

Identification and Management of Perioperative Anaphylaxis



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The authors present a case of a patient with multiple episodes of perioperative anaphylaxis. The incidence and the most common causes of perioperative anaphylaxis are reviewed. The most common causes can vary by country and the type of perioperative medications used. The unique environment and the multiple medications and substances used in the anesthesia and surgical setting that make a definitive diagnosis challenging are outlined. A systematic strategy to recognize the reaction, identify the culprit, and direct future management are demonstrated. Management of the patient experiencing perioperative anaphylaxis requires close collaboration between the anesthesia, surgical, and allergy teams. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2134-42)

Key words: Perioperative period; Anaphylaxis; Intraoperative; Anesthesia; Hypersensitivity reactions

BACKGROUND

Anaphylactic reactions during anesthesia may be life-threatening events and are a result of the medications or substances used for anesthesia or surgery. The incidence of anaphylactic reactions during procedures or surgery has shown wide variations from 1 in 1,250 to 1 in 20,000.¹⁻⁶ The mortality is higher than from other causes of anaphylaxis and ranges from 3% to 9%.⁷ The primary risk factor for intraoperative anaphylaxis is a history of a reaction during procedures or surgery. Although nearly all the medications and substances used in anesthesia and surgery have been implicated as causes (including hypnotics, opioids, local anesthetics, colloids, and dyes), the most common causes of intraoperative anaphylaxis are neuromuscular blocking agents (NMBAs), antibiotics, disinfectants, and latex.^{7,8} The most common causes of intraoperative anaphylaxis vary by country. The inciting agent remains unknown in approximately

30% to 50% of cases of intraoperative anaphylaxis, despite evaluation.⁸⁻¹⁰ Initial evaluation of the type of reaction, with measurement of mediators and subsequent allergy evaluation of the possible culprits, is critical in management of the patient experiencing perioperative anaphylaxis and in preventing further episodes. Outlining a comprehensive plan for future procedures is of utmost importance.

CASE REPORT, PART 1

The patient is a 70-year-old man who was evaluated in the Allergy Clinic of our institution following an allergic reaction that occurred in the setting of a bilateral femoral endarterectomy. The medications that he received at induction of anesthesia included thiopental, succinylcholine, vecuronium, fentanyl, and midazolam. Following endotracheal general anesthesia, the urinary catheter could not be introduced. A cystoscopy was performed, urethral stricture dilated, and a urinary catheter successfully placed. During this procedure, the patient developed widespread urticaria, starting in the groin and pelvic region. He also developed significant swelling of the face, lips, and mouth. There was a transient decrease in his blood pressure to 80 mm Hg systolic, but otherwise cardiopulmonary function remained stable. He responded to treatment with epinephrine, dexamethasone, and diphenhydramine, and the bilateral femoral endarterectomy could be completed without further incident. Cefazolin and hydromorphone were given at a later time point, after the reaction.

Further history revealed he had allergic reactions after every procedure or surgery that he had undergone over the 8 previous years at other institutions. The patient's first episode occurred near the completion of a total hip arthroplasty and was manifested by widespread urticaria and hypotension, with systolic blood pressures as low as 64 mmHg. Two years later with left carotid stent placement, he again developed widespread urticaria and hypotension, with systolic blood pressures in the low 60s. Subsequently, 3 years later (3 years before this evaluation) with stent placement in the right lower extremity and a balloon dilatation of the left lower extremity, he developed hypotension, with systolic blood pressures in the 60s and widespread urticaria near completion of the procedure. Later that year when transurethral retropubic prostatectomy was performed, he again developed widespread urticaria and hypotension. Subsequently, with a cystoscopy procedure performed in a urology office, he developed hives, pruritus, and hypotension. His allergy-like symptoms had only occurred at the time of procedures and surgeries, not at any other times. His previous evaluations for these episodes elsewhere included skin testing to lidocaine, bupivacaine, and latex, all with negative results. Tryptase levels were not obtained at the time of the reactions.

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Abbreviation used

NMBA- Neuromuscular blocking agent

Incidence

Over the years, multiple series from various countries have estimated the incidence of perioperative anaphylaxis to range from 1 in 1,250 to 1 in 20,000.¹⁻⁶ The variability is related to finding the true denominator of surgical procedures, and identifying and defining a perioperative reaction. Most recently, the National Audit Project 6 from the United Kingdom estimated the incidence of severe perioperative anaphylaxis (grade 3-5 on a 1-5 scale, with 5 being death) at 1 in 10,000.¹¹ (Table I). However, the incidence potentially was higher at 1 in 7000 but could not be confirmed because of lack of complete data on all the patients.¹¹

Pathophysiology

Approximately 60% of intraoperative anaphylaxis reactions are thought to be mediated by IgE. The primary non-IgE-mediated driver of anaphylaxis is direct mediator release from mast cells and basophils. In addition, nonspecific complement activation may play a role. Recently described Mas-related G-protein-coupled receptor X2 can activate mast cells independent of IgE with exposure to opioids and neuromuscular blockers.¹⁴ Both IgE- and non-IgE-mediated (ie, formerly known as anaphylactoid reactions) hypersensitivity reactions can present similarly and result in increased serum tryptase.

