



Perioperative Anaphylaxis: Evaluation and Management

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Abstract

Perioperative anaphylaxis (PA) is a rare but life-threatening condition that poses diagnostic and management challenges in the operating room. The incidence of severe perioperative reactions is estimated to be approximately 1:7000–10,000. Management involves both immediate stabilization of the patient and identifying the culprit agent. Identification is essential to prevent recurrence of the event in subsequent surgeries and to avoid unnecessary labeling of drug allergy. Identifying all possible exposures including medications, disinfectants, latex, and dyes and choosing the appropriate tests are essential for proper evaluation. To identify the culprit, primary testing modalities include tryptase at the time of the reaction with subsequent levels and skin testing with nonirritating concentrations to the medications and substances utilized during the procedure and those potentially used as alternates. This strategy provides guidance for future surgeries and procedures. Close collaboration between the allergy, anesthesiology, and surgery teams is essential for appropriate management of these patients at the time of the reaction, during the post event evaluation and in preparation for subsequent surgeries.

Keywords Perioperative hypersensitivity · Intraoperative · Anaphylaxis · Drug allergy · Anesthesia

Abbreviations

PA	Perioperative anaphylaxis
POH	Perioperative hypersensitivity
US	United States of America
ASA	American Society of Anesthesiologists
ACE	Angiotensin converting enzyme
IgE	Immunoglobulin E
NAP6	National Audit Project 6
PAGS	Perioperative Anaphylaxis Grading System
ISPAR	International Suspected Perioperative Allergy Group
IV	Intravenous
SC	Subcutaneous
NMBA	Neuromuscular blocking agents
UK	United Kingdom
MRGPRX2	MAS Related GPR Family Member X2
HIV	Human immunodeficiency virus
Hev b	Hevea brasiliensis
FDA	Food and Drug Administration
SPT	Skin prick test
IDT	Intradermal testing

IDHR	Immune-mediated drug hypersensitivity reaction
DPT	Drug provocation test
NSAID	Non-steroidal anti-inflammatory drugs

Introduction

“Perioperative period” is the time when the patient is under the care of an anesthetist (for general or regional anesthesia or sedation or managed anesthesia care) at any site in the hospital from the time of receiving first administration of the drug until post-procedural transfer to the care of the team in a ward or critical care unit. “Hypersensitivity” is an umbrella term that encompasses reproducible symptoms that occur in response to a defined stimulus resulting from effects beyond predicted in most people [1, 2]. This includes both allergic and non-allergic reactions. Perioperative hypersensitivity (POH) reactions have a wide spectrum of presentation that can be classified from Grades 1 to 5, in the order of increasing severity (Tables 1 and 2). Grades 3–5 are typically life threatening and fulfill the criteria for perioperative anaphylaxis (PA) [1]

PA is rare with estimated worldwide incidence in the range of one in 353 to one in 18,600 anesthetic procedures based on various studies from different countries [3, 4]. A large retrospective study done in the USA reported an incidence of 15.3 cases per 100,000 procedures [5]. Mortality

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Table 1 Anaphylaxis classification using modified Ring and Messmer grading system [17, 20]

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Not life threatening		Life threatening		
Mucocutaneous signs Example: Rash, erythema and/or swelling	Multisystem involvement Example: Unexpected hypotension, bronchospasm (neither requiring treatment), Grade 1 features	Single or multisystem involvement (Severe) Example: Unexpected severe hypotension, severe bronchospasm, swelling with actual or potential airway compromise	Circulatory or respiratory arrest	Fatal

rates reported range from 1.4 to 4.8% [6–10]. This variation is likely a result of factors such as differences in local practices and drug preferences, variability in ascertainment, referral practices, comprehensiveness of allergy evaluation, and genetic or environmental factors.

Previous history of perioperative reaction is the primary risk factor for PA. Other risk factors include old age, female sex, race, and procedure type [3, 5, 10–13]. Comorbidities such as chronic pulmonary disease, coagulopathy, malignancy, fluid and electrolyte disorders, higher American Society of Anesthesiologists (ASA) physical status, obesity, and coronary artery disease also increase the risk of PA [5, 12]. Intake of beta blockers and ACE inhibitors that were described as risk factors earlier has been contradicted by more recent studies [5, 6, 11, 14, 15]. Patients with PA have higher mortality rates, increased median length of hospitalization, and inpatient costs when compared to those who had a procedure without a PA [5]. PA is challenging to diagnose due to simultaneous use of multiple drugs, overlap of the effects of various anesthetic drugs with the features of hypersensitivity, inability of patient under anesthesia to report symptoms, and differential diagnosis in the operating room that can act as PA or POH mimics. A further challenge is the inciting agent remains unknown in approximately 30 to 50% of cases of intraoperative anaphylaxis, despite evaluation.

Evaluation

PA is a presumed clinical diagnosis at the time of presentation. Appropriate initial management is essential to prevent fatal outcomes and depends on identification of clinical signs and their severity, chronology of events, and the time interval between introduction of possible agents to reaction onset. Investigations such as mediator levels, biological markers, skin, and serological tests help in determining the nature of the reaction, identifying the culprit agents and recommendations regarding future procedures in the patient. IgE-mediated reactions in the perioperative period are important to be identified due to the risk of a future reaction with increased severity. Mertes and colleagues reported that 50–60% of anaphylactic reactions are IgE-mediated reactions [16]. There is a wide variation in the proportion of reactions that are IgE-mediated across studies (Table 3). Evaluation and management of PA has been briefly summarized in Fig. 1.

