Perioperative Anaphylaxis

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Anesthesiologists routinely manage patients in multiple clinical settings, including surgery, intensive care, procedural interventions, and/or trauma. In these settings, patients receive a variety of drugs, blood products, or imaging agents, all of which have the potential for adverse reactions, including immediate hypersensitivity reactions. Because the most life-threatening presentation of an immediate hypersensitivity reaction is anaphylaxis, clinicians must be ready to diagnose and manage the life-threatening cardiopulmonary dysfunction that can occur. In the perioperative setting, patients may be under the effects of general or regional anesthesia, or, in the intensive care unit, patients may be sedated and mechanically ventilated with potential causes for hypotension and complicate making the diagnosis. In this review, we will examine the incidence, pathophysiology, presentations, and acute management of perioperative anaphylaxis.

Overview of Anaphylaxis

Anaphylaxis is the most severe form of immediate hypersensitivity reaction due to the massive release of multiple physiologically active mediators by inflammatory cells. In immunoglobulin E–mediated anaphylaxis, the mechanism most frequently encountered in the perioperative setting, mast cells and basophils are the main cells involved.[1] However, the immunoglobulin E–mediated mechanism is identified in only about 60% of perioperative anaphylaxis, which raises the question of other mechanisms involved, including immunoglobulin G–mediated reactions or complement activation.[2] Previously, non-immunoglobulin E–dependent reactions were called anaphylactoid, but this term is no longer used. The term anaphylaxis refers to the clinical presentation but not the mechanism.[3]

Pathophysiology of Anaphylaxis

Triggering Mechanisms Requiring Previous Sensitization

Substances to which patients have developed an allergic reaction are referred to as antigens. The molecular configuration of an antigen can be either a protein or a drug.[1,4,5] Proteins are processed by antigen-presenting cells and presented *via* the major histocompatibility complex to T cells, which then recruit B cells. This process results in the production of antigen-specific immunoglobulin E antibodies that bind to their specific high-affinity receptor, FcεRI, present on the surface of mast cells and basophils (fig. 1). On reexposure, binding of the antigen to these FcεRI-bound immunoglobulin E antibodies triggers the massive release of vesicle contents, resulting in the hypersensitivity response of anaphylaxis. To trigger the response, FcεRIs must be cross-linked with antigens. Allergic responses to drugs have attracted the attention of immunologists because most drugs require binding to larger host protein such as albumin or α-2 macroglobulin (hapten-carrier concept) to produce an immune response. This mechanism is still debated, and other mechanisms leading to drug sensitization and immunoglobulin E production have been suggested.[6]

Another mechanism involving a sensitization process has been proposed to explain perioperative anaphylaxis without identifying an immunoglobulin E–mediated mechanism.[4] For example, patients could develop specific immunoglobulin G antibodies to certain drugs. The interaction between the immune complexes formed by these antibodies and antigens and the FcγRIIA receptor, present on neutrophils, basophils, and platelets, leads to the activation of these cells and the release of their vesicular contents.[7,8] This mechanism has been described to explain reactions to dextrans or aprotinin and has been suggested to explain some reactions to neuromuscular blocking agents such as rocuronium.[9,10]

Triggering Mechanisms without Previous Sensitization

Several mechanisms other than mast cell activation may be involved with perioperative anaphylaxis on the first exposure to drugs.[11] Nonspecific histamine release from mast cells and basophils has been described in drugs such as atracurium, mivacurium, or morphine.[12] Contamination of unfractionated heparin by oversulfated chondroitin in early

