

Management of Anaphylaxis



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KEYWORDS

- Anaphylaxis • Epinephrine • Subcutaneous immunotherapy • Allergic rhinitis
- Asthma

KEY POINTS

- Cutaneous manifestations including urticaria, angioedema, and flushing are the most common physical examination findings in anaphylaxis.
- Intramuscular epinephrine should be administered in any patient suspected of having an anaphylactic episode with 0.2 to 0.5 mL at a concentration of 1:1000 for adults and 0.01 mg/kg in pediatric patients.
- Serum tryptase is currently the most helpful laboratory test to evaluate for anaphylaxis, although other tests are investigated that may increase the sensitivity of testing.
- Patients receiving subcutaneous immunotherapy should be observed for at least 30 minutes after injection. Screening for asthma and dose reduction during pollen season may decrease the risk of anaphylaxis.

INTRODUCTION

Definition and Epidemiology

Although first described in 1901, a meaningful and accurate definition of anaphylaxis is still being refined. Anaphylaxis is defined as a severe systemic reaction that is potentially fatal and caused by exposure to an allergy-causing substance.¹ The lifetime risk of anaphylaxis in the US population is approximately 1.6% and the frequency of hospital admissions are reportedly increasing, likely owing to the increase seen in food allergy, although mortality has slightly decreased.^{2,3}

The causes of anaphylaxis are complex and diverse, including foods, medications, insect stings, and systemic mast cell degranulating disorders. Food triggers are the most common cause of anaphylaxis, followed by medications, and hospital admissions for food-related anaphylaxis in children more than doubled from 2000 to 2009.⁴ The most common foods that cause anaphylaxis are peanuts, tree nuts, shellfish, fish, egg, and cow's milk.⁵ Risk factors for fatal food-related anaphylaxis include

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adolescent age, history of allergy to peanuts or tree nuts, asthma, and patients without obvious cutaneous symptoms.

The 2 most common medications causing anaphylaxis are antibiotics (beta-lactam) and nonsteroidal antiinflammatory drugs.^{2,5} Testing for medication-induced anaphylaxis remains lacking and history continues to be important in determining the etiology. The most common etiology for anaphylaxis in the allergy office is the administration of subcutaneous immunotherapy (SCIT), which warrants appropriate training and continued education of staff, as well as preparedness to treat this potentially fatal reaction.

DIAGNOSIS OF ANAPHYLAXIS

Signs and Symptoms of Anaphylaxis

Cutaneous manifestations are the most common, with urticaria and angioedema occurring in up to 90% of patients and flushing of the skin in more than one-half of patients.⁶ It is uncommon for patients to have pruritus without urticaria. Respiratory symptoms include dyspnea or wheezing is seen in approximately 50% of patients and upper airway angioedema in more than one-half of all patients. Gastrointestinal symptoms such as nausea, vomiting, diarrhea, and discomfort can also occur, and have been reported in approximately one-third of patients. Hypotension and shock occur in severe episodes.

Elements of the history that are important to obtain in patients suspected of experiencing anaphylaxis include foods and medications ingested within 6 hours of the episode, activity during the episode, duration, time of day, location, stings or bites, heat or cold exposure, associated symptoms, recurrence of symptoms, and treatment provided.⁵

Differential Diagnosis of Anaphylaxis

Several other conditions can present with symptoms similar to anaphylaxis, including vasovagal reactions and disorders that cause flushing of the skin, angioedema, and/or vocal cord dysfunction. Vasovagal reactions are quite common and should be differentiated from anaphylaxis. Pallor, diaphoresis, bradycardia, hypotension, and a lack of cutaneous manifestations such as urticaria, pruritus, angioedema, and flushing characterize vasovagal reactions. Bradycardia can also occur during anaphylaxis, but tachycardia is often a precursor to bradycardia in an anaphylactic episode.⁵

Flushing of the skin can be caused by medications such as niacin, angiotensin-converting enzyme inhibitors, vancomycin, and ingestants such as alcohol, monosodium glutamate, and scombroid fish. Scombroidosis occurs after consuming spoiled fish containing increased levels of histamine. In these cases the tryptase levels would be normal.⁷ Other syndromes such as mastocytosis, carcinoid, vasointestinal polypeptide tumors, and medullary carcinoma of the thyroid can cause flushing of the skin that may be confused with anaphylaxis.

