

# Anaphylaxis in Children and Adolescents



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## KEYWORDS

• Anaphylaxis • Anaphylactic reaction • Allergic reaction • Anaphylactoid

## KEY POINTS

- Anaphylaxis is an acute, potentially life-threatening systemic hypersensitivity reaction that should be recognized promptly.
- Food allergy is the most common cause of anaphylaxis, followed by drugs.
- Signs and symptoms of anaphylaxis include urticaria, angioedema, respiratory distress, nausea, vomiting, diarrhea, and hypotension.
- Up to 10% of patients with anaphylaxis can present without cutaneous findings. This lack of skin/mucosal involvement can lead to misdiagnosis or delayed diagnosis of anaphylaxis.
- Epinephrine is the first drug of choice for treating anaphylaxis. Delayed epinephrine administration is associated with increase in morbidity and mortality.

## INTRODUCTION

Anaphylaxis is an acute, potentially life-threatening systemic hypersensitivity reaction. Classically anaphylaxis is an immunoglobulin (Ig) E-mediated reaction; however, IgG or immune complex complement-related immunologic reactions that lead to degranulation of mast cells can also cause anaphylaxis. Food allergy is the most common cause of anaphylaxis, followed by drugs. The most common foods causing anaphylaxis are cow's milk in infants, peanuts in children, and tree nuts and shellfish in young adults. Beta-lactam antibiotics are the most common culprits of drug-induced anaphylaxis.

Patients with anaphylaxis commonly present with symptoms involving skin or mucous membranes, followed by respiratory and gastrointestinal symptoms. By definition, anaphylaxis involves at least 2 body systems. Anaphylaxis is also considered if

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only hypotension occurs without other clinical findings after exposure to a specific allergen known to the individual.<sup>1–4</sup> Epinephrine is the first drug of choice in treating anaphylaxis. Patients and caregivers should be educated in the use of epinephrine autoinjectors. Delayed epinephrine injection increases the risk of hospitalization and death from anaphylaxis.

## **PATHOGENESIS AND CLASSIFICATION**

Traditionally anaphylaxis is an IgE-mediated immunologic reaction that leads to the release of mediators from mast cells and basophils; however, IgG (animal models only) and immune complex/complement-mediated immunologic reactions can also cause anaphylaxis.

Nonimmunologic mechanisms such as direct release of mast cell and basophil mediators or complement activation are also known to cause anaphylactic reactions.<sup>2</sup> These non-IgE-mediated or non-immune systemic reactions were previously termed anaphylactoid reactions. However, the World Allergy Organization has categorized anaphylaxis as allergic anaphylaxis, when the reaction is mediated by immune mechanisms (either from IgE, IgG, or immune complex) and nonallergic anaphylaxis, when the reaction is not immunologically mediated, thus eliminating the term anaphylactoid.<sup>5</sup> Both the IgE-mediated and non-IgE-mediated mechanisms release platelet-activating factor, whereas only the IgE-dependent mechanism releases histamine. Regardless of the pathogenesis, the symptoms of anaphylaxis are identical.

## **EPIDEMIOLOGY, MORBIDITIES, AND MORTALITIES**

The lifetime risk of anaphylaxis is at least 1.6% in the general population in the United States.<sup>5,6</sup> The hospital admission rate for anaphylaxis in the United States for both children and adults had increased from 2000 to 2011.<sup>5</sup> Children between 0 and 4 years of age are at the highest risk for hospitalization because of anaphylaxis, with the main cause being food allergy.<sup>5</sup>

Overall fatality rates from anaphylaxis remain stable at 0.63 to 0.76 per million US adults per year.<sup>5,7</sup> This prevalence is higher than that reported from the United Kingdom (0.33 per million),<sup>8</sup> similar to the rate reported from Australia (0.64 per million),<sup>9</sup> but lower than that reported from France (0.83 per million).<sup>10</sup> In the United States, the most common causes of anaphylaxis fatalities in adults are medications (58.8%), followed by unspecified causes (19.3%), venoms (15.2%), and foods (6.7%).<sup>7</sup> Fatal anaphylaxis is significantly associated with African American ethnicity and older age.<sup>7</sup> However, fatal anaphylaxis caused by venom is more common in white people.<sup>7</sup>

