

Continued Learning

A Patient With an Allergy Emergency

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Anaphylaxis is a severe life-threatening systemic reaction that otolaryngologists may come in contact with through emergency cases, or in their offices when delivering allergy immunotherapy. Rapid recognition of the entity should be followed by epinephrine administration. Anaphylaxis causes, including a hypothetical scenario, are described. Various risk factors for anaphylaxis, such as β -blocker use, are discussed. The differential diagnosis of anaphylaxis and adjunct treatment are explained.

JAMA Otolaryngol Head Neck Surg. doi:10.1001/jamaoto.2015.8
Published online February 12, 2015. Corrected on March 27, 2015.

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Anaphylaxis is a rapid, severe allergic reaction that may cause death.¹ The wording was carefully chosen to be concise and grave to reflect the necessity for expeditious and accurate diagnosis and treatment of this disease.

The lifetime prevalence of anaphylaxis is estimated as 2%² in the general population and seems to have increased in recent decades, particularly among children.^{3,4} The most common trigger for anaphylaxis in the pediatric population is food allergens (71%), most often peanuts followed by tree nuts then fruit.^{3,5,6} For adults, insect stings and contrast dye are more common triggers.³ Individuals with a history of allergic rhinitis, asthma, eczema, and atopy are more likely to experience anaphylaxis in their lifetime.³ The association with atopy is stronger with food allergens than drug allergens.⁶ Certain groups are at increased risk for reactions to particular allergens leading to anaphylaxis. For example, health care workers and children with spina bifida and genitourinary abnormalities are at increased risk for latex allergy.^{2,6}

Briefly, the pathophysiologic mechanism of anaphylaxis involves the classical pathway whereby IgE reacts with receptors on mast cells and basophils, leading to cross-linking, degranulation, and release of histamine, tryptase, chymase, platelet-activating factor, prostaglandins, and leukotrienes.^{2,3} Mast cells can also initiate the complement cascade.³ Complement can further stimulate histamine release. Histamine causes coronary vasoconstriction and intropathy. Platelet-activating factor induces additional histamine release in the lungs and peripheral blood vessels.³ Platelet-activating factor plays a critical role in the anaphylaxis reaction, and high levels have been found in patients with severe anaphylaxis episodes.⁷ There also exists non-IgE-mediated anaphylaxis, or anaphylactoid reactions associated with exercise or use of aspirin, nonsteroidal anti-inflammatory drugs, and contrast dye.^{2,3}

Evaluation

The primary diagnostic tool in assessment of anaphylaxis is an accurate history including the time of symptom onset, associated allergen exposure, previous anaphylactic episodes, medications used, and medical history.⁶ Clinical diagnosis of anaphylaxis is made when any of the following criteria are met: The first criterion states that

anaphylaxis is highly likely if skin or mucosal involvement is present (such as urticaria, pruritus, flushing, or oral swelling) and if respiratory compromise, hypotension, or end organ damage is identified. The second criterion requires 2 of the following: respiratory compromise, hypotension, gastrointestinal symptoms, or end organ damage. The third criterion identifies the presence of hypotension within minutes to hours after exposure to a known allergen for the patient.^{1,8,9} By correctly applying these 3 consensus diagnostic criteria, anaphylaxis can be correctly identified with a sensitivity of 95% (Box 1).¹

Confirmatory laboratory testing including serum histamine and tryptase levels may be performed but is informative only if blood is sampled near the time of exposure and should never take precedence over initiation of life-saving interventions. Histamine levels are expected to be elevated only during a short window between 15 and 60 minutes after exposure. Similarly, tryptase levels stay elevated 15 minutes to 3 hours after exposure.^{1,3,6,8}

Whereas cutaneous symptoms are the most prevalent, up to 20% of anaphylactic reactions to food allergens can occur without any cutaneous signs at all. Therefore, it is important to vigilantly assess for multisystem involvement in other organ systems.³

Box 1. Criteria for Diagnosing Anaphylaxis

1. Acute-onset illness with skin or mucosal involvement and 1 of the following:
 - A. Respiratory compromise
 - B. Reduced blood pressure or symptoms of end organ failure
2. Two or more of the following that occur rapidly after exposure to a likely allergen:
 - A. Involvement of skin or mucosa
 - B. Respiratory compromise
 - C. Reduced blood pressure or associated symptoms
3. Reduced blood pressure after exposure to a known allergen
 - A. Infants and children: age-specific low systolic blood pressure or a greater than 30% decrease
 - B. Adults: systolic blood pressure less than 90 mm Hg or a greater than 30% decrease

