

Recognition, Treatment, and Prevention of Anaphylaxis



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KEYWORDS

• Anaphylaxis • Epinephrine • Management • Observation • Prevention

KEY POINTS

- Anaphylaxis remains a clinical diagnosis based on probability and pattern recognition.
- The evidence base for the treatment of anaphylaxis is weak and largely based on consensus expert recommendations and anecdotal reports.
- Intramuscular epinephrine is the treatment of choice for acute anaphylaxis.
- Education, avoidance, and prevention are critically important because some anaphylactic reactions are so severe that death occurs despite rapid recognition and treatment.

INTRODUCTION

Anaphylaxis, an acute and potentially lethal multisystem allergic reaction, occurs in a variety of clinical scenarios and is almost unavoidable. Immunologic reactions to medications, foods, and insect stings cause most episodes, but virtually any substance capable of inducing systemic degranulation of mast cells and basophils can produce anaphylaxis. International studies suggest the lifetime prevalence is 0.05% to 2% with a mortality of 1%.^{1,2} An expedient diagnosis of anaphylaxis can be challenging. Prevention of future episodes involves collaborative efforts between patients and their family members, community, and health care professionals. This article focuses on current recommendations for the recognition, treatment, and prevention of anaphylaxis.

Conflicts of interest: Dr S.F. Kemp has served as an anaphylaxis advisor for Sanofi US Services (Bridgewater, NJ). The other authors have no potential conflicts of interest to declare.

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CLINICAL RECOGNITION OF ANAPHYLAXIS

Anaphylaxis remains a clinical diagnosis based on pattern recognition and probability. No evaluation can prove causation of anaphylaxis conclusively without directly challenging the patient with the suspected agent, which is a course of action that is generally contraindicated by ethical and safety concerns. Cause and effect often are confirmed historically in patients who experience objective findings of anaphylaxis after inadvertent reexposure to the causal agent.

As highlighted in symposia jointly sponsored by the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network, anaphylaxis is defined as a “serious allergic reaction that is rapid in onset and may cause death” and is considered likely if any 1 of 3 criteria is satisfied within minutes to hours: (1) acute onset of illness with involvement of skin, mucosal surface, or both, and at least 1 of the following: respiratory compromise, hypotension, or end-organ dysfunction; (2) 2 or more of the following occur rapidly after exposure to a likely allergen: involvement of skin or mucosal surface, respiratory compromise, hypotension, or persistent gastrointestinal symptoms; (3) hypotension develops after exposure to a known allergen for that patient: age-specific low blood pressure or decreased systolic blood pressure more than 30% compared with baseline.³ A retrospective cohort study of 214 emergency department patients ascertained that these criteria had a positive predictive value of 69% and a negative predictive value of 98%.⁴ However, anaphylaxis occurs as part of a clinical continuum that can begin with minor symptoms such as itchy skin, eyes, or nose and rapidly progress to life-threatening respiratory or cardiovascular manifestations. In clinical practice, the ultimate severity of an anaphylactic reaction is difficult to predict at its onset.

Anaphylaxis is associated with 1 or more of the following signs and symptoms: diffuse erythema and pruritus, urticaria, angioedema, bronchospasm, laryngeal edema, hyperperistalsis (eg, abdominal cramps, emesis, diarrhea), uterine cramps, hypotension, or cardiac arrhythmias. Urticaria and angioedema are the most common manifestations, but cutaneous findings may be delayed or absent in rapidly progressive anaphylaxis or they may vary with certain populations (eg, in children or in perioperative anaphylaxis).^{2,5} The next most common manifestations of anaphylaxis are respiratory symptoms, followed by dizziness, syncope, and gastrointestinal symptoms. The more rapid the occurrence of anaphylaxis after exposure to a stimulus, the more likely the reaction is to be severe and potentially life threatening.^{1,2}

Anaphylactic reactions may be immediate and uniphasic or they may be delayed in onset, biphasic (recurrent), or protracted. The reported time of onset of the late phase of biphasic anaphylaxis varies from 1 to 72 hours after apparent resolution of the initial phase.^{6,7} Protracted anaphylaxis may persist for up to 32 hours.⁷ Neither biphasic nor protracted anaphylaxis can be predicted from the severity of the initial phase of an anaphylactic reaction because they have occurred after what were perceived initially to be mild episodes.