Data about fatal anaphylaxis in the pediatric population are insufficient and variable from country to country.<sup>11–13</sup> For example, in the United States and Australia, medications were found to be the most common cause of pediatric fatalities caused by anaphylaxis. However, a study from the United Kingdom identified foods as the most common cause of fatal anaphylaxis in patients less than 30 years of age. Factors associated with a higher risk for fatal food-induced anaphylaxis include adolescent age, history of a reaction, allergy to peanuts or tree nuts, asthma, and the absence of cutaneous symptoms.<sup>1</sup>

## **CAUSES**

### ***Food***

Food allergy is the most common cause of anaphylaxis. The most common foods causing anaphylaxis are cow's milk (infants), peanuts (children), and tree nuts and

shellfish (young adults).<sup>1,2,5</sup> Rare, delayed anaphylaxis occurring several hours after eating mammalian red meat are widely reported caused by IgE antibodies against the carbohydrate structure galactose- $\alpha$ -1,3-galactose. This reaction has been linked to sensitization from multiple tick bites.<sup>1,5</sup>

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### **Drugs**

Drugs are the second most common cause of anaphylaxis. The most common culprit of medication-induced anaphylaxis is beta-lactam antibiotics, followed by nonsteroidal antiinflammatory drugs (NSAIDs).

Reactions to vancomycin, known as red man syndrome or red neck syndrome, can mimic anaphylaxis. These reactions are non-IgE mediated, caused by direct mast cell activation, and can therefore occur with the first administration of vancomycin. Such reactions are preventable by slowing the infusion rate and premedicating with antihistamines.

Radiocontrast media reactions are also caused by direct mast cell activation and/or activation of coagulation/complement cascades. The use of lower osmolality preparations and premedication with steroid and antihistamines is recommended to minimize its occurrence.

Multiple agents may be involved in perioperative anaphylaxis, including antibiotics, neuromuscular blocking agents, blood products, chlorhexidine, and natural rubber latex.<sup>1,5</sup> Detailed clinical investigation may elucidate the cause of perioperative anaphylaxis.

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### **Latex**

Incidence of latex-induced anaphylaxis in the United States has stabilized because of the use of nonlatex products in hospitals and clinics, although latex allergy remains an important cause of anaphylaxis outside the United States.<sup>5</sup>

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### **Hymenoptera**

Another important cause of anaphylaxis is insect sting hypersensitivity reaction. The culprit insects include flying hymenopterans (yellow jacket, hornet, wasp, honeybee) and imported fire ant.<sup>14</sup>

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### **Exercise-induced Anaphylaxis**

Exercise-induced anaphylaxis (EIA) occurs after physical exertion and can be a difficult diagnosis. Direct mast cell activation is thought to play role in EIA. Some EIA can be related to certain foods, particularly wheat. A supervised exercise challenge test is not helpful in all cases. Avoiding exercise in the immediate postprandial period, exercising with a partner, prompt recognition of anaphylactic symptoms, and self-use of epinephrine autoinjectors are recommended.<sup>1</sup>

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### **Idiopathic**

Idiopathic anaphylaxis is a diagnosis of exclusion. Idiopathic anaphylaxis in children is very rare. In contrast, the cause of anaphylaxis in adults may remain undetermined in up to two-thirds of the cases when evaluated by specialists per survey studies.<sup>2</sup> Important considerations should include mast cell disorders and mastocytosis for these patients.

