Anaphylaxis in Urgent Care:

How New Data May Change How You Treat

Webinar for the Society for Pediatric Urgent Care (SPUC)

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Disclosures

• No commercial or grant funding conflicts of interest to report.

• I am an allergist at the VA and Medical College of Wisconsin and work at the VA, at Children’s Wisconsin, and at Froedtert Hospital.

• Clinical/research interests in mast cell disorders and severe asthma.

• Off-label use of medications will be discussed without brand names.

• Brand names of pharmaceuticals will be mentioned given proprietary delivery devices, however without preference.
Learning Objectives

1. Understand pathophysiology and time-course of anaphylaxis

2. Understand WAO anaphylaxis criteria and how to differentiate from urticaria

3. Understand new data-driven guidance which may shift management from Emergency Room to Urgent Care for milder reactions
An Incredibly Abridged History of Anaphylaxis...
Scientific Discovery of Anaphylaxis

• Drs. Portier and Richet studied vaccination against toxins at the turn of the 20th century

• Hypothesis: akin to tolerance to narcotics, habituation to toxins would be induced with vaccination

• Methodology: vaccinating dogs with venom, then later re-exposing dogs to venom to assess tolerance
Scientific Discovery of Anaphylaxis

Most dogs were protected

but... a few had immediate onset symptoms... to even 1/20th of a lethal dose

Symptoms included:
• vomiting, diarrhea
• fainting, unconsciousness
• choking, death
Scientific Discovery of Anaphylaxis

These severe reactions did not fit the habituation hypothesis pre-treatment with toxin lead to increased sensitivity symptoms were not venom toxicity... only some dogs affected...

So what happened?
HISTORY OF ANAPHYLAXIS

Naming of Anaphylaxis

The diagnosis of anaphylaxis was made, with a made-up name.

*ana* = against

*phylaxis* = protection

Anaphylaxis is a Syndrome of Systemic Immediate Hypersensitivity.
**Prevalence of Signs/Symptoms**

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Percentage of cases†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cutaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Urticaria and angioedema</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Flush</td>
<td>85–90</td>
</tr>
<tr>
<td>Pruritus without rash</td>
<td>45–55</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea, wheeze</td>
<td>40–60</td>
</tr>
<tr>
<td>Upper airway angioedema</td>
<td>45–50</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>50–60</td>
</tr>
<tr>
<td><strong>Dizziness, syncope, hypotension</strong></td>
<td>15–20</td>
</tr>
<tr>
<td><strong>Abdominal</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhea, cramping pain</td>
<td>30–35</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>25–30</td>
</tr>
<tr>
<td>Substernal pain</td>
<td>25–30</td>
</tr>
<tr>
<td>Seizure</td>
<td>1–2</td>
</tr>
</tbody>
</table>

*Based on a compilation of 1784 patients reviewed in reference 2.
†Percentages are approximations (see text).
Guidelines for Diagnosis of Anaphylaxis

For years, there were no uniform criteria. Over the past decade, that has all changed.

- **WAO (World Allergy Organization) Guidelines**

- **AAAAI/AACAI (American) Practice Parameter**
  • 2010, 2020 (Lieberman, P. et al)

- **EAACI (European) Guidelines**
  • Muraro, A. et al 2014, pending review 2020
Anaphylaxis by Criteria
World Allergy Organization 2011

3 separate criteria

each criteria is sufficient to diagnose anaphylaxis

only basic diagnostic equipment needed
**Anaphylaxis by Criteria**  
**World Allergy Organization 2011**

SuDDEN ONSET skin/mucus symptoms  
(hives/flushing/swelling/itching)  
AND respiratory **OR** low BP / end organ dysfunction

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**Criterion #1**

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

1. Sudden onset of an illness (minutes to several hours), with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, itching or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

- **Skin and mucosal involvement:**
  - Sudden respiratory symptoms (e.g., shortness of breath, wheeze, cough, stridor, hypoxemia)
  - Sudden reduced BP or symptoms of end-organ dysfunction (e.g., hypotonia [collapse], incontinence)

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Simons et al 2011
DEFINITION AND DESCRIPTION

Anaphylaxis by Criteria
World Allergy Organization 2011

Criterion #2

TWO OR MORE symptoms SUDDENLY after exposure to likely allergen
Anaphylaxis by Criteria
World Allergy Organization 2011

Criterion #3

Reduced blood pressure (BP) after exposure to a **known allergen** for that patient (minutes to several hours):

Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP

Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

REDUCED BLOOD PRESSURE after exposure to a **KNOWN ALLERGEN**
Criteria Validation from ED

The good news:
Criteria great CATCHING anaphylaxis
Criteria great at EXCLUDING anaphylaxis

The bad news:
Criteria could miss other medical problems with similar symptoms

- **Negative Predictive Value**: 98%
  - True negative rate: No anaphylaxis / all negative screens

- **Positive Predictive Value**: 67%
  - True anaphylaxis / all positive screens

- **Sensitivity**: 97%
  - True positive rate

- **Specificity**: 82%
  - True negative rate
If not anaphylaxis, then what?