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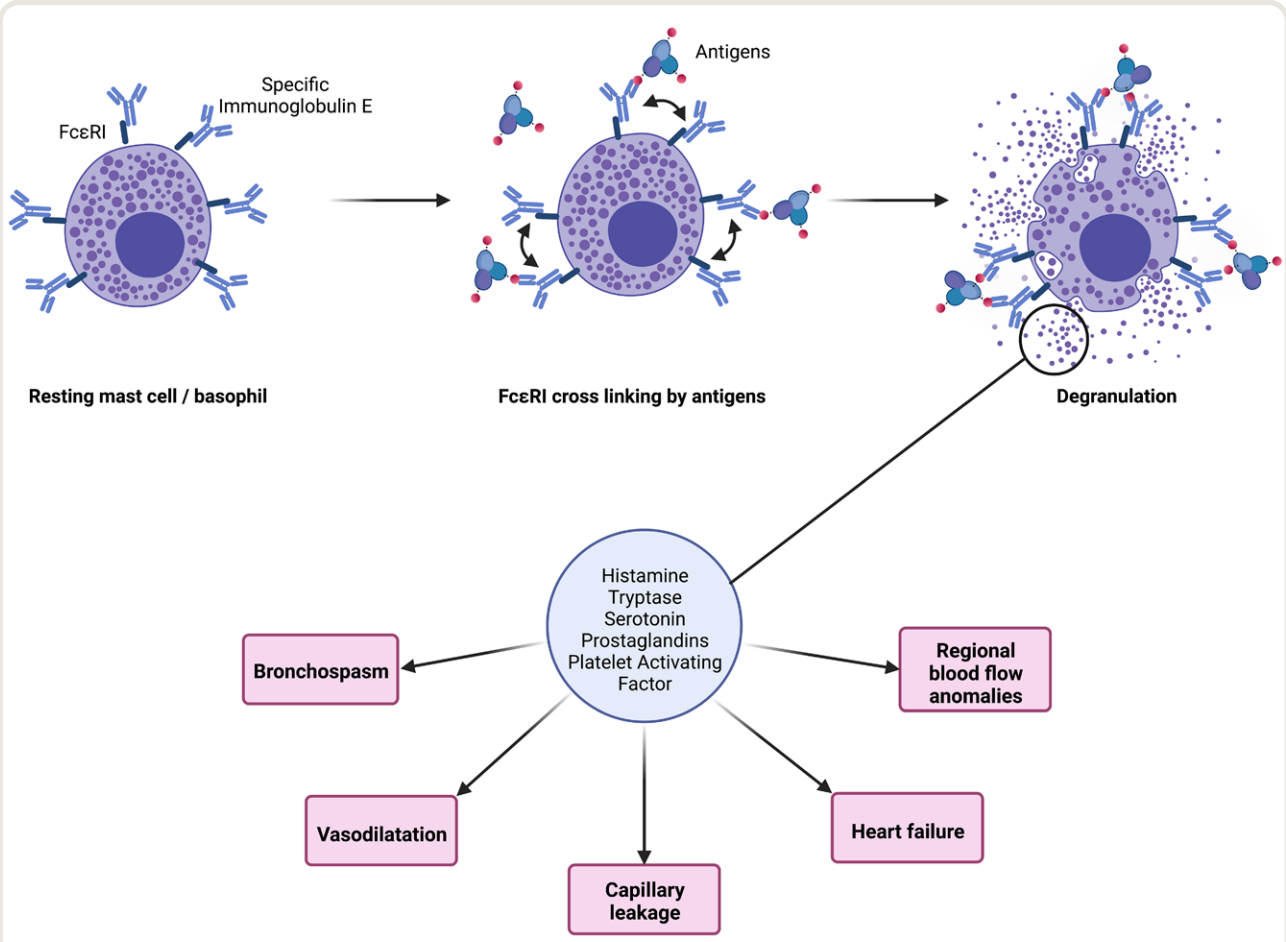

Fig. 1. Immunoglobulin E–mediated activation of mast cells and basophils and pathophysiologic effects of released mediators. Mast cells in the perivascular tissue and basophils that circulate in the blood are the effector cells of immunoglobulin E–mediated anaphylaxis, as shown in the figure. Immunologic activation occurs after antigen exposure and bridging two immunoglobulin E antibodies on the cell surface in a patient with previous exposure to the antigen and sensitization. Antigen–antibody binding produces cellular activation with the release of multiple vasoactive mediators from the stored secretory granules to produce acute cardiovascular and pulmonary effects. In the vasculature, vasodilation and increased capillary permeability causing vasodilation, hypotension, increased vascular permeability, anomalies in regional blood flow and angioedema are the end-organ effects. In the lung, bronchial smooth muscle contraction and bronchospasm occur, as well as hypersecretory changes, including increased mucus formation. Several mediators have negative inotropic effects.

2007 after changes in the manufacturing process led to severe reactions and death through complement and kinin-kallikrein system activation to produce vasodilation and/or shock.[13,14]

Another consideration for antibiotics, drugs, and imaging agents are that they can directly release histamine and other mast cell–stored mediators, including tryptase, through activation of the Mast-cell Related G-coupled Protein Receptor X2 (MRGPRX2) receptor.[15–17] This receptor experimentally triggers mast cell activation when stimulated by certain opioids, neuromuscular blocking agents, vancomycin, fluoroquinolones, substance P, and other peptidergic molecules like bradykinin. The clinical relevance of this mechanism is still debated because MRGPRX2 activation is not different between healthy subjects and patients with perioperative anaphylaxis.[18]

