Therapeutic Class Overview
Epinephrine for Anaphylaxis Agents

Therapeutic Class

- **Overview/Summary:** Anaphylaxis, a potentially fatal disorder, is an acute, multisystem syndrome resulting from a sudden release of mast cell- and basophil-derived mediators into circulation.[1] Most commonly it results from immunologic reactions to foods, medications and insect stings. In humans the heart, vasculature system and lungs are predominately affected during an anaphylactic reaction, and fatalities can result from circulatory collapse and respiratory arrest.[1,2] Epinephrine is essential for the treatment of anaphylaxis. It is recognized as the treatment of choice because the benefits associated with epinephrine are greater than any other available pharmacologic intervention (e.g., antihistamines, bronchodilators, glucocorticoids). Epinephrine is the only agent that prevents and reverses airflow obstruction in the upper and lower respiratory tracts, as well as cardiovascular collapse. The therapeutic actions of epinephrine result from α1, β1 and β2 adrenergic receptor agonist effects and include increased vasoconstriction, increased peripheral vascular resistance, decreased mucosal edema, increased inotropy, increased chronotropy, increased bronchodilation and decreased release of mediators of inflammation from mast cells and basophils.[3]

  The epinephrine for anaphylaxis agents (Adrenaclick®, Auvi-Q®, EpiPen® and EpiPen Jr®) which are all Food and Drug Administration approved for the emergency treatment of severe allergic reactions. All agents are available as single use, auto-injectors to be administered as an intramuscular or subcutaneous injection into the anterolateral aspect of the thigh.[4-7] Based on clinical trial data, intramuscular administration is preferred as it consistently provides a more rapid increase in the plasma and tissue concentrations of epinephrine.[2,8,9] These agents are intended for immediate administration in patients with a history of anaphylactic reactions. Furthermore, these agents are designed for emergency supportive therapy and are not intended to substitute immediate medical care. In conjunction with the administration of one of these agents, patients should seek the appropriate medical care. Differences among the various agents are minimal and include specific packaging and administration requirements. Auvi-Q® is the first epinephrine auto-injector with audio instructions that directs patients and caregivers through the injection process.[4-7] Each agent is available as a 0.15 and 0.3 mg injection. Generic epinephrine for anaphylaxis agents are currently available.

Table 1. Current Medications Available in the Therapeutic Class[4-7]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Epinephrine (Adrenaclick®*, Auvi-Q®, EpiPen®, EpiPen Jr®)	Emergency treatment of severe allergic reactions (Type 1) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants), biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as anaphylaxis to unknown substances (idiopathic anaphylaxis) or exercise-induced anaphylaxis	Injection: 0.15 mg/0.15 mL (Adrenaclick®*, Auvi-Q®*, epinephrine*) 0.15 mg/0.3 mL (EpiPen Jr®*) 0.3 mg/0.3 mL (Adrenaclick®*, Auvi-Q®*, epinephrine*, EpiPen®*)	✔

*Generic available in at least one dosage form and/or strength.

Evidence-based Medicine

- It has been noted that controlled clinical trials evaluating epinephrine for this indication will never be performed, due to ethical considerations in a disease that can kill within minutes and mandates

prompt epinephrine administration.[3] As noted in the Food and Drug Administration-approved package labeling of the various agents, epinephrine is essential for the treatment of anaphylaxis.[4-7]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Epinephrine is the first drug that should be used in the emergency management of a child having a potentially life-threatening allergic reaction.
  - Epinephrine injection is available in a number of self-administration delivery devices.
  - There are no contraindications to the use of epinephrine for a life-threatening allergic reaction.
  - In patients who have had anaphylactic reactions, it is recommended that epinephrine be given at the start of any reaction occurring in conjunction with exposure to a known or suspected allergen.
  - In situations where there has been a history of a severe cardiovascular collapse to an allergen, the physician may advocate that epinephrine be administered immediately after an insect sting or ingestion of the offending food and before any reaction has begun.
  - Epinephrine should be kept in locations that are easily accessible and not in locked cupboards or drawers.
- Other Key Facts:
  - Generic products are available.
  - Auvi-Q® is the first epinephrine auto-injector with audio instructions that directs patients and caregivers through the injection process.[4-7]