MANAGEMENT OF ANAPHYLAXIS

Systematic reviews have noted the lack of optimal, randomized controlled trials of epinephrine, antihistamines, and glucocorticoids in anaphylaxis.^{8–11} Pending a stronger evidence base for the treatment of anaphylaxis, practice parameters and consensus emergency management guidelines afford the best clinical guidance.^{12–15} However, physicians and other health care professionals may not follow them.^{16–18}

Clinicians who perform procedures and administer medications should have the appropriate medications and equipment available to treat anaphylaxis.^{2,12,15} A sequential approach to the management of anaphylaxis is outlined in **Box 1**. The prompt,

Box 1**Management of acute anaphylaxis**

1. Immediate intervention:
 - a. Assessment of airway, breathing, circulation, and adequacy of mentation
 - b. Administer IM epinephrine every 5 to 15 minutes, as necessary, to control anaphylaxis signs and symptoms and prevent progression to more severe symptoms (eg, respiratory distress, hypotension, and unconsciousness)
 - c. Place patient in recumbent position and elevate lower extremities, as tolerated
2. Subsequent measures depending on response to IM epinephrine:
 - a. Consider call for assistance and transportation to an emergency department or an intensive care facility
 - b. Establish and maintain airway
 - c. Administer oxygen
 - d. Establish venous access
 - e. Use IV (IO) crystalloid (eg, 0.9% saline or Ringer's lactate) for fluid replacement
3. Specific measures to consider after epinephrine injections, where appropriate:
 - a. Consider dilute epinephrine infusion
 - b. Consider H₁ and H₂ antihistamines
 - c. Consider nebulized beta2-agonist (eg, albuterol) for bronchospasm resistant to epinephrine
 - d. Consider systemic glucocorticoids
 - e. Consider vasopressor (eg, dopamine)
 - f. Consider glucagon for patient taking β -blocker
4. Observation and subsequent outpatient follow-up:
 - a. Observation periods after apparent resolution must be individualized
 - b. After recovery from the acute episode, every patient should receive epinephrine autoinjectors and be instructed in proper technique
 - c. Every patient after anaphylaxis requires a careful diagnostic evaluation in consultation with an allergist-immunologist

Abbreviations: IM, intramuscular; IO, intraosseous; IV, intravenous.

Data from Lieberman P, Nicklas RA, Oppenheimer J, et al. Joint Task Force on Practice Parameters. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol* 2010;126:480, e32.

judicious use of intramuscular epinephrine and the maintenance of airway, adequate oxygenation, and effective circulatory volume are paramount considerations. Patients should be monitored continuously to facilitate prompt detection of any new clinical findings or treatment complications. When a patient should be transferred to an emergency facility depends on the severity of the anaphylaxis, the response to treatment, the expertise of the individual clinician, the estimated time of arrival of assistance, and possibly other scenario-dependent factors.

Epinephrine

Epinephrine is the treatment of choice for anaphylaxis and should be administered as soon as the clinician makes the clinical diagnosis of anaphylaxis ([Table 1](#); Kemp and

Table 1

Therapeutic agents for anaphylaxis

Intervention	Dose and Route of Administration	Comments
Epinephrine 1:1000 v/v (1 mg/mL)	0.2–0.5 mg IM thigh (adult); 0.01 mg/kg (up to 0.3 mg) IM thigh (child)	Give immediately; repeat every 5–15 min as needed. Monitor for toxicity
Epinephrine infusion	1 mg of 1:1000 v/v (1 mg/mL) dilution added to 250 mL D5W (or NS) (ie, 4 µg/mL concentration) infused at 1–4 µg/min (15–60 drops/min with microdrop), increasing to maximum 10 µg/min	Give if hypotensive shock and no response to IM epinephrine and IV (IO) fluids; titrate to blood pressure response Continuous use requires critical care monitoring. Monitor for toxicity
Volume Expansion		
Normal saline Ringer's lactate	Adult, 1–2 L rapidly IV/IO (5–10 mL/kg in first 5 min); child, ^a 20 mL/kg in first hr	Rate is titrated to blood pressure and pulse rate. Insert the largest catheter possible into the largest, most secure peripheral vein available. Use an administration set that permits rapid infusions. Monitor for volume overload
Antihistamines		
Diphenhydramine	Adult, 25–50 mg IV (IO); child, ^a 1 mg/kg IV (IO) up to 50 mg infused over 10 min	Second-line agents: H ₁ and H ₂ agents might work better in combination than H ₁ agents alone in urticarial suppression. Standard oral doses might suffice in milder episodes
Ranitidine	Adult, 50 mg IV (IO) (adults); child, ^a 12.5–50 mg, infused over 10 min	—
Glucocorticoids		
Methylprednisolone	1–2 mg/kg/d IV (IO)	Second-line agents: exact dose not established; no role in acute anaphylaxis
Prednisone	0.5 mg/kg/d PO	—
Vasopressor		
Dopamine	400 mg in 500 mL D5W (or NS) infused at 2–5 µg/kg/min	Consider if hypotensive and no response to epinephrine and fluids; titrate to maintain blood pressure; continuous use requires critical care monitoring
Glucagon	Initial dose, 1–5 mg slow IV (IO), then 5–15 µg/min infusion	Consider if treatment complicated by β-adrenergic blockade; emesis precautions needed; titrate to blood pressure
Methylene blue	Single bolus, 1.5–2 mg/kg in 100 mL D5W infused over 20 min has been used	Optimal dose unknown; should avoid in patients with G6PD deficiency, pulmonary hypertension, acute lung injury