Causes of anaphylaxis are summarized in [Table 1](#).<sup>1,2,5</sup>

| Table 1<br>Common causes of anaphylaxis       |                                                                                                                                                                                                                              |
|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pathophysiology of Anaphylaxis                | Common Causes                                                                                                                                                                                                                |
| Classic IgE-mediated anaphylaxis              | Food (milk, egg, peanuts, tree nuts, seafood, soy, wheat), drug (antibiotics, NSAIDs, biologic agents, neuromuscular blocking agents, barbiturates), latex, insect sting, subcutaneous allergen immunotherapy, seminal fluid |
| Immune complex complement-related anaphylaxis | Blood products, hemodialysis                                                                                                                                                                                                 |
| Nonimmunologic anaphylaxis                    | RCM, opioids, ethanol, physical exercise, cold, heat, sunlight/UV radiation                                                                                                                                                  |
| Idiopathic anaphylaxis                        | Unknown                                                                                                                                                                                                                      |

Abbreviations: RCM, radiocontrast media; UV, ultraviolet.  
Data from Refs.<sup>1,2,5</sup>

Signs and Symptoms

The most common clinical findings in anaphylaxis involve the skin/mucosa (62%–90%), followed by respiratory (45%–70%) and gastrointestinal symptoms (25%–45%).<sup>2,3</sup> Urticaria, pruritus, and angioedema are among the common skin/mucosal presentations of anaphylaxis. Angioedema may involve eyelids, conjunctiva, lips, tongue, uvula, and oral pharyngeal mucosa. In some cases, pruritus can be seen alone without evidence of hives or urticaria on physical examination.<sup>2</sup>

Upper airway obstruction, wheezing, and/or hypoxia are frequently seen in anaphylaxis and can be life threatening. Abdominal pain, nausea, vomiting, and/or diarrhea are also commonly observed. Notably, 10% of the patients can present with immediate, profound shock without cutaneous involvement, making the diagnosis of anaphylaxis more challenging.<sup>2,3</sup> Clinical features of anaphylaxis are summarized in Table 2.<sup>2,3</sup>

Biphasic anaphylaxis is reported in 0.4% to 23.3% of patients with anaphylaxis.<sup>1,5</sup> It is described as a second anaphylactic reaction that occurs within 12 hours after the

| Table 2<br>Common signs and symptoms of anaphylaxis by organ systems |                                                                                                                                             |
|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Organ System Involvement                                             | Presentations                                                                                                                               |
| Skin/mucosa (62%–90%)                                                | Pruritus with or without rash, urticaria, flushing, angioedema of the lips/tongue and/or uvula, conjunctival edema, periorbital edema       |
| Respiratory (45%–70%)                                                | Nasal congestion, rhinitis, dyspnea, stridor, sensation of throat closing, choking, wheezing, hypoxia                                       |
| Gastrointestinal (25%–45%)                                           | Nausea, vomiting, diarrhea, abdominal pain                                                                                                  |
| Cardiovascular (10%–45%)                                             | Diaphoresis, chest pain, presyncope/syncope, tachycardia, bradycardia (caused by Bezold-Jarisch reflex), hypotension, end-organ dysfunction |
| Central nervous system (5%–15%)                                      | Confusion, unconsciousness, hypotonia, headache, incontinence, seizure                                                                      |

Data from Adkinson NF Jr. BB, Busse WW, Holgate ST, Lemanske RF Jr., Simons FER and Middleton's Allergy: Principles and Practice. 7th ed. St. Louis: Mosby, Inc; 2009 and Simons FE. Anaphylaxis, killer allergy: long-term management in the community. Allergy Clin Immunol. 2006;117(2):367-377.

resolution of the initial anaphylaxis and without new exposure to allergens. Protracted anaphylaxis is an anaphylactic reaction that can last from hours to several days without resolution of symptoms.