Tests that can help to establish a diagnosis of anaphylaxis during or in the immediate subsequent period include serum tryptase, histamine, 24-hour urinary histamine metabolites, and urinary prostaglandin D₂. Typically, serum tryptase is considered the most helpful test to establish a diagnosis of anaphylaxis, although studies have shown that plasma histamine levels, cysteinyl leukotrienes, and prostaglandins may be more sensitive and remain under further investigation.⁸ Tryptase peaks up to an hour and a half after the initial onset of anaphylaxis and can remain elevated several hours afterward.

Tests to identify the cause of anaphylaxis include skin and in vitro testing to identify specific immunoglobulin E to foods and medications. Using fresh food for skin prick testing can be more sensitive than commercially developed extracts. Because foods are the most common cause of anaphylaxis, it is recommended that anyone experiencing an anaphylaxis episode be tested for hypersensitivity to the most common food triggers. If there is delayed anaphylaxis occurring several hours after a meal, especially in the setting of a possible tick bite and ingestion of meat, testing should be considered for immunoglobulin E to galactose- α -1,3-galactose, which is present in the tissue of nonhuman mammals. A commercially available benzylpenicilloyl polylysine skin test can be useful to evaluate for penicillin allergy in adults and in children with a negative predictive value of 95% to 99%, although history can obviate the need for testing in low-risk patients.^{9,10}

Mastocytosis and mast cell-activating disorders can also be the cause of anaphylactic episodes. These patients often have elevated baseline serum tryptase, histamine, 24-hour urine histamine metabolites, and/or prostaglandin D₂. Although a tryptase level of 20 ng/mL has been conventionally used as a cutoff level for diagnosis, lower levels can be present. A blood test screening for the 816V mutation can be helpful for the diagnosis of mastocytosis, but bone marrow biopsy currently is the definitive method to establish the diagnosis.^{11,12} Other methods of testing under investigation include component-resolved diagnosis and basophil activation tests, which in the future may be able to provide a more accurate diagnosis.

TREATMENT OF ANAPHYLAXIS

Early Epinephrine Administration

Prompt recognition of anaphylaxis symptoms with appropriate treatment is critical to minimizing mortality. The most important first-line therapy for anaphylaxis is intramuscular injection of epinephrine. Epinephrine should be administered in the midlateral thigh (vastus lateralis muscle), the inciting allergen should be removed if possible, and the patient should be assessed for airway, breathing, circulation, and mental status.^{2,5,13,14} In the office setting, appropriate assistance should be sought immediately from appropriate staff and emergency medical personnel.

The dose of epinephrine is 0.2 to 0.5 mL at a concentration of 1:1000 for adults. The pediatric dose is 0.01 mg/kg with a maximum dose of 0.3 mg. Patients with severe symptoms should be provided a higher dose and repeat dosing can be administered every 5 to 15 minutes in conjunction with establishing intravenous access and transfer to a higher level of intensive care if required. In more than one-third of patients, a repeat dose was required to adequately treat an anaphylactic episode.¹⁵

Epinephrine is the first choice of medical therapy in anaphylaxis owing to its α -1 agonist effects that can help to prevent and treat airway edema, hypotension, and shock, as well as its β -1 agonist effects on cardiac function and β -2 agonist effects leading to bronchodilation.^{16–19} Early administration of epinephrine, defined as before arriving in the emergency department, has been associated with decreased hospitalization (17% vs 43%; $P < .001$) in a study of 384 emergency visits.²⁰ Delayed epinephrine administration has been associated with fatal anaphylaxis with only 23% of patients receiving the medication before cardiac arrest and, in another study, epinephrine was used correctly in only 47% of fatalities (9 of 19 patients).^{21,22} As of this writing, there is no absolute contraindication to the use of epinephrine in a patient suspected of having anaphylaxis.