Abbreviations: D5W, 5% dextrose in water; G6PD, glucose-6-phosphodiesterase; IM, intramuscular; IO, intraosseous; IV, intravenous; NS, normal saline; PO, orally; v/v, volume/volume.

^a Child dosage is age independent and determined by prepubertal state and weight less than 40 kg.

Adapted from Kemp SF. Office approach to anaphylaxis: sooner better than later. *Am J Med* 2007;120:666; and Kemp AM, Kemp SF. Pharmacotherapy in refractory anaphylaxis: when intramuscular epinephrine fails. *Curr Opin Allergy Clin Immunol* 2014;14:375.

colleagues¹⁹ discuss some of the complexities involved in decision making).^{3,12–15,20–22} Westfall and Westfall²³ provide a detailed review of the pharmacology of epinephrine. Note that there is no absolute contraindication for epinephrine administration in anaphylaxis.^{12,19} All subsequent therapeutic interventions depend on the initial response to this medication.^{12,19} Fatalities from anaphylaxis can result from delayed or inadequate doses of epinephrine and from severe respiratory or cardiovascular complications.^{12,24} Delayed epinephrine administration might also contribute to the likelihood of biphasic anaphylaxis.^{6,7,12} Even with optimal treatment, some patients still die from anaphylaxis.^{2,12,15,24}

The α -adrenergic, vasoconstrictive effects of recommended dosages of intramuscular epinephrine reverse peripheral vasodilation and alleviate hypotension and reduce generalized cutaneous erythema, urticaria, and angioedema. Local injection of epinephrine might reduce further absorption of antigen from a sting or injection site, but this has not been studied systematically. The β -adrenergic properties of epinephrine cause bronchodilation, increase myocardial output and contractility, and suppress further mediator release from mast cells and basophils.^{19,23}

Epinephrine administration enhances coronary blood flow. Two mechanisms are probably responsible: an increased duration of myocardial diastole compared with systole and a vasodilator effect caused by increased contractility. These actions usually offset the vasoconstrictor effects of epinephrine on the coronary arteries.^{19,23}

Common pharmacologic effects of epinephrine that occur at recommended doses via any route of administration include agitation, anxiety, tremulousness, headache, dizziness, pallor, or palpitations.^{19,23} Rarely, and usually after excessive doses, epinephrine administration might contribute to or cause myocardial ischemia or infarction, pulmonary edema, prolonged QTc interval, ventricular arrhythmias, accelerated or malignant states of hypertension, and intracranial hemorrhage. Nonetheless, some patients have survived massive doses of epinephrine without evident myocardial ischemia or residual complications.¹⁹

The evidence base supporting the prompt use of epinephrine in anaphylaxis is less robust than the evidence base for treatment used in other common medical conditions (eg, asthma) and likely will remain so for ethical, clinical, and logistic considerations.^{8,11,15,25} A systematic review concluded that, despite suboptimal evidence, intramuscular injections of epinephrine remain the treatment of choice for anaphylaxis.⁸

THERAPEUTIC OPTIONS AFTER INTRAMUSCULAR EPINEPHRINE

Oxygen and Beta2-agonists

Practice parameters and international guidelines support the use of oxygen and beta2-agonists in anaphylaxis, but no high-quality studies have evaluated their implementation.^{11–14,21,22,26} Thus, oxygen should be administered and pulse oximetry monitored during anaphylaxis for patients who require multiple doses of epinephrine, have protracted anaphylaxis, or have preexisting hypoxemia or myocardial dysfunction. The rate of oxygen flow depends on the clinical response and the device used. A nasal cannula at 4 to 6 L/min delivers 25% to 40% oxygen, whereas a simple face mask at 8 to 12 L/min delivers 50% to 60% oxygen.¹²

Patients with epinephrine-resistant bronchospasm usually respond to inhaled beta2-agonists (eg, albuterol) delivered with oxygen nebulization. Recommended dosages are extrapolated from asthma management guidelines.