It is important to distinguish and identify clinical mimickers of anaphylaxis as listed in [Table 3](#).<sup>1</sup>

## DIAGNOSIS

The diagnosis of anaphylaxis is often challenging and missed, compromising the well-being of patients. The diagnosis of anaphylaxis should be considered in the following 3 situations:

1. Patients who experience acute onset and rapidly progressive symptoms (minutes to hours) involving the skin and/or mucous membranes plus either respiratory symptoms or hypotension/end-organ dysfunction.
2. Patients who experience acute onset of symptoms (minutes to hours) after exposure to a likely allergen and have at least 2 organ systems involved.
3. Patients who experience an acute decrease in blood pressure (minutes to hour) after exposure to a known allergen, even without other symptoms.

## LABORATORY FINDINGS

Anaphylaxis is essentially a clinical diagnosis and most laboratory tests are not commonly required.<sup>1,5</sup>

Serum histamine levels decrease to the baseline within an hour after the onset of anaphylaxis and are unlikely to be helpful.<sup>1</sup> However, serum tryptase can be useful for confirming the diagnosis of anaphylaxis, especially in cases of clinically ambiguous presentations. Serum tryptase levels remain increased for up to 6 hours after the onset of anaphylaxis<sup>1</sup> and could theoretically be obtained in the emergency department (ED) if needed.

Persistent increase of serum tryptase level for more than 24 hours after the resolution of anaphylaxis indicates underlying mast cell disorders and mastocytosis.<sup>1</sup> These patients can present with recurrent idiopathic anaphylaxis. Further laboratory evaluation and a referral to a specialist are recommended.

Other laboratory tests that are helpful for identifying the cause of anaphylaxis include skin prick testing and allergen-specific serum IgE levels. Because of high sensitivity and lower specificity, skin prick testing and allergen-specific serum IgE levels should focus only on suspected allergen exposure suggested by history.<sup>1,2,15</sup> Testing with broad allergen panels is not recommended and can lead to false-positive tests and unnecessary allergen avoidance, especially food.<sup>15</sup> A referral to a specialist should be considered to identify the cause of anaphylaxis. Typically, skin prick testing is delayed for 6 weeks after anaphylaxis because of the possibility of specific IgE consumption that occurred during the reaction; however, the evidence supporting this practice is controversial.

[Table 4](#) summarizes laboratory tests that may be useful for diagnosis and in identifying the cause of anaphylaxis.<sup>1,2,15</sup>

## MANAGEMENT

### *Acute Management of Anaphylaxis*

Epinephrine at 0.01 mg/kg (maximum dose of 0.5 mg) per single dose is the first drug of choice for treating anaphylaxis. There are no absolute contraindications to epinephrine. Transient side effects of epinephrine, such as pallor, tremor, palpitations,

