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Allergy And Anaphylaxis: Principles Of Acute Emergency Management

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Abstract

Allergic reactions and anaphylaxis are potentially life-threatening processes that present with a variety of clinical symptoms. Emergency clinicians must be able to recognize these presentations and make prompt clinical decisions regarding management of a patient's airway, treatment options, and disposition of a patient who improves after initial presentation. Furthermore, emergency clinicians may be faced with patients who have atypical presentations or require special consideration, such as high-risk patients with comorbid conditions and patients who do not respond to first-line treatments. An increasing number of patients in the United States carry allergy diagnoses, and it is expected that this subset of the population will continue to seek care in the emergency department. This review assesses the research and evidence on the diagnosis, etiology, and treatment of anaphylaxis, as well as the utilization of epinephrine, both in and out of the hospital setting.

CME Objectives

Upon completion of this article you should be able to:

1. Identify the clinical criteria and common causes of anaphylaxis.
2. Diagnose anaphylaxis and differentiate it from similar processes.
3. Determine appropriate treatment (acute and prophylactic).
4. Identify high-risk patients or patients who may be difficult to treat.

Prior to beginning this activity, see "Physician CME Information" on the back page.

Case Presentations

A 55-year-old man with no significant medical history presents to the ED after breaking out in an "itchy" rash on day 3 of using an antibiotic for a sinus infection, but he can't recall the name of the medication. He has no other recent exposures or food allergies. His girlfriend once had a similar reaction to a medication, and just prior to arrival she gave the patient her epinephrine auto-injector to use. The patient reports abdominal cramping and wheezing, and he states that he feels a tingling in his lips, although there is no lip swelling, and he is breathing without difficulty. He notes that the rash seems to be spreading to different parts of his body, and resolves in one place only to reappear somewhere else. He denies any history of allergy to medications in the past, and says he has taken many different types of antibiotics without untoward effects. His vital signs are: temperature, 37°C; blood pressure, 130/80 mm Hg; heart rate, 90 beats/min; and respiratory rate, 12 breaths/min. The patient also took diphenhydramine 25 mg by mouth 30 minutes prior to arrival in the ED, and he notes that the rash and itching seem to be improving, although he has residual abdominal cramping and mild wheezing. The patient wants to go home, and you wonder if that's a good idea.

A 40-year-old woman with a history of hypertension who takes 100 mg a day of metoprolol is brought to the ED by EMS after experiencing a sensation of throat tightening and dizziness about 10 minutes into her normal indoor exercise routine on a treadmill. She has no other medical problems and no significant family history. In an effort to eat more healthfully, she has been consciously increasing her intake of green vegetables lately, and consumed 16 ounces of a juice comprised of celery and kale 1 hour prior to exercise. She denies chest pain or pressure, and the initial ECG from EMS shows sinus tachycardia at 120 beats/min, without any other concerning changes for acute coronary syndromes. En route to the ED, she developed a diffuse, pruritic rash and received diphenhydramine and methylprednisolone from EMS, but does not appear better. Her vital signs are: temperature, 37.2°C; blood pressure, 90/60 mm Hg; heart rate, 120 beats/min; and respiratory rate, 16 breaths/min. Her physical examination is remarkable for a diffuse rash, expiratory wheezing, and uvula and posterior oropharyngeal mucosal swelling. Although she adamantly denies any food and drug allergies and has not had exposure to any new medications, you proceed to treat her for an anaphylactic reaction and administer 0.5 mg of a 1:1000 solution of intramuscular epinephrine to the anterolateral thigh. However, soon after the administration of epinephrine, you note that she is no better, and, in fact, her heart rate has now increased to 140 beats/min, and her blood pressure has dropped to 80/50 mm Hg. Your nurse and medical student look a bit concerned, and your student asks why this is happening when epinephrine is the first-line drug for anaphylaxis. The medical student wonders out loud whether there is anything else you might give this patient to help her, and whether you could be missing a cardiac event...

Introduction

Allergic reactions occur when hypersensitivity to a foreign protein or antigen that normally would not be deleterious is acquired. On the spectrum of allergic responses, anaphylaxis is a profound reaction. Historically, anaphylaxis has lacked a standard, universally accepted definition, which has hampered the ability to consistently diagnose it. The National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network consensus defines anaphylaxis clinically as a continuum of a constellation of acute symptoms affecting multiple systems in the body after exposure to an allergen. Anaphylaxis is probable when any of the following criteria are met: (1) the presence of skin signs or symptoms together with respiratory involvement or signs of organ dysfunction or hypotension; (2) the involvement of at least 2 organs or systems after recent exposure to an allergen; or (3) signs of organ dysfunction or hypotension after exposure to a known allergen.[1] The areas of organ dysfunction are skin and mucosal tissue, as well as respiratory, neurologic, and vascular systems.

Anaphylaxis is caused by an immediate hypersensitivity response mediated by immunoglobulin-E (IgE) that releases inflammatory mediators from mast cells in tissues and from basophils into circulation. This IgE-mediated response follows a previous exposure to an allergen and sensitization to it, and it results in a rapid, potentially life-threatening reaction.

An anaphylactoid reaction is an immediate systemic reaction that, similar to an anaphylactic reaction, also releases inflammatory mediators via the stimulation of mast cells and basophils. However, unlike anaphylaxis, it is not IgE-mediated and, because the formation of IgE is not a prerequisite, an anaphylactoid reaction may occur on the initial exposure to an allergen. Clinically, anaphylactoid reactions are often indistinguishable from anaphylaxis. For this reason, the World Allergy Organization has suggested abandoning use of this terminology and referring to anaphylactic and anaphylactoid reactions as IgE-mediated anaphylaxis and nonallergic anaphylaxis, respectively.[2] Some triggers of anaphylaxis include radiocontrast dye, ethanol, N-acetylcysteine, and opioids.[3]

Angioedema is localized, nonpitting edema of the subcutaneous and submucosal tissues, resulting from mast cell mediators or bradykinin. It may be the result of a hereditary or acquired defect modulating bradykinin-related peptides and complement activation, as a result of a C1-esterase inhibitor deficiency. Furthermore, it may occur secondary to drugs, especially angiotensin-converting enzyme (ACE) inhibitors, or via an allergic/IgE-related mechanism.

The emergency clinician must confidently iden-

tify anaphylaxis and allergic reactions, and implement definitive and rapid interventions. Delays in treatment and inadequate treatment may have dire consequences. This issue of *Emergency Medicine Practice* presents a review of the current evidence that guides the evaluation and treatment of anaphylaxis and allergy, and focuses on the clinical scenarios that are most often seen in common practice.

Critical Appraisal Of The Literature

A literature search was performed using PubMed and Ovid MEDLINE® with the search terms *anaphylaxis, allergy*, and *hypersensitivity*. The search focused on English-language articles limited to humans that included systematic reviews, clinical trials, multicenter studies, or meta-analyses. References pertinent to emergency treatment were selected, and used for additional manual literature searches. Due to the plethora of literature on allergy and anaphylaxis, the search focused on literature from 1986 to 2014, including clinical diagnosis in the emergency setting and on prehospital and hospital diagnosis and treatment. In addition, a search of the National Guideline Clearinghouse (www.guideline.gov), using these refined search terms, produced guidelines and practice parameters from 2010 and 2011. A review of the Cochrane Database of Systematic Reviews yielded approximately 13 reviews on the general category of allergy and anaphylaxis. Several of these were specific to emergency management and covered the following topics: H1 antihistamines in anaphylaxis, glucocorticoids and heliox use in allergy and asthma, epinephrine auto-injectors, and an emergency action plan for people at risk of anaphylaxis. Overall, approximately 550 articles were reviewed, and 104 of these are included here for reference.

Due to the ethical challenges of randomized placebo-controlled trials of treatment for anaphylaxis, most studies are retrospective or based on clinical observations. Although a preponderance of the literature is from the field of allergy and immunology, a smaller number of references were found in the emergency medicine and pediatric emergency care literature.

Epidemiology, Etiology, And Pathophysiology

Epidemiology

There are little data on the prevalence of anaphylaxis. The burden of disease has historically been challenging to quantify because of a lack of consensus on diagnostic criteria, a lack of consistent standards for reporting cases, and ICD-9 miscoding, leading to an under-reporting of anaphylaxis in studies and in the databases.[4,5,6] Clinical studies have been performed in many different locations with natural variations in allergen exposure from place to place, which may also contribute to the wide range of prevalence estimates.[4] Nonetheless, with these factors taken into consideration, in the United States, the lifetime prevalence of anaphylaxis from all triggers is estimated to be between 0.05% and 2%, with anaphylactic reactions on the rise.[2,7,8]

The fact that anaphylaxis is on the rise was confirmed by Decker et al in a 10-year study from 1990 to 2000. They found that the overall incidence rate of anaphylaxis was more than double the rate that had been reported previously, particularly in young people (aged 0-19 years).[9,10] When age-specific and sex-specific incidence rates were examined by Harduar-Morano et al in a population-based study of 2751 patients with anaphylaxis-related ED visits in Florida, it was found that the highest incidence among male subjects was in young children, with a rate of 8.2 out of 100,000 male Floridians aged 0 to 4 years experiencing anaphylaxis.[11] Among female subjects, the highest incidence rate, 10.9 out of 100,000 female Floridians, was seen in subjects who were aged 25 to 34 years.