The importance of patient history cannot be overstated in the workup of a patient with suspected anaphylaxis. Specifically, certain medications and comorbid medical conditions can substantially affect the progression of anaphylaxis, the patient's response, and outcome. For example, use of antihistamines and corticosteroids can mask the initial signs and symptoms of anaphylaxis. β -blocker use can interfere with the efficacy of epinephrine therapy.^{2,3} Angiotensin-converting enzyme (ACE) inhibitor therapy may intensify allergic reactions. Tricyclic antidepressant use can worsen anaphylaxis by preventing reuptake of epinephrine.^{2,3} Asthma and heart disease are associated with more severe presentations of anaphylaxis.² In addition, such factors as exercise, acute infection, emotional stress, and premenstrual status can amplify the anaphylactic reaction.¹ Certain populations are at higher risk for increased severity of anaphylaxis, such as pregnant women (risk of hypoxic ischemic encephalopathy), elderly individuals with underlying cardiovascular disease, infants (from whom it is difficult to elicit history and symptoms), and teenagers at risk for substance use.¹ Furthermore, certain factors can predict severity of allergic reaction. The most strongly associated is a history of severe anaphylactic reaction.⁹ In fact, 22% and 18% of patients with fatal anaphylaxis to food and venom allergens, respectively, had experienced at least 1 previous severe anaphylaxis episode.⁹ Delayed administration of epinephrine is also associated with more severe reactions.⁵

Differential Diagnosis

The differential diagnosis for anaphylaxis is broad, including acute asthma, syncope, anxiety attack, myocardial infarction, pulmonary embolism, aspiration of foreign body, seizure, autonomic epilepsy, postprandial scombroidosis (histamine poisoning from fish), pollen-food allergy syndrome (food allergens having cross-reactivity with pollen, resulting in itching, tingling lips and tongue in high pollen season), systemic mast cell disorder, acute poisoning, mastocytosis, basophilic leukemia, menopause, carcinoid syndrome, pheochromocytoma, medullary thyroid cancer, systemic capillary leak syndrome, paradoxical vocal cord dysfunction, hyperventilation, psychosomatic disorder, shock (hypovolemic, cardiogenic, distributive, or septic), hereditary angioedema, ACE inhibitor-associated angioedema, Redman syndrome, and hypoglycemia.^{1-3,8} Probably the most commonly mistaken diagnosis in the differential for anaphylaxis is acute vasovagal episode, which in contrast to anaphylaxis lacks dyspnea, urticaria, and angioedema. In a vasovagal episode, the skin is usually cool and pale, and it is initially associated with bradycardia rather than tachycardia as in anaphylaxis (Table).⁸

Biphasic presentation of anaphylaxis is the recurrence of symptoms after treatment and resolution of symptoms and can occur within the first 8 to 72 hours. Biphasic reactions occur in up to 20% of cases of anaphylaxis and are more common with severe initial presentations.^{2,3,6}

The practice of allergy immunotherapy in many otolaryngology offices necessitates special emphasis on anaphylaxis. Anaphylaxis in patients receiving intradermal allergy testing (IDT) and subcutaneous immunotherapy (SCIT) administration is a rare but important complication.⁶ The risk of systemic reaction in patients receiving intradermal testing is 0.009%.¹⁰ Most of these reactions (82%) occur within 20 minutes of exposure to the allergen in pa-

Table. Anaphylaxis vs Vasovagal Manifestations

Manifestation	Anaphylaxis	Vasovagal
Cardiopulmonary system		
Pulse	Tachycardia	Bradycardia
Blood pressure	Hypotensive	Normal
Hoarseness, stridor	Present	Absent
Cough, wheeze	Present	Absent
Integumentary (skin)		
Color	Red	Pale
Urticaria, angioedema	Present	Absent

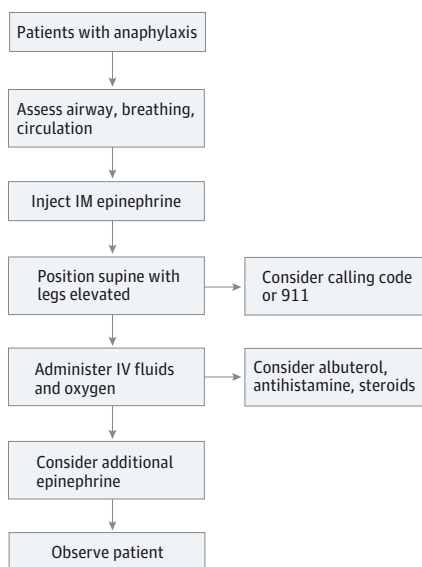
tients receiving IDT or SCIT.¹⁰ Since 1985, there have been 64 recorded deaths from anaphylaxis related to SCIT and 3 related to IDT.¹⁰ The death rate from allergy immunotherapy has been estimated to be 0.7 deaths per 1 million injections (0.00007%).¹¹ The main risk factors associated with developing a reaction to an immunotherapy injection appear to be (in order of frequency) buildup phase of immunotherapy, active asthma, first injection from a new vial, prior systemic reaction, vial prepared in another office, β -blocker use, and error (wrong patient vial).¹² A vial test to initiate each new vial is advised, as well as patient self-verification of their vial prior to receiving each dose.¹²

