Anaphylaxis

December 10, 2016 by Josh Farkas

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clinical findings & definition

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### Clinical Findings

- **Cardiovascular**
  - Hypotension
  - Tachycardia
  - Syncope, presyncope

- **Pulmonary/Airway**
  - Upper airway obstruction (stridor, tongue/uvula swelling, voice change)
  - Bronchospasm (wheeze originating in lower airways on auscultation)
  - Dyspnea, cough

- **GI**
  - Nausea, vomiting
  - Abdominal discomfort
  - Diarrhea

- **Skin/mucosa (involved in ~90% of patients)**
  - Flushing
  - Itch
  - Urticaria
  - Angioedema (~80% sensitive) – may involve lips, eyelids, airway, hands, feet, genitalia.
  - Conjunctivitis, conjunctival swelling, tearing
  - Nasal discharge & congestion

### Timing of Anaphylaxis Onset

- Anaphylaxis due to intravenous medication or bee sting usually begins within <30 minutes.
  - Initiation of reaction immediately following exposure is a poor prognostic sign.
- Anaphylaxis due to food or oral medication usually begins within a few hours.
- Among patients who die, the time between exposure & death is (10931122):
  - ~5 minutes for iatrogenic anaphylaxis (e.g. IV medication induced).
• ~15 minutes for insect venom anaphylaxis.
• ~30 minutes for food anaphylaxis.

approach to the diagnosis: main pieces to consider

• [1] Exposure history and chronicity
  • Exposure to known causative agent increases index of suspicion.
  • Some patients can have *idiopathic* anaphylaxis, so absence of a trigger doesn't exclude anaphylaxis.

• [2] Number of organ systems involved
  • Having two organ systems involved strongly supports the diagnosis.
  • The diagnosis of anaphylaxis can be made on the basis of only one organ, within a highly suggestive clinical context.

• [3] Competing diagnoses (when in doubt, it's generally wise to treat *empirically* for anaphylaxis while continuing to investigate other diagnostic possibilities).

causes

- Foods, especially:
  - Peanuts
  - Seafood
- Insects (e.g. bees)
- Medications, especially:
  - Antibiotics (especially penicillin & first-generation cephalosporins)
  - NSAIDs, aspirin
  - Monoclonal antibodies (e.g. anti-TNF antibodies)
  - Radiocontrast dye
  - Paralytics
  - Protamine
  - Local anesthetics (e.g. lidocaine, benzocaine, mepivacaine)
- Blood products in an IgA deficient person
- Exercise, cold or heat exposure

* The reaction to NSAIDs, aspirin, or radiocontrast dye is technically an anaphylactoid reaction, not anaphylaxis. The two disorders are treated the same fashion, however.

differential diagnosis

- Asthma
  - Severe asthma is a risk factor for anaphylaxis.
  - Wheeze and dyspnea in an “asthmatic” is likely to be *presumed* due to asthma.
- Angioedema due to bradykinin accumulation (see chapter on [angioedema](https://emcrit.org/bcc/angioedema/)).
- Systemic mastocytosis.
- Red person syndrome due to vancomycin.
- Scombroidosis (“histamine fish”).
- Upper airway obstruction of any etiology (e.g. vocal cord dysfunction, epiglottitis, abscess compressing airway).
- Acute pulmonary deterioration (e.g. pulmonary embolism, pneumothorax).
- Sepsis, toxic shock syndrome.

investigation


**tests for anaphylaxis**

- There are no tests to immediately diagnose anaphylaxis.
- Tryptase levels won’t come back for a long time, but may eventually help clarify whether the patient had anaphylaxis.

**evaluation of competing diagnoses**

- Depending on the presentation, it may be necessary to evaluate for other diagnostic possibilities.
- *Clinical example.* A patient presents with vasodilatory shock and urticaria. Anaphylaxis is suspected, but there is also a concern for septic shock. The patient is treated empirically for both conditions (with IV epinephrine infusion, steroid, antihistamine, and antibiotic). Infectious workup is pursued with chest X-ray, procalcitonin, and blood cultures. The infectious evaluation is negative, so antibiotics are stopped – leaving the patient with a *clinical diagnosis* of anaphylaxis.

