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Anaphylaxis Rescue: Abbreviated Class Review

Month/Year of Review: November 2014 **End date of literature search:** September 2014
Drugs Included: Epinephrine auto-injector (Adrenaclick®, Auvi-Q™, EpiPen®, EpiPen Jr®)

Current Management: Anaphylaxis rescue is not currently listed as a drug class on the Preferred Drug List (PDL).

Research Questions:

- What is the evidence for efficacy and safety of epinephrine for the treatment of anaphylaxis rescue?
- What is the comparative efficacy and safety evidence of different self-administered formulations of epinephrine?
- Are there subgroups of patients where one formulation may be more effective or safer?

Conclusions:

- There is insufficient evidence from randomized, double-blind, placebo-controlled clinical trials to define the benefits from administering epinephrine for anaphylaxis due to ethical concerns.[1–3]
- There is moderate evidence from one systematic review[1] that intramuscular injection is superior to subcutaneous route.
- There is insufficient evidence comparing the effectiveness of administering epinephrine via auto-injector versus other injectable formulations.[3]
- Epinephrine is recommended as first-line initial therapy for anaphylaxis in both children and adults.[4–6] In addition, the auto-injector is recommended as the preferred injectable formulation in the community.[4–6]

Recommendations:

- Add “Anaphylaxis Rescue” as a drug class to the PDL under “Allergy/Cold” to include all auto injector products as preferred on the PDL.

Reason for Review:
Epinephrine, H_1-antihistamines, H_2-antihistamines, and systemic glucocorticosteroids are used for the initial treatment of anaphylaxis.[7] Epinephrine is the best studied medication in anaphylaxis[8]; however, it is not on the Preferred Drug List (PDL). This review will examine place in therapy for PDL placement and class inclusion.

Background:

Anaphylaxis is a serious allergic or hypersensitivity reaction that is rapid in onset and may cause death.[9,10] There are three recognized temporal patterns of anaphylaxis: uniphasic, biphasic, and protracted.[11] Uniphasic anaphylactic reactions are the most common type, accounting for an estimated 80 to 90 percent of all episodes. A uniphasic response usually peaks within 30 minutes to one hour after symptoms appear and resolves either spontaneously or with treatment within the next 30 minutes to one hour; a protracted anaphylactic reaction lasts hours to days without clearly resolving completely and biphasic reactions are characterized by a uniphasic response, followed by an asymptomatic period of an hour or more, and then a subsequent return of symptoms without further exposure to antigen.[11] In the United States, the lifetime prevalence of anaphylaxis is reported to be 1.6 percent, based on strict clinical diagnostic criteria.[12] The most common trigger factors include foods, insect venom, and medications.[4] In the health care setting, epinephrine, H_1-antihistamines, H_2-antihistamines, and systemic glucocorticosteroids are used for the initial treatment of anaphylaxis.[7] In anaphylaxis, no randomized controlled trials without methodological problems have been performed with above medications.[7] Epinephrine is the best studied medication in anaphylaxis. However, the evidence for its use comes from observational studies during anaphylaxis, randomized controlled clinical pharmacology studies at baseline, studies of anaphylaxis in animal models, and epidemiologic studies, including fatality studies. The evidence for use of H_1-antihistamines in anaphylaxis is extrapolated from their use in urticaria.[13,14] The evidence for the use of glucocorticosteroids in anaphylaxis is extrapolated from their use in acute asthma.[8]

Epinephrine is a α- and β- adrenergic agonist which results in relaxation of smooth muscle of the bronchials, cardiac stimulation (increasing myocardial oxygen consumption), and dilation of skeletal muscle vasculature.[7] It is frequently cited as first-line therapy and the single most important agent in the treatment of anaphylaxis.[4–6] Anaphylaxis often occurs in the community, in the absence of trained health care professionals; hence the development and popularity of self-injectable epinephrine that can be administered by patients or caregivers. In the United States, the generally recommended intramuscular (IM) epinephrine dose for adults is 0.3mg of a 1:1000 (1 mg/mL) solution or 0.01mg/kg (up to 0.3 mg) of a 1:1000 solution for children.[15] Self-injectable epinephrine is currently available in two auto-injector dosage formulations: 0.3mg/0.3 mL (typically for adults) and 0.15mg/0.15 mL (typically for children).[15]

Methods:

A MEDLINE Ovid search was conducted using the terms: anaphylaxis, anaphylaxis treatment, adrenaline or epinephrine. The search was limited to meta-analysis, systematic review, English language, and to studies conducted in humans in the last 10 years. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, Oregon Evidence-based Practice Center, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs (VA) and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality and relevant systematic reviews. The AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

Systematic Reviews and Meta-analyses: (See Appendix 1 for abstract)

