American Red Cross

Scientific Advisory Council

ARC SAC Scientific Review
Epinephrine Auto-Injector

Questions to be addressed:

Should lay rescuers be taught how to assist patients by administering epinephrine (auto-injector) during an anaphylactic reaction?

Review Process and Literature Search of Evidence Since Last Approval Performed

Search Strategy:

- Cochrane Database for systematic reviews.
- PubMed via OVID, UVA, 2006 to 2012
- Key word search for (epinephrine OR Epipen OR 'autoinjector') AND (anaphylaxis) in PubMed (231 hits, 27 selected for possible further review)
- Key word search for (first aid) AND (anaphylaxis) in PubMed (24 hits, 13 included for review
- MESH headings, title or abstract search for "epinephrine" AND "autoinjector" OR "Epipen" in PubMed (31 hits, 9 included for review)
- MESH headings for "epinephrine" AND "first aid" (28 hits, 12 included for review)
- Review of references from articles retrieved.
- Review of findings and recommendations from the 2010 ARC/AHA International First Aid Science Advisory Committee Worksheets FA-302A and B (Does the administration of a second dose of injectable epinephrine improve outcome from a severe allergic reaction?) and FA-303B (Can the first aid provider appropriately recognize signs and symptoms of anaphylaxis?).

Inclusion and Exclusion Criteria:

- English only, humans only, links to full text, abstracts, 2006 - 2011; Articles about epinephrine treatment by routes such as inhalation or sublingual were excluded. Selected major review articles included to assist with identifying studies not found in initial literature search. After elimination of duplicate citations and screening for relevance, a total of 19 articles were included for this review.

Updated Scientific Foundation:

Summary of Key Articles/Literature Found and Level of Evidence:

- **Anaphylaxis is a serious allergic reaction of rapid onset and that may be fatal within minutes.** The definition of anaphylaxis has varied in the past depending on the author, but the definition above is now commonly used in the medical literature and based on a similar definition originally proposed at a symposium sponsored by the National Institute of Health and the Food Allergy and Anaphylaxis Network (Sampson, 2006). The four most common triggers are foods, insect stings, medications, and natural rubber latex (Sheikh, 2008). Skin symptoms and signs such as angioedema or urticaria are the most common manifestation (90%), followed by respiratory (70%), gastrointestinal (40%) and cardiovascular symptoms (hypotension, 10 – 30%). The median time to respiratory or cardiac arrest is reported to be 30 minutes for food and 15 minutes for venom-induced anaphylaxis (Pumphrey 2004, 2007). More than 1% of the general population may be affected by anaphylaxis (Sheikh, 2008).
- **Epinephrine is widely considered the initial treatment of choice for anaphylaxis** (Lieberman 2010, Kemp 2008, Sheik 2008, Sicherer 2007, Simons 2010). There are no randomized, controlled trials of epinephrine in anaphylaxis, and placebo controlled trials are considered unethical since all anaphylaxis guidelines and the WHO state that epinephrine is fundamentally important in anaphylaxis management (Sheik 2010). The use of epinephrine for anaphylaxis is based on longstanding clinical use, fatality studies, epidemiologic studies, prospective studies in animal models, dramatic observational nonrandomized uncontrolled studies of patients experiencing anaphylaxis at the time of the investigation, and randomized controlled studies in patients not experiencing anaphylaxis at the time of the investigation. (Simons 2010).
- **The standard of first aid treatment for anaphylaxis occurring in the community, non-medical setting is self-injectable intramuscular epinephrine** into the anterolateral thigh using an epinephrine autoinjector such as EpiPen, AnaPen,or Twinject (Sheikh 2008, Sicherer 2007, Simons 2010).
- **Delayed injection of epinephrine in anaphylaxis is potentially associated with poor outcomes including fatal anaphylaxis or biphasic reactions** (Greenberger 2007, Simons 2010, Bock 2001, Sampson 2006, Pumphrey 2004, 2007). **Urticaria may be less common in fatal cases**. *(Greenberger 2007)*
- **The initial dose of epinephrine for anaphylaxis**, 0.01 mg/kg of a 1:1000 formulation to a maximum dose of 0.5 mg in an adult or 0.3 mg in a child, is based on tradition and clinical consensus. **Between 18 and 35% of those receiving epinephrine will require a second dose**, usually within 5 – 15 minutes after the first dose (Sicherer 2007, Golden 2004, Gaines 2007). Studies on use of a second dose of epinephrine are retrospective observational epidemiologic studies with no standardized criteria for the decision to administer a subsequent dose of epinephrine (Markenson 2010, Worksheet FA-302A)
- The **currently available epinephrine auto injectors** in the USA are expensive and have limited shelf life. They include:
    - EpiPen 0.3mg (adult) and EpiPen Jr 0.15mg (pediatric), both of which are available as a 2-pack. The Epipen Jr is intended for use in pediatric patients between 33 and 66 lbs. Infant dose epinephrine autoinjectors are not available.

