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*Review*

# Recognition, treatment, and prevention of perioperative anaphylaxis: a narrative review

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**Abstract:** Perioperative anaphylaxis events are allergic reactions which occur in the perioperative period when patients are exposed to a multitude of agents, received anesthesia, and undergo a procedure. These reactions are rare and can be life-threatening, with the common signs being hypotension, hypoxia, elevated airway pressures and urticaria. Perioperative anaphylaxis can be mediated by immunoglobulin E (IgE) or non-IgE mechanisms. Globally, the incidence of reactions and frequency of specific triggers varies considerably. Perioperative anaphylaxis events often result in discontinuation of surgery, extended hospital stays, unanticipated intensive care admissions and increased morbidity and mortality. Common causative agents include neuromuscular blocking agents (NMBA's), beta-lactam antibiotics, chlorhexidine, and latex. The primary treatment of perioperative anaphylaxis is removal of the offending agent, epinephrine, and adequate fluid resuscitation. Post-operative workup involves serial serum tryptase measurements, skin testing, in-vitro testing and challenges to determine the culprit agent. Several countries including the UK, Spain, France, Australia, and New Zealand have established guidelines, reporting systems, and specialized clinics dedicated to perioperative hypersensitivity reactions. Future efforts should address diagnostic challenges as well as increasing awareness of other perioperative anaphylaxis triggers. This narrative review will provide an overview of the epidemiology, diagnosis, management, and prevention of perioperative anaphylaxis events.

**Keywords:** perioperative; anaphylaxis; hypersensitivity; allergy; anesthesia

**Abbreviations:** ACE: Angiotensin converting enzyme; ACLS: Advanced cardiovascular life support; ANZAAG: Australian & New Zealand Anaesthetic Allergy Group; ICU: Intensive care unit; IgE: Immunoglobulin E; IM: Intramuscular; IV: Intravenous; GERAP: Groupe d'etude des reactions anaphylactoides peranesthesiques; MRGPRX2: Mas-related G-protein coupled receptor member X2; NAP6: 6th National Audit Project; NMBA: Neuromuscular blocking agents; $T_H2$: T helper 2

## 1. Introduction

Anaphylaxis events in the perioperative period are systemic hypersensitivity reactions due to IgE-mediated or non-IgE mechanisms. Both mechanisms result in mast cell degranulation resulting in systemic symptoms of hypotension, tachycardia/bradycardia, hypoxemia, bronchospasm, urticaria, and angioedema. For brevity, this review will use the term "perioperative anaphylaxis" to include both IgE-mediated reactions and non-IgE reactions.

Anaphylaxis reactions in the perioperative environment are rare with global variation in reported incidence between 1:10000–1:11000 and a mortality rate between 1.4–4.75% as outlined in Table 1 [1–6]. Perioperative anaphylaxis events have significant negative impacts on patient outcomes causing surgical abandonment, prolonged hospital stays, unanticipated intensive care admissions, increase morbidity, and create angst for future anesthetic exposure [7]. Most literature regarding perioperative anaphylaxis comes from France, Australia, and the United Kingdom, as these countries have both reporting systems and dedicated perioperative anaphylaxis clinics [3,8,9]. This review will provide an overview of the epidemiology, pathophysiology, triggers, clinical presentation, treatment, and workup of perioperative anaphylaxis summarized from international literature.

## 2. Materials and methods

Searches were conducted via PubMed, MEDLINE, Google Scholar, and Web of Science using combinations of the keywords: "perioperative anaphylaxis", "intraoperative anaphylaxis" "anaphylaxis", "anaphylactoid", "allergy", "hypersensitivity", "general anesthesia", and "anesthesia". For example, search queries included "anaphylaxis AND general anesthesia", "anaphylactoid AND anesthesia", and "allergy AND anesthesia". Secondary combinations were combined with individual drugs: "antibiotics", "cefazolin", "beta lactam", "Neuromuscular blocking agents", "Rocuronium", "succinylcholine", "atracurium", "sugammadex", "chlorhexidine", "patent blue", "latex", "local anesthetic" AND "anaphylaxis". Abstracts were screened by EL, JR, and JF for content and articles were eligible if they were published in or prior to December 2021. Additional articles were found by searching through references listed in eligible papers.

## 3. Incidence

Several studies have undertaken the challenging task of examining the incidence of perioperative anaphylaxis. Not only are these events rare, but many of these studies rely on voluntary reports from physicians [10] or referrals to specialized perioperative allergy clinics [9], likely leading to

underestimates of the true incidence. As a result of true differences in incidence or variations in study design, the reported incidence of perioperative anaphylaxis differs from geographical region to region as summarized in Table 1. The 6th National Audit Project (NAP6), a large, nationwide survey based study conducted in the UK estimates the incidence of anaphylaxis to be 1 in 11 000 anesthetics [5]. An 8 year, national-scale study done by the Groupe d'etude des reactions anaphylactoides perianesthesiques (GERAP) group in France reported the incidence of perioperative anaphylaxis to be 1 in 10000 procedures [9]. In Western Australia, a 9-year study estimates incidence at 1 in 11000 [3]. A Japanese survey conducted between 2009–2011 reported an incidence of 1 in 18600 [11], while a more recent paper based on retrospective, multi-center data from 2012–2016 proposes a higher incidence of 1 in 2778 [12]. Reactions may be more frequent in Spain, where a prospective study capturing the years 2008–2010 has reported an incidence of 1 in 737 anesthetic procedures [13]. A retrospective study done in the US between 2005–2014 estimates incidence at 1 in 6536 procedures [14]. In France, the incidence of reactions is roughly 1 in 6455 for females but 1 in 18000 for males [9]. Female predominance has also been observed in the US, where one study reported 63% of perioperative anaphylaxis cases occurred in females [15]. It has been hypothesized that sex hormones may be involved in the potentially higher incidence found in females. In the aforementioned French study, the increased incidence of perioperative anaphylaxis was only observed in adults [9]. Estrogen is an immunomodulator that promotes $T_H2$ responses [16] and has also been shown to enhance IgE-associated mast cell activation [17]. However, the incidence of perioperative anaphylaxis was not significantly different between males and females in a 2015 US study [15] and a 50/50 female to male ratio has been reported in Spain [13].

