CRITICAL REVIEW FORM:

Resident: Jaqui Sugameli **Date: 2/26/24**

Citation: Dodd A, et al. Evidence update for the treatment of anaphylaxis. Resuscitation. 2021 Apr 23;163:86-96

Study Objective: There are over 8 organizations with published guidelines regarding the emergency treatmet of anaphylaxis. This is an evidence and consensus-based update from the Resuscitation Council of the United Kingdom

Study Methodology:
Anaphylaxis Working Group of the REsuscitation Council UK(RCUK) completed an evidence review using "an internationally accepted approach for adoption, adaptation, and de novo guideline development based on the previously validated Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence to decision (EtD) framework, referred to as GRADE-ADOLOPMENT

In brief:

1. identify and review key research questions (from previously published guidelines)
2. reviewed existing guidelines/systemic reviews by two independent assessors
3. working group determines whether consensus of previously published recommendation stands ("Adopted"), needs to be modified ("Adapted") or an entirely new recommendation needed to be developed.
4. overall recommendations were assigned as either strong or weak.
5. evidence for individual recommendations was either high, moderate low or very low
6. a Working Group using the Grade evidence to decision framework determined whether recommendation was adopted, adapter or warranted rewriting .

Question: Is adrenaline effective for the treatment of anaphylaxis?

1. **ADOPT: adrenaline as first line treatment for anaphylaxis (strong recommendation, moderate certainty evidence)**
    a. weakness of this recommendation is that there aren't a lot of studies comparing epi vs. no epi due to risk of patient harm.
    b. meta-analysis of 365,577 anaphylaxis events shows that only 2.2% of reactions will fail to respond to 2 doses of epi (95% CI 1.1-4.1)
    c. meta-analysis of 27 studies (2758 patients) reported 5% biphasic reactions and no impact of adrenalin on biphasic reactions (OR 0.91, 95% CI 0.6-1.4)

Question: What is the optimal timing of adrenaline in the treatment of anaphylaxis?

2. **ADOPT: give adrenaline early (weak recommendation,low certainty)**
    a. prospective study of 430 anaphylaxis reactions (>30mins after symptoms) associated with higher rate of biphasic reaction (OR 3.39, 95%CI1.13-10.18)

Question: What is the optimal route of adrenaline to treat anaphylaxis?

3. **ADOPT: IM Epi is better initially than IV (strong recommendation, low certainty of evidence)**

a. IM vs. IVonly in one case series, "IVbolus administration was assocaitedwith 13% increasein incidence of adrenaline overdoseand 8% increase in incidence of cardiovascular eventscomparedwith IM administration"

Question: What is the optimal dose of intramuscular adrenaline in the treatment of anaphylaxis?

Table 4 – Recommended doses of IM adrenaline.

Adrenaline IM dose – adults	
500 micrograms (0.5 mg) IM (0.5 mL of 1 mg/ml [1:1000] adrenaline)	
Adrenaline IM dose – children	
>12 years	500 micrograms IM (0.5 mL) i.e. same as adult dose
	300 micrograms (0.3 mL) if child is small or prepubertal
6–12 years	300 micrograms IM (0.3 mL)
6 months–6 years	150 micrograms IM (0.15 mL)
<6 months	100–150 micrograms IM (0.1–0.15 mL)

The equivalent volume of 1 mg/ml [1:1000] adrenaline is shown in brackets.

Question: Are additional doses of adrenaline effective in the treatment of anaphylaxis reactions refractory to initial treatment with adrenaline?

4. **ADAPT: Repeat IM adrenaline dosing q5 mins depending on patient response**
    a. in patients whose symptoms are refractory to initial treatment (weak recommendation, low certainty evidence)
    b. if respiratory/CV features persist despite two doses use IV administration (strong recommendation, low certainty)

****this is a change to include greater emphasison early recognition of refractory reactions, preferring low dose IV adrenaline infusions)**

rationale includes the biphasic nature of IM epi absorption (initialy peak 5-10 mins after administration)

Question: Are intravenous fluids effective as an adjuvant treatment for anaphylaxis?

5. **ADAPT: Give IV Fluids**
    a. **with hemodynamic compromise (weak recommendation, very low certainty evidence)**
    b. **if refractory to initial epi in order to improve drug distribution (weak recommendation, very low certainty evidence)**

**** this represents a change from prior guidelines to include giving fluids to treat refractory cases even in the absence of hemodynamic compromise**

rationale: in order to restore circulatory volume (IM epi found to have limited effect in restoring strokevolume)

Question: Are antihistamines effective in the treatment of anaphylaxis?

6. **ADAPT: Antihistamines should NOT be used as initial treatment for anaphylaxis (weak recommendation, low certainty evidence)**
    a. treat skin symptoms (weak recommendation, low certainty evidence)

** represents a change from prior guidelines due to concern that antihistamine administration may delay use of epi.

rationale: no role in CV or respiratory resolution, no role in survival improvement, researcherse had concern for how many patients arrive having taken antihistamines but not epi. concerns could be distracting from appropriate pre-hospital management.