Clinical patterns of reaction

Anaphylaxis occurring during the perioperative time frame is a clinical syndrome involving the release of primarily mast cell mediators involving multiple organ systems. The clinical presentation can be variable given underlying comorbidities, medications, surgical procedures, and anesthetics. Delay in diagnosis can occur because of the setting, because the patient is usually intubated, sedated, and draped, and so early skin signs and typical symptoms (eg, pruritus, feeling faint, and dyspnea) are not easily delineated. In addition, the anesthetics can cause cardiovascular changes that can mimic early anaphylaxis and make early recognition difficult. Inhaled anesthetics cause a decrease in systemic vascular resistance and consequently a drop in mean arterial pressure.¹⁵ In addition, inhaled anesthetics can cause an increase in heart rate. Of note, sudden changes in anesthetic concentration can cause a more profound effect on the cardiovascular system (ie, hypotension and tachycardia). Some of the inhaled anesthetics, such as isoflurane and desflurane, are pungent and can irritate the airways when used at higher levels. This effect may be exacerbated in patients with reactive airway disease, leading to bronchospasm. The most commonly used intravenous anesthetic for induction, propofol, causes a dose-dependent decrease in blood pressure that may be associated with a compensatory tachycardia. Propofol can also be used for a total intravenous anesthetic for maintenance of anesthesia. Deep levels of total intravenous anesthetic can also cause hypotension and tachycardia.

The clinical manifestations can vary from mild cutaneous exanthema to cardiovascular collapse. A suspected allergic or anaphylactic event can be categorized on the basis of severity. A modified Ring and Messmer scale has been used to grade the

perioperative event.¹⁶ Grade I (skin manifestations) and II (mild, but multiple system involvement) reactions are not life-threatening and more commonly associated with non-IgE-mediated reactions. The grade III (life-threatening symptoms) and IV (cardiac and/or respiratory arrest) reactions are more commonly associated with IgE-mediated reactions.²

It is important to note that isolated hypotension or cardiovascular collapse without any skin symptoms may be the initial presentation of intraoperative anaphylaxis.¹⁷ In the surgical setting, it is important to consider anaphylaxis when hypotension or bronchospasm does not respond to usual therapy or cardiovascular collapse occurs unexpectedly.

Differential diagnosis

Early cardiovascular symptoms of anaphylaxis often include hypotension and tachycardia. Any condition predisposing to shock can lead to hypotension as the initial presentation. These commonly include myocardial ischemia, cardiac arrhythmias, pulmonary embolism, hemorrhage, sepsis, and hypovolemia. In addition, hypotension can be seen on induction of anesthesia, particularly in patients taking antihypertensive or tricyclic antidepressant medications.¹⁸ Tachycardia can result from inadequate anesthesia.

Upper airway mimickers of anaphylaxis include airway swelling as a result of a difficult intubation, angiotensin-converting enzyme inhibitor-related angioedema, or C1-esterase-deficient hereditary and acquired angioedema.¹⁸ Airway manipulation in patients with underlying airway hyperreactivity, or with undiagnosed or insufficiently treated asthma, can also lead to bronchospasm. Bronchospasm can also present in patients with chronic obstructive pulmonary disease following intubation or due to light anesthesia. Other causes of bronchospasm include histamine release from medications, mucus plugs, mechanical obstruction, pulmonary aspiration, pulmonary edema, pulmonary embolism, and pneumothorax.¹⁹

Evaluation

The timing between the administration of the suspected allergen and the clinical signs and symptoms can sometimes be helpful. In general, when symptoms occur within the first 30 minutes of anesthesia, the primary culprits are neuromuscular blockers, antibiotics, and hypnotics. When symptoms begin after 30 minutes of anesthesia, causes include chlorhexidine, latex, dyes, plasma expanders, blood products, and sugammadex. The following are the most commonly identified causes of intraoperative anaphylaxis.