**Table 1.** Reported incidence and mortality of perioperative anaphylaxis from countries that have reporting systems.

| | Australia [3] | France [9] | UK [5] | USA [14] | Japan [11] |
|---|---|---|---|---|---|
| Incidence | 1:11000 | 1:10000 | 1:11752 | 1:6536 | 1:18600 |
| Mortality | 0–1.4% | 4% | 3.8% | 4.0% | 4.75% |

## 4. Morbidity and mortality

While perioperative anaphylaxis events are uncommon, they are associated with significant morbidity. In the UK's NAP6 study, perioperative anaphylaxis events resulted in a median unplanned hospital stay of one day, ranging to a longest stay of 150 days [7]. A multi-center US study reported a three day increase of median hospital stay for patients with perioperative anaphylaxis compared to those without [14]. Unanticipated intensive care admission were also a common outcome ranging from 38% in the UK [7] to 71% in one US based study [18]. The most common long term morbidity outcome reported in the NAP6 was anxiety about future anesthetic use, with associated post-traumatic stress disorder in three cases [7]. A small number of cases resulted in serious sequelae such as myocardial infarction, acute kidney injury, new shortness of breath, and transient ventricular dysfunction [7,18].

One of the biggest decisions to be made in the event of perioperative anaphylaxis is whether to continue or abandon surgery. The intended surgery was not started in over half of the cases reported in the NAP6 [7], while 39% of surgeries were aborted due to perioperative anaphylaxis in a US study [18]. Similarly, one review reported surgery was abandoned in 39% of chlorhexidine-associated

perioperative anaphylaxis events [19]. In some instances, the benefits of continuing surgery may outweigh the risk even in the face of severe anaphylaxis. One case report outlined successful renal transplant after severe intraoperative anaphylactic reaction to cefazolin [20]. In this patient, the decision to proceed with transplant was made as the donor kidney was an excellent immunological match [20].

While anaphylaxis is a life-threatening condition, mortality due to perioperative anaphylaxis is rare across the globe. The outcomes of anaphylaxis events in the community are much more variable, depending on the personnel and equipment available. The perioperative setting is equipped with Anesthesiologists who are experts in the art of monitoring and resuscitation and are equipped with the necessary equipment for resuscitation. The 9-year Western Australian aforementioned estimates mortality at 0–1.4% of perioperative anesthesia cases (number of deaths due to perioperative anesthesia divided by number of cases of perioperative anaphylaxis in the study period) [3], while reported mortality in other countries is slightly higher—France at 4.1% [21], the UK at 3.75% [5], the US at 2% [14], and Japan at 4.76% [22]. The NAP6 study reported the incidence of death from perioperative anaphylaxis to be 1 in 313000 procedures over 1 year [5]. A 10-year study done in US centers reported the incidence of fatal and near-fatal perioperative anaphylaxis to be 1.26 in 100000 procedures [14]. Mortality rates are likely similarly low in other regions, though more studies should be done to elucidate local trends.

## 5. Mechanisms of perioperative anaphylaxis

Perioperative anaphylaxis events can be mechanistically divided into IgE-mediated reactions or non-IgE mediated reactions [1]. As depicted in Figure 1, IgE-mediated reactions involve pre-sensitization to a specific allergen, with IgE production and binding on mast cell and basophil membranes [23,24]. Repeat allergen exposure leads to IgE crosslinking with subsequent mast cell and basophil release of mediators such as histamine, tryptase, proteoglycans, and carboxypeptidase A [24]. Other mediators produced further downstream include prostaglandins, leukotrienes, heparin and platelet activating factor [24]. Non-IgE mediated reactions involve mast cell and basophil degranulation by non-IgE mechanisms meaning there is no requirement of previous exposure [23]. The clinical features of anaphylaxis reactions are predominantly attributable to histamine, leukotrienes, and prostaglandin D2, though many other mediators are involved [23,24]. Histamine induces vasodilation, increased vascular permeability, and has cardiovascular effects including hypotension and cardiac arrest [23,24]. Leukotrienes stimulate bronchoconstriction and increase vascular permeability, while prostaglandin D2 is implicated in both bronchoconstriction and vasodilation [24]. Non IgE mechanisms are poorly understood, though factors such as C5a receptor, MRGPRX2, and C3a pathways have been implicated [25,26]. Regardless of the mechanism, perioperative IgE mediated and non-IgE mediated reactions present similarly and alone cannot be distinguished clinically during the initial reaction [5,9,15]. However, post reaction the mechanism of anaphylaxis can often be speculated once a culprit agent is discovered. Most studies report IgE mediated anaphylaxis if a culprit agent was indeed discovered. Therefore, non-IgE mechanisms were suspected if a culprit agent was not discovered [9]. The proportion of IgE-mediated vs non-IgE mediated reactions varies globally. Approximately 70% of perioperative anaphylaxis reactions are IgE mediated in France [9] and Norway [27]. In other countries, reactions are roughly divided between IgE and non-IgE mechanisms, such as the USA [15,18] and Spain [13,28]. These numbers can often contain error as the identification

of culprit causes can be influenced by allergy testing, omission of agents exposed in the operating room, or false negatives that can occur.

