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Drug Class Literature Scan: Anaphylaxis Rescue Agents

Date of Review: May 2017

Date of Last Review: November 2014
Literature Search: 2/8/17-2/14/17

Current Status of PDL Class: All epinephrine auto-injectors (EAI) are on the PDL
See **Appendix 1**.

Conclusions:

- Three new guidelines on anaphylaxis management from the American Heart Association (AHA) and the Red Cross (RC), the European Academy of Allergy and Clinical Immunology (EAACI) and the American Academy of Pediatrics (AAP) have been published since the last review.[1–3] Guidelines recommend first aid responders administer an intramuscular (IM) dose of epinephrine, or assist a patient with their own device, if there is an anaphylactic reaction. The dose of epinephrine when using the auto-injectors should be 0.3 mg IM for adults and children greater than 30 kg and 0.15 mg IM for children 15-30 kg.
- There is insufficient comparative evidence between EAI products. There is insufficient evidence in subgroups populations.

Recommendations:

- No changes are recommended to the OHP PDL based on the review of current evidence. After review of comparative drug costs in the executive session, no changes to the PDL were recommended.

Previous 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.
- There is moderate evidence from one systematic review 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.
- Epinephrine is recommended as first-line initial therapy for anaphylaxis in both children and adults. In addition, the auto-injector is recommended as the preferred injectable formulation in the community.

Previous Recommendations:

- The Committee recommended adding “anaphylaxis rescue” as a drug class to the PMPDP under the Allergy/Cold section and to include epinephrine auto-injector products as preferred.
- After comparative costs in executive session, the Committee recommended making all auto-injector products preferred on the PMPDP.

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Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
No systematic reviews were identified.

New Guidelines:

American Heart Association and Red Cross First Aid Guidelines
The AHA and RC formed an International Liaison Committee on Resuscitation (ILCOR) First Aid Task Force to evaluate the literature related to first aid preparation and management. The Committee used Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to evaluate the evidence. Evidence related to first aid management is limited due to the difficulty of obtaining high quality data in emergency situations. The AHA/RC anaphylaxis recommendations are as follows:

- A first aid responder should administer epinephrine or assist a person with anaphylaxis with their own epinephrine if they are having a reaction.
- The recommended dose is epinephrine 0.3 mg IM for adults and children greater than 30 kg, 0.15 mg IM for children 15-30 kg or the dose prescribed by a physician.
- Providers of first aid should call 9-1-1 immediately when assisting a person with a severe allergic reaction or anaphylaxis.
- A second epinephrine dose should be given if there is not an adequate response to the first dose.

Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology
The EAACI provided guidance on the diagnosis and management of anaphylaxis in 2014.[2] Recommendations were based on 2 systematic reviews on the epidemiology and treatment of anaphylaxis as well as complementary anaphylaxis guidelines. The Appraisal of Guidelines for Research and Evaluation (AGREE II) tool was used for guideline development and recommendations were assigned a level and grade of evidence. IM adrenaline is recommended as first-line and there are no absolute contraindications to its use (based on descriptive studies or extrapolation from primary evidence). An IM injection in the thigh should be given at a dose of 0.01 ml/kg to a max dose of 0.5 ml. Patients weighing 7.5 –25 kg and using an auto-injector should receive 0.15 mg dose and patients weighing 25-30 kg should move up to the 0.3 mg dose.[2] Patients weighing 25 kg or more should also receive the 0.3 mg dose. Repeat doses can be given every 5 minutes if needed. An adrenaline infusion may be appropriate for patients not responding to IM adrenaline. Second-line interventions include removal of the trigger,

administration of high-flow oxygen, intravenous (IV) fluid for cardiovascular instability and inhaled short-acting beta-2 agonists for patients with bronchoconstriction. H1- and H2-antihistamines are considered third-line and have only demonstrated relief of cutaneous symptoms during anaphylaxis. Oral and IV glucocorticoids are an additional third-line treatment as a mechanism to prevent protracted anaphylaxis symptoms. Glucagon may be useful in patients, especially in those taking beta-blockers, with anaphylaxis who fail to respond to adrenaline.