Mechanisms Responsible for Perioperative Hypersensitivity Reactions

Activation of mast cells and basophils triggers the release of stored inflammatory mediators such as histamine, tryptase, or serotonin, and induces the production of other mediators such as platelet-activating factors and prostaglandins.[1,11,19] These mediators are responsible for the acute cardiovascular and pulmonary manifestations of anaphylaxis. Characteristic pathophysiologic manifestations include any combination of acute airway responses with bronchospasm and upper airway edema, vasodilation, increased vascular permeability,

tachycardia, flushing, and urticaria. Acute cardiac dysfunction has also been described recently, probably underestimated due to the massive vasoplegia and reduction of the cardiac afterload.[20] In anaphylaxis, regional blood flows are altered with splanchnic vasoconstriction, pulmonary hypertension, and loss of cerebral autoregulation.[21–24]

Acute shock during anaphylaxis is classically characterized as distributive shock, associated with profound hypovolemia resulting from the effects of vasoactive mediators on the cardiopulmonary system. Vasoplegia and shock result from the effects of released inflammatory mediators on endothelial and vascular smooth muscle responses. Multiple mediators are responsible for this response. In classical immunoglobulin E responses, inflammatory cells release several mediators, including histamine, nitric oxide, arachidonic acid metabolites, and platelet-activating factor, which have multiple vascular effects, including vasodilation and increased vascular permeability.[25,26] These mediators also affect bronchial smooth muscle, resulting in bronchoconstriction. Histamine also stimulates endothelial release of nitric oxide and prostacyclin.[27] Nitric oxide production is increased due to the activation of the endothelial form of nitric oxide synthase that occurs in vascular smooth muscle cells and endothelial cells.[28,29] Nitric oxide activates soluble guanylate cyclase in vascular smooth muscle, and prostacyclin activates soluble adenylate cyclase, both of which result in vasodilation.

Diagnosing Anaphylaxis

Diagnosing anaphylaxis can be difficult, especially in unconscious patients, because most anesthetic agents used for induction cause cardiovascular changes, including hypotension and vasodilation, due to direct and indirect effects on the heart, vasculature, and adrenergic responses. Patients who are hypovolemic and have underlying cardiovascular disease and hypovolemia may often have hemodynamic instability; therefore, hypotension is not always a diagnostic sign of an anaphylactic reaction.

The onset of the reaction after exposure to an antigen may be immediate (less than 5 min), particularly for immunoglobulin E–mediated reactions, but in some cases, it may be delayed for up to 20 min. In addition, the expression and course of anaphylaxis due to parenteral, subcutaneous (*e.g.*, for dyes such as patent blue), cutaneous (*e.g.*, for skin disinfectants), or potentially oral exposure varies among individuals. Previous reports of perioperative anaphylaxis include a spectrum of clinical manifestations ranging from urticaria and slight arterial hypotension to cardiopulmonary collapse due to vasodilatory shock, refractory bronchospasm, acute pulmonary edema, and/or ventricular fibrillation/electromechanical dissociation.[30] The paradox of anaphylaxis is its unpredictability, especially in the absence of an allergic history, and the variable severity of responses to the same amount of drug.

For the diagnosis of anaphylaxis, clinicians rely on the appearance of specific signs and symptoms (table 1) after exposure to an antigen within a time frame consistent with the route of exposure. Severity of anaphylaxis can be graded using the modified Ring and Messmer classification (table 2).[34]

Table 1. Signs and Symptoms of Perioperative Anaphylaxis

System	Symptoms	Signs
Cardiovascular	Diaphoresis	Cardiac arrest
	Dizziness	Hypotension or cardiovascular collapse
		Decrease in $Etco_2$
	Palpitations	Tachycardia/bradycardia
		Dysrhythmias
Respiratory	Acute hoarseness	Acute respiratory failure
	Chest discomfort	Bronchospasm/increased inspiratory pressures during ventilation
	Short of breath	Decreased pulmonary compliance
	Wheezing	Laryngeal edema
		Stridor
Mucosa/skin	Burning	Flushing
	Itching	Diffuse erythema
	Tingling	Cutaneous/mucosal edema
		Urticaria (hives)
Neurologic	Sense of impending doom	Loss of consciousness
	Malaise	Confusion
Gastrointestinal	Abdominal cramps	Diarrhea
	Nausea	Vomiting

Table 2. Classification of the Severity of the Reaction According to the Modified Ring and Messmer Classification[31–33]

Grade of Severity	Clinical Signs
Grade I	Cutaneous signs: generalized erythema, urticaria, angioedema
Grade II	Measurable but not life-threatening symptoms. Cutaneous signs, hypotension, tachycardia Respiratory disturbances: cough, difficulty inflating
Grade III	Life-threatening symptoms: cardiovascular collapse, tachycardia or bradycardia, arrhythmias, bronchospasm
Grade IV	Cardiac and/or respiratory arrest

In the awake patient, specific symptoms such as itching after administration of medication or acute dyspnea may occur. One of the most dramatic results is the patient's sense of impending doom or lack of well-being.