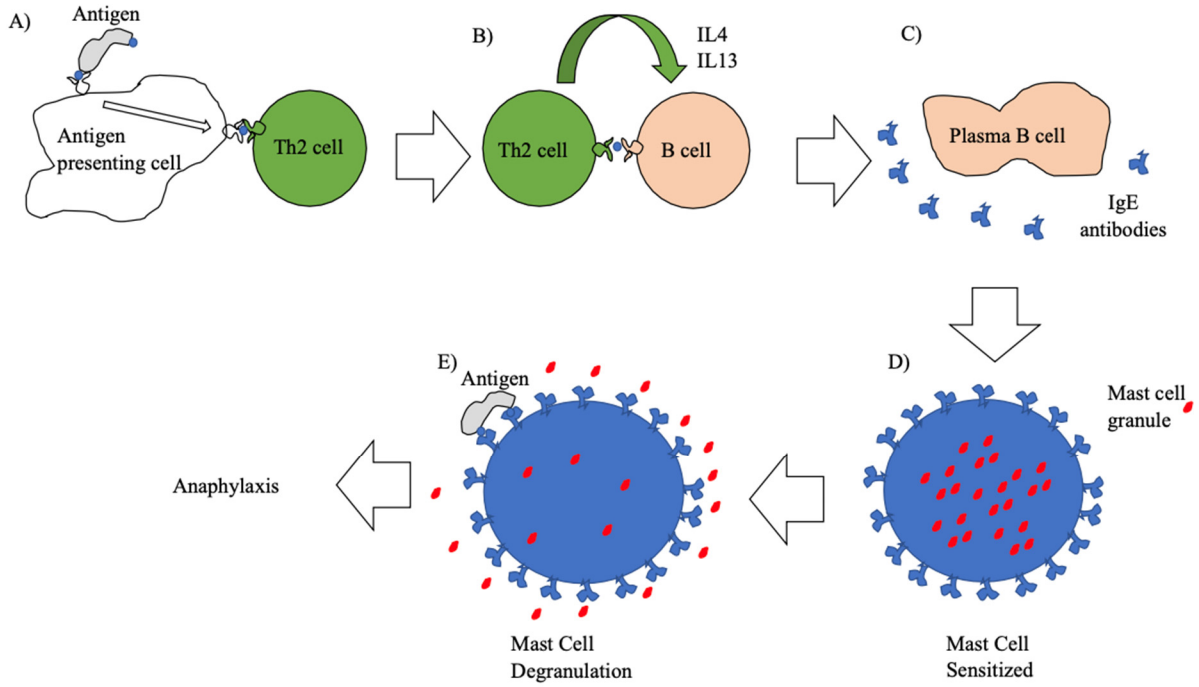


**Figure 1.** Simplified pathophysiology of Anaphylaxis: IgE-mediated reactions involve pre-sensitization to a specific allergen, with IgE production and binding on mast cell and basophil membranes (A) An antigen is recognized by an Antigen Presenting Cell and presents it to the T Helper 2 cell (TH2). (B) The TH2 cell will present the antigen to a B cell and activate by interleukins. (C) The B cell will proliferate to become a plasma B cell through class switch mechanisms it produces IgE antibodies. (D) IgE antibodies will bind to the high affinity IgE receptors on surface of mast cell. This process known as sensitization. The mast cell granules contain multiple chemicals that trigger anaphylaxis. (E) Mast cell recognize antigen re exposure by the preformed IgE receptors and release mast cell granules that cause symptoms of anaphylaxis.

## 6. Clinical features and classification

Clinical manifestations of anaphylaxis in the perioperative period can be difficult to detect as patients are under general anesthesia. The clinical features of perioperative anaphylaxis reactions are mainly cardiovascular, respiratory, and cutaneous (Table 2). Hypotension is reported in most if not all patients [5,15]. Bronchospasm is another common sign, present in 49% of cases in the UK [5] and 43% in the USA [15]. There, is some speculation on whether patients with an IgE-mediated reaction present more severely and were more likely to have elevated levels of tryptase, a mast cell mediator [9]. The aforementioned French study by Mertes and colleagues found differences in the occurrence of bronchospasm (41% in IgE vs 19% in non-IgE mediated reactions), cardiovascular symptoms (54% in IgE vs 11% in non-IgE mediated reactions), and cutaneous manifestations (70% in IgE-mediated

reactions vs 95% in non-IgE reactions) [9]. However, it cannot be concluded that these clinical presentations can reliably differentiate between mechanisms of anaphylaxis.

**Table 2.** Clinical features of perioperative anaphylaxis reactions.

| Cardiovascular | Respiratory | Cutaneous |
|---|---|---|
| Unexplained hypotension | Hypoxemia | Urticaria |
| Tachycardia<br>Bradycardia | Bronchospasm | Angioedema |
| Arrhythmia | Laryngeal edema | Flushing |
| Cardiac arrest | Difficult ventilation | |
| | Respiratory arrest | |

Further, presentation of anaphylaxis can be further complicated by co-morbidities. For instance, in the NAP6, bronchospasm was more likely to be the presenting feature of anaphylaxis in asthmatics and obese patients [5]. Similarly, in the same study, hypotension was more commonly a presenting feature in patients with coronary artery disease, on beta-blockers, or on angiotensin converting enzyme (ACE) inhibitors [5].