Clinical Presentation

Cutaneous signs, one of the early and common signs of anaphylaxis, are often absent at presentation in PA and may only appear after resuscitation, or not be apparent in draped

Table 2 Grading of perioperative anaphylaxis [22]

	Grade A—Moderate perioperative anaphylaxis (Measurable derangements in one or more major organ systems that are unexpected for the stage of the patient's perioperative course, non-life-threatening)	Grade B—Life-threatening perioperative anaphylaxis (life-threatening cardiovascular or respiratory derangement, or both)	Grade C—Cardiac arrest with or without respiratory arrest associated with perioperative anaphylaxis
Cardiovascular system	Hypotension, Tachycardia or bradycardia, Arrhythmia	Systolic blood pressure of <60 mm Hg, life-threatening tachyarrhythmia or bradyarrhythmia	Cardiac arrest
Respiratory system	Cough, wheeze, difficult ventilation, oxygen desaturation, difficulty swallowing, Rhinorrhea	Oxygen saturation <90%, Inspiratory pressures of >40 cm H ₂ O, Severe difficulty inflating the lungs, airway angioedema	Respiratory arrest or complete failure of ventilation
Other systems	Unexpected change in consciousness, agitation, gastrointestinal upset		
Cutaneous signs	Signs such as flushing, urticaria, angioedema may or may not be present. At least one other system is involved for the diagnosis of anaphylaxis		

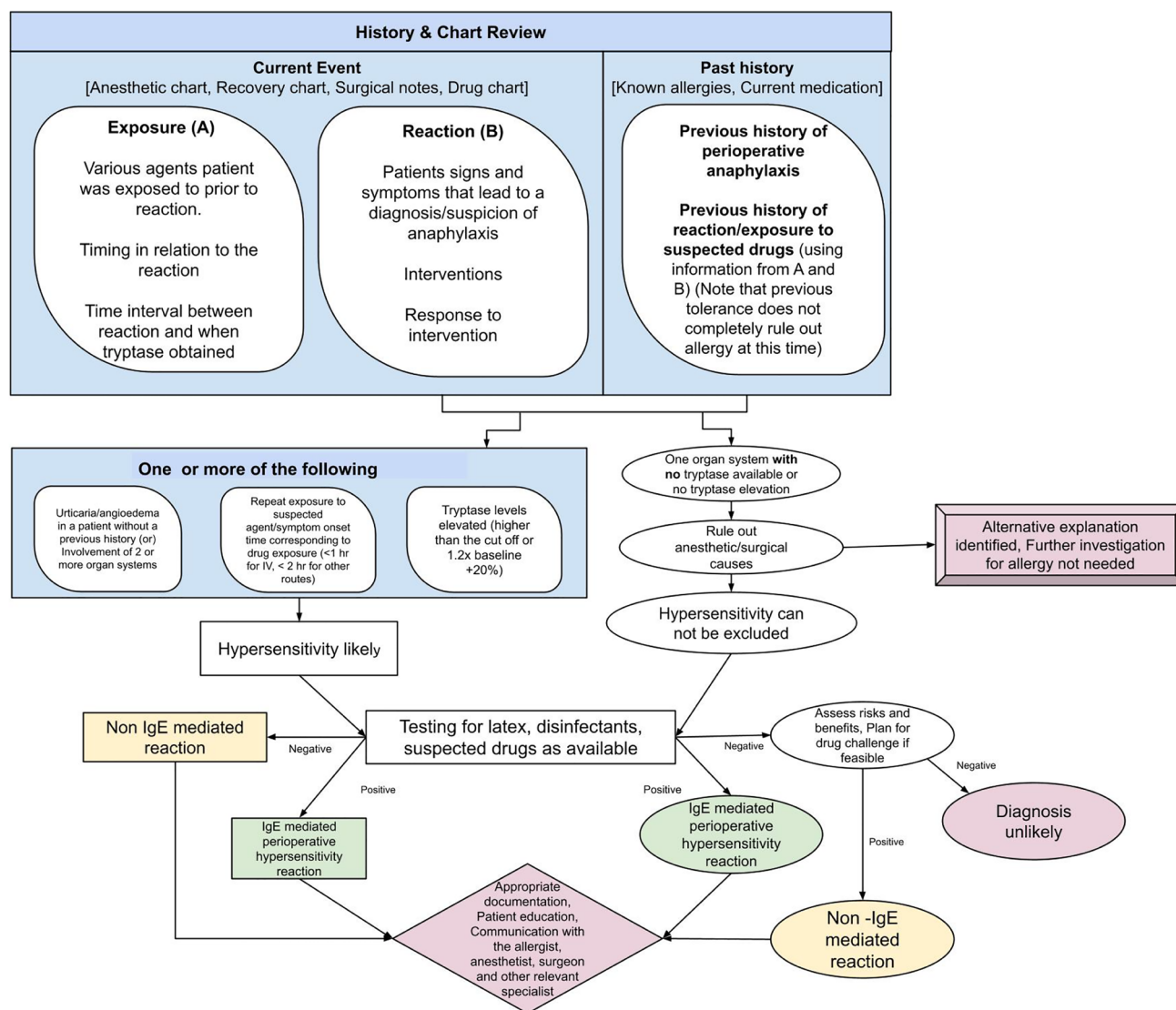
Table 3 Percentage of perioperative hypersensitivity reactions that are IgE mediated

	Geographical location
73%	United Kingdom (NAP6) [12]
47%	United States (Mayo Clinic 2011) [32]
57%	United States (Cleveland Clinic 2014) [47]
17%	United States (Massachusetts General Hospital 2015) [33]
72%	France (2011) [3]
54%	Australia (1993) [132]

patients [12, 17, 18]. In NAP6, the largest prospective study of suspected PA, hypotension was present in all patients during a severe episode although the clinical features at presentation varied (Fig. 2). A small minority of patients

also present with isolated organ system involvement. [12] Bronchospasm is more commonly present in patients with a history of increased airway hyperactivity and obesity [12, 17–19].

