

To EPI OR NOT TO EPI: ALLERGIC EMERGENCIES IN THE ED

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- I. Anaphylaxis is a true emergency that transcends all medical specialties
 - a. Onset: rapid and often unpredictable
 - b. Symptoms: potentially lethal
 - c. Treatments: fortunately they are effective and widely available
 - d. Patients: often affects those who are young, otherwise healthy, and at the prime of their lives

- II. Setting the stage
 - a. There are many types of hypersensitivity reactions
 - i. Gell & Coombs classification schema
 - ii. However, allergic emergencies fall under Gell & Coombs Type I, acute hypersensitivity reactions
 1. IgE mediated
 - b. Pathophysiology of anaphylaxis
 - i. Sensitization
 1. Allergen exposure leads to IgE formation
 2. IgE binds to the surface of:
 - a. Mast cells – located in tissues
 - b. Basophils – located in the bloodstream
 - ii. Re-exposure to the inciting allergen
 1. Leads to the release of various pro-inflammatory mediators from mast cells and basophils
 - a. Pre-formed mediators → histamine, tryptase others
 - b. Newly synthesized mediators → leukotrienes, others
 - i. IgE stimulation effectively “turns on” intracellular machinery, ultimately leading to continued inflammatory mediator production and release
 - iii. Inflammatory mediators lead to clinical symptoms
 - c. Clinical syndrome – target systems
 - i. Respiratory
 1. “ENT” → angioedema anywhere from lips to hypopharynx
 2. lower airways → bronchospasm
 - ii. Cardiovascular
 1. Spectrum of manifestations

2. Mild → pre-syncope/lightheadedness
3. Severe → hypotension, malignant dysrhythmia, cardiovascular collapse
- iii. Gastrointestinal
 1. Often caused by intestinal wall angioedema
 2. Nausea, vomiting, cramping
- iv. Dermatologic
 1. Flushing
 2. Urticaria, angioedema
 - a. Urticaria → superficial layers
 - b. Angioedema → same pathophysiological process as urticaria, but involves deeper layers
 3. Itching/pruritis
- v. Central nervous system
 1. Altered mental status
 2. CNS symptoms typically result from disturbance of other systems
 - a. Cardiovascular → poor perfusion
 - b. Respiratory → hypoxia
- d. Important caveat: Not all allergic emergencies are associated with skin findings!
 - i. We most frequently look for confirmatory skin findings to “rule-in” the diagnosis of anaphylaxis (eg, “it can’t be anaphylaxis because there is no urticaria, itching or flushing”
 - ii. However, cutaneous findings may be absent entirely in 10-15% of cases.¹
 - iii. Importantly, severe anaphylaxis can occur without cutaneous manifestations whatsoever.^{2,3}

III. Definition of Anaphylaxis

- a. “We all know it when we see it; yet, it’s hard to define!”
- b. From the 2nd National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis (FAAN) symposium: “a serious allergic reaction that is rapid in onset and may cause death.”⁴
- c. Sure, great...But, completely **useless** to us in the ED setting in terms of making real-time clinical decisions!
- d. So, why does the definition matter?
 - i. Anaphylaxis is a medical emergency
 - ii. Treatments need to be enacted swiftly and aggressively
 - iii. Our treatments for **anaphylaxis** differ in some ways from those used in “lesser” allergic reactions
- e. Think of allergic emergencies as a SPECTRUM
 - i. Mild end of the spectrum → isolated skin findings
 - ii. Severe end of the spectrum → respiratory failure or cardiovascular collapse
 - iii. And, of course, everything in-between!