Etiology

There is a wide range of etiologies that may cause anaphylaxis. **(See Table 1, page 4.)** A 2011 analysis of etiologies of anaphylaxis in adult patients found that 34% of anaphylactic reactions were triggered by medications, 31% by food, 20% by insect stings, 7.5% by environmental allergens, 2.6% by latex, 1.2% by exercise, and 11% by unknown factors.[8] General food allergy in children, not solely restricted to anaphylaxis, has an estimated prevalence of 8% in the United States, with approximately 150 deaths per year due to such allergies.[12,13] Most of these fatalities are in young adults and adolescents, and the vast majority of these patients have known pre-existing food allergies or asthma.

Anaphylaxis To Food

Food allergy has become the most common cause of anaphylaxis overall in the United States, and it is the most prevalent provoking factor in children and young adults.[12,14,15,16] Nuts, fish, and shellfish allergies are among the most common.[17] In fact, in a case review by Bock et al, in the United States, tree nuts and peanuts were responsible for 30 out of 32 cases (94%) of fatal food anaphylaxis.[12] Patients may react to the oils of shellfish or nuts, and they should avoid contact with these products, including contact with areas where these foods are prepared.

Exercise-Induced Anaphylaxis

There is a phenomenon of food-triggered anaphylaxis that is induced by exercise. It is more common in women than in men, and the reaction may occur after the ingestion of a wide range of foods that

may not commonly be the cause of general food allergies. Exercise-induced anaphylaxis occurs most frequently within 1 to 4 hours of eating, and wheat, corn, garlic, celery, vegetables, and shellfish are the foods most commonly implicated.[18,19] It is believed that these food triggers interact with changes in creatine phosphokinase (CPK), lactate, endorphin, and serum pH levels that are seen with exercise. The ingestion of these trigger foods in the absence of exercise does not seem to invoke an anaphylactic response, and prevention involves avoidance of such foods within the 4 hours before exercise.

Anaphylaxis To Drugs

In adults, the most common triggers of allergic reactions are medications, particularly beta-lactam antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and muscle relaxants.[20,21] Dermatologic manifestations, such as urticaria and pruritus, are most common with drug reactions, but effects on any organ system are possible. Adverse drug reactions may be nonimmune-mediated or immune-mediated in origin (IgE, immunoglobulin-G [IgG], or immunoglobulin-M [IgM]), with the vast majority falling into the nonimmune-mediated category. Immune-mediated reactions represent just a fraction of all drug reactions (5%-10%), but they are deemed to be true allergic responses. Nonimmune adverse drug reactions are not truly allergic in nature, and generally do not carry the same potential mortality as immune-mediated-IgE reactions.

Emergency clinicians must be cautious not to misclassify simple adverse drug reactions as "allergic reactions," as this can erroneously limit the array of medications a patient may be offered in the future. (See the "Pathophysiology" section.) Hypersensitivity reactions to certain agents, such as NSAIDs and radiocontrast media, can be triggered via both the immune and nonimmune pathways.

Insect Sting Anaphylaxis

Stinging insects in the *Hymenoptera* order are the main cause of insect-related anaphylaxis. The families of *Hymenoptera* of clinical importance are Apidae (honeybees and bumblebees), Vespidae (yellow jackets, hornets, and wasps), and Formicidae (ants). The venom from the insects' stings contain proteins and vasoactive amines (such as histamine), and are implicated in anaphylaxis, due to their toxic effects.[22] The Africanized honeybee (the "killer bee") poses a danger not only due to its venom (which is similar to that of other types of bees), but also because of its swarm-and-attack behavior, the number of stings deposited, and the resultant high allergen load.[23,24] Among the small number of true IgE-mediated reactions that occur due to stings, the majority may be fatal on the initial event.

Table 1. Common Etiologies Of Anaphylaxis

Category	Allergens
Foods	• Children: eggs, milk, soy • Adults: peanuts, tree nuts, shellfish
Drugs	• Antibiotics, anesthetics, aspirin, NSAIDs
Hymenoptera	• Apidae (honeybee, bumblebee) • Vespidae (yellow jacket, hornet, wasp) • Formicidae (fire ant)
Natural rubber latex	• Heat-stable proteins and additives in processing
Exercise-induced	• Temperature extremes, food-triggered
Idiopathic	• Diagnosis of exclusion

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug.

Environmentally Induced Anaphylaxis

Allergy to natural rubber latex may be a delayed hypersensitivity reaction (such as contact dermatitis) or it may be an immediate IgE-mediated reaction that may cause a life-threatening reaction. The portal of entry of the allergen may be through the skin, mucous membranes, vasculature, or via inhalation. This can be a major cause of iatrogenic anaphylaxis in the hospital setting as a result of exposure to medical materials (gloves, urinary catheters, intravenous catheters). Due to more-stringent guidelines and a public health approach, in the past 2 decades, environments that are natural-rubber-latex-safe and controlled have been established in healthcare settings, and these iatrogenic reactions have been significantly reduced.[24]

Idiopathic Anaphylaxis

When no inciting source of anaphylaxis can be determined after obtaining a detailed history, a diagnosis of idiopathic anaphylaxis may be given. These cases occur in women more often than in men in a 2:1 ratio, and they most frequently arise between the second and sixth decades of life.[25] Idiopathic anaphylaxis cases are often benign, with minimal clinical manifestations and spontaneous resolution; however, the presentation may also be unpredictable and recurrent, and a minority of cases may be life-threatening.[26,27,28]

Pathophysiology

Immune-Mediated Hypersensitivity

The mechanism of an immune-mediated allergic reaction was first classified by Gell and Coombs. **(See Table 2, page 5.)** It is helpful to distinguish between the different types of hypersensitivity reactions. The most common reactions seen in the ED are Type I (IgE-mediated and immediate), which may manifest as anaphylaxis, angioedema, or urticaria; and Type IV (T-lymphocyte-mediated and delayed), which may manifest as contact dermatitis. After prior sensitization to an allergen and after repeated exposure to it, an immune-mediated response (IgE, IgG, IgM) may occur. During the classic Type I response,

antigen-processing cells, such as macrophages, alert the body to a foreign allergen. Allergen-specific IgE is produced, and it binds to high-affinity receptors for IgE (FcεRI) on mast cells and basophils.

When re-exposure occurs and a subsequent antigen binds to the already-existent IgE-mast cell or IgE-basophil complex, degranulation results, and preformed mediators and other agents are released (including histamine, leukotriene, prostaglandin, and tryptase). Histamine increases blood flow and the leakage of proteins and fluid into tissue spaces. Leukotrienes, prostaglandins, and tryptase have roles as mediators of inflammation. They work together to produce the clinical manifestations of edema, rash, pruritus, vascular compromise, and the respiratory difficulties seen in anaphylaxis.

At the far end of the spectrum, anaphylactic shock leads to clinical signs of worsening systemic edema and vascular collapse. The pathophysiologic mechanism of anaphylactic shock involves a large number of allergic mediators. Histamine, in particular, is a strong vasodilator of both arterioles and veins, and ultimately leads to decreased venous return to the heart. This further reduces filling pressures and cardiac output, resulting in a mixed hypovolemic-distributive shock.[29]

The degree of hypersensitivity reaction depends upon IgE concentration, the number of mast cells and basophils, the route of exposure to the antigen, the sensitivity of target organs, and the suddenness of symptom onset.[30] A history of atopy (the genetic predisposition to develop allergic diseases such as allergic rhinitis, asthma, and atopic dermatitis) also seems to predispose individuals to more-severe hypersensitivity reactions. Individuals with atopy have a heightened immune response to common extrinsic allergens and a higher level of IgE at baseline, although they are not predisposed to an increased risk of anaphylaxis, per se.[31] Rarely, anaphylaxis may occur through other immune mechanisms that are non-IgE-mediated, such as IgG or complement, as has been documented in the past with infliximab (Remicade®) and contaminants in heparin, respectively.[32]

Nonimmune-Mediated Hypersensitivity

The pathophysiology of idiopathic anaphylaxis, a diagnosis of exclusion, is clinically similar to anaphylaxis secondary to an extrinsic allergen, except that mast cells are activated in a nonimmunologic fashion, and the reaction is not antigen-dependent.[26,29] Such patients should have close follow-up with an allergist, and prophylactic measures should be instated because of the unpredictability of the response and the potential for serious fatal reactions.[28] It should be noted that patients with frequently recurrent idiopathic anaphylaxis may, in fact, truly be suffering from mastocytosis, which is characterized by the abnormal accumulation of mast cells in the skin or internal organs. This results in excessive endogenous histamine release and subsequent pruritus, abdominal pain, diarrhea, dyspnea, tachycardia, or hypotension.[33] Anaphylactoid reactions may occur on the first exposure, since antibody mediators do not need to be primed.

The emergency clinician should not attempt to determine which pathway has been activated, as anaphylaxis and anaphylactoid reactions are both treated in the same fashion and with urgency. Differentiation may be of interest in terms of risk stratification after the acute phase and for follow-up testing, as anaphylactoid reactions are not predicted with skin testing. **(See Figure 1, page 6.)**

Differential Diagnosis

Anaphylaxis can present similarly to a variety of other conditions. **(See Table 3, page 6.)** Some of these require swift evaluation and initiation of treatment, and the history will help direct resuscitation and medication administration. Exposure to a potential trigger accompanied by multiple systemic manifestations strongly points to anaphylaxis. However, anaphylactic shock may mimic other hypoperfusion states, such as hypovolemic, endotoxic, hemorrhagic, cardiogenic, or vasovagal reactions, particularly if the anaphylactic response lacks cutaneous/mucosal manifestations such as pruritus, urticaria, or flushing.