Skin manifestations may occur, but in the patient who is draped may go unnoticed. In addition, cutaneous manifestations may be absent, especially in severe reactions, due to compromised skin perfusion. In these cases, cutaneous signs usually appear secondarily, after systemic perfusion has been restored.

In intubated and unconscious patients, anaphylaxis usually presents as acute cardiopulmonary dysfunction with changes in oxygen saturation or acute hemodynamic

instability with varying degrees of hypotension to complete cardiac arrest.[30,5,36]Decreased end-tidal carbon dioxide is a marker of decreased cardiac output but also reduced tissue perfusion that correlates well with the severity of the reaction.[37] However, as mentioned, there are multiple causes of acute cardiopulmonary dysfunction that must be considered in the differential diagnosis and evaluation of patients, as shown in table 3.

Epidemiology of Perioperative Anaphylaxis

Incidence

It is difficult to determine the incidence of low-frequency events, and most data on anaphylaxis in general surgery come from retrospective reports. The frequency of perioperative anaphylaxis ranges from 1:353 to 1:18,600 procedures with a wide frequency range due to the method of reporting, reactions considered, and country.[31] Most of these data come from European reports. A recent report evaluated the 2005 to 2014 Nationwide Inpatient Sample for anaphylaxis,[38] defined as anaphylaxis complicated by cardiac or respiratory arrest. Throughout a 9-year period, there were 5,223 anaphylaxis events, with a reported incidence of 1 in 6,825 procedures. In France, crossed analysis of several databases allowed an estimation of the incidence of allergic perioperative anaphylaxis at 100.6 [76.2 to 125.3] reactions per million anesthesia.[39]

Mortality of Anaphylaxis

The mortality associated with perioperative anaphylaxis is estimated to be 1.4 to 6%, with approximately 2% of survivors developing anoxic cerebral injury.[40,41] The U.S. data by Gonzalez-Estrada evaluated fatal and near-fatal outcomes incidence in perioperative examining a 2005 to 2014 Nationwide Inpatient Sample. From their 9-year evaluation of 5,223 anaphylaxis events, 7% were fatal or near-fatal cases, of which 2% were fatal and 5% near-fatal.[38] In France, the mortality rate was estimated at 4.1% after neuromuscular blocking agent–related reaction and 5% after intensive care unit admission for severe anaphylaxis.[42,43]

Table 3. Differential Diagnosis

Other causes of isolated respiratory or airway symptoms
• Acute bronchospasm/asthmatic reaction
• Air embolus
• Aspiration
• Endotracheal tube malposition
• Postextubation stridor
• Pulmonary edema
• Tension pneumothorax
• Transfusion-related acute lung injury (TRALI)
Other causes of hypotension/vasoplegia
• Arrhythmias
• Cardiac tamponade
• Cardiogenic shock
• Hemorrhage
• Overdose of vasoactive drugs
• Partial sympathectomy from spinal/epidural anesthesia
• Pulmonary embolus
• Sepsis
• Vasovagal reaction
• Venous air embolism

The differential diagnosis of an allergic or anaphylactic reaction during or following general anesthesia includes a broad list of reactions and physiologic events.[30,33] Tryptase levels should be *normal* in all of these other disorders to rule out anaphylaxis.

Agents Implicated in Perioperative Anaphylaxis

In surgical patients, multiple agents are administered, often in close temporal sequences to each other, making it sometimes challenging to determine the causative agent based on history regarding what agent may have been responsible for producing anaphylaxis. The agents most often implicated in immunoglobulin E–mediated reactions are antibiotics, neuromuscular blocking agents, dyes, and chlorhexidine. Other agents, such as transfusion therapies or blood products and sugammadex, are also involved in perioperative reactions, although the mechanism is not clearly understood. Table 4 summarizes the main allergens identified in immunoglobulin E–mediated reactions. Unfortunately, identifying the causative agent is challenging, and some may not be identified in approximately 40% of cases.[2]

Most of the medications or agents responsible have been reported in different countries, although the rank order may differ, potentially due to differences in clinical practice, differences in the environment or in reporting. From limited U.S. reporting, antibiotics are the most commonly reported causes of perioperative anaphylaxis. The situation is similar in the United Kingdom but is in distinct contrast to neuromuscular blocking agents most often implicated in European reports.[44,45]