- f. Our task is to pick a point along this spectrum where we distinguish anaphylaxis from lesser allergic phenomena
 - i. Again, our treatments for **anaphylaxis** differ from those used in “lesser” allergic reactions... as such, this distinction impacts real-time clinical decision making
- g. Consensus, not evidence → a reasonable working definition of anaphylaxis involves allergic signs/symptoms with one or both of the following features:
 - i. respiratory compromise
 - 1. upper airways – areas that matter from an ENT perspective
 - a. tongue, posterior pharynx, hypopharynx, larynx
 - ii. hemodynamic instability
 - 1. symptoms ranging from pre-syncope to cardiovascular collapse
- h. What about lip swelling?
 - i. Not infrequent, particularly with food allergens
 - ii. Lesson that can be gleaned from what we know about a pathophysiologically different, yet related, condition: bradykinin-mediated angioedema (eg, ACE-I or ARB associated angioedema)...
 - 1. anything inside the oral cavity (eg, from lingual aspect of dentition, inwards) matters⁵
 - iii. Isolated lip swelling is not as concerning, unless it is rapidly progressive
- i. Anaphylactoid reactions
 - i. Preferred term → “non-allergic anaphylaxis”
 - ii. An immediate systemic reaction resulting from the release of identical mediators from mast cells and basophils
 - iii. Differs from anaphylaxis in that it is **not IgE mediated**
 - iv. Therefore, unlike allergic anaphylaxis, adverse reactions may occur on first exposure to the inciting agent
 - 1. prior sensitization is not required
 - v. Clinical presentation and management is exactly the same as for anaphylaxis

IV. Etiologies

- a. Foods
 - i. Most common etiology seen in ED setting^{6 7}
 - ii. Early in life
 - 1. Eggs, milk, soy
 - 2. Often outgrown
 - iii. Later in life
 - 1. Peanuts, tree-nuts (almonds, hazelnuts, etc), fish, shellfish

2. Frequently life-long, even if they initially develop during childhood
- b. Medications
 - i. Antimicrobials
 - ii. NSAIDs
 - iii. Many others
- c. Stinging insects (Hymenoptera)
- d. Latex
- e. Exercise-induced
 - i. Occurs during exercise
 - ii. May be a food anaphylaxis variant
- f. Idiopathic
 - i. Etiologic culprit may be forever elusive in up to 20% of cases⁸

V. Treatments

- a. Controlled data is lacking
 - i. it would, of course, be unethical to enroll patients in the placebo arm of an anaphylaxis treatment trial!
 - ii. Therefore, therapeutic recommendations based on:
 1. Clinical observations
 2. Interpretation of underlying pathophysiology
 3. And, to some extent, animal models
 - iii. There are may published consensus guidelines
 1. Limitation: lack a consistent definition of anaphylaxis
 2. Limitation: consensus guidelines are only as good as the evidence that goes into formulating the guidelines
 - a. And in the case of anaphylaxis, the evidence is largely absent!
- b. Treatments we can all agree on:
 - i. Supplemental oxygen
 - ii. Intravenous fluids
- c. Pharmacologic treatments and the questions they often raise:
 - i. Epinephrine – in which cases, by what route, safety, when to avoid?
 - ii. Antihistamines
 1. H1 blockers – any alternatives to diphenhydramine?
 2. H2 blockers – any additive benefit compared with an H1 alone?
 - iii. Corticosteroids – in which cases, by what route (PO? IV?)
 - iv. Bronchodilators – in which cases?
 - v. Others
 1. Glucagon – any role?
 2. Alternate vasopressors – any alternative to epinephrine?