| <b>Table 3</b><br><b>Differential diagnosis of anaphylaxis</b> |                                                                                                                                                                                                                                                                                    |
|----------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Differential Diagnosis</b>                                  | <b>Distinguish Clinical Features</b>                                                                                                                                                                                                                                               |
| <i>Flushing syndromes</i>                                      |                                                                                                                                                                                                                                                                                    |
| Drug/ingestant induced                                         | Flushing with history of exposure to alcohol, ACE inhibitors, niacin, nicotine, or catecholamines                                                                                                                                                                                  |
| Pheochromocytoma                                               | Flushing, headaches, diaphoresis, tachycardia, with hypertension. Increased neuropeptide levels                                                                                                                                                                                    |
| Carcinoid tumor/vasointestinal polypeptide tumors              | Flushing with secretory diarrhea, abdominal pain, diaphoresis, bronchospasm, and tremor. Increased neuropeptide levels                                                                                                                                                             |
| Medullary carcinoma of the thyroid                             | Facial/upper-extremity flushing, telangiectasias, thyroid nodules<br>Increased serum calcitonin and CEA levels                                                                                                                                                                     |
| Mastocytosis and mast cell activating syndrome                 | Symptoms mimic those of anaphylaxis<br>Typically recurrent. May have urticaria pigmentosa; positive Darier sign is supportive for the diagnosis. Need further laboratory tests to help diagnosis (see <a href="#">Table 4</a> )                                                    |
| Vasodepressor reactions or vasovagal reactions                 | Hypotension, weakness, pallor, diaphoresis, nausea, vomiting, and bradycardia without cutaneous manifestations                                                                                                                                                                     |
| <i>Restaurant syndromes</i>                                    |                                                                                                                                                                                                                                                                                    |
| Monosodium glutamate                                           | Flushing with headache, nausea, diaphoresis, numbness, or burning in the mouth/throat. Typically after exposure to food from Chinese restaurant                                                                                                                                    |
| Scombroidosis                                                  | History of exposure to spoiled, scombroid fish (tunas, mackerels, bonitos). More than 1 person with symptoms. Skin finding is flushing (sunburnlike) rather than urticaria. Normal serum tryptase level                                                                            |
| <i>Nonorganic disease</i>                                      |                                                                                                                                                                                                                                                                                    |
| Panic attacks                                                  | Sudden periods of intense fear, palpitations, diaphoresis, shortness of breath, numbness without cutaneous findings except for possible mild flushing                                                                                                                              |
| VCD                                                            | Throat tightness, dyspnea, dysphonia, stridor, wheezing, coughing, without cutaneous findings<br>Pulmonary function test showed extrathoracic airway obstruction of flattening of the inspiratory flow volume loop. Flexible laryngoscopy showed abnormal adduction of vocal cords |
| Munchausen stridor (factitious anaphylaxis)                    | Symptoms of vocal cord dysfunction. Patients consciously produce symptoms of illness for secondary gain                                                                                                                                                                            |
| Undifferentiated somatoform anaphylaxis                        | Symptoms of dyspnea, throat tightness, syncope without physical findings of wheezing, hypotension, or cutaneous manifestations                                                                                                                                                     |
| <i>Miscellaneous</i>                                           |                                                                                                                                                                                                                                                                                    |
| HAE accompanied by rash                                        | History of recurrent episodes of angioedema without pruritus that are commonly self-limited and resolve within 2–5 d without treatment. A family history of angioedema is helpful for the diagnosis                                                                                |

(continued on next page)

**Table 3**  
(continued)

| Differential Diagnosis  | Distinguish Clinical Features                                                                                                          |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Red man syndrome        | History of vancomycin administration with symptoms of flushing and pruritus on the face, neck, and upper body. Hypotension is possible |
| Capillary leak syndrome | Recurrent angioedema, gastrointestinal symptoms, shock with hemoconcentration, usually associated with monoclonal gammopathy           |

*Abbreviations:* ACE, angiotensin-converting enzyme; CEA, carcinoembryonic antigen; HAE, hereditary angioedema; VCD, vocal cord dysfunction.

Data from Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis—a practice parameter update 2015. *Ann Allergy Asthma Immunol.* 2015;115(5):341-384.

anxiety, headache, and dizziness, are common with the therapeutic doses and generally not cause for concern.<sup>3,16</sup> Delayed epinephrine injection increases the risk of hospitalization and death from anaphylaxis.<sup>5</sup>

Prompt recognition of anaphylaxis and early administration of epinephrine, even before the ED arrival, are strongly encouraged. Epinephrine should be administered intramuscularly in the midouter thigh or intravenously if intravenous access is readily available. Subcutaneous injection is discouraged because of poor circulation to subcutaneous tissue in anaphylaxis. Epinephrine can be repeated up to 3 times every 5 to 15 minutes if the patient is not clinically responding.

After epinephrine administration, the patient should be removed from the inciting allergen if exposure continues to occur; for example, discontinuing infusion of a medication or removing the patient from the nesting area of stinging insects. Cardiopulmonary resuscitation; assessment of airway, breathing, circulation; and activation of the emergency medical services should be initiated.<sup>1</sup> Adults and adolescents should be placed in a recumbent position. Young children should be placed in a comfort position, and pregnant women should be placed on the left side. Supplemental oxygen should also be initiated. Intravenous access and fluid replacement for hypotension should be started as soon as possible. Intraosseous access can be considered if intravenous access is not readily available.

