
Presented by
Scott Russell, MD

December 7, 2016
Welcome!

Made possible through a 2016 grant from:

www.foodallergy.org
Scott Russell, M.D.
Division Chief and Medical Director,
Pediatric Emergency Medicine
Medical University of South Carolina
Epi First, Epi Fast. Ask Questions Later

Scott Russell, MD
Division Chief and Medical Director,
Pediatric Emergency Medicine
Medical University of South Carolina
12/7/2016
Acknowledgements:

The content presented in this discussion are modified from a presentation at the ASAnaphylaxis Summit in 2016

Content prepared by the speaker in conjunction with Drs. Dana Wallace, Stan Fineman, and Wes Sublett

Drs. Wallace, Fineman, and Sublett are really, really smart Allergists and the speaker is the medical equivalent of a caveman (i.e. an emergency physician)
Definition of Anaphylaxis

**Food allergy**: adverse reaction to a food allergen caused by immunologic mechanisms.¹

**Systemic reaction**: an allergic reaction which is not immediately life threatening, is limited to a single organ system, and has cutaneous/mucosal symptoms, if present, extending beyond the immediate area of allergen contact. (allergist’s definition)

**Anaphylaxis**: a severe, potentially life-threatening systemic hypersensitivity reaction.²

**Allergic reaction**: a local or generalized immunological reaction following contact with a specific allergen to which one has been previously exposed and sensitized. (allergist’s definition)

Muraro et al, Allergy 2014;69:1046-57
Muraro et al, Allergy 2014;69:1026-45
Classification of Human Anaphylaxis

Human Anaphylaxis

Immunologic

IgE, FcεRI
Foods, venoms, latex, drugs

Non-IgE, Non-FcεRI
Non-IgE, Non-FcεRI
Dextran, OSCS, contaminants in heparin, transfusion reactions

Idiopathic

ANAPHYLACTOID

Non-IgE, Non-FcεRI

Other

Radiocontrast media, aspirin, opioids, NSAIDs

Physical

Exercise, cold

IgE, immunoglobulin E; FcεRI, high-affinity IgE receptor; NSAIDs, nonsteroidal anti-inflammatory drug; OSCS, oversulfated chondroitin sulfate.
NIAID/FAAN: Clinical Criteria for Diagnosing Anaphylaxis

Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both

OR

≥2 of the following that occur rapidly after exposure to a likely allergen (minutes to several hours):

- Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
- Respiratory compromise
- Reduced BP or associated symptoms of end-organ dysfunction
- Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

OR

Reduced BP after exposure to known allergen (minutes to several hours):

AND AT LEAST 1 OF THE FOLLOWING

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm)
- Reduced BP or associated symptoms of end-organ dysfunction

*Low systolic blood pressure (SBP) for children is defined as <70 mm Hg from 1 month to 1 year, <70 mm Hg plus (2x age) from 1 to 10 years, and <90 mm Hg from 11 to 17 years.

Cave Man Diagnosis

- Textbook definition great for allergists
- Clinical definition great for retrospective studies
- Gut check definition best bet for ED practitioners…and parents
Signs and symptoms of **Anaphylaxis**

- **Swelling of the conjunctiva**
- **Central nervous system**
  - lightheadedness
  - loss of consciousness
  - confusion
  - headache
  - anxiety
- **Runny nose**
- **Swelling of lips, tongue and/or throat**
- **Respiratory**
  - shortness of breath
  - wheezes or stridor
  - hoarseness
  - pain with swallowing
  - cough
- **Heart and vasculature**
  - fast or slow heart rate
  - low blood pressure
- **Skin**
  - hives
  - itchiness
  - flushing
- **Pelvic pain**
- **Gastrointestinal**
  - crampy abdominal pain
  - diarrhea
  - vomiting
  - Loss of bladder control
Treatment of Anaphylaxis

1. Have a written emergency protocol for recognition and treatment of anaphylaxis and rehearse it regularly.

2. Remove exposure to the trigger if possible, e.g., discontinue an intravenous diagnostic or therapeutic agent that seems to be triggering symptoms.

3. Assess the patient’s circulation, airway, breathing, mental status, skin, and body weight (mass).

4. Promptly and simultaneously, perform steps 4, 5, and 6.

   - Call for help: resuscitation team (hospital) or emergency medical services (community) if available.

5. Inject epinephrine (adrenaline) intramuscularly in the mid-anteronatal aspect of the thigh; 0.01 mg/kg of a 1:1000 (1 mg/mL) solution, maximum of 0.5 mg (adult) or 0.3 mg (child); record the time of the dose and repeat it in 5-10 minutes, if needed. Most patients respond to 1 or 2 doses.