American Pediatric Society: Clinical Guidance on First-Aid Management

The APS released a clinical report on the guidance for first-aid management of anaphylaxis.[3] Recommendations for the identification of pediatrics at risk of anaphylaxis and the appropriate use of EAI is discussed. Methodology of guideline development was based on clinical expertise but due to the paucity of evidence on anaphylaxis management the recommendations will be included. Epinephrine is recommended as the treatment of choice for anaphylaxis. Intramuscular administration given in the outer thigh at a dose of 0.01 mg/kg, up to 0.3 mg in pre-pubertal children and 0.5 mg in teenagers. EAI can be used to deliver the recommended dose of 0.15 mg for patients weighing 15 to 30 kg and 0.3 mg for patients over 30 kg. Repeated epinephrine doses can be given up to two additional times at intervals of 5 to 15 minutes if symptoms of anaphylaxis persist. Adverse events seen with epinephrine include transient pallor, tremor, anxiety and palpitations, similar to endogenous epinephrine.

New Formulations:

No new formulations were identified.

New FDA Safety Alerts:

In May of 2016 the FDA issued safety labeling changes for all EAI.[4–7] Reports of serious infections at in the injection site due to necrotizing fasciitis and myonecrosis caused by Clostridia have been identified. To minimize this risk, it is recommended that EAIs are not injected into the buttock. Reports of injection-related complications have also been reported in small children who are uncooperative during injections given in the thigh. Movement should be minimized when injecting to prevent lacerations, bent needles and embedded needles.

Safety labeling changes were updated for Adrenaline® 30 mL multi-dose vial, advising against ophthalmic use due to potential ophthalmic injury.[4] The multi-dose vial contains chlorobutanol which may be harmful to the cornea.

References:

1. Singletary EM, Charlton NP, Epstein JL, et al. Part 15: First Aid: 2015 American Heart Association and American Red Cross Guidelines Update for First Aid. *Circulation*. 2015;132(18 Suppl 2):S574-589. doi:10.1161/CIR.0000000000000269.

2. Muraro A, Roberts G, Worm M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2014;69(8):1026-1045. doi:10.1111/all.12437.

3. Sicherer S, Simons E. Epinephrine for First-aid Management of Anaphylaxis. Pediatrics. 2017;139(3):e20164006. doi:10.1542/peds.2016-4006.

4. The Food and Drug Administration. Safety Information - Adrenalin (epinephrine injection, USP). Available at: http://www.fda.gov/safety/medwatch/safetyinformation/ucm505854.htm. Accessed February 9, 2017.

5. The Food and Drug Administration. Safety Information - Twinject, Adrenaclick & Epinehrine Injection USP Auto-Injector. Available at: http://www.fda.gov/safety/medwatch/safetyinformation/ucm505917.htm. Accessed February 9, 2017.

6. The Food and Drug Administration. Safety Information - EpiPen and EpiPen Jr. (epinephrine injection) Auto-Injector. Available at: http://www.fda.gov/safety/medwatch/safetyinformation/ucm505913.htm. Accessed February 9, 2017.

7. The Food and Drug Administration. Safety Information - AUVI-Q Autoinjector (epinephrine injection, USP). Available at: http://www.fda.gov/safety/medwatch/safetyinformation/ucm505855.htm. Accessed February 9, 2017.

Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
IM	AUTO INJCT	ADRENACLICK	EPINEPHRINE	Y
IM	AUTO INJCT	EPIPEN JR	EPINEPHRINE	Y
IM	AUTO INJCT	EPIPEN	EPINEPHRINE	Y
IM	AUTO INJCT	EPINEPHRINE	EPINEPHRINE	Y

Appendix 2: New Comparative Clinical Trials

A total of 48 citations were manually reviewed from the initial literature search. After further review, none of the citations were included because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to January Week 4 2017

Search Strategy:

#	Searches	Results
1	Epinephrine/	11993
2	Anaphylaxis/	7491
3	1 and 2	929
4	limit 3 to (english language and humans and yr="2014 -Current")	187
5	limit 4 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or practice guideline or randomized controlled trial or "review" or systematic reviews)	48