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

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Running title: Allergic conditions and peri-operative setting

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Summary / abstract

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 peri-operative management.

Follow-up investigation should be performed after a peri-operative immediate hypersensitivity to establish a diagnosis and provide advice for subsequent anesthetics; the main risk factor for peri-operative IgE-mediated anaphylaxis being a previous uninvestigated peri-operative immediate hypersensitivity reaction. The concept of cross-reactivity between drugs used in the peri-operative 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 characterized 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 NPH-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 peri-operative risk associated with the potential for exacerbation of the various conditions.

Key words: adverse effects; Anaesthesia; Drug Hypersensitivity; Food Hypersensitivity; Peri-operative Period

Editor's key points

- The main peri-operative risk factor for anaphylaxis is a previous uninvestigated peri-operative immediate hypersensitivity reaction.
- The main concerns are potential uncontrolled asthma in atopy, strict avoidance of all 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 peri-operative protocols in α -gal syndrome regarding the use of heparin, or in chronic urticaria, except 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 pre-operative evaluation as they may result in peri-operative life-threatening conditions. The acquired knowledge during the past decades has helped us to better characterize the different conditions and identify their peri-operative risks, which are displayed in this review.

The sole identified peri-operative risk factor for anaphylaxis is a previous un-investigated peri-operative immediate hypersensitivity reaction. The concept of cross-reactivity between drugs used in the peri-operative 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 IgE-mediated drug allergy but the potential peri-operative risk is linked to the disease itself. Finally, the peri-operative 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) characterize and distinguish the clinical patterns of pre-existing allergic conditions from other confounding non-allergic clinical entities; ii) identify the potential peri-operative 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 peri-operative setting; iv) discuss a rational approach to the identification of the culprit agent that allows for a safe subsequent management of patients experiencing peri-operative 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 (MeSH) 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; Peri-operative Period; Povidone-Iodine; Propofol; Protamines; Shellfish Hypersensitivity; Soybeans; succinylated gelatin; surgery and combinations of those. Conferences abstracts were not considered. Searches were performed from January 1998 to August 2018. Key publications prior to 1998 reporting major findings or paradigm shifts that remain cornerstones of current understanding were also included.

Outcomes

Our searches failed to retrieve any randomized 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 sub-section. Relevant records, based on title and abstract, were provisionally selected. Identified citations were independently reviewed by the authors of the corresponding sub-sections. Full texts of the included titles and abstracts were then extensively reviewed by these authors to reach a final list.

Risk factors for peri-operative IgE-mediated allergy

The risk factors of a peri-operative allergic reaction include the propensity of certain drugs to elicit IgE-mediated allergy and patient factors. Peri-operative 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 due to agents unrelated to anaesthetics (*e.g.* patent blue dye, succinylated gelatin, iodinated contrast agent, latex, sugammadex, chlorhexidine).¹⁻³

The main risk factor for peri-operative IgE-mediated anaphylaxis is a previous uninvestigated peri-operative immediate hypersensitivity reaction.⁴⁻⁷ Uneventful previous exposure to a NMBA or an antibiotic does not exclude IgE-mediated allergy during a subsequent exposure while 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 drugs⁸ while genetic modifiers and other host factors, as well as gene-environment interactions, may influence the development, clinical presentation and/or severity of IgE-mediated allergy.⁹ The onset of drug allergy may be modulated by cofactors which lower “the allergen dose” necessary to elicit the clinical features. This has been clearly demonstrated in food allergy.¹⁰ Furthermore, stress and/or infection might be cofactors involved in the peri-operative setting. Finally, fatalities after peri-operative anaphylaxis may be influenced by a higher ASA physical status, associated comorbidities (obesity, coronary artery disease), ongoing β -blockers and/or 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 effective long-term treatment attenuating airway inflammation decreases the incidence of peri-operative pulmonary complications.^{13, 14} The largest overall phenotype in children and adults is allergic asthma (*See section on 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 peri-operative bronchospasm is uncontrolled asthma.¹⁵⁻¹⁷ In addition, co-existing obesity is associated with a poor asthma control in both children and adults. The pre-operative 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 intravenous corticosteroid along with inhaled β_2 -agonist may be required to prevent the onset of peri-operative bronchospasm. In case of emergency surgery, repeated aerosolized β_2 -agonist/glucocorticoid along with intravenous corticosteroid may be required. Bronchodilators should be continued up to the time of surgery whenever possible.¹⁸

In summary, the main peri-operative 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 following latex-exposure; iii) *Spina Bifida* patients; iv) multiple surgeries especially in childhood; v) occupational latex-exposure; vi) allergy to exotic fruits (avocado, banana, kiwi...). 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} while 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 allergy

Egg, soy and peanut allergy are among 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/or 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.