Etiologies

Neuromuscular blocking agents. NMBAs have traditionally been identified as the most common cause of perioperative anaphylaxis, particularly in France, the United Kingdom, Norway, Australia, and New Zealand, accounting for 50% to 70% of perioperative anaphylaxis events.^{2,20} Recently, though, other countries including the United States, Spain, and Denmark have found it as a less common cause and accounts for approximately 30% of cases in these countries.²¹⁻²⁴

NMBAs appear to cause anaphylactic reactions through both an IgE-mediated mechanism and a non-IgE-mediated mechanism via direct nonspecific mast cell activation.^{14,25,26} The IgE recognition site for the neuromuscular blockers is their substituted ammonium ions and molecular environment.^{25,27}

TABLE I. Grading of perioperative hypersensitivity/anaphylaxis

Grade	Features	Clinical presentation
1	Cutaneous-mucous signs	Rash, erythema, swelling (any of)
2	Moderate multivisceral signs	Unexpected hypotension-not severe,* bronchospasm-not severe,* or both $\pm$ grade 1 features
3	Life-threatening mono- or multivisceral signs	Unexpected severe hypotension, $\pm$ severe bronchospasm, $\pm$ swelling with actual or potential airway compromise, $\pm$ grade 1 features
4	Cardiac arrest	Fulfilling indications for CPR
5	Fatal	Death

CPR, Cardiopulmonary resuscitation.

Modified from Cook et al¹² and Ring and Messmer.¹³

*Not requiring treatment.

Given the ammonium structures, possible sensitization can occur to these agents with exposure to materials containing tertiary and quaternary ammonium groups including many over-the-counter drugs, cosmetics, disinfectants, and food products. This is hypothesized, though not clearly defined, to explain a higher incidence of neuromuscular blocker sensitivity in females than in males. Females have a 3-fold risk of developing anaphylaxis than do males.²⁸ In support of nonclinical exposures as sensitizers, hairdressers through exposure to their work products have been found to have a higher rate of sensitization to neuromuscular blockers and quaternary ammonium compounds.²⁹ Because there is no sex difference in the incidence of anaphylaxis before puberty, another hypothesis supports hormonal involvement. This may be related to the effects of female hormones on T_H2 polarization.³⁰ In Norway, high rates of sensitivity to neuromuscular blockers were noted and were associated with consumption of pholcodine, an opioid antitussive.³¹ On removal of pholcodine from the market, declines were seen in clinical reactions to neuromuscular blockers and sensitization to quaternary ammonium ion products.³²

Cross-sensitivity is approximately 60% to 70% among the neuromuscular blockers.³³ The patterns of cross-reactivity can be quite variable, though only 7% show sensitivity to all the neuromuscular blockers.² The pairs of pancuronium and vecuronium, succinylcholine and gallamine, and cis-atracurium and atracurium often show cross-sensitivity.^{2,34,35} The presence of multiple possible cross-sensitivities emphasizes the importance of a systemic approach to the evaluation of a patient with perioperative anaphylaxis. This applies not just in finding the initial cause, but in providing a guidepost for outlining neuromuscular blockers (those with negative skin test results) that may be used in subsequent surgery.³⁶

Many factors influence the choice of a specific neuromuscular blocker depending on the clinical context and overall availability. Patterns of neuromuscular blocker use are variable between medical centers and from region to region. These differences can make it difficult to determine which neuromuscular blockers are more likely associated with allergic reactions. In general, succinylcholine and rocuronium are thought to be associated with increased allergic risk and atracurium, cis-atracurium, and pancuronium with less risk.³⁷ However, atracurium is associated with histamine release, which may lead to bronchospasm and hypotension.

Antibiotics. Antibiotics, frequently given before or during anesthesia, are an increasing cause of perioperative anaphylactic reactions. They are the most common cause of intraoperative

anaphylaxis in the United States and Spain accounting for 40% to 55% of reactions. The most common antibiotics identified were beta lactam antibiotics, with cefazolin being the most common.²¹⁻²³

In France, the percentage of antibiotics increased from causing approximately 2% of perioperative reactions in the late 1980s to approximately 20% now.⁸ The type of antibiotic causing the reaction will vary by region, but in general penicillins and cephalosporins are the most common culprits. Vancomycin and quinolones have also been implicated, but difficulty with testing has made confirmation problematic. In the most recent data from the United Kingdom, antibiotics were the most common cause of perioperative anaphylaxis.¹¹ The 2 most common culprits were co-amoxiclav (also known as amoxicillin clavulanate) and teicoplanin, accounting for more than 87% (82 of 94) of antibiotic culprits identified. Teicoplanin is not available in the United States and is not a Food and Drug Administration–approved product. The reactions to the antibiotics occurred within 5 minutes in 74% of cases, between 6 and 10 minutes in 18%, and between 11 and 15 minutes in 5%.¹¹ The authors comment that the use of teicoplanin was related to a noted penicillin allergy on the chart in 56% of those receiving the teicoplanin. The penicillin allergy label played an important role in the high incidence of teicoplanin reactions. Because most (more than 98% in some studies) cases of penicillin allergy are incorrectly labeled when testing is done, it is recommended to evaluate penicillin allergy before surgery.^{38,39}