EpiPens have recently been redesigned to address concerns of needle exposure pre and post use, accidental digital injection of epinephrine, and inadequate needle length to reach thigh musculature. The 2-pack EpiPen costs $272 at one popular pharmaceutical supplier online.

  - TwinJect 0.15 mg (pediatric) and 0.3 mg (adult), allow use of a second injection and costs $177 at one popular pharmaceutical supplier online.
  - Intellijject has received initial FDA approval for their novel Epicard autoinjector device for administration of epinephrine. This device has potential advantages of smaller size/greater likelihood of being carried by the recipient, voice prompts and ease of use including 5 second injection time vs 10 seconds for alternative brands (Guerlain 2/2010 and 12/2010)
  - All epinephrine autoinjectors have an expiration of 12 – 20 months when stored at room temperature. Epinephrine degrades rapidly at higher temperatures and may need to be replaced as often as every 3 months at 38 degrees. Autoinjectors now include a window to view the epinephrine solution, and if the fluid is discolored or cloudy, it should be discarded.

- **Studies looking at the use of epinephrine autoinjectors by first-aiders are few, but there is new evidence that first aid providers have difficulty in assessing and recognizing signs and symptoms of anaphylaxis and are less likely to use epinephrine autoinjectors for anaphylaxis with respiratory or circulatory compromise than are paramedics** (Markenson 2010, Capps (2010). Capps concluded that the lack of correlation between clinical severity and epinephrine use by first aiders suggests that they may often not understand the correct clinical indications for the drug. This is consistent with findings by Epstein in FA 303-B, Jan 2010 (Can the First Aid Provider Appropriately Recognize the Signs and Symptoms of Anaphylaxis?) which concludes “the evidence evaluated does not support expanding the role of the first aid provider to ‘diagnose’ an anaphylactic reaction in a victim not previously diagnosed with anaphylaxis”, and that “even trained medical professionals have difficulty making a correct assessment and diagnosis” (Markenson 2010).
- Thus, the current review of evidence supports the previously approved statement that **first aiders should be restricted to use of epinephrine autoinjectors in individuals who identify themselves as having a diagnosis of anaphylaxis/severe allergies, have been previously prescribed and provide an epinephrine autoinjector, and state they are having an anaphylactic or severe allergic reaction and require assistance.** First aid education should clearly describe signs and symptoms of anaphylaxis (acute onset of illness with skin or mucosal involvement PLUS respiratory difficulty or syncope/collapse), indications for use /assisting in the administration of epinephrine autoinjectors, and technique for use of the various autoinjectors commonly available.

Citations

Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol. 2001; 107:191–193

Summary: A retrospective review of fatalities from anaphylaxis due to food. LOE 2C

Capps JA, Sharma V, Arkwright PD: Prevalence, outcome and pre-hospital management of anaphylaxis by first aiders and paramedical ambulance staff in Manchester, UK. Resuscitation 81 (2010) 653–657.

Summary: A retrospective study of all emergency calls for allergic reactions within Greater Manchester in a 12-month period by the North West Ambulance Service of the United Kingdom. Results: 816 (0.2%) of 401,152 incidents were due to allergic reactions (32/100,000/year). No patients died. In 457 (56%) patients this was the first allergic reaction. Intramuscular adrenaline was administered to 116 (14%) patients. Patients with respiratory/circulatory compromise were significantly more likely to be given intramuscular adrenaline by paramedics (14 (4.4–45)), but not by first aiders (1.9 (0.98–3.6)). Administration of adrenaline by first aiders was more likely in patients with a past history of allergic reactions (4.3 (2.3–8.1)) and where reactions occurred at non-residential addresses (4.6 (2.6–8.2)). Conclusions…Most cases were successfully managed without intramuscular adrenaline. Adrenaline appeared to be used appropriately by paramedics. The lack of correlation between clinical severity and adrenaline use by first aiders suggests that they may often not understand the correct clinical indications for this drug. LOE 2B

Gaines AD: Self-injectable Epinephrine for First-Aid Management of Anaphylaxis. (letter) *Pediatrics* 2007;120;238.