Nebulized albuterol should be considered in patients with lower airway obstruction and can be repeated every 15 minutes, if required. Glucagon should be administered in patient on  $\beta$ -blockers who do not respond to epinephrine. Advanced airway management may be needed in patients with severe stridor or laryngeal edema. Consider dopamine infusion, in addition to epinephrine infusion, in patients with refractory hypotension caused by anaphylaxis.<sup>1</sup>

H1 and H2 antihistamines and corticosteroids are considered as optional or adjunctive medications for anaphylaxis. These medications are not lifesaving and should not be given as monotherapy or the initial treatment of anaphylaxis.<sup>5</sup> First-generation and second-generation H1 antihistamines have a delayed onset of action and do not stop mast cell degranulation. Although they can relieve dermatologic symptoms, including urticaria, H1 antihistamines cannot relieve the hypotension or airway obstruction caused by anaphylaxis and hence should not replace epinephrine. Because they are to be considered only as adjunctive therapies, there are no well-designed, randomized, placebo-controlled trials establishing the use of H2 antihistamines in the treatment of anaphylaxis.<sup>1,5</sup>

Glucocorticoids also have no role in the initial treatment of anaphylaxis. In addition to a slow onset of action, their use and dosage in anaphylaxis are extrapolated from

| Table 4<br>Laboratory tests for the diagnosis or establishing the cause of anaphylaxis                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|--------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Test                                                                                                   | Features/Usage                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Histamine                                                                                              | Serum histamine level is increased 2–15 min after the onset of anaphylaxis and decreased to baseline by 1 h. This short period of detection makes serum histamine not practical for diagnosis of anaphylaxis in clinical settings<br>However, urine histamine can be helpful for the diagnosis of anaphylaxis. This test is practically challenging because it requires a standard 24-h urine collection and, ideally, a second baseline sample 24 h after the resolution of anaphylaxis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Tryptase                                                                                               | Serum tryptase level peaks at 60–90 min after the onset of anaphylaxis and remains increased up to 6 h. This test can be useful for confirming the diagnosis of anaphylaxis, although it may not be increased in food-induced anaphylaxis<br>If serum tryptase remains increased 24 h after the resolution of anaphylaxis, further tests for mastocytosis and mast cell activation syndrome should be entertained (discussed in the text in relation to bone marrow biopsy)<br>Patients who experienced insect sting anaphylaxis should have baseline serum tryptase tested because of high risk of having occult systemic mastocytosis<br>Serum tryptase level is also increased in nonanaphylaxis conditions such as acute myelocytic leukemia, myelodysplastic syndromes, acquired C1 esterase deficiency in non-Hodgkin lymphoma, hypereosinophilic syndrome associated with the FIP1 L1-PDGfra mutation, and end-stage renal disease with increased levels of endogenous stem cell factor |
| Skin and in vitro tests for serum-specific IgE                                                         | Useful for determining the cause of anaphylaxis for suspicious food or drug allergens<br>For food-induced anaphylaxis, these tests should be focused on foods suspected of provoking the reaction. Fresh food prick skin test may be needed in cases of fruit or vegetable allergy, or when extracts for foods are not available<br>Oral food challenge may be needed if the diagnosis of food anaphylaxis remains unclear                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Bone marrow aspiration/ biopsy and mutational analysis of KIT showing a codon 816 mutation (Asp816Val) | Useful for confirming the diagnosis of mast cell disorders as a differential diagnosis of anaphylaxis<br>Bone marrow specimen showed coexpression of CD2 and CD25 in CD117 (KIT)-positive mast cells by flow cytometry                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

Abbreviation: CD, cluster of differentiation.  
Data from Refs.<sup>1,2,15</sup>

studies on acute asthma. The use of steroids for preventing biphasic or protracted anaphylaxis is also not strongly supported in many studies.<sup>1,5,17,18</sup>