References

1. Kemp SF. Pathophysiology of anaphylaxis. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Jun 21]. Available from: http://www.utdol.com/utd/index.do.
2. No authors listed. Part 10.6: anaphylaxis. Circulation. 2005;000:IV-143-IV-145.
3. Estelle F, Simons R. Anaphylaxis: rapid recognition and treatment. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Jun 21]. Available from: http://www.utdol.com/utd/index.do.
4. Adrenaclick® [package insert]. Horsham (PA): Amedra Pharmaceuticals LLC.; 2013 Apr.
5. Epinephrine [package insert]. Horsham (PA): Lineage Therapeutics; 2013 Apr.
6. EpiPen®, EpiPen Jr® [package insert]. Basking Ridge (NJ): Mylan Specialty L.P.; 2012 Aug.
7. Auvi-Q® [package insert]. Bridgewater (NJ): Sanofi-Aventis.; 2012 Sep.
8. Simons FER, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular vs subcutaneous injection. J Allergy Clin Immunol. 2001;108(5):871.
9. Simons FER, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol. 1998;101(1 pt 1):33.
10. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2013 Jun 21]. Available from: http://www.thomsonhc.com/.
11. Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol. 2010 Sep;126(3):477-80.
12. National Institute of Allergy and Infectious Diseases: Guidelines for the Diagnosis and Management of Food Allergy in the United States (2010). 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 Dec;126(6 Suppl):S1-58.
13. American College of Allergy, Asthma, & Immunology. Food allergy: a practice parameter. Ann Allergy Asthma Immunol. 2006 Mar;96(3 Suppl 2):S1-68.
14. [No authors listed]. Anaphylaxis in schools and other childcare settings. AAAAI Board of Directors. American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 1998 Aug;102(2):173-6.
15. Golden DB, Moffitt J, Nicklas RA, Freeman T, Graft DF, Reisman RE, et al. Stinging insect hypersensitivity: a practice parameter update 2011. J Allergy Clin Immunol. 2011 Apr;127(4):852-4.e1-23.

Therapeutic Class Review
Epinephrine for Anaphylaxis Agents

Overview/Summary

Anaphylaxis, a potentially fatal disorder, is an acute, multisystem syndrome resulting from a sudden release of mast cell- and basophil-derived mediators into circulation.[1] Most commonly it results from immunologic reactions to foods, medications and insect stings. In humans the heart, vasculature system and lungs are predominately affected during an anaphylactic reaction, and fatalities can result from circulatory collapse and respiratory arrest.[1,2]

Epinephrine is essential for the treatment of anaphylaxis. It is recognized as the treatment of choice because the benefits associated with epinephrine are greater than any other available pharmacologic intervention (e.g., antihistamines, bronchodilators, glucocorticoids). Specifically, epinephrine is the only agent that prevents and reverses airflow obstruction in the upper and lower respiratory tracts, as well as cardiovascular collapse. The therapeutic actions of epinephrine result from α1, β1 and β2 adrenergic receptor agonist effects and include increased vasoconstriction (α1), increased peripheral vascular resistance (α1), decreased mucosal edema (α1), increased inotropy (β1), increased chronotropy (β1), increased bronchodilation (β2) and decreased release of mediators of inflammation from mast cells and basophils (β2).[3]

In general, pharmacologic treatment of anaphylaxis is based upon extrapolation from therapies utilized in cardiac arrest and asthma, as well as from uncontrolled clinical trials with humans who develop anaphylaxis during insect sting challenges, randomized controlled trials of interventions such as epinephrine in people not experiencing anaphylaxis at the time of administration and animal anaphylaxis models. Randomized, placebo-controlled trials that meet current standards have not been performed for any pharmacologic intervention in humans experiencing anaphylaxis. Of note, placebo-controlled trials with epinephrine will never be performed, due to ethical considerations in a disorder that can kill within minutes and mandates prompt epinephrine administration.[3]

