

AANA Journal Course

Update for Nurse Anesthetists



Anesthetic-Induced Anaphylaxis

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The purpose of this course is to update nurse anesthetists about anesthetic-induced anaphylaxis. This course discusses the pathophysiologic process of anaphylaxis with descriptions of the allergic immune response and the mediators and mechanisms of mast cell activation. The preoperative identification of patients at high risk and the assessment of potential anesthetic triggers of a hypersensitivity and/or allergic reaction are prudent strategies to minimize the risk of anaphylaxis. Other practices recommended for clinicians include suggestions for anesthetic management

to decrease threat of an allergic response in high-risk patients. Furthermore, the identification of the severity grade of hypersensitivity reactions and the appropriate treatment of perioperative anaphylaxis is discussed. In addition, postoperative and follow-up interventions, including testing for patients who have had an anesthetic-induced hypersensitivity reaction, are considered.

Keywords: Anaphylaxis, anesthesia, hypersensitivity reaction, IgE.

Objectives

After completion of this course, the reader should be able to:

1. Recognize the pathophysiologic process of anaphylaxis, its mediators and mechanisms, and the primary cells involved, including mast cells and basophils.
2. Describe the symptoms and determine the severity of anesthetic-induced anaphylaxis.
3. Identify preoperative surgical patients who are at a higher risk for anaphylaxis during anesthesia.
4. Identify anesthetic drugs that may trigger anaphylactic reactions, and examine strategies to prevent perioperative anaphylaxis.
5. Formulate an appropriate treatment protocol for anesthetic-induced anaphylaxis, and suggest the diagnostic tests essential for the evaluation of drug hypersensitivity.

Introduction

Anaphylaxis is a severe allergic reaction that can be life threatening with rapid onset and can occur with or without exposure to a known allergen.¹ The incidence during anesthesia ranges from 1 in 4,000 to 1 in 25,000 patients.² If not promptly diagnosed and treated, a sudden, severe, or prolonged reaction can lead to car-

diovascular collapse resulting in perioperative death.³ Anaphylaxis is fatal in 3% to 10% of surgical cases.⁴ Hypersensitivity to anesthetic drugs remains a substantial hazard for patients at increased risk because it is difficult to promptly recognize; consequently, the proper treatment may be delayed.⁵ In addition, the lack of specific molecular markers for confirmation of anaphylaxis impedes accurate diagnosis.⁶ The unreported financial burden resulting from perioperative anaphylaxis may be unknown but substantial; food-induced anaphylaxis costs were more than \$500 million in 2007.⁷

Pathophysiologic Process

• **Types of Allergic Reactions.** Type I allergic hypersensitivity reactions resulting in anaphylaxis are now defined as immunoglobulin E (IgE)-triggered and non-IgE-triggered (previously known as anaphylactoid) reactions.¹ Types II, III, and IV reactions do not result in anaphylaxis (Figure 1).³ Type I IgE-mediated anaphylaxis occurs on subsequent exposure after a patient is sensitized to an antigen. The production of an antigen-specific IgE is critical to eliciting an anaphylactic response. On reexposure, the antigenic protein binds to IgE antibodies on the high-affinity receptor for IgE (FcεRI) on the cell walls of mast cells and basophils. Multivalent allergens need to cross-link with at least 2 IgE receptor sites on

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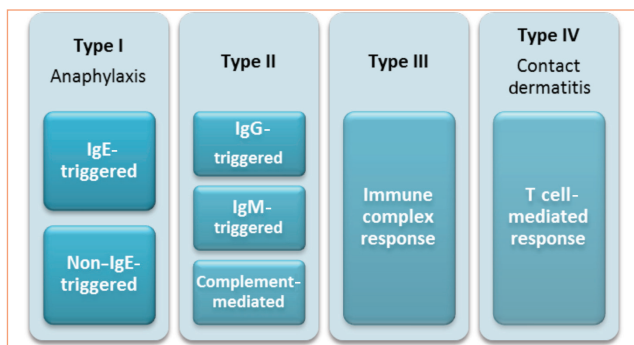


Figure 1. Types of Allergic Hypersensitivity Reactions³
Abbreviation: Ig, immunoglobulin.

the surface of the cell membrane to induce the release of inflammatory mediators.⁸ Allergen activation causes the eruption of potent preformed and newly generated inflammatory mediators from mast cells and basophils (Figure 2).^{3,9-12}

Type I non-IgE immunologic reactions can occur with the first exposure to the antigen and can be indistinguishable from IgE-mediated responses.⁹ Nonimmunologic mechanisms may be idiopathic or may result from a combination of mechanisms. Non-IgE reactions may directly trigger the release of histamine, may occur in response to complement or bradykinin activation, or can be mediated by an IgG antigen (see Figure 2).^{3,9-12} In an 8-year survey of surgical patients who experienced anaphylaxis, IgE-mediated reactions were more frequent ($n = 1,816$ [72.2%]) and severe (grade 3; $n = 1,092$; [60%]) than non-IgE reactions, which occurred less frequently ($n = 700$; [27.8%]) and were milder (grade 1; $n = 372$; [53%]).¹³

- **Mast Cells and Basophils.** Although mast cells are present in all tissues, basophils circulate in the vasculature. Mast cells are found within most organs and tissues, especially in the heart, vasculature, respiratory and gastrointestinal tracts, and integument. The release of cell mediators is controlled by calcium channel receptors. Mast cells and basophils have similar receptors and functions: to respond to signals of innate and adaptive immunity and to release inflammatory mediators, but the role of basophils has not been defined in human anaphylaxis.⁸

The early phase of an allergic reaction that induces mast cell degranulation may be followed by a late phase reaction with the release of cytokines that can interact with T-helper type 2 cells. In turn, cytokines such as interleukin 4 (IL-4) stimulate B cells to generate IgE and further stimulate mast cells and eosinophils.¹⁴ Lipids, free radicals, and/or inflammatory proteins and enzymes also regulate the innate immune response. The cascading complement system (C_{3a} - C_{5a}) directly activates the release of mediators through non-IgE mechanisms.¹¹ Allergic sensitization occurs when T lymphocytes are signaled by an antigen-presenting cell such as dendritic cells in the lymphatic system and then interact with B cells

to induce IgE production. The B lymphocytes develop into plasma cells that secrete immunoglobulin antibodies such as IgG or IgE or memory cells with receptors that remember antigens. Because gene segments encode the formation of hundreds of allergen-specific B and T cells, millions of different receptors can develop with long-lasting memory.¹⁵

