



EM CASES SUMMARY

Episode 78 –Anaphylaxis & Anaphylactic Shock Live from EM Cases Course

With Dr. David Carr

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Anaphylaxis is *the* quintessential medical emergency. We *own* this one. While the vast majority of anaphylaxis is relatively benign, about 1% of these patients die from anaphylactic shock. And usually they die quickly. Observational data show that people who die from anaphylaxis and anaphylactic shock do so within about 5-30mins of onset, and in up to 40% there's no identifiable trigger. The sad thing is that many of these deaths are because of 2 simple reasons:

1. The anaphylaxis was misdiagnosed and
2. Treatment of anaphylaxis and anaphylactic shock was inappropriate.

Diagnostic Criteria for Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to hours), with involvement of the skin, mucosal tissues, or both AND at least one of the following:
 - Respiratory compromise
 - Reduced blood pressure or associated symptoms of end-organ dysfunction
2. Two or more of the following that occur rapidly (minutes to hours) after exposure to a likely antigen for that patient:
 - Involvement of the skin - mucosal tissue
 - Respiratory compromise
 - Reduced blood pressure or associated symptoms of end-organ dysfunction
 - d. Persistent gastrointestinal symptoms
3. Reduced blood pressure after exposure to a known allergen for that patient (minutes to hours)
 - Infants and children: low systolic blood pressure (age-specific) or >30% decreased in systolic blood pressure
 - Adults: systolic blood pressure <90 mm Hg or >30% decrease from that patient's baseline

Adapted from: Sampson HA, Munoz-Furlong A, Bock SA, et al. Symposium on the definition and management of anaphylaxis: summary report. J Allergy Clin Immunol 2005; 115:584-91.

Note that according to this definition of anaphylaxis, isolated hypotension after an allergen exposure can be diagnostic for

anaphylaxis, and that anaphylaxis can occur without any skin manifestations.

The importance of epinephrine timing, location and dose in anaphylaxis

All patient who fulfill the criteria for anaphylaxis require the administration of epinephrine. Epinephrine is the *only* drug to show a mortality benefit in the management of anaphylaxis.

#1



TIMING



LOCATION



DOSE



Epinephrine should be administered as soon as the diagnosis of anaphylaxis is made intramuscularly in the anterolateral thigh.

Administering epinephrine IM in the deltoid muscle is *not* recommended.



LOCATION



That means, the patient needs to disrobe in order to access the thigh. Intramuscular administration of epinephrine in the anterolateral thigh reaches the maximal epinephrine serum concentration seven approximately 7 times faster compared to the arm. Subcutaneous injections should be avoided. Peak concentrations of epinephrine occurs in approximately 8 minutes when administered intramuscularly compared to approximately 34 minutes for subcutaneous injections.

Dose of Epinephrine in Anaphylaxis

The correct dose of epinephrine for the treatment of anaphylaxis is **0.01mg/kg (to a max of 0.5mg) IM**, repeated after 5 mins if there's no clinical improvement. It is common practice to under-dose epinephrine in this setting. A 180 lb man should NOT be getting only 0.3mg IM. Any patient weighing 50Kg or more should receive 0.5mg of epinephrine IM.

Take home point #1:

The most common cause of death in anaphylaxis is not giving epinephrine at the right time at the correct dose

Second line agents for anaphylaxis

What's the evidence for the effectiveness of the addition of H2 blockers to H1 blockers in the symptomatic relief in allergic reactions and anaphylaxis?

One study from The Annals of EM in 2000 looked at 91 adults presenting to the ED with urticaria, acute angioedema, acute unexplained stridor or acute pruritic rash within 12 hours of ingested food, drug or contact with latex. They found that the combination of 50mg of diphenhydramine plus 50mg of ranitidine compared to diphenhydramine plus placebo was significantly more likely to result in absence of urticaria at 2 hours (91.7% in the ranitidine group vs 73.8% in the placebo group).

While the addition of H2 blockers to H1 blockers may help resolve urticaria faster, the true clinical significance of this is unknown. Certainly, there is no evidence in the literature to suggest that either H1 or H2 blockers have a mortality benefit in the treatment of anaphylaxis.

What about steroids? Which patients require steroids in the ED for anaphylaxis?

There is a paucity of evidence for the efficacy of steroids in patients with allergic reactions or anaphylaxis. Nonetheless, corticosteroids are standard care for patients with anaphylaxis. Our expert's practice is that if the patient fulfills the diagnostic criteria for anaphylaxis, give epinephrine AND steroids. While there is no good evidence in the literature that the addition of steroids to epinephrine has a mortality benefit or prevents a biphasic reaction, it is still recommended by our expert, but only if the setting of true anaphylaxis.

If the patient does *not* fulfill the diagnostic criteria for anaphylaxis, then steroids are *not* indicated.