The epinephrine for anaphylaxis agents (Adrenaclick®, Auvi-Q®, EpiPen® and EpiPen Jr®) which are all Food and Drug Administration approved for the emergency treatment of severe allergic reactions. All agents are available as single use, auto-injectors to be administered as an intramuscular or subcutaneous injection into the anterolateral aspect of the thigh.[4-7] Based on clinical trial data, intramuscular administration is preferred as it consistently provides a more rapid increase in the plasma and tissue concentrations of epinephrine.[2,8,9] These agents are intended for immediate administration in patients with a history of anaphylactic reactions. Furthermore, these agents are designed for emergency supportive therapy and are not intended to substitute immediate medical care. In conjunction with the administration of one of these agents, patients should seek the appropriate medical care. Differences among the various agents are minimal and include specific packaging and administration requirements. Auvi-Q® is the first epinephrine auto-injector with audio instructions that directs patients and caregivers through the injection process.[4-7] Each agent is available as a 0.15 and 0.3 mg injection. Generic epinephrine for anaphylaxis agents are currently available.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Epinephrine (Adrenaclick®*, Auvi-Q®, EpiPen®, EpiPen Jr®)	Anaphylaxis agents	✔

*Generic available in at least one dosage form and/or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[4-7]

Indication	Epinephrine
Emergency treatment of severe allergic reactions (Type 1) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants), biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as anaphylaxis to unknown substances (idiopathic anaphylaxis) or exercise-induced anaphylaxis	✔

Pharmacokinetics

The pharmacokinetic data associated with the epinephrine for anaphylaxis agents are not clinically significant.[10]

Clinical Trials

A thorough literature search failed to retrieve any clinical trials evaluating the epinephrine for anaphylaxis agents in their Food and Drug Administration (FDA)-approved indications. It has been noted that controlled clinical trials evaluating epinephrine for this indication will never be performed, due to ethical considerations in a disease that can kill within minutes and mandates prompt epinephrine administration.[3] As noted in the FDA-approved package labeling of the various agents, epinephrine is essential for the treatment of anaphylaxis.[4-7]

Special Populations

Table 3. Special Populations[4-7]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Epinephrine	No dosage adjustment required in the elderly. No dosage adjustment required in children.*	No dosage adjustment required.	No dosage adjustment required.	C	Unknown

*Since the doses of epinephrine delivered from the various agents within this class are fixed, physicians should consider other forms of injectable epinephrine if doses lower than those available from these agents are felt to be necessary.

Adverse Drug Events

The potential for an epinephrine for anaphylaxis agent to produce any of the adverse events outlined in Table 4 does not contraindicate its use in an acute, life-threatening allergic reaction.[4-7]

Table 4. Adverse Drug Events (%)[4-7]

Adverse Event(s)	Epinephrine
Angina	✔
Anxiety, transient moderate	✔
Apprehensiveness	✔
Arrhythmias	✔
Dizziness	✔
Headache	✔
Hypertension, acute	✔
Nausea and vomiting	✔
Pallor	✔
Palpitations	✔
Respiratory difficulties	✔

Adverse Event(s)	Epinephrine
Restlessness	✔
Sweating	✔
Tremor	✔
Weakness	✔

✔ Percent not specified.

Contraindications/Precautions

There are no absolute contraindications to the use of the epinephrine for anaphylaxis agents in a life-threatening allergic reaction.[4-7]

Epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions should be instructed about the circumstances under which epinephrine should be administered. It should be determined that the patient is at risk of future anaphylaxis, since there are some concerns in specific patients with epinephrine administration. Epinephrine should be administered with caution to patients with cardiac arrhythmias, coronary artery or organic heart disease or hypertension, or in patients who are on medications that may sensitize the heart to arrhythmias. In patients with coronary insufficiency or ischemic heart disease, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias. The presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation.[4-7]

The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors.[4-7]

Some patients may be at a greater risk of developing adverse events after administration of epinephrine, including those with hyperthyroidism, cardiovascular disease, hypertension and diabetes, as well as the elderly and pregnant women. Despite these concerns, patients with these conditions, or any other person who might be in a position to administer epinephrine to a patient with these conditions experiencing anaphylaxis, should be instructed about the circumstances under which epinephrine should be administered.[4-7]

Epinephrine is not intended as a substitute for immediate medical care; in conjunction with its administration, patients should seek appropriate medical care. More than two sequential doses of epinephrine should only be administered under direct medical supervision.[4-7]