Inflammatory Mediators

Inflammatory mediators released from mast cells and basophils such as histamine, proteases (among which is tryptase), leukotrienes, and prostaglandins elicit immediate symptoms of an allergic reaction such as pruritis, wheezing, or hypotension, and can induce cardiovascular collapse (Table 1).^{3,8,9,12} The inflammatory mediators released from cardiac mast cells such as cysteinyl leukotrienes and prostaglandins decrease myocardial perfusion and contractility. Platelet-activating factor can constrict the coronary arteries, decrease coronary perfusion and contractility, and can contribute to coronary plaque rupture. Furthermore, cardiac mast cells can release chymase and carboxypeptidase, which activate the renin-angiotensin system.¹⁶

Histaminergic System

Four types of histamine (H) receptors are distributed throughout the body. The H_4 receptors are found in the innervations of the vasculature and cells of the blood, lung, liver, spleen, and gut; stimulation of the H_4 receptors precipitates inflammation. The central nervous system is regulated by H_1 , H_2 , and H_3 receptors. The H_3 neurons in the tuberomammillary nucleus of the hypothalamus control neurotransmitters. The release of histamine is modulated by feedback from the H_3 autoreceptors and from muscarinic, α_2 -adrenergic, and peptidergic receptors. The tuberomammillary nucleus controls the release of acetylcholine and other neurotransmitters. This hypothalamic center is regulated by H_3 autoreceptors that are inhibited by histamine. Inflammatory mediators released by tissues stimulate the afferent sensory fibers to the central nervous system, which causes the efferent vagus nerve release of acetylcholine. At the parasympathetic ganglion via autoinhibitory mechanisms of the postganglionic nerves, the nicotinic or muscarinic receptors release acetylcholine.¹⁴ Stimulation of the H_3 receptors of the presynaptic terminals of sympathetic nerves inhibits epinephrine release from the adrenals, heart, and the peripheral vasculature.³

The H_2 receptors regulate cognitive brain function and the function of the gastric and immune systems. The H_2 receptors in the gut stimulate proton pump secretion of gastric acid. The H_1 receptors are distributed widely throughout the entire body and nervous system. The release of histamine stimulates the H_1 receptors of smooth muscle, causing constriction of the bronchi and

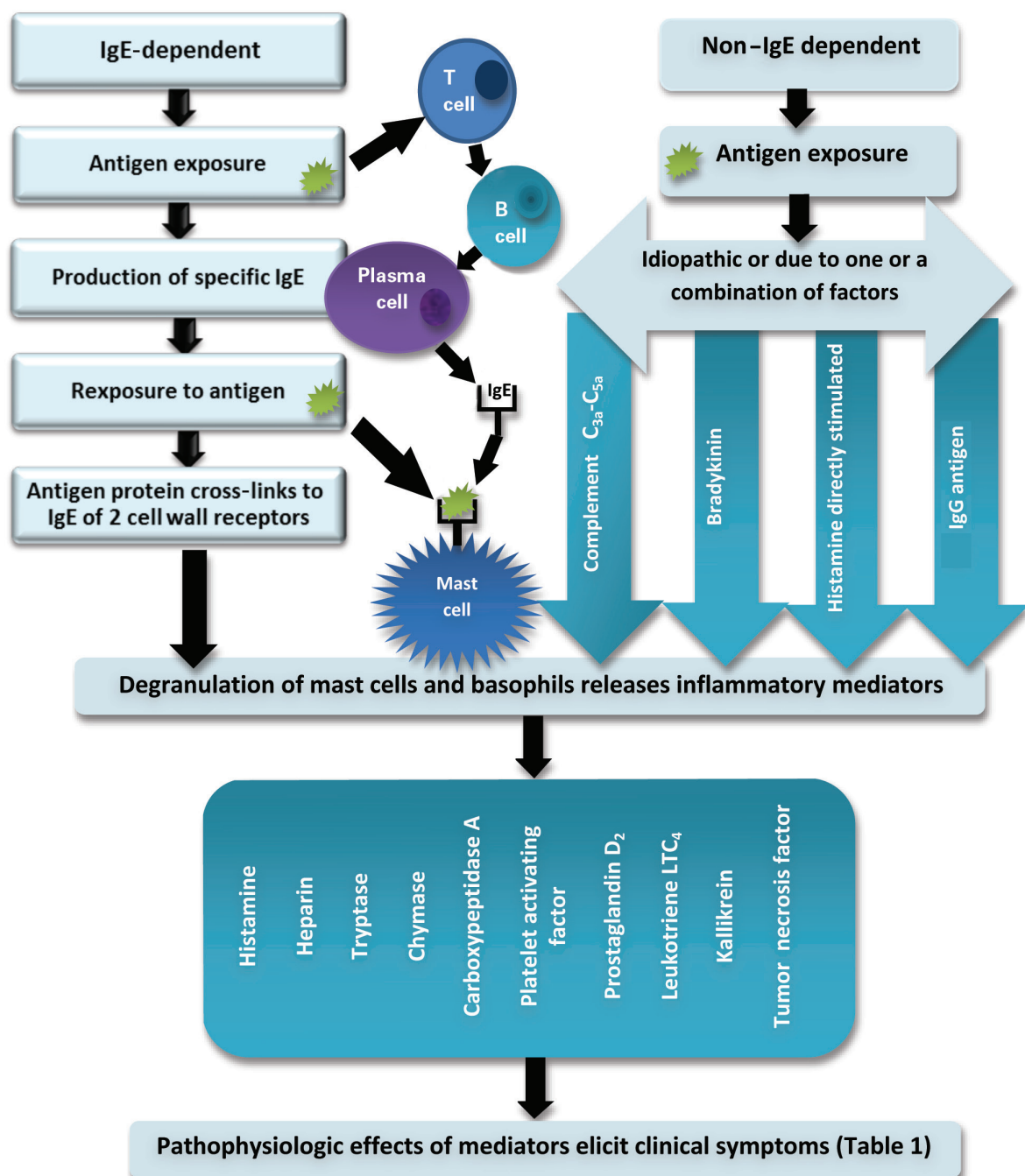


Figure 2. Physiologic Pathways to Type I Hypersensitivity Reactions^{3,9,10,12,15}

Abbreviations: Ig, immunoglobulin; PAF, platelet-activating factor.

vasodilation.¹⁷ Activation of the H₁ receptors in the coronary vasculature may precipitate dysrhythmias, myocardial ischemia, cardiac depression, hypotension, shock, and cardiac arrest.¹⁶