Swelling Disorders:
- hives / angioedema
- bradykinin induced angioedema

Flushing Syndromes
- Peri-menopause
- Carcinoid syndrome
- Autonomic disorders
- Medullary thyroid carcinoma
- Red man syndrome
- Pheochromocytoma

Pulmonary / Cardiovascular
- vasodepressor syncope
- asthma
- heart attack
- pulmonary embolism
- sepsis/shock
- systemic capillary leak syndrome
- choking
- aspiration

Neuro/Psychiatric Disease
- Vocal cord dysfunction
- Hyperventilation
- Somatoform disorder
- Panic attack
- Seizure
- Stroke
Poll Question #1

What is FALSE about Bradykinin mediated angioedema (hereditary angioedema)?
<table>
<thead>
<tr>
<th>Ultrasound/Angioedema:</th>
<th>Bradykinin-induced angioedema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (&lt;6 weeks)</td>
<td>• hereditary (onset 10-30 years old)</td>
</tr>
<tr>
<td>Chronic (≥ 6 weeks)</td>
<td>• acquired (onset &gt;50 years old)</td>
</tr>
<tr>
<td></td>
<td>• ACE-I (more common in Af. Amer)</td>
</tr>
</tbody>
</table>

**Tips:**

<table>
<thead>
<tr>
<th>Skin symptoms ALONE</th>
<th>Never associated with hives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Often more chronic (more days than not)</td>
<td>Can cause nausea/vomiting, severe abdominal pain from gut angioedema</td>
</tr>
<tr>
<td>Improves with antihistamines, steroids</td>
<td>Never improves with epinephrine, antihistamines, steroids</td>
</tr>
<tr>
<td>Rapid onset/offset</td>
<td>Crescendos over 24 hours without treatment, resolves over days</td>
</tr>
<tr>
<td>No risk of fatality</td>
<td>Risk of asphyxiation high</td>
</tr>
</tbody>
</table>
DEFINITION AND DESCRIPTION

Triggers of Anaphylaxis

**IgE dependent**
- food, venom, meds

**IgE independent**
- NSAID/Aspirin
- CT contrast

- direct mast cell activation
  - narcotics, alcohol, meds
  - cold water immersion
  - mast cell disorders

Simons et al 2011
MECHANISM OF ANAPHYLAXIS

Major Mediator Cells

Mast Cells
Tissue resident

Basophil
in blood and tissue resident

Land Mine

U:http://www.pathologyoutlines.com/topic/bonemarrowbasophils.html
lower:science.howstuffworks.com
L:http://www.bu.edu/histology
MECHANISM OF ANAPHYLAXIS

Degranulation as Initial Event

Resting Mast Cell

Degranulating Mast Cell
MECHANISM: IgE Crosslinking

**PREFORMED MEDIATORS**
seconds-minutes

- HISTAMINE
- NEUTRAL PROTEASES
  - tryptase, chymase, cathepsin G, and carboxypeptidase
- PROTEOGLYCANS
  - heparin
- TNF alpha

**RAPIDLY PRODUCED**
minutes-hours

- PAF, PGD$_2$, LTC$_4$, S1P

**SLOWLY PRODUCED**
hours-days

Image: Abbas & Lictman Basic Immunology 2008
Altered Vascular Tone
- vasodilation
- flushing
- fluid extravasation
- intravascular volume depletion
- hypotension

Smooth Muscle Spasm
- bronchospasm
- GI / GU tract
**MECHANISM**

Biphasic (second phase) Anaphylaxis

**Incidence:** ~4.7%

**Risk factors:**
- unknown or non-food trigger
- hypotension
- mod-severe reactions
- late EPI treatment

**Onset:**
- typically ~8 hours (range: 1-78)
- beyond 10 hours in 40%
- beyond 20 hours in 20%

Average ED visit: 3.8 hrs
New Data: Biphasic Anaphylaxis

Corticosteroids did not help prevent biphasic anaphylaxis

also...