While 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 reported³⁰⁻³⁴; 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 3 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 characterized by oesophageal dysfunction, 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-sensitized or allergic patients with or without EoE (Table 1). In one case, generalized 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.³⁹ 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, 40} and some authors agree that propofol can be 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®) in egg- or soy allergy⁴¹ while 1% propofol and 10% Intralipid® share the same egg lecithin/soy oil content and 20% intralipid has double the amount of soy oil. Based on actual data, the *American Academy of Allergy, Asthma and Immunology* recently states 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 (10-13kDa) heat-stable muscle protein parvalbumin, a calcium-binding protein.⁴² The high clinical cross-reactivity among fishes has been attributed to parvalbumins cross-reactive IgE from several species. Other fish allergens have been characterized *e.g.* glycolytic enzymes (aldolase A, β -enolase) or collagen isolated from muscle tissues and/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 among 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 drugs allergy

Iodinated contrast media (ICM) and povidone-iodine are the main iodinated drugs used in the peri-operative setting. ICM are chemical modifications of a 2,4,6-tri-iodinated benzene ring. IgE-mediated⁴³⁻⁴⁵ and delayed hypersensitivity⁴⁵⁻⁴⁷ to ICM have been documented. ICM present different degree of cross-reactivity in both immediate and delayed hypersensitivity. 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 following 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 unproven.⁵⁶

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

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 while 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 to 0.06% in other cardiac surgical patients, no protamine allergy was evidenced. Recently, 3 cases of protamine allergy were reported.⁶² 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.

α -gal syndrome, gelatin-based colloid and heparin

Over the past decade, the α -gal syndrome has been recognized as an IgE-mediated red meat allergy and identified as a singular syndrome involving the carbohydrate (galactose- α -1,3-galactose; α -gal) determinant, a sensitisation *via* tick bites and a delayed onset of the clinical features *i.e.* 3-6h after meat-exposure.^{29, 63} The oligosaccharide is present in many mammalian foods, including meat and gelatin. IgE to α -gal was initially recognized 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 due to 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 symptoms onset disproves its role, no IgE-mediated heparin allergy was evidenced while un-investigated drugs used in the peri-operative 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 while 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 COX-1-selective nonsteroidal anti-inflammatory drugs (NSAIDs). This condition has been referred 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 peri-operative management of NSAID-exacerbated respiratory disease is 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 prior to surgery. The intraoperative 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.

Prior to surgery, the pre-operative assessment/treatment of uncontrolled asthma and/or 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 aerosolized β_2 -agonist/steroid along with intravenous 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 blockade 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 (less than 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 sub-types, *i.e.* chronic spontaneous or 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 characterized 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 while 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, use of 2nd generation H₁-antihistamines to prevent mast cell mediators release. Omalizumab, an anti-IgE monoclonal antibody, is effective in chronic urticaria unresponsive to H₁-antihistamines⁷⁹ 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 while 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 urticaria⁷⁹, unless it is clear that the patient is currently tolerating NSAIDs. Ten clinical cases regarding chronic inducible urticaria peri-operative 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 7 cases.⁸²⁻⁸⁸ Preoperative H₁/H₂ antihistamines and steroids were mostly started a few days or hours prior to surgery, repeated before rewarming and after surgery. In the 3 remaining cases, pharmacological or physical factors triggered mild/moderate peri-operative features.⁸⁹⁻⁹¹

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

Mastocytosis

Mastocytosis is the most important mast cell clonal disorder characterized 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} Estimated incidence is 1:10,000.⁹⁴ Mastocytosis is classified according to the age of onset (pediatric 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 mediators release. Cutaneous mastocytosis is the most frequent phenotype characterized 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.

There is no evidence showing a higher prevalence of IgE- or non IgE-mediated drug-induced immediate hypersensitivity in mastocytosis when compared to the general population.^{95, 96} Various triggers *i.e.* histamine-releasing agents, mechanical (skin irritation, tourniquet) or physical (hypo- or hyperthermia) factors and anxiety may elicit non-specific immediate hypersensitivity. Attention to the peri-operative patient safety (homeothermy, positioning, anxiolysis) makes these factors less likely to induce clinical features.⁹⁶ The *Ring and Messmer* scale is appropriate to characterize peri-operative immediate hypersensitivity in mastocytosis.⁹⁵ Their incidence remains unknown. The 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 peri-operative 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 2 adults. The role of anaesthetics remains unproven in the 2 other cases. Uneventful procedures have been reported in 4 retrospective case-series including parturients^{99, 100} and children.^{101, 102} Since 1998, the peri-operative management of 21 cutaneous or systemic mastocytosis patients undergoing 25 procedures has been published (Table 4).¹⁰³⁻¹²² No peri-operative event occurred in 52% (n=13) of the procedures. Pretreatment regimen was administered in most of the patients. Concurrent allergy (NMBA, gelatin) was proven or may have been involved in four cases while non-specific triggers including drugs (antibiotics, atracurium) or mechanical factors were identified in five. The role of mastocytosis remained speculative in the 3 other cases.