Antibiotics

Patients receive antibiotics for prophylaxis as part of most surgical procedures, usually before but sometimes during

Table 4. Agents Implicated in Perioperative Hypersensitivity Reactions

Frequently reported
• Antibiotics: penicillins, cephalosporins, glycopeptides
• Neuromuscular blocking agents: mainly succinylcholine and rocuronium
• Chlorhexidine
• Dyes (particularly patent blue)
• Sugammadex
Less commonly reported
• Latex
• α-Galactosidase; gelatins
• Allogeneic blood components
• Hypnotics
• Opioids
• Radiocontrast media
Very rare
• Local anesthetics

the induction period. In studies reported from France, antibiotics were the causative agents for 18% of reported cases, mainly due to β-lactams with an increased involvement of cephalosporins, particularly cefazolin.[2,31] In studies reported from Germany that included 107 patients, 53 cases were able to determine the drug responsible, of which 24 (45%) were due to antibiotics.[46] A prospective United Kingdom registry reported 286 cases through a 1-year period,[40] that identified the culprit agent in 199 cases, of which 47% percent were from antibiotics, mainly teicoplanin. In the United States, 50% of documented immunoglobulin E–mediated reactions were due to antibiotics.[45,47] Of the different antibiotics administered, penicillin and cephalosporin (β-lactam agents) due to immunoglobulin E–mediated anaphylaxis, and vancomycin or teicoplanin (glycopeptides) are most often reported.

Neuromuscular Blocking Agents

Neuromuscular blocking agents are one of the main allergens involved in perioperative anaphylaxis and represent the first or second cause of perioperative anaphylaxis in many countries. In France, neuromuscular blocking agents accounted for 60% of immunoglobulin E–mediated perioperative anaphylaxis in the latest Groupe d'Étude Des Réactions Anaphylactiques Périopératoires survey.[2] The incidence is estimated at 184 [139 to 230] reactions per million anesthesia with a high female predominance (251 [190 to 313] reactions per million anesthesia).[39] Neuromuscular blocking agent–related reactions are also common in countries such as the United Kingdom, Spain, Australia, New Zealand, Norway, and Belgium.[31] These reactions appear to be less common in the United States, Denmark, or Sweden. The risk of reaction appears to be different between neuromuscular blocking agents, with a higher risk with succinylcholine and rocuronium and the lower risk with cisatracurium.[2,48,49] Cross-reactions are common between neuromuscular blocking agents and are not predictable based on the pharmacologic class. Thus, without appropriate allergic investigation, the use of an neuromuscular blocking agent after a reaction should be carefully considered.

Several suggestions can be made to explain the difference among countries. The immunoglobulin E recognition site for neuromuscular blocking agents is the quaternary ammonium group, which is also present in other drugs and certain environments. The frequency of neuromuscular blocking agent–related reactions decreased significantly in Norway after the withdrawal of pholcodine, a cough suppressant that contains a quaternary ammonium compound and may contribute to neuromuscular blocking agent sensitization.[50] Moreover, a recent case-control analysis showed that exposure to pholcodine was associated with an increased risk of neuromuscular blocking agent–related reaction.[49] Some topical cosmetics and cleaning agents also contain quaternary ammonium compounds, and exposure to such an environment has been associated with an increased prevalence of anti-quaternary ammonium sensitization.[51]

Chlorhexidine

Chlorhexidine is an antiseptic agent used for skin preparation/surgical scrub that accounted for 9% of the cases in the United Kingdom prospective registry previously described.[40] These reactions are also frequently reported in Belgium, Australia, and Denmark, whereas they remain infrequent in France, probably due to the predominant use of povidone-iodine in the operating room.[32] Patients may have previous sensitization due to extensive previous exposure to antiseptic mouthwashes, topical solutions, or previous antiseptic use.

Sugammadex

Sugammadex is a large molecular weight (2,178 Da) cyclodextrin used to reverse steroidal neuromuscular blocking agents by binding to the inner cyclic structure. From a systematic review in 2014, it was estimated to produce anaphylaxis in 1:3,500 to 1:20,000 exposures, but from the 2018 United Kingdom evaluation, the rate was 1:64,000 exposures.[40,52] Reactions to sugammadex appear to be particularly frequent in Japan.[53] A recent investigation evaluated the hypersensitivity responses and mechanisms of reactions after rechallenging sugammadex administration in a blinded placebo-controlled study of volunteers randomly assigned to receive three repeat intravenous administrations. Hypersensitivity was noted in 0 of 150 subject receiving placebo, 1 of 148 subjects receiving 4 mg/kg, and 7 of 150 subjects receiving 16 mg/kg.[54] Evaluating tryptase and other sensitive biomarkers for anaphylaxis, and the dose-dependent response indicates that observed reactions were not immunologically mediated by immunoglobulin E/immunoglobulin G but rather suggest another mechanism of immediate hypersensitivity reaction.