Summary: Patients 16 years of age and younger who have experienced cutaneous systemic reactions without other allergic manifestations have approximately a 10% chance of having a systemic reaction if re-stung. If a systemic reaction does occur, it is likely to be limited to the skin, and usually a milder reaction than the initial one. LOE 7.

Golden DB, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Outcomes of allergy to insect stings in children, with and without venom immunotherapy. N Engl J Med. 2004; 351:668 – 674

Summary/Abstract: Follow-up data were obtained on 89 children with initial mild cutaneous systemic reactions who had not received venom immunotherapy. When subsequently stung, 87% of the children had no systemic reaction, 6.74% had another mild cutaneous systemic reaction, 6.74% had a moderate systemic allergic reaction, and none had a severe allergic reaction. A moderate systemic reaction was defined as "signs and symptoms of a cutaneous reaction as well as discomfort in the throat or chest, mild symptoms of airway obstruction, light-headedness, and dizziness or mild hypotension," a description that is consonant with the current definition of anaphylaxis. LOE 3B.

Greenberger PA, Rotskoff BD, Lifschultz B. Fatal anaphylaxis: postmortem findings and associated comorbid diseases. Ann Allergy Asthma Immunol. 2007 Mar; 98(3):252-7. PMID:17378256

Summary: A retrospective case review of 25 unselected cases of documented fatal anaphylaxis. Each case report contained details of the fatal reaction, a review of the medical record, and laboratory and autopsy findings. LOE 2C.

Guerlain S, Wang L, Hugine A. Intellijject's novel epinephrine autoinjector: sharps injury prevention validation and comparable analysis with EpiPen and Twinject. Ann Allergy Asthma Immunol. 2010 Dec;105(6):480-4. PMID:21130387

Summary: Description of new epinephrine autoinjector and benefits of use. LOE 6

Guerlain S, Hugine A, Wang L: A comparison of 4 epinephrine autoinjector delivery systems: usability and patient preference. Ann Allergy Asthma Immunol. 2010 Feb;104(2):172-7. PMID:20306821

Summary: Trial use by compensated volunteers that found the majority preferred using a novel epinephrine autoinjector. Funded by manufacturer. LOE 6.

Kemp SF, Lockey RF, Simons FE; World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy. 2008 Aug;63(8):1061-70. Review. PubMed PMID: 18691308.

Abstract:
Anaphylaxis is an acute and potentially lethal multi-system allergic reaction. Most consensus guidelines for the past 30 years have held that epinephrine is the drug of choice and the first drug that should be administered in acute anaphylaxis. Some state that properly administered epinephrine has no absolute contraindication in this clinical setting. A committee of anaphylaxis experts assembled by the World Allergy Organization has examined the evidence from the medical literature concerning the appropriate use of epinephrine for anaphylaxis. The Committee strongly believes that epinephrine is currently underutilized and often dosed suboptimally to treat anaphylaxis, is under-prescribed for potential future self-administration, that most of the reasons proposed to withhold its clinical use are flawed, and that the therapeutic benefits of epinephrine exceed the risk when given in appropriate i.m. doses.

Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM: The diagnosis and management of anaphylaxis practice parameter: 2010 Update. J Allergy Clin Immunol 2010; 126:477-80

Summary/Abstract: Practice parameters developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma and Immunology. Confirms: The initial drug of choice is epinephrine.33-37 The following are salient points regarding administration of epinephrine:
-The concentration is1:1000 and the adult dose is 0.2 to 0.5 ml (mg). The dose in a child is 0.01 ml (mg)/kg. The time to highest blood concentration (Cmax), when studied in asymptomatic subjects, is shorter when injection is given intramuscularly in the vastus lateralis muscle (lateral thigh) than when it is administered either subcutaneously or intramuscularly in the deltoid muscle of the arm. There are no outcome data comparing these routes of administration during anaphylaxis. There are no data indicating that epinephrine is ineffective when administered either subcutaneous or intramuscular in the deltoid muscle of the arm.
- Epinephrine may be administered every 5 to 10 minutes as necessary.
-All patients should carry epinephrine auto injectors and exercise with a partner who can recognize symptoms and administer epinephrine if necessary.