Fluid Resuscitation for Persistent Hypotension

Increased vascular permeability during anaphylaxis can shift up to 35% of intravascular volume into the extravascular compartment within 10 minutes, potentially

resulting in inadequate venous return to the heart.^{27,28} Placement in the recumbent position with the legs elevated, as tolerated, thus is highly recommended in anaphylaxis, and it is essential in hypotensive patients because it provides autotransfusion of approximately 1 to 2 L of fluid into the central vascular compartment.²⁹

No high-quality studies have evaluated the therapeutic use of intravenous fluids in anaphylaxis and there is insufficient conclusive evidence from various other clinical conditions to provide general guidance for the optimal administration of isotonic crystalloid fluid resuscitation.^{11,30} A Canadian survey observed that the selection of 0.9% saline versus lactated Ringer's solution varies by specialty; internists tend to prefer the former, whereas surgeons and anesthesiologists tend to prefer the latter.³¹ Aggressive use of 0.9% saline potentially risks hyperchloremic metabolic acidosis, whereas large volumes of lactated Ringer's potentially risk respiratory acidosis.³²

Practice parameters and international guidelines promote the use of the crystalloid solution, 0.9% saline, for epinephrine-resistant hypotension in anaphylaxis (see **Table 1**).^{12–15,20,26} Large volumes might be required (eg, 7 L).^{2,12} If multiple liters of saline are necessary, 0.45% saline can be substituted to help prevent hyperchloremic metabolic acidosis. A critical care setting permits monitoring of electrolytes as part of the emergency care.

Any drug or fluid that is administered intravenously can also be given intraosseously in any age group.³³ Thus, clinicians who are proficient at obtaining intraosseous cannulation might consider it if intravenous access is delayed or unsuccessful because it provides safe and efficacious access to a noncollapsible venous plexus.

Intravenous Epinephrine

No scientifically rigorous studies presently permit recommendations concerning the use of intravenous epinephrine in anaphylaxis.¹¹ However, parameters and international guidelines support its use in refractory anaphylaxis (see **Table 1**).^{12–15} Because of the risk for potentially lethal arrhythmias, epinephrine characteristically is administered intravenously only in patients with cardiac arrest or to unresponsive or hypotensive patients who fail to respond to fluid resuscitation and multiple epinephrine injections.^{2,12} One group of investigators suggests that the early use of intravenous epinephrine is effective and well tolerated when the rate of administration is titrated to the clinical response, but no cohort study has systematically compared this modality with intramuscular injections of epinephrine.^{2,34} Continuous hemodynamic monitoring is optimal, but its absence should not preclude the use of intravenous epinephrine if considered essential after several epinephrine injections. In this special circumstance, monitoring by available means (eg, every-minute measurements of pulse rate and blood pressure) should be considered.¹²

SECOND-LINE THERAPEUTIC AGENTS FOR ANAPHYLAXIS

Parameters and international guidelines support the consideration of antihistamines, glucocorticoids, vasopressors, and glucagon for the treatment of anaphylaxis after initial use of epinephrine and fluids (see **Table 1**).^{12–15,20–22} However, the quality of evidence is presently insufficient to permit recommendations concerning their use.^{9–11,35–37}

Antihistamines

Skidgel and colleagues³⁸ provide a detailed review of H₁ and H₂ antihistamine pharmacology. Antihistamines act much more slowly than epinephrine; they have minimal favorable influence on blood pressure and they should not be administered alone for anaphylaxis treatment.¹² Even at maximum dosages, they cannot abort anaphylaxis if

other inflammatory mediators are involved. However, antihistamines can attenuate cutaneous manifestations (eg, urticaria or pruritus). Intravenous administration ensures that effective dosing will not be diminished by hemodynamic compromise, which impairs gastrointestinal or intramuscular absorption, but maximal therapeutic effect might not be observed for 1 hour.³⁹ Caution should be taken, because intravenously administered H₁ antihistamines can also cause hypotension.⁴⁰