Epinephrine should only be injected into the anterolateral aspect of the thigh. Avoid accidental injection into the hands or feet as this may result in loss of blood flow to the area. Furthermore, epinephrine should not be injected into the buttock. If an accidental injection occurs, patients should inform a health care provider when he/she goes to the nearest emergency room for further treatment of anaphylaxis.[4-7]

Possible inadvertent intravascular administration should also be avoided. Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to a sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effect of epinephrine if there is such inadvertent administration.[4-7]

Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations even though Adrenaclick®, Auvi-Q®, epinephrine contain sodium bisulfate and EpiPen® and EpiPen Jr® contain sodium metabisulfite, which are sulfites that may, in other products, cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. Because the alternatives to epinephrine in a life-threatening situation may not be satisfactory, the presence of a sulfite should not deter administration of the agent for the treatment of serious allergic or other emergency situations, even in a sulfite-sensitive patient.[4-7]

Drug Interactions

Table 5. Drug Interactions

Generic Name	Interacting Medication or Disease	Potential Result
Epinephrine	β-blockers	Concurrent use may result in an initial hypertensive episode, followed by bradycardia.
Epinephrine	Furazolidone	Furazolidone may increase the pressor sensitivity to epinephrine, possibly resulting in hypertension.
Epinephrine	Guanethidine	Guanethidine may potentiate the effects of epinephrine and inhibit the effect of epinephrine that depends upon the release of norepinephrine for activity.
Epinephrine	Methyldopa	Concurrent use may result in an increased pressor response, possibly resulting in hypertension.
Epinephrine	Monoamine oxidase inhibitors	Concurrent use may cause hypertensive crisis.
Epinephrine	Rauwolfia alkaloids	Rauwolfia alkaloids may potentiate the pressor response of epinephrine which may result in hypertension.
Epinephrine	Tricyclic antidepressants	Tricyclic antidepressants may potentiate the pressor response of epinephrine; dysrhythmias have occurred.

Dosage and Administration

The epinephrine for anaphylaxis agents are available as self-administered auto-injectors, which deliver one dose of epinephrine at strength of either 0.15 or 0.3 mg. Any remaining volume that is left after administration cannot be further administered and should be discarded with the device. As mentioned previously, these agents are not intended as a substitute for immediate medical care. In conjunction with its administration, patients should seek appropriate medical care. More than two sequential doses of epinephrine should only be administered under direct medical supervision.[4-7]

Table 6. Dosing and Administration[4-7]

Generic Name	Usual Dose	Availability
Epinephrine	Emergency treatment of severe allergic reactions (Type 1) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants), biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as anaphylaxis to unknown substances (idiopathic anaphylaxis) or exercise-induced anaphylaxis: Injection: 0.15 (15 to 30 kg) or 0.3 mg (≥30 kg)	Injection: 0.15 mg/0.15 mL (Adrenaclick®*, Auvi-Q®*, epinephrine*) 0.15 mg/0.3 mL (EpiPen Jr®*) 0.3 mg/0.3 mL (Adrenaclick®*, Auvi-Q®*, epinephrine*, EpiPen®*)

*Only available in a two pack containing two auto-injectors.

Clinical Guidelines

Table 7. Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology and the Joint Council of Allergy,	Evaluation and management of the patient with a history of episodes of anaphylaxis • In the management of a patient with a previous episode of anaphylaxis, education is necessary. Emphasis on early treatment, specifically the self-administration of epinephrine, is essential. • Instruct patient to wear and/or carry identification denoting the