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**anaphylaxis vs bradykinin-mediated angioedema**

**clinical characteristics of histamine-mediated versus bradykinin-mediated angioedema**

<table>
<thead>
<tr>
<th></th>
<th>Allergic angioedema (Histamine-mediated)</th>
<th>Non-allergic angioedema (Bradykinin-mediated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigger?</td>
<td>- Allergic trigger (medications, foods, insects, etc.)</td>
<td>- ACE/ARB commonly involved. Can be triggered by minor trauma.</td>
</tr>
<tr>
<td>Distribution</td>
<td>- Typically diffuse, symmetric.</td>
<td>- Often focal/asymmetric.</td>
</tr>
<tr>
<td></td>
<td>- More often involves lips &amp; eyes.</td>
<td>- Often primarily involves tongue.</td>
</tr>
<tr>
<td>Eyelids in %</td>
<td>Eyelids in 4%</td>
<td>Eyelids in 2%</td>
</tr>
<tr>
<td>Lips in %</td>
<td>Lips in 30%</td>
<td>Lips in 24%</td>
</tr>
<tr>
<td>Tongue in %</td>
<td>Tongue in 33%</td>
<td>Tongue in 42%</td>
</tr>
<tr>
<td>Larynx in 3% (stridor, hoarse)</td>
<td>Larynx in 17%</td>
<td></td>
</tr>
<tr>
<td>Extremities in %</td>
<td>Extremities in 11%</td>
<td>Extremities in 4%</td>
</tr>
<tr>
<td>Rapidity of onset</td>
<td>Fast (may evolve over minutes).</td>
<td>Slower (evolves gradually over many hours).</td>
</tr>
<tr>
<td>Associated skin findings</td>
<td>Urticaria, flushing, or generalized pruritus may be seen.</td>
<td>- No urticaria or pruritus.</td>
</tr>
<tr>
<td></td>
<td>Erythema or itching in 53%</td>
<td>Erythema or itching in 1%</td>
</tr>
<tr>
<td>Involvement of other organs</td>
<td>May occur in context of anaphylaxis with involvement of other organs (e.g., hypotension, wheeze, nausea/vomiting, diarrhea).</td>
<td>Usually doesn’t involve other organs, although can involve bowel (causing pain, diarrhea, nausea).</td>
</tr>
<tr>
<td>Response to therapy</td>
<td>Responds to antihistamines, steroid. 90-100% will improve</td>
<td>Unresponsive to antihistamine/steroid.</td>
</tr>
</tbody>
</table>

Numbers obtained from Lenschow 2018 PMID 29721614 [Internet Book of Critical Care, by @PulmCrit](https://emcrit.org/wp-content/uploads/2019/07/numbersangiodiff.svg)

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**approach to sorting out the etiology of angioedema**

- Clearly differentiating the cause of angioedema is important (because the treatments are entirely different).
- Anaphylaxis is histamine-mediated, so it will almost always respond rapidly to aggressive treatment (with epinephrine, antihistamine, and steroid, as discussed below). In contrast, bradykinin-mediated angioedema won’t respond to these treatments (and tends to progress slowly, over a period of hours). Therefore, an immediate therapeutic trial of therapies for anaphylaxis can be used as a diagnostic/therapeutic approach to differentiating anaphylaxis versus bradykinin-mediated angioedema (29721614 [https://www.ncbi.nlm.nih.gov/pubmed/29721614](https://www.ncbi.nlm.nih.gov/pubmed/29721614)).
Anaphylaxis - EMCrit Project

2/13/2020

[Anaphylaxis - EMCrit Project](https://emcrit.org/ibcc/anaphylaxis/)

Intravenous epinephrine infusion

Intramuscular epinephrine

Intravenous epinephrine infusion

Source control

- Any potentially causative infusion (e.g. drug, blood transfusion) must be stopped.
- Consider placing a tourniquet proximal to site of sting or antigen infiltration (e.g. local anesthetic).

**Epinephrine**

**Indications for epinephrine** = any of the following:

- A = Airway involvement
- B = Breathing difficulty
- C = Circulation (hypotension)
- C = Involvement of any two organ systems (e.g. nausea/vomiting plus urticaria).