Galactose-α-1,3-galactose Allergy

After a tick bite, patients can develop an allergic reaction to a carbohydrate allergen called galactose-α-1,3-galactose.[55,56] Patients sensitized to galactose-α-1,3-galactose develop allergic reactions to red meat, but also potentially animal-derived products such as gelatin from topical hemostatic agents or intravascular volume expanders. The role of galactose-α-1,3-galactose continues to be determined, especially in geographical areas where sensitization to galactose-α-1,3-galactose is known to be present. As noted, a positive history does not preclude animal-derived product use, such as heparin, but the surgical team should have increased vigilance so that reactions are detected promptly.

Others Causes

Dyes, mainly used by surgeons during surgery (*e.g.*, for sentinel node mapping) are the third most common cause

of perioperative anaphylaxis in France. In the last survey from the Groupe d'étude Des réactions Anaphylactiques périopératoires, dyes and mainly patent blue were responsible for 5.4% of all perioperative anaphylactic reactions. These reactions often occur during or at the end of the procedure due to the route of administration.[2,57]

Allergic reactions to latex were common in the 1990s. The human immunodeficiency virus epidemic led to a high demand for latex, which led to the use of lower-quality latex with higher protein content, ultimately leading to an increase in patient and staff sensitization. The implementation of primary and secondary prevention measures, as well as the use of powder-free gloves with better quality latex, has led to a significant reduction in latex-induced perioperative hypersensitivity in recent years.[58,59]

Allergic reactions due to local anesthetics are very rare, and most hypersensitivity reactions are due to the intravascular passage of epinephrine added to the local anesthetic solution.[60]

Patients at Increased Risk

Perioperative anaphylaxis is not predictable; however, certain patients may be at a higher risk. For example, multiple previous surgeries, patients with spina bifida, latex fruit syndrome, and healthcare workers are at risk for latex allergy.[33,34] Patients with mastocytosis or other mast cell disorders are at risk for hypersensitivity reactions to drugs, although not specifically to anesthetics. A previous perioperative anaphylactic reaction is a major risk for recurrence and should prompt the anesthesiologist to review the previous reaction.

Several factors are not *per se* risk factors for perioperative anaphylaxis but contribute to the severity of the reaction. Urgent surgery, higher American Society of Anesthesiology physical status score, obesity, β-adrenergic blocker, and/or angiotensin-converting enzyme inhibitor therapy have been identified as potential risk factors for adverse outcomes and increased mortality.[40,42] An asthma history was not associated with an increased risk of developing intraoperative bronchospasm or anaphylaxis.[61]

Table 5 lists a potential management strategy for patients with specific allergies in the perioperative period if allergy workup has not been performed or is not available.

Table 5. What Should the Anesthesiologist Do When the Patient Claims to be Allergic to Something Without Having Done an Allergy Test?[33,61–71]

Claimed Allergy	Management
During a previous general anesthesia	Consider performing local-regional anesthesia If not possible: avoid all neuromuscular blocking agents and histamine-releasing drugs. Consider latex-free environment.
Local anesthetics	Consider general anesthesia
Codeine/morphine	Avoid codeine and morphine. All the other opioids can be used.
Chlorhexidine/povidone iodine	Switch the skin disinfectant class.
ß-Lactams	Substitution for surgical prophylaxis in accordance with local protocols for patients or surgery at low risk of infectious complication. Consider aztreonam and carbapenems for antibiotic therapy (if suspected allergy to ceftazidime, aztreonam should be avoided).
Latex	Inform all relevant parties of the latex allergy. Latex-free environment. Program the patient in the first position in the operating list.
Latex fruit syndrome: allergy to banana, kiwi, chestnut, avocado.	Consider performing the surgery in a latex-free environment if not standard practice*
Egg or soy	Propofol can be used, no contraindication.
Peanut	No known contraindication for any anesthetic drug
Seafood	No known contraindication for any iodinated drugs or protamine
Red meat or galactose-α-1,3-galactose	Avoid gelatin colloids and gelatin-containing glues

*Although most operating rooms have eliminated latex products

Clinical Management of Anaphylaxis

Initial Management

Early recognition and prompt cardiopulmonary resuscitation with epinephrine and a potential multimodal strategy are listed in table 6.[33] Unlike out-of-hospital anaphylaxis where intramuscular epinephrine is the cornerstone of management, intravenous epinephrine, and potentially other vasoactive agents are important for initial management, as noted in advanced cardiac life support algorithms titrated to specific effects. Volume administration is required due to the profound hypovolemia that can occur during perioperative anaphylaxis.