Preoperative H₁- and/or H₂-antihistamine and/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 Caution has been recommended with benzylisoquinoline-NMBAs due to their histamine-releasing potency.

In summary, the peri-operative 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).^{123, 124} Acquired angioedema is less common and due to C1-inhibitor deficiency.¹²⁵ It might be associated with C1-INH auto-antibodies with/without an underlying condition (*e.g.* lymphoma). Given the role of bradykinin, the latest guidelines classify angioedema related to the use of angiotensin-converting-enzyme inhibitor (ACE-I) or angiotensin receptor blocker as acquired, though C1-INH deficiency or dysfunction is absent.¹²⁴

C1-INH deficiency/dysfunction results in inappropriate or excessive activation of the complement pathway allowing kallikrein activation. This leads to 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 above. Symptoms are similar in hereditary and acquired angioedema. In hereditary angioedema, swelling often begins during childhood and worsens around puberty. In acquired angioedema, onset of symptoms is later, family history of angioedema is absent and facial angioedema more frequent.¹²⁵ ACE-I-induced angioedema frequently occurs within the first month or after years of treatment. Angioedema may occur spontaneously or be precipitated by various stimuli (*e.g.* mechanical trauma, stress, emotion). Upper airway manipulation, including dental surgery and tracheal intubation, is at particularly high-risk due to upper airway and laryngeal angioedema.^{123, 124, 126, 127}

Only 4 retrospective case-series regarding the hereditary or acquired angioedema peri-operative management were published since 1998 (Table 6). One study investigated 705 tooth extractions in 171 hereditary angioedema patients with/without C1-INH prophylaxis.¹²⁸ 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.¹²⁹ In most cases, angioedema was located at the site or region of surgery, though laryngeal angioedema was documented in 3 patients. A recent study included 24 hereditary or acquired angioedema patients who underwent 38 procedures.¹³⁰ Short-term prophylaxis was administered in all hereditary and in 6 acquired angioedema patients. Upon tracheal extubation, oral angioedema requiring re-intubation occurred in an 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.¹³¹

National, International and/or Society guidelines regarding the hereditary or acquired angioedema overall management, including the peri-operative 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.^{123, 124, 126} If short-term prophylaxis should be considered prior to all medical, surgical and dental procedures in Canada¹²⁶ and the US¹²³, 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 aero-digestive tract.¹²⁴ Short-term prophylaxis can be achieved by FFP¹²³ as a second-line agent.¹²⁴ Attenuated androgens (*e.g.* danazol) may be used in light of their adverse effects.^{123, 124, 126} Tranexamic acid is no longer recommended.¹²⁴ In the UK, no specific short-term prophylaxis regimen has been outlined.¹²⁷ Despite short-term prophylaxis, angioedema may occur even after minor procedures. Specific acute treatment should be available during and after any procedure, though short-term prophylaxis was administered.^{123, 124, 126, 127}

All attacks are considered for on-demand treatment while any attack affecting or potentially affecting the upper-airway is treated.¹²⁴ Hereditary and acquired angioedema fail to respond to corticosteroids, antihistamines or epinephrine. Early treatment with 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 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.^{123, 124, 126, 132} 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; iii) as the first-line acute therapy in pregnancy or during breastfeeding.^{124, 132} 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 is available during pregnancy or breastfeeding. Close follow-up is recommended for at least 72 hours after delivery.

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

Anaesthesia for the patient with previous peri-operative immediate hypersensitivity

Follow-up allergological investigation should be performed after a peri-operative immediate hypersensitivity or any peri-operative context without obvious explanation *i.e.* unexplained prolonged hypotension or circulatory arrest. The peri-operative management of the patient

labelled as “penicillin allergic” is reviewed in detail elsewhere in this issue of the *British Journal of Anaesthesia*.

Allergological investigation

The clinical history is crucial to establish the diagnosis of peri-operative immediate hypersensitivity and the *Ring and Messmer* scale is useful to describe the clinical features.^{5, 6, 20} All the grades (I to IV) of this scale require subsequent investigation. Combined acute plasma histamine and tryptase measurements are recommended in France⁴ and in the US¹³³ while only tryptase measurement has been retained in Scandinavia⁵, the UK⁷, Australia and New Zealand¹³⁴ and Spain.¹³⁵ Skin testing remains the “gold standard” to identify the culprit agent, the pathophysiologic (allergic *versus* non-allergic) mechanism involved and provide advice for subsequent anaesthetics.^{5-7, 20, 133, 134} Skin testing requires experience and time and is best performed in dedicated clinics.¹³⁶