Clinical Guideline	Recommendations
Asthma and Immunology: **The Diagnosis and Management of Anaphylaxis Practice Parameter: 2010 Update (2010)**[11]	condition and have telephone numbers for paramedic rescue squads and ambulance services on hand. • A written action plan can be helpful in this regard. <u>Office management of anaphylaxis</u> • Anaphylaxis is an acute, life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden systemic release of mediators from mast cells and basophils. • The more rapidly anaphylaxis develops, the more likely the reaction is to be severe and potentially life-threatening. • Prompt recognition of signs and symptoms of anaphylaxis is crucial. If there is any doubt, it is generally better to administer epinephrine. • Epinephrine and oxygen are the most important therapeutic agents administered in anaphylaxis. Epinephrine is the drug of choice, and the appropriate dose should be administered promptly at the onset of apparent anaphylaxis. • Appropriate volume replacement either with colloid or crystalloids and rapid transport to the hospital are essential for patients who are unstable or refractory to initial therapy for anaphylaxis in the office setting. <u>Anaphylaxis to foods</u> • The rapid use of injectable epinephrine has been shown to be effective in the initial management of food-induced anaphylaxis, but subsequent doses may be needed. • Patients who experience anaphylaxis should be observed for longer periods if they have experienced food-induced anaphylaxis. • Food-dependent, exercise-induced anaphylaxis (EIA) is a unique clinical syndrome in which anaphylaxis occurs within a few hours of specific food ingestion or any meal, and exercise. <u>Natural rubber latex–induced anaphylaxis</u> • Patients with a diagnosis of natural rubber latex allergy by history and/or skin testing can wear a medical identification bracelet, carry a medical identification card, or both. • If patients have a history of anaphylaxis to natural rubber latex allergy, it is important for them to carry auto-injectable epinephrine. <u>EIA</u> • All patients with EIA must be advised to stop exercising immediately at the first sign of symptoms because continued exertion causes the attacks to worsen. • All patients should carry epinephrine auto-injectors and exercise with a partner who can recognize symptoms and administer epinephrine if necessary. • Prophylactic medications are not effective for preventing attacks in the majority of patients, although a small subset does appear to benefit from daily administration of H1 antihistamines. <u>Idiopathic anaphylaxis</u> • Empiric use of oral corticosteroids combined with H1 antagonists has been demonstrated to reduce the frequency/severity of episodes. • Patients with idiopathic anaphylaxis should carry epinephrine, should

Clinical Guideline	Recommendations
	know the indications for self-administration, and can carry information denoting their condition. Insect sting anaphylaxis • Patients discharged from emergency care for anaphylaxis should be given auto-injectable epinephrine, receive instruction in its proper use and indications for use, and be advised to set up an appointment with an allergist-immunologist. • Patients should understand that using auto-injectable epinephrine is not a substitute for emergency medical attention. • Venom immunotherapy (VIT) should be recommended for patients with systemic sensitivity to stinging insects because this treatment is highly (90 to 98%) effective.
National Institute of Allergy and Infectious Diseases: **Guidelines for the Diagnosis and Management of Food Allergy in the United States (2010)**[12]	Treatment in the hospital based setting • Prompt and rapid treatment after onset of symptoms. The benefits of appropriate treatment for anaphylaxis begin with intramuscular (IM) epinephrine injection. Benefits of epinephrine treatment far outweigh the risks of unnecessary dosing. • Delays in instituting therapy with epinephrine are associated with risks of death and morbidity. • IM epinephrine is recommended over subcutaneous injection because it provides a more rapid increase in plasma and tissue concentrations of epinephrine. • The IM dose should be given in the anterolateral thigh in the vastus lateralis muscle. The needle used should be of adequate length to reach the muscle beneath the subcutaneous adipose tissue over the vastus lateralis muscle. • IM injection into the thigh may be impossible in overweight or obese individuals, especially women who have thicker subcutaneous fat tissue. In the circumstance of inadequate IM dosing, subcutaneous dosing will provide some benefit but will be less effective than IM dosing. • When an epinephrine auto-injector is used, children weighing less than 25 kg should receive the 0.15 mg dose. • Children over 25 kg through adults should receive the 0.3 mg dose auto-injector. When a 1:1,000 epinephrine solution is used, patients should receive a dose of 0.01 mg/kg with a maximum dose of 0.5 mg. • Intravenous (IV) epinephrine (1:10,000 solution) is recommended for patients who do not respond to an initial (or repeated) IM injection of epinephrine and fluid resuscitation and may not be adequately perfusing muscle tissues. • For the treatment of bronchospasm not responsive to IM epinephrine, inhaled bronchodilators such as albuterol should be used as needed and should be considered to be adjunctive therapy to the administration of epinephrine. • Albuterol does not relieve airway edema (for example, laryngeal edema) and should not be substituted for IM epinephrine dosing in the treatment of anaphylaxis. • Very limited scientific evidence supports the use of H1 antihistamines in the emergency treatment of anaphylaxis. • H1 antihistamines are useful only for relieving itching and urticaria but do not relieve stridor, shortness of breath, wheezing, gastrointestinal symptoms, or shock.