Latex. Latex has been identified traditionally as one of the more common causes of perioperative anaphylaxis. Latex allergy reached its peak in the 1990s in the setting of increased production of high protein content latex gloves to meet the demand of hospital hygiene practices during the HIV epidemic. Those with increased exposure were sensitized and risk groups were identified, which included those with spina bifida, those undergoing multiple procedures and surgeries, health care workers, and non–health care workers exposed to latex. Certain patient populations such as atopic individuals with increased IgE levels are also at increased risk for allergic reactions to latex.^{5,40}

Over time, latex sensitization has decreased, with manufacturers substituting other materials for latex and use of powder-free latex gloves. Furthermore, the Food and Drug Administration mandated that manufacturers label products that contain latex.⁴⁰ The incidence of cases of latex anaphylaxis has decreased as a result of identification of at-risk patients and the use of preventive measures such as latex-free equipment (primary prevention) and the use of powder-free gloves.⁴⁰ In the French studies, the percentage of

patients with an identified cause of perioperative anaphylaxis showed latex ranging from 2% in the period 1984 to 1989 to 18% in the period 2005 to 2007, and decreased to 5% from 2011 to 2012.^{2,41} Recent studies from many countries have shown a decline in perioperative anaphylaxis attributed to latex.^{11,42}

Reactions to latex tend to occur later in the surgery, typically after significant mucosal exposure. To decrease the likelihood of a reaction in the latex-allergic individual with a subsequent surgery, the surgery should be performed in a latex-free operating room and as the initial case of the day if latex-powdered gloves are being used in the institution.^{5,40}

Disinfectants (chlorhexidine, povidone iodine, bacitracin). Chlorhexidine is widely used as an antiseptic in medical, procedural, and surgical settings. Chlorhexidine is used to clean the skin before insertion of epidural catheters, arterial lines, and central venous lines. It is also used on the skin of the abdomen, chest, or other body part prepared for surgery. Urinary catheters are passed using chlorhexidine gel. Initial reports of chlorhexidine sensitivity were confined to localized contact skin (type 4 hypersensitivity) reactions.⁴³ Subsequently, immediate, systemic allergic reactions (type 1 hypersensitivity) ranging from widespread urticaria to anaphylactic shock have been reported to chlorhexidine via topical skin application, ophthalmic wash solution,⁴⁴ chlorhexidine bath,⁴⁵ coated central venous catheter,⁴⁶ and urethral gels.⁴⁷ Most initial reports came from Denmark and New Zealand.^{47,48}

In 12 patients with perioperative chlorhexidine reactions, most were male with a median age of 64 years, with nearly half the reactions occurring during urologic surgeries or procedures.⁴⁷ A literature review of 36 articles of chlorhexidine reactions during surgery noted similarly that urologic procedures were most common, and a male predominance.⁴⁹ The most common exposure was the chlorhexidine-containing lubricant for the urinary catheter followed by chlorhexidine-impregnated central venous catheters.⁴⁹ Overall, intensive care admissions occurred in 28% of cases. Reactions to chlorhexidine can occur early or later in a surgery. In a study of 4 patients, chlorhexidine sensitivity occurred 20 to 40 minutes into the surgical procedure.⁵⁰ Sensitization to chlorhexidine can occur from home products such as mouthwash, toothpaste, dressings, ointments, and over-the-counter disinfectant solutions for cuts and wounds. During procedures, chlorhexidine exposure is enhanced by absorption through mucosal surfaces (eg, urethra and bladder) and skin (eg, incision and epidural), especially if the chlorhexidine is not dry before the initiation of the procedure. Chlorhexidine skin testing has been shown to be predictive of allergic sensitivity and to correlate with *in vitro* chlorhexidine specific IgE testing.⁵¹

Although much less common, there are a few case reports of reaction to povidone-iodine. These are usually associated with the application of the povidone-iodine to the mucosa or skin. These reactions can occur at variable times during surgery.⁵² Of note, povidone iodine can be safely used in patients with shellfish allergy, because the allergenic component of shellfish is tropomyosin.⁵³

Intraoperative anaphylaxis has also been reported with bacitracin. These can occur in various settings including bacitracin irrigation, lavage, and the implantation of bacitracin-soaked devices.⁵⁴ The reactions to these compounds underscore the importance of studying antiseptics in the comprehensive diagnostic approach to perioperative anaphylaxis.

Dyes. Dyes are becoming increasingly recognized as a cause of perioperative anaphylaxis. In the National Audit Project 6 investigation in the United Kingdom, patent blue dye was the fourth most identified culprit in perioperative anaphylaxis behind antibiotics, neuromuscular blockers, and chlorhexidine.¹¹ Blue dyes are used to identify sentinel lymph nodes in melanoma and breast cancer. The 2 most commonly used dyes are patent blue V and isosulfan blue. They are structurally very similar and cross-reactive.⁵⁵ Methylene blue, however, is structurally different. Although cross-reactivity would not be expected between methylene blue and patent blue V, it has been reported.⁵⁶ Reactions to the blue dyes can be delayed compared with the intravenously administered medications. This may be due to slow absorption from the lymphatics and subcutaneous tissue.