<u>Question:</u> Are corticosteroids effective in the treatment of anaphylaxis?

7. **ADAPT: Corticosteroids should not be used to treat anaphylaxis (weak recommendation, very low certainty evidence)**
    a. **treat asthma/shock in third line (weak recommendation, low certainty evidence)**

** represents change due to concerns of efficacy to prevent biphasic reactions and increased need for hospitalization (in one study)

<u>rationale:</u> steroids down-regulate late phase inflammatory response. slow absorption means likely not playing a role in treating acute phase. reactions.

(Canadian C-CARE registry showed hospitalization/admissino to ICU was associated with prehospital corticosteroids(OR 2.84, 95% CI 1.55-6.97)

Question: Are inhaled beta-2 agonists effective in the treatment of anaphylaxis?

8. **ADAPT: Beta-2-agonists- may be useful in treating lower respiratory symptoms following IM epi (weak recommendation, very low certainty evidence)**
    a. if persisting respiratory symptoms, beta-2-agonists) should not be used instead of IV epi (strong recommendation, very low certainty evidence

** represents a change, using bronchodilators as an adjunct rather than replacement

Question: How long should patients be observed in hospital following anaphylaxis?

9. **ADAPT: instead of observe for 6 hours, consider risk-stratified approach (weak recommendation,very low certainty evidence)**
    a. **because often biphasic reactions occur more than the recommended 6 hour obs time, updated study shows that 2.5% of fatalities happened >6hr after allergen exposure, 6-12 hours of obs will miss 50%of biphasic reactions.**
    b. **consider especially in patients requiring more than 1 dose of adrenaline**

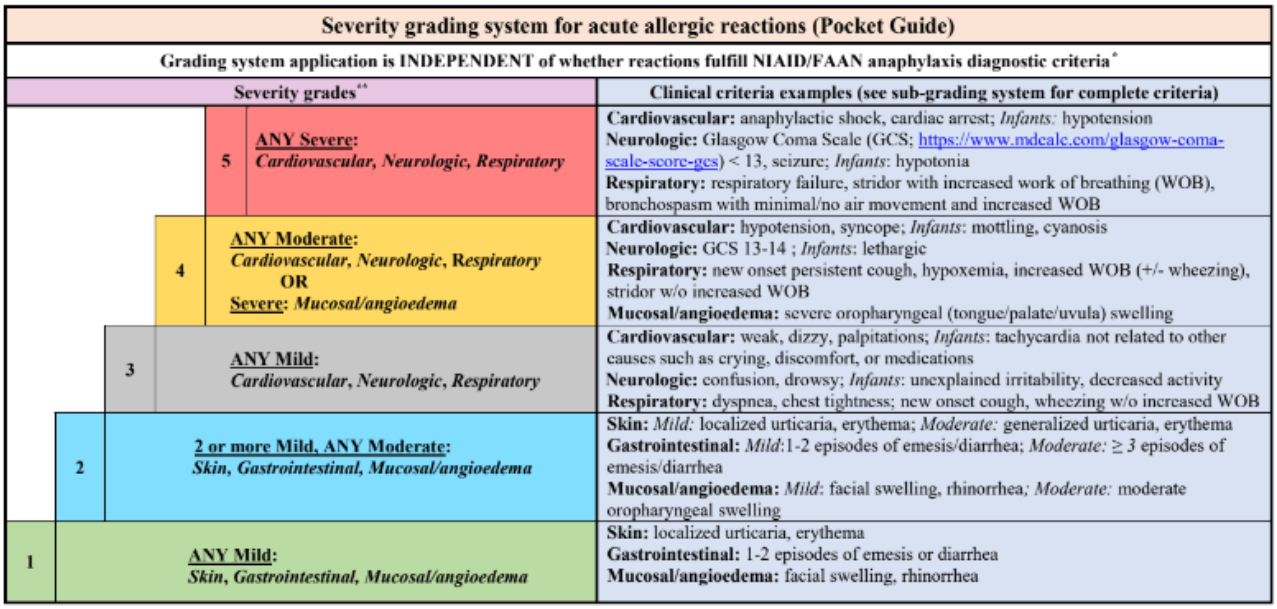
Low risk - should capture 95% of biphasic reactions (95% CI 99.9-97.3)
only extended to 98.2% at 12 hours (95% CI 96.7-99.1)

Table 5 – Suggested observation times following anaphylaxis.