Remember that steroids take 4-6hrs to become effective, so (in contradistinction to epinephrine) there is no rush to administer them.

If you *do* give steroids, our expert recommends single dose dexamethasone in the ED, which has the advantage of a long half-life of 53hrs, thus negating the need for prescribing steroids upon discharge.

Take home point #2

If you don't give epinephrine (ie the patient does not have anaphylaxis) then don't give steroids.

Observation time in anaphylaxis

How long to do you need to keep patients with allergic reactions with or without anaphylaxis in the ED? Which patients might you want to observe for a prolonged period of time in the ED?

While traditionally patients with anaphylaxis are observed in the ED for 4-6hrs before discharge, there is no literature to support this practice. Some experts recommend observing patients until they become asymptomatic regardless of time. It may be prudent to observe patients longer who have been shown in observational studies to be at high risk for severe anaphylaxis.

The risk factors for severe anaphylaxis are:

- patients taking anti-hypertensive medication
- early symptom onset and late treatment initiation
- asthmatics
- past history of severe reactions

Biphasic reactions in anaphylaxis

Do we need to worry about biphasic reactions in deciding how long to observe patients for? How effective are steroids at preventing biphasic reactions in anaphylaxis?

Observational data have shown that biphasic reactions in anaphylaxis can occur any time between 1 hour and 7 days after the initial anaphylactic episode in approximately 2-5% of patients.

Recent literature has found that the rate of biphasic reactions may be lower than previously stated. In a Canadian observational study out of *Annals of EM* in 2013 of 496 anaphylactic patients and 2,323 allergic reactions, clinically important biphasic reactions occurred in only 0.18% of patients with no deaths. While it is tempting to conclude from this study that biphasic reactions are so rare that they become almost irrelevant, this study was *not* confined to patients with anaphylaxis. The vast majority of these patients did not fulfill the criteria for true anaphylaxis and likely had minor allergic reactions which would have gotten better by themselves, *regardless* of medications.

In another Canadian retrospective cohort study from *Annals of EM* in 2015 of 473 anaphylactic patients and 2,701 allergic reactions, they looked at the number of subsequent allergy-related ED visits within 7 days (a "relapse") in steroid and non-steroid exposed groups. They found that the 7-day bounce back rate was 5.8% in the steroid group vs 6.7% in the no steroid group. The number needed to treat (NNT) to prevent one ED relapse visit was 176. Again, the issue with this study, was that only a small proportion of patients actually fulfilled the criteria for true anaphylaxis, with only 54% receiving epinephrine.

Therefore, we cannot assume from these studies that steroids play *no* role in preventing relapses or biphasic reactions in anaphylaxis. Until large validated RCTs can show definitely that steroids are not effective in this respect, it still remains standard care to administer steroids along with epinephrine for patients with true anaphylaxis.

Take home point number #3

While there is no good evidence that steroids decrease the relapse rate or rate of biphasic reactions, further studies are required to abandon steroids for the treatment anaphylaxis.

The administration of epinephrine in adequate doses early in the illness course may prevent biphasic reactions.

What counseling do you provide patients who you are discharged from the ED after anaphylaxis?

One of the more common causes of death in anaphylaxis, is the patient not self-administering the epinephrine auto-injector (even if they are carrying it on their person) or not administering it properly. It is therefore imperative not only to give the patient a script for epinephrine auto-injectors on discharge from the ED, but to take the time to counsel patients on the use of them. It is recommended for patients to carry 2 epinephrine auto-injectors as the adult ones only contain 0.3mg of epinephrine, and many patients will require 2 doses. In one study only 32% of patients could demonstrate that they knew how to use the epinephrine auto-injector correctly. In the same study, only 36% of pediatric residents showed they could use

an auto-injector correctly and, sadly, only 18% of attending physicians could do so.

Epinephrine auto-injector instructions for patients being discharged from the ED after anaphylaxis

1. Remove the auto-injector from its case
2. Remove the safety release mechanism, making sure that the blue end points away and the orange end points to the thigh ("Blue to the Sky, Orange to the Thigh")
3. Firmly push the auto-injector against the middle of the outer thigh (through the pants if necessary) until a clicking sound is heard
4. Hold the auto-injector firmly in place against the thigh for 10 seconds to deliver the medication
5. Remove the device from the thigh and call 911

Anaphylactic Shock

Can isolated hypotension be the only finding in anaphylaxis?

As outlined above in the diagnostic criteria of anaphylaxis, isolated hypotension after exposure to a presumed allergen is enough to make the diagnosis of anaphylaxis. Observational studies show that up to 20% of patients do *not* have a rash with their anaphylaxis. While this patient could be suffering from septic shock, and consideration should be given to this in the work-up and management, he also fulfills the diagnostic criteria for anaphylactic shock which is a more time-sensitive emergency than septic shock.