Therapeutic Measures

Treatment of anaphylaxis should be divided into 2 categories: acute and long term. In the event of an acute anaphylaxis episode, it is important to immediately assess the patient's airway, breathing, circulation, and adequacy of mentation. The offending allergen should be removed if possible. The patient needs to be placed in a supine position with the lower extremities elevated to prevent empty vascular syndrome or pulseless electrical activity. After the airway is established and maintained, hemodynamic monitoring should be applied and maintained throughout the episode. Oxygen can be applied if necessary in addition to obtaining intravenous access and starting fluid resuscitation. Intravenous (IV) fluids should be provided because massive fluid shifts can occur rapidly in anaphylaxis as a result of increased vascular permeability (Figure and Box 2).²

Medication treatments for anaphylaxis include epinephrine, inhaled albuterol, antihistamines, and corticosteroids. Epinephrine is the treatment of choice for anaphylaxis and should be the first medication to be administered to any patient with a suspected anaphylactic episode.^{2,5,8} In a series investigating more than 200 anaphylaxis deaths, the median time from onset of symptoms to fatal cardiopulmonary arrest was less than 30 minutes irrespective of the trigger or mechanism of anaphylaxis; thus, the initial management remains the same: to administer epinephrine as soon as the diagnosis is made.³ The dose of epinephrine to be administered is 0.01 mg/kg of a 1:1000 aqueous solution to a maximum of 0.5 mg in adults and 0.3 mg in children.¹ Epinephrine works through both the α -adrenergic effect, which reverses peripheral vasodilation, and the β -adrenergic effect, which increases myocardial output and contractility.¹ Epinephrine can be given intramuscularly (IM) or subcutaneously; however, IM administration is more effective, with the preferred site being the thigh because it allows for more rapid absorption and

Figure. Anaphylaxis Algorithm



Box 2. Hypothetical Patient Vignette

- A 25-year-old woman has been progressing with an immunotherapy regimen. She has had several large local reactions during advancement but no systemic reactions. She has no history of asthma or β -blocker use. She passed a vial test and received 0.05 mL of her vial (containing mainly concentrate and level-1, or 1:5 dilution of concentrate, antigens). One week later, she arrived for advancement to a 0.10-mL dose. After confirming the appropriate vial, she received the 0.10-mL dose in the ear, nose, and throat allergy clinic. Several minutes after receiving her dose, she approaches the allergy nurse complaining of a tight sensation in her throat and chest and an extreme anxious feeling. The nurse notes erythema on the skin of her neck and chest.
- The patient is quickly escorted into a patient examination room. She is seated in an examination chair and 0.3 mg epinephrine is administered intramuscularly in her thigh. The chair is flattened out while vital signs are obtained including pulse oximetry. Her pulse is 125 beats per minute, blood pressure 90/60 mm Hg, respiration 14 breaths per minute, and she has 97% arterial oxygen saturation on room air. Intravenous access is obtained, and a normal saline infusion is started. Intravenous diphenhydramine hydrochloride is administered, followed by 10 mg dexamethasone. A tourniquet is applied on the arm above the immunotherapy injection site.
- The patient seems to improve as seen amidst the flurry of multiple actions treating her apparent anaphylactic episode. Her visible anxiety lessens, and she confirms that her sense of dread has passed. Her vital signs normalize, with a pulse of 70 beats per minute, blood pressure 120/70 mm Hg, respiration of 14 breaths per minute, and 100% arterial oxygen saturation while receiving 2 L oxygen via nasal cannula. She is transferred from the ear, nose, and throat allergy clinic to the hospital for extended observation.

higher plasma level compared with subcutaneous administration.² It should be noted that IM injection is more difficult to administer in obese patients because of body habitus. The IM epinephrine should be given every 5 minutes as needed to control symptoms and maintain blood pressure. There is no absolute contraindication to admin-

istering epinephrine, as shown in a Cochrane review.¹³ Relative contraindications for epinephrine use include patients using monoamine oxidase inhibitors, tricyclic antidepressants, stimulant medications, or illicit substances. Use of these drugs may predispose patients to an increased risk of adverse effects of epinephrine therapy. In addition, caution is needed in patients with recent intracranial surgery, aortic or cerebral aneurysms, uncontrolled hyperthyroidism, or hypertensive emergencies.