Differential diagnoses following allergological investigation

The allergological assessment includes review of the details of the reaction. A suggestive clinical history, usually life-threatening reaction, associated with increased histamine and/or tryptase levels linked to skin tests positivity to the culprit agent prove the diagnosis of IgE-mediated allergy. The absence of tryptase increase does not preclude IgE-mediated allergy.^{5, 7, 20, 133} Conversely, a suggestive clinical history (usually mild/moderate reaction) associated with skin tests negativity, with or without increased histamine and tryptase (tryptase may be slightly elevated) levels suggest a non-allergic reaction (*e.g.* histamine release induced by benzylisoquinoline NMBAs, suxamethonium, propofol, 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.¹³⁷ Discontinuation of the vancomycin infusion and H₁-antihistamines may reduce/prevent most of the reactions. Other antibiotics (*e.g.* fluoroquinolones, 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) and/or pharmacological (*e.g.* histamine-releasing drugs) triggers in uncontrolled airway hyperreactivity.^{15, 17}

Systemic mastocytosis should be suspected in cases of severe cardiovascular disturbances associated with cutaneous signs and highly increased peak tryptase level compared to the grade of the clinical presentation. Baseline tryptase level and, when available testing for KIT D816V mutation in peripheral blood, may be useful followed by 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.¹³⁵ Drug challenge test with negative skin tested anaesthetics 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 and/or atopic and/or stressed patients. Severe clinical presentation is also reported. Following mild/moderate non-allergic immediate hypersensitivity, the culprit drug is not contra-indicated 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.^{135, 138}

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 standardized in France⁴, the protocol has been adapted by others^{5, 7, 139} and endorsed by the *European Academy of Allergy and Clinical Immunology*.¹⁴⁰ 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 only¹⁴¹, combined prick-tests and intradermal tests¹⁴²⁻¹⁴⁵ or combined skin tests and basophil activation test.¹⁴⁶ The use of lower dilutions of NMBAs than those recommended and/or intradermal tests only^{141, 147, 148}, inadequate communication¹⁴⁵ or false negative skin tests¹⁴³ may explain second reactions to a negative skin-tested 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.

Conclusion

The main identified risk factor of peri-operative drug anaphylaxis is a previous un-investigated peri-operative immediate hypersensitivity reaction. However, peri-operative 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 following peri-operative immediate hypersensitivity highly contributes to the quality and safety in subsequent peri-operative care.

Contribution of authors

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Design of the study: all authors

Data collection, analysis & interpretation: all authors

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PDW: i) has received lecture and travel fees from MSD France (Courbevoie, France); ii) has received lecture and travel fees from Bracco Imaging France (Courcouronnes, France); iii) Expert for a Task Force Group dedicated to *“Neuromuscular Blocking Agents and Anaphylactic Reactions”* (until 2016), Agence Nationale de Sécurité du Médicament et des Produits de Santé, Saint-Denis, France; iv) belongs, until October 2019, to a MSD Expert Board on *“Neuromuscular Blocking Agents and Fast-Tracking Anaesthesia”*

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Table 1: Retrospective studies evaluating the use of propofol in egg-, soy- or peanut allergy with or without eosinophilic esophagitis (EoE)

Reference	Patient (n =) Age [range, yrs]	Study design	Propofol injection (n =)	Clinical history	Peri-operative event	Skin testing to propofol
Murphy ³⁵ [2011]	28 [1-15]	- monocentric - 1999-2010	43	egg-sensitization: 28 <ul style="list-style-type: none"> egg allergy: 19 (68%) previous egg anaphylaxis: 2/19 	generalized urticaria 15 min. after the 2 nd propofol dose EoE child with previous egg anaphylaxis (n = 1)	PT (neat): 3mm (pos) IDT: not done
Molina- Infante ³⁶ [2014]	60 [14-56]	- bi-centric - 2009-2013	404	EoE: 60 egg, soy or peanut sensitization: 52 (86%) <ul style="list-style-type: none"> egg, soy or peanut allergy: 18/52 (35%) previous clinical reaction or anaphylaxis: egg: 1, legume: 4, peanut: 13 	<ul style="list-style-type: none"> intubation-induced bronchospasm adolescent with uncontrolled asthma (n = 1) 	PT (neat): neg
Asserhoj ³⁴ [2016]	99 (adults)	- monocentric - 2004-2012	171	<ul style="list-style-type: none"> egg, soy or peanut sensitization: 99 egg, soy or peanut allergy: 44 (44%) 	none	

Mehta ⁴⁰ [2017]	144 (children)	- monocentric - 2013-2014	65	egg or soy allergy: 144 previous egg anaphylaxis: 6 (4%) EoE: 76 (53%)	none	
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PT: prick-test; IDT: intradermal test; neg: negative; pos: positive