Clinical Guideline	Recommendations
	• They should be considered adjunctive therapy and should not be substituted for epinephrine. • For oral and IV dosing, first generation H1 antihistamines such as diphenhydramine are used. • Minimal evidence supports the use of H2 antihistamines in the emergency treatment of anaphylaxis. • Very little evidence supports or refuted the use of corticosteroids for the treatment of acute anaphylaxis. Empiric use is prevalent and supported by many health care professionals. • Corticosteroids are not helpful in the treatment of acute anaphylaxis due to their slow onset of action (four to six hours). These agents often are given because of their anti-inflammatory properties that benefit allergic and inflammatory disease and also because they may help prevent biphasic or protracted reactions. • Patients who have persistent hypotension despite the administration of epinephrine and IV fluids should receive vasopressor medications titrated to the desired effect of restoring blood pressure. • In patients treated with β adrenergic antagonists, glucagon should be administered because it has inotropic and chronotropic effects that are not mediated through β receptors. • A single dose of 1 to 5 mg in adults (in children, 20 to 30 mg/kg, to a maximum of 1 mg) administered intravenously over five minutes is recommended, which may be repeated or followed by an infusion of 5 to 15 mg/minute. • Consider IV administered atropine for patients with bradycardia. • Oxygen should be administered initially to all patients experiencing anaphylaxis, especially those with evidence of hypoxia or respiratory distress. • Many patients with anaphylaxis require IV fluids. Any patient who does not respond promptly and completely to injected epinephrine should be assumed to have intravascular volume depletion causing persistent hypotension despite maximum vasoconstriction. • These patients should receive large-volume fluid resuscitation, with normal saline being the preferred treatment. • Large-volume fluid resuscitation should be initiated immediately in patients who present with orthostasis, hypotension, or incomplete response to IM epinephrine. <u>Therapy for patients at discharge</u> • Epinephrine auto-injector prescription (two doses) and instruction. • Education on avoidance of allergen. • Follow-up with primary care physician. • Consider referral to an allergist. <u>Adjunctive treatment</u> • H1 antihistamine: diphenhydramine every six hours for two to three days. • H2 antihistamine: ranitidine twice daily for two to three days. • Corticosteroid: prednisone daily for two to three days.
Joint Council of Allergy, Asthma and Immunology: **Food Allergy: A Practice Parameter (2006)**[13]	• Management entails avoiding foods or beverages that contain the implicated additive and using self-injectable epinephrine for life-threatening reactions, especially for individuals who are sulfite

Clinical Guideline	Recommendations
	sensitive. • Although aqueous epinephrine solutions are sulfited, their sulfite content is only 0.3 mg per usual dose. This is below the level at which known sulfite-sensitive individuals will react; therefore, epinephrine should not be withheld from sulfite-sensitive patients and should be used to treat anaphylaxis. • Management of food-dependent EIA entails avoiding exercising in proximity to food consumption, carrying self-injectable epinephrine, exercising with a "buddy," and wearing medic-alert jewelry. • Delay in the administration of injectable epinephrine is a common feature of fatal food allergic reactions. • Schools and childcare centers should have policies ensuring prompt treatment of food anaphylaxis, including a requirement for physician-prescribed treatment protocols for food allergic students, staff education regarding recognition and treatment of anaphylaxis, and the ready availability of injectable epinephrine. • If there is a history of suspected or proven IgE-mediated systemic reactions to foods, injectable epinephrine should be given to patients and/or caregivers to carry with them and they should be instructed in its use.
American Academy of Allergy, Asthma and Immunology: **Anaphylaxis in Schools and Other Child-Care Settings (2005)**[14]	• Epinephrine is the first drug that should be used in the emergency management of a child having a potentially life-threatening allergic reaction. • Epinephrine injection is available in a number of self-administration delivery devices. • There are no contraindications to the use of epinephrine for a life-threatening allergic reaction. • In patients who have had anaphylactic reactions, it is recommended that epinephrine be given at the start of any reaction occurring in conjunction with exposure to a known or suspected allergen. • In situations where there has been a history of a severe cardiovascular collapse to an allergen, the physician may advocate that epinephrine be administered immediately after an insect sting or ingestion of the offending food and before any reaction has begun. • All individuals receiving emergency epinephrine should immediately be transported to a hospital even if symptoms appear to have resolved. • In the majority of cases, epinephrine will be effective after one injection; however, further treatments may be required, and therefore observation in a hospital setting is necessary for at least four hours after initial symptoms subside because delayed and prolonged reactions may occur even after proper initial treatment. • Additional epinephrine should be available during transport and may be administered every 15 to 20 minutes as required, preferably following medical advice. This should only be given in situations where the allergic response is not under adequate control (e.g., the patient's breathing becomes more labored or the patient has a decreasing level of consciousness). • The need for multiple injections indicates the need for other emergency drugs. Therefore it is important when planning trips or camping outdoors that everyone consider how they would manage a medical emergency. • Epinephrine should be kept in locations that are easily accessible and