**Intramuscular epinephrine**

- Traditional approach, useful in most situations.
- Start with 0.3-0.5 mg IM into the mid anterolateral thigh.
- If symptoms recur, then consider a repeat dose or initiation of an IV epinephrine infusion (as below).

**Intravenous epinephrine infusion**

- May be useful for anaphylaxis which occurs in a context where providers are well versed in the use of IV epinephrine (e.g. ICU, OR, emergency department).
- Advantages of IV epinephrine:
  - i) Faster onset (if the patient has an IV placed and if IV epinephrine is available, this is the fastest way to get the medication into circulation).
  - ii) Smoother tapering – the infusion can be gradually weaned off in a controlled fashion.
  - iii) Ability to withdraw the epinephrine if problems are encountered (e.g. hypertension). This is unlike IM epinephrine, where the epinephrine cannot be immediately withdrawn.
  - iv) Patients who are already shocked may not perfuse their muscle tissue well, so they may have poor absorption of IM epinephrine.
- A regimen for using IV epinephrine in anaphylaxis is shown below.
- “Dirty Epi Drip”
  - If a pre-mixed bag of epinephrine isn’t immediately available, one may be created as follows:
  - Inject a 10-ml syringe of cardiac epinephrine (1:10,000) into a 1-liter bag of normal saline or lactated ringers. (Or a 1-ml vial of 1:1,000 epinephrine – either form will work perfectly here, since both contain a total of 1 mg of epinephrine). Shake it up. This creates a 1 microgram/ml solution of epinephrine.
  - Titrate:
    - 2 micrograms/min = 2 ml/min = 120 ml/hour
    - 5 micrograms/min = 5 ml/min = 300 ml/hour

https://emcrit.org/ibcc/anaphylaxis/
10 micrograms/min = 10 ml/min = 600 ml/hour
16 micrograms/min = 16 ml/min = 960 ml/hour

- Push-doses of 20 mcg epinephrine can be given as 20-ml boluses (using a 20-cc syringe).
- Diluting epinephrine in a liter of saline makes it difficult to give it fast enough to kill someone. Even if this solution is run in wide open, it will result in administration of ~20-30 mcg/min infusion – which shouldn't be dangerous in a monitored setting and might be an appropriate dose during the first few minutes.

- Peripheral IV epinephrine is safe, so a central line is **neither required nor recommended** (https://emcrit.org/pulmcrit/phenylephrine-epinephrine-central-access/).

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### Approach to IV epinephrine dosing in anaphylaxis

- **Is patient peri-arrest** (e.g., bradycardic, profoundly hypotensive, about to die)
  - No
  - Yes: Bolus ~20-50 mcg IV epinephrine

### Loading epinephrine infusion at 20 mcg/min

- Mild-moderate anaphylaxis: Continue at this infusion rate for ~2 minutes
- Severe anaphylaxis with hypotension: Continue at this rate until MAP increases >65 mmHg

### Maintenance epinephrine infusion of 10 mcg/min

- Titrated to effect within a range of roughly 5-15 mcg/min.

### Wean off epinephrine

- Begin weaning after ~20-30 minutes of clinical improvement (ideally patient will have received anti-histamine therapy by then).
- Target discontinuation in under ~2 hours (you can always re-start PRN)

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### Physiology of epinephrine in anaphylaxis

- Effects of epinephrine:
  - Hemodynamic stabilization (vasoconstriction, inotropy, chronotropy)
  - Stabilization of mast cells (prevents ongoing mediator release)
  - Reduction of airway edema
  - Bronchodilation (via beta-2 receptors)

- Key points:
  - (1) Epinephrine has many beneficial effects in anaphylaxis (above and beyond hemodynamics). Even if the patient's hemodynamics are stable, epinephrine can still be life-saving.
  - (2) Epinephrine is the only real **disease-modifying** medication for acute anaphylaxis. For example, anti-histamines may make the patient less itchy, but they don't do much else.