The recognition and diagnosis of perioperative anaphylaxis is challenging when a patient is under general anesthesia and undergoing a surgical procedure as the differential diagnosis can be broad. Confounders, such as drugs with cardiovascular effects, respiratory disease, and anesthesia related physiological disturbances can obscure features of a perioperative anaphylaxis reaction, further complicating initial recognition and diagnosis in the perioperative period [29]. The UK audit determined that 25% of anaphylaxis had a delayed recognition because of a wide differential diagnosis that included: tension pneumothorax, pulmonary embolism, $CO_2$ embolism, high neuraxial sympathectomy, uncontrolled hemorrhage, and primary cardiac event [7]. Additionally, pharmacological effects of medications administered for routine general anesthesia can cause hypotension, tachycardia, and bradycardia which can delay recognition. Urticaria and other cutaneous features are difficult to detect in a draped patient, while subjective symptoms such as pruritus and nausea are impossible to identify when patients are unconscious under general anesthesia. As such, an international group of Anesthesiologists, Allergists, and Immunologists have proposed a scoring system to classify the likelihood of a perioperative event representing an immediate hypersensitivity reaction [29]. A numerical score is calculated based on cardiovascular, respiratory, and dermal/mucosal features as well as the timing of the suspected reaction in relation to possible intravenous (IV) triggers, with the option of incorporating tryptase measurements [29]. Reactions are then classified as unlikely, possible, likely, very likely, or almost certain to be an immediate perioperative hypersensitivity reaction [29]. For grading the severity of anaphylaxis reactions, a classification that is widely used is the Ring and Messmer system [30]. The original system includes grades I to IV, with grade I characterized by cutaneous symptoms and grade IV defined by circulatory or respiratory arrest [30]. A modified version of the Ring and Messmer classification used by the Scandinavian perioperative anaphylaxis management guidelines extends it to grade 5, representing death [31]. A modified version of the Ring and Messmer classification is used by the International Suspected Perioperative Allergic Reaction group [32]. A consensus classification for severity grading of perioperative anaphylaxis reactions would not only guide management but would also facilitate

treatment algorithms and other areas of research. As such, multidisciplinary, multinational efforts should be made to create a single, widely used stratification system.

The timing of anaphylaxis presentation in the perioperative setting is quite variable. One Japanese study observed that 29% of anaphylaxis reactions presented during induction of anesthesia and 68% during anesthesia maintenance [22]. In contrast, a study conducted in Spain reported that most cases presented during induction (57%) compared to 20% presenting during the course of the procedure and 23% in the PACU [13]. The UK's NAP6 study found that 58% of perioperative anaphylaxis cases occurred in the operating room and that in 83% of cases, anaphylaxis occurred within 10 minutes of exposure to the trigger [33]. Interestingly, this study noted that the speed of anaphylaxis onset varied with the causative agent—antibiotics and neuromuscular blocking agents (NMBAs) resulted in fast onset whereas chlorhexidine or patent blue dye-triggered reactions had a slow onset likely related to route of exposure [33]. The variability in international reported onset of anaphylaxis is potentially attributed to the differing prevalence of triggers internationally. In addition, the timing of anaphylaxis can be confounded by delayed recognition and lower severity of anaphylaxis. Agents that patients are exposed to vary over the course of anesthesia administration, thus, anaphylaxis would present at different stages of surgery depending on the trigger.

## 7. Triggers

### *7.1. Antibiotics*

Antibiotics are a common trigger of perioperative anaphylaxis reactions. In the UK, Spain, and the United States, antibiotics account for roughly half of perioperative anaphylaxis events with an identified cause [5,13,15,18,28]. Beta-lactams account for 90% of antibiotic-induced anaphylaxis cases in one US-based study, of which, Cefazolin and co-amoxiclav were the most common [5,15,18]. Notably, 89% of antibiotic-induced cases in the UK were attributed to either co-amoxiclav or teicoplanin [5], though these agents only accounted for 22% and 8.9% of all perioperative antibiotic exposures respectively [34]. In the NAP6 Allergen survey, the decision to use teicoplanin or vancomycin was influenced by the patients allergy, accounting for the high rate of teicoplanin anaphylaxis in the UK [34]. The variations demonstrate that the antibiotic used as prophylaxis in the region, resulted in the highest rates of sensitization. Therefore, the rates of anaphylaxis to antibiotics in question would depend on the population's exposure.

### *7.2. Neuromuscular blocking agents*

Another common trigger of perioperative anaphylaxis are NMBA's. In France, the incidence of IgE-mediated reactions to NMBA's is estimated at 184 per million anesthetics, representing 58% of all identifiable triggers [9]. Rates of NMBA-associated perioperative anaphylaxis are lower in the US, UK, and Spain, where NMBA's account for 20–30% of identified triggers [5,13,15,28]. Some studies suggest a higher incidence of anaphylaxis with rocuronium than with other NMBA's [35,36]. Succinylcholine and atracurium are also commonly implicated NMBA's [5,9]. Interestingly, while multiple NMBA's have been shown to provoke mast cell activation through non-IgE mechanisms [25], atracurium has been shown to be a particularly potent inducer of mast cell activation and histamine release [25,37]. NMBA-associated cases of anaphylaxis also illustrate the role of sensitizing exposures