Sugammadex. Sugammadex, a reversal agent for neuromuscular blockers, is one of the newest causes of perioperative anaphylaxis. It was approved by the US Food and Drug Administration in late 2015, after previously being used in Europe since 2008 and Japan since 2010, because of concerns about allergic reactions. Japan has been considered the highest user of sugammadex, with sugammadex being used in approximately 10% of anesthetic cases. The incidence of perioperative reactions to sugammadex was found to be approximately 1 in 2500 cases when measured retrospectively at a single Japanese hospital.⁵⁷ A study of all phase 1 to 3 sugammadex clinical studies, composed of 42 trials with approximately 3500 patients who received sugammadex, demonstrated a low incidence of hypersensitivity reactions that were comparable to those in the placebo and the neostigmine groups.⁵⁸ Reactions to sugammadex occur late in the surgery because they are given to reverse neuromuscular blockade. The sensitizing trigger to sugammadex is not definitively known. Cyclodextrin, though, is found in food additives and cosmetics and this potentially could be sensitizing. Because the cyclodextrin content in foods and cosmetics varies between countries, this may lead to a different incidence of sugammadex hypersensitivity from region to region. In addition to reacting to sugammadex alone, there are reports of patients reacting to a sugammadex-rocuronium complex.⁵⁹ In these instances, testing to rocuronium and sugammadex individually may be negative, but when combined result in a positive test result.

Less common causes of intraoperative anaphylaxis (hypnotics, opioids, colloids, blood products)

Hypnotic agents. There are a number of medications and substances that are very rarely associated with perioperative anaphylaxis. The hypnotic induction agents commonly include propofol, ketamine, midazolam, and etomidate. With the removal of Cremophor EL as a solvent, the rate of reactions to these agents has dropped further. In recent studies from France, hypnotics were causative in 2% of intraoperative anaphylaxis cases and in the recent National Audit Project 6 from the United Kingdom, only 1 case was identified.^{2,11} Propofol (2-6-diisopropyl-phenol) is currently formulated in a lipid vehicle containing 10% soybean oil, 1.2% egg lecithin, and 2.25% glycerol. True allergic reactions to propofol are likely to be secondary to the 2 isopropyl groups.⁶⁰ Questions have been raised about the safety of propofol in patients with egg, soy, and peanut allergy. Although case reports have implicated an association in children, recent studies show that propofol is safe to use in children and adults with egg, soy, or peanut allergy.^{11,61,62}

Opioids. Incidence of allergic reactions to opioids is 1 in every 100,000 to 200,000 anesthetics. Many opioids (eg, morphine and meperidine) cause the direct release of histamine, causing dermatologic manifestations including urticaria, itching, and vasodilation.^{5,63} Large doses of morphine used during cardiac anesthesia did not show any bronchospasm or angioedema. Non-IgE hypersensitivity reactions to codeine and morphine have been reported; however, negative results have been seen on skin testing in affected patients.⁵

Colloids. Albumin, dextran, hetastarch, and gelatin are colloids commonly used in the operating room, and gelatin is the colloid most likely to lead to an allergic reaction.⁶⁴ Gelatins and dextrans are more likely than albumin or hetastarch to cause an allergic reaction. Albumin is the colloid least likely to lead to an allergic reaction.⁶⁴ IgE-mediated anaphylaxis has been proven by demonstrating IgE antibodies and positive intradermal test results against gelatins. Increased circulating IgG dextran-reactive antibodies are found in most adults with dextran anaphylaxis, and ELISA is used for detecting hetastarch- and dextran-reactive antibodies (IgG and IgM) in human sera.⁶³ Although there is no known cross-reactivity between the different groups of colloids, colloids that belong to the same group such as Hemacel and Gelofusin (which are both gelatins) have been proven to have cross-reactivity.

Blood products. Urticarial reactions are seen in 0.5% of all transfusions with frozen plasma. Because there is a small amount of plasma in all the blood products, allergic reactions to red blood cells and platelets may occur as well. The reaction may present as itching, swelling, or a rash. These symptoms can be avoided with diphenhydramine pretreatment in patients who previously had severe urticarial reactions. In addition, it is recommended to transfuse with saline washed cells. The prophylactic use of acetaminophen before transfusion is controversial because it has potential toxicity and studies have not shown that it prevents transfusion reactions.