Few guidelines support consideration of H₂ antihistamines in anaphylaxis after the initial use of epinephrine and fluids.^{12–14,21} Ranitidine is usually recommended when H₂ antihistamines are considered in anaphylaxis. Hypotension may result from rapid intravenous administration of cimetidine.¹²

Glucocorticoids

Schimmer and Funder⁴¹ provide a detailed review of the pharmacology of glucocorticoids. Systemic glucocorticoids may not exert appreciable effects for several hours, but they might prevent biphasic or protracted reactions in some patients. However, the data concerning possible preventive benefits are conflicting and limited.^{6,7,35} Patients with asthma or other conditions recently treated with glucocorticoids might be at an increased risk for severe or fatal anaphylaxis and might receive additional benefit if glucocorticoids are administered to them during anaphylaxis. Recommended dosages are extrapolated from acute asthma management.

Vasopressors

Vasopressors (eg, dopamine) are reserved for the rare occurrence when epinephrine and fluids both fail to alleviate hypotension in anaphylaxis.^{2,12–15} A critical care specialist may be needed for these events. A systematic review concluded that the effect of vasopressors on patient-relevant outcomes in hypotensive shock remains controversial and thus evidence-based recommendations to support one investigated vasopressor rather than another are not possible.³⁶

Glucagon

Usual doses of epinephrine administered during anaphylaxis may not have the desired clinical effect in patients taking β -blockers and may instead exert predominately α -adrenergic effects. In such circumstances, isotonic volume expansion and glucagon administration are both recommended.^{12,15,37} By directly activating adenylyl cyclase, glucagon bypasses the β -adrenergic receptor and thus may reverse refractory hypotension and bronchospasm associated with anaphylaxis, as shown in limited case reports.³⁷ Airway protection is especially important in severely drowsy patients because glucagon can cause emesis and increase the risk for aspiration.

Methylene Blue

Parameters and international guidelines briefly mention methylene blue, which might be an emerging consideration as a second-line therapeutic agent for anaphylaxis (see [Table 1](#)).^{12,20} Seven case reports describe the use of methylene blue for the treatment of anaphylactic shock refractory to epinephrine, intravenous fluids, vasopressors, and intra-aortic balloon pump, and 1 report describes its successful use in a normotensive patient with refractory anaphylaxis.^{42–44} The optimal dosage for use in anaphylaxis has not been determined. Methylene blue presumably exerts its therapeutic effects by blocking nitric oxide-mediated relaxation of vascular smooth muscle. However, the administration of methylene blue itself can precipitate anaphylaxis in some individuals.^{45,46}

OBSERVATION AFTER ANAPHYLAXIS

The best evidence suggests that observation periods after complete resolution of uniphasic anaphylaxis should be individualized, particularly because there are no reliable predictors of biphasic anaphylaxis. An observation period based on the severity and response to treatment is appropriate. Initial phases of anaphylaxis characterized by hypotension, respiratory failure or hypoxemia, repeated doses of epinephrine, poorly controlled asthma, or prior history of biphasic anaphylaxis are reasonable indications for an observation period of at least 24 hours. At discharge, all patients should be provided epinephrine autoinjectors and receive proper instruction on how to self-administer them in case of a subsequent episode. Patients should also have ready access to emergency medical services for prompt transportation to the closest emergency department for treatment. Further prospective studies on biphasic anaphylaxis are needed.^{6,7,12,14,47}

PREVENTION OF ANAPHYLAXIS

Education, avoidance, and prevention are critically important because some anaphylactic reactions are so severe that death occurs despite rapid recognition and treatment. **Box 2** outlines basic principles for the prevention of future anaphylaxis. An allergist-immunologist can provide comprehensive professional advice on these matters.

Box 2
Preventive measures in anaphylaxis

General measures

- Obtain thorough history to identify the causes of anaphylaxis and those individuals at risk for future attacks
- Provide instruction on proper reading of food and medication labels, where appropriate
- Avoid drugs immunologically or biochemically cross reactive with any agents to which the patient is sensitive
- Manage comorbid conditions
- Administer drugs orally rather than parenterally, when possible
- Implement a waiting period of 20 to 30 minutes after injections of drugs or other biologic agents
- Consider a waiting period of 2 hours if a patient receives a particular oral medication for the first time in the office
- Consult allergist-immunologist for assistance

Specific measures for high-risk patients

- Individuals at high risk for anaphylaxis should carry epinephrine autoinjectors at all times and receive instruction in proper use with placebo trainer (includes patients receiving monoclonal antibody therapy)
- MedicAlert (MedicAlert Foundation, Turlock, CA) or similar warning bracelets or chains
- Avoid β -adrenergic blockers, angiotensin-converting enzyme inhibitors, monoamine oxidase inhibitors, and tricyclic antidepressants, if possible
- Where appropriate, use specific preventive strategies, including pharmacologic prophylaxis, provocative dose challenge, and desensitization

Adapted from Kemp SF. Office approach to anaphylaxis: sooner better than later. Am J Med 2007;120:667.