Table 2. Gell And Coombs Classification Of Hypersensitivity Reactions

Classification	Mechanism	Clinical Manifestations	Timing of Reaction
Type I (IgE-mediated)	Allergen IgE binds to mast cells with inflammatory mediators released	Anaphylaxis, urticaria, angioedema	Immediate; minutes to hours
Type II (cytotoxic)	IgG and IgM bind to allergen on target cell; complement mediated	Neutropenia, thrombocytopenia, hemolytic anemia	Variable
Type III (immune complex)	Tissue deposition of IgG, bound to allergen; activated by complement	Serum sickness, vasculitis, glomerulonephritis	1-3 weeks postexposure
Type IV (delayed, cell-mediated)	T-lymphocytes, macrophages	Contact dermatitis	48-72 hours

Abbreviations: IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M.

Adapted from "Allergies And Anaphylaxis: Analyzing The Spectrum Of Clinical Manifestations," by Jonathan E Davis, MD, *Emergency Medicine Practice,* Vol. 7(10), 2005, Table 2, page 3, Copyright EB Medicine.

One notable distinction is that reflex tachycardia and a wide pulse pressure from distributive shock most often accompany the hypotension of anaphylaxis.[34,35] A landmark study in the anesthesia literature tracked the hematocrit levels of 205 patients who experienced anaphylactic shock while under anesthesia, and extravasation of up to 35% of circulating blood volume was found to occur within 10 minutes of the onset of anaphylactic shock.[36] Hypotension from a vasovagal response is most commonly associated with bradycardia, since vasovagal episodes are neurally mediated with a combination of increased vagal tone and sympathetic withdrawal. Flush syndromes such as carcinoid, decreased circulating estrogen levels in menopause, and "restaurant" syndromes (scombroid and monosodium glutamate [MSG] reactions) may all resemble anaphylaxis as well.

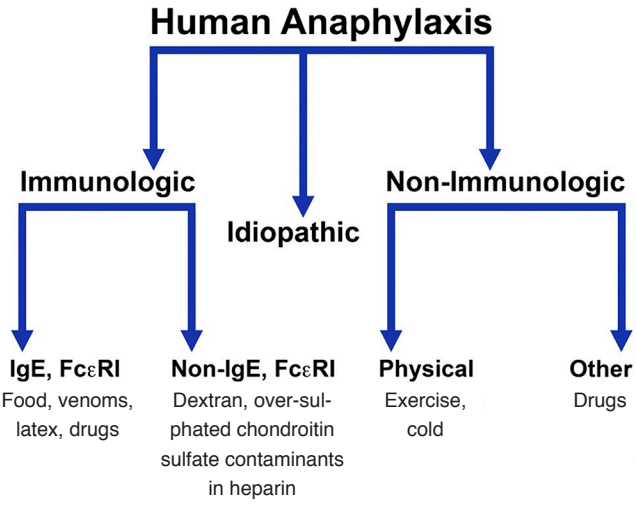
Scombroid poisoning results from eating spoiled fish, particularly dark meat, such as tuna. Histidine on the fish muscle is broken down by bacteria into histamine, and when eaten, leads to self-limited skin flushing, headache, and a variety of gastrointestinal complaints.[37] Additionally, MSG syndrome may present with nausea, diaphoresis, and headache after ingestion of foods containing this additive.[38] It is important to distinguish these food-induced reactions from anaphylaxis, as treatment includes simple supportive measures, along with the administration of antihistamines for scombroid poisoning.

ACE inhibitors may precipitate mast cell-mediated reactions through a nonallergic mechanism and increased levels of bradykinin, a vasodilator that generally requires ACE to be broken down. ACE-inhibitor-induced angioedema (ACEIIA) can occur at any time in the treatment course in 0.1% to 0.7% of patients, although the majority of cases occur in the first weeks after starting the medication.[27,38,39] Angioedema may present with mild swelling of the lips to dramatic involvement of the tongue and oropharynx.[40] In a large multinational, multicenter study of patients with angioedema, urticaria and flushing were reported 7% and 28% of the time, respectively, demonstrating overlapping symptoms with anaphylaxis.[41,42] Patients with angioedema induced by an ACE inhibitor must immediately stop taking the inciting medication in order to prevent future reactions.

Hereditary angioedema is due to a decrease in the amount or function of C1-esterase inhibitors and a subsequent increase in bradykinin. Hereditary angioedema lacks the pruritus of allergy, but has a high rate of gastrointestinal involvement (93%), and it may resemble an allergic reaction in this regard.[43,44] Case reports support treatment for ACE-inhibitor-induced anaphylaxis and hereditary angioedema (both bradykinin-mediated) with plasma-derived products (such as fresh-frozen plasma) rather than epinephrine.[45,46,47] Epinephrine is generally ineffective in nonallergic, bradykinin-mediated reactions.

Finally, cutaneous mastocytosis involves a preponderance of mast cells in the skin, while the systemic form may show a rapid production of mast cells in the lymph nodes, spleen, bone marrow, or liver.[23] These disorders may mimic anaphylaxis, as patients generally present with histamine-related flushing, pruritus, diarrhea, nausea, abdominal pain, and possible hypotension.[48]

Figure 1. Mechanisms Underlying Human Anaphylaxis



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Prehospital Care

Prehospital care of anaphylaxis and severe allergy should focus on maintaining the airway, breathing, and circulation, with a focus on evaluation of airway patency

Table 3. Differential Diagnosis Of Anaphylaxis

Type	Differential Diagnosis
Cardiac	Myocardial infarction, arrhythmia
Pulmonary	Pulmonary embolism, inhaled foreign body, asthma, obstructive lung disease
Flush	Carcinoid, postmenopause, carcinoma
Restaurant	Scombroid, monosodium glutamate syndrome
Shock	Septic, cardiogenic, hemorrhagic
Histamine	Systemic mastocytosis, leukemia, urticaria pigmentosa
Psychological	Anxiety, Munchausen stridor
Neurologic	Cerebrovascular accident, seizure
Other	Antiotensin-converting-enzyme-inhibitor angioedema, hereditary angioedema, and pheochromocytoma

as a crucial factor in the early assessment period. The airway may be compromised, resulting in stridor from upper airway laryngeal edema and/or wheezing from lower airway inflammation and bronchospasm.[35,39] Patients with potential anaphylaxis also require rapid assessment of vital signs, supplemental oxygen, large-bore intravenous access, and cardiac monitoring.

After initial airway management, attempts should focus foremost on shortening the time between anaphylaxis and epinephrine administration, as up to 50% of deaths occur within the first hour of a reaction.[7] In order to control symptoms and increase blood pressure, 0.3 to 0.5 mL (0.01 mg/kg in children, max 0.3 mg dosage) of aqueous epinephrine in a 1:1000 dilution (1 mg/mL) should be given intramuscularly in the lateral aspect of the thigh. Under no circumstance should epinephrine be withheld until a patient is in extremis. Patients with a prior history of allergy or anaphylaxis may carry an epinephrine auto-injector in the prehospital setting.[50,51,52] Most emergency medical services (EMS) protocols are written for the swift delivery of epinephrine; however, epinephrine may be underutilized, with as few as 14% of cases receiving the medication appropriately in the prehospital setting.[53] Studies have shown that prehospital epinephrine administration by EMS personnel in the field is safe and used appropriately in the overwhelming number of situations.[54]

Evidence also exists to support intravenous crystalloid administration for cardiovascular compromise. One should not underestimate the potential for hemodynamic collapse in the setting of severe allergy and anaphylaxis. Clinicians should administer aggressive fluid boluses to increase preload and place patients in a supine position with legs elevated.[2,35,47] Furthermore, in the case of *Hymenoptera* envenomations, the stinger should be removed as soon as possible. This will decrease the allergen load by preventing the venom sac attached to the stinger from injecting additional venom into the patient.

In addition to epinephrine, some patients may receive inhaled beta agonists as well as glucocorticoids to assist with bronchospasm. Despite little evidence from the literature to support the use of these drugs specifically for anaphylaxis, it is known that beta agonists are effective in the treatment of allergic asthma and upper airway obstruction, and that steroids block arachidonic acid production, thus reducing inflammation and decreasing the likelihood of protracted anaphylaxis. In the critical prehospital setting, use of these drugs in a "shotgun" approach is reasonable in a patient with upper airway symptoms (use inhaled beta agonists) or signs of edema from severe allergy (use corticosteroids).

Furthermore, evidence exists to support the use of antihistamines (H1- and H2-blockers) as second-line drugs in anaphylaxis, as they help to decrease further histamine release.[55] It is recommended that they should be given in the prehospital setting, with diphenhydramine dosed at 1 to 2 mg/kg or 25 to 50 mg/dose parenterally, and with ranitidine administered at 50 mg in adults and 1 mg/kg in children.[2]

Emergency Department Evaluation

Initial Stabilization

ED evaluation begins with rapid triage and measurement of vital signs. Evaluate airway, breathing, and circulation, and place the patient on continuous electrocardiography and pulse oximetry monitoring. Patients in respiratory distress with stridor or wheezing should immediately be placed in a resuscitation area. Frequently reassess the need for intubation or awake, fiberoptic intubation, even in initially stable patients, and closely monitor all patients, keeping advanced airway equipment close at hand.[54,56]

History

The American Academy of Allergy, Asthma, and Immunology Joint Task Force on Practice Parameters has recently revised guidelines for the diagnosis and treatment of anaphylaxis and have determined that history is the most reliable tool in determining whether a patient has had an anaphylactic episode.[2] Furthermore, guidelines set forth by the National Institute of Allergy and Infectious Diseases have emphasized updated clinical criteria to diagnose anaphylaxis.[1] **(See Table 4, page 8.)** It is also crucial to recognize the variability of allergic reactions and that anaphylaxis exists on a continuum of reactions, with a threshold of clinical signs and symptoms for diagnosis that is often difficult to define.