Author: B Liang, Pharm.D Date: November 2014

The most recent systematic review by **Dahimi S et al**[1] in November 2013 evaluated the effectiveness of interventions for the acute and long-term management of anaphylaxis. The review searched for systematic reviews, randomized controlled trials (RTCs), quasi-randomized controlled trials, controlled clinical trials, controlled before-after studies and interrupted time series and, case series in relation to adrenaline investigating the effectiveness of interventions in managing anaphylaxis. Fifty - five studies were evaluated. Case fatality register studies have demonstrated the deaths can occur within minutes of the onset of an anaphylactic reaction. Therefore the consistent guidelines recommendation of prompt management with pharmacological interventions. The authors found some evidence investigating the role of epinephrine - the main drug advocated in guidelines; however the evidence was derived from case series, fatality registers and a limited number of trials in people not experiencing anaphylactic reactions. There were some evidence based on two RTCs that in both children and adults, maximum plasma concentration occurs quicker with the intramuscular than with subcutaneous route. The authors found no evidence from primary studies for other potential treatments such as glucocorticosteroids, antihistamines, methylxanthines and brochodilators.

Chipps BE (2013)[2]conducted a systematic review to update the pediatrician on the treatment of anaphylaxis in pediatrics. The author reviewed the literature published between 2007 and 2012. This review found food to be the most common trigger in children, but insect venom and drugs are other typical causes. Clinical diagnostic criteria include dermatological, respiratory, cardiovascular and gastrointestinal manifestation. Epinephrine is the drug of choice for acute reactions and is the only medication shown to be lifesaving properties when used promptly based on guidelines from World Allergy Organization. Auto-injector formulation provides unique advantage of prompt administration with proper training of caregivers.

A **Cochrane** review[3] from 2008 and last updated in 2010 assessed the effectiveness of epinephrine auto-injectors in relieving respiratory, cardiovascular and other symptoms during episodes of anaphylaxis that occur in the community. The authors found 1,328 studies relating to anaphylaxis and epinephrine auto-injector use but no randomized controlled trials on this subject. No new recommendations on the effectiveness of epinephrine auto-injectors for the treatment of anaphylaxis were made. Although randomized, double-blind, placebo-controlled clinical trials of high methodological quality are necessary to define the true extent of benefits from the administration of epinephrine in anaphylaxis via an auto-injector, such trials are unlikely to be performed in individuals experiencing anaphylaxis because of ethical and methodological concerns. There is, however, a need to consider trials in which, for example, auto-injectors of different doses of adrenaline and differing devices are compared in order to provide greater clarity on the dose and device of choice. Such trials would be practically challenging to conduct. In the absence of appropriate trials, the authors recommend that epinephrine administration by auto-injector should still be regarded as the most effective first-line treatment for the management of anaphylaxis in the community.

Treatment guidelines:

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World Allergy Organization (WAO) Anaphylaxis Guidelines

In 2013 WAO published updated the guidelines with a focus on the epidemiology, risk factors, triggers, diagnosis and the management of anaphylaxis.[3] Epinephrine remains the first line initial treatment. Patients at risk for anaphylaxis in community settings should be equipped with epinephrine. Epinephrine auto-injectors are the preferred formulation;[16] ampules/syringes or prefilled syringes can be alternative formulations. H_1-antihistamines are not appropriate for initial anaphylaxis treatment due to lack of ability to relieve life-threatening respiratory symptoms or shock. Similarly, systemic glucocorticosteroids are not drug of choice in initial anaphylaxis treatment because of the relatively slower onset of action. However, glucocorticosteroids remain important options for anaphylaxis because they potentially prevent biphasic anaphylaxis.

Working Group of the Resuscitation Council of United Kingdom (UK) Emergency Treatment of Anaphylactic Reaction Guidelines

An updated guidance on the recognition, acute management and follow-up of adults with anaphylaxis was published by the Resuscitation Council (UK) in 2008.[5] The use of an airway, breathing, circulation, disability and exposure approach to recognize and treat anaphylaxis was emphasized in the guidelines. The guidelines has Grade C recommendation that designate epinephrine the most important drug for the treatment of anaphylaxis and it should be given to all patients with life-threatening features. All patients and caregivers should be given instructions on how to properly administer epinephrine auto-injector. (Grade C).

European Academy of Allergy and Clinical Immunology (EAACI) Task Force

Due to lack of specific guidelines for anaphylaxis in children, the EAACI task force released a position paper that outlined the epidemiology, clinical presentation and the management of anaphylactic reactions in children.[6] Intramuscular epinephrine is the acknowledged first-line therapy for anaphylaxis in the hospital and in the community as soon as the condition is recognized. There is no absolute contraindication to administering epineprhine in children. Additional therapies such as volume support, nebulized bronchodilators, antihistamines or glucocorticosteroids are supplementary to epinephrine.The prescription of epinephrine auto-injector is part of a larger, comprehensive approach to the management of anaphylaxis. Epinephrine auto-injector is mandatory for high risk children, especially in children with prior cardiorespiratory reactions.