VI. Epinephrine

- a. Punch lines:
 - i. Undisputed first line agent in the treatment of anaphylaxis⁹
 - 1. This is why distinguishing ***anaphylaxis*** from lesser allergic phenomena becomes so important!
 - ii. Very effective
 - iii. Safer than you may think
 - 1. Safety concerns regarding epinephrine are generally exaggerated over-stated, particularly for administration by a non-IV route
 - iv. However, with all of these great things said...
 - 1. Epinephrine remains under-utilized, and
 - 2. It is often used incorrectly (wrong clinical setting, inappropriate route/dose of administration, etc.)
- b. Epinephrine – what’s the best route?
 - i. Most important point: *Virtually all adverse outcomes result from Intravenous (IV) administration!*
 - ii. I repeat: *Virtually all adverse outcomes result from it’s Intravenous (IV) administration!*
 - iii. So, what about the other parenteral routes: IM vs. SQ
 - 1. Randomized study of children at risk for anaphylaxis showed more rapid peak plasma levels after IM as compared with SQ¹⁰
 - 2. Follow-up study in adults showed similar benefits of IM (thigh) as compared with SQ (deltoid)¹¹
 - iv. So, what’s the problem with SQ?
 - 1. SQ absorption is dependent on cutaneous blood flow
 - 2. In healthy volunteers at risk for anaphylaxis (studies noted directly above), SQ absorption was delayed and variable
 - 3. Complicating matters, take the case of anaphylaxis...
 - a. A state of distributive shock: cutaneous blood flow is diminished
 - b. Furthermore, epinephrine is a potent local vasoconstrictor: cutaneous blood flow is further diminished
 - 4. Taken all together, the current “evidence” suggests IM over SQ in a patient of any age (pediatric, adult)
 - v. However, the critics: is IM really that much better, as all of the guidelines suggest?
 - 1. Issues with this recommendation:
 - a. Data leading to this conclusion from healthy volunteers at risk for anaphylaxis (and not from patients actually suffering from an anaphylactic reaction)
 - b. Recommendation based on two studies with a total of 30 patients (17 children, 13 adults)

- c. Data is not outcomes based
- d. Finally, the side-effect profile of IM epinephrine as compared with SQ epinephrine is largely unknown...
- vi. With all of this said, there is still a role for IV epinephrine
 - 1. However, it is critical to remember: *Virtually all adverse outcomes result from Intravenous (IV) administration!*
 - a. Major adverse events
 - i. Dilution Errors: Inadequate dilution
 - ii. Dosing Errors: Excessive dosage
 - iii. Administration Errors: Given too rapidly
 - 2. IV epinephrine should be reserved for our sickest patients
 - a. “Shock” with impaired peripheral absorption
 - b. Failure to respond to repeated IM dosing
 - 3. If you do give IV epinephrine, it is recommended that you use a very dilute solution (see below)
- vii. Epinephrine Dosing
 - 1. IM (or SQ) Dosing
 - a. Adult: 0.2-0.5 mg of a 1:1,000 dilution (“high-test”)
 - b. Pediatric: 0.01 mg/kg, up to max 0.3 mg
 - c. May repeat every 5 to 15 minutes prn
 - 2. IV Dosing
 - a. Regimens not firmly established
 - b. 1:100,000 dilution may be safest^{12,13}
 - i. take 0.1 mg of epinephrine
 - 1. 0.1 ml of 1:1K dilution, or
 - 2. 1 ml of 1:10K dilution
 - ii. mix in sterile NS to create 10 ml volume of solution
 - 1. 0.1 mg = 100 µg in 10 ml
 - 2. Therefore, a 10 µg per ml solution
 - iii. administer 10 ml over 5 to 10 minutes in adult
 - 1. 10-20 µg per minute dilute infusion
 - 2. compare with routine adult epinephrine infusion (1-4 µg per min)
- c. Epinephrine – is it safe?
 - i. When we worry: higher risk patients
 - 1. Elderly
 - 2. Hypertensive
 - 3. Coronary/vascular disease

- ii. For routes *other than IV*, epinephrine is safer than many of us think!
 - 1. A study of SQ epinephrine use in asthmatics showed a favorable safety profile across spectrum of age (15 to 96 year of age)¹⁴
- iii. Decision needs to be made on a case-by-case basis, and needs to be risk-benefit driven
- iv. Importantly, untreated anaphylaxis is not without its consequences!
 - 1. Anaphylaxis is a life-threatening emergency
 - 2. Physiologic derangements in and of themselves are worrisome, particularly in higher risk patients
 - a. Respiratory: increased work of breathing +/- hypoxia
 - b. Cardiovascular: decreased preload, decreased coronary perfusion pressure
- v. Taken all together, the risk of withholding epinephrine may outweigh the risk of the treatment itself in certain cases
- d. Epinephrine – in which cases do we actually “pull the trigger” and give it?
 - i. Symptom trajectory is key!