Grading the severity of an episode helps to guide treatment decisions. A variety of anaphylaxis classification systems have been developed. The most commonly quoted grading system is the one developed by Ring and Messmer that features a scale of 1 to 4 [20]. This has been modified with the addition of another category, where Grade 5 is death [17, 21] (Table 1). A perioperative anaphylaxis grading system (PAGS) has also been developed in an effort to promote rapid stratification of patients and appropriate treatment (Table 2) [22]. A clinical grading scale to assess the likelihood of a hypersensitivity reaction was recently suggested by the ISPAR group [23]. This grading scale can also

**Fig. 1** Algorithm for evaluation and management of perioperative anaphylaxis [55, 128]

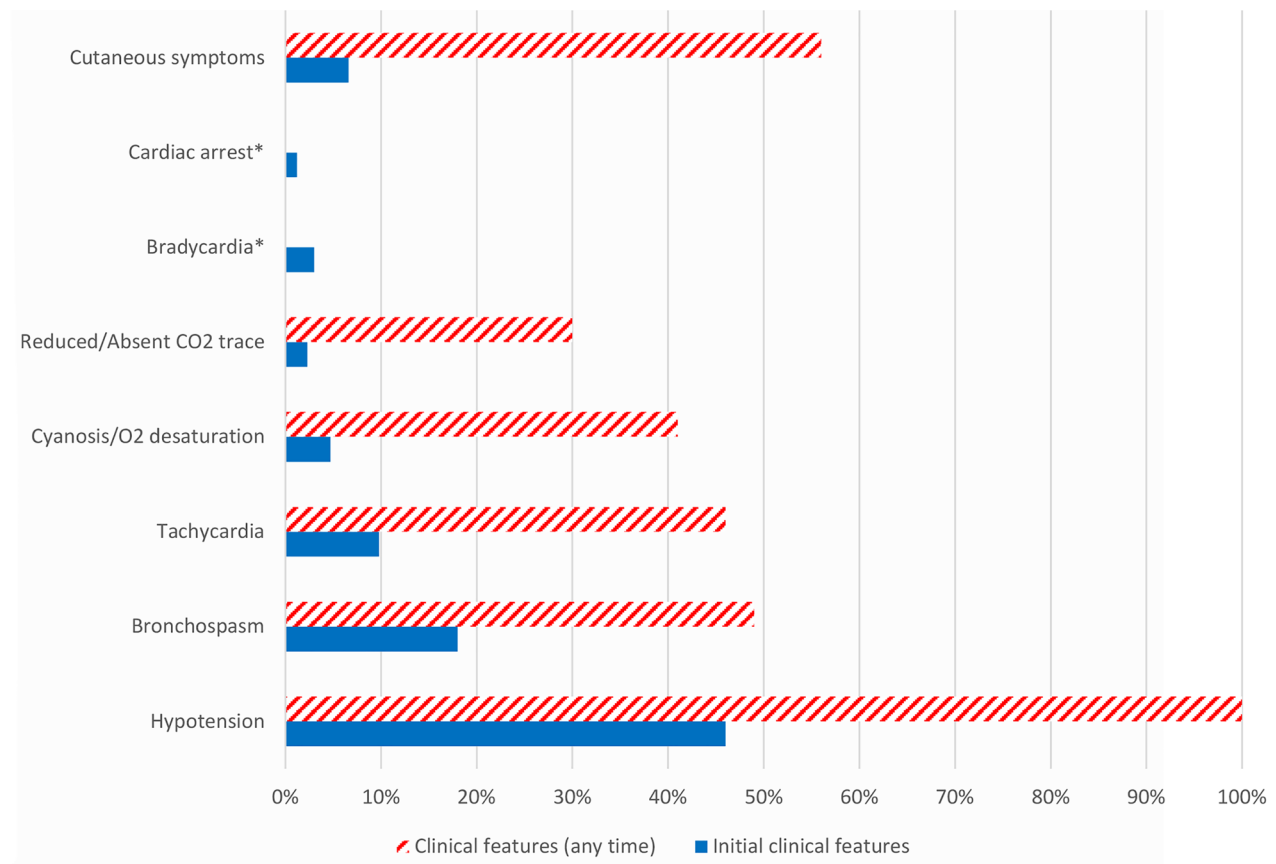


Fig. 2 Clinical features in perioperative anaphylaxis based on NAP6 report [12]. *Exact data points not available for clinical features at any time for bradycardia and cardiac arrest

be used to assess the sensitivity of tests intended to confirm perioperative hypersensitivity reaction and to identify the culprit agent.

Time from exposure to reaction can vary based on several factors. A study on fatal anaphylaxis reported that median time to cardiac arrest was 5 min after IV injection, 15 min after SC injection, and 30 min after oral intake [24]. In NAP6, most cases presented within 10 min of exposure, as was expected as most drugs are delivered intravenously in the perioperative setting. The exceptions to this were chlorhexidine and Patent Blue dye, where presentation was more likely to be modestly (>10 min) or significantly (>30 min) delayed. A delay of more than 120 min was also reported with these substances [12]. Significant delays in onset could be observed with oral drugs due to time lag in absorption. Hence, most recommendations advise that all agents given to the patient at least up to 120 min prior to exposure should be investigated. In general, the common culprits are neuromuscular blockers, antibiotics, and hypnotics when symptoms occur within first 30 min of anesthesia. When symptoms begin after 30 min of anesthesia, primary cause include chlorhexidine, latex, dyes, plasma expanders, blood

products, and sugammadex [25] (Fig. 3). However, timing alone should not be used to identify the culprit or limit testing, as this approach has been shown to be imprecise [26, 27].

Potential Culprits

Neuromuscular Blocking Agents

Neuromuscular blocking agents (NMBAs) have been the most common suspected culprits for POH worldwide. They continue to be the top suspects in France, Norway, Belgium, and Australia accounting for 50 to 70% of perioperative anaphylaxis events [28–31] and are now the second most common culprit in the UK [12]. They are less common in USA, Spain, Sweden, and Denmark [32–36] (Table 4).