Table 2: Clinical cases of IgE-mediated allergy to povidone-iodine (since 1998)

Reference	F/M age	Site Onset delay	Clinical features	Skin testing	Tryptase
Lopez-Saez ⁴⁸ [1998]	M 27	- skin wound - immediately	pruritus of the soles, generalized urticaria, facial angioedema (Grade I)	- PT (10 ⁻²) PVP-iodine: pos - PT (neat) PVP: pos - PT (neat) Lugol solution: neg - PT (neat) 2 ICM: neg	ND
Adachi ⁴⁹ [2003]	F 59	- mucosa - 10 min	pruritus in the genital area, erythema, generalized urticaria, SAP: 40 mmHg, dyspnea (Grade III)	- PT (0.1%, 10%) PVP-iodine: pos - PT (0.001%) PVP: pos - PT (2%) iodine: neg	ND
Le Pabic ⁵⁰ [2003]	M 32	- surgical wound - a few min.	clinical features not detailed (Grade IV)	- PT (neat) PVP-iodine: pos - IDT (10 ⁻⁴) PVP-iodine: pos - PT (neat) PVP: pos - IDT (10 ⁻⁴) PVP: pos	T0 + ? min: 39 (N < ? µg/l)
Pedrosa ⁵¹ [2005]	M 9	- skin - 10 min	• urticaria, facial angioedema, dyspnea (Grade II) • one previous clinical reaction after oral intake of flubendazole (containing povidone): (Grade IV)	- PT (neat) PVP-iodine: pos - PT (neat) PVP: pos - PT (neat) flubendazole: pos	ND

Caballero ⁵² [2010]	M 42	- surgical wound - 15 min	<ul style="list-style-type: none"> • skin preparation with PVP-iodine: no event • PVP-iodine on surgical wound: generalized urticaria, tongue swelling, SAP: 94 mmHg, moderate bronchospasm (Grade II) 	<ul style="list-style-type: none"> - PT (neat) PVP-iodine: pos - PT (neat) iodine: neg 	ND
Gray ⁵³ [2013]	F 12	- skin wound - unknown	<ul style="list-style-type: none"> • clinical features not detailed • one previous clinical reaction following PVP-iodine application on skin wound (Grade II) 	<ul style="list-style-type: none"> - PT (neat) PVP-iodine: pos 	ND
Castelain ⁵⁴ [2016]	M 56	- knee wound - immediately	pruritus on the knee spreading to the whole body, generalized erythema, sweating, SAP: 70 mmHg, HR ↑ (?) (Grade II)	<ul style="list-style-type: none"> - PT (neat) PVP-iodine: pos - PT (10⁻¹) PVP: pos 	<ul style="list-style-type: none"> • T0 + ? min: 94 • baseline: 3.7 (N < 11 µg/l)
Moreno-Escobosa ⁵⁵ [2017]	M 4	- skin wound - 20 min	<ul style="list-style-type: none"> • eyelids angioedema, generalized urticaria, AP: 80/40 mmHg, HR: ? (Grade II) • 2 subsequent clinical reactions following: <ul style="list-style-type: none"> - facial application of a suncream (Grade I) - prednisolone oral intake (Grade II) <p>(suncream & prednisolone both contain PVP)</p>	<ul style="list-style-type: none"> - PT (10⁻¹) PVP-iodine: pos - PT (neat) suncream: pos - PT (neat) prednisolone: pos 	ND

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; SAP: systolic arterial pressure; HR: heart rate

IDT: intradermal test; PT: prick-test; neg: negative; pos: positive; ND: not done

PVP: povidone; ICM: iodinated contrast medium

Table 3: Clinical cases reporting the peri-operative course of cold-induced urticaria during normothermic or hypothermic cardiopulmonary bypass (CPB) (since 1998)

Reference	F/M age	Surgery	Pretreatment regimen	CPB duration	Core temperature	Peri-operative event
Lancey ⁸² [2004]	M 69	coronary bypass grafting	<ul style="list-style-type: none"> • anti-H₁ + anti-H₂ • methylprednisolone - 5 days prior to surgery - before rewarming - up to 6 hrs after surgery 	?	32°C	none
Irani ⁸³ [2007]	F 34	mitral valve repair	<ul style="list-style-type: none"> • anti-H₁ + anti-H₂ • methylprednisolone - 6 hrs prior to surgery 	109 min	37°C	none
Bakay ⁸⁴ [2010]	F 41	coronary bypass grafting	<ul style="list-style-type: none"> • anti-H₁ (single dose) • methylprednisolone -12 hrs prior to surgery - up to 3 days after surgery 	80 min	36°C	none
Booth ⁸⁵ [2011]	F 67	coronary bypass grafting	<ul style="list-style-type: none"> • anti-H₁ + anti-H₂ • hydrocortisone 	140 min	from 35.6 to 37.3°C	none

