An Evidence-Based Review Of Pediatric Anaphylaxis

It is 9 pm on a busy Friday, and you are seeing a 10-year-old girl with a chief complaint of syncope. Thirty minutes ago, she felt dizzy and fainted after eating dinner at a friend’s house. She is currently complaining of abdominal cramping and has vomited twice. Her past medical history is significant for tree nut and peanut allergies and 2 hospitalizations for asthma in the last year. She has no prior episodes of syncope. On examination, her heart rate is 90, blood pressure is 90/50, respiratory rate is 22, and oxygen saturation is 95%. Her weight is 32 kilograms. She has diffuse wheezing and is in moderate respiratory distress. She was not carrying her albuterol inhaler and hasn’t received any medications yet. You wonder if the syncope is related to her wheezing and abdominal symptoms. Could this presentation be related to her food allergies?

Anaphylaxis is a diagnosis that all pediatricians and emergency medicine clinicians must be comfortable treating. Common teaching is that patients should immediately be treated with epinephrine, H1 and H2 receptor blocking antihistamines, and corticosteroids. This treatment regimen is so ingrained that few question the evidence behind these treatments.

The more common clinical question is who to treat for anaphylaxis. We all know to aggressively treat the hypotensive, stridulous patient with diffuse urticaria or the child with a known serious peanut allergy who presents with symptoms after accidental exposure. What about the asthmatic child who looks well with diffuse urticaria and wheezing? Or the child with food allergies who presents with symptoms after accidental exposure. A patient with diffuse urticaria or the child with a known serious peanut allergy who presents with symptoms after accidental exposure.

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The more common clinical question is who to treat for anaphylaxis. We all know to aggressively treat the hypotensive, stridulous patient with diffuse urticaria or the child with a known serious peanut allergy who presents with symptoms after accidental exposure. What about the asthmatic child who looks well with diffuse urticaria and wheezing? Or the child with food allergies who presents with abdominal cramping, diarrhea, and wheezing after eating away from home? Since all the signs and symptoms of anaphylaxis are commonly seen in other disease processes, atypical presentations of anaphylaxis are not uncommon. It is important to recognize these presentations and treat them accordingly. After completing this activity, you should be able to:

1. Develop a working definition for the clinical diagnosis of anaphylaxis.
2. Cite first- and second-line anaphylaxis treatments recommended in national guidelines.
3. Identify risk factors for fatal anaphylaxis.
4. Recognize other disease entities which may present with similar signs and symptoms to those of anaphylaxis.

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anaphylaxis can easily be missed and undertreated. This issue of Pediatric Emergency Medicine Practice will focus on the identification of patients with anaphylaxis including those with atypical presentations. A recent collaboration between the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network developed consensus guidelines for the clinical diagnosis of anaphylaxis. (See Table 1.) We use those criteria for the diagnosis of anaphylaxis. This issue will also review the literature behind the treatment of anaphylaxis and review recent guidelines on the topic (See Table 2).

Critical Appraisal Of The Literature

The literature review was performed using Ovid MEDLINE and PubMed databases. Additionally, the references of each identified article were reviewed for relevant citations. A search of the Cochrane Database of Systematic Reviews yielded a 2007 review of H1 antihistamines in anaphylaxis, a 2009 review of epinephrine, and a 2010 review of glucocorticoids. A search of the National Guideline Clearinghouse (www.guidelines.gov) yielded 1 guideline.

The literature on anaphylaxis is difficult to compare because there was no standard definition for anaphylaxis until publication of consensus guidelines in 2006. Incidence and outcomes vary greatly from study to study, likely due to lack of a standard definition and variability in reporting.

Most studies of anaphylaxis are retrospective with associated limitations. There are no randomized, placebo-controlled studies of medications used for the treatment of anaphylaxis in adults or children. When available, studies restricted to pediatric patients were reviewed and included. However, most studies on anaphylaxis include all ages, so pediatric-specific data are not always available, and many of the references in this review involve combined pediatric and adult data. Relevant adult-only studies are included when necessary to supplement limited pediatric data.

Table 1. Clinical Criteria For Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND at least 1 of the following:
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence); persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

Abbreviations: PEF, Peak expiratory flow; BP, blood pressure

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Epidemiology

Establishing the incidence of anaphylaxis in large populations is difficult. Studies based on self-reports or emergency department (ED) data may focus on severe reactions and underestimate the true incidence of anaphylaxis. Mild anaphylactic reactions and first-time events may be missed in these studies. Two recent studies found that about half of patients meeting criteria for food-related anaphylaxis did not receive a discharge diagnosis of anaphylaxis. Furthermore, ED studies do not capture anaphylaxis in hospitalized patients. Patients who are hospitalized might have a higher rate of anaphylaxis due to exposure to anesthetics, multiple medications, and contrast agents. Nonetheless, the most recent reviews of anaphylaxis suggest that the frequency is rising, particularly in younger individuals.

One working group of anaphylaxis experts performed a comprehensive literature review and estimated a lifetime prevalence of 0.05% to 2%. It is believed that anaphylaxis is more likely to occur in children than in adults and likely underreported in the youngest patients. Anaphylaxis in infants may be missed because symptoms of facial flushing, vomiting, and loose stools are nonspecific and easily attributed to other diagnoses. After puberty, anaphylaxis appears to be more common in women than men. In contrast, studies in children show either a male predominance or no gender difference.

Population-based anaphylaxis mortality data are likely to be inaccurate due to incorrect diagnosis coding and non-specific autopsy findings. The risk of death from anaphylaxis is considered to be low. In a pediatric study of patients hospitalized for anaphylaxis, 2% of cases were fatal. However, the fatality rate is likely higher in hospitalized patients. Several studies of pediatric ED patients with anaphylaxis have found a mortality rate less than 1%. Other studies of pediatric and adult populations have also found the rate of fatal anaphylaxis to be less than 1%.

Table 2. Relevant Guidelines For The Management Of Anaphylaxis

<table>
<thead>
<tr>
<th>Year</th>
<th>Organization</th>
<th>Title</th>
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<tr>
<td>2005</td>
<td>Joint Task Force of the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology</td>
<td>The diagnosis and management of anaphylaxis: an updated practice parameter</td>
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<td>2006</td>
<td>Symposium convened by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (13 participating organizations including the American College of Emergency Physicians and the American Academy of Pediatrics)</td>
<td>Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium</td>
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<tr>
<td>2007</td>
<td>European Academy of Allergology and Clinical Immunology</td>
<td>The management of anaphylaxis in childhood: position paper of the European Academy of Allergology and Clinical Immunology</td>
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<tr>
<td>2008</td>
<td>Resuscitation Council (UK)</td>
<td>Emergency treatment of anaphylactic reactions: guidelines for healthcare providers</td>
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Etiology And Pathophysiology

Anaphylaxis in children is most commonly due to food, possibly due to an increased incidence of food allergies in this age group. Peanuts and tree nuts are the most common foods to cause anaphylaxis. Vaccine-related anaphylaxis is very rare, with an incidence of about 1.5 per 1 million vaccinations administered. In contrast to the predominance of food-related anaphylaxis in children, anaphylaxis in adults is more likely to be triggered by medications, radiocontrast dye, or insect stings. As a group, adults are exposed to a greater number of medications and diagnostic studies requiring radiocontrast dye, potentially accounting for this difference. Common causes of anaphylaxis are listed in Table 3 on page 4.