and allergic reactions in the case study of pholcodine. In the mid 2000's, Florvaag and colleagues noted that despite their shared border, anaphylaxis reactions to NMBAs were six times more frequent in Norway compared to Sweden [38]. Testing found that IgE activity to a variety of household chemicals did not differ between the two countries with the sole exception of pholcodine, which 6% of healthy Norwegian sera and no Swedish sera were IgE-sensitized to [38]. Pholcodine and its parent molecule morphine are both monovalent for the quaternary ammonium ion [39] while NMBAs are bivalent for the same ion [40]. Studies have demonstrated that quaternary ammonium and tertiary amine groups are allergenic epitopes recognized by IgE [41]. At the time of 2005 Florvaag study, pholcodine was widely accessible in Norway as a component of over-the-counter cough suppressants but was not available in Sweden [38]. The structural link between pholcodine and NMBAs as well as the cross-border difference in pholcodine exposure proved to be damning evidence—in 2007, pholcodine was pulled from the Norwegian market and has resulted in a reduction of cases of anaphylaxis to rocuronium [6,42].

### *7.3. Sugammadex*

Sugammadex is a cyclodextrin molecule which acts by binding ammonium neuromuscular blocking agents such as rocuronium and vecuronium. The rates of anaphylaxis for sugammadex vary substantially in the literature with a single case reported in the UK data from NAP6 ranging to Japan demonstrating sugammadex as one of the top three leading triggers of perioperative anaphylaxis [5,43]. The product monograph from Merck quotes the hypersensitivity incidence is 0.3% based on one prospective study of healthy volunteers [44]. However, this prospective study has received criticism based on the inclusion of all hypersensitivity reactions, including only skin reactions, and no confirmatory allergy testing. Secondly, the study used the highest dose recommended of 16 mg/kg, and raises the suspicion that higher doses led to increased rates of reaction [45]. A retrospective Japanese study recently showed the incidence of sugammadex anaphylaxis was 0.02%, making it the leading cause of perioperative anaphylaxis [12,43]. One important aspect of anaphylaxis resulting from sugammadex, which is still early in hypothesis testing, seems to be the exact mechanism. Since sugammadex is unique in that it encapsulates rocuronium, there is a change in structure to the potential allergenic moiety [46]. Therefore, there is inconclusive evidence to the exact structure which causes anaphylaxis whether it is sugammadex alone or sugammadex complexed with rocuronium.

### *7.4. Latex*

Natural rubber latex, made from *Hevea brasilensis*, is widely used in many types of medical devices. Latex allergy became prominent in the 1980's and peaked during the 1990s, likely due to increased use of powdered gloves and airborne sensitization. From 1997–2004, the estimated incidence of latex-associated IgE-mediated perioperative reactions in France was 59.1 reactions per 1 million anesthetics [9]. Risk of latex allergy is elevated in certain populations, such as children with spina bifida [47], healthcare workers [48], and others with frequent occupational latex exposure [49]. Latex allergy is also associated with hypersensitivities to certain foods, commonly kiwi, banana, avocado, and potato, in a phenomenon known as latex-fruit syndrome [50–53]. Mechanistically, this is thought to be due to IgE cross-reactivity, as several studies have identified IgE cross-reactive to both latex and fruit allergens in the serum of patients with latex-fruit syndrome [51,54]. The major latex allergens

implicated in latex-fruit syndrome are hevein, beta-1,3-glucanase, and patatin-like protein, while major plant allergens include chitinases, and patatin [50,52,53]. In recent years, the incidence of latex-associated reactions has diminished as a result of decreased latex exposure. In a 2014–2015 European study, there was only one latex-triggered anaphylaxis event that occurred out of roughly 31000 pediatric anesthetic procedures [55]. Additionally, there were no reports of latex-induced perioperative anaphylaxis in the UK [5]. Preventative strategies implemented include the use of latex-free gloves, reducing glove protein content, and banning powdered gloves which has indeed translated into decreasing rates of latex-triggered perioperative events as well as latex allergy [56–59].

### *7.5. Dyes*

Patent blue dye is also known to cause perioperative anaphylaxis and is responsible for 5% of cases in the UK; Nine cases were identified, all of which were females and most episodes occurred during breast cancer surgery [5].

### *7.6. Chlorhexidine*

Chlorhexidine has been associated with increasing rates of anaphylaxis and is the third leading cause of anaphylaxis in the UK [5]. While some patients may experience mild cutaneous reactions, others can suffer near fatal anaphylactic reactions to chlorhexidine [60–62]. These hypersensitivity responses can be very severe and may be accompanied by protracted hypotension or cardiovascular collapse, which often require aggressive treatment with epinephrine and some reports of venoarterial extracorporeal membrane oxygenation [63]. What makes chlorhexidine especially risky is that it may not be suspected as the causative agent due to its hidden nature in perioperative equipment, such as central lines, delayed symptom onset and the potential for anaphylaxis to occur even after previous repeated uneventful administration [64].

### *7.7. Other agents*

Other, less typical triggers include hypnotics, colloids, opioids, and local anesthetics [6,59]. Of note, some opioids are able to induce histamine release from mast cells independent of IgE [65], though opioid-provoked anaphylaxis events are often mislabeled as IgE-mediated reactions [6].

## 8. Immediate management and resuscitation of perioperative anaphylaxis

Professional societies of Allergists and Anesthesiologists in countries such as France [66], Australia and New Zealand [67], Spain [68], the UK [32], and Scandinavia [31] have published guidelines for the treatment and management of suspected perioperative anaphylactic reactions. However, there remains discrepancy between many recommendations. Recently in 2019, a consensus from 26 international experts was conducted to provide the most updated recommendations on management which is summarized in Figure 2 [32].

