

REVIEW ARTICLE

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

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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

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 ($N < ? \mu\text{g L}^{-1}$)
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 $\uparrow$ (?) (Grade II)	(i) PT (neat) PVP-iodine: pos (ii) PT (10^{-1}) PVP: pos	(i) T_{0+} ? min: 94 (ii) baseline: 3.7 ($N < 11 \mu\text{g L}^{-1}$)
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

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 Europe⁷² 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 post-operative 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 H₁ antihistamines to prevent mast-cell-mediator release. Omalizumab, an anti-IgE monoclonal antibody, is effective in chronic urticaria unresponsive to H₁ 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 H₁ antihistamines may be useful, whilst H₂ 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 H₁/H₂ 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 thromboendarterectomy	(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 pre-treatment 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 H₁ or H₂ 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 benzyli-soquinoline 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 Canada¹²⁷ and in the USA,¹²⁴ the latest international guidelines provide that C1-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 FFP¹²⁴ 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 ($N < 13 \text{ U L}^{-1}$)
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 ($N < 1 \text{ ng ml}^{-1}$)
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) $T_0 + 90 \text{ min}$: 37 (ii) Baseline: 36 ($N < 15 \text{ } \mu\text{g L}^{-1}$)
		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, remifentanyl, 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) $T_0 + 90 \text{ min}$: 69 (ii) Baseline: 73 ($N < 10 \text{ } \mu\text{g L}^{-1}$)
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 ($N < 14 \text{ ng ml}^{-1}$)
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	$T_0 + ? \text{ min}$: 154 ($N < 11 \text{ ng ml}^{-1}$)
		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	$T_0 + ? \text{ min}$: 56 ($N < 11 \text{ ng ml}^{-1}$)

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 SpO 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, remifentanyl, 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 France⁴ 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 H₁ 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 hyper-reactivity.^{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 H₁ 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 tests¹⁴⁴ 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 anaesthesia: 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. Physiopathology 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 Invest 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. Anaphylactic shock due to povidone. *J Paediatr Child Health* 2017; 53: 517
56. Dooms-Goossens A, Deveyllder 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- α -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- α -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/GA²LEN/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, Quezada 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. *Pediatr 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. Renaud 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 Torno 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, Ansoategui 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 Sagner 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

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