Once the patient is hemodynamically stable, obtain a detailed history of events from the patient, family members, or bystanders to help clarify a diagnosis of anaphylaxis. Specific attention should be placed on the time of onset and initial symptoms, potential food triggers, medications, and insect stings. Inquire about the chronic use of medications such as beta blockers, as this may affect the treatment response.[57] Eliciting a prior history of severe allergies or asthma is important, since these factors are associated with recurrent life-threatening episodes of anaphylaxis and will influence decisions to admit and observe patients.[1] Inquire about medications that were administered in the prehospital setting by caregivers or by EMS. It should be recognized that a patient may require additional epinephrine, even if an initial dose was given in the prehospital setting.[54,57] In a retrospective review, it was found that close to 20% of patients with food-induced anaphylaxis required a second dose of epinephrine in the ED after prehospital administration of the first dose.[58]

Physical Examination

Check vital signs immediately in all patients with potential anaphylaxis, paying particular attention to pulse oximetry and blood pressure (hypotension). Perform a careful assessment of airway patency, looking for stridor, wheezing, dyspnea, or voice change. There are a wide range of signs and symptoms of anaphylaxis that occur with varied frequency. **(See Table 5.)** The majority of patients with anaphylaxis will exhibit a rash; however, mucosal or cutaneous involvement may be absent or unrecognized in 10% to 20% of patients.[2] The rash of anaphylaxis often presents as generalized flushing or frank urticaria, although, in some cases, a localized cutaneous reaction or even physical evidence of an insect bite may be enough to tailor the diagnosis towards an allergic etiology.[59,60]

Anaphylaxis should be strongly considered when there is a rash and other organ system involvement. Carefully document gastrointestinal symptoms, as nearly 50% of patients may present with rapid onset of nausea, vomiting, or abdominal pain, followed by delayed diarrhea.[7] Syncope or dizziness due to hypotension, as well as cardiovascular manifestations, may be present approximately 50% of the time, especially in adults, and emergency clinicians should be aware of isolated syncope as a potential presentation of anaphylaxis.[1,4,7]

All patients suspected of having an anaphylactic reaction should be undressed and inspected for a potential trigger. If an insect stinger is present, it should be scraped off rather than compressed, as the latter method may release additional venom. If a food allergen is suspected, induction of vomiting is not recommended.

Diagnostic Studies

Treatment should be initiated in the presence of clinical suspicion and hemodynamic compromise, as anaphylaxis is truly a clinical diagnosis. Blood tests have no role in the acute diagnosis of severe allergy and anaphylaxis. However, certain acute biomarkers are helpful, retrospectively, in cases where the diagnosis may not be clear, or to assist in guiding the allergist consultant in future therapeutic management. In severe allergic reactions, elevations in tryptase, histamine, and platelet-activating factor (a vasoactive mediator) were noted in 61%, 75%, and nearly 100% of patients, respectively, in a study by Vadas et al.[61]

Tryptase and histamine assays are the tests most often requested by allergists in the acute ED setting, as the half-life of platelet-activating factor is 3 to 13 minutes, which renders it impractical to capture elevated levels.[62,63]

Tryptase is released mainly by mast cells, peaks within 90 minutes, and may be tested in serum up to 3 hours after symptom onset.[64] However, a normal tryptase level does not exclude anaphylaxis and, notably, tryptase has less utility in food-based allergies than in anaphylaxis of other etiologies, as it is less likely to be elevated after allergens have been ingested.[64] Histamine levels peak within 10 minutes and disappear in 1 hour, making them less useful in establishing a diagnosis of anaphylaxis. If detected

Table 4. Clinical Criteria To Diagnose Anaphylaxis

Anaphylaxis is likely when any 1 of the 3 criteria below is satisfied:

1. The acute onset of a reaction (within minutes to hours) with involvement of the skin, mucosal tissue, or both, and at least 1 of the following:
   - Respiratory compromise
   - Reduced blood pressure or symptoms of end-organ dysfunction (eg, syncope, angina, or arrhythmias)
2. ≥ 2 of the following that occur rapidly (within minutes to hours) after exposure to a likely allergen:
   - Involvement of the skin/mucosal tissue
   - Respiratory compromise
   - Reduced blood pressure or associated vascular symptoms
   - Persistent gastrointestinal symptoms
3. Reduced blood pressure after exposure to a known allergen (within minutes to hours):
   - Infants and children: low systolic blood pressure for age or > 30% decrease from baseline in systolic blood pressure
   - Adults: systolic blood pressure < 90 mm Hg or > 30% decrease from baseline

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Table 5. Frequency Of Occurrence Of Signs And Symptoms Of Anaphylaxis

Signs and Symptoms	Frequency of Occurrence
Cutaneous	
Urticaria and angioedema	85%-90%
Flushing	45%-55%
Pruritus without rash	2%-5%
Respiratory	
Dyspnea, wheezing	45%-50%
Upper airway angioedema	50%-60%
Rhinitis	15%-20%
Dizziness, syncope, hypotension	30%-35%
Abdominal	
Nausea, vomiting, diarrhea, cramping	25%-30%
Miscellaneous	
Headache	5%-8%
Substernal pain	4%-6%
Seizure	1%-2%

Reprinted from the *Journal of Allergy and Clinical Immunology,* Vol. 126(3), Phillip Lieberman, Richard A. Nicklas, John Oppenheimer, et al, "The Diagnosis and Management of Anaphylaxis Practice Parameter: 2010 Update. Pages 477-480, Copyright 2010, with permission from Elsevier.

early in an emergent episode, however, elevated histamine and tryptase levels may be used most reliably to help guide the diagnosis of allergy by comparing them to baseline convalescent levels.

Treatment

Secure And Monitor The Airway

Definitive airway management takes precedence. Emergency clinicians should observe for edema, accessory muscle use, retractions, and signs of altered mental status, as these may suggest hypoxia. Furthermore, airway obstruction may cause hypercarbia, leading to stridor and dysphonia. Patients with anaphylaxis and severe dyspnea require immediate high-flow supplemental oxygen at the highest concentration, using a mask with an oxygen reservoir. Heliox may be added, as it improves ventilation by reducing airway turbulence, particularly in patients with severe airway compromise and a history of asthma.[65]

Patients may present with some degree of labial or facial swelling. Patients with lingual edema and oropharyngeal swelling are at particular risk of airway compromise. The American Heart Association guidelines recommend early elective intubation for patients observed to develop hoarseness, lingual edema, stridor, or oropharyngeal swelling.[54]

Orotracheal rapid sequence intubation (RSI) is the most commonly employed definitive airway maneuver in the ED. However, in the setting of pronounced airway edema, RSI may create potential problems. Specifically, patients given paralytics for RSI who fail intubation may experience compromised effectiveness of ventilation via bag-valve mask. Several advanced airway techniques offer alternatives and adjuncts to traditional RSI. These include apneic oxygenation, delayed sequence intubation, and awake intubation. Apneic oxygenation utilizes a nasal cannula at 15 L/min. This technique has been shown in clinical trials to extend the duration of safe apnea and blunt desaturation. Delayed sequence intubation incorporates an intentional pause after the sedative is initiated to allow for adequate preoxygenation without risking gastric insufflation or aspiration. **Table 6** outlines the technique for awake intubation.

Address Breathing And Monitor Respiratory Rate

Careful auscultation of the patient's lungs may reveal wheezing and/or diminished breath sounds. This may represent upper airway edema or lower airway bronchospasm. According to the Diagnosis and Management of Anaphylaxis Practice Parameter: 2010 Update guidelines developed by the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma, and Immunology, inhaled beta-2 agonists, such as albuterol (2.5 mg via nebulizer), may be employed if wheezing is present or bronchospasm is suspected, especially if the patient does not respond to intramuscular epinephrine. Furthermore, despite the presence of only anecdotal evidence that inhaled epinephrine (0.5 mL epinephrine nebulized in 2.5 mL saline) may be useful in mitigating both bronchospasm and laryngeal edema, there is little downside to its administration, and we recommend it as an adjuvant to other treatment in cases of refractory airway difficulties.

Patients should be placed in a position of comfort. Patients with airway compromise generally prefer to sit upright, while patients with hypotension should lie flat, with or without their legs elevated.[3] Deaths have been reported if the patient assumes the upright sitting position prematurely.[66]

The patient's respiratory rate should be carefully monitored, as decreased effort and rate of breathing may represent a fatigued patient and signal impending respiratory failure. A potential adjunct to airway management is end-tidal carbon dioxide monitoring. A meta-analysis by Waugh et al found that such monitoring detects hypoventilation earlier than methods such as pulse oximetry and pulse rate alone, particularly when supplemental oxygen is administered.[67]

Ensure Adequate Circulation

Patients suffering from anaphylaxis are at high risk of circulatory collapse and eventual shock, and they require serial automated blood pressure monitoring. Hypotensive patients require 2 large-bore intravenous lines and a rapid intravenous fluid challenge of 500 to 1000 mL of isotonic crystalloid solution (such as normal saline) as soon as possible.