6. Place patient on the back or in a position of comfort if there is respiratory distress and/or vomiting; elevate the lower extremities; tachycardia can occur within seconds if patient stands or sits suddenly.

7. When indicated, give high-flow supplemental oxygen (8-10 L/min), by face mask or oropharyngeal airway.

8. Establish intravenous access using needles or catheters with wide-bore cannula (14-16 gauge). When indicated, give 1-2 litres of 0.9% (isotonic) saline rapidly (e.g., 5-10 mL/kg in the first 5-10 minutes to an adult; 10 mL/kg to a child).

9. When indicated at any time, perform cardiopulmonary resuscitation with continuous chest compressions.

10. In addition,

    - At frequent, regular intervals, monitor patient’s blood pressure, cardiac rate and function, respiratory status, and oxygenation (monitor continuously, if possible).
Guidelines Position Epinephrine as First-line Emergency Treatment of Anaphylaxis

- Epinephrine has a primary role in the management of anaphylaxis
- Prompt intramuscular injection of epinephrine, the first-line medication, should not be delayed by taking the time to draw up and administer adjunctive medications, such as antihistamines and glucocorticoids
- Epinephrine is the drug of choice for the treatment of anaphylaxis
- The appropriate dose of epinephrine should be given promptly at the onset of apparent anaphylaxis
- Epinephrine is the first-line treatment in all cases of anaphylaxis
- When there is suboptimal response to the initial dose of epinephrine dosing remains first-line therapy over adjunctive treatments
- Upon discharge, 2 doses of epinephrine autoinjector should be prescribed
- Patients must be educated on when and how to use the epinephrine autoinjector device

If Epinephrine Is Standard of Care, Why Is Everyone So Scared To Use It?
Reasons Patients Report Why They Did Not Use an Auto-injector

- Not prescribed by physician
- Not affordable/not filled
- Not accessible when reaction occurred
- Previous reaction improved quickly
- Current reaction seemed mild or improved quickly
- Used another medication to treat episode
- Patient taking another medication that interfered with using the EAI
- Didn’t want to go to ED
- Patient was unsure when to inject or injected too late
- Rapid progression of reaction

Reasons Why Providers May Not Use Epi

- Historical bias
- Timing of presentation/Resolution of symptoms
- Diagnosis bias?
- We treat a lot of allergic reactions…severe ones are rare
- Fear of dosing error
- Cost of EAI
- Access to subspecialty care
- Time investment to properly educate
- ED throughput
NIAID Guidelines
Standard of Care

1) Use of IM epinephrine as treatment of choice
2) Educational instruction at discharge
3) Prescription for an Epinephrine Autoinjector (EAI)
4) Referral to a specialist

Do We Practice What We Preach?

- Pediatric Health Information System (PHIS) database 1/1/09-9/20/13
- 10,442 patients with ICD-9 diagnosis code for anaphylaxis
- 35 Children’s Hospitals
- Rate of ED diagnosis rose from 5.7-11.7 patients per 10,000 ED visits

- THEY DID NOT MEASURE EPINEPHRINE USAGE…even though variations were measured in adjutive treatment.
Do We Practice What We Preach?

  - 124 patients with clinical anaphylaxis
  - 54% epinephrine dosing rate
  - Antihistamine dosing rate of 92%
  - Corticosteroid dosing rate of 78%
Do We Practice What We Preach?


- Prevalence of food allergy among children doubled from 1997-2007
- Pre- and post-guideline epi use in the ED 57% and 41%, respectively
- IM route use pre- and post- in ED 6% and 46%, respectively
- Antihistamine use pre- and post- in ED 92% and 93%
- Steroid use pre- and post- in ED 75% and 73%
WE DO NOT PRACTICE WHAT WE PREACH!!!!
Reasons Why That Fear Is Bunk…

I conclude that there is as much sense in nonsense as there is nonsense in sense.

— Anthony Burgess —
Mild adverse effects of epinephrine: May be GOOD

- Transient pharmacologic effects after a recommended dose of epinephrine by any route of administration include:
  - Pallor, tremor, anxiety, palpitations, dizziness, and headache
- These symptoms indicate that a therapeutic dose has been given
- Serious adverse effects:
  - Ventricular arrhythmias, hypertensive crisis, and pulmonary edema potentially occur after an overdose of epinephrine by any route of administration
  - Typically, serious adverse effects are reported after intravenous epinephrine dosing