Pitfall: *Assuming the patient does not have anaphylaxis just because they don't have a rash*

How would you administer epinephrine in the scenario of anaphylactic shock resistant to two doses of IM epinephrine?

After 2 intramuscular injections of 0.01mg/kg (max 0.5mg) epinephrine 5 minutes apart, it's time to move on to IV epinephrine.

Steps for drawing up epinephrine for push dose epinephrine and epinephrine infusion

- Inject **1 mg** of epinephrine 1:10,000 (one amp of crash cart epi) into a **1L bag of normal saline**
- Draw up 10mL from the 1L bag in a 10mL syringe (The concentration of epinephrine in the syringe is **now** 1 mcg/mL)

Push Dose: 10 mL every 2-5 minutes (10 mcg)

- note that the onset = 1 minute and duration = 5-10 minutes

Dose of epinephrine given via infusion: 1 mL/min (1 mcg/min) and titrate to a maximum of 20mL/min

Note that starting May 2016, the current 1:1,000 vs 1:10,000 concentration of epinephrine will be replaced by 1mg/mL and 0.1mg/mL respectively to minimize confusion leading to medication dosing error.

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What is your next move after maxing out on your IV epinephrine infusion?

Do not underestimate profound vasodilatory shock that occurs in anaphylactic shock. First, aggressive fluid resuscitation is indicated for patients with anaphylactic shock via rapid infuser or short large peripheral IVs with pressure bags. Second, consideration may be given to a second vasopressor. There exists some anecdotal evidence for vasopressin, however our expert recommends whatever vasopressor with alpha properties that you are most familiar with.

Vasopressin dose: 1-5mg IV bolus followed by infusion of 1-5mg/hr

Take home point #4

Anaphylaxis, can present with isolated hypotension, or hypotension plus vomiting, or hypotension plus wheezing without rash.

Not recognizing this in a timely manner can lead to misdiagnosis and death.

Pearl: a cognitive forcing strategy that can be employed whenever you are presented with a patient who appears to be in septic shock, is to ask yourself "could this be anaphylactic shock" and inquire about possible recent allergen exposure, previous anaphylaxis and the rapidity of onset.

CASE: A 43 year-old is brought to the ED by his wife with an allergic reaction to Cloxacillin. He complained of nausea, vomited once and some shortness of breath along with his urticarial rash. He was

given epinephrine 0.5mg IM, and soon after started complaining of chest pain. His ECG shows an obvious STEMI.

Q: What happened here? Did you cause an MI with your IM epinephrine? Did this man have underlying coronary disease that you should have asked about as a contraindication to epinephrine?

Epinephrine in the *correct* dose for anaphylaxis generally does *not* cause MIs. There are no absolute contraindications to epinephrine in severe anaphylaxis.

The diagnosis is in this case is *Kounis Syndrome*.

Kounis Syndrome: Anaphylaxis of the coronary arteries

Kounis syndrome is essentially an allergic myocardial infarction; an acute coronary event in the setting of an anaphylactic reaction. There are 3 subtypes of Kounis Syndrome:

Type I - normal coronary arteries and no cardiovascular risk factors
Type II - pre-existing coronary artery disease
Type III - coronary stent thrombosis due to anaphylaxis

A bit of basic pathophysiology is helpful to understanding how one ends up with a STEMI after anaphylaxis:

There is a high density of mast cells present in the coronary arteries in people with coronary artery disease. When anaphylaxis occurs, chemical mediators induce coronary artery vasospasm as well as

platelet activation. In patients with existing CVD, these conditions can promote plaque rupture and stent thrombosis.

The management of patients with Kounis syndrome is challenging. The emergency provider must treat both the allergic and cardiac manifestations of anaphylaxis. Unfortunately, no guidelines exist for the management of patients with acute coronary events in the setting of anaphylaxis. Theoretically, epinephrine may worsen coronary vasospasm and worsen myocardial ischemia. Notwithstanding, epinephrine should still be given as the initial treatment of choice. In a recent case series, approximately 24% of patients with Kounis syndrome received epinephrine and there were no deaths. Cardiac catheterization with intracoronary vasodilator infusion has been used successfully to treat patients with Type I Kounis syndrome. Similarly, catheterization with thrombus evacuation has been successfully used to treat patients with Type III Kounis syndrome.

Take home points:

1. The number one cause of death in anaphylaxis is failure to give epinephrine in a timely manner, in the correct location and in the correct dose.
2. There are no contra-indications to epinephrine when it comes to severe anaphylaxis.
3. Consider anaphylaxis in every patient who presents in shock, cuz anaphylaxis can present with isolated hypotension

Dr. Helman and Dr. Carr have no conflicts of interest to declare.

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