Epinephrine is the undisputed first-line medication for treatment of anaphylaxis. Its alpha-agonist effects significantly increase vascular tone and its beta-agonist activity improves cardiac contractility, which improves circulation in the shock state. Furthermore, it blocks the release of cyclic-adenosine-monophosphate-dependent allergic mediators, reducing the allergen load on the body.

Table 6. Awake Intubation Technique

1. Administer glycopyrolate 0.2 mg intravenously as a drying agent.
2. Administer ondansetron 4 mg intravenously to blunt the gag reflex.
3. For best results, wait 10-15 minutes before proceeding.
4. Suction and pat entire mouth dry with gauze.
5. Utilize nebulized lidocaine (5 mL of 4%) at 5 L/min.
6. Spray atomized lidocaine into oropharynx.
7. Apply viscous lidocaine 4% to the patient's tongue to be swallowed.
8. Preoxygenate the patient with a nasal cannula and nonrebreather mask at 15 L/min.
9. Utilize mild sedation with ketamine 20 mg every 2 minutes.
10. Intubate with a bougie, pass the tube, and confirm placement.

Route Of Epinephrine Administration

Epinephrine is confirmed to be a life-saving medication, and its administration should be considered as soon as the diagnosis of anaphylaxis is suspected.[1,2,68,69,70] Unfortunately, epinephrine is underutilized, and its administration is often delayed, putting patients at significant risk of death.[68] Although previous recommendations have advocated for the subcutaneous route of epinephrine administration, ideally epinephrine should be given intramuscularly into the anterolateral aspect of the middle third of the thigh, as it achieves more-rapid peak plasma concentrations in both children and adults in this fashion. The evidence from 2 separate randomized, double-blinded studies using healthy volunteers at risk for anaphylaxis supports this. The studies demonstrated that blood concentrations of epinephrine reached higher levels in shorter time periods when administered intramuscularly in the thigh rather than subcutaneously or intramuscularly in the deltoid.[71,72] Although this was performed in healthy subjects, results from these studies can be extrapolated to patients in anaphylactic shock. Such patients are hemodynamically unstable and have reduced perfusion and circulation, particularly at the surface of the skin, which reduces subcutaneous absorption.

The American Heart Association, the American Academy of Allergy, Asthma & Immunology, and the Cochrane Collaboration all regard the administration of epinephrine intramuscularly as first-line treatment for the management of anaphylaxis.[1,54,73]

Epinephrine Dosing

Intramuscular Epinephrine Administration

Epinephrine should be administered as soon as the diagnosis of anaphylaxis is suspected. The recommended dose of intramuscular epinephrine is 0.3 to 0.5 mg of 1:1000 (1 mg in 1 mL) solution, which calculates to 0.3 to 0.5 mL. It may be administered every 5 to 10 minutes as necessary, and the 5-minute interval between injections can be liberalized to promote more-frequent administration if the patient's cardiovascular and/or respiratory status further deteriorates.[2] Epinephrine is not contraindicated in patients with underlying ischemic heart disease. The adverse effects from hypotension and decreased filling pressure in anaphylaxis may worsen ischemia, but this risk outweighs any potential side effects of the drug itself, although monitoring is recommended.

Intravenous Epinephrine Administration

At least 1 trial has shown that intravenous administration of epinephrine may be beneficial in patients with cardiovascular collapse who do not respond to the intramuscular route.[34] One option for intravenous use is to add 0.1 mg (1 mL of a 1:10,000 solution) to 9 mL normal saline for a total of 10 mL of a 1:100,000 dilution that can be given over 5 to 10 minutes.[54] However, it may prove more effective to initiate a continuous epinephrine infusion rather than administering epinephrine in a push-dose fashion. There are no quality studies that support the use of intravenous terbutaline, a beta-2 adrenergic receptor agonist, over epinephrine for anaphylaxis.

Epinephrine Infusion

Several dosing regimens for epinephrine infusion exist. One prospective study demonstrated efficacy using an intravenous infusion of 1 mg of 1:1000 epinephrine in 100 mL normal saline (1:100,000, 10 mcg/mL) intravenously by infusion pump.[34] It is recommended that infusions should be initiated at 30 mL/h to 100 mL/h (5-15 mcg/min), and patients should be monitored for signs of epinephrine toxicity that may manifest as tachycardia, tremor, and pallor in the setting of a normal or elevated blood pressure. The infusion should be stopped 30 minutes after life-threatening signs and symptoms of anaphylaxis have resolved.[34]

Antihistamines As Second-Line Medications

It has been recommended that antihistamines can be used as second-line drugs in the treatment of anaphylaxis after epinephrine has been given.[1,74,75] Nonetheless, there are no randomized or placebo-controlled trials of H1-receptor blockers in anaphylaxis. However, a randomized double-blind, placebo-controlled trial of 91 adults with acute allergic reactions did demonstrate the benefit of combining H1-receptor blockers and H2-receptor blockers for treatment over using H1-receptor blockers alone.[76] Therefore, it is recommended that, when employing antihistamines for anaphylaxis, emergency clinicians should treat with both H1-receptor blockers and H2-receptor blockers. These medications take 30 to 45 minutes to take effect even when given intravenously.

The mechanism of action of the antihistamine is to prevent the additional release of histamine, not to alter levels of histamine already in circulation. Thus, antihistamines may be given as second-line agents in conjunction with first-line epinephrine, but they should never be given in lieu of epinephrine. Antihistamines may treat cutaneous manifestations of anaphylaxis but will not alter shock or airway symptoms. **Table 7** provides dosing options for antihistamines. There is no conclusive evidence to guide therapeutic duration.

Table 7. Dosing Options For Antihistamines

Antihistamine	Dosing
H1-receptor antagonists (eg, diphenhydramine)	25-50 mg intravenously
H2-receptor antagonists (eg, ranitidine)	50 mg intravenously

Corticosteroid Use In Anaphylaxis

A 2012 Cochrane review produced no relevant evidence to support the use of corticosteroids in acute anaphylaxis.[77] The justification for giving glucocorticoids has been based on their proven role in asthma and on the presumption that corticosteroids would prevent a biphasic allergic reaction. Yet there is no firm evidence that steroids prevent a biphasic response in anaphylaxis.[78] However, because of the known mechanism of action of steroids, their blockade of arachidonic acid production through cell membrane stabilization, and their subsequent ability to reduce inflammation, steroids have been employed in the treatment of severe allergic reactions in the emergency setting. Some consensus guidelines have recommended their inclusion in the treatment of anaphylaxis as second-line agents, after epinephrine, with a dosage of 1 mg/kg by mouth of prednisone or 125 mg of methylprednisolone intravenously. As with antihistamines, there is a delay in the onset of action of steroids and, even when given intravenously, these medications take 4 to 6 hours to have an effect.[78,79] Thus, corticosteroids should never replace the administration of first-line epinephrine in the treatment of anaphylaxis. If corticosteroids are used as second-line drugs, there is no recommendation in the literature on the duration of therapy.

Fluid Resuscitation

Intravenous fluids through large-bore catheters should be initiated on all anaphylaxis patients. If intravenous access cannot be obtained, intraosseous access has been demonstrated in several studies to be safe and effective.[80,81] Normal saline is the fluid of choice. Adult patients should initially receive a 500-mL to 1000-mL bolus of normal saline, with additional boluses given as necessary, particularly in patients taking beta blockers, where the need may be substantially greater. Children should receive 30 cc/kg in the first hour of resuscitation.

Special Circumstances

Refractory Anaphylaxis

Glucagon may have a role in the treatment of refractory anaphylaxis, and it should be considered in patients with a history of hypertension who are on beta-blockers and for whom first-line therapy with epinephrine has failed. These patients can face 2 issues: (1) They have a tendency toward more-severe anaphylactic reactions because, at a cellular level, the blockade of beta-adrenergic receptors increases the likelihood of release of inflammatory intermediaries. This contributes to a greater degree of shock by decreasing cardiac contractility and potentiating bronchospasm; and (2) the patient's anaphylaxis may be refractory to epinephrine administration secondary to a lack of its efficacy at the beta-receptors.

Epinephrine reduces the load of allergic mediators by increasing cyclic adenosine monophosphate through beta-adrenergic receptors. If these receptors are blocked, the epinephrine effect is blunted, and it may cause unopposed alpha-adrenergic effects that can worsen existing symptoms of the allergic response. These patients can benefit from the administration of glucagon, which increases cyclic adenosine monophosphate via pathways other than the beta-adrenergic system.[83] Glucagon is extremely short-acting; therefore, it should be dosed at 1 to 2 mg intravenously and repeated every 5 minutes as needed. Patients may require a glucagon drip at 1 to 5 mg/hr. In children, the dose is 20 to 30 mcg/kg (maximum 1 mg) intravenously over 5 minutes, although it is rarely used in this population.