## The Facts: Epinephrine Fatal Events in Treating Anaphylaxis

<table>
<thead>
<tr>
<th>Age</th>
<th>Physiologic effect</th>
<th>Dose</th>
<th>Route</th>
<th>Given for</th>
<th>Overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Pulmonary Edema</td>
<td>3.5 mg</td>
<td>IV</td>
<td>Mild Symptoms</td>
<td>Yes</td>
</tr>
<tr>
<td>63</td>
<td>Pulmonary Edema</td>
<td>2.5 mg</td>
<td>IV</td>
<td>Antibiotic Rx</td>
<td>Yes</td>
</tr>
<tr>
<td>Infant</td>
<td>Fluid overload</td>
<td>Multiple doses</td>
<td>??</td>
<td>Persistent Pallor</td>
<td>Yes</td>
</tr>
<tr>
<td>38</td>
<td>Aspiration of vomitus</td>
<td>1.0 mg</td>
<td>IV</td>
<td>Vomiting from nuts</td>
<td>Yes</td>
</tr>
</tbody>
</table>

A Higher Proportion of Subsequent Reactions Are Severe and Require Epinephrine


*Indicates a reaction significantly greater than prior reaction ($P<.05$).

Data from the 1st 5,149 patients in a voluntary registry for peanut and tree nut allergy.
Fatal Anaphylactic Reactions Are Often Associated With:

- Delay between time of symptom onset and administration of treatment
- History of asthma
- Adverse therapeutic event as the etiology of anaphylaxis, e.g., drug reaction
- But fatal reactions can be unpredictable

Pumphrey, *Curr Opin Allergy Clin Immunol* 2004
Pumphrey, *Clin Exp Allergy*, 2000
Evidence that Delay in Epinephrine is a Risk Factor in Biphasic Anaphylaxis

- Of those who had a biphasic reactions, the median time from the onset of symptoms to the initial administration of subcutaneous epinephrine was 190 minutes, versus 48 minutes for those without a biphasic reaction\(^1\)
- When comparing patients with uniphasic and biphasic anaphylaxis, there was a significant higher rate of epinephrine use in the uniphasic group\(^2\)
- A time delay to epinephrine treatment longer than 90 minutes from the onset of the initial reaction was significantly associated with a biphasic reaction\(^3\)

Biphasic Anaphylaxis

<table>
<thead>
<tr>
<th>Time</th>
<th>Classic Model</th>
<th>New Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 to 12 hours</td>
<td>Treatment</td>
<td>Treatment</td>
</tr>
</tbody>
</table>

1st Phase
- Asymptomatic

Symptom Score

Antigen Exposure

Predictors of Biphasic Reactions

Epidemiology and clinical predictors of biphasic reactions in children with anaphylaxis

Waleed Alqurashi, MD, MSc; Ian Stiell, MD, MSc; Kevin Chan, MD, MPH; Gina Neto, MD; Abdulaziz Alsadoon, MD; and George Wells, PhD

Table 3
Independent predictors of biphasic reaction as determined by stepwise logistic regression analysis for anaphylaxis episodes

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>P value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 6–9 y</td>
<td>1.28</td>
<td>.01</td>
<td>3.60</td>
<td>1.5–8.58</td>
</tr>
<tr>
<td>Delay in presentation to ED &gt; 90 min</td>
<td>0.95</td>
<td>.001</td>
<td>2.58</td>
<td>1.47–4.53</td>
</tr>
<tr>
<td>from onset of initial reaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wide pulse pressure at triage</td>
<td>1.07</td>
<td>&lt;.001</td>
<td>2.92</td>
<td>1.69–5.04</td>
</tr>
<tr>
<td>Treatment of initial reaction with &gt;1</td>
<td>0.99</td>
<td>.03</td>
<td>2.70</td>
<td>1.12–6.55</td>
</tr>
<tr>
<td>dose of epinephrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration of inhaled β-agonists in ED</td>
<td>0.87</td>
<td>.01</td>
<td>2.39</td>
<td>1.24–4.62</td>
</tr>
</tbody>
</table>
Practice Parameter Summary: Clinical Impact of Biphasic Response

- Patients may require ≥2 doses because of severity, biphasic reactions, or protracted course.
- The need for ≥2 doses occurs in ~15% to 35% of patients who received epinephrine.
- A 2nd dose can be administered within the 1st 5 minutes of the previous dose.
- *There is no way to predict who will require ≥2 doses based upon the severity of previous events alone.*

Why Epi and Not Benadryl?
Maximum PD effect occurs before 10 minutes

- Systolic pressure
- Diastolic pressure
- Heart rate

Pharmacokinetics and Pharmacodynamics of H1-antihistamines

<table>
<thead>
<tr>
<th>H₁-antihistamine</th>
<th>$t_{max}$</th>
<th>Onset of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>1.7 ± 1 h</td>
<td>2h</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>2.1 ± 0.4 h</td>
<td>2h</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>1 ± 0.5 h</td>
<td>1h</td>
</tr>
<tr>
<td>Desloratadine</td>
<td>1-3 h</td>
<td>2h</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>2.6 h</td>
<td>2h</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>0.8 ± 0.5 h</td>
<td>1h</td>
</tr>
<tr>
<td>Loratadine</td>
<td>1.2 ± 0.3 h</td>
<td>2h</td>
</tr>
</tbody>
</table>