VII. Antihistamines

- a. Second line agents in the treatment of ***anaphylaxis***
 - i. Again, why distinguishing ***anaphylaxis*** from lesser allergic phenomena becomes so important (may be first line in the case of less concerning allergic symptoms)
- b. H1 antihistamines
 - i. Role “well established,” although according to a recent Cochrane review, evidence supporting their role is lacking¹⁵
 - ii. Most commonly utilized: diphenhydramine (Benadryl®)
 - iii. Other options: less-sedating/non-sedating antihistamines
 - 1. Limitation: none are available in the U.S. for IV use
 - 2. Well established track record in the treatment of milder allergic phenomena (eg, urticaria)
 - 3. Options: cetirizine (Zyrtec®), loratidine (Claritin®), etc
- c. H2 antihistamines
 - i. Utilized with varying frequency in the treatment of allergic emergencies as compared with H1 blockers
 - ii. ED based evidence supports their adjunctive use:
 - 1. Randomized, double-blind, placebo-controlled trial of 91 ED patients with acute allergic syndromes demonstrated benefit of the H1 (diphenhydramine) and H2 (ranitidine) antagonist combination, as compared with H1 antagonist alone¹⁶

2. A second ED study found that the combination of diphenhydramine (H1 blocker) and cimetidine (H2 blocker) was more effective than diphenhydramine alone for the treatment of acute urticaria¹⁷
3. Very safe, generally well-tolerated, so an overall very low-risk intervention with some potential additive benefit

VIII. Corticosteroids

- a. From the Updated Anaphylaxis Practice Parameter published by the American Academy of Asthma Allergy & Immunology¹:
“Glucocorticosteroids have not been shown to be effective for the acute treatment of anaphylaxis...”
 - i. “What!,” you may ask (which is a reasonable and anticipated response)
- b. As it turns out, along with many other interventions in anaphylaxis management, the role of corticosteroids has not been adequately evaluated with controlled trials
- c. Furthermore, the role of corticosteroids in anaphylaxis treatment is not to impact the release of the pre-formed pro-inflammatory mediators; rather, it is to potentially quell the production of newly-synthesized mediators (see ‘pathophysiology’ section above)
- d. So, the punch lines with corticosteroids in allergic emergencies:
 - i. Use them. However...their use as a **sole** agent is discouraged for the reasons indicated above
 - ii. They may be beneficial in preventing multi-phasic (or recurrent) anaphylaxis...more on this below...

IX. Disposition

- a. Often the most challenging aspect of care from the emergency physician’s perspective
- b. Disposition is readily apparent for many patients:
 - i. Those at either end of the “spectrum” do not pose significant challenges
 1. Isolated urticaria, looks great → home
 2. Cardiovascular collapse → ICU
- c. However, what about the ~90% of patients who fall somewhere in-between? Options include:
 - i. Admit for observation – and if so, admit to what setting (floor, intermediate care, ICU?)
 - ii. Observe in the ED – and for how long (2 hours? 23 hours? Somewhere in-between?)
 - iii. “Bite the bullet,” so to speak, and just send the patient home
- d. We need to be concerned regarding disposition decisions for a few reasons:
 - i. Symptom progression