Clinical Guideline	Recommendations
	not in locked cupboards or drawers. • All staff members should know these locations. Children old enough to self-administer epinephrine should carry their own kits. • For younger children, the epinephrine device should be kept in the classroom and passed from teacher to teacher as the child moves through the school. • All students, regardless of whether they are capable of epinephrine self-administration, will still require the help of others because the severity of the reaction may hamper their attempts to inject themselves. Adult supervision is mandatory. • This should include additional formal training on how to use epinephrine devices. Training programs may be through health departments or physicians' groups to ensure that all individuals in schools and other areas of child care are qualified in these techniques.
American Academy of Allergy, Asthma & Immunology, American College of Allergy, Asthma & Immunology and the Joint Council of Allergy, Asthma and Immunology: **Stinging Insect Hypersensitivity: A Practice Parameter Update 2011 (2011)**[15]	• Most insect stings cause mild local reactions for which no specific treatment is usually required. • Some local reactions are manifested by extensive swelling surrounding the sting site that can persist for several days or more and might be accompanied by itching, pain, or both. • Cold compresses might help to reduce local pain and swelling. Oral antihistamines and oral analgesics might also help to reduce the pain or itching associated with cutaneous reactions. • Many physicians use oral corticosteroids for large local reactions, although definitive proof of efficacy through controlled studies is lacking. • Because the swelling (and even lymphangitis) is caused by mediator release and not by infection, antibiotics are not indicated unless there is evidence of secondary infection (a common misdiagnosis). • Large local reactions are usually IgE mediated but are almost always self-limited and rarely create serious health problems. • Patients who have previously experienced large local reactions often have large local reactions to subsequent stings, and up to 10% might eventually have a systemic reaction. Some patients who have had large local reactions seek guidance on insect avoidance measures. • In patients who have had large local reactions, it is optional to prescribe injectable epinephrine for use if the patient experiences a systemic reaction in the future. • The vast majority of patients with large local reactions need only symptomatic care and are not candidates for testing for venom-specific IgE or for VIT. • There is, however, growing evidence that VIT significantly reduces the size and duration of large local reactions and thus might be useful in affected subjects with a history of unavoidable, frequent, or both large local reactions and detectable venom-specific IgE. • Injectable epinephrine should be provided, and the patient should be instructed in its proper administration and use. • Patients should also consider obtaining and carrying a medical identification bracelet or necklace. • A patient with a history of severe reaction should have injectable epinephrine prescribed because even if the test result for venom-specific IgE is negative, there is a small risk of another systemic reaction.

Clinical Guideline	Recommendations
	• Referral to an allergist is appropriate for any patient who has had an allergic reaction and is indicated for any patient who is a potential candidate for immunotherapy. • Preventive management includes measures to prevent subsequent stings and to prevent subsequent systemic reactions if the patient is stung.