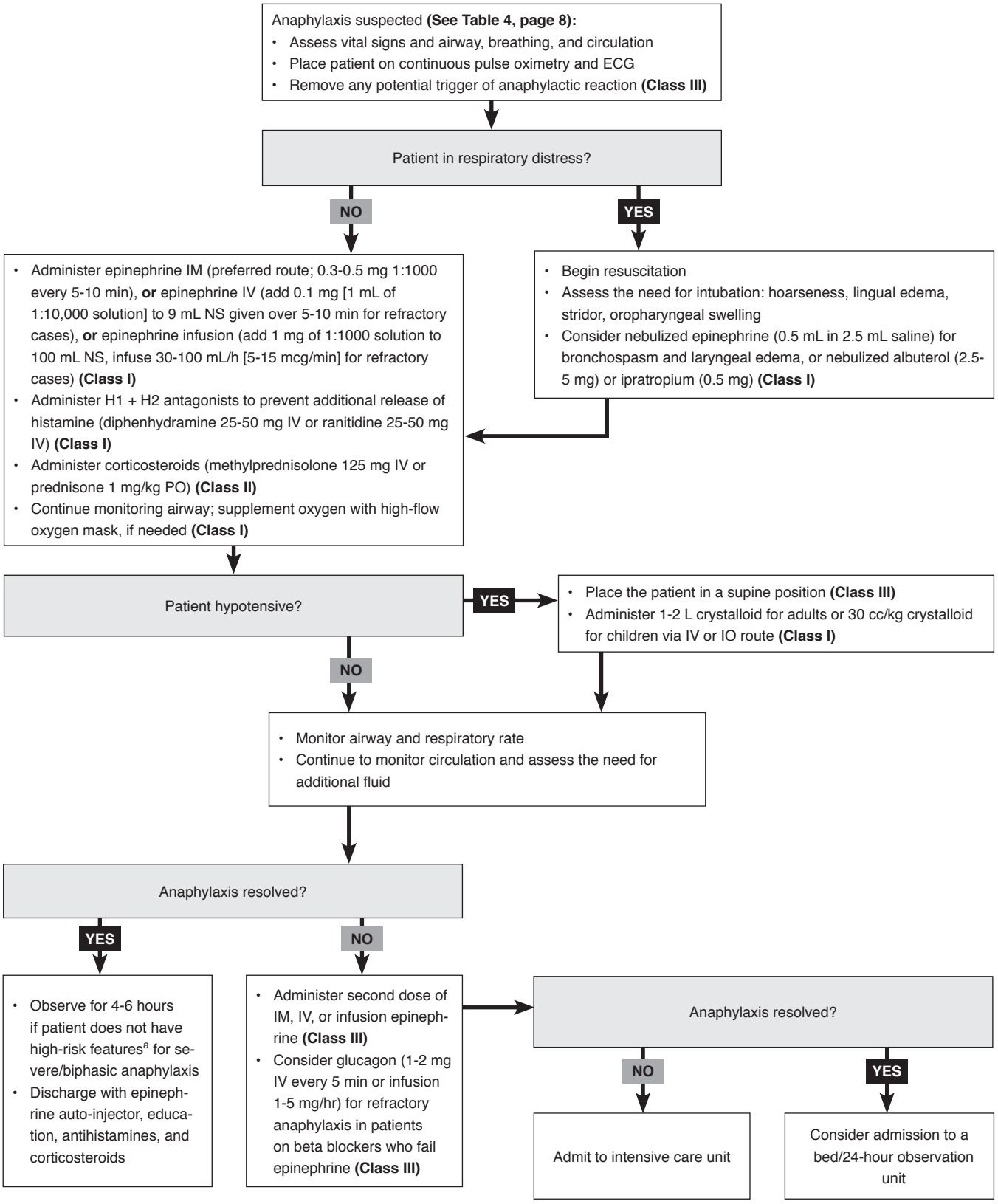
Side effects of glucagon include hyperglycemia, nausea, and vomiting, and airway assessment and monitoring should continue any time glucagon is employed.[83,84] However, in spite of the biological justification for glucagon, the evidence to support its use in epinephrine-resistant anaphylaxis is based on only a few case reports in patients with anaphylactoid reactions in response to intravenous contrast media.[1,83,85]

Controversies And Cutting Edge

Epinephrine remains the first-line, proven treatment for anaphylaxis. Pharmaceutical companies have focused on different delivery methods, epinephrine auto-injectors (EAIs), and patient education.[86,87,88] Trials have shown near-perfect administration of epinephrine via auto-injectors when accompanied by instructional labels, although ED or clinical teaching by medical staff is still preferred in conjunction with this.[87,89-91] Furthermore, there are newer EAI devices that are the size of a credit card and possess retractable needles, as well as a novel auto injector with voice-recorded directions.[92,93]

Perhaps the most promising new potential development is not in the realm of general anaphylaxis itself, but rather in the specific area of ACEIIA with the trial of ecallantide, a kallikrein inhibitor. After approval of the use of this drug for hereditary angioedema in December 2009, a multicenter, double-blinded, randomized, controlled phase 2 trial was undertaken to determine its effectiveness in ACEIIA. However, results published in August 2014 did not show a significant difference between the placebo and ecallantide groups, and supportive care and airway management still remain the standard of care for ACEIIA.[94] A prospective double-blinded, placebo-controlled study of a similar drug, icatibant, a bradykinin-receptor inhibitor, is currently ongoing to determine its use in ACEIIA. A prior case series of 8 patients examined icatibant use for ACEIIA against a control group. The study found complete resolution of angioedema symptoms within 4 hours in patients who received 30 mg of the drug subcuta-

Clinical Pathway For Management Of Allergy And Anaphylaxis In The Emergency Department



Abbreviations: ECG, electrocardiogram; IM, intramuscular; IO, intraosseous; IV, intravenous; NS, normal saline.

[a]High-risk features include patients on beta blockers, history of nut allergies and asthma, young age, or those with limited access to phone or emergency services.

See page 13 for Class of Evidence definitions.

neously, and within 33 hours in the control group.[95] More extensive randomized controlled trials are needed to determine its acceptability, effectiveness, and safety for treatment of anaphylaxis.

Another novel development in the treatment of anaphylaxis has centered on investigations into the role of omalizumab, a monoclonal antibody that has previously been used in IgE-mediated disorders such as rhinitis, dermatitis, and urticaria that have an allergic etiology. A few case reports exist on its utility in anaphylaxis via one of its theoretical modes of action, as a reducer of serum IgE. Methylene blue has been explored in animal studies as a potential treatment for anaphylactic shock through its inhibition of vasodilatation, and has also been discussed in a few case reports. From these sources, it has been suggested as a potential rescue drug for anaphylaxis that is refractory to first-line epinephrine.[96,97]

Disposition

Admission And Length Of Observation Period

Observation periods and admissions for patients experiencing allergic reactions should be individualized and based upon the severity of the reaction and the response to treatment.[78] Any patient who experiences an anaphylactic reaction that is resistant to initial treatment and who requires intravenous epinephrine, an epinephrine infusion, or glucagon administration should be admitted to an intensive care unit (ICU) setting for continued monitoring. Similarly, there should be a low threshold to admit patients to the ICU if ACEIIA is present with clinical findings of stridor or changes in phonation. In fact, a single-center, retrospective chart review of 80 patients by Ishoo et al identified patients who exhibited angioedema with tongue or larynx involvement as needing admission to the ICU in 67% and 100% of cases, respectively.[98]

Admission to an inpatient setting, although not necessarily an ICU, should strongly be considered in patients with limited access to phone or emergency services, patients on beta-blockers, and patients with a prior history of anaphylaxis, underlying asthma, renal disease, or congestive heart failure, who might be at risk for volume overload after intravenous fluid treatment. These high-risk features have been reported to lead to increased rates of death, and admission to the hospital or observation for at least 24 hours is recommended.[12,72,98]

For patients who are not at high risk, whose symptoms improve completely, and who may be discharged home, there is no established time period for ED observation, and the American Academy of Allergy, Asthma & Immunology Joint Task Force on Practice Parameters recommends tailoring observation times to individuals.[2] Other consensus guidelines from the National Institute of Allergy and Infectious Diseases and the Food Allergy Research & Education groups recommend that most patients should have an observation time of 4 to 6 hours after the height of the clinical reaction, while the Resuscitation Council (United Kingdom) advises at least 6 hours of monitoring.[1,99] This allows emergency clinicians to monitor for rebound reactions and to treat them early.

Rebound or biphasic anaphylaxis may occur even after complete resolution of symptoms, yet studies have not consistently identified factors that predispose a subset of patients to rebound anaphylaxis.

Biphasic reactions have been reported to occur in 5% to 20% of patients, and the latency period is variable, according to research.[100] A 2007 prospective study of 103 patients in a Canadian tertiary care center showed that the majority of biphasic anaphylaxis occurred around 10 hours after the initial anaphylaxis had cleared.[101] Another retrospective study examined ED presentations for allergy and anaphylaxis from 2001 to 2013, and the authors of that study found that 4.5% of all anaphylactic reactions were biphasic, and that the rebound response tended to occur within 8 hours of the resolution of the primary reaction.[102] Moreover, even among patients who experienced a clinically important biphasic reaction,

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

there were no deaths in this study or in another similar study.[102,103] Thus, prolonged observation after symptoms have resolved is unnecessary, given that biphasic reactions are rare and that patient safety is not likely to be impacted by additional monitoring.

In summary, the most reasonable recommendation, given the varying study conclusions and what is known about biphasic reactions, is that patients with nonsevere allergic reactions without high-risk features whose symptoms resolve in the ED with intramuscular epinephrine and/or antihistamines may be discharged after a 4-hour to 6-hour observation period from the height of the clinical reaction. Patients with severe allergic reactions that do not resolve after initial therapy, who are determined to be at high risk, or who have continued cardiorespiratory symptoms should be considered for admission to either a monitored bed or an ICU setting, depending upon the extent of the reaction.