1. Trajectory of symptoms may progress (pick-up-steam) with time
2. Protracted/refractory anaphylaxis has been reported¹⁸
3. Delayed onset anaphylaxis has been reported, particularly with stinging insects¹⁹
- ii. Symptom recurrence
 1. Allergic phenomena may re-emerge following the resolution of the original reaction
 - a. Termed multi-phasic, or **recurrent anaphylaxis**
 - b. Recurrence rates reported as high as 20%²⁰
 - c. Recurrence may occur upwards of 72 hours following the original event.²¹
 - d. Recurrence may occur with any allergen, and in any age group²²
- e. Recurrent anaphylaxis in the ED setting
 - i. Retrospective ED study: of 67 cases, recurrent anaphylaxis was noted in 2 patients who had been released from the ED, with only minor recurrent allergic manifestations (urticaria) in both cases²³
 - ii. Retrospective ED: biphasic reactions occurred in 18% of 34 patients with anaphylaxis, with the second phase developing after more than 29 hours in one patient²⁴
 - iii. Retrospective ED: biphasic reactions in 5% of 282 patients
 1. Importantly: Three patients with stable vital signs on presentation developed **hypotension or severe dyspnea** on recurrence
 2. Note: these 3 initially non-concerning patients developed recurrent symptoms that meet criteria for **anaphylaxis!**
 3. Although we certainly can't base our practice solely on observational data, this certainly is illustrative of the concerns regarding disposition!
- f. So, what to do? How do we make sense of all of this information regarding recurrent anaphylaxis?
 - i. Important to recognize that the incidence is greater than generally appreciated
 1. Wide range of "asymptomatic intervals"
 2. Recurrence has occurred despite corticosteroids¹
 - a. Again, the theoretical role of steroids is to quell the second wave of mediator release (newly-synthesized mediators), which is thought to play a role in recurrent anaphylaxis
- g. Back to the recommended period of Observation...
 - i. The "magic number" (in terms of minutes or hours of ED observation) has not been established

- ii. Several hours (range 3-6 hours) appears reasonable for a mild episode (with a re-assuring trajectory of symptoms)
- iii. Longer observation appears reasonable following:
 - 1. a severe episode
 - 2. a stagnant (or worsening) symptom trajectory
 - 3. or in the presence of “High-Risk” features
- h. High risk features: lessons can be gleaned on very limited retrospective data on fatal anaphylaxis
 - i. Risk factors for fatal anaphylaxis include:
 - 1. Specific allergens^{25 26 27}
 - a. Peanuts
 - b. Tree nuts
 - 2. Comorbidities
 - a. Asthma, history of reactive airways²⁸
 - 3. Patient characteristics
 - a. Adolescents²⁹
- i. When we decide to discharge, ensure the following:
 - i. Reliable caretaker who will be with the patient, at least for the first 24 hours or so to monitor trajectory and for signs of recurrence
 - ii. Access to EMS/9-1-1 in case symptoms progress or return
- j. Discharge medications
 - i. Self-injectable epinephrine
 - 1. Prescription should be given whenever epinephrine has been utilized (or strongly considered for use) in the ED
 - 2. Confusion remains regarding the role of self-injectable epinephrine at the time of ED discharge:
 - a. Short term use (for initial 72 hours following a reaction)
 - i. Treats recurrent anaphylaxis should it occur in the out-of-hospital setting
 - ii. Use for any allergen
 - b. Long term use
 - i. Not an ED decision, per se
 - ii. Multi-disciplinary decision (primary care, allergist, others)
 - iii. Only needed for unavoidable allergens
 - 1. Peanuts, tree nuts, stinging insects, etc.
 - 2. Also for exercise-induced anaphylaxis
 - c. Complicating this distinction, however, is the fact a precipitating etiology may not be uncovered during the ED encounter (and will never be uncovered in up to 20% of cases! – eg, idiopathic anaphylaxis)

- d. Bottom line is that we prescribe self-injectable epinephrine for short term use, then refer for follow-up regarding continued use
3. Self-injectable epinephrine: only 2 available dosages²⁹
 - a. Adult – 0.3 mg
 - i. Recommended for adults
 - ii. Recommended for children > 25 kg
 - b. Junior – 0.15 mg
 - i. For children 10-25 kg
 - c. Ampule-needle-syringe method
 - i. For children less than 10 kg
- ii. Other medications
 1. H1 antihistamine
 - a. Once daily
 - b. Less-sedating/non-sedating agent preferred by many patients (and may be equivalent in treating symptoms)
 - c. If once daily less-sedating/non-sedating agent selected, can also utilize Benadryl as a “qhs booster” at nighttime for symptom relief
 2. H2 antihistamine
 - a. Typically twice daily
 3. corticosteroid
 - a. Once daily
 4. H1 + H2 + corticosteroid treatment for 3-7 days
 - a. “3 day” treatment recommendation based on observed presentation of recurrent anaphylaxis up to 72 hours after initial event
 - b. However, there is no firm data to support these broad recommendations

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