All individuals at risk for anaphylaxis should carry and know how to self-administer epinephrine. Because the potential benefit of epinephrine outweighs the risk of untreated anaphylaxis, patients should be strongly encouraged to self-administer epinephrine in any case of doubt.^{19,21} Data are limited concerning the frequency with which 2 or more doses of epinephrine are needed to treat anaphylaxis (reports range from 16%–36%), and multiple cofactors may be involved.¹⁹

Demonstration of proper self-administration technique with a placebo trainer autoinjector is strongly recommended for patients and their family members, but many receive improper or no instructions.¹⁹ Patients should promptly seek precautionary medical attention after self-administration of epinephrine. **Table 2** lists the single-dose epinephrine autoinjectors commercially available in North America.

The agent responsible for anaphylaxis in an individual must be identified, whenever possible, and instructions provided on how to minimize future exposure. The relative and relevant benefits and risks of certain medications (eg, angiotensin-converting enzyme inhibitors, β -blockers, monoamine oxidase inhibitors, and some tricyclic antidepressants) should be discussed, where applicable, with patients and their health care professionals and these medications should be discontinued if feasible.^{2,12,15}

Patients with food-triggered anaphylaxis should scrutinize food labels and mitigate risk of ingesting food cross-contaminated during preparation. Accidental ingestion of peanuts and tree nuts is common.²¹ Education is of paramount importance, and Food Allergy Research & Education (FARE; 800–929–4040; www.foodallergy.org) is a helpful nonprofit resource for many food-allergic individuals.

Specific immunoglobulin E (IgE) skin testing may help ascertain the potential for anaphylaxis in some circumstances (eg, allergy to β -lactam antibiotics or to protein excipients of certain vaccines). However, the immunochemistry of most drugs and biologic agents is not well defined.

Table 2
Single-dose epinephrine autoinjectors commercially available in North America

Name of Device	Manufacturer	Dose Injected IM in the Anterolateral Thigh
Adrenaclick ^a	Amedra Pharmaceuticals, Horsham, PA	Adults, 0.3 mg/0.3 mL Child ≥ 30 kg, 0.3 mg/0.3 mL Child <30 kg, 0.15 mg/0.15 mL
Allerject	Sanofi Canada, Laval, Quebec	Adults, 0.3 mg/0.3 mL Child ≥ 30 kg, 0.3 mg/0.3 mL Child <30 kg, 0.15 mg/0.15 mL
Auvi-Q	Sanofi US, Bridgewater, NJ	Adults, 0.3 mg/0.3 mL Child ≥ 30 kg, 0.3 mg/0.3 mL Child <30 kg, 0.15 mg/0.15 mL
EpiPen	Mylan Specialty US (Basking Ridge, NJ); also sublicensed through Pfizer Canada	Adults, 0.3 mg/0.3 mL IM Child ≥ 30 kg, 0.3 mg/0.3 mL
EpiPen Jr	—	Child <30 kg, 0.15 mg/0.3 mL

Adrenaclick and EpiPen/EpiPen Jr. are penlike devices with written instructions on each syringe barrel.

The Auvi-Q/Allerject is approximately the size of a credit card and features blinking lights at the needle end and a voice recording that guides the user throughout administration.

^a Counterpart is not available in Canada.

Situations may arise in which it is necessary to administer a medication that previously caused anaphylaxis. Numerous protocols are available to assist in decreasing the risk of severe adverse reactions. These desensitization protocols should be conducted in clinical settings only where anaphylaxis, if it occurs, can be properly managed. Techniques used in these protocols include antihistamine and glucocorticoid prophylaxis to prevent or reduce the severity of IgE-independent reactions (eg, radiographic contrast media); administration of incremental doses of medication gradually over several hours (eg, short-term desensitization to penicillin, carboplatin); or the highly effective, long-term risk reduction with venom immunotherapy for insect stinging anaphylaxis. Therapeutic preparations of anti-IgE monoclonal antibodies (omalizumab) may mitigate risk in some scenarios (eg, frequent idiopathic anaphylaxis), but more data are needed.¹⁵

SUMMARY

Education, avoidance, and prevention are critically important because some anaphylactic reactions are so severe that fatalities occur despite rapid recognition and treatment. Allergist-immunologists can provide comprehensive professional assistance. The treatment of choice for anaphylaxis is intramuscular epinephrine. Improving the evidence base for various treatment and preventive modalities through controlled trials may further help minimize fatalities from anaphylaxis.