Clinical Presentation

- **Symptoms.** Surgical patients experiencing anaphylaxis may have early cutaneous symptoms such as pruritis, flushing, erythema, urticaria, or angioedema. Cutaneous

signs can be followed by respiratory, gastrointestinal, or cardiovascular symptoms with hypotension and organ dysfunction.¹⁸ A systemic allergic response can quickly progress to respiratory problems with rhinorrhea, shortness of breath, cough, chest or throat tightness, wheezing, hypoxia, hypercarbia, and increased peak airway pressure. An allergic reaction during anesthesia can suddenly occur with cardiovascular collapse, resulting in hypotension, tachycardia, dysrhythmias, shock, or

Mediators	Pathophysiologic effects
Histamine	H ₁ : Mucus secretion, edema, cardiac depression, coronary vasoconstriction, renin release; H ₂ : gastric acid secretion, nitric oxide induction, vasodilatation, tachycardia; H ₃ : decreased norepinephrine level; H ₄ : chemotaxis, inflammation
Heparin	Anticoagulation, activates prekallikrein and contact systems, bradykinin
Tryptase	Activates prekallikrein and complement, bradykinin, anaphylatoxins
Chymase	Renin production, compensatory norepinephrine secretion, dysrhythmias
Carboxypeptidase A	Prostaglandin and leukotriene synthesis, inflammation
Platelet-activating factor	Bronchoconstriction, decreased coronary blood flow and contractility, nitric oxide induction, vasodilatation, hypotension, platelet aggregation, recruitment of neutrophils and eosinophils, biphasic late response, anticoagulation
Prostaglandin D ₂	Bronchoconstriction, pulmonary and coronary vasoconstriction, peripheral vasodilatation, vascular permeability, hypotension, flushing, urticaria
Leukotriene LTC ₄	Bronchoconstriction, airway remodeling, angioedema, nitric oxide induction, increased vascular permeability, hypotension
Kallikrein	Renin production, complement activation, fibrinolysis, clotting
Tumor necrosis factor	Neutrophil activation, chemokines, cytokines, effector cell recruitment

Table 1. Major Mediator Actions of Mast Cells and Basophils Implicated in Anaphylaxis^{3,8,9,15}

death.³ An allergic reaction can cause acute coronary spasm or myocardial infarction (Kounis syndrome).¹⁹ Gastrointestinal distress (nausea, vomiting, diarrhea, abdominal pain, or incontinence) and neurologic symptoms (headache, anxiety, diaphoresis, presyncope, confusion, unconsciousness, or seizures) may be associated with inadequate tissue perfusion due to hypotension and hypoxia.¹⁸ Anaphylaxis can also result in decreased renal output with acute tubular necrosis or disseminated intravascular coagulation.³

Anaphylaxis Severity Scale

The severity of anaphylaxis symptoms is rated by using the Ring and Messmer severity scale (Table 2).^{18,20} Mild grade I reactions show cutaneous or mucosal signs. A moderate grade II reaction can result in multiorgan involvement with possible cutaneous signs and cardiovascular, respiratory, and gastrointestinal symptoms. Grades III and IV reactions may be life threatening. A severe grade III systemic reaction manifests with cardiovascular collapse and profound hypotension leading to inadequate tissue perfusion and arrhythmias; bronchospasm and hypoxia ($\text{Sao}_2 \leq 92$) are common; neurologic symptoms (confusion or unconsciousness) may develop; and gastrointestinal distress or incontinence may occur. Death can rapidly occur after the sudden onset of a serious grade IV reaction. A critical grade IV reaction manifests as pulseless electrical activity or cardiac arrest.^{18,20}

Risk Factors for Anaphylaxis

- **Female Sex.** In Spain, a 5-year study of anesthetic hypersensitivity reactions reported a male-female ratio of 2:3.²¹ Anaphylaxis to sodium thiopental is 3 times more

likely to occur in females.² A patient with previous exposure to cosmetics may subsequently become sensitized to haptens that initiate the development of antibodies predisposing sensitization to anesthesia drugs.²

- **Older Age and Infirmary.** Anaphylaxis is more common and severe in older patients who may have chronic pulmonary or cardiovascular disease. Patients with an upper respiratory infection may have a worsened outcome if anaphylaxis suddenly occurs. Although people with asthma are not at increased risk of hypersensitivity reactions, they are at higher risk of death if anaphylaxis occurs.²⁰

- **Food Allergy.** In a survey of surgical patients who experienced anaphylaxis, patients who reported food intolerance more frequently had IgE-mediated reactions (8.49 vs 3.64; $P < .0001$).¹³ Patients with food allergies may have decreased levels of enzymes that degrade platelet-activating factor, increasing the risk of anaphylaxis. A gelatin food allergy may sensitize patients to colloid volume expanders, resulting in a reaction.²² However, propofol may be derived from egg lecithin, and no strong evidence of cross-reactivity of food allergens with propofol exists. The main allergen of egg is ovalbumin (found in the egg white), and the lecithin in propofol is derived from the egg yolk protein, which may explain the low incidence of propofol allergy. Also, the soy and peanut oils in propofol are refined to eliminate allergenic proteins.²³ Patients with food allergies to fruits (such as banana, pear, kiwi, fig, mango, passion fruit, and papaya), nuts (such as chestnuts, hazelnuts, walnuts, or peanuts), and avocado have been associated with latex cross-sensitivity.²⁴

- **Latex Allergy.** Latex has been a common cause

Grade I	Grade II	Grade III	Grade IV
Cutaneous	Cutaneous	Cardiovascular	Cardiovascular
Erythema	Grade I signs	Grade II signs plus	Pulseless electrical activity
Pruritis	Cardiovascular	Cardiovascular collapse	Cardiac arrest
Urticaria	Hypotension	Profound hypotension	Death
Angioedema	Tachycardia	Bradycardia	
	Presyncope	Dysrhythmia	
	Respiratory	Respiratory	
	Dyspnea	Bronchospasm	
	Wheezing	Hypoxia ($\text{SaO}_2 < 92\%$)	
	Gastrointestinal	Gastrointestinal	
	Nausea	Grade II signs plus	
	Vomiting	Incontinence	
	Diarrhea	Neurologic	
	Abdominal pain	Confused	
		Unconscious	