LOE 5.

Markenson D, Ferguson JD, Chameides L, Cassan P, Chung KL, Epstein JL, Gonzales L, Hazinski MF, Herrington RA, Pellegrino JL, Ratcliff N, Singer AJ; First Aid Chapter Collaborators. Part 13: First aid: 2010 American Heart Association and American Red Cross International Consensus on First Aid Science With Treatment Recommendations. Circulation. 2010 Oct 19;122(16 Suppl 2):S582-605.
PMID: 209562615

Summary:
Recognition of Anaphylaxis by First Aid ProvidersFA-303B
Consensus on Science
Four LOE 417–20 and 3 LOE 521–23 studies documented the difficulty that first aid providers have in assessing and recognizing signs and symptoms of anaphylaxis. Evidence from 1 LOE 4 study24 demonstrated that parents of children with multiple anaphylactic reactions can more accurately begin to recognize the signs and symptoms indicating the need for administration of an auto-injector, but with a lack of training and experience, they are unable to provide appropriate care.
Treatment Recommendation
First aid providers should not be expected to recognize the signs and symptoms of anaphylaxis without repeated episodes of training and encounters with victims of anaphylaxis.
Knowledge Gaps
How can a first aid provider determine that a witnessed allergic reaction needs epinephrine? Are there anaphylactic reactions that do not respond to epinephrine?
Second Dose of EpinephrineFA-302A, FA-302B
Consensus on Science
One small, retrospective LOE 4 chart review,25 1 LOE 4 retrospective patient survey,26 and 1 LOE 4 retrospective chart review of children with food allergy27 found that 12% to 36% of patients with anaphylactic reactions received a second dose of epinephrine because the first dose did not relieve symptoms. Two LOE 428,29 and 2 LOE 5 studies30,31 documented adverse reactions, including fatalities, due to misdiagnosis of an anaphylactic reaction, inappropriate route of administration, or excessive doses of epinephrine. One LOE 3 retrospective study32 demonstrated that 20% of anaphylactic reactions are biphasic, with a mean of 10 hours between 2 symptomatic episodes.
Treatment Recommendation
There is insufficient evidence for or against the routine first aid administration of a second dose of epinephrine.
LOE 5.

Pumphrey RS. Fatal anaphylaxis in the UK, 1992–2001. Novartis Found Symp. 2004;257:116–128

Summary: Retrospective review of 196 fatalities due to anaphylaxis with identification of causes, time to death, and common features. LOE 2C

Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999-2006. J Allergy Clin Immunol. 2007 Apr;119(4):1018-9.

Summary: Additional data from retrospective review of fatalities in the UK due to anaphylaxis, including information on fatalities in individuals who used epinephrine autoinjectors. LOE 2C

Sampson HA, Mendelson LM, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. N Engl J Med. 1992;327:380–384.

Summary: Retrospective review of fatalities in 6 children/adolescents due to anaphylaxis. LOE 2C.

Sampson HA, Munoz-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;117:391–397

This article describes: Clinical Criteria for Diagnosing Anaphylaxis (Fulfilling Any 1 Criterion Indicates That Anaphylaxis Is Highly Likely):
Criterion 1:
Acute onset of an illness (minutes to several hours) with involvement of the skin and/or mucosal tissue (eg, generalized hives, pruritus, or flushing, swollen lips/ tongue/uvula) and at least 1 of the following:
a. Respiratory compromise (eg, dyspnea, wheeze/ bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
Criterion 2:
Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin/mucosal tissue (eg,, generalized hives, itch/flush, swollen lips/tongue/uvula) b. Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
c. Reduced blood pressure or associated symptoms(eg, hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
Criterion 3:
Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)

LOE 5

Shaker M, Woodmansee D, Kay Wolfson M, Goodman D: Self-injectable Epinephrine for First-Aid Management of Anaphylaxis. (letter) *Pediatrics* 2007;120;238