Other immediate measures to be taken include placing the patient in a recumbent position. Pregnant women should be placed in the left lateral position. Vital signs

including pulse oximetry should be used if available and oxygen provided if needed. Oxygen is considered the second important therapeutic intervention after epinephrine and critical for all patients experiencing anaphylaxis, especially in the patient experiencing respiratory or cardiovascular effects. A facemask can be used to deliver 100% oxygen at a rate of 6 to 10 L/min to keep oxygen saturation at greater than 93%.^{5,19} Intravenous access should be established for fluid and medication administration if required. Fluid replacement with 1 to 2 L of 0.9% normal saline within 5 minutes for adults and up to 30 mL/kg in the first hour for children may be necessary for hypotension.

Additional measures include albuterol via nebulizer for lower airway obstruction, such as symptoms of wheezing, coughing, and shortness of breath. The adult dose is 2.5 to 5.0 mg/3 mL in saline and 2.5 mg/3 mL in children. Glucagon is indicated for patients who are on beta-adrenergic blockers and are not responsive to epinephrine. Glucagon 1 to 5 mg can be given intravenously over 5 minutes. The mechanism of action is by direct activation of adenylyl cyclase, bypassing the beta-adrenergic receptor.

Refractory anaphylaxis has been observed in patients who are on beta-adrenergic blocker therapy, including ophthalmic medications. The symptoms described are paradoxical bradycardia, hypotension secondary to decreased cardiac contractility, and persistent bronchospasm.^{23,24} Unfortunately, patients who are on selective beta-1 antagonists do not have a lower risk of anaphylaxis because both beta-1 and beta-2 antagonists can inhibit the receptor. Patients who are on beta-blocker therapy may also have symptoms more resistant to epinephrine therapy and unopposed alpha-adrenergic stimulation, leading to significant hypertension.

The intravenous administration of epinephrine can be provided for patients not responding to intramuscular epinephrine, by adding 1 mg (1 mL of 1:1000) epinephrine to 1 L of 0.9% normal saline and providing 2 µg/min (2 mL/min) to be titrated up to 10 µg/min (10 mL/min) if required.^{2,5} Intraosseous access can be used if intravenous access is not possible for administration of intravenous fluids and epinephrine. Patients who develop laryngeal edema may require endotracheal intubation or emergent cricothyroidotomy in severe cases when ventilation by bag-mask is ineffective. Vaso-pressors such as dopamine are indicated in addition to epinephrine if the patient is unresponsive to the treatments discussed. These interventions would be performed in a monitored setting if possible.

Second-line therapies include H1 antihistamines and corticosteroids, although efficacy in the emergent setting has not been established for these medications. Guidelines concur that these medications should not be used as a first-line or sole therapy.^{2,5,16,17} Although H1 antihistamines are effective for allergic symptoms such as rhinitis, pruritus, and urticaria, they are not effective in treating airway obstruction or cardiovascular compromise. The use of H2 antihistamines is not supported by the evidence in the literature and may increase hypotension. Both medical professionals and patients alike may delay the administration of epinephrine owing to the misconception that the antihistamine may help to treat anaphylaxis, resulting in increased severity of symptoms and death. The evidence for corticosteroids in treating the biphasic or prolonged episodes of anaphylaxis has been extrapolated from asthma data, and these medications should not be used as initial therapy for anaphylaxis.^{16,19} Corticosteroids have an onset of action of between 4 and 6 hours, and dosing is typically 1 to 2 mg/kg per dose of methylprednisolone or equivalent.

Monitoring and Education after Anaphylaxis

The decision for monitoring should be based on symptom severity and risk factors. Hospital admission should be considered in patients who have upper or lower airway

edema, prolonged symptoms, when an allergen has been ingested, risk factors for severe anaphylaxis such as asthma, and/or when more than 1 dose of epinephrine was required to treat the patient.^{5,17,18} A study of 541 patients diagnosed with anaphylaxis showed that 4% (21 patients) developed biphasic reactions with a median time of 7 hours from the initial onset of symptoms to the onset of the biphasic reaction.²⁵ In this study, increased risk was associated with history of prior anaphylaxis, an unknown cause of anaphylaxis, or symptoms of diarrhea or wheezing. Biphasic reactions in the literature have been reported to range from 0.4% to 23.0%.^{25,26} Monitoring should be individualized to the patient's risk factors, reliability, and access to care.