Anaphylactic reactions from NMBAs may occur through an IgE or a non-IgE-mediated mechanism via direct non-specific mast cell activation [37, 38]. Substituted quaternary and tertiary ammonium ions have been implicated as the IgE recognition site for the neuromuscular blockers

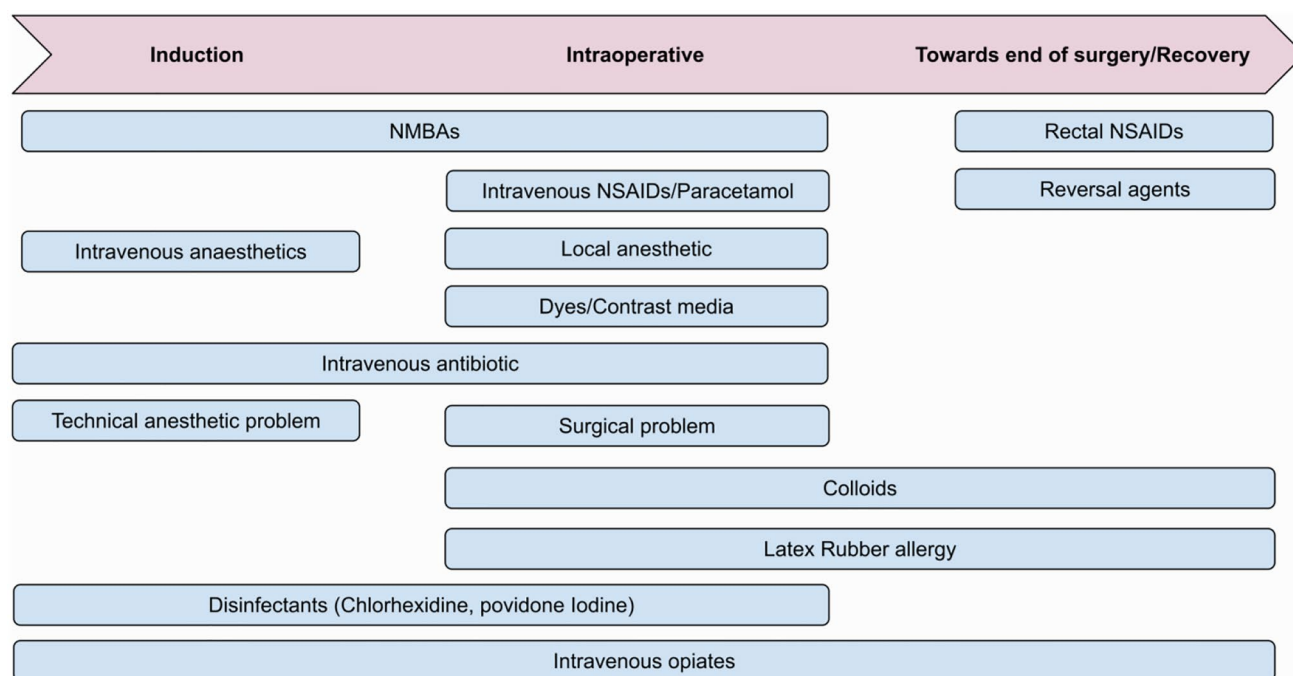


Fig. 3 Likely culprit based on time of reaction [44]

[25, 39]. Cross sensitization with several agents containing ammonium groups such as over-the-counter drugs (pholcodine), cosmetics (hair dyes for example), disinfectants, and food products have been hypothesized [25, 40–43]. Cross sensitivities within and amongst different classes of NMBAs are also widely reported. The NMBAs are classified as aminosteroids (rocuronium, vecuronium,

pancuronium), benzylisoquinolones (atracurium, cisatracurium), and others (succinylcholine). Interestingly, cross-reactivities are not always class related. Cross reactive patterns can vary according to the agent responsible for the initial event. For example, patients with initial reaction to succinylcholine infrequently reacted to other agents, while those initially reacting to vecuronium reacted to other aminosteroid agents and succinylcholine, whereas after initial atracurium reaction, patients reacted to cisatracurium and succinylcholine but rarely with aminosteroids [29]. Hence, a systematic approach for evaluation using skin test and serology is important both for finding the initial cause and to establish safe alternatives. Though the skin tests are not entirely standardized, guidelines are available [1, 44, 45]. It is important to be aware in a minority of patients; allergic reactions to NMBAs can occur despite negative skin testing [45].

Many factors influencing the choice of a specific neuromuscular blocker and lack of standardized testing can make it difficult to determine which neuromuscular blockers are more frequently associated with allergic reactions. Rocuronium is one of the main inducers of IgE-mediated anaphylaxis among NMBAs and succinylcholine the most commonly cross-reacting drug [29, 30, 34]. Cis-atracurium, pancuronium, and vecuronium are associated with lower incidences of IgE-mediated anaphylaxis [46]. Non-IgE-mediated anaphylactic reactions may occur with atracurium and mivacurium, perhaps due to recognition by MRGPRX2 on the surface of mast cells [12, 37].

Table 4 Causes of PA by country

Agent	Percentage of time identified as cause	Geographical Location
NMBA	41.5%	Belgium [137]
	55%	Norway [30]
	32.7%	UK [12]
	23%, 11.1%	United States [32, 47]
	60.6%	France [28]
	37%	Spain [34]
Chlorhexidine	7.7%, 9%	UK [12, 135]
	10.3%	Belgium [137]
	9.6%	Denmark [63]
Antibiotics	47.2%	UK [12]
	59%, 50%	US [32, 47]
	15.3%	Belgium [137]
	18.2%	France [28]
	44%	Spain [34]
Patent Blue dyes	4.5%	UK [12]
	2.3%	Belgium [137]
	5.4%	France [28]

Antibiotics

Antibiotics are the one of the main causes of PA in several countries and are the most common cause of anaphylaxis in the USA, Spain, and UK accounting for around 50% of cases [12, 34, 47] (Table 4). There is substantial variability based on local drug preferences and differences in bacterial resistance patterns. Beta lactams especially amoxicillin (co-amoxiclav) and cefazolin are the most frequently identified due to their widespread use for perioperative prophylaxis. Teicoplanin is also associated with high incidence of PA in the UK where it is commonly used as an alternative in patients with a history of penicillin allergy. Vancomycin and quinolones have also been implicated, but difficulty with testing has made confirmation challenging [12, 25, 27]. In the NAP6, the onset of anaphylaxis for antibiotics noted was within 5 min in 74% of cases, within 10 min in 92% and in all cases within 30 min.