Table 2. Severity Grades for Anaphylaxis Signs and Symptoms^{18,20}

of perioperative anaphylaxis for more than 2 decades, although the incidence is decreasing. Latex gloves are the most common trigger.²⁴ Of the surveyed patients experiencing latex anaphylaxis, a significant association with a history of atopy, asthma, or food intolerance was found ($P < .0001$).¹³ However, atopic patients or patients with an allergy history are not considered at risk for anaphylaxis if they are not exposed to the trigger. But, atopic healthcare workers are at an increased risk of latex allergy. Patients who have frequent multiple surgeries with exposure to latex products (such as for spina bifida) and healthcare workers may be at higher risk of anaphylaxis due to sensitization to latex. Patients who are allergic to latex should be scheduled for the first case of the day with all latex products removed from the room.²⁴ Latex may be considered the triggering agent if the causative agent of a hypersensitivity reaction cannot be identified.²⁵

- **Cardiovascular Disease.** Patients with ischemic heart disease or dilated cardiomyopathy may have severe allergic reactions because of a greater density of myocardial mast cells.¹⁶ Patients undergoing cardiac surgery are at risk of anaphylaxis because they receive multiple drugs, polypeptides (such as aprotinin, latex, or protamine), blood, and volume expanders.¹⁰ Patients with cardiac conduction defects, increased vagal tone, or taking sympatholytic medications may not have tachycardia if anaphylaxis occurs. In addition, surgical patients taking β -adrenergic receptor antagonists (β -blockers) may have an inadequate response to treatment for anaphylaxis. Administration of β -blockers can predispose patients to bronchospasm or hypotension and bradycardia due to decreased cardiac contractility. Patients taking β -blockers

can become severely hypertensive when epinephrine is administered because of unopposed α -adrenergic tone and reflex vagotonic effects. Furthermore, people who are taking angiotensin-converting enzyme inhibitors may also be less responsive to epinephrine. Patients taking angiotensin-converting enzyme inhibitors may have a substantially increased severity of allergic reactions. An increased serum bradykinin level due to low serum angiotensin-converting enzyme levels and decreased platelet-activating factor acetylhydrolase levels may increase the risk of anaphylaxis. Patients taking angiotensin II blockers may also be resistant to epinephrine.²

- **Previous Anaphylaxis.** A history of perioperative anaphylaxis is the greatest risk factor for anesthetic-induced anaphylaxis. Patients who have reported urticaria or angioedema during anesthesia are at higher risk for another reaction. A family history of anesthetic allergy or multiple drug allergy syndromes may also indicate the potential for hypersensitivity.²³

- **Mast Cell Diseases.** Patients with mastocytosis or clonal mast cell diseases can have exaggerated release of histamine, leukotrienes, and prostaglandins during anesthesia. Patients with diseases such as hereditary or acquired angioedema that cause increased release of inflammatory mediators may also be sensitive to anesthesia. The patients are at risk for the development of severe angioedema during anesthesia and surgery due to an increased bradykinin level.²⁶ According to Castells, director of the Allergy Immunology Training Program, Harvard Medical School, Boston, Massachusetts:

Mastocytosis patients should receive anti- H_1 and [anti-] H_2 histamine receptor blockers, steroids, and leukotriene blockers preoperatively. One protocol includes prednisolone

(Prednisone), 0.5 mg/kg orally (20 mg for children [younger than 12 years]), 12 hours and 1 hour prior to surgery. One hour preoperatively, they also should take orally either hydroxyzine (Atarax), 25 mg; or diphenhydramine (Benadryl), 25-50 mg (12.5 mg, [younger than 12 years]); ranitidine (Zantac), 150 mg (20 mg, [younger than 12 years]); and montelukast (Singulair), 10 mg (4 mg, [younger than 12 years]). If mast cell stabilizing drugs such as disodium cromoglycate or ketotifen have been previously prescribed, the patient should continue these drugs prior to surgery. To prevent a reaction, all medications, [intravenous] infusions, and local anesthetics administered should be preservative- and alcohol-free solutions. Any β -blocker or other drug that interferes with epinephrine or that contributes to mast cell activation or histamine release should be withheld (Figure 3). Additionally, placing a preoperative arterial blood pressure line and obtaining a baseline serum tryptase level are prudent strategies. If the patient becomes hypotensive, a mature (formerly known as β -) tryptase level should be drawn to compare with baseline values. Maintenance of normothermia also helps to minimize risk in mastocytosis patients (M. C. Castells, MD, PhD, personal communication, March 26, 2011).

- **Triggers.** The anesthetic technique should minimize the risk of hypersensitivity and exposure of high-risk patients to their triggers of anaphylaxis. A patient who has had a previous reaction to a drug should not receive the drug again except during a desensitization process.³ Substitutes should be used if a patient has an allergy to latex or a drug such as an antibiotic or a nonsteroidal anti-inflammatory drug. Although a slow rate of intravenous (IV) administration may prevent a more severe allergic reaction to a drug by minimizing the administered dose of an allergen, a test dose will not prevent anaphylaxis. If a test dose is necessary, wait at least 20 minutes after a small amount is given before administering a drug to a highly allergic patient (M. C. Castells, MD, PhD, personal communication, March 26, 2011). The risk of an allergic reaction may be lowered by avoiding the use of muscle relaxants during general anesthesia and using an alternative to intubation such as a laryngeal mask airway. Regional techniques are preferred over general anesthesia for high-risk patients to minimize the use of drugs that are potential triggers.²² If a patient has had a previous reaction to ionic contrast media, a lower osmolality, nonionic contrast medium should be administered and an ultrasound or magnetic resonance imaging may be more appropriate.²⁶

Impediments to the Recognition of Anaphylaxis

- **Altered Presentation.** Anaphylaxis symptoms can differ slightly in clinical manifestations and severity during a perioperative allergic reaction. A patient's subjective symptoms of anaphylaxis such as itching, nausea, abdominal pain, confusion, and shortness of breath may be masked by unconsciousness or sedation of anesthesia and analgesia. In addition, the common early cutaneous signs such as urticaria cannot always be viewed because patients are covered by drapes during surgery.^{3,26} However, severe perioperative anaphylaxis may not always manifest urticaria or angioedema because of the rapid onset of vasoconstriction, which may impede recognition of

Analgesics	Nonsteroidal anti-inflammatory drugs AVOID morphine or codeine derivatives Meperidine
Anesthetics	Ester local anesthetics
Antibiotics	Amphotericin B AVOID Vancomycin Polymyxin B
Cardiovascular	α -Adrenergic receptor blockers β -Adrenergic receptor blockers Anticholinergics
Muscle relaxants	Atracurium Rocuronium Succinylcholine
Preservatives	Ethanol or other alcohol solutions Metabisulfites
Other	Dextran Dextromethorphan Quinine