Upon discharge from medical care patients should be prescribed an epinephrine autoinjector and educated regarding proper use. At least 2 doses should be provided; about one-third of patients will require a second dose of epinephrine to treat anaphylaxis.^{15,27} Commercially available autoinjectors are provided in 0.15-mg and 0.30-mg formulations. An identification bracelet or equivalent should be worn and an anaphylaxis action plan should be provided to the patient. There are examples available on the websites of the American Academy of Allergy, Asthma, and Immunology and the American Academy of Pediatrics. Referral should be provided to an allergist or an immunologist for further management.

Prevention of Anaphylaxis

It is difficult to predict the severity of future anaphylaxis episodes based on prior events, and diagnostic testing is inadequate to predict anaphylaxis severity. Patients who are diagnosed with hypersensitivity to a specific trigger such as a food, medication, or insect sting should be counseled on avoidance measures. Education regarding reading food labels carefully including possible hidden sources of the food trigger can be helpful. Currently, desensitization to foods is still under investigation and avoidance is recommended. Cross-reactivity between allergens in foods as well as in medications can trigger reactions, and appropriate education and counseling should be provided regarding avoidance measures.

If a patient will be exposed to a known trigger for systemic reaction, such as radiocontrast material or to prevent recurrent episodes of idiopathic anaphylaxis, it is reasonable to use pharmacologic prophylaxis such as treatment with antihistamines and corticosteroids. Pretreatment for patients sensitive to radiocontrast material is 50 mg of prednisone orally before exposure (at 13 hours, 7 hours, and at 1 hour) and 50 mg of diphenhydramine 1 hour before administration.²⁸

Patients who have anaphylaxis to insect stings may be candidates for desensitization via immunotherapy. Skin testing to venom should be performed in patients who have experienced anaphylaxis from "flying hymenoptera" and to whole-body extract for bites from a fire ant. Baseline tryptase levels should be performed in all patients who have had anaphylaxis from a hymenoptera sting to rule out systemic mastocytosis. Venom immunotherapy is 80% to 98% effective and, therefore, should be considered in patients with prior systemic reactions.^{5,18}

Because epinephrine is the single most important medication for the early treatment of anaphylaxis and prevention of possible complications, appropriate counseling on carrying an epinephrine autoinjector at all times and its correct use should be provided.

Anaphylaxis to Subcutaneous Immunotherapy

Allergen immunotherapy is the only disease-modifying treatment of allergic disease and is efficacious for symptom relief, decreased need for medications, prevention of new sensitizations, and the prevention of asthma.^{29–31} The most serious side effect

of SCIT, however, is anaphylaxis, with symptoms ranging from mild pruritus and urticaria to death. The World Allergy Organization has developed a grading system ranging from 1 to 5 to systematically characterize reactions from SCIT (Table 1).³² Fatalities from SCIT-related anaphylaxis are rare, with estimates of approximately 3.4 deaths per year or 1 in every 2.5 million injections.³³ A recent surveillance study evaluating data from 2008 to 2013 on 28.9 million injection visits for 344,480 patients reported a total of 4 fatalities from SCIT and no fatalities reported for sublingual immunotherapy.³⁴ Systemic reactions occurred in 1.9% of patients on SCIT (grade 3, 0.08%; grade 4, 0.02%) and 1.4% of patients on off-label sublingual immunotherapy (grade 3, 0.03%; grade 4, 0%). The study also confirmed that screening for asthma and dose reduction during peak pollen seasons may help to decrease the risk of systemic reactions. One of the fatalities described occurred under the care of an otolaryngologist during the surveillance period 2012 to 2013 in which a patient left the office without complying with the recommended observation period. The patient collapsed outside the office and died shortly after the anaphylaxis episode. Epinephrine was not available and, therefore, not administered for this patient. It was also reported that the patient had asthma, but it is unknown regarding the level of the patient's asthma control or severity. This fatality does highlight the importance of observing patients after the injection as well as the importance of expedient administration of epinephrine by trained personnel when anaphylaxis occurs. Most severe anaphylactic episodes occur within 30 minutes of an injection. It is recommended that allergy injections be provided in a supervised clinic setting with personnel trained in the recognition and treatment of anaphylaxis.^{5,19,30,34} The office should be prepared with epinephrine, oxygen, and methods to maintain an airway and to establish intravenous access for fluids and medications. It is not recommended that allergy injections be administered at home secondary to the risks of anaphylaxis, with the rare exception when the benefits may outweigh the risks, such as in life-threatening hypersensitivity reactions to stinging insects.³⁰ The assessment of asthma control should be done before each injection because most fatal reactions occur in patients who have uncontrolled asthma.^{5,30,33} Anaphylaxis related to angiotensin-converting enzyme inhibitors and SCIT have been reported in a few case reports with hymenoptera venom immunotherapy. Severe hypotension occurred within minutes of the injection, but fortunately all patients were successfully resuscitated and also could resume immunotherapy without a reaction when the angiotensin-converting enzyme inhibitor was held