			- single dose			
Ellis ⁸⁶ [2013]	M 70	aortic aneurysm repair	<ul style="list-style-type: none"> • anti-H₁ + anti-H₂ • methylprednisolone • montelukast - 7 days prior to surgery - before rewarming - up to 6 hrs after surgery 	159 min	28°C	none
Fitzsimons ⁸⁷ [2015]	M 57	pulmonary thrombo- endarterectomy	<ul style="list-style-type: none"> • anti-H₁ + anti-H₂ • hydrocortisone - 13 hrs prior to surgery - and anti-H₁ before rewarming 	≈ 240 min	from 17 to 21.6°C	none
Maddy ⁸⁸ [2017]	F 66	aortic aneurysm repair	<ul style="list-style-type: none"> • anti-H₁ + anti-H₂ • hydrocortisone - single dose 	135 min	from 15.4 to 24.7°C	none

Table 4: Clinical cases reporting the peri-operative course in cutaneous (CM) or systemic (SM) mastocytosis (since 1998)

References	F/M age	Premedication	Agents and Surgery	Peri-operative event	Trigger	Tryptase
Borgeat ¹⁰³ [1998]	F, 30 SM	MDZ anti-H ₂ steroid	<ul style="list-style-type: none"> • fentanyl, propofol, vecuronium • splenectomy 	none		<ul style="list-style-type: none"> • during surgery: 10 (N < 13 U/L)
Vaughan ¹⁰⁴ [1998]	M, 43 SM	none	<ul style="list-style-type: none"> • fentanyl, propofol, isoflurane, morphine, atracurium • olecranon fracture 	immediately after intubation: electromechanical dissociation followed by MOF and death	atracurium allergy likely involved	<ul style="list-style-type: none"> • T0 + ? : 18 (N < 1 ng/ml)
Damodar ¹⁰⁵ [2006]	F, 14 SM	anti-H ₁ , anti-H ₂ steroid	<ul style="list-style-type: none"> • MDZ, fentanyl, pancuronium • cardiac surgery 	none		ND
Russell ¹⁰⁶ [2006]	F, 60 SM	none	<ul style="list-style-type: none"> • SA (bupivacaine), midazolam, propofol, tropisetron • knee arthroplasty (postponed) 	after SA and propofol: extreme bradycardia then circulatory arrest	- role of SM ? - likely due to the additive effects of SA and propofol	<ul style="list-style-type: none"> • T0 + 90 min.: 37 • baseline: 36 (N < 15 µg/l)
		none	<ul style="list-style-type: none"> • 2nd surgery: MDZ, morphine, propofol, vecuronium, desflurane • knee arthroplasty 	none		ND
Villeneuve ¹⁰⁷	F, 37	anti-H ₁ , anti-H ₂	<ul style="list-style-type: none"> • CSE (lidocaine, fentanyl), nitrous 	none		ND

[2006]	CM		oxide, oxytocin, naproxen, paracetamol • cesarean section			
Konrad ¹⁰⁸ [2009]	F, 52 SM	anti-H ₁ MDZ	• sufentanil, propofol, rocuronium, sevoflurane • hysterectomy	none		ND
	M, 45 SM	anti-H ₁ steroid	• sufentanil, remifentanil, propofol • tonsillectomy	none		ND
Renauld ¹⁰⁹ [2011]	F, 69 CM	anti-H ₁	• sufentanil, propofol, atracurium, desflurane morphine, nefopam • hysterectomy	2-3 min after atracurium: AP: 77/50 mmHg, HR: 120 b/min, generalized erythema	atracurium (allergy excluded)	• T0 + 90 min.: 69 • baseline: 73 (N < 10 µg/l)
Bridgman ¹¹⁰ [2013]	F, 58 SM	none	• MDZ, fentanyl, propofol, sevoflurane, cefazolin, paracetamol, ropivacaine, dexamethasone • knee replacement	after tourniquet release: no erythema, SAP: 60 mmHg, HR: ?	tourniquet	• T0 + ? > 200 • baseline: 31 (N < 14 ng/ml)
Ulbrich ¹¹¹ [2013]	F, 33 SM	MDZ	• propofol, piritramid, clonidine, oxytocin, erythromycin • cesarean section	none		ND
Duggal ¹¹² [2015]	M, 53 SM	none	• MDZ, fentanyl, propofol, vecuronium, vancomycin	during vancomycin infusion: AP: 50 mmHg, HR: 60 b/min,	non-allergic reaction to vancomycin likely	• T0 + ? min: 154 (N < 11 ng/ml)