Figure 3. Drugs to Administer with Caution for Patients With Mast Cell Disease

(M. C. Castells, Personal communication, March 26, 2011.)

cutaneous signs.¹⁰ Most commonly during an anesthetic, anaphylaxis initially manifests with cardiac arrest and bronchospasm, resulting in oxygen desaturation from decreased inspired tidal volume.²⁷ However, anesthetic-induced anaphylaxis can sometimes occur without hypotension and bronchospasm. Tachycardia can be followed by bradycardia or cardiac arrest, probably due to the Bezold-Jarisch cardioinhibitory reflex originating in sensory receptors in the inferoposterior left ventricular wall.¹ Paradoxical bradycardia due to massive hypovolemia occurs in approximately 10% of severe cases.²⁷

- **Anesthetic Pharmacology.** The symptoms of anaphylaxis may be camouflaged during anesthesia because of the delivery of multiple anesthetic drugs administered in a short time during induction. Although cardiovascular instability is the most important sign of perioperative hypersensitivity, the rapid administration of IV anesthetic drugs can also cause profound cardiovascular changes.²² In addition, surgical patients may more commonly have a rapid onset of anaphylaxis and more severe symptoms because the triggering agent is a potent anesthetic drug administered by the IV route or by contact with the mucous membranes.³ Although prior sensitization, not the drug dose, determines the severity of response and a minute amount of any drug can provoke a reaction, a large dose of the allergen rapidly administered by the IV route can exacerbate severe anaphylaxis symptoms.²⁸

- **Differential Diagnoses.** The cardiovascular symptoms of an allergic reaction may be misdiagnosed as anesthetic overdose, dysrhythmias, hypovolemia or hemorrhage, gas embolism, vasovagal reaction, pericardial tamponade, and septic or cardiogenic shock.²⁶ Rapid IV administration of vancomycin may cause flushing (red man syndrome) and symptoms similar to those of anaphylaxis.²⁰ Allergic respiratory symptoms may mimic postextubation stridor, asthma, pulmonary embolism or edema, and pneumothorax.²⁶

Intraoperative Management

• Perioperative Agents as Triggers

• *Induction Drugs.* Most reactions to anesthetic induction agents are due to the direct release of histamine, especially when the drugs are administered with muscle relaxants. Although patients who are allergic to pentothal may have cross-reactions to other barbiturates, anaphylaxis to propofol is rare.²⁷ There is “no role to contraindicate propofol in egg-allergic, soy-allergic or peanut-allergic patients.”^{23(p320)} However, the administration of propofol to patients with a documented history of true anaphylaxis to eggs is controversial.²⁸ Anaphylaxis to etomidate is also extremely rare. Furthermore, induction with ketamine or midazolam rarely elicits an allergic reaction.²⁷ Preoperative benzodiazepines are indicated for highly allergic patients because stress can lead to mast cell degranulation (M. C. Castells, MD, PhD, personal communication, March 26, 2011). Anaphylaxis to inhaled anesthetics has not been reported,⁵ and sevoflurane inhibits mast cell activation (M. C. Castells, MD, PhD, personal communication, March 26, 2011).

Unusual allergic reactions may occur to amide local anesthetics such as lidocaine, prilocaine, and mepivacaine. Although allergic reactions are rare with amides, cross-reactive sensitization is possible with esters.²⁷ These responses are often type IV reactions or result from adverse effects due to inadvertent IV injection, vasoconstrictors, or preservatives or toxic effects of drugs.³

Opioids are more likely to cause a reaction from the direct release of histamine than from IgE mechanisms.²² Meperidine and morphine are the most histamine-stimulating narcotics.⁵ Although morphine and fentanyl may rarely cause anaphylaxis, these narcotics may stimulate the dermal mast cells, resulting in flushing or urticaria.² All opioids and muscle relaxants should be titrated cautiously because of histamine release.

• *Muscle Relaxants.* For surgical patients, the most common triggers of anaphylaxis are neuromuscular blocking agents (NMBAs), which are considered responsible for 50% to 75% of allergic reactions.²³ Most NMBAs directly stimulate histamine release.²⁷ Muscle relaxants, in particular steroid-derived drugs, may bind with biologic proteins, creating a hapten molecule that is recognized as an antigen.¹⁰ The development of allergic cross-reactivity may be due to antibodies to allergens that have chemical families or molecular structures similar to those of drugs. Hypersensitivity can occur during the first administration of an anesthetic due to cross-sensitization from similar quaternary ammonium ions in cosmetics, personal products (toothpastes, soaps, and shampoos), chemical additives in foods (metabisulfites, preservatives), and drugs (cough medicines).²² The tertiary ions or quaternary ammonium ions of NMBAs may cross-react with other NMBAs, morphine, acetylcholine, and neostigmine.²³ In a French survey of perioperative

anaphylaxis, succinylcholine was the most frequent trigger (n = 356 [33.4%]), followed by rocuronium (n = 313 [29.3%]), atracurium (n = 206 [19.3%]), and vecuronium (n = 109 [10.2%]).¹³ Although succinylcholine precipitates histamine release, an IgE-mediated reaction can also occur.¹ Cisatracurium has the lowest potential of the NMBAs to stimulate the release of histamine.⁵

• *Fluids and Blood.* Blood products can cause immunologic and nonimmunologic reactions during an anesthetic. Blood products expose patients to antigens that can cause anaphylaxis, hemolytic transfusion reactions, and transfusion-related acute lung injury.¹⁰ However, hydroxyethyl starch, albumin, dextran products, and gelatins used as plasma expanders have a low risk of allergic reaction.⁵

• *Antibiotics.* In the general population, the most common triggers for anaphylaxis are antibiotics (especially β -lactam) and nonsteroidal anti-inflammatory drugs. Cephalosporins, vancomycin, and quinolone antibiotics and irrigation with bacitracin or rifamycin have also elicited hypersensitivity reactions.² Rare cross-reactive allergic reactions may occur with penicillin, amoxicillin, and first-generation cephalosporins but not with second- or third-generation cephalosporins.²³

