurement of sIgE is possible for a limited number of drugs relevant for POH, for example some β-lactam antibiotics and NMBAs, NRL, CHX and EO. Sensitivity and specificity are high for NRL and CHX assays, but more variable for the remaining drugs. sIgE can be measured on the sample taken at the time of reaction, but if negative, it needs to be repeated 4-6 weeks later.[21,48,82] Specific IgE should ideally be interpreted in relation to the amount of total IgE. Diagnostic conclusions should not be made based on elevated sIgE without other confirmatory tests and a relevant clinical history.

6.4 | Basophil activation test (BAT)

Like mast cells, basophils may also be activated by IgE-mediated or non–IgE-mediated stimulation (see Figure 1). Upon activation, the appearance and/or up-regulation of surface activation and/or degranulation markers, such as CD63 and/or CD203c, can be quantified by flow cytometry. In theory, BAT can be performed for all drugs and can be used to identify both culprit drugs and potential safe alternatives. BAT with unstandardized drugs should only be performed in experienced laboratories.

6.5 | Histamine release (HR)

Histamine release can also be quantified by flow cytometry,[90] and the technique is applicable in POH.[82] Like BAT, HR can be done for all drugs, and additionally for solid materials, if they can be divided into small enough pieces to get into a test tube (eg, catheters).

6.6 | Drug provocation testing (DPT)

Full-dose DPT represents the "Gold Standard" when investigating immediate hypersensitivity to drugs.[91,92] It has had limited use in POH due to the strong pharmacologic effects of perioperative drugs, for example respiratory depression, paralysis and anaesthesia. Therefore, consensus on the use of DPT in this setting is lacking.[39,65,66] When considering DPT in POH, the principles recommended in drug hypersensitivity in general could be followed, that is that DPT can be performed when skin tests are equivocal/negative,

with the aim to exclude sensitization to the culprit drug or to test a safe alternative.[91,92]

When investigating drug groups where the mechanism is unlikely to be IgE-mediated, for example opioids or NSAIDs, DPT may be the only reliable test.[92-94]

It has been argued that without DPT, the causal relationship as well as sensitivity and specificity for skin tests, sIgEs and cellular tests cannot be reliably determined.[95]

An important drawback is the risk of inducing anaphylaxis, making DPT in POH a high-risk procedure, less likely to become an available option in most centres. In addition, full-dose DPT cannot be performed due to the potent pharmacological actions of many of the drugs, and in some centres, lower maximum doses are used.[96] Finally, even DPT does not display 100% sensitivity and specificity.

However, in some cases a reliable conclusion cannot be reached based on the available tests. DPT is being used for such cases in several centres. A case report of DPT being used to solve a diagnostic challenge in POH in Australia was recently published.[97] Recent guidelines on POH from Spain suggest that DPT can be undertaken for anaesthetic drugs in highly specialized centres with full monitoring and resuscitation facilities, for example in a recovery unit/operating room.[71] In the highly specialized Danish Anaesthesia Allergy Centre, DPTs have been done routinely since 2004 with most drugs, when skin tests are negative, inconclusive or suspected to be false positive.[21,33,41,45,47,98]

In smaller less specialized centres, it may be possible for allergists to collaborate with local anaesthetists about individual patients that might benefit from DPT with drugs used in the perioperative setting, after a careful risk-benefit evaluation.

7 | CONCLUSIONS WHEN INVESTIGATIONS ARE COMPLETED

When a culprit is found, a suitable alternative should be identified for drug groups with potential cross-reactivity, for example, for NMBAs, where a skin test-negative or BAT-negative substance may be used.[99-102]

As sensitivity and specificity are not 100% for any one test, a relevant correlation between positive test results and the clinical reaction is very important. To minimize the risk of false-positive testing, some groups require ≥2 positive test modalities before the drug can be considered the culprit.[21,101]

If all tests are negative, serum tryptase was not elevated, and another nonallergic explanation is more likely, all tested substances can be used in subsequent anaesthesia. If all tests are negative and serum tryptase is elevated, the case should be re-evaluated. All exposures including potential hidden exposures such as excipients and disinfectants should be identified, and the test results should be re-evaluated. Additional tests such as BAT and DPT should be considered,[40] and other tests may be repeated after 2-3 months. Lastly, a clonal mast cell disorder should be considered even in the presence of a normal baseline tryptase.[5,6,103] If an anaesthetic is needed before such re-evaluation, suspected drugs should be avoided and extra monitoring should be put in place to ensure early identification and treatment of symptoms of anaphylaxis.

When investigations have been concluded, the patient should be informed about conclusions and implications for further anaesthesia both verbally and in a letter with copies to referring doctor, other relevant specialists and general practitioner. If a culprit has been identified, the patient should be given a warning card or allergy passport according to local guidelines.[65,66,104]

Reporting of the reaction to the national/regional pharmacovigilance unit should be ensured.

8 | PREVENTION

8.1 | Premedication

British guidelines suggest that there is no evidence for premedication with antihistamines or steroids[61] and *Scandinavian*, *US and French guidelines* state that premedication with antihistamines or steroids is unlikely to prevent IgE-mediated events.[65,66,105] Spanish guidelines suggest premedication primarily for nonspecific reactions.[71]

Premedication with H_1-antihistamines, along with slow injection of incremental doses of drugs, may reduce/prevent mild reactions caused by nonspecific histamine release from mast cells and basophils[65,105] induced by histamine-releasing agents, for example opioids, NMBAs, vancomycin and thiopentone.[106] In this setting, oral H_1-antihistamines may be used as premedication for 2-3 days prior to anaesthesia to ensure effective blockade of histamine receptors.

Referral for allergy investigations is highly recommended in patients with a previous episode of POH, as a history of a previous POH or unexplained perioperative event is the only risk factor for a future POH. The presence of atopy, food allergy, other drug allergy, previous uneventful anaesthetic or familial history of anaesthetic or other drug allergy per se are not risk factors for POH.[65,107]

8.2 | Specific measures to reduce risk of POH

Several guidelines on POH, and the group behind the NAP6 project, recommend that iv antibiotics should be administered before anaesthetic induction to avoid the combination of effect of anaesthetic drugs and anaphylaxis.[23,66,71,105] If a hypersensitivity reaction does occur, fewer drugs will be suspected. It has also been suggested to administer antibiotics as slow infusion.[62]

Implementing a primary NRL-free environment in children with myelomeningocoele has proven to be effective in preventing sensitization to NRL.[108]

8.3 | Screening

There is no place for systematic preoperative screening for any drug or drug group in patients without a relevant history of a reaction.[109]

9 | CONCLUSIONS AND UNMET NEEDS

Due to the rare occurrence of POH, it is mandatory that collaborations are established both within and across specialties to form specialized centres that can build up expertise in this highly complex field. Similarly, international collaboration is needed.

Many issues are still to be resolved especially regarding the standardization of skin- and in vitro testing and finding the place for drug provocation in POH.

Finally, the successful implementation of recommendations in this position paper is dependent on the establishment of specialized collaborations between allergist/immunologists/dermatologists and anaesthesiologists and goodwill from administrators to support the logistics and the economic framework to enable the best care for this complex patient group.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors (LHG, DGE, PMM, PD, TG, PK, JJL, AC, IT, SV and KS) participated in two consensus meetings and contributed to first and subsequent drafts. First draft was prepared by LHG and reviewed by all authors. All authors reviewed and approved the final version.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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