Risk Management Pitfalls In Management Of Allergy And Anaphylaxis

(Continued on page 15)

1. **"The patient had an intravenous catheter in place, so I thought it seemed reasonable to give epinephrine through the intravenous line rather than to stick the patient again with an intramuscular injection."**
   Expert guidelines recommend administering epinephrine via the intramuscular route. It has a fast time of onset, and there is a lower likelihood of adverse arrhythmias from intramuscular administration versus intravenous administration of epinephrine. If a patient is not reacting appropriately to repeated doses of intramuscular epinephrine or has cardiovascular collapse, consider intravenous epinephrine at that time, and attempt to determine the causes of the refractory response (such as chronic use of beta blockers).

2. **"The patient has urticaria and wheezing after eating a cookie with nuts, but he looks good and is not hypotensive, so I won't give epinephrine yet. I'll try albuterol and an antihistamine first. Besides, he is 60 years old, and who knows if he has undiagnosed cardiac disease?"**
   Nothing should delay the administration of epinephrine in an anaphylactic reaction. Doing so increases the likelihood of a biphasic reaction and increases mortality. There are also no absolute contraindications to epinephrine use. The benefits of giving it in this situation outweigh the risks, as the adverse effects from hypotension and decreased filling pressure in anaphylaxis may actually worsen underlying ischemia.

3. **"My 21-year-old patient had a syncopal episode with bradycardia. It had to have been a vasovagal episode and not anaphylaxis. Besides, she didn't even have a rash."**
   Patients having an anaphylactic reaction who present with syncope generally have an accompanying tachycardia due to distributive shock and fluid extravasation. However, less frequently, patients may present with bradycardia-associated syncope, although there is some conjecture about the precise mechanism. Also, patients taking chronic beta blockers may not be able to mount a tachycardic response and may appear with a relative bradycardia. Even children and young adults may be prescribed these medications for a variety of reasons, and glucagon may be needed in such cases if they are refractory to first-line epinephrine. Furthermore, 10% to 20% of patients with anaphylaxis do not have urticaria or cutaneous findings on examination. Isolated hypotension or syncope after being exposed to a known allergen is sufficient to qualify the reaction as an anaphylactic one.

4. **"It's really busy tonight, so I will send the patient back to the allergist to get a prescription for an EAI in the morning. He seems perfectly stable."**
   All patients should be discharged from the ED with an EAI and guidance on how to self-administer it, even if their symptoms have resolved in the ED. Biphasic reactions can occur in 5% to 20% of patients, and auto-injectors can be effective in saving lives in the prehospital setting.

5. **"EMS already gave epinephrine to the patient. I just need to observe."**
   Severe anaphylaxis may necessitate more than one dose of intramuscular epinephrine. Though the first dose may be enough to abate the initial allergic reaction, it may not be sufficient to quell the multitude of symptoms. If the patient still manifests hemodynamic compromise, redosing of epinephrine is a necessity. In refractory cases, an epinephrine intravenous push or via infusion may be needed.

Discharge Counseling, Medications, And Follow-Up

Patients discharged from the ED after a period of observation should receive counseling regarding the indications that warrant a return to the ED, including any swelling, lightheadedness, or difficulty breathing. If the allergen responsible for the allergic reaction is known, counseling should be provided to avoid future exposure. Current evidence-based recommendations are that patients should receive a prescription for an EAI kit and instructions regarding its use and administration, as this can save lives in the community.[92,93] At the time of discharge from medical supervision, all patients should be instructed to follow up with a primary care provider, and patients with severe allergic reactions should be referred to an allergist/immunologist.

Discharged patients should receive a prescription for a short course of H1 and H2 antihistamines in combination. Some guidelines endorse a prescription for a short-course steroids as well.[76,77] Since there is no direct evidence of harm from a short

Risk Management Pitfalls In Management Of Allergy And Anaphylaxis

(Continued from page 14)

6. **"I'm writing a prescription for an EAI and sending the patient home. That should prevent another visit."**
   Patients who have a serious allergic reaction are more prone to recurrent or more-severe subsequent reactions. It is crucial that patients are not only in possession of EAIs, but that they also have a clear understanding of how and when to use them. There are data to support the fact that patient instruction labels are becoming more useful; however, this should not replace concomitant teaching in the ED, which should be a part of any discharge plan.

7. **"The patient with the severe allergic reaction is crashing, so I'll perform RSI. That should secure her airway."**
   Careful consideration must be taken when approaching airway management in anaphylaxis. In patients requiring orotracheal intubation, attention should be paid when giving paralytics in RSI. If the intubation attempt is unsuccessful, these patients may be difficult to effectively ventilate via bag-valve mask because of oropharyngeal edema and laryngeal constriction. Awake intubation, fiberoptic intubation, and delayed-sequence intubation offer alternatives to RSI. The emergency clinician may choose to involve an anesthesiologist in these procedures depending upon his or her degree of experience with these advanced airway techniques.

8. **"The patient had been taking his ACE inhibitor for years without a problem. I just treated his reaction in the ED and sent him home."**
   ACEIIA is a special circumstance of bradykinin-mediated (nonallergic-mediated) angioedema that may not be responsive to epinephrine and standard treatments. Airway management and fresh-frozen plasma may be indicated, and immediate cessation of the ACE-inhibitor is always necessary. Most ACE-inhibitor reactions occur in the weeks following the start of therapy; however, some patients develop symptoms years after being on the medication.

9. **"I did not give the patient epinephrine because his oropharyngeal edema pointed toward a diagnosis of angioedema."**
   Just because angioedema is present, an allergic-mediated etiology should not be ruled out. Angioedema is a physical sign, and it may be a manifestation of anaphylaxis or an allergic reaction, as well as a symptom in nonallergic, bradykinin-mediated pathways. If the history points toward such an allergic episode, angioedema is responsive to epinephrine, and it should be employed in treatment.

10. **"EMS is calling in for medications en route to the ED for a 27-year-old woman who has pruritus, wheezing, and low oxygen saturation after taking NSAIDs. They are only 5 minutes away so I would rather use my judgment and take a look at her myself before I order epinephrine. I'll just tell them to give antihistamines and steroids for now."**
    There should never be a delay in administering epinephrine, the undisputed first-line medication, for what appears to be anaphylaxis. Studies have shown that epinephrine administration in the field by EMS personnel is safe and used appropriately in the overwhelming number of situations. Continued efforts must be focused on increasing its use in the early phase of anaphylaxis.

course of corticosteroids, a prescription for 3 to 5 days of medication that does not require tapering is acceptable clinical practice.

Summary

Anaphylaxis and severe allergy are life-threatening episodes of sudden onset that involve inflammatory mediators. It is of paramount importance that emergency clinicians recognize and treat the symptoms early and aggressively to avoid airway compromise or cardiovascular complications in patients. Intramuscular administration of epinephrine remains the foundation of treatment, along with intravenous fluids for hypotension and distributive shock. Consensus guidelines consistently deem antihistamines and corticosteroids to be second-line treatments, and epinephrine should never be withheld while such other treatments are given.

Biphasic reactions are rare and are most likely to occur within 8 to 10 hours after resolution of initial anaphylaxis. However, because of the lack of fatalities seen from biphasic reactions in the general population, extended observation in the ED after resolution of anaphylaxis does not enhance patient safety or improve outcomes and is not routinely recommended. Self-administered auto-injectors can save lives outside of the ED, and they remain the most important tool (along with avoidance of the inciting allergen) to prevent fatal allergic episodes.

Time- And Cost-Effective Strategies

- Patients should be sent home with a prescription for 2 EAIs and teaching and instructions on the use of EAIs. When used correctly, autoinjectable epinephrine can save lives and reduce healthcare costs.
  Risk Management Caveat: Be certain that any prescribed medication is not only available (at a pharmacy), but also accessible to patients (affordable and the patient has the ability and time to fill the prescription). Patients who are unable to meet these requirements may need assistance from the ED pharmacy or hospital staff to ensure that they will be able to obtain the needed medication.
- Diagnostic laboratory testing is not indicated, as anaphylaxis and severe allergy are clinical diagnoses. Laboratory tests add little value and should not be performed routinely in the acute setting.
  Risk Management Caveat: In equivocal cases when the etiology of the reaction remains unclear, an allergist-immunologist in follow-up care may want a serum tryptase level drawn within the 90-minute peak time.
- Make the patient aware early on in the ED course that he will need an observation period, even if all symptoms resolved upon arrival. While most patients do not require admission after a mild anaphylactic episode, based on recent expert guidelines, some period of observation is recommended to monitor for a biphasic reaction, although this does not need to be a prolonged time period. After this, patients may be discharged home with a reliable adult.
  Risk Management Caveat: Any patient with high-risk features should be admitted to an inpatient setting or observation bed for further monitoring. This includes patients who exhibit signs of hemodynamic instability or airway distress, patients who need a dose of glucagon or a second dose of epinephrine, patients who have poorly controlled or active asthma, and patients who have limited access to a phone or emergency services.