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### Usual anaphylaxis cocktail (for non-beta-blocked patient)

1. **Epinephrine** dosed as above is **most important therapy**.
2. **Steroid**
   - 125 mg methylprednisolone IV x1 loading dose, then:
   - 60 mg methylprednisolone IV daily until no longer critically ill.
3. **H1-receptor antihistamine**
   - Diphenhydramine (BENADRYL) 50 mg IV Q4-6 hr.

4. **H2-receptor antihistamine**
   - Famotidine (PEPCID) 20 mg IV q12hr.
   - Ranitidine (ZANTAC) 50 mg IV q6hr.

5. +/- **Albuterol** for bronchospasm that persists *despite epinephrine (#1 above).*

**anaphylaxis in a beta-blocked patient**

- **Start with standard therapy** as shown above.
  - Epinephrine *remains* the front-line therapy.
  - For most patients who are on low or moderate-dose beta-blockers, epinephrine should still work fine.
- If the patient *fails* to respond adequately to standard treatment (and particularly if bradycardic), then try:
  - Glucagon
    - Start with 1-5 mg IV over five minutes.
    - If there is a response, may infuse at 0.3 – 0.9 mg/hour.
    - *This will often elicit vomiting,* so use caution if the patient has borderline ability to protect their airway.
  - Isoproterenol infusion (2-10 micrograms/minute) if available
    - Isoproterenol is a pure beta-agonist.

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**fluid resuscitation**

- Large volumes of crystalloid may be required for hemodynamic stability (e.g. several liters of lactated Ringers).
- Aggressive fluid resuscitation is particularly important for:
  - Patients requiring high doses of epinephrine to maintain hemodynamic stability.
  - Patients about to be intubated.
- Bedside echocardiography may guide fluid resuscitation (if available).

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**airway management**

**racemic epinephrine & heliox**

- **Nebulized racemic epinephrine** can temporize while preparing for intubation.
- **Heliox** may also be considered as a stop-gap measure to stabilize the patient sufficiently to organize the material and people required for intubation.

**indications for intubation**

- Precise indications are unclear. High-quality evidence is impossible to obtain, for the following reasons:
  - (#1) Physicians cannot be blinded to clinical features when they decide whether to intubate a patient.
  - (#2) Intubation is generally used as an *outcome* variable, but this may simply be a measurement of the decision algorithms which physicians employ when deciding whether to intubate (#1).
  - (#3) Truly determining which patients absolutely require intubation would require a decision to randomized patients and *never* intubate some patients and see which patients die – which is obviously impossible.
- Potential indications for intubation are as follows:
  - (1) Stridor, dyspnea – especially if worsening & not responding to therapy.
  - (2) Inability to handle secretions.
  - (3) Progressive deterioration of edema (intubation may become more difficult over time if edema worsens).
(4) Nasolaryngoscopy shows significant laryngeal edema or impending closure of the posterior pharynx. When in doubt, nasolaryngoscopy may help reveal whether there is significant laryngeal edema. The true threat to the airway is the larynx and posterior tongue – not the lips and anterior tongue.

**Intubation is fraught with hazard**

- Airway manipulation may worsen swelling.
- Laryngeal edema will often preclude the use of a laryngeal mask airway.
- In severe angioedema, orotracheal intubation may simply be impossible.
- There is a high risk of hemodynamic collapse following intubation: start epinephrine & give fluid beforehand.

**Scenario #1: the crashing anaphylaxis patient (extremely rare!)**

- **Description**
  - Patient is at immediate risk of losing their airway.
  - Patient is stridulous, sitting bolt upright, and struggling for breath.
  - Patient may be unable to lie down.
- **Potential management:** Ketamine-dissociated cricothyrotomy
  - Place the patient on 100% FiO2 using one of the following:
    - i) High-flow nasal cannula at 100% FiO2 and 60 liters flow.
    - ii) BiPAP mask.
    - iii) 100% Non-rebreather facemask set to flush rate (crank the flow rate well past the 15 liters/min mark).
    - iv) 100% non-rebreather facemask set to 15 liters/minute plus a nasal cannula underneath it running at 15 liters/minute.
  - Provide a dissociative dose of IV ketamine (e.g. 1.5-2 mg/kg) slowly over ~120 seconds. This should fully dissociate the patient, without impairing the respiratory drive. Patients with a history of alcoholism may require more ketamine to fully dissociate.
  - Perform a scalpel-finger-bougie cricothyrotomy. The patient should continue breathing throughout the entire procedure, so you should be able to take your time a bit with this. However, if asphyxiation occurs, the procedure should be achievable very rapidly.