Immunoglobulin type E (IgE) is central to the development of anaphylaxis. Upon exposure to an allergen, B cells become sensitized and produce allergen-specific IgE. Once produced, IgE binds to the Fc epsilon R1 (FcεRI) receptor found on basophils and mast cells. When an allergen binds to the IgE-mast cell complex, a signal is generated and the mast cell releases mediators of the anaphylactic response including histamine, leukotrienes, and prostaglandins. Higher IgE levels increase the probability that a reaction will occur with re-exposure to the antigen. Furthermore, IgE increases expression of its own receptor on basophils and mast cells, creating a positive feedback loop that results in a more vigorous anaphylactic response.

In addition to classic IgE-mediated anaphylactic reactions, non-allergic anaphylaxis or anaphylactoid reactions occur in response to a variety of triggers. Examples of triggers include radiocontrast dye, intravenous N-acetylcysteine, ethanol, and opiates. Recently, there were reports of a contaminant in heparin causing anaphylactoid reactions in hemodialysis patients and patients on heparin therapy. The underlying mechanism for anaphylactoid reactions...
is not completely understood. They are believed to circumvent the classic IgE-mediated pathway, with direct activation and release of mediators from basophils and mast cells. Some triggers cause anaphylaxis via both the traditional IgE-mediated and direct activation pathways. Other rare causes of anaphylaxis may exist. Some experts believe that anaphylaxis after infusion of human monoclonal antibody preparations such as infliximab is mediated by immunoglobulin type G (IgG).

### Differential Diagnosis

The differential diagnosis varies depending on the clinical presentation. If lip and tongue swelling are the predominant symptoms, idiopathic or hereditary angioedema should be considered. If hypotension is the predominant symptom, septic shock, cardiogenic shock, and other types of shock should be considered. The differential diagnosis of urticaria is broad. One unusual entity that may be considered in the differential is cold-induced urticaria. This is a familial or acquired disorder in which urticaria develops in response to cold exposure. Symptoms of histamine release can be severe and patients may develop hypotension.

### Anxiety

In patients with subjective symptoms of dyspnea, throat tightening, or difficulty swallowing without objective evidence of anaphylaxis, psychiatric causes such as panic attack should be considered. Patients with a known history of anaphylaxis may have a panic attack if they believe they have come in contact with a trigger.

### Scombroid Poisoning

One entity that can easily be confused with anaphylaxis is scombroid poisoning. Scombroid poisoning is thought to be caused by high levels of histamine in poorly refrigerated fish. Histidine, which is naturally present in the flesh of fish, is broken down by bacteria to histamine. Inadequate refrigeration accelerates this process. Fish may not appear spoiled and can taste and smell normal. Symptoms due to high histamine levels occur within minutes to hours of consumption. Symptoms include a peppery taste in the mouth, burning or tingling of the oral mucosa, headache, dizziness, flushing, sweating, rash, pruritus, abdominal cramping, diarrhea, nausea, and vomiting. Patients may have hypotension, tachycardia, and circulatory collapse. Time course and symptoms of scombroid poisoning and anaphylaxis are very similar. Since seafood is a common cause of anaphylaxis, the diagnosis is challenging. If more than 1 person presents with anaphylactic-like symptoms after eating fish, scombroid poisoning is the likely diagnosis. Scombroid poisoning should also be considered in patients with apparent anaphylaxis who have previously eaten the same fish multiple times without any allergic symptoms. If there is any question whether symptoms are due to scombroid poisoning or anaphylaxis, referral to an allergist for testing is appropriate.

### Mastocytosis

Another disorder that can have similar signs and symptoms or can be a cause of anaphylaxis is mastocytosis. Cutaneous mastocytosis is due to proliferation of mast cells in the skin. It is characterized by reddish-brown macules, papules, plaques, or blisters that develop urticaria in response to physical trauma. Systemic mastocytosis occurs when mast cells proliferate in other tissues including bone marrow, liver, spleen and lymph nodes. Usual signs and symptoms of systemic mastocytosis overlap with signs and symptoms of anaphylaxis. Flushing, pruritus, abdominal pain, diarrhea, dyspnea, and tachycardia are seen in both. Patients with recurrent, idiopathic anaphylaxis may in fact have underlying mastocytosis. Systemic mastocytosis is rare in children but might be considered with recurrent, otherwise unexplained anaphylaxis. Anaphylaxis can be seen in patients with both cutaneous and systemic mastocytosis and has been reported in children with severe diffuse cutaneous mastocytosis.

### Prehospital Treatment

Anaphylaxis is a relatively uncommon reason for emergency medical service (EMS) transport. Studies have estimated that 0.2% to 0.5% of EMS runs are for a chief complaint of allergy or anaphylaxis. As always, prehospital care should focus on the ABCs (airway, breathing, and circulation). Supplemental oxygen should be supplied as needed for hypoxia, and intravenous fluids should be given for hypotension or other evidence of shock. Because multiple studies have found an association between delay in epinephrine administration and death from anaphylaxis, intramuscular epinephrine should be administered as soon as possible to patients with evidence of anaphylaxis. Epinephrine administration is generally incorporated into paramedic advanced life support protocols.

### Table 3. Common Triggers Of Anaphylaxis

<table>
<thead>
<tr>
<th>Foods</th>
<th>Medications</th>
<th>Insects</th>
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<tr>
<td>Peanuts</td>
<td>Antibiotics, especially beta-lactams</td>
<td>Hymenoptera including bees, yellow jackets, wasps and ants</td>
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<tr>
<td>Tree nuts</td>
<td>Non-steroidal anti-inflammatories</td>
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<td>Shellfish</td>
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<td>Fish</td>
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<td>Egg</td>
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<td>Sesame</td>
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<td>Food additives</td>
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Evidence of posterior oropharyngeal swelling should raise concern for impending airway obstruction. The most common signs and symptoms of an anaphylactic reaction are dermatologic and respiratory. Most patients present with mucocutaneous symptoms such as urticaria, flushing, or angioedema. A minority of patients lack cutaneous manifestations. Patients may present with predominantly gastrointestinal or neurologic symptoms such as syncope or dizziness due to hypotension. If the patient is unable to provide a history, examine the skin for signs of an insect sting, which may be the trigger for the reaction. Reddish-brown papules or macules on the skin that become raised, red, and itchy after stroking may be indicative of mastocytosis.

**Diagnostic Studies**

Anaphylaxis is a clinical diagnosis. Since anaphylaxis must be treated immediately, laboratory tests are unlikely to be helpful in ED management. However, in cases in which the diagnosis is not clear, measurement of serum markers may be useful for long-term patient management. The 2 primary assays that may be performed during an episode of anaphylaxis are serum tryptase and histamine. Timing is critical for both of these assays. Histamine levels peak within 10 minutes of onset of anaphylaxis and return to baseline within 60 minutes. Total tryptase levels may be tested within 3 hours of symptom onset. In one study of insect-sting anaphylaxis, peak tryptase level correlated with severity of symptoms. Unfortunately, normal tryptase levels do not rule out a diagnosis of anaphylaxis. Tryptase measurement is more likely to be normal with food-related anaphylaxis than other types of anaphylaxis. Neither tryptase elevations nor histamine elevations are specific to anaphylaxis and either can occur in other circumstances.