REFERENCES

1. Khan BQ, Kemp SF. Pathophysiology of anaphylaxis. *Curr Opin Allergy Clin Immunol* 2011;11:319–25.
2. Brown SGA, Kemp SF, Lieberman PL. Anaphylaxis. In: Adkinson NF Jr, Bochner BS, Burks AW, et al, editors. *Middleton's allergy: principles and practice*. 8th edition. Philadelphia: Elsevier Saunders; 2014. p. 1237–59.
3. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. 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. *J Allergy Clin Immunol* 2006;117:391–7.
4. Campbell RL, Hagan JB, Manivannan V, et al. Evaluation of National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria for the diagnosis of anaphylaxis in emergency department patients. *J Allergy Clin Immunol* 2012;129:748–52.
5. Wood RA, Camargo CA Jr, Lieberman P, et al. Anaphylaxis in America: the prevalence and characteristics of anaphylaxis in the United States. *J Allergy Clin Immunol* 2014;133:461–7.
6. Tole JW, Lieberman P. Biphasic anaphylaxis: review of incidence, clinical predictors, and observation recommendations. *Immunol Allergy Clin North Am* 2007;27:309–26.
7. Kemp SF. The post-anaphylaxis dilemma: how long is long enough to observe a patient after resolution of symptoms? *Curr Allergy Asthma Rep* 2008;8:45–8.
8. Sheikh A, Shehata YA, Brown SGA, et al. Adrenaline for the treatment of anaphylaxis: Cochrane Systematic Review. *Allergy* 2009;64:204–12.
9. Sheikh A, Ten Broek V, Brown SGA, et al. H1-antihistamines for the treatment of anaphylaxis: Cochrane Systematic Review. *Allergy* 2007;62:830–7.
10. Nurmatov UB, Rhatigan E, Simons FER, et al. H2-antihistamines for the treatment of anaphylaxis with and without shock: a systematic review. *Ann Allergy Asthma Immunol* 2014;112:126–31.

11. Dhimi S, Panesar SS, Roberts G, et al. Management of anaphylaxis: a systematic review. *Allergy* 2014;69:168–75.
12. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol* 2010; 126:477–80.e1–42.
13. VandenHoek TL, Morrison LJ, Shuster M, et al. Part 12: cardiac arrest in special situations: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; 122(Suppl 3):S829–61.
14. Soar J, Perkins JD, Abbas G, et al. European Resuscitation Council guidelines for resuscitation 2010 section 8. Cardiac arrest in special circumstances: electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. *Resuscitation* 2010;81:1400–33.
15. Simons FER, Arduzzo LRF, Bilò MB, et al. World Allergy Organization guidelines for the assessment and management of anaphylaxis. *J Allergy Clin Immunol* 2011;127:587–93.e1–22.
16. Clark S, Bock SA, Gaeta TH, et al. Multicenter study of emergency department visits for food allergies. *J Allergy Clin Immunol* 2004;113:347–52.
17. Haymore BR, Carr WW, Frank WT. Anaphylaxis and epinephrine prescribing patterns in a military hospital: underutilization of the intramuscular route. *Allergy Asthma Proc* 2005;26:361–5.
18. Beyer K, Eckermann O, Hompes S, et al. Anaphylaxis in an emergency setting—elicitors, therapy and incidence of severe allergic reactions. *Allergy* 2012;67: 1451–6.
19. Kemp SF, Lockey RF, Simons FER. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. *Allergy* 2008;63:1061–70.
20. Simons FER, Arduzzo LRF, Dimov V, et al. World Allergy Organization anaphylaxis guidelines: 2013 update of the evidence base. *Int Arch Allergy Immunol* 2013; 162:193–204.
21. NIAID-Sponsored Expert Panel. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;126(Suppl 6):S1–58.
22. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011;127:S1–55.
23. Westfall TC, Westfall DP. Adrenergic agonists and antagonists. In: Brunton LL, Chabner BA, Knollman BC, editors. *Goodman and Gilman's the pharmacological basis of therapeutics*. 12th edition. New York: Access Medicine from McGraw-Hill; 2011. Chapter 12.
24. Pumphrey R. Anaphylaxis: can we tell who is at risk of a fatal reaction? *Curr Opin Allergy Clin Immunol* 2004;4:285–90.
25. Simons FER. Pharmacologic treatment of anaphylaxis: can the evidence base be strengthened? *Curr Opin Allergy Clin Immunol* 2010;10:384–93.
26. Simons FER, Arduzzo LRF, Bilò MB, et al. 2012 Update: World Allergy Organization guidelines for the assessment and management of anaphylaxis. *Curr Opin Allergy Clin Immunol* 2012;12:389–99.
27. Fisher MM. Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. *Anaesth Intensive Care* 1986;14: 17–21.
28. Pumphrey RS. Fatal posture in anaphylactic shock. *J Allergy Clin Immunol* 2003; 112:451–2.