Latex

Latex was a leading cause of perioperative anaphylaxis worldwide in the 1990s where many patients and health care workers were sensitized with the production of high protein content latex gloves to meet the demand of hospital hygiene practices during the HIV epidemic [25]. Its incidence has now decreased secondary to increased use of powder free gloves, improvement in the quality of latex products, and promotion of latex-safe health care facilities. Interestingly, no case in NAP6 was attributed to latex [12, 27, 28, 48–52]. Individuals at risk of developing latex allergy include atopic subjects and those who experience high latex exposure—such as health-care workers and patients who have undergone several procedures with exposure to rubber products [48, 53, 54].

Symptoms associated with latex allergy tend to appear in the maintenance phase of anesthesia. Natural rubber latex is derived from the *Hevea brasiliensis* tree, and Hev b 1, 3, 5, 6.02, and 7 are the allergens of clinical relevance. Diagnosis is based on a combination of skin testing and latex specific IgE levels. Patients with a diagnosis or suspicion of latex allergy should have the procedure performed in a latex free environment and preferably as the initial case of the day [19, 25, 48, 55].

Disinfectants

Chlorhexidine is a ubiquitous antiseptic in healthcare setting with an allergic potential. Exposure may occur through skin disinfection, ophthalmic wash solution, chlorhexidine coated central venous catheters, chlorhexidine bath, and urethral gels [25, 56–61]. POH from chlorhexidine is reported to be approximately 10% of all cases in the UK, Denmark and Belgium, while <1% in France [12, 28, 62, 63]. In 2017,

the FDA also issued an alert regarding allergic reactions to chlorhexidine skin antiseptics and a request that manufacturers of over-the-counter antiseptic products containing chlorhexidine gluconate add an allergy warning to their products' Drug Facts labels [61, 64]. Sensitization can occur from home products containing chlorhexidine. However, given the widespread use of chlorhexidine, the overall incidence of POH is low and it continues to be one of the most commonly used antiseptics in healthcare and the community.

Reactions may range from mild skin reactions to severe life-threatening reactions [63]. Time of symptom onset depends on the route of introduction. When the onset is delayed, it may coincide with the time of administration of other drugs leading to erroneous identification of the culprit agent. There are also reported cases with increasing severity of reaction due to continued exposure to the agent where a chlorhexidine coated catheter was not removed during anaphylaxis [60]. Diagnosis is best made with a combination of clinical history, skin test, and IgE testing. When allergy testing for chlorhexidine is positive during investigation of perioperative anaphylaxis, all other potential culprits should still be investigated, as there may be more than one sensitization. Operating theatres should have an accessible list of chlorhexidine-containing items. Appropriate alternatives should be available for patients with suspected or confirmed chlorhexidine allergy [12, 25, 63, 65].

Although not as common, there are a few case reports of reaction to other disinfectants such as povidone iodine and bacitracin. Of note, povidone iodine can be safely used in patients with shellfish allergy because the allergenic component of shellfish is tropomyosin [25, 66, 67]. Recent guidelines recommend testing all perioperative hypersensitivity patients with chlorhexidine or other locally used disinfectants as these are often not documented. [12, 27]

Dyes

Incidence of perioperative anaphylaxis from dyes is on the rise as they are increasingly used for identification of the sentinel node perioperatively. Common dyes used are patent blue V, isosulfan blue, and methylene blue. While the first two are structurally very similar and hence can be cross-reactive, methylene blue is structurally different [68]. However, cross reactivity between methylene blue with patent blue V has also been reported [69]. Patent blue dye was the fourth most commonly identified culprit in perioperative anaphylaxis in NAP6 [12]. Sensitization exists without known previous exposure in a medical context due to their widespread presence in objects of everyday life [70]. Reaction times to the blue dyes range from immediate to delayed. A delay of 30–60 min is likely due to slow absorption from the lymphatics and subcutaneous tissue. They are often severe with symptoms lasting for several hours. Skin

prick and intradermal testing may be used for diagnosis [69, 71, 72].

Reversal Agents

Neostigmine and sugammadex are commonly used reversal agents for NMBA. While there are very few reports for allergic reactions to neostigmine [73–75], the incidence of allergic reactions to sugammadex varies widely in different countries. Allergic reactions to sugammadex were as low as 0.0016% in NAP6 to 0.02% based on post market surveillance in the USA and a recent retrospective study from Japan [12, 76, 77]. Previously, a single-center study from Japan had reported an incidence of around 0.04% [78]. Combining data from different studies, NMBA/reversal combination with the highest incidence of anaphylaxis is rocuronium/sugammadex (19.23 cases per 100 000 patients), followed by succinylcholine/atracurium/neostigmine (15.25 cases per 100 000 patients) and atracurium/neostigmine (4.15 cases per 100 000 patients) [79].

Reactions to sugammadex occur late in the perioperative period as they are given to reverse neuromuscular blockade. Reaction onset is usually within 5 min of the drug administration. Cyclodextrin found in food additives and cosmetics could potentially be sensitizing [78]. There are also reports of patients reacting to a sugammadex-rocuronium complex [25]. There is conflicting evidence regarding the use of sugammadex for management of rocuronium-induced anaphylaxis [27, 80]. Though skin testing and IgG and IgE-specific antibodies to sugammadex have been identified, the mechanism of reactions is not yet completely understood [81].

Sedative Agents

Sedative agents are a rare cause of PA. Incidence of PA associated with hypnotics was reported as 2% in a French study, while only one case was identified in NAP6 [12, 28]. With decreased use, reactions to barbiturates are now rare. Reactions to other hypnotics such as midazolam, etomidate, ketamine, and inhalational agents are extremely rare [28, 82]. Reactions related to the most commonly used hypnotic agent, propofol, have been reported [83–85]. Immediate reactions involving propofol are most frequently due to isopropyl groups and phenol. Due to trace amounts of egg lecithin and soybean oil in propofol, there have been concerns about the use in egg and soy allergic patients. However, such a connection has not been confirmed and avoidance in egg and soy allergic patients is not recommended [50, 85, 86].