Once the diagnosis is suspected, perioperative anaphylaxis requires immediate aggressive treatment and effective communication with the entire perioperative team. First, the suspected trigger should be withdrawn, and immediate resuscitative measures initiated including: administration of 100%

oxygen, definitive airway support, epinephrine, and adequate fluid resuscitation [31,66–68]. Cardiopulmonary resuscitation should be initiated according to Advanced Cardiovascular Life Support (ACLS) guidelines if indicated [32,66–68].

Discontinuation of the triggering agent is one of the first steps that should be undertaken in the resuscitation of anaphylaxis. Up to 25% of the cases from the data in the UK demonstrated that the agent was not discontinued in the management of intraoperative anaphylaxis [7]. Calling for help early in the treatment of hemodynamically unstable patients under general anesthesia is a recognized step in managing any intraoperative emergency. However, it cannot be highlighted enough: the cognitive overload during resuscitation can be assisted and delegation of tasks including determination of the triggering agent and ensure its discontinuation. The Nap 6 study went on to show that the quality of resuscitation was adequate in only 46% of cases based on the timing of recognition, administration of epinephrine, and adequacy of fluid administration with correlation to adherence of published guidelines [7]. It is therefore important to highlight the use of cognitive aids and checklists during resuscitation to improve efficiency and adequacy of resuscitation.

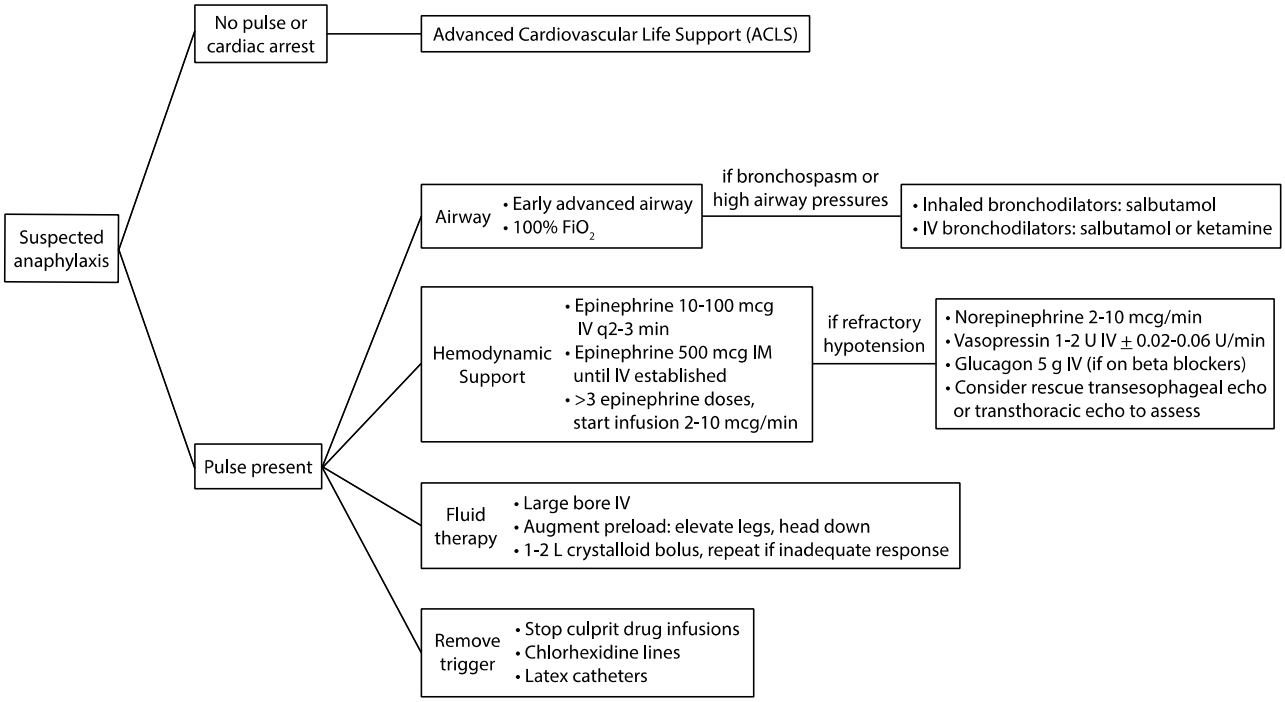


**Figure 2.** Immediate management of perioperative anaphylaxis summarized from international experts to provide the most updated recommendations on management [31,32,66–68].

### *8.1. Epinephrine*

Epinephrine must be administered promptly, with dosage titrated to severity of the reaction and response to therapy. French, Spanish, and Australian & New Zealand Anaesthetic Allergy Group (ANZAAG) guidelines grade severity of anaphylaxis from I to IV based on the Ring and Messmer classification mentioned previously, with Grade I representing mild reactions, Grade II moderate, Grade III life-threatening, and Grade IV defined by cardiac and/or respiratory arrest [66–68]. The dose of epinephrine varies between recommendations internationally due to the lack of randomized controlled trials and reliance on retrospective review and case reports. However, consensus and expert opinion have recommended initial epinephrine doses ranging from 10–30 microgram IV bolus for Grade II reactions and 50–200 microgram IV bolus for Grade III reactions [32,66–68]. For Grade IV reactions, the UK guidelines recommend an initial epinephrine dose of 1 mg IV with repeated 1 mg doses according to ACLS guidelines. If escalating doses of epinephrine are required, defined as three repeated doses, an IV infusion starting at 0.05–0.1 microgram/kg/min are suggested by the French, ANZAAG, UK, and Scandinavian guidelines [31,32,66,67]. Epinephrine can be given intramuscularly administered if IV access is not available, with suggested dosing ranging from 0.3–0.5 mg [66], and 0.5 [67]–0.8 mg [31].