Summary: The decision to prescribe prophylactic self-injectable epinephrine for children with generalized acute urticaria after an insect sting should not be a universal recommendation. LOE 7

Sheikh Aziz, Shehata Yasser A, Brown Simon GA, Simons F Estelle R. Adrenaline (epinephrine) for the treatment of anaphylaxis with and without shock. Cochrane Database of Systematic Reviews: Reviews 2008 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD006312.pub2 (last update 2010)

Abstract:
Background
Anaphylaxis is a serious hypersensitivity reaction that is rapid in onset and may cause death. Adrenaline is recommended as the initial treatment of choice for anaphylaxis.
Objectives
To assess the benefits and harms of adrenaline (epinephrine) in the treatment of anaphylaxis.
Search strategy
In the previous version of our review, we searched the databases until March 2007. In this version we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, Issue 11), MEDLINE (1966 to November 2010), EMBASE (1966 to November 2010), CINAHL (1982 to November 2010), BIOSIS (to November 2010), ISI Web of Knowledge (to November 2010 and LILACS

(1982 to November 2010). We also searched websites listing ongoing trials and contacted pharmaceutical companies and international experts in anaphylaxis in an attempt to locate unpublished material.

Selection criteria

We included randomized and quasi-randomized controlled trials comparing adrenaline with no intervention, placebo or other adrenergic agonists were eligible for inclusion.

Data collection and analysis

Two authors independently assessed articles for inclusion.

Main results

We found no studies that satisfied the inclusion criteria.

Authors' conclusions

Based on this review, we are unable to make any new recommendations on the use of adrenaline for the treatment of anaphylaxis. Although there is a need for randomized, double-blind, placebo-controlled clinical trials of high methodological quality in order to define the true extent of benefits from the administration of adrenaline in anaphylaxis, such trials are unlikely to be performed in individuals with anaphylaxis. Indeed, they might be unethical because prompt treatment with adrenaline is deemed to be critically important for survival in anaphylaxis. Also, such studies would be difficult to conduct because anaphylactic episodes usually occur without warning, often in a non-medical setting, and differ in severity both among individuals and from one episode to another in the same individual. Consequently, obtaining baseline measurements and frequent timed measurements might be difficult, or impossible, to obtain. In the absence of appropriate trials, we recommend, albeit on the basis of less than optimal evidence, that adrenaline administration by intramuscular (i.m.) injection should still be regarded as first-line treatment for the management of anaphylaxis.

LOE 5.

Sicherer SH, Simons FE; American Academy of Pediatrics, Section on Allergy and Immunology. Self-injectable epinephrine for first-aid management of anaphylaxis. Pediatrics. 2007;119: 638 – 646

Summary: This clinical report focuses on practical issues concerning the administration of self-injectable epinephrine for first-aid treatment of anaphylaxis in the community. The recommended epinephrine dose for anaphylaxis in children, based primarily on anecdotal evidence, is 0.01 mg/kg, up to 0.30 mg. Intramuscular injection of epinephrine into the lateral thigh (vastus lateralis) is the preferred route for therapy in first-aid treatment. Epinephrine autoinjectors are currently available in only 2 fixed doses: 0.15 and 0.30 mg. On the basis of current, albeit limited, data, it seems reasonable to recommend autoinjectors with 0.15 mg of epinephrine for otherwise healthy young children who weigh 10 to 25 kg (22–55 lb) and autoinjectors with 0.30 mg of epinephrine for those who weigh approximately 25 kg (55 lb) or more. This article also describes the clinical criterion for diagnosing anaphylaxis, as adapted from Sampson HA, Munoz-Furlong A, Campbell RL, et al. J Allergy Clin Immunol. 2006;117:391–397.

“It seems appropriate to switch most children from the 0.15-mg dose to the 0.30-mg dose at approximately 25 kg (55 lb)—that is, to provide a slightly higher dose (0.012 mg/kg) rather than an underdose (0.006 mg/kg) for a 25-kg (55-lb) child….There are no data at this time to support specific recommendations for children who weigh less than 15 kg (33 lb).”