Perioperative Blood Sampling

Because of the many possible differential diagnoses, characterization of mast cell activation is of particular interest to support the diagnosis of perioperative anaphylaxis. Although not all anaphylaxis is mast cell related (immunoglobulin G–mediated anaphylaxis, contact phase activation, nonspecific histamine release), the most common, immunoglobulin E–mediated anaphylaxis, involves mast cell activation.[62] Thus, an increase in tryptase levels is a strong argument for this mechanism. After the start of initial resuscitation, serum blood samples should be sent for tryptase measurement to support the diagnosis of anaphylaxis over other potential causes of hemodynamic instability. The serum tryptase level does not increase immediately after the reaction, and blood should be drawn from 30 min to 2 h after the start of the reaction, when the serum level is at its maximum, to avoid false negatives. Normal values

Table 6. Management Considerations for Perioperative Anaphylaxis

Initial therapy

1. Stop the administration of all suspected allergens. Call for help.
2. Maintain airway maintenance with 100% oxygen. Consider intubation if it is not already done.
3. Administer epinephrine as soon as possible and titrate to restore arterial blood pressure with initial dosing at 10 to 50 μg per bolus. Consider increased dose in case of treatment with β-blockers and continuous infusion if repeated boluses are required.
4. Initiate intravascular volume expansion using large intravenous catheters, with crystalloids up to 20 to 30 ml/kg as a first-line therapy. Additional intravascular volume administration should be considered based on invasive monitoring or echocardiography if available. Colloids could be considered as a second-line therapy if hypovolemia persists and if not suspected to be responsible for the reaction.
5. Asystole/pulseless electrical activity: Cardiac surgical patients should all have pacing capabilities, and ventricular, atrial, or atrioventricular pacing used.

Secondary therapy

6. In case of refractory hypotension:
   a. Consider intravenous vasopressin administration starting at doses of 1 to 2 units. In patients with cardiac arrest, 40 units are part of Advanced Cardiac Life Support guidelines.
   b. Consider norepinephrine in continuous infusion
   c. Consider methylene blue at 1.5 to 3 mg/kg for 30 min
7. In case of severe bronchospasm, consider nebulization of $ß_2$-agonists. Epinephrine should be preferred if cardiovascular signs are associated. Reassess ventilatory mode to be sure appropriate inspiratory/expiratory ratios for patients. Patients may develop bronchospasm and need longer exhalation times.
8. Sugammadex has been proposed for rocuronium-induced reactions. Data on its efficacy are lacking, and sugammadex itself may trigger reactions. It should only be used as a last-line rescue therapy.
9. Corticosteroids (methylprednisolone 1 mg/kg) should be considered because they may have value in the early hours of any postresuscitation period
10. In medical centers with additional potential for extracorporeal membrane oxygenation, patients with refractory shock or cardiac arrest may be a potential consideration.

Overall, when acute hypotension or shock occurs, initial resuscitation based on Advanced Cardiopulmonary Life Support (ACLS guidelines; A, B, C, D) should be considered. Specific therapy of anaphylactic shock includes epinephrine, the cornerstone of therapy, and intravascular volume administration. Management considerations should be multimodal with a plan in mind. A potential therapeutic plan is detailed in the table.

are defined as less than 11.4 μg/l by the manufacturers. A peak tryptase level greater than 9.8 μg/l has been associated with a positive allergy workup with good sensitivity and specificity, and a peak tryptase level greater than 33 μg/l was very specific in identifying an agent responsible for the reaction.[63] However, lower levels of peak tryptase have been associated with mast cell activation. Moreover, patients with hereditary α-tryptasemia or mastocytosis may have basal tryptase levels above this threshold, leading potentially to a wrong diagnosis of mast cell activation.[64] Thus, sampling of a basal serum tryptase level at least 24 h after resolution of anaphylaxis is recommended by several scientific societies and is particularly relevant if there is a small increase in the peak tryptase level. A tryptase peak greater than 1.2 × basal level + 2 μg/l defines mast cell activation in this case.[65]