### *8.2. Intravenous fluid therapy*

Intravenous fluid therapy is a mainstay of perioperative anaphylaxis treatment, as vasodilation, pooling of splanchnic circulation, and leaky capillaries result in large fluid shifts and subsequent hypovolemia [31,32]. The UK guidelines base initial crystalloid bolus volumes by reaction severity: 0.5 L for Grade II reactions, 1 L for Grade II reactions, and fluid therapy as per advanced life support standards for Grade IV reactions [32]. French, ANZAAG, and Scandinavian guidelines recommend crystalloid dosing at 20–30 mL/kg [31,66,67]. Further fluid therapy is dictated by clinical response and the underlying pathophysiology but guidelines agree on liberal fluid resuscitation [31,32,67]. Advanced methods to assess fluid responsiveness include transthoracic or transesophageal echocardiography to determine parameters such as left ventricle end diastolic volumes, ventricular function, and assessing for any confounding causes of hemodynamic instability [32].

### *8.3. Other management modalities*

Hypotension refractory to epinephrine may require the use of adjuvant cardiovascular support such as norepinephrine and vasopressin [31,32,66–68]. In patients on beta-blockers, glucagon can be given if there is no response to epinephrine [31,66–68]. Bronchospasm present without hypotension or not responsive to epinephrine should be treated with salbutamol either inhaled or as an IV infusion [32,66–68]. Leg elevation or changing head level of the operating table may also be helpful to increase preload [31,32,66,67]. Currently there is no strong recommendations for the use of sugammadex during resuscitation due to the risk of confounding the diagnosis and causing further hypersensitivity reactions [32,46]. Management of perioperative anaphylaxis in pregnant patients has additional measures such as left uterine displacement and consideration of postmortem caesarean section if indicated [66,67].

Intravenous antihistamines, such as dexchlorpheniramine or any locally available IV formulation, can be given for symptomatic management of urticaria, angioedema, pruritus and are indicated for mild grade I reactions [32,66,68] or to prevent relapse of symptoms after the initial reaction [31,67]. It should be noted that no studies have demonstrated improved outcomes after antihistamine use, but antihistamines have not been associated with harm either [7,32]. Corticosteroids may also be given for prophylaxis of delayed symptoms but there is limited evidence of outcome benefit [31,32,66,68]. Ultimately, the administration of corticosteroids and antihistamines are not a priority and should only be given once the patient is adequately resuscitated.

Once the patient is stabilized, the decision to proceed or cancel surgery, if not already decided on, should be made. The patient will require close postoperative monitoring, with consideration given to 24-hour ICU monitoring for severe reactions [31,67,68].

## 9. Post-operative workup

Generally, workup of suspected perioperative anaphylaxis reactions includes referral to an Allergist with expertise in drug allergy [69]. Referral should be made for all grade II–IV reactions to a specialized anesthetic allergy testing center (if available) for further investigation of the reaction as well as reporting to the appropriate pharmacovigilance centers [31,66–69]. Several countries, including France [9], the UK [8], Australia [3], and Canada [70] have clinics specialized in perioperative hypersensitivity reactions, staffed by both Allergists and Anesthesiologists. In addition to diagnosis and management, these dedicated clinics also facilitate the reporting of such events on the national level and constitute one of the predominant reasons why extensive epidemiological studies have been conducted in their respective countries. Investigation typically consists of a review of anesthesia charts, skin testing, tryptase measurements, in vitro testing, and drug provocation testing [32]. Once the causative agent(s) are identified, strategies for trigger avoidance and suggestions of suitable alternatives are prepared for future surgery, if needed [69]. Repeat anesthesia is uneventful in the majority of patients who undergo appropriate workup in drug-allergy clinics [71].

### *9.1. Serum tryptase*

Serum tryptase is a marker of mast cell degranulation that should be sampled acutely at the time of reaction and again at baseline for the purposes of investigation and workup [31,32,66–68]. Elevated serum tryptase above baseline levels is highly suggestive of mast cell degranulation and thus anaphylaxis, though normal levels do not necessarily exclude the possibility of anaphylaxis as false negatives can occur [32,68,72]. It is thought that elevated serum tryptase is more indicative of IgE-mediated anaphylaxis [73] but can be present in both IgE and non-IgE-mediated reactions [72]. Elevated baseline tryptase levels can also help identify mast cell disorders [32]. Serum tryptase peaks roughly 1 hour after an anaphylaxis event [31,72], with the timing of measurements varying from region to region. French guidelines suggest tryptase should be sampled 15–60 minutes post reaction for grades I–II and 30 minutes to 2 hours for grades III – IV [66], while Spanish and UK guidelines suggest sampling immediately after initial treatment, then repeated at 2 hours and 24 hours [68,72], and ANZAAG guidelines at 1 hour, 4 hours, and >24 hours [67]. In our centre, we routinely obtain an acute tryptase 30 minutes to 2 hours after the event and a baseline tryptase 24 hours after the event.

Absolute cut-offs are falling out of favor, with guidelines moving towards defining elevations as an individualized formula ( 2 + 1.2× increase above baseline levels) [32,68,69].