• *Other Drugs.* The incidence of allergic reactions to heparin has increased, especially if the heparin is contaminated. After heparin administration, an IgG antibody may form, predisposing the patient to thrombocytopenia and/or allergic reactions.¹⁰ Hypersensitivity reactions to protamine may be less likely to be caused by direct histamine release or through IgE or IgG antibodies and the activation of complement.³ High-osmolar iodinated ionic contrast media precipitate an allergic reaction more often than do low-osmolar, nonionic contrast media. Although aprotinin is no longer marketed, tissue sealants or fibrin glues may contain aprotinin that can trigger anaphylaxis.¹⁰ Other drugs associated with anesthetic hypersensitivity reactions include glycopyrrolate, chymopapain, hyaluronidase, oxytocin, chlorhexidine, and other antiseptics. Dyes used for sentinel node biopsy, such as patent blue or isosulfan blue, may also trigger anaphylaxis.⁵

Treatment of Anaphylaxis

When anaphylaxis occurs, the goals of treatment are to stop the administration of the allergen, abate the effects of the toxic mediator release, and prevent further mast cell degranulation.³ Table 3^{2,28} shows the drug therapy for anaphylaxis. The treatment strategy is shown in Figure 4 (M. C. Castells, MD, PhD, personal communication, March 26, 2011).^{2,26,27}

• *Recognize and Remove Triggers.* Prompt recognition of the severity of anaphylaxis and provision of the appropriate treatment are essential.³ The anaphylaxis severity grade is directly related to the swiftness of the

Drug	Dose
Epinephrine (titrated to severity of symptoms)	Adult, IV/IM, 1:1,000, 0.1-0.3 mg (in 10 mL NS IV), up to 1-3 mg every 3-5 min; infusion IV, 1 mg (1 mL) of 1:10,000 in 250 mL NS at 2-4 µg/min up to 10 µg/min; endotracheal, 2-2.5 mg in 10 mL; pediatric, IV, 0.1 µg/kg/min
Vasopressin	Adult, IV, 1-2 U initially for hypotension; 40 U IV for cardiac arrest
Dopamine	Adult, infusion IV, 400 mg in 500 mL NS at 2-20 mg/kg/min
Phenylephrine	Adult, bolus IV, 0.1-1 mg (maximum) repeated every 10-15 min; infusion IV, 40 mg diluted in 250 mL NS—0.1-0.18 mg/min (100-180 µg/min) titrate to effect for hypotension
Norepinephrine	Adult, infusion IV, 0.05 µg/kg/min or 2-4 µg/min
Methylene blue	Adult, bolus IV, 0.5-2 mg/kg; infusion IV, 0.5 mg/kg/h
Atropine	Adult, bolus IV, 0.4-1 mg
Albuterol	Adult, nebulized, 2.5-5 mg in 3 mL NS; bolus IV, 100-200 µg
Ipratropium bromide	Adult, nebulized, 500 µg (1 unit-dose vial) in 2.5 mL NS
Terbutaline	Adult, subcutaneous, 250-500 µg
Methylprednisolone	Adult, bolus IV/IM, 120 mg (0.5-1 mg/kg) followed by 0.8 mg/kg every 4-6 h
Hydrocortisone	Adult, bolus IV, 0.5-1 mg/kg IV initially, then 2.5 mg/kg every 4-6 h
Diphenhydramine	Adult, IV/IM/orally, 1-2 mg/kg or 25-50 mg; child younger than 12 y, 12.5-25 mg
Hydroxyzine	Adult, IV/IM, 25-100 mg; orally, 25 mg every 2-4 h; pediatric, 12.5-25 mg
Ranitidine	Adult, IV/IM, 1 mg/kg (maximum dose, 50 mg); pediatric, IV, 12.5-50 mg
Glucagon	Adult, bolus IV, 1-5 mg or 20-30 µg/kg; infusion IV, 5-15 µg/min; pediatric, IV, 20-30 µg/kg, up to 1 mg over 5 minutes, then 5-15 µg/min

Table 3. Pharmacologic Treatment of Anaphylaxis^{2,28}

Abbreviations: IV, intravenously; IM, intramuscularly; and NS, normal saline.

onset of symptoms.²⁷ After IV drug administration, anaphylaxis usually begins within 5 to 10 minutes, but it can occur as quickly as within a few seconds after exposure to an antigen.²² Most often, a reaction occurs immediately after IV induction of anesthesia, although it may occur at any time. Anaphylaxis may also occur after topical, mucosal, or intra-articular routes of antigen exposure.²⁸ The latex allergen is absorbed more slowly through the skin and mucosa; the symptoms of latex hypersensitivity may be delayed by 30 minutes after contact.²⁹

If anaphylaxis is suspected, a rapid assessment for possible causes of the abrupt symptoms should be determined to rule out other diagnoses. For diagnostic purposes, the timing of symptoms should be noted in relation to the previous drugs administered.¹² Whether a drug or latex is causing the allergic reaction, the trigger should be quickly removed from patient contact and help sought.²⁷ The administration of antibiotics and blood products should be stopped, anesthetic administration discontinued, and the surgery terminated.²⁸

- **Epinephrine.** Epinephrine is the mainstay of treatment for anaphylaxis. It is preferred because the α_1 effect of epinephrine constricts the peripheral vasculature to support blood pressure; in addition, its β_2 effect causes bronchodilation.³ Epinephrine also inhibits the cellular release of the chemical mediators of anaphylaxis to suspend the allergic reaction and stop vascular dilation.

Delayed epinephrine treatment may be associated with worsened outcomes.¹² If no IV line has been inserted, epinephrine can be injected intramuscularly in the vastus lateralis, or, in patients with laryngeal edema, it can be administered by nebulization or through an endotracheal tube.¹ The dose of epinephrine should be titrated according to the severity of the reaction. Patients with mild reactions (grade I) may need little to no treatment, whereas patients with grade II through V reactions may need escalating doses of epinephrine (see Figure 4) (M. C. Castells, MD, PhD, personal communication, March 26, 2011).^{2,26,27} High-dose epinephrine may be needed to treat pulseless electrical activity. If bradycardia occurs, the patient may also need to be treated with atropine or atrial or ventricular pacing.¹⁰ However, if bradycardia is treated without volume expansion, atropine administration may cause cardiac arrest. When the ventricle is empty because of decreased preload from massive hypovolemia, bradycardia is a physiologic compensation to increase ventricular filling time. Atropine causes pharmacologic opposition of the paradoxical cardioinhibitory reflex that elicits bradycardia; therefore, volume replacement and epinephrine are indicated instead of atropine for bradycardic hypotension during anaphylaxis.²⁸

- **Antihistamines.** Antihistamines are the second line of anaphylaxis treatment but should never be administered as an epinephrine substitute. Antihistamines—such