Proceeding with Surgery After a Reaction

The decision to proceed with surgery after anaphylaxis should be individualized depending on the severity of the reaction, cardiopulmonary stability, and the urgency of the procedural intervention. Ultimately, the clinicians involved must use clinical judgment to determine the most sensible course of action. In one retrospective analysis, proceeding with surgery was without reported complications after grade 1 or 2 anaphylactic reactions (limited to cutaneous signs and/or vital sign changes that are not life-threatening). After grade 3 reactions (profound hypotension or severe bronchospasm), the risk of adverse events attributable to the reaction was higher but did not differ in cases where surgery was continued or abandoned.[66] Surgical procedures were frequently abandoned after grade 4 reactions (associated with cardiac arrest and/or inability to ventilate) in this study, although there was no evidence of further harm as a result of proceeding with emergency or partially completed major surgery. In the 2018 United Kingdom prospective registry, the surgical procedure was not started or abandoned in more than one-half of the cases with a grade 3 or higher anaphylactic reaction, including 10% where surgery was urgent.[67]

If the patient is stabilized after the reaction, it may be worthwhile to proceed with the surgery to avoid the need for further anesthesia, keeping in mind that all suspected allergens should be avoided, including all neuromuscular blocking agents (if suspected, not just the one causing the reaction).

What Anesthesiologists Should Know about Allergy Workup

If perioperative anaphylaxis is suspected, European guidelines suggest the patient should be referred to an allergist.[68] Because most allergists do not have extensive experience with perioperative anaphylaxis and are unfamiliar with the anesthetic agents, if the patient is to be referred, in Europe, a specialized center with expertise in perioperative anaphylaxis evaluation is often used where skin testing can be performed to determine the potentially responsible drug and/or use the results to evaluate alternative agents.

A detailed history of the anesthetic protocol and reaction is mandatory for an allergic investigation, including communication between anesthesiologists and allergists. Providing a copy of the anesthesia record can be helpful to allergists, as well as a detailed history of the reaction, temporal sequences of drug exposure, and potential drugs implicated. To avoid false-negative skin tests (due to skin anergy after massive mast cell degranulation), allergy consultation should occur at least 6 weeks after the reactions and, if possible, within the first year.

Because provocation tests using anesthetic agents involve a high level of risk for the patient, the allergy workup is

mainly based on skin tests (skin prick test and intradermal reactions) using different nonirritating drug concentrations validated on a cohort of healthy volunteers.[69] Skin tests to neuromuscular blocking agents evaluated in these conditions have a good negative predictive value (95%) allowing for identification of a safe anesthetic protocol in most cases.[70]

When skin tests are uninterpretable (dermographism, skin anergy), several diagnostic tools can be useful. Several types of specific immunoglobulin E assays have been developed to detect specific immunoglobulin E antibodies to quaternary ammoniums (for neuromuscular blocking agents, either by the Immunocap method (c260, c202) or by radioimmunoassay), latex, thiopental, chlorhexidine, galactose-α-1,3-galactose, or penicillin. Most of these specific immunoglobulin E antibodies have a good specificity in case of perioperative reaction (high pretest probability of having an allergy to anesthetics) but their specificity is not evaluated in the general population (very low pretest probability of having an allergy to anesthetics), which excludes the use of these specific immunoglobulin E antibodies to predict the risk of a reaction. The *in vitro* basophil activation test has been reported, although the place of this test in the diagnostic strategy is not well defined.[71]

At the end of the allergic workup, the drug responsible for the reaction is not always identified (up to 40% of cases in certain series), which may lead to difficulties during subsequent anesthesia. Several teams around the world are currently trying to define a safe provocation test protocol for general anesthesia. These provocation tests should be performed with caution and, due to the lack of guidelines, should only be performed in clinical studies.[68,72]

In certain immunoglobulin E–mediated reactions, especially due to antibiotics, it may be possible to desensitize patients if a crucial antibiotic is required; however, data for anesthetic agent desensitization are not available. In certain nonimmunologic reactions, including those to radiocontrast media, pretreatment with antihistamines and glucocorticoids or the use of lower osmolar contrast can reduce the severity or frequency of the reaction.

Conclusion

Perioperative anaphylaxis is a rare complication of anesthesia but can be associated with major morbidity and mortality. Prompt recognition of the reaction and early administration of epinephrine and fluid resuscitation are the cornerstones of its management. Blood sampling for tryptase can help support the diagnosis of mast cell activation. It is worthwhile to perform an allergic workup after the reaction to identify the culprit agent and provide guidance for future anesthetics.

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Competing Interests

Dr. Iba received research grants from Japan Blood Products Organization (Tokyo, Japan) and Asahi Kasei Pharmaceuticals (Tokyo, Japan). Dr. Levy has served on steering committees, safety monitoring boards, or advisory boards for Instrumentation Labs (Bedford, Massachusetts), Octapharma (Lachen, Switzerland), Leading Biosciences (Solana Beach, California), and Merck (Kenilworth, New Jersey). Dr. Tacquard declares no competing interests.

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