**Cost-Effective Strategies**

1. **Limit laboratory testing in patients with anaphylaxis.** Anaphylaxis is a clinical diagnosis, and laboratory testing is rarely helpful. Unless the diagnosis is in question or an allergy-immunologist has requested testing during an acute episode, histamine and tryptase levels are not necessary.

2. **Admission is not necessary in all patients.** Most patients do not benefit from prolonged observation. Two published expert guidelines support a 6-hour observation period. Good discharge instructions and discharge with an epinephrine auto-injector and teaching are vital.

*Risk Management Caveat:* Consider admission for patients with severe anaphylaxis or risk factors such as uncontrolled asthma, slow response to epinephrine, need for bolus fluids, or a second dose of epinephrine. Ensure that patients are able to fill their prescription for the epinephrine auto-injector and are comfortable using it. Consider admission if the family doesn’t have a phone and is unable to access emergency medical services.
disease processes. If tryptase or histamine levels are elevated but the patient doesn’t clearly have anaphylaxis, repeat levels should be drawn under normal clinical circumstances. Vast differences between the 2 points in time support a diagnosis of anaphylaxis.

In general, ED measurement of tryptase and histamine are not necessary for patients with a clear diagnosis of anaphylaxis. Histamine levels must be drawn within an hour of symptom onset, limiting its utility. Tryptase levels remain elevated longer, but normal tryptase levels do not rule out the diagnosis of anaphylaxis. Histamine and tryptase levels may be useful if the diagnosis is uncertain. In patients being followed for recurrent episodes in which the diagnosis of anaphylaxis is in question, the patient’s allergy-immunologist may request levels to be drawn during an acute episode.

Treatment

**Intramuscular Epinephrine**

Epinephrine is the most important medication in the treatment of anaphylaxis. The pediatric dose is 0.01 mg/kg of the 1:1000 solution (1 mg/mL) administered intramuscularly. The adult dose is 0.3 to 0.5 mg. All national and international guidelines recommend early treatment of anaphylaxis with intramuscular epinephrine.1,33,44-48

There are multiple theoretical reasons that epinephrine would be beneficial in the treatment of anaphylaxis. Epinephrine increases peripheral resistance and has positive chronotropic and inotropic cardiac effects, treating hypotension associated with anaphylaxis. The increase in peripheral vasoconstriction reduces flushing, urticaria, and angioedema.47 The beta-adrenergic effects treat associated bronchospasm.47 In addition to the immediate cardiorespiratory effects, epinephrine is thought to decrease further release of inflammatory mediators from basophils and mast cells and may play a role in preventing biphasic or late reactions.47,49

Although epinephrine is theoretically and anecdotally beneficial in the treatment of anaphylaxis, clinical data is lacking. There are no randomized controlled trials of epinephrine for the treatment of anaphylaxis. A recent Cochrane Systematic Review on the use of epinephrine in anaphylaxis found no eligible randomized or quasi-randomized trials.50 Epinephrine is accepted as effective, and untreated anaphylaxis is potentially fatal. Thus, a randomized controlled trial comparing epinephrine and placebo cannot be ethically justified.

There is limited indirect evidence that epinephrine is effective in the treatment of anaphylaxis. Delay in administration of epinephrine has been associated with fatal or biphasic anaphylaxis.13,34 In a study of fatal anaphylaxis in children, all 6 children with fatal anaphylaxis had a significant delay from time of allergen exposure to administration of epinephrine.34 The vast majority of patients described in 2 series of fatal anaphylaxis did not receive early epinephrine.35,36 In a study of biphasic anaphylaxis, delay in administration of epinephrine was associated with an increased risk of having a biphasic reaction.13

Traditionally, epinephrine was administered subcutaneously for anaphylaxis. Limited data suggests that, in both adults and children, peak plasma epinephrine levels are reached more quickly with intramuscularly administered epinephrine than with subcutaneously administered epinephrine.51,52 Data in adults supports the administration of epinephrine in the vastus lateralis.52 This research was performed in patients not actively experiencing anaphylaxis and the clinical significance of these findings has not been demonstrated in clinical trials. However, until further data is available, it is prudent to administer epinephrine as an intramuscular injection, and guidelines generally recommend intramuscular injection in the anterolateral thigh.

Although intramuscular epinephrine is recommended as first-line treatment for anaphylaxis in all guidelines, it is underused in practice. Retrospective studies of ED treatment of anaphylaxis in adults and children have found rates of epinephrine administration ranging from 16% to 67%,7,9,53-55 Even in patients admitted to the hospital, epinephrine administration is suboptimal. In a retrospective study of pediatric patients hospitalized for anaphylaxis, only 89% had received epinephrine.13 Despite national guidelines emphasizing epinephrine as the first-line treatment, several studies have found that patients diagnosed with anaphylaxis are more likely to receive corticosteroids and antihistamines than epinephrine.54,56 One recent pediatric study found that the majority of ED epinephrine doses were administered subcutaneously rather than intramuscularly.56

Not only is epinephrine underused in the ED setting, but patients also underuse their epinephrine auto-injectors. Research conducted in an allergy clinic found that although 86% of pediatric patients prescribed an epinephrine auto-injector stated they had the device with them at all times, only 55% actually had an unexpired injector with them at the clinic visit.57 One-quarter stated that the auto-injector was not available at school.57

Multiple studies of anaphylaxis deaths have demonstrated that only a minority of patients prescribed an epinephrine auto-injector administered it appropriately during their fatal reaction. Many did not even have their auto-injectors available at the time of the fatal reaction.19,58,59

Patients who carry epinephrine auto-injectors don’t necessarily know how to use them. In a clinic-based study, most anaphylaxis patients and their families were not able to correctly demonstrate use of an epinephrine auto-injector.57 Additionally, most resident and attending physicians could not demonstrate appropriate use of an epinephrine auto-injector.57
1. “The epinephrine auto-injector is self-explanatory and I’m busy. They’ll figure it out if they ever need to use it.”
   Physicians frequently neglect to counsel patients on epinephrine auto-injector use. Studies show that many patients don’t know how to use their auto-injectors properly. Time spent teaching a patient how to use the auto-injector may be life-saving during a future episode of anaphylaxis.

2. “The nurse is questioning my intramuscular epinephrine order because he’s always given epinephrine subcutaneously.”
   Traditional teaching was to administer epinephrine subcutaneously, but onset appears to be faster with intramuscular administration. Expert guidelines recommend intramuscular, rather than subcutaneous administration.

3. “The patient doesn’t have cutaneous findings, so it couldn’t be anaphylaxis.”
   The diagnosis of anaphylaxis does not require cutaneous findings. Acute onset of any 2 of the systems listed in Table 1 or hypotension after exposure to a known allergen is sufficient for the diagnosis of anaphylaxis. In one study, the majority of patients with fatal anaphylaxis lacked cutaneous signs, so treatment should not be delayed because the patient doesn’t have urticaria.

4. “This patient said she felt short of breath after eating a cookie which may have contained peanuts. She is extremely anxious. Her physical examination is completely normal with the exception of a rapid respiratory rate.”
   Patients with a history of allergy or anaphylaxis may have a panic attack if they think that have come in contact with a trigger. Consider panic attack in patients who have no objective evidence of anaphylaxis.

5. “Two patients arrived from the same restaurant with anaphylaxis. Is that a coincidence?”
   Scombroid poisoning presents with similar signs and symptoms to those of anaphylaxis. It is the likely diagnosis if multiple patients present with anaphylaxis-like symptoms after eating the same fish.