Biphasic risk if ≤1 EPI dose OR no IV fluids

PPV poor NPV 99%

As such, mild reactions rarely triggered biphasic reactions
Our primary treatment for prevention didn’t work

Guideline updates were needed.....
2020 Updated AAAAAI Guidelines

Extended observation is suggested for patients with resolved severe anaphylaxis and/or those with need for >1 dose of epinephrine.

Number needed to treat:
- for >1 EPI = 13
- for severe anaphylaxis = 41

Risk factors associated with biphasic reactions:
- severe anaphylaxis
- >1 dose of epinephrine
- wide pulse pressure
- unknown anaphylaxis trigger
- cutaneous signs and symptoms
- drug trigger in children
2020 Updated AAAAI Guidelines

Antihistamines and/or glucocorticoids are not reliable interventions to prevent biphasic anaphylaxis but may be considered as secondary treatment.

- NNT antihistamines = 72
- NNT glucocorticoids = 161

After diagnosis and treatment of anaphylaxis, all patients should be kept under observation until symptoms have fully resolved.

- 1-hour observation 95% NPV
- 6-hour or longer 97.3% NPV
2020 Updated AAAAI Guidelines

All patients with anaphylaxis should receive education about anaphylaxis, risk of recurrence, trigger avoidance, self-injectable epinephrine, and thresholds for further care, and they should be referred to an allergist for follow-up evaluation.
Implications for Urgent Care

Urgent care settings were not mentioned in this guideline!

Could mild cases (without risk factors) be managed in UC?
- Could brief 1-hour observation in urgent care replace transport by EMS to ED? Is 95% CI acceptable?
- Would UC management an appropriate burden?
- How to incorporate a prolonged stay/observation/monitoring?
- How to uniformly educate providers/nurses on observation/management?

How to prevent the discharge problems found in EDs?
- Could UC provide initial patient anaphylaxis teaching?
- Could referrals to specialist completion be improved?
- Would epinephrine injector dispensing from clinic help improve fills?
Severe/Fatal Anaphylaxis
Epidemiology for Fatal Anaphylaxis

Frequency of fatal anaphylaxis is ~30-950 per 100,000 persons in US
- ~50/yr venom-induced
- ~150/yr food induced
- ~600/yr antibiotic induced

True incidence uncertain due to:
- lack of a national anaphylaxis registry in US
- varied ICD codes for allergic reactions
Causes for Fatal Anaphylaxis

**Drugs:**
- beta-lactams (up to 75%), NSAIDs
- radiocontrast, neuromuscular blockers

**Food:** peanut/tree nuts (>90%), cow’s milk, seafood

**Parasite:** hydatid (echinococcosis) cyst

**Iatrogenic:** latex, allergen immunotherapy (6 fatalities 2001-7)

**Venom:** Hymenoptera
Estimated risk of fatal anaphylaxis less than death due to fire, murder for comparison

Turner et al J Allergy Clin Immunol Pract 2017;5:1169-78
Risk Factors for Fatal Anaphylaxis

**Age related factors**
- Infants
- Adolescents
- Pregnancy
- Elderly

**Co-morbid diseases**
- Asthma / chronic respiratory diseases
- Cardiovascular diseases
- Mastocytosis
- Allergic rhinitis and eczema
- Depression
- Cognitive dysfunction

**Drugs**
- β adrenergic blockers
- ACE inhibitors
- Psychotropic meds/drugs of abuse
- NSAID

**Co-factors that amplify anaphylaxis**
- Exercise
- Acute infection
- Emotional stress
- Premenstrual status
Prior severe reactions RARELY predict fatal reactions

**Venom:**
> $\frac{2}{3}$ rd had **no prior history of reaction**

**Drug:**
> $\frac{4}{5}$ th had **no prior history of reaction**

**Food:**
Majority had **MILD prior reactions**
Poll question #2

What position is recommended during management of anaphylaxis?
DEFINITION AND DESCRIPTION

Empty Heart/Ventricle Syndrome

4 of 10 deaths from occurred “within seconds” of change to upright posture

• “the individual stood up after sitting slumped or lying down”

• “the individual was made to sit in a chair after lying in bed”

• “driver stepped out of his vehicle during a reaction to a sting”

• “each individual (of 5 venom reactions) had been supported sitting up after shock caused loss of consciousness”