Table 1 World Allergy Organization subcutaneous immunotherapy systemic reaction grading system	
Grade	Description of Criteria
1	Pruritus, urticaria, angioedema (not upper airway), rhinitis, throat clearing, cough, nausea, headache
2	Asthma responding to an inhaled bronchodilator or gastrointestinal symptoms or uterine cramps
3	Asthma not responding to an inhaled bronchodilator or laryngeal, uvular, or tongue angioedema
4	Respiratory failure with or without loss of consciousness or hypotension with or without loss of consciousness
5	Death

Adapted from Cox L, Larenas-Linnemann D, Lockey RF, et al. Speaking the same language: The World Allergy Organization subcutaneous immunotherapy systemic reaction grading system. J Allergy Clin Immunol 2010;125(3):571; with permission.

Table 2
First-line anaphylaxis medications and supplies

Basic Supplies	Airway and IV Resuscitation Equipment	Medications
Stethoscope	Bag–valve–mask	Epinephrine 1:1,000, 3 doses or 1 multidose vial
Blood pressure cuff	Face masks	O ₂ E-cylinder >1100 psi
Pulse oximeter	Oropharyngeal airways	Albuterol inhalational solution 0.5%
IV catheters (14-, 16-, 18-, 20-, and 22-gauge)	Nasal pharyngeal airways	Glucagon 1 mg/mL (2 vials)
IV butterfly needles (19-, 21-, and 23-gauge)	O ₂ nasal cannula and tubing	
Syringes (1, 10, and 20 mL)	IV administration set and connection tubing	
Needles (1–2 inches, 18-, 21-, and 23-gauge)	Nebulizer with face mask, tubing	
Latex-free gloves		

Abbreviation: IV, intravenous.

Adapted from Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis—a practice parameter update 2015. *Ann Allergy Asthma Immunol* 2015;115(5):362; with permission.

for at least 24 hours before injection.^{35,36} Whether all patients on SCIT should be prescribed and required to carry an epinephrine autoinjector is controversial and remains at the discretion of the treating physician.

OTOLARYNGIC ALLERGY OFFICE PREPARATION FOR ANAPHYLAXIS

Education of office staff regarding recognition and expedient treatment of anaphylaxis is important to prevent progression of symptoms and mortality. Prompt recognition of a systemic reaction and early use of epinephrine can be life saving. Quality improvement programs that stress continued education, development of a standardized protocol, safety checks, and mock anaphylaxis drills can help to decrease the risk of anaphylaxis related to SCIT administration.^{37–39} In addition, informed consent and a written contract with the patient regarding the risks of allergy testing, SCIT, and the required postinjection wait time can be helpful to educate the patient regarding the risks of treatment and establish standardized care. Important first-line medications and supplies to treat anaphylaxis adapted from recent practice parameters are listed in **Table 2**. Development of an office action plan for the management of anaphylaxis is also critical to appropriately treat the patient in an emergent setting.

SUMMARY

Anaphylaxis can present in many forms with varied etiologies. Prompt diagnosis and early treatment with epinephrine is critical to minimizing mortality. There is no absolute contraindication to providing epinephrine for a patient suspected of experiencing anaphylaxis. Once a diagnosis of anaphylaxis is established, patients should be appropriately counseled on preventive strategies; advances in diagnosis and treatment continue to evolve for the management of anaphylaxis, especially in the areas of food allergy, desensitization, and understanding mast cell disorders. In the allergy office, proactive measures to improve safety can decrease anaphylaxis and improve quality of care. Recent surveillance data highlight the importance of postinjection wait times and the potential to decrease risk of anaphylaxis by screening for asthma control, as well as dose reduction during peak pollen season.

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