6. “I won’t prescribe an epinephrine auto-injector because the patient will follow up with the pediatrician tomorrow. The pediatrician can write for it.”
   Even if patients have prolonged observation in the ED, biphasic reactions after discharge are possible. All patients with anaphylaxis should be discharged with an epinephrine auto-injector.

7. “My 18-month-old patient had anaphylaxis, but he only weighs 12 kg so I can’t prescribe him an epinephrine auto-injector.”
   A clinical report published by the American Academy of Pediatrics recommends prescription of the 0.15 mg auto-injector to otherwise healthy children weighing from 10 to 25 kg.

8. “My patient has wheezing and diffuse urticaria and flushing after eating a peanut butter sandwich. He’s not hypotensive so epinephrine would be overkill. I’ll give an albuterol treatment and diphenhydramine and see if he improves.”
   Delay in epinephrine treatment has been identified as a risk factor for biphasic reactions and fatal anaphylaxis. All guidelines emphasize early treatment with epinephrine.

9. “Paramedics are calling for an order to give epinephrine to a 5-year-old with a history of bee sting anaphylaxis who now has stridor, diffuse wheezing, and an oxygen saturation of 92% after a bee sting. It sounds like anaphylaxis, but I’d rather examine the patient myself before giving any medications.”
   Again, all guidelines emphasize early treatment with epinephrine.

10. “My patient had an anaphylactic reaction with syncope, urticaria, and shortness of breath at home. The mother gave epinephrine and her symptoms completely resolved before she arrived. I’m not sure why they even came to the ED.”
    There is a risk of biphasic reactions after symptom resolution. Guidelines vary in their recommendations, but all recommend some period of observation. The patient will also need a prescription for a replacement epinephrine auto-injector.
Intravenous Epinephrine
Most cases of anaphylaxis respond to intramuscularly administered epinephrine. In cases of hypotension refractory to multiple doses of intramuscularly administered epinephrine, intravenous epinephrine is an option. No evidence-based dosing recommendations are available. Recommended doses vary from guideline to guideline. The report from the Second Symposium on the Definition and Management of Anaphylaxis recommends bolus doses of 0.2 mcg/kg to a maximum of 10 mcg for persistent hypotension.1 The guidelines published by the Resuscitation Council of the UK give the option of intravenous bolus doses of 1 mcg/kg of 1:10,000 epinephrine to a maximum of 50 mcg of intravenous epinephrine in cases requiring repeated intramuscular doses of epinephrine.33 Other experts recommend epinephrine infusions rather than bolus doses.5

Epinephrine Pitfalls
Multiple case reports of epinephrine dosing errors in patients with anaphylaxis have been published.58,60-63 These reports describe inadvertent intravenous administration of 1:1000 solution or intravenous administration of cardia arrest dose epinephrine.58,60,61 The smaller volume of medication and intramuscular administration of the 1:1000 concentration are less familiar.

One case series found a 2.4% incidence of potentially life-threatening complications from inappropriate epinephrine administration for anaphylaxis in a single ED.60 Serious outcomes after epinephrine overdose in children and young adults without underlying cardiac disease have been described. It is impossible to know if the cardiac complications were due to the epinephrine overdose or the underlying hypoxia or hypotension that led to epinephrine administration, but epinephrine overdose does have the potential to cause serious harm. In one reported case in the UK, a 13-year-old girl developed fatal pulmonary edema after intravenous administration of 3.5 mg of epinephrine.68 One case report describes a 5-year-old boy who received a 10-fold overdose of subcutaneous epinephrine and subsequently developed ventricular dysrhythmias and myocardial ischemia.62 A case of takotsubo cardiomyopathy in a 24-year-old woman after an overdose of intramuscular epinephrine has also been published.63

The reasons for dosing errors are likely multifactorial. Besides the familiarity with cardiac arrest dosing and intravenous administration, the 1:1000 concentration is less familiar. The authors of one concept paper published in Annals of Emergency Medicine recommend that EDs add easy-to-read labels to epinephrine syringes to distinguish intramuscular and intravenous preparations and avoid inadvertent intravenous administration of concentrated epinephrine.60 Another problem is that the concentration is expressed as a ratio (1:1000) and providers are more accustomed to mass concentrations (1 mg/mL).64,65 One study found that practitioners took longer to calculate doses and were more likely to give an incorrect dose when calculating doses using ratios rather than mass concentrations.66 As always, there is more room for error when calculating weight-based pediatric doses. Adult ED providers are used to the adult dose of 0.3 mg of 1:1000 epinephrine, but there is more room for error and confusion when calculating pediatric doses. Computerized emergency dosing calculators are available and may help decrease dosing errors.66,67

Antihistamines
One common recommendation in the treatment of anaphylaxis is to administer an antihistamine.1,33,44,45,68 There is some data that antihistamines are beneficial in preventing anaphylactoid reactions when given before intravenous radiocontrast material.69,70 However, there are no published data to support the use of antihistamines in established anaphylaxis. A recent Cochrane Systematic Review on the use of antihistamines found no randomized or quasi-randomized controlled trials of H1 receptor blockers in anaphylaxis.71 We were also unable to identify placebo-controlled studies of antihistamines in anaphylaxis. Several studies in adults demonstrate that the combination of H1 and H2 receptor blockers is superior to an H1 receptor blocker alone in the treatment of cutaneous symptoms of mild allergic reactions.72,73 Therefore, antihistamines may be helpful as a second-line adjunct agent to treat cutaneous symptoms of anaphylaxis, but they do not relieve airway symptoms, shock, or hypotension.

Expert guidelines vary in their recommendations probably because of the paucity of evidence supporting or refuting the use of antihistamines. See Table 4 on page 9. All guidelines emphasize that antihistamine administration is at best a second-line treatment and should never delay administration of epinephrine. If antihistamines are given, there is no evidence to guide duration of treatment.

Corticosteroids
Another common treatment recommendation is to administer a corticosteroid.1,33,44,45 However, little evidence supports use of corticosteroids in the treatment of anaphylaxis. A Cochrane Systematic Review of glucocorticoids did not identify any randomized controlled trials in adults or children.74 The reason cited for giving corticosteroids is to prevent biphasic or protracted reactions. Few studies have addressed this question. In the 2 pediatric studies of biphasic reactions, similar percentages of patients with biphasic and uniphasic reactions received corticosteroids, and it did not appear that administration of steroids
was protective.\textsuperscript{13,14} However, both were retrospective studies with small numbers of patients with biphasic reactions. One study with 19 adult and pediatric patients with biphasic reactions found a statistically insignificant trend towards decreased incidence of biphasic reaction in patients receiving corticosteroids.\textsuperscript{75} This is a question in need of further research. It is possible that larger studies would show a clinically significant difference.

Guidelines vary in their recommendations on steroid administration in anaphylaxis. (See Table 5 on page 12.) As with antihistamines, all guidelines emphasize that steroids are at best an optional or second-line treatment and should never delay the administration of epinephrine. If steroids are administered, there is no evidence to guide duration of therapy.