Thus, lying down and elevating the legs part of WAO guidelines
TREATMENT: EPINEPHRINE

### Fatal Anaphylaxis Case Series

<table>
<thead>
<tr>
<th></th>
<th>Minutes to arrest</th>
<th>First adrenaline</th>
<th>Resuscitated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
<td>None</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>5</td>
<td>1–80</td>
<td>6</td>
</tr>
<tr>
<td>Food</td>
<td>30</td>
<td>6–360</td>
<td>13</td>
</tr>
<tr>
<td>Venom</td>
<td>15</td>
<td>4–120</td>
<td>29</td>
</tr>
</tbody>
</table>

- Iatrogenic —> shock common, 5 min to arrest
- Venom —> shock common, 15 min to arrest
- Food —> respiratory arrest only, 30 min to arrest

EPI was administered **AFTER ARREST** or **NOT GIVEN** in most.

Post-resuscitation survival was **very poor**: 3 hours-30 days.

anoxic brain injury primary cause of death
Treatment of Anaphylaxis
Most Important Treatment is Rapid Administration of EPINEPHRINE
Second Most Important Treatment is Rapid Administration of EPINEPHRINE
Third Most Important Treatment is Rapid Administration of EPINEPHRINE

epinephrine is the only medication demonstrated to reduce hospitalization and death
Poll Question #3

What are the contraindications to epinephrine?
How does EPINEPHRINE help with anaphylaxis?

**Works like:**

- **At alpha-1 adrenergic receptor**
  - Increases vasoconstriction & vascular resistance
  - Increases blood pressure
  - Decreases mucosal edema in the airways
  
- **At beta-1 adrenergic receptor**
  - Increases cardiac contraction force
  - Increases heart rate

- **At beta-2 adrenergic receptor**
  - Decreases mediator release
  - Bronchodilates / relaxes smooth muscle
FDA Approved EPINEPHRINE IM Injectors

**EpiPen® & Generic (both Mylan)**
0.15mg (JR) & 0.3mg

**Generic (Teva)**
0.15mg & 0.3mg

**Adrenaclick® & generic (Amendra)**
0.15mg & 0.3mg

**Auvi-Q (kaléo)**
0.10mg, 0.15mg & 0.3mg

**Symjepi (Adamis)**
0.15mg, 0.3mg

http://www.epinephrineautoinject.com/what_is_epinephrine_injection_USP_auto_injector.php
http://www.auvi-q.com/about-auvi-q
Why is EPI given IM? Pharmacokinetics

Different effects of EPI
SQ = vasoconstriction
IM = vasodilation

**FIG. 1.** Mean plasma epinephrine concentration versus time plot after injection of epinephrine subcutaneously in nine children and after injection of epinephrine intramuscularly in eight children.

- **t<sub>max</sub>**
  - SUBCUTANEOUS: 34 ± 14 min
  - INTRAMUSCULAR: 8 ± 2 min
Poll question #4:

Why might treating anaphylaxis in an obese patient be more difficult?
Problems with EPI: Needle Length

EPIPEN Jr needle in infants may be too long:
- under 9kg, 90% had skin-to-bone distance < 12.7mm
- under 11kg, 53% had skin-to-bone distance < 12.7mm

EPIPEN needle in higher BMI, female children & adults may be too short:
Problems with EPI: Overdose

- EPI has a **NARROW** therapeutic index

- Pharmacologic Side-Effects:
  - pallor
  - tremor
  - anxiety
  - palpitations
  - dizziness
  - headache

Overdose:
- ventricular arrhythmia ($QT_c$ prolongation)
- hypertensive crisis
- pulmonary edema
- theoretical risk with COMT inhibitors: tolcapone, entacapone
We need to do more than just give EPINEPHRINE however.
## Recommended Basic Management of Anaphylaxis

### 1. Have a Protocol

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

### 2. Remove Allergen Exposure

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

### 3. Assess Circulation/Airway/Breathing/Mental Status/Skin exam/Weight

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

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

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

### 4. High flow supplemental O₂

**Inject epinephrine** (adrenaline) intramuscularly in the mid-outer lateral aspect of the thigh, 0.01 mg/kg of a 1:1,000 (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 5-15 minutes, if needed. Most patients respond to 1 or 2 doses.