Adapted from Middleton’s Allergy Principles & Practice 7th edition, Table 87.4
Antihistamines Take Time

Time to 50% Suppression of Histamine-induced Flare

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median T&lt;sub&gt;50&lt;/sub&gt; Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fexofenadine IM</td>
<td>101.2</td>
</tr>
<tr>
<td>PO Diphenhydramine</td>
<td>79.2</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>51.7</td>
</tr>
</tbody>
</table>

Why give benadryl?
“Benadryl is what you give patients so that they don’t itch while they die of anaphylaxis.”

- Carlos Camargo, MD
What is the best and safest dose of epinephrine?

- **Emergency department treatment dose of epinephrine (1:1000):**
  - 0.01 mg/kg up to 0.30 ml for children and up to 0.05 for adults administered IM
- **Auto-injectors package labeling in USA**
  - 0.15 mg for child 15-30 kg
  - 0.30 mg for child >30 kg
- May be safer to treat children <15 kg with auto-injector than with a syringe and bottle of epinephrine, as errors can be made by caretakers
- Optimal dosing regimen is unknown

Is it ever better to “overdose” epinephrine in children?

- The ideal dose best on weight and available epinephrine auto-injectors is unavailable for many children.
- Consider “overdosing” with the 0.30 mg dose when:
  - Asthma is a concurrent diagnosis
  - Culprit food is peanut, tree nut, milk, egg, fish, or seafood
  - Poor access to emergency medical services
  - Dysfunctional family situation
  - History of previous life-threatening reaction
- In infants, the 0.15 mg dose is preferred to no EAI at all.

Low cost epinephrine solutions don’t really work

- Drawing up epinephrine from an ampule takes too long and the dose is often inaccurate \(^1\)
- Using an unsealed syringe prefilled with epinephrine by the patient's physician has a shelf-life of only 3–4 months \(^2\)

Difficulty Drawing Epinephrine From an Ampule in the Real World

Cases: What Do They All Have In Common?
Case 1

- A 2 year old female, with known egg and milk allergy, attends a county fair with her parents where she ingest a dinner roll purchased from a food vendor. Within 30 minutes, her parents note she is very irritable, has developed flushing, and has several episodes of emesis. She also appears to be scratching her face around the mouth.

- History of allergic rhinitis, asthma, and atopic dermatitis
Case 2

A 8 year old male, with known peanut allergy, is on a school field trip. His teachers and school administrators are aware of his peanut allergy. He ingest a cupcake which were given to the students during the field trip. Within 10 minutes, he reports to his teachers his stomach hurts and needs to use the restroom. On the way to the restroom, the child has several episodes of emesis and appears to have several urticarial lesions on his face. The teacher fearing an allergic reaction calls EMS. When EMS arrives, the child still appears flushed, has mild urticarial lesions on his face. The student reports he is feeling better.

- History of allergic rhinitis, asthma, and atopic dermatitis
Case 3

- A 14 year old asthmatic female, with known tree nut allergy, is at school with friends setting up a stand to sell candy for a school band fund. Her teachers and school administrators are aware of her tree nut allergy and asthma. She ingests a coffee flavored chocolate covered protein bar which was given to her by a friend. Within 30 minutes, she reports her stomach hurts and needs to use the restroom. On the way to the restroom, she has several episodes of emesis and develops chest tightness and shortness of breath. She approaches a teacher who calls EMS fearing she is having problems with her asthma. When EMS arrives, the child still appears flushed and tachypneic. EMS supplies supplemental oxygen, and the student reports it helps her breathing. Upon arrival to the ER, the student’s symptoms have not changed.

- History of allergic rhinitis, asthma, and atopic dermatitis
Anaphylaxis Deaths

- From 2006 to 2009, the overwhelming majority of hospitalizations or ED presentations for anaphylaxis did not result in death, with an average case fatality rate of 0.3%.

- Although anaphylactic reactions are potentially life-threatening, the probability of dying is actually very low.

When it’s your child, the statistics don’t count. Be an advocate
Thank you!

Made possible through a 2016 grant from:

Mylan
Seeing is believing

www.foodallergy.org
Don’t Miss Our Next Webinar

When Should I Use Epinephrine? Why Am I Afraid of it?

Jonathan M. Spergel, M.D., Ph.D.
Monday, December 12, 2016

12:00 – 1:00 PM ET

Registration Now Open!

www.foodallergy.org