### *9.2. Skin testing*

Skin testing for diagnosis of IgE-mediated allergic reactions is indicated in almost all investigations of perioperative anaphylaxis reactions [32,68,69,72,74]. Most guidelines recommend skin testing be undertaken 4–6 weeks after the reaction at a specialist center [31,66,68]. In skin prick testing, a drop of diluted concentration containing the allergen in question is placed on the skin then pricked into the epidermis with a lancet [31,72,74]. Intradermal testing involves intradermal injection of the allergen and is more sensitive but less specific than skin prick testing [72]. The results are read in 15–20 minutes for skin prick tests and 20–30 minutes for intradermal tests [72], with a wheal and flare response representing a positive result [31,74]. Skin testing is most useful for NMBA's, antibiotics, and latex [68,72]. The dilutions and final concentrations of allergen used vary internationally but have been outlined in Spanish, French, and ANZAAG guidelines [66,68,74]. The heterogeneity in the testing concentrations used by different centres, cause uncertainty when comparing the incidence of triggers among different regions.

### *9.3. Further testing*

Further testing can supplement skin testing. Specific IgE antibodies can be measured for latex, chlorhexidine, succinylcholine, and selected antibiotics, but the sensitivity and specificity of these assays vary [32,68,72]. Basophil activation tests can also be used but is not widely available [32,68,74]. Drug provocation testing is the gold standard in diagnosis of drug allergy but is rarely used in the workup of perioperative anaphylaxis given the nature of the drugs investigated and requirement for cardiorespiratory monitoring [31,66,68]. The decision to carry out provocation testing requires careful risk-benefit analysis, informed consent, and facilities with personnel capable of managing cardiopulmonary events that may occur [32,68].

## 10. Prevention

Prevention of perioperative anaphylaxis begins with awareness of the issue. Anesthesiologists, as the first ones to encounter and manage perioperative reactions, are a crucial group to target. The UK's NAP6 project surveyed over 11000 anesthetists to assess their current perception of perioperative anaphylaxis [33]. 76% of anesthetists reported seeing a case of perioperative anaphylaxis during their career, with a median of two cases per respondent [33]. 4% of respondents saw a death related to perioperative during their career, roughly equivalent to one death per 311 years of practice [33]. Notably, 26% of anesthetists reported avoiding specific agents due to concerns about perioperative anaphylaxis—the most common reason cited was personal or colleague experience with such an event [33]. Frequency of agent avoidance did not always correlate with the proportion of reactions caused by the agent. For example, only 0.1% of respondents reported avoiding chlorhexidine even though it is suspected of precipitating 1 in 25 reactions [33]. Of the 18 chlorhexidine-triggered cases included in the NAP6 report, 3 of the cases were deemed avoidable via history taking [33]. Thus,

education of anesthesiologists on best practices could limit provocative exposures in the operating room and is a crucial first step in prevention.

Knowledge of common triggers, supported by epidemiological studies, could also lead to large-scale changes in policies and regulations. The pholcodine case of Norway illustrates how links between sensitization and anaphylactic outcomes can be identified and changed through national regulatory action. Three years after the withdrawal of pholcodine from the Norwegian market, the number of perioperative anaphylaxis reactions to NMBA decreased to almost half of the pre-withdrawal numbers [42]. As mentioned previously, reactions to latex, historically a leading cause of perioperative anaphylaxis, have also decreased in recent years due to institutional regulation of latex exposure [59]. A potential agent to target for prevention of perioperative anaphylaxis is sugammadex, a rocuronium reversal agent [75]. In Japan, the incidence of sugammadex-triggered anaphylaxis has been estimated to be 0.02–0.039% (sugammadex-triggered anaphylaxis events divided by total number of sugammadex administrations) [12,76]. The incidence of sugammadex-associated events seems to be rare in other parts of the world—in the UK's NAP6, the estimated incidence was 0.0016% [5]. The comparatively high incidence of sugammadex-induced anaphylaxis in Japan may be due in part to its frequent usage compared to other countries, with sugammadex being used in 90% of anesthetic reversals in Japan compared to 8% of reversals in the UK [34,75]. However, a comparison of UK NAP6 data [5] and Japanese data reported by Orihara et al. [12] as done by Savic et al. suggests the combination of rocuronium/sugammadex is more likely than other NMBA/reversal agent combinations to trigger adverse events [75]. As such, the issue of sugammadex-induced anaphylaxis should be considered by not only Japan, but other regions as well. Prevention is the most effective cure, but like all other treatments, needs to be supported by evidence. By identifying problematic exposures, and perceptions, tangible steps can be made to reduce negative outcomes associated with these reactions.

## 11. Conclusions

Perioperative anaphylaxis reactions are rare but carry significant risk of morbidity and mortality. There are considerable epidemiological variations on a regional basis, including differences in anaphylaxis triggering agents. The clinical presentation of perioperative anaphylaxis is characterized by unexplained hypotension, bronchospasm, and less often skin manifestations. Core management principles are early recognition, trigger discontinuation, epinephrine, and resuscitative IV fluids. Steroids and antihistamines are supportive and should only be given once the patient is stabilized. Acute and baseline tryptase measurements are crucial to making the diagnosis post event. Further diagnostic skin testing, and in vitro assays, should be arranged in the post-operative period to confirm the diagnosis, identify the trigger agent, and provide recommendations for future perioperative exposures.

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## Conflicts of interest

All authors declare no conflicts of interest in this paper.

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