### 5. CPR when indicated

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

**When indicated, give high-flow supplemental oxygen** (5-8 L/min), by face mask or oropharyngeal airway.

### 6. Establish IV access

**Establish intravenous access** using needles or catheters with wide-bore cannulae (14-16 gauge). When indicated, give 2-3 litres of 0.9% (normal) saline rapidly (e.g., 5-10 mL/kg in the first 5-10 minutes to an adult; 10 mL/kg to a child).

### 7. Frequently monitor patient

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

**At frequent, regular intervals, monitor patient’s blood pressure, cardiac rate and rhythm, respiratory status, and oxygenation** (monitor continuously, if possible).
Efficacy Data is Lacking

“We found no studies that satisfied the inclusion criteria.”

- Glucocorticoids for the treatment of anaphylaxis (2012)
- Auto-injectors in community (2012)
- H1 antihistamines (2007, revised 2012)
- H2 antihistamines (2014)
Obstacles to Early Treatment with Epinephrine
Underdiagnosis, Undercoding, Undertreatment

Anaphylaxis is underdiagnosed, undertreated often by EMS
Epi given to 17% of anaphylaxis patients
higher odds if d/t venom or respiratory symptoms

Anaphylaxis is under-diagnosed in EDs (Klein & Yocum)

• “allergic reaction” was code in 53% rather than anaphylaxis
• “anaphylaxis” was often not coded if no shock
• diagnosis of “anaphylaxis” more likely to receive epinephrine than “systemic allergic reaction”

Disparities of care
Epinephrine prescribed preferentially to high income patients
Cost of Epinephrine

- EPIPEN® 2 pak; AUVI Q ~ $600
- Mylan generic ~$300
- Adrenaclick® generic ~$100
- Cost of 0.3mg vial of epinephrine ~$1-12
Within 1 year after discharge, 46% had filled an Epinephrine and 29% had A/I follow-up (n=18,279)
Psychology of Delaying Treatment: TV case of Illana Wexler
Illana’s Justifications:
“I know my limit”
Wait till it gets worse
Someone else will inject me
Temptation – food is too good!
Young Adults at Highest Risk for Non-Adherence

29-53% of food anaphylaxis deaths occur in 18-30 age group

Cannuscio et al. Ann Allergy Asthma Immuno 2015

6.6% of college students with food allergies carry EPI injector yet 60% engaged in risky eating behavior


54% of 13-21 year olds engaged in risky behavior, such as eating small amounts of allergens

Recognize anaphylaxis as a syndrome with **varied presentations**

- urticaria is common, but **not** necessary criterion
- most fatal cases don’t present with urticaria
- hypotension may be the only sign after a known allergen exposure
- consider posting the WAO criteria [https://www.worldallergy.org/disease-focus/anaphylaxis](https://www.worldallergy.org/disease-focus/anaphylaxis)

**TAKE HOME PEARLS**
PEARLS

Recognize and respond quickly

- don’t delay epinephrine
  there are no absolute C/I

- don’t forget about IV fluids, recumbency, oxygen, immediate airway assistance, repeat epinephrine, serial vitals/exam

- consider WAO poster on the wall
  https://www.worldallergy.org/disease-focus/anaphylaxis
Prior reactions don’t determine severity of future reactions
• Consider analogy of earthquakes: mild common, severe rare, but ultimately unpredictable
PEARLS

Great supportive resources available

- FARE (foodallergy.org) emergency action form
- Criteria don’t exactly match WAO anaphylaxis criteria

TAKE HOME PEARLS
Questions?

jsteinberg@mcw.edu

Thank you!
Non-Classical Mechanisms of Anaphylaxis

mice lacking mast cells, basophils, IgE, IgE receptors can still develop anaphylaxis!

Patients receiving first dose of certain drugs can have anaphylaxis reactions, too fast to develop IgE antibodies!

What explains this?
MECHANISMS OF ANAPHYLAXIS: Overview

IgE
Via FcεRI

IgG
Via FcγRIII, FcγRI, FcγRIIA

Complement
Via C3αR, C5αR

Direct MC activation
Via MRGPRX2 and other receptors

Food
Insect
Drugs

Lipid incipients
Micellar drugs
Liposomes
Nanoparticles
Polygols
Cellulose

Biologicals
Drugs
Dextrans
Aprotinin
Transfusion

NSAIDS/ Aspirin
Vancomycin
Opiates
Local Anesthetics
Fluoroquinolones
NM Blockers
Octreotide
Leuprolide

Derived from table from Finkelman, F, Kohodoun, Strait . Journal of Allergy and Clinical Immunology Volume 137, Issue 6, June 2016, Pages 1674-1680