At least 4 to 8 hours of direct observation and monitoring is recommended for moderate to severe anaphylaxis. A longer observation should be considered in patients who are at risk of severe anaphylaxis (eg, asthmatics, medical comorbidities, requiring more than 1 dose of epinephrine, prolonged symptoms of anaphylaxis, exposure to ingested allergens, or pharyngeal edema). Biphasic anaphylaxis occurs in between 0.4% and 23.3% of anaphylaxis episodes and usually occurs in patients presenting

with hypotension or with unknown triggers. Therefore, routine prolonged monitoring is no longer necessary in patients whose anaphylaxis symptoms have resolved. However, patients and caregivers should be provided with and instructed in the use of epinephrine autoinjectors and educated to recognize anaphylaxis on all hospital discharges.<sup>1,5</sup>

### ***Long-term Management of Anaphylaxis***

#### ***Self-treatment: autoinjectable epinephrine and emergency action plan for anaphylaxis***

Autoinjectable epinephrine should be prescribed to all patients who have experienced anaphylaxis or those who are at risk for anaphylaxis. At least 2 epinephrine autoinjectors should be given because up to 30% of anaphylactic patients require the second dose of epinephrine.<sup>1</sup> Historically, 2 doses of the epinephrine autoinjectors have been available in the United States: 0.15 mg (for patient weights of <30 kg) and 0.3 mg (for patient weights of  $\geq 30$  kg). In early 2018, a new 0.1-mg dose of the epinephrine autoinjector was made available for children weighing 7.5 to 15 kg. As stated earlier, the recommended dose for epinephrine in anaphylaxis is 0.01 mg/kg, with a maximum single dose of 0.5 mg. Therefore, a single 0.3-mg dose may be suboptimal in teens as well as obese children, requiring repeat injection of epinephrine. In addition, the needle length of the autoinjectors may be too short to reach the thigh muscles in obese patients.<sup>16</sup> Given the safety profile of epinephrine and the potential for subtherapeutic treatment, providers should consider choosing a slightly higher dose for some patients.<sup>1</sup>

The most significant obstacle for long-term management of anaphylaxis is the underprescription and underuse of epinephrine. Available epinephrine autoinjectors vary in size, shape, color, needle size, method of use, ease of use, and portability.<sup>5,16</sup> Health care providers should be familiar with the device prescribed and able to instruct patients and parents in its use. Epinephrine autoinjectors should be kept at 20°C to 25°C to protect against degradation of the medication and ensure the mechanical integrity of the devices. Higher temperatures can increase the degradation of epinephrine. Exposure to freezing temperatures for a few days does not cause medication degradation but the device should be completely thawed before use.<sup>5</sup>

Personalized emergency action plans should be provided to all patients at risk for anaphylaxis (available at the American Academy of Allergy, Asthma, and Immunology Web site, [www.aaaai.org](http://www.aaaai.org)). Plans should include common signs and symptoms of anaphylaxis, instructions for epinephrine autoinjector use, and contact information for emergency medical services for transportation to an ED.<sup>15</sup> Patients at risk for anaphylaxis should also wear medical identification listing their anaphylactic triggers, comorbidities, and concurrent medications. Such identification could be in the form of Medic-Alert jewelry or an anaphylaxis wallet card (also available at [www.aaaai.org](http://www.aaaai.org)).<sup>1,16</sup>

#### ***Prevention of recurrence of anaphylaxis and specialist referral***

A referral to an allergist/immunologist should be considered in all patients who have experienced anaphylaxis. Specialist referrals have shown improved clinical outcomes and reduced hospital admissions caused by early diagnosis in addition to identification of anaphylaxis-inducing allergens. Regular follow-up of such patients also showed long-term risk reduction of anaphylaxis.<sup>1,5</sup> All patients and caregivers should be provided with written and specific information on avoidance of known allergens. Personalized emergency action plans should be reviewed periodically at follow-up visits.<sup>3,5,16</sup>