29. Caroline NL. Emergency care in the streets. 2nd edition. Boston: Little, Brown; 1983. p. 57–98.
30. Kemp AM, Kemp SF. Pharmacotherapy in refractory anaphylaxis: when intramuscular epinephrine fails. *Curr Opin Allergy Clin Immunol* 2014;14:371–8.
31. McIntyre LA, Hebert PC, Fergusson D, et al. A survey of Canadian intensivists' resuscitation practices in early septic shock. *Crit Care* 2007;11:R74.
32. Takil A, Eti Z, Irmak P, et al. Early postoperative respiratory acidosis after large intravascular volume infusion of lactated Ringer's solution during major spine surgery. *Anesth Analg* 2002;95:294–8.
33. Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010;122(Suppl 3):S729–67.
34. Brown SGA, Blackman KE, Stenlake V, et al. Insect sting anaphylaxis: prospective evaluation of treatment with intravenous adrenaline and volume resuscitation. *Emerg Med J* 2004;21:149–54.
35. Sheikh A. Glucocorticosteroids for the treatment and prevention of anaphylaxis. *Curr Opin Allergy Clin Immunol* 2013;13:263–7.
36. Havel C, Arrich J, Losert H, et al. Vasopressors for hypotensive shock. *Cochrane Database Syst Rev* 2011;(5):CD003709.
37. Thomas M, Crawford I. Best evidence topic report. Glucagon infusion in refractory anaphylactic shock in patients on beta-blockers. *Emerg Med J* 2005;22:272–3.
38. Skidgel RA, Kaplan AP, Erdös EG. Histamine, bradykinin, and their antagonists. In: Brunton LL, Chabner BA, Knollman BC, editors. *Goodman and Gilman's the pharmacological basis of therapeutics*. 12th edition. New York: Access Medicine from McGraw-Hill; 2011. Chapter 32.
39. Simons FE. Advances in H1-antihistamines. *N Engl J Med* 2004;351:2203–17.
40. Ellis BC, Brown SGA. Parenteral antihistamines cause hypotension in anaphylaxis. *Emerg Med Australas* 2013;25:92–3.
41. Schimmer BP, Funder JW. ACTH, adrenal steroids, and pharmacology of the adrenal cortex. In: Brunton LL, Chabner BA, Knollman BC, editors. *Goodman and Gilman's the pharmacological basis of therapeutics*. 12th edition. New York: Access Medicine from McGraw-Hill; 2011. Chapter 42.
42. Evora PR, Simon MR. Role of nitric oxide production in anaphylaxis and its relevance for the treatment of anaphylactic hypotension with methylene blue. *Ann Allergy Asthma Immunol* 2007;99:306–13.
43. Del Duca D, Sheth SS, Clarke AE, et al. Use of methylene blue for catecholamine-refractory vasoplegia from protamine and aprotinin. *Ann Thorac Surg* 2009;87:640–2.
44. Bauer CS, Vadas P, Kelly KJ. Methylene blue for the treatment of refractory anaphylaxis without hypotension. *Am J Emerg Med* 2013;31:264.e3–5.
45. Dewachter P, Castro S, Nicaise-Roland P, et al. Anaphylactic reaction after methylene blue-treated plasma transfusion. *Br J Anaesth* 2011;106:687–9.
46. Nubret K, Delhoume M, Orsel I, et al. Anaphylactic shock to fresh-frozen plasma inactivated with methylene blue. *Transfusion* 2011;51:125–8.
47. Scranton SE, Gonzalez ED, Waibel KH. Incidence and characteristics of biphasic reactions after immunotherapy. *J Allergy Clin Immunol* 2009;123:493–8.