			<ul style="list-style-type: none"> • aortic aneurysm (postponed) 	erythema, urticaria	involved	
		anti-H ₁ , anti-H ₂ steroid	<ul style="list-style-type: none"> • 2nd surgery: fentanyl, propofol, lidocaine, succinylcholine, linezolid • aortic aneurysm (postponed) 	during linezolid infusion: AP < 65 mmHg, HR: ? erythema, urticaria	non-allergic reaction to linezolid	<ul style="list-style-type: none"> • T0 + ? min: 56 (N < 11 ng/ml)
		anti-H ₁ , anti-H ₂ steroid MTK	<ul style="list-style-type: none"> • 3rd surgery: fentanyl, lidocaine, propofol, succinylcholine, linezolid, cefuroxime, protamine • aortic aneurysm 	none		ND
Tew ¹¹³ [2015]	F, 6 CM	anti-H ₁	<ul style="list-style-type: none"> • fentanyl, propofol, sevoflurane, nafcillin, paracetamol, oxycodone • lumbar laminectomy 	none		ND
Aloysi ¹¹⁴ [2016]	F, 19 CM	anti-H ₁	<ul style="list-style-type: none"> • propofol, suxamethonium • electroconvulsive therapy 	none		ND
Ten Hagen ¹¹⁵ [2016]	M, 70 ISM	none	<ul style="list-style-type: none"> • SA (bupivacaine), propofol, ketamine, cefazolin, tranexamic acid, naproxen, ondansetron, paracetamol • hip arthroplasty 	after cement implantation: AP: 60/40 mmHg, HR ?, SpO ₂ : 80%, no cutaneous signs	bone cement (unrelated to ISM)	ND
Bryson ¹¹⁶ [2017]	M, 41 SM	anti-H ₁	<ul style="list-style-type: none"> • MDZ, propofol, rocuronium, neostigmine • electroconvulsive therapy 	none		ND

de la Fuente Tornero ¹¹⁷ [2017]	M, 50 ISM	MDZ anti-H ₂	<ul style="list-style-type: none"> • fentanyl, lidocaine, propofol, rocuronium, sevoflurane, cefazolin, succinylated gelatin • spinal surgery 	immediately after gelatin: AP: 60/30 mmHg, HR: 40 b/min, EtCO ₂ : 9 mmHg and circulatory arrest	gelatin allergy likely involved	<ul style="list-style-type: none"> • T0 + 120 min: 410 • baseline: 50 (N < 11 ng/ml)
Richter ¹¹⁸ [2017]	M, 49 MMAS	anti-H ₁ , anti-H ₂ steroid	<ul style="list-style-type: none"> • fentanyl, lidocaine, propofol, rocuronium, heparine, protamine • pulmonary embolectomy 	6 hrs after ICU arrival: pruritus (chest, legs), vasoplegia	mast cell activation may have contribute to vasoplegia	<ul style="list-style-type: none"> • immediately and every 6 hrs during 24 hrs < N (N < ? ng/ml)
Unterbuchner ¹¹⁹ [2017]	M, 45 ISM	anti-H ₁ , anti-H ₂ steroid	<ul style="list-style-type: none"> • sufentanil, propofol, rocuronium, ceftriaxone, metronidazole, sugammadex • emergency laparotomy 	none		<ul style="list-style-type: none"> • after induction: 18 • after sugammadex: 20 (N < 11 ng/ml)
Chatterjee ¹²⁰ [2018]	F, 57 ISM	none	<ul style="list-style-type: none"> • propofol, atracurium • thyroidectomy (postponed) 	2 min. after atracurium: AP: 50/32 mmHg, HR: 153 b/min SpO ₂ : ↓, bronchospasm, erythema	atracurium allergy likely involved	<ul style="list-style-type: none"> • T0 + 45 min: > 200 • baseline: 161 (N < ? ng/ml)
Dewachter ¹²¹ [2018]	F, 62 ISM	none	<ul style="list-style-type: none"> • sufentanil, propofol, rocuronium, desflurane, sugammadex • appendectomy 	2 min after rocuronium: AP: 55/28 mmHg, HR: 130 b/min EtCO ₂ : 23 mmHg, SpO ₂ : 90%	rocuronium allergy proven	<ul style="list-style-type: none"> • T0 + 40 min: > 200 • baseline: 86 (N < 13 µg/l)

				generalized erythema		
Ishii ¹²² [2018]	F, 43 SM	anti-H ₂	<ul style="list-style-type: none"> • epidural (?), fentanyl, sevoflurane, vecuronium, MP flomoxef • colectomy (postponed) 	colon traction: ↑HR (?), severe hypotension, flushing (face, chest)	colon traction	ND
		anti-H ₁ , anti-H ₂ steroid	<ul style="list-style-type: none"> • 2nd surgery: same protocol, no antibiotic • colectomy 	none		ND

ISM: indolent systemic mastocytosis; MMAS: monoclonal mast cell activation syndrome