True anaphylactic reactions to blood products are infrequent (0.6 per 1000 transfusions),⁶⁵ except in patients with head injury or IgA deficiency who may have been previously sensitized either by a transfusion or by a previous pregnancy.⁶³

CASE REPORT, PART 2: TESTING

Given that all the medications and substances used were potentially causative, further evaluation was performed. Skin prick testing was performed to fentanyl (50 µg/mL), thiopental (25 mg/mL), succinylcholine (20 mg/mL), vecuronium (1 mg/mL), and midazolam (5 mg/mL), and all results were negative. Intradermal testing was performed to these medications, starting with 1:100,000 of the base concentration and decreasing sequentially by 10-fold to a final intradermal concentration of 1:100-1:10 using the most concentrated nonirritating concentrations. These results were all negative. Skin test results to latex was negative. Skin prick testing was performed to chlorhexidine using a 2% solution. The patient had a markedly positive response, with a 7 × 8 mm wheal and 25 mm by 30 mm flare. Skin prick test results to chlorhexidine performed on 4 control staff members were negative. On the basis of his reactions with the previous surgeries and procedures and the current episode, the patient was diagnosed with chlorhexidine allergy. Chlorhexidine was a constant for all his previous episodes, tying

the picture together. Evaluation after this episode included tryptase level, which was obtained 6 hours after the reaction, and this was within normal limits at 1.27 ng/mL. The tryptase level was not obtained at the optimal time to help identify an allergic reaction, but serves as a reminder that tryptase level may not always be elevated in perioperative anaphylaxis.

Skin prick and intradermal testing (medications/substances)

Skin testing remains the primary means for identifying the allergen in intraoperative anaphylaxis. Skin prick testing followed by intradermal skin testing can be performed to the medications and substances received during the procedure. Difficulties with skin testing include a nonspecific irritant reaction to the medications and inability to identify a non-IgE-mediated reaction. These tests are not standardized and sensitivity, specificity, and positive and negative predictive values are not well defined for most medications encountered. A positive skin test result to nonirritating drug concentrations is consistent with an allergic mechanism; however, the sensitivity and specificity remain unknown. Given the absence of this data, recommendations for testing are primarily based on nonirritating skin test concentrations. Guidelines have been published outlining a nonirritating concentration of the drug for testing.^{16,66-68} See Table II for reported nonirritating concentrations for skin prick and intradermal testing for medications and substances encountered in intraoperative anaphylaxis. Skin testing to latex has not been standardized and the extract can be prepared with latex from an industry source, elution from soaked latex gloves, or prick through gloves. This is variable depending on the clinic and based on its experience with the process. Given the number of possible antibiotics and the variation in skin testing to antibiotics, they are not included in this table.

Specific IgE testing for medications and substances

Specific IgE testing for medications and substances encountered in perioperative anaphylaxis currently has a limited role due to lack of availability and sensitivity. Latex specific IgE and penicillin G IgE are commercially available in the United States. Suxamethonium, morphine, gelatin, and individual beta lactam antibiotics' specific IgE is available in some countries but their sensitivity is moderate at less than 60%.⁷⁰ Chlorhexidine specific IgE, where available, has shown a sensitivity and specificity near 100%.⁵¹

Role of tryptase and other markers of anaphylaxis

The primary mediator of anaphylaxis is histamine. An increase in histamine indicates activation of mast cells and is observed during anaphylactic and non-IgE hypersensitivity reactions. The plasma half-life of histamine, though, is only 20 minutes and can be difficult to measure. Tryptase, a mast cell protease, is a pre-formed enzyme that is also released during mast cell activation. Tryptase serum levels peak approximately 15 minutes to 120 minutes after the anaphylactic reaction onset, and declines under first-order kinetics with a half-life of approximately 2 hours. This kinetics makes measurement of tryptase the easiest way to assess mast cell activation, with elevation often seen 1 to 4 hours after the event.

A recent multicenter study from the United Kingdom of 161 patients, where the cause of intraoperative anaphylaxis was identified in 70% of cases, used a tryptase value of more than 15.7 mg/L as the cutoff. The sensitivity was 63.9%, specificity