**Airway Management**

Guidelines on the treatment of anaphylaxis do not discuss indications for tracheal intubation of patients with anaphylaxis. A literature search did not find any studies of airway management in ED patients with anaphylaxis or guidelines on airway management in anaphylaxis. In the absence of expert guidelines or published studies, clinicians must rely on their best judgment in airway management. One consideration is that if anaphylaxis is protracted and progressing despite appropriate treatment, airway edema may progress, and early intubation may be beneficial. Patients with mucosal edema should be considered to have difficult airways. Management of the difficult airway is beyond the scope of this review, but alternatives to traditional oro-tracheal intubation, such as a fiber optic laryngoscope and a cricothyroidotomy kit, should be available if tracheal intubation is attempted.

### Table 4. Expert Guideline Recommendations On Antihistamines For Treatment Of Anaphylaxis

<table>
<thead>
<tr>
<th>H1 Blockers</th>
<th>H2 Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Joint Task Force representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology\textsuperscript{44}</strong></td>
<td><strong>Consider as second-line</strong></td>
</tr>
<tr>
<td>• Consider as second-line</td>
<td>• Consider as second-line</td>
</tr>
<tr>
<td>• Diphenhydramine 1-2 mg/kg to 50 mg parenterally</td>
<td>• Ranitidine 1 mg/kg to 50 mg intravenous</td>
</tr>
<tr>
<td><strong>National Institute of Allergy and Infectious Diseases; Food Allergy and Anaphylaxis Network\textsuperscript{1}</strong></td>
<td><strong>Second-line treatment</strong></td>
</tr>
<tr>
<td>• Second-line treatment</td>
<td>• Second-line treatment</td>
</tr>
<tr>
<td>• Diphenhydramine 1-2 mg/kg to 50 mg parenterally or orally in mild cases</td>
<td>• Ranitidine or cimetidine (No dosing guidelines)</td>
</tr>
<tr>
<td><strong>European Academy of Allergology and Clinical Immunology\textsuperscript{45}</strong></td>
<td><strong>Not adequately tested in children</strong></td>
</tr>
<tr>
<td>• Recommended, options given: Chlorphenamine, cetirizine, levocetizine, loratidine, desloratadine, fexofenadine, oxatomide</td>
<td></td>
</tr>
<tr>
<td><strong>Resuscitation Council of the UK\textsuperscript{33}</strong></td>
<td><strong>Insufficient evidence to support routine use</strong></td>
</tr>
<tr>
<td>• Recommended as second-line</td>
<td></td>
</tr>
<tr>
<td>• Chlorphenamine dosing:</td>
<td></td>
</tr>
<tr>
<td>12 years: 10 mg</td>
<td></td>
</tr>
<tr>
<td>6 - 12 years: 5 mg</td>
<td></td>
</tr>
<tr>
<td>6 months - 6 years: 2.5 mg</td>
<td></td>
</tr>
<tr>
<td>&lt; 6 months: 250 mcg/kg</td>
<td></td>
</tr>
</tbody>
</table>

---

**Beta-blockers**

Multiple case reports describe patients on beta-blockers who had unusually severe episodes of anaphylaxis and anaphylaxis refractory to usual treatment.\textsuperscript{76} These case reports involve triggers of medications, food, insect stings, and radiocontrast media. Two retrospective case-control studies demonstrated an increased risk of moderate or severe anaphylactoid reactions after radiocontrast exposure in patients on beta-blockers.\textsuperscript{77,79} Although beta-blockade is less common in children than adults, children may be prescribed beta-blockers for supraventricular tachycardia, congenital heart disease, or other indications.

Epinephrine increases cyclic adenosine monophosphate (cAMP) through beta-adrenergic stimulation, and this pathway is less effective in patients on beta-blockers. Glucagon increases cAMP via pathways other than the beta-adrenergic system and has chronotropic and inotropic effects that are not affected by beta-blockers.\textsuperscript{79} Therefore, glucagon has been proposed as a treatment for epinephrine-resistant anaphylactic shock in patients on beta-blockers. Several case reports have been published describing patients in which administration of glucagon reversed radiocontrast-induced hypotension refractory to usual treatments in adults on beta-blockers.\textsuperscript{80,81} There is not sufficient evidence to change recommendations for treatment of anaphylaxis in patients on beta-blockade. To our knowledge, use of glucagon in anaphylaxis or an anaphylactoid reaction has never been described in a pediatric patient. However, in patients failing usual treatment, glucagon may be considered. One practice parameter recommends a pediatric dose of 20 to 30 mcg/kg to a maximum dose of 1 mg.\textsuperscript{44}
Clinical Pathway For The Diagnosis Of Anaphylaxis

Does patient have acute onset of the following without a more plausible explanation?
- Mucocutaneous signs (urticaria, generalized flushing, pruritis, angioedema)
- One of the following: Respiratory compromise (wheeze, stridor, hypoxemia, dyspnea) OR hypotension, collapse, syncope, incontinence

**YES**

Initiate treatment for anaphylaxis.

**NO**

Does the patient have at least 2 of the following AFTER recent exposure to a likely allergen?
- Mucocutaneous signs (urticaria, generalized flushing, pruritis, angioedema)
- Respiratory compromise (wheeze, stridor, hypoxemia, dyspnea)
- Hypotension, collapse, syncope, incontinence
- Persistent gastrointestinal symptoms (vomiting, crampy abdominal pain)

**YES**

Initiate treatment for anaphylaxis.

**NO**

Does the patient have a known allergen AND hypotension* within hours of exposure to that allergen?

*or drop of at least 30% from baseline blood pressure

**YES**

Initiate treatment for anaphylaxis.

**NO**

Consider alternate diagnoses

Clinical Pathway For The Treatment Of Anaphylaxis

Is patient in cardiopulmonary arrest?

YES

Initiate Pediatric Advanced Life Support or Advanced Cardiac Life Support

NO

Administer epinephrine 1:1000 (1 mg/mL)
0.01 mg/kg to a maximum of 0.3-0.5 mg intramuscularly (Class II)
PLUS
Oxygen and airway management as needed

Are life-threatening symptoms of hypotension, respiratory distress, or stridor resolved?

YES

• Consider an H1 blocker for cutaneous symptoms (Class III)
• Consider an H2 blocker for cutaneous symptoms (Class III)
• Consider a corticosteroid to prevent biphasic reactions (Class Indeterminate)

NO

Repeat epinephrine every 3-5 minutes as necessary.
Give fluid bolus as necessary.
Consider inhaled B-agonists for persistent wheezing.

Are symptoms resolved?

YES

Consider admission to a monitored bed.

NO

Consider intravenous epinephrine boluses or an epinephrine drip for persistent hypotension.

Admit to pediatric intensive care unit (PICU).

Class Of Evidence Definitions

Each action in the clinical pathways section of Pediatric 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
• Non-randomized or retrospective studies: historic, cohort, or case control studies
• Less robust RCTs
• 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


This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient’s individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

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Exercise-Induced Anaphylaxis
A unique type of anaphylaxis occurs only during exercise. Some patients have a variant called food-dependent exercise-induced anaphylaxis in which anaphylaxis occurs during exercise only after eating certain foods which are normally tolerated by the patient. Multiple foods have been implicated, most commonly wheat. The pathophysiology of this disorder is debated, but emergent treatment is the same as for other forms of anaphylaxis.