**Scenario #2: the non-crashing anaphylaxis patient**

- **Description**
  - The patient requires intubation, but isn't actively crashing.
  - There is time to call for help and additional equipment.
- **Suggested management:** The awake double setup:
  - Obtain an experienced intubator and someone competent at scalpel-finger-bougie cricothyrotomy *(Note: it doesn't matter whether this person is a surgeon, what matters is skill in this specific procedure).*
  - Perform awake fiberoptic intubation. These patients often have tongue swelling, so the best approach is often nasotracheal intubation (for taller patients, consider obtaining an extra-long ETT for nasotracheal intubation).
  - During the intubation procedure, the second operator should be prepared to perform cricothyrotomy if the airway is lost.

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**Recovery**

**Weaning epinephrine**

- The one drawback of using an epinephrine infusion is that it tends to stay on forever.
- Aggressive attempts should be made to wean the epinephrine off, ideally within some hours of admission.
- Follow the patient carefully after stopping epinephrine, and resume the infusion if symptoms recur.

**Steroid**

- Duration of steroid therapy is unknown.
- Prolonged courses are probably unnecessary (e.g. may be stopped within 2-3 days).

**Extubation**
Patients can generally be extubated reasonably rapidly (e.g. after <24 hours). The primary determinant of readiness to extubate is visual confirmation that airway edema has improved – rather than any arbitrary time interval (30480175).

Evaluation of airway patency:
- Wait for external swelling to subside (if there is observable swelling).
- Under deep sedation, very gently insert a hyperangulated videolaryngoscope blade (e.g. a glidescope blade or a C-MAC D-blade). This should allow for direct visualization of the airway, including the epiglottis.
- Presence or absence of cuff leak may provide some adjunctive information.
- When in doubt, consider extubation over an airway exchange catheter:
  - Leave the airway exchange catheter in place temporarily to ensure that the airway is patent.
  - If stridor occurs, re-intubation can be performed immediately over the exchange catheter.

duration of observation in the hospital

- Recurrent (biphasic) reactions can occur, but they are rare and tend to be less severe.
- There is no evidence supporting any specific duration of time to observe the patient prior to discharge.

discharge instructions

- (1) Patients should be prescribed an EpiPen and taught how to self-administer it.
- (2) Efforts should be made to avoid the causative agent.
- (3) Patients should be instructed to return to the hospital if a recurrent reaction occurs.
- (4) Many patients will be discharged with a short course of steroids (e.g. 3-5 days).
  - This seems reasonable but isn't supported by any high-level evidence.

To keep this page small and fast, questions & discussion about this post can be found on another page here.
Attempting intubation without sufficient preparation/planning.

Going further:

- **Epinephrine**
  - [How to use IV epinephrine for anaphylaxis](https://emcrit.org/pulmcrit/iv-epinephrine-anaphylaxis/) (PulmCrit)
  - [IV bolus epinephrine for anaphylaxis?](https://emcrit.org/emcrit/iv-bolus-epinephrine-for-anaphylaxis/) (EMCrit with Ashley Mogul)
  - [Dirty Epi Drip](https://www.aliem.com/dirtyepi/) (Zlatan Coralic, ALIEM)

- [Anaphylaxis](https://lit.com/anaphylaxis/) (Chris Nickson, LITFL)
- [Management of severe anaphylaxis in the ED](https://rst10em.com/anaphylaxis/) (Justin Morgenstern, First10EM)
- [Anaphylaxis](https://wikem.org/wiki/Anaphylaxis) (WikEM)
- [Anaphylaxis mock trial with Mike Weinstock](https://emcrit.org/emcrit/refractory-anaphylaxis-mock-trial/) (EMCrit)


The Internet Book of Critical Care is an online textbook written by Josh Farkas (@PulmCrit), an associate professor of Pulmonary and Critical Care Medicine at the University of Vermont.

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