“Prompt administration of epinephrine is clearly indicated for treatment of significant respiratory or cardiovascular symptoms of anaphylaxis, but considerable judgment is required in many actual or possible allergic reactions in which life-threatening symptoms have not yet developed but may develop. Previous guidelines have suggested that epinephrine should be administered promptly at the onset of symptoms after exposure to an allergen that had previously caused anaphylaxis and possibly even in the absence of symptoms if there was a known exposure to an allergen that previously caused anaphylaxis with cardio-vascular collapse.

LOE 5.

Simons KJ and Simons FE: Epinephrine and its use in anaphylaxis: current issues. Current Opinion in Allergy and Clinical Immunology 2010, 10:354–361.

Abstract: We review the practical pharmacology of epinephrine in anaphylaxis, its intrinsic limitations, and the pros and cons of different routes of administration. We provide a new perspective on the adverse effects of epinephrine, including its cardiac effects. We describe the evidence base for the use of epinephrine in anaphylaxis. We discuss the role of epinephrine auto-injectors for treatment of anaphylaxis in community settings, including identification of patients who need an auto-injector prescription, current use of auto-injectors, and advances in auto-injector design. We list reasons why physicians fail to prescribe epinephrine auto-injectors for patients with anaphylaxis, and reasons why patients fail to self-inject epinephrine in anaphylaxis. We emphasize the primary role of epinephrine in the context of emergency preparedness for anaphylaxis in the community. Summary
Epinephrine is the medication of choice in the first-aid treatment of anaphylaxis in the community. For ethical reasons, it is not possible to conduct randomized, placebo- controlled trials of epinephrine in anaphylaxis; however, continued efforts are needed towards improving the evidence base for epinephrine injection in this potentially fatal disease. LOE 5.

Valentine M, Schuberth K, Kagey-Sobotka A. The value of immunotherapy with venom in children with allergy to insect stings. N Engl J Med. 1990;323:1601–1603.

Summary: 242 venom-allergic children 2 to 16 years of age with isolated cutaneous symptoms were randomly assigned to insect-venom immunotherapy or observation. In the treated group, 84 stings in 36 patients resulted in 1 systemic reaction (1.2% of stings). In contrast, 196 stings in 86 untreated children resulted in 18 systemic reactions (9.2% of stings). Of these 18 reactions, 16 were judged to be milder than the index reaction, 2 were similar, and none were more severe.

LOE 1A

Level of Evidence	Definitions (See manuscript for full details)
Level 1a	Population based studies, randomized prospective studies or meta-analyses of multiple studies with substantial effects
Level 1b	Large non-population based epidemiological studies or randomized prospective studies with smaller or less significant effects
Level 2a	Prospective, controlled, non-randomized, cohort or case-control studies
Level 2b	Historic, non-randomized, cohort or case-control studies
Level 2c	Case series: convenience sample epidemiological studies
Level 3a	Large observational studies
Level 3b	Smaller observational studies
Level 4	Animal studies or mechanical model studies
Level 5	Peer-reviewed, state-of-the-art articles, review articles, organizational statements or guidelines, editorials, or consensus statements
Level 6	Non-peer reviewed published opinions, such as textbook statements, official organizational publications, guidelines and policy statements which are not peer reviewed and consensus statements
Level 7	Rational conjecture (common sense); common practices accepted before evidence-based guidelines
Level 1-6E	Extrapolations from existing data collected for other purposes, theoretical analyses which is on-point with question being asked. Modifier E applied because extrapolated but ranked based on type of study.

Overall Recommendation

The available scientific evidence supports the position that early administration of epinephrine in an individual experiencing anaphylaxis plays a key role in reducing mortality.

Recommendations and Strength

Standards: There is no evidence to support a standard treatment.

Guidelines: The lay rescuer should be trained to assist with the administration of epinephrine by auto-injector or (where State regulations permit) to administer epinephrine by auto-injector when the patient indicates that they are having a severe allergic reaction or anaphylaxis, are awake, and provide a prescribed epinephrine auto-injector.

Options: A second dose of epinephrine may be required for continued signs or symptoms of anaphylaxis within 5 – 15 minutes after the first dose.

Implementation Suggestions

It is suggested that an epinephrine auto-injector training program be provided for lay rescuers, family members, and those at risk of anaphylaxis. This program would include an overview of allergic reactions including signs and symptoms of anaphylaxis, indications for use of epinephrine auto-injectors for anaphylaxis, as well as familiarization with techniques for administration of commonly available epinephrine auto-injectors.