References:

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Appendix 1: Abstract of Selected Systemic Reviews and Meta-analyses

1. **Management of anaphylaxis: a systematic review.**
   Dhami S, Panesar SS, Roberts G, et al. *Allergy* 2014;69(2):168-175. doi:10.1111/all.12318.

   Abstract

   To establish the effectiveness of interventions for the acute and long-term management of anaphylaxis, seven databases were searched for systematic reviews, randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before-after studies and interrupted time series and - only in relation to adrenaline - case series investigating the effectiveness of interventions in managing anaphylaxis. Fifty-five studies satisfied the inclusion criteria. We found no robust studies investigating the effectiveness of adrenaline (epinephrine), H1-antihistamines, systemic glucocorticosteroids or methylxanthines to manage anaphylaxis. There was evidence regarding the optimum route, site and dose of administration of adrenaline from trials studying people with a history of anaphylaxis. This suggested that administration of intramuscular adrenaline into the middle of vastus lateralis muscle is the optimum treatment. Furthermore, fatality register studies have suggested that a failure or delay in administration of adrenaline may increase the risk of death. The main long-term management interventions studied were anaphylaxis management plans and allergen-specific immunotherapy. Management plans may reduce the risk of further reactions, but these studies were at high risk of bias. Venom immunotherapy may reduce the incidence of systemic reactions in those with a history of venom-triggered anaphylaxis.

2. **Update in pediatric anaphylaxis: a systematic review.**
   Chipps BE. *Clin. Pediatr. (Phila.)* 2013; 52(5):451-461. doi:10.1177/0009922812474683.

   Abstract

   Anaphylaxis is common in children and has many differences across age groups. A systematic review of the literature from the past 5 years was conducted with the goal of updating the pediatrician. Food is the most common trigger in children, but insect venom and drugs are other typical causes. Clinical diagnostic criteria include dermatological, respiratory, cardiovascular, and gastrointestinal manifestations. A biphasic reaction is seen in some, with recurrence usually within 8 hours of the initial episode. Epinephrine is the drug of choice for acute reactions and the only medication shown to be lifesaving when administered promptly, but it is underutilized. Patients should have ready access to ≥2 doses of an epinephrine auto-injector, with thorough training regarding correct use of a given device and an emergency action plan. Management of anaphylaxis in schools presents distinct challenges. Pediatricians are in a unique position to assess and treat these patients chronically.

3. **Adrenaline auto-injectors for the treatment of anaphylaxis with and without cardiovascular collapse in the community.**
   Sheikh A, Simons FER, Barbour V, Worth A. *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2012.

   Abstract

Background: Anaphylaxis is a serious hypersensitivity reaction that is rapid in onset and may cause death. Adrenaline (epinephrine) auto-injectors are recommended as the initial, potentially life-saving treatment of choice for anaphylaxis in the community, but they are not universally available and have limitations in their use.

Objectives: To assess the effectiveness of adrenaline (epinephrine) auto-injectors in relieving respiratory, cardiovascular, and other symptoms during episodes of anaphylaxis that occur in the community.

Search methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2012, Issue 1), MEDLINE (Ovid SP) (1950 to January 2012), EMBASE (Ovid SP) (1980 to January 2012), CINAHL (EBSCO host) (1982 to January 2012), AMED (EBSCO host) (1985 to January 2012), LILACS, (BIREME) (1980 to January 2012), ISI Web of Science (1950 to January 2012). We adapted our search terms for other databases. We also searched websites listing on-going trials: the World Health Organization International Clinical Trials Registry Platform, the UK Clinical Research Network Study Portfolio, and the meta Register of Controlled Trials; and contacted pharmaceutical companies who manufacture adrenaline auto-injectors in an attempt to locate unpublished material.

Selection criteria: Randomized and quasi-randomized controlled trials comparing auto-injector administration of adrenaline with any control including no intervention, placebo, or other adrenergic agonists were eligible for inclusion.

Data collection and analysis: Two authors independently assessed articles for inclusion.

Main results: None of the 1328 studies that were identified satisfied the inclusion criteria.

Authors' conclusions: Based on this review, we cannot make any new recommendations on the effectiveness of adrenaline auto-injectors for the treatment of anaphylaxis. Although randomized, double-blind, placebo-controlled clinical trials of high methodological quality are necessary to define the true extent of benefits from the administration of adrenaline in anaphylaxis via an auto-injector, such trials are unlikely to be performed in individuals experiencing anaphylaxis because of ethical concerns associated with randomization to placebo. There is, however, a need to consider trials in which, for example, auto-injectors of different doses of adrenaline and differing devices are compared in order to provide greater clarity on the dose and device of choice. Such trials would be practically challenging to conduct. In the absence of appropriate trials, we recommend that adrenaline administration by auto-injector should still be regarded as the most effective first-line treatment for the management of anaphylaxis in the community. In countries where auto-injectors are not commonly used, it may be possible to conduct trials to compare administration of adrenaline via auto-injector with adrenaline administered by syringe and ampoule, or comparing the effectiveness of two different types of auto-injector.

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