Opioids

Immediate type hypersensitivity to opioids is rare with incidence of 1 in every 100,000 to 200,000 perioperative

reactions. Cutaneous symptoms such as urticaria, itching, and vasodilation may result from histamine release because of nonspecific activation of mast cells [4, 7, 25, 27]. There are a few case reports of anaphylaxis to codeine and fentanyl confirmed with skin test and oral challenge [87–90]. A study evaluating the role of SPT in opioid hypersensitivity showed that opiate-sensitive individuals responded similarly as the control study in the SPT, suggesting that placebo-controlled challenge should be considered when possible [91].

Others

Plasma substitutes such as albumin, hydroxyethyl starch compounds, gelatin, and dextrans account for 1 to 4% of perioperative anaphylaxis cases [30, 92]. Albumin-based colloids are not contraindicated in egg allergy patients since the allergenic proteins are different [93].

Heparin hypersensitivity is rare. Reactions have been reported in patients undergoing cardiovascular surgery, hemodialysis, and with heparin-lock flush injection [94]. Hypersensitivity reactions may occur in isolation or in concurrence with heparin-induced thrombocytopenia. Protocols for skin testing with various heparin preparations have been described and may be useful in identifying alternative agents [94].

IgE-mediated hypersensitivity reactions to local anesthetics are extremely rare [28, 95, 96]. It is however important to note that these can act as hidden undocumented allergens due to frequent use in the form of sprays and gels by the anesthetist [65]. It is important to inquire about possible exposure in unidentified cases of PA. Non-irritant concentrations for skin testing have been identified (Table 8).

An allergic reaction to blood and blood products are considered as a diagnosis of exclusion after investigating all other drugs used in the perioperative setting. True anaphylactic reactions are rare (0.6 per 1000 transfusions), except in patients with head injury or IgA deficiency who may have been previously sensitized either by a transfusion or by a previous pregnancy [97]. Reactions such as itching, swelling, or rash in a patient with a previous history of similar reaction may be prevented with a premedication regimen [4, 25, 65, 97].

Differential Diagnosis

The most recent large prospective study by NAP6 reported an incidence of PA to be 1 in 10,000 anesthetic procedures with an estimate of it being 70% higher (or 1 in 7000) due to methodological limitations [12]. True rates of anaphylaxis may be higher than the reported levels due to lack of recognition secondary to various PA mimics that can occur in the operating room. A high index of suspicion and vigilance is needed to recognize PA. In NAP6, there was delay

in starting anaphylaxis-specific treatment in 25% of cases, illustrating the potential difficulties inherent in recognition of perioperative anaphylaxis [6]. Any skin signs of an anaphylactic reaction may pass unnoticed as patients are usually fully draped for procedures. It is prudent to check for cutaneous signs when a patient presents with other signs of an allergic reaction. It is also important to rule out other causes for patients presenting symptoms to ensure proper management. Differential diagnosis for PA is wide, and the most common are summarized in Table 5.

Management

If anaphylaxis is suspected, intravenous epinephrine administration and fluid therapy are generally agreed to be the mainstay of treatment [17, 18, 98, 99]. Epinephrine is not contraindicated in patients with coronary artery disease, as untreated anaphylaxis could further reduce coronary artery perfusion. However, excessive dose or over-rapid IV administration can cause arrhythmias [100]. Cardiopulmonary resuscitation should be administered, if necessary, without delay [101]. Further management depends on the particular clinical presentation of the patient. Other therapies recommended as second line or in the management of refractory anaphylaxis include metarminol, vasopressin, and glucagon (in patients taking beta blockers) [18, 99, 102, 103]. Corticosteroids and antihistamines may also be used to help reduce symptoms though there is no strong evidence

available on their role in PA. Sugammadex is not recommended as a treatment for rocuronium-induced anaphylaxis as it appears itself to be potentially allergenic [76, 104, 105]. Summary of immediate management of PA from guidelines or consensus recommendations has been summarized in Table 6 [106]. Measurement of mediator levels are best done immediately after the reaction with peak tryptase levels usually occurring 1 h into the reaction, whereas allergy testing to specific agents are recommended 28 days to 6 months from the time of reaction [107].

Measurement of Mediator Levels

Several mast cell mediators are released during an anaphylactic reaction. Histamine is a primary mediator of anaphylaxis, but its measurement is challenging as the plasma half-life of histamine is only 20 min. Histamine levels may increase in both anaphylactic and non-IgE hypersensitivity reactions.

Tryptase, a serine protease, is a preformed enzyme that is also released during mast cell activation. It is stable in room temperatures, and the serum levels peak approximately 15 to 120 min after the anaphylactic reaction onset and declines under first-order kinetics with a half-life of approximately 2 h [25]. Optimum time for sampling is 1–4 h since the start of reaction and a baseline tryptase (preferably 24 h after the reaction) should be taken for comparison. Recent recommendations consider tryptase levels to be elevated if reaction tryptase $> (1.2 \times \text{baseline tryptase level}) + 2$ as this has

Table 5 Differential diagnosis for perioperative Anaphylaxis [44, 98]

Anesthesia related
Anesthesia technique
Airway irritation from misplaced ET tube
Airway edema
Subcutaneous emphysema
Aspiration
Inadequate depth of anesthesia
Pharmacological effects
Overdose
Hypotension from vasodilation induced by spinal/epidural, drugs such as propofol
Bradycardia and hypotension after opiates
Malignant hyperthermia
Drug interactions: ACE inhibitor—elicited angioedema, nonspecific histamine release from a combination of drugs
Procedure related
Major blood loss
Amniotic fluid embolism
Overdose of oxytocin
Autonomic parasympathetic effects—with peritoneal traction, laparoscopy, arthroscopy etc
Patient comorbidity related
Hyperreactive airways: untreated asthma, smokers, viral infection
Pulmonary embolism
Cardiac disorders: myocardial ischemia, congestive heart failure, arrhythmia
Septicemia
Chronic urticaria or angioedema exacerbation
Mast cell disorders—may develop have mast cell activation with or without an allergen