Controversies/Cutting Edge
Alternate Routes Of Epinephrine Administration
One problem in the treatment of anaphylaxis is that patients are reluctant to administer epinephrine auto-injectors. One factor may be fear of needles. Investigators have explored alternate routes of delivery for epinephrine administration. Several animal studies show promise for rapidly dissolving sublingual epinephrine tablets. Human research is needed to investigate this possibility. One study evaluated the potential of epinephrine administration by metered dose inhaler instead of auto-injectors. The authors found that despite coaching, children were unable to self-administer a sufficient number of inhalations to be effective.

Table 5. Expert Guideline Recommendations On Corticosteroids For Treatment Of Anaphylaxis

| Joint Task Force representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology | Consider for patients with a history of idiopathic anaphylaxis or asthma and patients severe or prolonged symptoms: • Intravenous glucocorticosteroids at 1-2 mg/kg/day given every 6 hours • For less critical patients: oral prednisone 0.5 mg/kg |
| National Institute of Allergy and Infectious Diseases; Food Allergy and Anaphylaxis Network | Option IV methylprednisolone at 1-2 mg/kg/dose given every 6 hours or Oral prednisone 1 mg/kg for milder attacks |
| European Academy of Allergy and Clinical Immunology | Should not be considered first-line Methylprednisolone or hydrocortisone IV options |
| Resuscitation Council of the UK | Recommended Hydrocortisone IV or IM • 12 years of age: 200 mg • 6-12 years of age: 100 mg • 6 months - 6 years of age: 50 mg • < 6 months: 25 mg |

Vasopressin
Most cases of pediatric anaphylaxis respond well to epinephrine and intravenous fluid. The evidence base for treatment of epinephrine-resistant anaphylaxis is lacking. There are multiple adult case reports of successful use of vasopressin in patients with anaphylaxis resistant to usual treatment. To our knowledge, the only reported case of use of vasopressin for anaphylaxis in a pediatric patient was in a 17-year-old girl with anaphylaxis occurring during induction of anesthesia. The dose administered in most case reports ranged from 2 to 10 international units given as a bolus dose. No guidelines incorporate use of vasopressin for treatment of anaphylaxis in children. At this time, there are no dosing recommendations for use of vasopressin for anaphylaxis in children. This is another area that requires further research, but vasopressin is an option in patients refractory to usual treatment.

Disposition
Length Of Observation Period
Any patient with protracted anaphylaxis resistant to therapy should be admitted to an intensive care unit for ongoing care. However, most patients will have resolution of symptoms. Determination of an appropriate observation period for those patients is difficult. Only 2 of the guidelines discussed offer specific recommendations. The Resuscitation Council of the UK recommends at least 6 hours of observation for most patients. The statement published by the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network with input from the American College of Emergency Physicians and the American Academy of Pediatrics states that a 4 to 6 hour observation period is appropriate for most patients. Longer observation periods may be considered for patients with severe reactions or with risk factors for biphasic or fatal anaphylaxis.

Data on current United States practice varies greatly from study to study. A 1999 study found that 7% of patients with anaphylaxis were admitted, followed by a 2004 study found that 6% were admitted, and a 2005 study found that only 3% were admitted. Studies published in 2010 and 1996 found that 27% and 28% of patients were admitted, respectively. The dose of epinephrine administered was 0.01 mg/kg every 5 minutes in most patients. In the last decade found that in patients discharged from the ED, the average length of stay was less than 3 hours. In the 1996 study, no admitted patient whose symptoms resolved completely in the ED had a biphasic reaction. Three studies published in the last decade found that in patients discharged from the ED, the average length of stay was less than 3 hours.

Biphasic Reactions
The reason to observe patients whose symptoms have resolved is to monitor and initiate early treatment for biphasic or recurrent anaphylaxis.
Prolonged observation could be avoided in many patients if at-risk patients could be accurately identified. Unfortunately, the available studies have not consistently demonstrated which patients are at risk of experiencing a biphasic reaction.

Rates of biphasic reactions vary greatly from study to study. Rates range from less than 1% to up to 20% of patients with anaphylaxis. Unfortunately, studies use different definitions of anaphylaxis and frequently include patients who did not receive appropriate initial treatment. Some studies include recurrence of very mild symptoms not requiring treatment as biphasic reactions. Therefore, the rate of biphasic reactions requiring intervention in patients who receive appropriately aggressive initial treatment is unknown. Three mainly adult studies identified biphasic reactions in 18% to 20% of patients. However, multiple studies have found rates of biphasic reactions closer to 5%. One combined pediatric and adult study reported that 5% of outpatients and 7% of hospitalized patients had a biphasic reaction. Another combined pediatric and adult study found a 5% rate of biphasic anaphylaxis. A study of 67 patients with anaphylaxis found a 3% rate of biphasic reactions. The 2 biphasic reactions seen in this study were both mild, consisting of urticaria only, and both were delayed beyond 24 hours. A study of pediatric anaphylaxis reported that 11% of patients had a biphasic reaction, but in most of these patients, the second phase was not considered to be an anaphylactic reaction. Another study of biphasic reactions in children found a 6% rate of biphasic reactions in children hospitalized for anaphylaxis. Only 3% of patients had a biphasic reaction requiring treatment. None of the episodes of biphasic anaphylaxis in any of the above studies were fatal.

Length of time to development of a biphasic reaction varies considerably from study to study. In one pediatric study, 3 biphasic reactions occurred after asymptomatic intervals of 5.8, 11.4, and 28.4 hours. The authors of that study concluded that only 2% of patients benefitted from an admission for 24-hour observation. Multiple authors have described patients with biphasic reactions after an asymptomatic period of more than 24 hours. Therefore, there is a small risk of deterioration after discharge even if patients are admitted for 24 hours of observation.

Several studies have tried to determine risk factors for a biphasic reaction. One study reported that no biphasic reactions occurred in patients whose symptoms completely resolved within 30 minutes of initiation of treatment. In another study, all patients with a biphasic reaction required a second dose of epinephrine or a fluid bolus during their initial resuscitation. Several studies have identified need for higher total doses of epinephrine for symptom resolution to be a risk factor for biphasic anaphylaxis. Another study found that patients with biphasic reactions had a longer delay from onset of symptoms to epinephrine administration than patients with uniphasic reactions. Until more data is available, requirement of a second dose of epinephrine, or a fluid bolus, slow response to epinephrine, and delay in epinephrine administration should be considered risk factors for biphasic reactions.

### Fatal Anaphylaxis

Multiple small studies have examined which patients are at risk for death from anaphylaxis. Asthma is reported to be a risk factor for fatal food-related anaphylaxis. In one series, all 13 pediatric patients with fatal or near fatal food-related anaphylaxis had asthma. Larger studies of adults and

<table>
<thead>
<tr>
<th>Table 6. Expert Guidelines Recommendations On Duration Of Observation For Patients With Anaphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint Task Force representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology</td>
</tr>
<tr>
<td>National Institute of Allergy and Infectious Diseases; Food Allergy and Anaphylaxis Network</td>
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<td>Resuscitation Council of the UK</td>
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</table>

- **Difficulty responding to deterioration including evening and night presentations and areas without easy access to emergency care**
children have also found that most patients with fatal food-related anaphylaxis have asthma.\textsuperscript{35,36} Age has also been identified as a risk factor. Most food-related anaphylaxis deaths occur in adolescents and young adults.\textsuperscript{35,36} One reason that older children and adolescents are thought to be at higher risk is that they are less likely to avoid known triggers or carry their epinephrine auto-injectors.\textsuperscript{97}

Although the majority of patients with anaphylaxis demonstrate cutaneous symptoms, in one case series of fatal anaphylaxis, only 1 of the 6 patients with fatal anaphylaxis had cutaneous symptoms.\textsuperscript{34} It is unclear if this was due to chance, if lack of cutaneous symptoms is a marker for severe anaphylaxis, or if recognition of anaphylaxis and initiation of appropriate treatment was delayed because urticaria was absent. Regardless, clinicians should aggressively treat patients with symptoms consistent with anaphylaxis even in the absence of cutaneous signs.