Conclusions

Anaphylaxis, a potentially fatal disorder, is an acute, multisystem syndrome resulting from a sudden release of mast cell- and basophil-derived mediators into the circulation.[1] Foods, medications and insect stings that cause a subsequent immunologic reaction are the most common reason for an anaphylactic reaction to occur. In humans, the heart, vasculature system and lungs are predominantly affected during anaphylaxis, and fatalities can result from circulatory collapse and respiratory arrest.[1,2] Epinephrine is the recognized treatment of choice for such severe allergic reactions, as it is the only pharmacologic intervention that prevents and reverses obstruction to airflow in the upper and lower respiratory tracts.[11-15] Acting as an agonist at α1, β1 and β2 adrenergic receptors, epinephrine works in the emergency treatment of anaphylaxis by causing increased vasoconstriction (α1), increased peripheral vascular resistance (α1), decreased mucosal edema (α1), increased inotropy (β1), increased chronotropy (β1), increased bronchodilation (β2) and decreased release of mediators of inflammation from mast cells and basophils (β2). Of note, clinical trials evaluating epinephrine for emergency anaphylaxis treatment will never be performed, due to ethical considerations in a disorder that can kill within minutes and mandates prompt epinephrine administration.[3]

Included in this review are the epinephrine for anaphylaxis agents (Adrenaclick®, Auvi-Q®, EpiPen® and EpiPen Jr®) which are all Food and Drug Administration (FDA)-approved for the emergency treatment of severe allergic reactions. As noted in their FDA-approved package labeling, epinephrine is essential for the treatment of anaphylaxis and these agents are designed for emergency supportive therapy. They are not intended to substitute immediate medical care; in conjunction with the administration of one of these agents, patients should seek the appropriate medical care.[4-7]

All of the epinephrine for anaphylaxis agents are available as single use, auto-injectors to be administered, by the patient or caregiver, as an intramuscular or subcutaneous injection into the anterolateral aspect of the thigh.[4-7] Differences among the various epinephrine agents are minimal and include specific packaging and administration requirements. Auvi-Q® is the only epinephrine auto-injector that contains with audio instructions to guide patients and caregivers through the injection process. Each agent is available as a 0.15 and 0.3 mg injection, and generics are available within the class.

References

1. Kemp SF. Pathophysiology of anaphylaxis. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Jun 21]. Available from: http://www.utdol.com/utd/index.do.
2. No authors listed. Part 10.6: anaphylaxis. Circulation. 2005;000:IV-143-IV-145.
3. Estelle F, Simons R. Anaphylaxis: rapid recognition and treatment. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2013 [cited 2013 Jun 21]. Available from: http://www.utdol.com/utd/index.do.
4. Adrenaclick® [package insert]. Horsham (PA): Amedra Pharmaceuticals LLC.; 2013 Apr.
5. Epinephrine [package insert]. Horsham (PA): Lineage Therapeutics; 2013 Apr.
6. EpiPen®, EpiPen Jr® [package insert]. Basking Ridge (NJ): Mylan Specialty L.P.; 2012 Aug.
7. Auvi-Q® [package insert]. Bridgewater (NJ): Sanofi-Aventis.; 2012 Sep.
8. Simons FER, Gu X, Simons KJ. Epinephrine absorption in adults: intramuscular vs subcutaneous injection. J Allergy Clin Immunol. 2001;108(5):871.
9. Simons FER, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. J Allergy Clin Immunol. 1998;101(1 pt 1):33.
10. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Reuters (Healthcare) Inc.; Updated periodically [cited 2013 Jun 21]. Available from: http://www.thomsonhc.com/.
11. Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol. 2010 Sep;126(3):477-80.
12. National Institute of Allergy and Infectious Diseases: Guidelines for the Diagnosis and Management of Food Allergy in the United States (2010). 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 Dec;126(6 Suppl):S1-58.
13. American College of Allergy, Asthma, & Immunology. Food allergy: a practice parameter. Ann Allergy Asthma Immunol. 2006 Mar;96(3 Suppl 2):S1-68.
14. [No authors listed]. Anaphylaxis in schools and other childcare settings. AAAAI Board of Directors. American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 1998 Aug;102(2):173-6.
15. Golden DB, Moffitt J, Nicklas RA, Freeman T, Graft DF, Reisman RE, et al. Stinging insect hypersensitivity: a practice parameter update 2011. J Allergy Clin Immunol. 2011 Apr;127(4):852-4.e1-23.