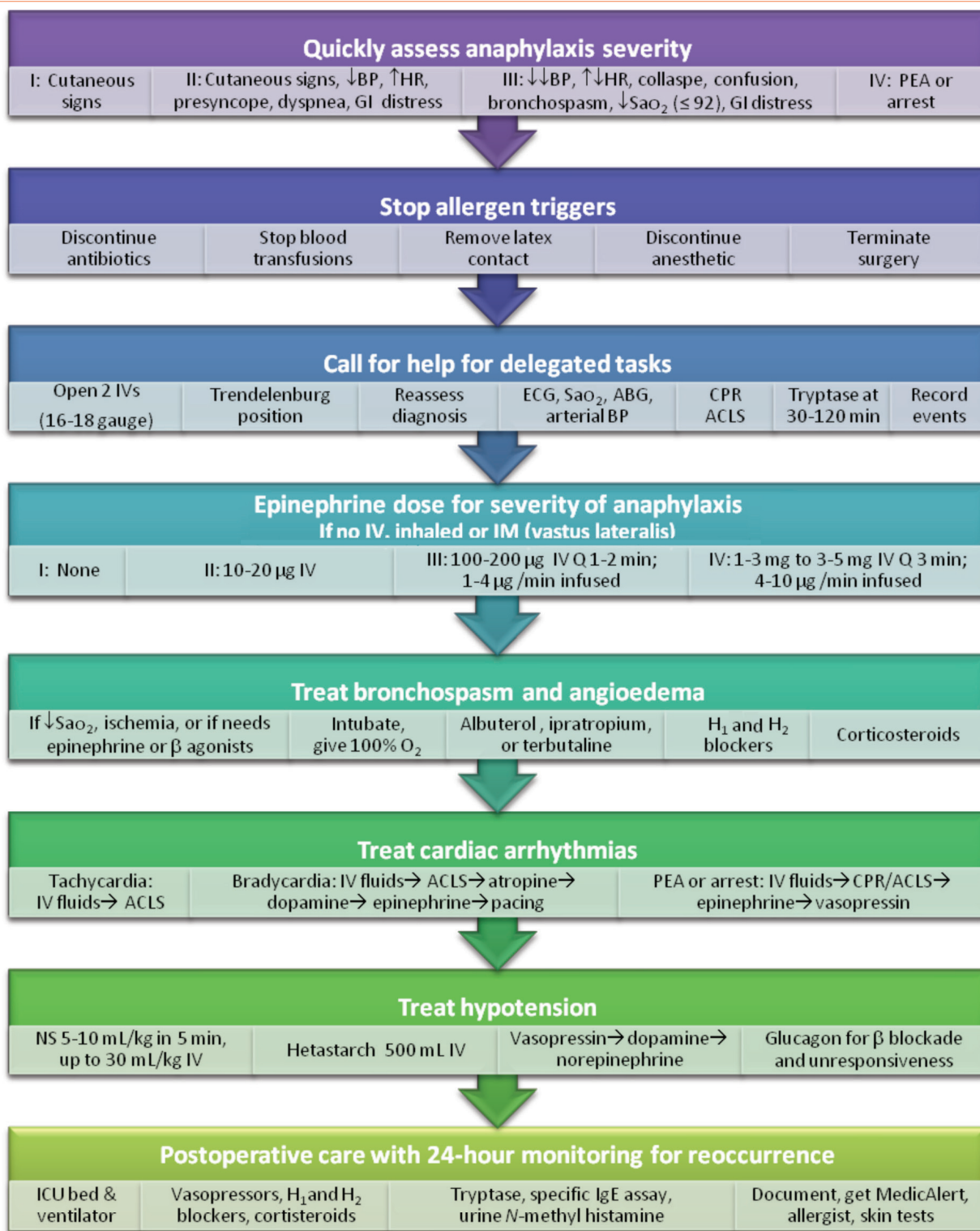


Figure 4. Treatment Strategy for Anesthetic-Induced Anaphylaxis^{2,27}

Abbreviations: BP, blood pressure; HR, heart rate; ↑, increased; ↓, decreased; ↑↓, increased or decreased; →, proceed to administration; GI, gastrointestinal; PEA, pulseless electrical activity; IV, intravenous, intravenously, or intravenous line; ECG, electrocardiogram; ABG, arterial blood gases; Sao₂, oxygen saturation; CPR, cardiopulmonary resuscitation; ACLS, advanced cardiac life support; IM, intramuscularly; Q, every; H, histamine; NS, normal saline; and ICU, intensive care unit.

Hydroxyethyl starch (Hetastarch, Teva Parenteral Medicines Inc., Irvine, CA); MedicAlert (MedicAlert Foundation, Turlock, California). (M. C. Castells, personal communication, March 26, 2011.)

as diphenhydramine and hydroxyzine (H_1 antagonists) and ranitidine and cimetidine (H_2 antagonists)—should be given early and are superior when given in combination than when given alone. An H_2 antagonist should also be administered early in the presence of hypotension. However, after cardiovascular collapse, H_1 blockade is controversial.³

- **Bronchodilators.** The β_2 -agonist drugs albuterol and terbutaline and the anticholinergic ipratropium bromide are indicated to treat bronchospasm. Any patient with hypoxemia or myocardial dysfunction or who requires epinephrine or β -agonist treatment should be given 100% oxygen. Pulse oximetry and an arterial line should be monitored for hypoxic or hypotensive patients. The patient's airway should be maintained and intubated, if necessary.^{20,27} Extubation should be delayed in patients with airway edema, so admission to an intensive care unit and use of a ventilator should be anticipated.³ The symptoms of a severe reaction can continue for up to 32 hours, despite treatment. After the reaction has subsided, symptoms can reoccur for another 72 hours.¹ Up to 23% of patients who experience anaphylaxis have biphasic responses with repeated symptoms,²⁷ with onset usually in 10 hours.¹

- **Corticosteroids.** Although no consensus exists for the use of corticosteroids or histamine antagonists for anaphylaxis, histamine blockade and glucocorticosteroids may be indicated to treat airway edema and hives. Corticosteroids should not be given before or instead of epinephrine.² Hydrocortisone is preferred because it has a faster onset of action, although methylprednisolone may also be given for anaphylaxis.³ Within the first few hours of a reaction, glucocorticoids may help prevent a worsened or prolonged anaphylactic episode or late recurrence, but they do not help in the acute setting. Preventing prophylaxis in surgical patients is an “elusive ideal”^{2(p480.e16)} because of its episodic rarity and unpredictability, multiple triggering mechanisms, and difficulty determining allergen sensitization and subsequent risk of anaphylaxis. However, preoperative glucocorticoids and antihistamines may decrease the recurrence of anaphylaxis in patients with previous idiopathic anaphylaxis or a reaction to radiographic contrast.²