Death appears to be uncommon if epinephrine is immediately administered, but it has been reported. Three of 48 patients in one series died despite appropriate self-administration of epinephrine.\textsuperscript{59} In another case series, 2 of 32 deaths occurred in patients who had not responded to self-administered epinephrine.\textsuperscript{35}

In 1 study of 164 cases of fatal anaphylaxis, the longest time from exposure to the trigger to death was 6 hours.\textsuperscript{58} (See Figure 1.) The vast majority of deaths occurred within 4 hours of exposure to the trigger. The delayed deaths were due to ingested allergens, either food or drug. A study of 6 children with fatal food-related anaphylaxis demonstrated similar results.\textsuperscript{34} Five of the children died within 4 hours of exposure to the trigger and a 6\textsuperscript{th} died 5 hours after exposure. In that study, 3 of the patients had improvement in symptoms before dying. These 2 studies of fatal anaphylaxis do support a 6-hour observation period for patients with anaphylaxis.

\section*{Discharge Medications And Referrals}

Current recommendations are to discharge the patient with an epinephrine auto-injector and refer him or her to an allergist.\textsuperscript{1,33,44,45} Additionally, there is a small risk of recurrent symptoms after discharge, so the child must be discharged to a reliable adult who is able to administer the epinephrine auto-injector and access emergency services in case of a biphasic reaction.

One problem with prescribing epinephrine auto-injectors is that only 2 doses are available in the United States, 0.15 milligrams and 0.3 milligrams. Food and Drug Administration-approved drug labels for auto-injectors state that the 0.15 milligram dose should be used for children weighing at least 15 and up to 30 kilograms and the 0.3 milligram dose should be used in children weighing 30 kilograms or more. However, this would result in a significant undertreatment in children weighing close to 30 kilograms. Children receiving larger doses of epinephrine experience more side effects from the medication,\textsuperscript{98} but given the risks of undertreated anaphylaxis, a small overdose may be preferable to an underdose. A clinical report by the American Academy of Pediatrics’ Section on Allergy and Immunology published in \textit{Pediatrics} recommends prescribing the 0.15 milligram auto-injector for children weighing 10 to 25 kilograms and the 0.3 milligram auto-injector to children weighing 25 kilograms or more.\textsuperscript{48} In a survey of 29 pediatricians, 80\% stated they would prescribe a 0.15 milligram epinephrine auto-injector to a 10 kilogram child and 70\% would prescribe it to a 20 kilogram child.\textsuperscript{48} One expert review states that most allergists dispense the 0.15 milligram auto-injector to children who weigh 10 to 20 kilograms and the 0.3 mg auto-injector to children who weigh 28 kilograms or more.\textsuperscript{99} Dosing for children weighing less than 10 kilograms is even more difficult. Unless manufacturers begin marketing more doses of epinephrine auto-injector, the only alternative is to prescribe an ampoule of 1:1000 epinephrine with syringes and have parents draw up the appropriate dose. One study tested parents’ ability to do that and found that parents were unable to reliably draw up the correct dose.\textsuperscript{100} The authors concluded that despite the fact that the pediatric epinephrine auto-injector delivers too large a dose for infants, it is preferable.
to dispensing ampoules and syringes to parents. There is a potential for a much larger dosing error with an ampoule and syringe than with the epinephrine auto-injector.

Many studies demonstrate a need for improvement in ED discharge medications and instructions for patients with anaphylaxis. One study of food allergy showed that only 35% of patients with food-related anaphylaxis were given instructions to avoid the offending food. In the United States, 22% to 63% of patients diagnosed with anaphylaxis were discharged with an epinephrine auto-injector and 13% to 33% were referred to an allergist. An Australian study found that only 17.5% of pediatric patients with anaphylaxis were discharged with a prescription for an epinephrine auto-injector, but 54% of children were discharged with an H1 blocker and 28% were discharged with steroids. Furthermore, when epinephrine is prescribed, patients are frequently not trained in its use. A survey of 29 attending pediatricians found that only 17% generally demonstrated use of an epinephrine auto-injector and only 24% gave written information at the time of prescription. All physicians prescribing epinephrine auto-injectors should be comfortable with their use. Training auto-injectors and online videos demonstrating proper use are available from manufacturers.

Summary

Anaphylaxis can present with a variety of signs and symptoms and is frequently underdiagnosed. Early recognition and treatment of this potentially fatal disorder are vital. Intramuscular epinephrine is the cornerstone of treatment. As reviewed in this issue, evidence for other treatment options is lacking. Expert guidelines agree that antihistamines and corticosteroids are at best second-line treatments and should never replace or delay epinephrine administration. Patients diagnosed with anaphylaxis should be discharged with an epinephrine auto-injector, instructions on allergen avoidance, and instructions to follow-up with an allergy-immunologist.

Case Conclusions

The 10-year-old patient is accompanied to the ED by her friend’s mother. The patient admits that she doesn’t always ask how food is prepared. The friend’s mother was unaware of the patient’s food allergies and prepared a meal fried in peanut oil. You diagnose anaphylaxis and immediately administer 0.3 mg 1:1000 epinephrine intramuscularly in the anterolateral thigh. You decide not to administer antihistamines because she doesn’t have urticaria or other cutaneous signs. She is wheezing and has a history of asthma so you administer 60 mg (2 mg/kg) of methylprednisolone intravenously. The patient’s symptoms resolve completely. You consider the patient high-risk because she has poorly controlled asthma and she ingested an allergen. Furthermore, it is late at night and recognition of symptom recurrence might not occur at home. Therefore, you decide to admit the patient to a monitored bed on the pediatric ward. When the patient’s parents arrive, you counsel the patient and her parents on the importance of allergen avoidance, carrying an epinephrine auto-injector, and allergy follow-up.

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, such as the type of study and the number of patients in 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.


64. Rolle S, Harper NJ. Ability of hospital doctors to calculate drug doses. BMJ. 1995;310:1173-1174. (Survey and written test, 150 physicians)
68. Andreae DA, Andreae MH. Should antihistamines be used to treat anaphylaxis? BMJ. 2009;339:b2489. (Review)
93. Lieberman P. Biphasic anaphylactic reactions. Ann Allergy
3. Which of the following is true regarding fatal anaphylaxis?
   a. Approximately 5% of episodes of anaphylaxis are fatal.
   b. Most deaths from anaphylaxis occur at least 4 hours after exposure to the trigger.
   c. Delayed anaphylaxis deaths are more commonly due to ingested allergens.
   d. Most pediatric anaphylaxis deaths are due to medications administered in a hospital setting.