**Food.** Avoidance of culprit food allergens remains the mainstay of treatment of food-induced anaphylaxis. Patients and caregivers should be educated on how to read and interpret product ingredient labels, inquire about allergen exposure at restaurants, as well as avoid cross-contamination and eating cross-reactive foods.<sup>1,3,5,16</sup> Evaluation by an allergist, including skin prick testing, food allergen component testing, or oral food challenge, can help confirm the cause of anaphylaxis and also determine whether patients have outgrown their sensitivity, particularly to milk or egg. In cases of multiple dietary restrictions, a referral to a nutritionist should be considered. Desensitization by oral or sublingual immunotherapy has been achieved in multiple randomized controlled research trials but has not yet been approved for clinical use.<sup>1,5,16</sup>

Exclusive breastfeeding is recommended for the first 4 to 6 months of life. Specific food allergen avoidance by mothers during pregnancy or breastfeeding has not proved effective for primary prevention of food allergies.<sup>15</sup> Introduction of solid foods, including common allergenic foods, should not be delayed beyond 6 months of age. In children at high risk for food allergies (eg, children with early development of severe atopic disease or whose parent or sibling has confirmed peanut allergy), specific IgE testing (serum or skin prick testing) for milk, egg, and peanut can be considered before the introduction of these highly allergenic foods. The widespread use of specific IgE testing in children who are not at high risk for food allergy is not recommended because such testing can lead to unnecessary dietary restrictions.<sup>15</sup>

**Drug.** Patients with drug-induced anaphylaxis should strictly avoid the culprit medication. They also should be educated regarding other drug therapies that might cross-react. An alternative, non-cross-reacting medication from a different class should be offered, if possible. An allergist consultation for a desensitization procedure may be needed if the anaphylaxis-inducing medication cannot be avoided. An outpatient referral to an allergist can also aid in confirmation of drug allergy by means of skin prick testing, intradermal testing, and/or graded challenge of the medication, particularly in patients with penicillin allergy.<sup>3,5,16</sup>

**Hymenoptera.** Patients with insect-induced anaphylaxis should be educated on measures to avoid insect stings. They should be referred to an allergist for considerations of venom testing and immunotherapy because immunotherapy can significantly reduce the risk of recurrent severe systemic reaction on subsequent stings.<sup>5,14</sup> Hymenoptera venom and whole-body extract (fire ant) skin testing and venom immunotherapy are recommended for all patients with anaphylaxis or patients greater than or equal to 16 years old with cutaneous systemic reaction because of high risk of anaphylaxis with subsequent sting in these patients. In contrast, venom testing or immunotherapy is not indicated for children younger than 16 years of age who have cutaneous systemic reaction, or for patients who developed only large local reactions because of the low risk of anaphylaxis with subsequent stings.<sup>14</sup>

## SUMMARY

Anaphylaxis is a life-threatening reaction that should be recognized promptly. The most common causes of anaphylaxis are foods and medications. Common symptoms of anaphylaxis include urticaria, angioedema, respiratory distress, nausea, vomiting, diarrhea, and hypotension. The symptoms can occur within minutes to hours after allergen exposure. Up to 10% of patients with anaphylaxis can present without cutaneous findings. This lack of skin/mucosal involvement can lead to misdiagnosis or

delayed diagnosis of anaphylaxis. Epinephrine is the drug of choice for treating anaphylaxis. The most significant obstacle for long-term management of anaphylaxis is the underprescription and underuse of epinephrine. Delayed epinephrine administration in anaphylaxis is associated with increase in morbidity and mortality. At least 2 epinephrine autoinjectors should be prescribed because up to 30% of anaphylactic patients require the second dose of epinephrine. Patients and caregivers should be educated on the use of epinephrine autoinjectors with periodic review of symptoms and emergency action plan for anaphylaxis. A referral to an allergist/immunologist should be considered in all patients who have experienced anaphylaxis. Specialist referrals have shown improved clinical outcomes and reduced hospital admissions caused by early diagnosis in addition to identification of anaphylaxis-inducing allergens.

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