TABLE II. Reported nonirritating maximal concentrations for SPT and IDT

Table 1. Reported Nontitrating Maximal Concentrations for SPT and IDT					
Agent	Undiluted	SPT (mg/mL)		IDT (mg/mL)	
		Dilution	Max []	Dilution	Max []
NMBA					
Atracurium	10	1/10	1	1/1000	0.01
Cis-atracurium	2	Undiluted	2	1/100	0.02
Mivacurium	2	1/10	0.2	1/100	0.002
Pancuronium*	2	Undiluted	2	1/100	0.02
Rocuronium	10	Undiluted	10	1/200	0.05
Vecuronium*	4	Undiluted	4	1/100	0.04
Suxamethonium	50	1/5	10	1/500	0.1
Hypnotics					
Etomidate	2	Undiluted	2	1/10	0.2
Midazolam*	5	Undiluted	5	1/100	0.05
Propofol	10	Undiluted	10	1/10	1
Thiopental	25	Undiluted	25	1/10	2.5
Ketamine	10	Undiluted	10	1/10	1
Opioids					
Alfentanil	0.5	Undiluted	0.5	1/10	0.05
Fentanyl	0.05	Undiluted	0.05	1/10	0.005
Sufentanil	0.005	Undiluted	0.005	1/10	0.0005
Remifentanil	0.05	Undiluted	0.05	1/10	0.005
Morphine*	10	1/10	1	1/2000	0.005
Dyes					
Methylene blue	10	Undiluted	10	1/100	0.1
Patent blue*	25	Undiluted	25	1/100	0.25
Antiseptics					
Chlorhexidine	5 (0.5%)	Undiluted	5	1/2500	0.002
NMBA reversal					
Sugammadex	100	Undiluted	100	1/10	10

IDT, Intradermal testing; SPT, skin prick testing.

Adapted from Mertes et al,¹⁶ Volcheck and Mertes,⁶⁶ Brockow et al,⁶⁷ Kam de et al,⁶⁹ and Garvey et al.⁶⁸

*Note decreased IDT testing concentrations based on recent European Academy of Allergy and Clinical Immunology (EAACI) position paper.⁶⁸

73.7%, positive predictive value 82.1%, and negative predictive value 51.9% for IgE-mediated anaphylaxis.⁷¹ In the French series where 259 patients had tryptase level measured, the sensitivity of tryptase for the diagnosis of intraoperative anaphylaxis was 64%, specificity 89%, positive predictive value 93%, and negative predictive value 54%.⁷² In a study of 75 patients with IgE-mediated anaphylaxis causing severe cardiovascular collapse or cardiac arrest perioperatively, compared with nonallergic cardiovascular collapse, tryptase levels of more than 7.35 µg/L showed sensitivity and specificity of 92%. When tryptase level of more than 12.5 µg/L was used as the cutoff, sensitivity was 82.7% and specificity 96%.⁷³ The calculated positive and negative predictive values for tryptase levels of more than 7.35 µg/L were 99.4% and 44.3%, respectively. The tryptase levels did not change in the control groups with resuscitation. This study suggests that the threshold for tryptase should be reduced when measured during a life-threatening reaction. An acute serum tryptase level greater than $\{[1.2 \times \text{serum baseline tryptase}] + 2\}$ µg/L has been recommended to confirm acute mast cell degranulation. When this formula was compared with an acute tryptase level of more than 11.4 µg/L in 85 patients with perioperative anaphylaxis with adequate timing of the samples, the sensitivity, specificity, positive predictive value, and

negative predictive value were 75%, 86%, 94%, and 53%, respectively, compared with 53%, 95%, 97%, and 40%, respectively, for acute tryptase value of more than 11.4 µg/L.⁷⁴

Clearly, a normal tryptase level does not rule out an IgE-mediated anaphylactic event. If the tryptase level is elevated during the reaction, a follow-up level should be obtained at a later time point to check for an underlying mast cell disorder. Although not as common, tryptase levels can also be elevated in non-IgE hypersensitivity reactions.

Other measurements of mast cell activation are not widely available and include spot and 24-hour urine measurements for *n*-methyl histamine, 2,3 dinor beta prostaglandin F2a, prostaglandin D2, and leukotriene E4. These markers have not been studied in perioperative anaphylaxis.

CASE REPORT, PART 3: SUBSEQUENT MANAGEMENT FOR SURGERY

Six months later the patient required hip arthroplasty. The primary recommendation was strict chlorhexidine avoidance, which was communicated to the patient and the surgical and anesthetic teams. He underwent right total hip arthroplasty receiving propofol, succinylcholine, fentanyl, and cefazolin.

Povidone-iodine (ie, Betadine) was used as the topical antiseptic agent. The patient tolerated the surgery well without the development of any allergic signs or symptoms.

Acute treatment of intraoperative anaphylaxis

The first step in the treatment of an anaphylactic reaction consists of the withdrawal of the drug likely to be the cause of the reaction. Early administration of epinephrine is mandatory to avoid airway compromise and cardiovascular collapse.⁷⁵ Epinephrine leads to the interruption of the effects of the preformed mediators and the prevention of further mediator release. Epinephrine doses of 5 to 10 µg intravenously (0.2 µg/kg) are used in the treatment of mild to moderate hypotension, and are titrated to effect. Doses of 0.1 to 0.5 mg intravenously are used in the presence of cardiovascular collapse.^{16,76,77} An immediate assessment of the airway, breathing, and circulation is also essential during the early stages of anaphylaxis. In addition, it is important to decrease or discontinue anesthetic agents likely to cause vasodilation such as inhalational agents, as well as any medications with negative inotropic effects.