- **Volume and Vasopressors.** Because of the release of vasoactive mediators during anaphylaxis, vasodilation and profound hypotension may quickly occur. The altered vascular permeability can transfer 50% of the intravascular volume into the extravascular tissues in 10 minutes.²⁸ Two large-bore IV lines should be opened wide to give a fluid bolus. Normal saline should be infused, 5 to 10 mL/kg IV in the first 5 minutes, up to 30 mL/kg, followed by colloids, preferably IV hydroxyethyl starch (Hetastarch, Teva Parenteral Medicines Inc, Irvine, California), 500 mL.²⁷ The Trendelenburg position slows the hemodynamic compromise. Death can occur if the

patient is positioned upright.¹ Vasopressor infusions such as epinephrine, phenylephrine, dopamine, or norepinephrine may also be indicated to treat hypotension (see Table 3).^{2,27}

For patients in anaphylactic shock due to vasodilation who are unresponsive to epinephrine, arginine vasopressin (AVP) is the preferred drug.⁴ During anaphylaxis, α -adrenergic compensation may be ineffective because anaphylaxis has multiple mechanisms for vasodilation, such as excess nitric oxide synthesis, and metabolic acidosis causes vasodilation because it activates vascular smooth muscle potassium channels.⁴ Vasopressin blocks numerous mediators and signaling pathways that contribute to vasodilation such as excess nitric oxide synthesis, which causes vascular relaxation and the activation of vascular potassium channels. In addition, AVP inhibits the receptors that control vasodilation.²⁸ Vasopressin may be effective for catecholamine failure during anaphylaxis because its vasoconstrictive effects are mediated by nonadrenergic vasopressin-1 vascular receptors. Vasopressin has an additive effect with other vasopressors.⁴ However, if AVP is given before epinephrine or in high doses, it may have adverse effects. Vasopressin is a superior treatment to methylene blue for anaphylaxis.²⁸ Nevertheless, methylene blue has been effective for non-responsive anaphylaxis because it also interferes with nitric oxide relaxation of vasculature.³⁰

- **Glucagon.** In addition to vasopressin, glucagon may be indicated for the treatment of hypotension and bronchospasm for patients taking β -blockers who are unresponsive to epinephrine. Glucagon is an effective antidote because it directly activates adenyl cyclase, precluding β -receptors. Whether or not treatment requires glucagon, a prolonged resuscitation for refractory anaphylaxis is recommended because a good outcome is likely.¹

Laboratory Testing for Anaphylaxis

Laboratory tests are valuable in the diagnosis of anaphylaxis, although no test is a specific and sensitive marker for an allergic hypersensitivity reaction.⁵ Detection of the causative allergen is based on retrospective analysis of the clinical manifestations and timing of the onset of symptoms (such as hypotension) after the administration of a trigger, the measurement of tryptase levels, and the severity and symptoms of the reaction and the epinephrine dose needed to effectively treat the reaction.²⁷

- **Preoperative Testing.** Before surgery, patients with mast cell disease need proper evaluation and challenge tests to determine which drugs are best tolerated. However, skin testing should not be used for preoperative screening without a clinical history of hypersensitivity (M. C. Castells, MD, PhD, personal communication, March 26, 2011).

- **Intraoperative Testing.** If anaphylaxis is suspected intraoperatively, serum markers of mast cell activation

should be analyzed. Tryptase confirms an immune-mediated reaction because it is released by mast cells and basophils.²³ Biological evidence of anaphylaxis includes a total tryptase and β -tryptase level within 30 to 120 minutes after the onset of symptoms. A baseline total tryptase level should be tested within 24 hours. Because histamine is degraded very quickly, a serum histamine level is not a reliable marker. A 24-hour urine collection for histamine and *N*-methyl histamine urine levels may be diagnostic. Serum-specific IgE assays may be useful retrospectively. Test results should correlate with the history and the results of skin testing.²⁷

• **Postoperative Testing.** After anaphylaxis, a detailed record of the events, drugs administered, and laboratory test results must be recorded for postoperative consultation and diagnostic purposes. An evaluation by an allergist-immunologist is necessary to prevent future reactions through diagnosis of the triggering IgE antibody.²³ Following an episode of anaphylaxis, allergy testing may be needed for high-risk patients to confirm the trigger; skin-prick tests, allergen-specific serum IgE levels, and allergen challenge tests may be ordered to verify the trigger.²⁹ Allergological evidence based on review of the clinical history guides the skin testing to identify the triggering agent and to determine the mechanisms precipitating the reaction. Skin testing by prick or intradermal injection of a dilute concentration of the allergen is recommended postoperatively to confirm the allergen.²⁷ Currently, skin tests are the most reliable method to determine the trigger and whether the reaction was IgE-mediated and to direct future safe administration of anesthetics. However, the sensitivity and specificity of skin tests are not perfect.³¹ After anaphylaxis, systemic depletion of mast cell mediators precludes skin testing for 4 to 6 weeks.³

A commercial IgE test (quaternary ammonium morphine) with 84% sensitivity may be diagnostic of NMBA allergy in conjunction with skin tests. Other novel tests to assess drug allergy include basophil activation tests, radioallergosorbent tests, Immuno-Cap (Quest Diagnostics, Madison, New Jersey), enzyme-linked immunosorbent assay, enzyme-linked immunospot assays, and T-cell proliferation tests.³² Once the allergen is confirmed, the patient should be provided with a letter to document the reaction and the potential causative agent.²⁹ The patient should obtain a MedicAlert (MedicAlert Foundation, Turlock, California) bracelet for identification of the allergen.¹² Desensitization is possible for highly allergic patients who have no other options, but with a history of allergy to NMBAs, patients can remain sensitive for 30 years.³

Conclusion

Anaphylaxis is a major anesthetic challenge that increases the morbidity and mortality of surgical patients.

Although anaphylaxis is rare, it can be fatal, even in healthy patients. Preoperative assessment of patients at risk and recognition of anaphylaxis with prompt treatment are essential for survival. Protocols are needed in anesthesia departments to anticipate an unexpected anaphylactic crisis. Simulator practice drills for anaphylaxis are recommended.^{1,20} Within advanced cardiac life support, specific training, including algorithms for the treatment of anaphylaxis, could ostensibly improve the outcomes of surgical patients at risk for anesthetic-induced hypersensitivity reactions.

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