Table 6 Immediate management of PA—recommendations from various guidelines [106]

Guideline	Epinephrine (IV)		IV fluids	
	Grade 3	Grade 4	Grade 3	Grade 4
ISPAR [98]	50 mcg or 100 mcg bolus -If inadequate response at 2 min - 200 mcg bolus Repeat every 2 min	1 mg Repeat as per ALS guidelines	1 L bolus Review results and repeat as needed up to 30 ml/kg	Per ALS guidelines
ANZC and ANZAAG [99]	100–200 mcg bolus - Repeat every 2 min Increase dose if unresponsive	1 mg (repeat 1–2 min) Follow ALS guidelines	If hypotensive—elevate legs, bolus crystalloid fluid 2L, repeat as needed	
Spanish–SEAIC and SEDAR [133]	100–200 mcg	1 mg	Not defined	
French–SFAR and SFA [50]	100–200 mcg bolus - Repeat every 1–2 min, Increase dose if unresponsive IV infusion at a dose of 0.05–0.1 mcg/kg/min helps reduce the need for repetitive bolus	1–2 mg bolus (repeat every 1–2 min) Initiate cardiac massage	Lower limb elevation Rapid infusion of crystalloid solutions Colloid substitution when volume of crystalloid infused exceeds 30 ml/kg	

shown a high positive predictive value [27]. Several studies that have investigated the specificity, sensitivity, and positive and negative predictive values for various cut off levels of tryptase in perioperative anaphylaxis have been summarized in Table 7. An elevation of the follow-up baseline serum tryptase levels may indicate an underlying mast cell disorder [108]. A normal tryptase level does not rule out an IgE-mediated anaphylactic event, and further investigations should be done wherever clinical features are suggestive of PA. Although not as common, tryptase levels can also be elevated in non-IgE hypersensitivity reactions [65, 98].

Spot and 24-h urine measurements for n-methyl histamine, 2,3 dinor beta prostaglandin F2a, prostaglandin D2, and leukotriene E4 are other markers of mast cell activation. They have not been studied in perioperative anaphylaxis and are less widely available.

Allergen specific Testing

It is a general practice to use a combination of history, skin test, and drug provocation tests for diagnosis and

determination of reaction risk on re-exposure. As always, test results should be correlated with the clinical history.

Skin Tests

Skin prick test (SPT) followed by intradermal testing (IDT) (when SPT is negative) is the most commonly used method used to identify the culprit agent in PA. Inconclusive SPT or IDT should always be repeated. Testing is done starting with the lowest concentrations and not exceeding the maximum nonirritant concentration. Preservative free solutions may be used if there is a question that the preservative in the medication is causing the reaction. Table 8 summarizes the concentrations recommended by various guidelines. Though the risk of anaphylaxis during IDT is very low, the risk of milder systemic reactions increases with higher concentrations, large volumes or multiple tests [25, 27].

Specific Serum IgE Measurement

Serum IgE levels are not routinely recommended for the identification of the culprit agent in PA as only a limited number of

Table 7 Tryptase levels cut offs and their predictive values [25, 108, 134, 135]

Cut off level	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Reference
7.35 mg/L	92%	92%	99.4%	44.3%	[134]
11.4 mg/L	53%	95%	97%	40%	[108]
12.5 mg/L	82.7%	96%			[134]
15.7 mg/L	63.9%	73.7%	82.1%	51.9%	[135]
(1.2 × Baseline serum tryptase) + 2	75%	86%	94%	53%	[108]

Reference [134] patient population only included life threatening reactions

Table 8 Recommendation on highest non-irritative concentration by drug type [27, 44, 50, 99, 136] (Concentrations as recommended by EAACI (2019) have been listed first. Any variations in recommendation in other guidelines have also been noted)

Drug class/name	SPT	IDT
Neuromuscular blocking agents		
Atracurium	1 mg/ml	0.01 mg/ml
Cisatracurium	2 mg/ml	0.02 mg/ml
Mivacurium	0.2 mg/ml	0.002 mg/ml
Rocuronium	10 mg/ml	0.05 mg/ml 0.1 mg/ml [99]
Vecuronium	4 mg/ml	0.04 mg/ml 0.2 mg/ml [44]
Pancuronium	2 mg/ml	0.2 mg/ml 0.02 mg/ml [99]
Suxamethonium	10 mg/ml 50 mg/ml [44]	0.1 mg/ml
Reversal agents		
Sugammadex	100 mg/ml	10 mg/ml 1 mg/ml [99]
Opiates		
Fentanyl	0.05 mg/ml	0.005 mg/ml
Alfentanil	0.5 mg/ml	0.05 mg/ml
Sufentanil	0.005 mg/ml	0.0005 mg/ml
Remifentanyl	0.05 mg/ml	0.005 mg/ml
Morphine	1 mg/ml	0.005 mg/ml
High risk of false positive tests consider provocation in skin test positive patients	0.00001 mg/ml [99] 0.01 mg/ml [136] 0.001 mg/ml [50]	
Antiseptics		
Povidone iodine	100 mg/ml	No IDT 1 mg/ml [99] 10 mg/ml [50]
Chlorhexidine	5 mg/ml 0.2 mg/ml [99] 0.5 mg/ml [50]	0.002 mg/ml (sterile uncolored alcohol free solution) 0.0002 [99] 0.005 [50]
Plasma expanders		
Dextran	Skin tests not useful. (IgG-mediated mechanism)	
Hydroxyethyl starch	60 mg/ml	6 mg/ml
Modified fluid gelatins	40 mg/ml	4 mg/ml
Sentinel node dyes		
Methylene blue	10 mg/ml Undiluted [136]	0.1 mg/ml 0.01 mg/ml [99]
Patent blue	25 mg/ml	0.25 mg/ml 2.5 mg/ml [50]
Additives		
PEG/macrogol	Undiluted	High risk of systemic reactions on IDT
300	50% w/v	
3000	50% w/v	
6000		
Polysorbate 80	20% w/v	
Poloxamer 407	10% w/v 0.5–1 mg/ml [136]	
Carboxy methyl	SPT 1% w/v	0.05 mg/ml [99]
Cellulose	5 mg/ml [99] 5–10 mg/ml [136]	1 mg/ml [136]