Other important steps in the treatment of anaphylaxis include airway support with 100% oxygen to compensate for the increased oxygen consumption, intravenous crystalloid replacement (2–4 L) to compensate for the peripheral vasodilation, bronchodilators if bronchospasm is present (nebulized albuterol and/or ipratropium bromide), and glucocorticoids (hydrocortisone) to decrease late airway swelling and prevent recurrence of symptoms.

Perioperative anaphylaxis is a common simulation scenario due to its low frequency and the lack of experience of providers in managing anaphylaxis.⁷⁸ The use of cognitive aids (eg, emergency manuals and checklists) has been demonstrated to lead to improved teamwork and task performance during simulated intraoperative emergencies such as anaphylaxis.⁷⁹

Management of a patient with suspected perioperative anaphylaxis

In this situation, the patient had a history of numerous episodes of procedural and perioperative anaphylaxis, but only minimal evaluation. A careful and complete review of the clinical and perioperative history is essential before any procedure in patients with previous perioperative reactions because they are at increased risk of a recurrence during subsequent anesthetics. It is strongly recommended that the anesthesia and surgical teams communicate their concerns and that an allergy consult be obtained if there is a concern for an allergic reaction. An allergy assessment based on the clinical and surgical history should then be performed to identify the culprit drug or substance. The anesthesia record should be reviewed in detail to determine the accurate timeline of all the medications and substances administered in relationship to changes in monitored vital signs and symptom development. The type of treatment administered and response should also be reviewed. If the information is difficult to obtain or unclear, the anesthesia team from the procedure should be contacted whenever possible. Often substances used in the procedure including antiseptics, gels, dyes, and hemostatic agents are not documented. It is important to remember these during the evaluation and, if unclear, to contact the previous operating room team (anesthesia, nursing, and surgery) for the information. These substances in particular can vary among hospitals. See Table III for management overview.

TABLE III. General evaluation/management of patient with suspected perioperative reaction

Immediate
Treat anaphylaxis (epinephrine, fluids, secure airway)
Discontinue any suspected medications/substances
Obtain serum tryptase level
Obtain urine mediators (<i>n</i> -methyl histamine, leukotriene E4, 2,3 dinor beta prostaglandin F2alpha, prostaglandin D2, if able)
Obtain Allergy consultation
Allergy consultation
Careful review of anesthesia record, exact timeline of medications, substances, symptom development
If record not obtainable or questions, contact anesthesia/surgery team
Skin test ± specific IgE testing to all medications and substances administered and latex and chlorhexidine
If positive to NMBA, skin test to other NMBA's to aid future use
If allergen identified, document in Allergy section medical record, counsel patient on the allergen and its significance
Notify anesthesia and surgical teams before future surgery
Emergent management in patient with previous perioperative reaction not previously evaluated
Use latex-free environment, minimize antiseptics if able
Use local/regional anesthesia or general anesthesia without NMBA or histamine-releasing products
Minimize number of medications
Avoid penicillin and cephalosporin if used during previous anesthetic
Have high index of suspicion for early signs of anaphylaxis

There are no prospective randomized studies that have evaluated the use of a specific protocol of premedication for the prevention of perioperative anaphylaxis.¹⁶ Therefore, it is critical to identify and evaluate at-risk patients before any surgical procedure. The most important component is identification of the culprit agent. Premedication with H₁- and/or H₂-receptor antagonists or steroids is not universally recommended because their effects have never been thoroughly evaluated.^{30,76,80}

SUMMARY

The most commonly involved agents in perioperative anaphylaxis are NMBA's, antibiotics, antiseptics, latex, and dyes. However, any medication or substance the patient comes into contact with perioperatively can be a potential cause. The primary risk factor is a previous perioperative anaphylaxis or allergy to the medications or substances used in the procedure. Immediate discontinuation of the offending agent, epinephrine administration, and volume resuscitation are the cornerstones of treating anaphylaxis. Tryptase level obtained approximately 1 hour into the reaction can help identify the reaction as mast cell-mediated (either IgE or non-IgE). Prevention is the most important component to decrease the incidence of anaphylaxis. Prevention starts with the recognition of anaphylaxis during the initial event, documentation of all the medications and substances used in relation to the development of symptoms, referral to an allergist for identification of the causative drug, and appropriate labeling of the patient. Guidelines are available for the highest nonirritating concentrations used for skin prick and intradermal testing to commonly used perioperative medications and substances. Avoidance of drugs and products that produced anaphylaxis and cross-reactive medications and substances during

a previous anesthetic has been demonstrated to prevent an episode of anaphylaxis from recurring. The most effective management uses communication between the anesthesia and surgery teams and the allergist. It is essential to document the tests done and their results. Appropriate labeling of the patient's allergies is mandatory in the electronic record. It is of utmost importance to educate the patient about the culprit agent and the medications to avoid.

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