If the patient continues to experience symptoms of anaphylaxis despite IM administration of epinephrine, then depending on the clinician's comfort level, an IV epinephrine infusion can be started while continuing hemodynamic monitoring. Early administration of epinephrine in pediatric patients was associated with a lower rate of hospitalization.⁵ Fatalities during witnessed anaphylaxis usually result from delayed administration of epinephrine and from severe respiratory and/or cardiovascular complications.⁸

There are several other agents that can be administered in addition to epinephrine for management of anaphylactic events. Antihistamine use may prevent hives and pruritus but does not reverse upper or lower airway obstruction or cardiovascular compromise. Cochrane systematic review¹⁴ has not found randomized clinical trials that support the use of H1 antihistamine in anaphylaxis. Antihistamine therapy thus is considered adjunctive to epinephrine and should not be used alone as the treatment for anaphylaxis. Nebulized albuterol can also be administered in cases of bronchospasm not responding to epinephrine therapy. If the patient continues to have refractory hypotension, a vasopressor such as IV dopamine hydrochloride 2 to 20 $\mu\text{g}/\text{kg}/\text{min}$ can be administered and titrated to maintain adequate blood pressure. If the patient takes β -blockers, which can counter the effect of epinephrine, IV glucagon 20 to 30 $\mu\text{g}/\text{kg}$ (with a maximum of 1 mg in children) can be administered over the course of 5 minutes followed by an infusion at a rate of 5 to 15 $\mu\text{g}/\text{min}$. Adverse effects of glucagon therapy include emesis if infused too quickly; thus, the patient will need to be observed for aspiration. Glucocorticoids can also be administered for the theoretical benefit that they may reduce the number of biphasic episodes; however, they have not been shown to be effective for the acute treatment of anaphylaxis because they have a slow onset of action.³ In addition, a recent Cochrane systematic review¹⁵ concluded that there is insufficient high-quality evidence to either support or not support the use of glucocorticoids in the management of anaphylaxis.

A patient who has experienced anaphylaxis and received epinephrine treatment should be transferred to the emergency department or intensive care unit because up to 20% of patients will experience biphasic or protracted symptoms. The patient should be observed for at least 4 to 6 hours to monitor for biphasic response or possible recurrence of the reaction as the epinephrine wears off. The patient will need to be prescribed 2 epinephrine autoinjectors and instructed on their use prior to discharge from the hospital. The disadvantage of epinephrine autoinjectors and standard needles is that they may not provide IM access in obese individuals.

After acute management, long-term management will need to be considered. The patient should be evaluated by an otolaryngologic or general allergist. The goal is to identify and confirm the cause of anaphylaxis and be able to educate the patient on appropriate avoidance strategies. In addition, the clinician should work with the patient to draft an anaphylaxis action plan and advise regarding

whether immunotherapy is appropriate. An anaphylaxis action plan is a comprehensive, individualized plan that includes emergency contacts, allergens and triggers, signs and symptoms of anaphylaxis, and medications to be used. Patients and their caregivers should be educated about agents or exposures that may place them at risk for future reactions. A patient's comorbidities that can contribute to anaphylaxis such as asthma, chronic obstructive pulmonary disease, ischemic cardiac disease, and systemic mastocytosis should be managed. Last, use of certain drugs that might increase a patient's susceptibility and/or complicate the management of an anaphylactic event, such as β -blockers, ACE inhibitors, or angiotensin receptor blockers, should be reassessed and avoided if possible.

Future treatment options include inhaled or sublingual epinephrine, although neither is widely available, nor do they have proven consistent efficacy.³ Oral immunotherapy and sublingual immunotherapy are under investigation for treatment of patients with food allergy.⁷ Recently, omalizumab therapy was also evaluated as part of anaphylaxis treatment. Omalizumab works by depleting free IgE and downregulating Fc ϵ RI receptors on mast cells and basophils. In addition, methylene blue has been used for the treatment of refractory anaphylaxis because it may prevent platelet-activating factor-mediated anaphylaxis by blocking nitric oxide-mediated vascular smooth muscle relaxation.³ However, methylene blue itself may cause anaphylaxis in sensitized patients.

ARTICLE INFORMATION

Submitted for Publication: December 21, 2013; final revision received November 6, 2014; accepted January 2, 2015.

Published Online: February 12, 2015.
doi:10.1001/jamaoto.2015.8.

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Author Contributions: Drs Houser and Weng had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Houser, Weng.
Acquisition, analysis, or interpretation of data: Weng, Liu.

Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Administrative, technical, or material support: Houser, Weng.

Study supervision: Houser.

Conflict of Interest Disclosures: None reported.

Correction: This article was corrected on March 27, 2015, for a typographical error.

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