Table 8 (continued)

Drug class/name	SPT	IDT
Sedation		
Propofol	10 mg/ml	1 mg/ml
Etomidate	2 mg/ml	0.2 mg/ml
Ketamine	100 mg/ml	0.1 mg/ml 1 mg/ml [44, 50, 136]
S-ketamine	25 mg/ml	0.25 mg/ml
Thiopental	25 mg/ml	2.5 mg/ml
Midazolam	5 mg/ml 1 mg/ml [99]	0.05 mg/ml
Local anesthetics		
• Skin testing without vasoconstrictor if possible		
• Risk of false positive IDT consider provocation if IDT doubtful		
Amide type LA		
Lidocaine	10 mg/ml	1 mg/ml
Articaine	20 mg/ml	2 mg/ml
Prilocaine	20 mg/ml 10 mg/ml [99]	2 mg/ml 10 mg/ml [99]
Bupivacaine	2.5 mg/ml	0.25 g/ml 2.5 g/ml
Levobupivacaine	7.5 mg/ml	0.75 mg/ml
Mepivacaine	20 mg/ml	2 mg/ml 10 mg/ml [99] 1 mg/ml [50]
Ropivacaine	10 mg/ml 2 mg/ml [50]	1 mg/ml 0.2 mg/ml [50]
Ester type LA		
Chloroprocaine	10 mg/ml	1 mg/ml

drug specific serum IgE immunoassays are available and most of them are not validated or have low sensitivity [27, 110]. High IgE levels may affect specificity of specific serum IgE immunoassays; calculating the serum IgE: Total IgE ratio may improve the specificity of the assay in this situation [109–112]. Chlorhexidine-specific serum IgE immunoassay may be the most reliable with a sensitivity and specificity around 90% but is not commercially available in the USA [63, 107, 113, 114]. Latex-specific IgE and penicillin G IgE are commercially available in the USA but do not have reliable predictive values, and routine use is not recommended. Furthermore, latex IgE false positive may occur from grass-pollen cross-sensitization [98, 115].

Basophil Assays

Stimulation by specific allergens can result in the degranulation of basophils which can be studied with direct measurement of the released mediators or using flow cytometry to analyze upregulation of surface markers such as CD63 and CD203c. The utility of basophil assays in identification of IDHR of certain drugs such as NMBA, beta-lactams, opiates, and fluoroquinolones has been studied. These tests have good specificity but low sensitivity and are not widely used

at present [116–125]. Standardization of cut off values and testing methodologies with improvement in reproducibility will help in further widespread use of these assays.

Drug Provocation Tests

DPTs are considered the gold standard method for the diagnosis of drug hypersensitivity but are not always feasible due to ethical and practical considerations. Despite the limitations to the use of DPTs outside of the perioperative setting due to the pharmacologic effects of the perioperative drugs, they can be useful in the investigation of certain drugs such as antibiotics, local anesthetics, opiates, and NSAIDs. These should be done in specialized centers where collaboration between allergist and anesthetist, full monitoring, and resuscitation facilities are available [65, 117, 126, 127].

Plan for Future Surgeries

Test results and their clinical correlation are helpful in diagnosis and identification of the culprit agent. Once, diagnosed, the culprit substance should be communicated to the patient,

general practitioner, anesthetist, and other relevant specialists. Alternatives to the culprit should be identified wherever necessary. Once a culprit is confirmed, other suspected drugs that tested negative may be used for future procedures [65, 128]. If no culprit agents are identified, repeat testing and reevaluation should be considered. Drug provocation can be considered at this point, and this can help with ruling out a suspected drug as the cause [82]. Other differential diagnoses including clonal mast cell disorders should also be considered [129–131]. In patients with mastocytosis, there is not a large increase in perioperative anaphylaxis. Preoperative use of H1, H2 blockers, or corticosteroids are often used as pretreatment; however, this strategy has not been assessed [130].

Repeated perioperative reactions with isolated mild skin symptoms without increasing severity are likely caused by nonspecific histamine release. Reassurance and pretreatment with oral antihistamines for a few days prior to anesthesia may remove or minimize symptoms for these mild reactions [27, 65]. When an anesthetic is needed prior to completion of evaluation, suspected drugs should be avoided, and procedure may be done with the use of suitable alternative agents and with additional monitoring in place. Reporting reactions to the appropriate pharmacovigilance agency should be done wherever appropriate [25, 27, 65].

Summary

PA is a rare but significant event resulting in a higher mortality than other causes of anaphylaxis. Proper identification of possible culprits is essential to prevent further episodes and to outline a comprehensive plan for future surgeries and procedures. Diagnosis of PA with certainty is not always possible at the time of presentation; hence, clinical suspicion is critical, realizing cardiovascular collapse may be the only presentation. Strides have been made in optimizing skin testing concentrations to identify the culprit agent with published organizational guidelines. Currently, a causative agent is only identified approximately 50–60% of the time, emphasizing the need for further research in this area. Tryptase level should be obtained 1–2 h into the event to aid in the diagnosis. Allergen skin testing should be optimally obtained 4 weeks to 6 months after the event to identify the cause. Appropriate labeling of the allergy, identifying alternative medications, and educating the patient on the diagnosis and communication with the health care team are critical. Collaboration between allergy/immunology and anesthesiology is essential in identifying the culprit and will pave the way to improve the diagnosis and management of this condition.

Declarations

Conflict of Interest The authors declare no competing interests.

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