Case Conclusions

After use of his girlfriend's EAI and after ED administration of diphenhydramine, ranitidine, corticosteroids, and an albuterol nebulizer, the 55-year-old man who suffered a reaction to antibiotics improved significantly. His symptoms completely resolved after 4 hours in the ED, and he lacked high-risk features that would steer you toward admitting him. The patient's girlfriend appeared in the ED shortly after his arrival, and brought the bottle of amoxicillin/clavulanate pills that he had been taking. You counseled the patient about discontinuing the beta-lactam drug, educated him about anaphylaxis, and provided him with a prescription for his own EAI. You also gave him prescriptions for antihistamines and a short course of corticosteroids and recommended that he follow up with an allergist.

Your 40-year-old patient who had eaten celery and kale just prior to her exercise routine was, indeed, not experiencing a cardiac event, but rather food-triggered, exercise-induced anaphylaxis. Her repeat ECG showed sinus tachycardia, and she remained free of chest pain. Because she was taking a beta blocker daily, she was refractory to epinephrine administration and its usual beneficial effects on beta-adrenergic receptors in anaphylaxis. Her symptoms actually worsened after epinephrine was given, and she required aggressive volume resuscitation and a glucagon drip. Although her blood pressure and symptoms improved after this, she was admitted to the ICU for close monitoring because of her high-risk feature of beta blocker use with a refractory response to epinephrine.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.

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CME Questions

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1. What is the most likely diagnosis in a mother and a daughter who present simultaneously with abdominal pain, flushing, pruritus, and headache after eating at a restaurant together?
- a. Gastroenteritis
- b. Hereditary angioedema
- c. Scombroid poisoning
- d. Early anaphylaxis

2. The most common cause of fatal anaphylactic reactions is:
- a. Bronchospasm and respiratory failure
- b. Shock due to circulatory collapse
- c. Complications from epinephrine administration in patients with underlying cardiac disease
- d. Upper airway edema

3. A 12-year-old boy who is otherwise healthy would be most likely to exhibit a reaction to which type of allergen?
- a. *Hymenoptera* sting
- b. Peanut butter
- c. Aspirin
- d. Latex

4. Glucagon might be used with most effect in which patient?
- a. A man who has a history of hypertension and a tachyarrhythmia.
- b. A woman with a history of asthma and atopy.
- c. A teenager with a history of prior allergic reaction to penicillin.
- d. An elderly woman with inflammatory bowel disease and infliximab infusion.

5. Which patient does NOT meet the criteria for anaphylaxis?
- a. A 45-year-old woman with pruritus and vomiting after eating a peanut 30 minutes earlier.
- b. A 20-year-old with a history of asthma and known nut allergy who presents with wheezing and abdominal cramping shortly after eating a nut-containing granola bar.
- c. A 12-month-old girl with a blood pressure of 80/65 mm Hg who just tried soy milk for the first time, but who otherwise appears well with normal heart rate and oxygen saturation.
- d. A 65-year-old man with a history of hypertension who presents with an episode of syncope and mucosal edema after being stung by a wasp 20 minutes prior.

6. What is the proper way to initially administer epinephrine for an adult?
- a. 0.3 mg IV epinephrine, 1:1000 concentration
- b. 0.3 mg IV epinephrine, 1:10,000 concentration
- c. 0.1 mg IM epinephrine, 1:10,000 concentration
- d. 0.3 mg IM epinephrine, 1:1000 concentration

7. A patient in anaphylactic shock is unresponsive to epinephrine, and his medication list includes a beta blocker. What medication should be given next?
- a. Methylprednisolone
- b. Diphenhydramine
- c. Glucagon
- d. Cimetidine

8. Which is the preferred initial route of administration of epinephrine in the setting of anaphylactic shock?
- a. Subcutaneous
- b. Intramuscular
- c. Intravenous
- d. Nebulized

9. For patients discharged from the ED following an allergic reaction, it would be reasonable to prescribe which of the following?
- a. Diphenhydramine
- b. Prednisone
- c. Epinephrine auto-injector
- d. All of the above

10. Which of the following is TRUE of epinephrine auto-injectors?
- a. They are underused by patients.
- b. A prescription for an epinephrine auto-injector does not need to be written in the ED.
- c. They are easy to use, and no patient education is needed prior to ED discharge.
- d. If prescribed, a patient needs only 1 epinephrine auto-injector upon discharge.

Coming Soon In *Emergency Medicine Practice*

Current Emergency Department Management And Evaluation Methods For Patients With Pharyngitis

Pharyngitis, the combination of sore throat, fever, and pharyngeal inflammation, is a very common chief complaint. Emergency clinicians need to be able to quickly assess and treat pharyngitis, as well as identify life-threatening airway complications. There is still considerable disagreement in major guidelines regarding the diagnosis and management of pharyngitis, primarily group A beta-hemolytic streptococci (GABHS)-caused pharyngitis. There is a broad differential for this complaint, and differentiation of viral pharyngitis from GABHS and other bacterial causes of pharyngitis is key to appropriate management. A systematic approach, as outlined in this review, will guide the emergency clinician through the history and physical examination, diagnostic testing, and treatment of this chief complaint.

TIME- AND COST-EFFECTIVE STRATEGIES

- Do not treat patients with antibiotics if primarily viral symptoms (eg, cough, coryza, conjunctivitis, diarrhea) are present. These symptoms indicate that it is unlikely that the patient has GABHS.
- Administer penicillin or amoxicillin unless the patient is allergic. Other options are more expensive and have not proven to be any more effective against GABHS.
- Do not send a rapid antigen detection test if the patient will be treated based on clinical diagnosis. Either treat empirically or treat based on the RADT.
- Do not send throat cultures in adults for negative RADTs. The sensitivity of RADTs is high, the incidence of GABHS is low, and the incidence of serious complications in adult patients is even lower.

Managing Patients With Toxic Alcohol Exposure In The Emergency Department

The ability to identify the patient with potential toxic alcohol exposure and initiate management is a critical skill in emergency medicine. This issue provides an introduction to toxic alcohols by reviewing common sources of exposure, basic mechanisms of toxicity, physical examination and laboratory findings that may guide rapid assessment and management, and indications for hemodialysis, antidotal therapy, and adjunctive therapies. Potential sources of toxic alcohol exposure include ethylene glycol, a nephrotoxic substance commonly found in antifreeze; methanol, which is toxic to optic nerve cells and commonly found in windshield washer fluid and solid cooking fuels; diethylene glycol, an industrial solvent that is both nephrotoxic and neurotoxic; propylene glycol, a diluent commonly used in intravenous medications that causes a lactic acidosis; and isopropyl alcohol or isopropanol, a readily available intoxicating alcohol that may be substituted for ethanol by some ethanol abusers. Treatment considerations include the antidotes fomepizole and ethanol, which are competitive inhibitors of the enzyme alcohol dehydrogenase; hemodialysis for removal of both parent compound and toxic metabolites of the toxic alcohol as well as correction of acid-base disturbances; and adjunctive therapies which may enhance clearance of the toxic alcohol or metabolites.

TIME- AND COST-EFFECTIVE STRATEGIES

- Consider early initiation of antidotal therapy while laboratory testing is pending. Toxic alcohol concentrations may be difficult to obtain in some institutions, and care should not be delayed while this workup is pending.
- Consider weighing the cost of a prolonged course of antidotal therapy versus hemodialysis. In patients with markedly elevated toxic alcohol concentrations, a prolonged course of fomepizole or ethanol therapy may be needed. At some institutions, a course of hemodialysis may be a more cost-effective approach. The risks and benefits of these treatment approaches should be discussed with the poison center toxicologist and the hospital nephrologist.

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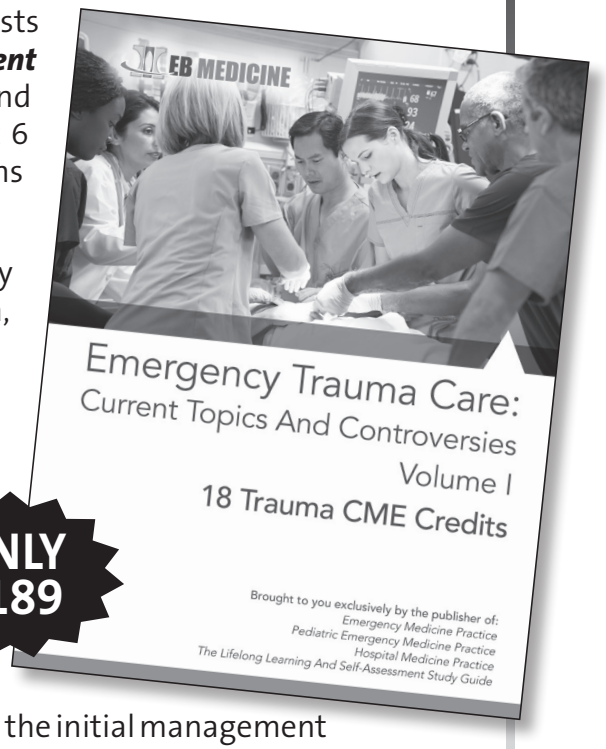

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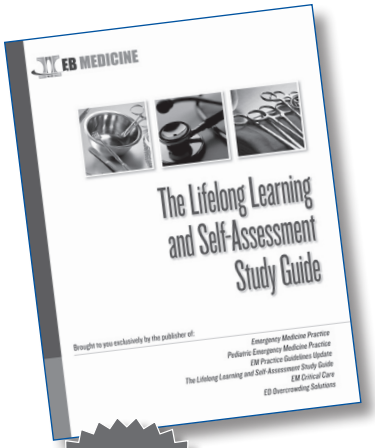

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