4. Which is the most appropriate initial dose of epinephrine in a 30 kg child with hives, stridor, and lip swelling?
   a. 0.5 mL nebulized racemic epinephrine
   b. 0.3 mL 1:1000 epinephrine administered subcutaneously in the upper arm
   c. 0.3 mL 1:1000 epinephrine administered intramuscularly in the thigh
   d. 3 mL 1:10,000 epinephrine administered intravenously

5. What is the likely diagnosis in 2 teenaged sisters who both present with flushing, vomiting, abdominal cramping, and pruritis after eating sushi together?
   a. Scombroid poisoning
   b. Bacterial gastroenteritis
   c. Familial anaphylaxis
   d. Anaphylaxis in one sister and panic attack in the other

6. Which of the following is TRUE regarding use of antihistamines in anaphylaxis?
   a. H1 receptor blockers have been demonstrated to reduce mortality and the incidence of biphasic reactions.
   b. H2 receptor blockers have been demonstrated to reduce mortality and the incidence of biphasic reactions.
   c. The combination of H1 and H2 receptor blockers have been demonstrated to reduce mortality.
   d. Neither H1 or H2 receptor blockers have been demonstrated to reduce mortality or biphasic reactions.
7. Which of the following patients does NOT meet criteria for anaphylaxis?
   a. A 10-year-old patient with a known peanut allergy with a blood pressure of 85/30 after accidentally eating a peanut-containing dessert at a party
   b. A 12-year-old patient who presents with an episode of syncope and sudden onset of diffuse urticaria and mucosal edema after a bee sting
   c. A 9-month-old with diffuse urticaria and pruritis but otherwise normal vital signs and physical examination after eating an egg for the first time
   d. A 5-year-old with a peanut allergy with acute onset of 4 episodes of vomiting, crampy abdominal pain, and wheezing after eating at a Chinese restaurant

8. Which of the following is TRUE regarding biphasic reactions?
   a. Early administration of corticosteroids has definitively been shown to decrease the incidence of biphasic reactions.
   b. Need for a second dose of epinephrine has been identified as a possible risk factor for a biphasic reaction.
   c. Biphasic reactions occur in about a quarter of pediatric patients with anaphylaxis.
   d. Biphasic reactions generally occur at least 6 hours after the initial reaction.

9. Which of the following is true regarding laboratory testing for anaphylaxis?
   a. Histamine remains elevated for up to 3 hours from symptom onset.
   b. A normal tryptase rules out the diagnosis of anaphylaxis.
   c. Histamine returns to baseline levels more rapidly than tryptase.
   d. Tryptase and histamine should routinely be ordered in patients with suspected anaphylaxis.

10. Which of the following patients with severe anaphylaxis would be most likely to benefit from glucagon?
    a. 13-year-old with a history of asthma on daily inhaled steroids and albuterol
    b. 10-year-old with a severe peanut allergy
    c. 12-year-old on propranolol for Wolff-Parkinson-White syndrome
    d. 8-year-old who just received her first infliximab infusion for Crohn’s disease

11. Which of the following would be the most common trigger of anaphylaxis in a child?
    a. Peanuts
    b. Influenza vaccination
    c. Strawberries
    d. Azithromycin

12. Classic anaphylaxis is an IgE-mediated reaction, but similar reactions can occur via non-IgE-mediated pathways. A reaction to which of the following is most likely to be an IgE mediated reaction?
    a. Radiocontrast dye
    b. Ethanol
    c. Bee sting
    d. Infliximab infusion

13. Which of the following signs of anaphylaxis is most commonly seen?
    a. Syncope
    b. Urticaria
    c. Hypotension
    d. Abdominal cramping

14. What is the likely diagnosis in a 2-year-old child with multiple reddish brown macules on his trunk who presents with recurrent flushing and urticaria and no other symptoms?
    a. Cutaneous mastocytosis
    b. Idiopathic anaphylaxis
    c. Food allergies
    d. Nummular eczema

15. Which of the following is TRUE of epinephrine auto-injectors?
    a. Their use is absolutely contraindicated in children under 15 kilograms.
    b. They should only be prescribed by allergy-immunologists.
    c. They are self-explanatory and require no specific discharge instructions.
    d. They are underused by patients and their families.

16. Which of the following is TRUE regarding intravenous epinephrine for anaphylaxis?
    a. If an IV has been established, intravenous epinephrine is preferred over intramuscular epinephrine for first-line therapy.
    b. The 1:1000 concentration is recommended for intravenous administration in anaphylaxis
    c. It should not be used unless the patient is in cardiac arrest.
    d. It is indicated if multiple bolus doses of intramuscular epinephrine fail to reverse hypotension or other severe signs.
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EVIDENCE-BASED PRACTICE RECOMMENDATIONS

An Evidence-Based Review Of Pediatric Anaphylaxis
Santillanes G, Davidson J. October 2010; Volume 7, Number 10

This issue of Pediatric Emergency Medicine Practice will focus on the identification of patients with anaphylaxis including those with atypical presentations. The authors review the literature behind the treatment of anaphylaxis and review recent guidelines on the topic.

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<th>Key Points</th>
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<td>Anaphylaxis can present with a variety of signs and symptoms.</td>
<td>Consider the diagnosis even in patients who don’t present with classic symptoms of urticaria, angioedema, or wheezing. Two recent studies found that about half of patients meeting criteria for food-related anaphylaxis did not receive a discharge diagnosis of anaphylaxis.(^2,3)</td>
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<td>The observation period must be individualized but a 6-hour observation period is supported by several expert guidelines.</td>
<td>The Resuscitation Council of the UK recommends at least 6 hours of observation for most patients.(^23) The statement published by the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network with input from the American College of Emergency Physicians and the American Academy of Pediatrics states that a 4 to 6 hour observation period is appropriate for most patients.(^1) Longer observation periods may be considered for patients with severe reactions or with risk factors for biphasic or fatal anaphylaxis.</td>
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<td>Intramuscular epinephrine is recommended as the most important treatment in all anaphylaxis treatment guidelines.</td>
<td>Limited data suggests that, in both adults and children, peak plasma epinephrine levels are reached more quickly with intramuscularly administered epinephrine than with subcutaneously administered epinephrine.(^31,32) However, one recent pediatric study found that the majority of ED epinephrine doses were administered subcutaneously rather than intramuscularly.(^36) Not only is epinephrine underused in the ED setting, but patients also underuse their epinephrine auto-injectors.(^57)</td>
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<td>Patients diagnosed with anaphylaxis should be discharged with an epinephrine auto-injector and instructions to follow-up with an allergist. They should also be counseled in trigger avoidance.</td>
<td>Many studies demonstrate a need for improvement in ED discharge medications and instructions for patients with anaphylaxis. One study of food allergy showed that only 35% of patients with food related anaphylaxis were given instructions to avoid the offending food.(^53) A survey of 29 attending pediatricians found that only 17% generally demonstrated use of an epinephrine auto-injector and only 24% gave written information at the time of prescription.(^57)</td>
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<td>Antihistamines and corticosteroids are at best second line treatments for anaphylaxis.</td>
<td>Several studies in adults demonstrate that the combination of H1 and H2 receptor blockers is superior to an H1 receptor blocker alone in the treatment of cutaneous symptoms of mild allergic reactions.(^72,73) Therefore, antihistamines may be helpful as a second-line adjunct agent to treat cutaneous symptoms of anaphylaxis, but they do not relieve airway symptoms, shock, or hypotension. The reason cited for giving corticosteroids is to prevent biphasic or protracted reactions, though few studies have addressed this question.</td>
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REFERENCES


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