CSE: combined spinal epidural anesthesia; SA: spinal anesthesia; AP: arterial pressure; SAP: systolic arterial pressure, HR: heart rate

MDZ: midazolam; MTK: montelukast

MOF: multiorgane failure; ND: not done

Table 5: Drugs accepted and not recommended in mastocytosis

Family of drugs	Accepted	Not recommended
<i>Intravenous, inhalation and local anaesthetics</i>		
benzodiazepine	midazolam	
hypnotics	etomidate, ketamine, propofol, thiopental	
halogenated gases and nitrous oxide	desflurane, isoflurane, sevoflurane nitrous oxide	
local anaesthetics	amide-type, ester-type*	
<i>Neuromuscular blocking agents</i>		
depolarizing agent	suxamethonium	
steroidal agents	pancuronium, rocuronium, vecuronium	
benzylisoquinolines	cisatracurium	atracurium, mivacurium
<i>Reversal of neuromuscular blockade</i>		
anticholinesterase agent	neostigmine	
cyclodextrin	sugammadex*	
<i>Intravenous analgesics</i>		
opioids	alfentanil, fentanyl remifentanyl, sufentanyl	
morphine	requires titration	
analgesic	paracetamol (acetaminophen)	nefopam
<i>Other agents</i>		
antiseptics*	chlorhexidine, povidone-iodine	

plasma substitutes*	albumin, gelatin, hydroxyethylstarch	
miscellaneous	aprotinin* (topical glue), atropine ondansetron, oxytocin, protamine*	

* although there is no data concerning the use of these agents, there is no reason to avoid them

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Table 6: Retrospective case-series regarding the peri-operative and obstetric management in hereditary and acquired angioedema

Reference	Patient (n =) Phenotype	Study design	Type of procedure (n =)	Prophylaxis per procedure	Incidence of peri-operative angioedema per procedure
Bork ¹²⁸ [2011]	171 HAE	- monocentric - ?	- procedures: 705 - tooth extraction - local anaesthesia	<ul style="list-style-type: none"> • C1-INH: 128 (18%) • no prophylaxis: 577 (82%) 	<ul style="list-style-type: none"> • without prophylaxis: 21.5% (n = 124/577) - isolated facial angioedema: 88 - isolated laryngeal angioedema: 8 - facial and laryngeal angioedema: 28 • with prophylaxis: 12.5% (n = 16/128) - isolated facial angioedema: 9 - isolated laryngeal angioedema: 4 - facial and laryngeal angioedema: 3
Aygören-Pürsün ¹²⁹ [2013]	144 HAE	- monocentric - ?	- procedures: 335 - abdominal (113), ENT (71), gynecologic (58), orthopedic (45), other (48) - type of anesthesia: ?	<ul style="list-style-type: none"> • no prophylaxis 	<ul style="list-style-type: none"> • angioedema: 5.7% (n = 19/335) - site or region of surgery: 14 - other site or region of surgery: 2 - laryngeal: 3 (2 after ENT surgery, 1 after laparoscopy)

					<ul style="list-style-type: none"> • no event: 69.6% (n = 233) • missing data: 24.8% (n = 83)
Mac Beth ¹³⁰ [2016]	24 HAE: 13 AAE: 10 unknown: 1	- monocentric - 2000-2014	<ul style="list-style-type: none"> - procedures: 38 - general surgery (15), urology (6), endoscopy (4), orthopedic (2), other (11) - GA with tracheal intubation 	<ul style="list-style-type: none"> • androgen: 24 (HAE: 14, AAE: 9, unknown: 1) • C1-INH: 3 (HAE: 2, AAE: 1) • androgen + C1-INH: 5 (HAE) • androgen + FFP: 2 (HAE) • no prophylaxis: 4 (AAE) 	<ul style="list-style-type: none"> • with prophylaxis (androgen + FFP) - oral angioedema: 2.6% (n = 1)
Gonzalez-Quevedo ¹³¹ [2016]	61 HAE	- 5 centres - 2006-2010	<ul style="list-style-type: none"> - procedures: 125 - cesarean section: 15 (GA: 9, EPI: 6) - vaginal delivery: 110 (GA: 8, EPI: 25, LA: 3, no anaesthesia: 74) 	<ul style="list-style-type: none"> • C1-INH: 14 (11%) - cesarean section: 5 - vaginal delivery: 9 • no prophylaxis: 111 (89%) 	<ul style="list-style-type: none"> • cesarean section: none • vaginal delivery: 5.4% (n = 6/110) - mild local symptoms

AAE: acquired angioedema; HAE: hereditary angioedema; C1-INH: C1-inhibitor concentrate; FFP: fresh frozen plasma

EPI: epidural anaesthesia; GA: general anaesthesia; LA: local anaesthesia

ENT: ear, nose and throat