Consider fast-track discharge (after 2 h observation from resolution of anaphylaxis) if:	Minimum 6 h observation after resolution of symptoms recommended if:	Observation for at least 12 h following resolution of symptoms if any one of the following:
• Good response (within 5–10 min) to a single dose of adrenaline given within 30 min of onset of reaction; AND • Complete resolution of symptoms AND • The patient already has unused adrenaline auto-injectors (AAI) and has been trained how to use them. AND • There is adequate supervision following discharge	• 2 doses of IM adrenaline needed to treat reaction[a] OR • Previous biphasic reaction	• Severe reaction requiring >2 doses of adrenaline. • Patient has severe asthma or reaction involved severe respiratory compromise. • Possibility of continuing absorption of allergen e.g. slow release medicines. • Patient presents late at night, or may not be able to respond to any deterioration. • Patients in areas where access to emergency care is difficult.

[a] It may be reasonable for some patients to be discharged after 2 h despite needing no more than 2 doses of IM adrenaline e.g. following a supervised allergy challenge in a specialist setting.

Regarding Severity: Dribin et al developed a non-validated scoring system based upon review of 21 studies in an attempt to help standardize severity of anaphylaxis



Severity grading system for acute allergic reactions (Pocket Guide)	
Grading system application is INDEPENDENT of whether reactions fulfill NIAID/FAAN anaphylaxis diagnostic criteria*	
Severity grades**	Clinical criteria examples (see sub-grading system for complete criteria)
5 **ANY Severe:** ***Cardiovascular, Neurologic, Respiratory***	**Cardiovascular:** anaphylactic shock, cardiac arrest; *Infants:* hypotension **Neurologic:** Glasgow Coma Scale (GCS; https://www.mdcalc.com/glasgow-coma-scale-score-gcs) < 13, seizure; *Infants*: hypotonia **Respiratory:** respiratory failure, stridor with increased work of breathing (WOB), bronchospasm with minimal/no air movement and increased WOB
4 **ANY Moderate:** ***Cardiovascular, Neurologic, Respiratory*** **OR** **Severe:** ***Mucosal/angioedema***	**Cardiovascular:** hypotension, syncope; *Infants*: mottling, cyanosis **Neurologic:** GCS 13-14 ; *Infants*: lethargic **Respiratory:** new onset persistent cough, hypoxemia, increased WOB (+/- wheezing), stridor w/o increased WOB **Mucosal/angioedema:** severe oropharyngeal (tongue/palate/uvula) swelling
3 **ANY Mild:** ***Cardiovascular, Neurologic, Respiratory***	**Cardiovascular:** weak, dizzy, palpitations; *Infants*: tachycardia not related to other causes such as crying, discomfort, or medications **Neurologic:** confusion, drowsy; *Infants*: unexplained irritability, decreased activity **Respiratory:** dyspnea, chest tightness; new onset cough, wheezing w/o increased WOB
2 **2 or more Mild, ANY Moderate:** ***Skin, Gastrointestinal, Mucosal/angioedema***	**Skin:** *Mild:* localized urticaria, erythema; *Moderate:* generalized urticaria, erythema **Gastrointestinal:** *Mild*:1-2 episodes of emesis/diarrhea; *Moderate:* ≥ *3* episodes of emesis/diarrhea **Mucosal/angioedema:** *Mild*: facial swelling, rhinorrhea*; Moderate:* moderate oropharyngeal swelling
1 **ANY Mild:** ***Skin, Gastrointestinal, Mucosal/angioedema***	**Skin:** localized urticaria, erythema **Gastrointestinal:** 1-2 episodes of emesis or diarrhea **Mucosal/angioedema:** facial swelling, rhinorrhea

Limitations: Well-constructed GRADE compliant guideline however, many of the recommendations are based upon weak evidence including heterogeneous meta-analysis, underpowered RCT's, case reports, observational studies or consensus opinions Making changes in clinical practice based off self- identified "weak recommendations" seems challenging. For that matter how many are comfortable withholding steroids in those who meet criteria for anaphylaxis?

Clinical Bottom Line:

1. Use IM EPI early
2. Repeat IM Epi x1 q 5 mins, if still refractory consider low dose epi drip (but probably give third dose while getting epi drip set up
3. Consider IVF in refractory anaphylaxis even with no hemodynamic compromise
4. Don't let antihistamines delay epi administration
5. consider steroid use closely in acute phase, don't let it delay epi administration
    a. **clinical question, what about going home with steroids?**
6. don't let bronchodilators replace epi in continuing respiratory symptoms
7. Don't be lulled into false sense of security when it comes to observation times, make sure you are identifying higher risk people and keeping them longer. Also may be ok to observe some identified "low risk" for less time.
    a. 2 hr obs when- 1 dose epi, complete resolution of sx, has auto injector at home, has supervision following discharge
    b. 6 hr obs when- 2 doses OR hx biphasic rxn
    c. 12 hr when - >2 doses OR asthma/resp compromise, possibility of continued absorption of allergy, areas where emergency access is difficult, presents late at night (might be sleeping if deterioration occurs)