Anaphylaxis

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Course Objectives:

Upon completion of this presentation, the attendee will be able to:

1. Identify the newest diagnostic criteria for anaphylaxis
2. Identify the various signs and symptoms of anaphylaxis
3. Identify the most common triggers and mechanism of anaphylaxis
4. Be familiar with the treatment strategies for anaphylaxis
Definition

- Multi-system syndrome involving cutaneous, gastrointestinal, respiratory, cardiovascular systems
- Resulting from mast cell mediator release
- Acute onset
- Severity varies from mild to fatal attacks
Anaphylaxis Treatment

- Epinephrine
- Tourniquet
- O₂, airway maintenance
- IV fluids
- Diphenhydramine + cimetidine
- Vasopressors: dopamine
- Glucagon
Epinephrine Dosing

- < 10 kg consult resource
- 10-25 kg = 0.15 mg
- >25 kg = 0.30 mg
- Can dose up to 0.5 mg
- 1:1000 Solution IM
Epinephrine Self-Injection Rx

- Anyone with Anaphylaxis Hx
- Persons who have not experienced but are at increased risk
- Always Rx in conjunction with an emergency plan
Epinephrine Indications
Severity of an Episode Not Predictable

*Indicates a reaction more severe than the previous reaction.

Epinephrine Contraindications

- There is no absolute contraindication to the administration of epinephrine for anaphylaxis.
- It is unclear whether patients taking β-blockers are at increased risk of having an anaphylactic event, but they may worsen the event and complicate treatment.
- Anaphylaxis in patients taking β-blockers may be more severe and difficult to treat because of a reduced β-adrenergic response and an increased alpha-adrenergic response.
Epinephrine Route of Administration

Achieving high plasma and tissue concentration is critical for reversal of hypotension

*IM in Vastus Lateralis leads to peak plasma concentration*
Absorption of Epinephrine Faster With IM vs SC Injection

Time to $C_{\text{max}}$ After Injection (minutes)

SC = subcutaneous.

Epinephrine Auto-injector versus Ampule

- Median time to respiratory or cardiac arrest:
  - 30 minutes for food
  - 15 minutes for venom
  - 5 minutes for iatrogenic reactions
Difficulty Drawing Epinephrine From an Ampule in the Real World

$P < .05$ vs all control groups

Comparison of Auto-injectors: EpiPen

- **One-step, flip-top carrying case**
  Designed for single-handed opening.

- **Ergonomically designed grip**
  Allows for a firm grip and improves ease of handling.

- **Brightly colored orange tip**
  Aids in quick identification of needle end to reduce risk of accidental thumb puncture.

- **Blue safety-release cap**
  Designed to prevent unintentional activation.

- **Easy-to-read, illustrated instructions**
  Allows for rapid recognition of product usage instructions.

- **Built-in needle protection**
  The only epinephrine auto-injector that protects against needle exposure before and after use.

Available at: http://www.epipen.com/professionals/about-epipen/auto-injector
Comparison of Auto-injectors: Auvi-q

http://www.auvi-q.com/demo-video
Epinephrine Side Effects

- Common Side Effects:
  - Rapid HR
  - Sweating
  - Shakiness
  - Headache
  - Paleness
  - Nervousness, anxiety, over excitement
  - Weakness
  - Dizziness
  - N/V
  - Breathing Problems
Action of Epinephrine

Epinephrine

$\alpha_1$-adrenergic receptor
- ↑ Vasoconstriction
- ↑ Peripheral vascular resistance
- ↓ Mucosal edema

$\alpha_2$-adrenergic receptor
- ↓ Insulin release
- ↓ Norepinephrine release

$\beta_1$-adrenergic receptor
- ↑ Inotropy
- ↑ Chronotropy

$\beta_2$-adrenergic receptor
- ↑ Bronchodilation
- ↑ Vasodilation
- ↑ Glycogenolysis
- ↓ Mediator release
Biphasic Reactions Not Predictable

- Biphasic reactions
  - Occur in 1% to 23% of patients
  - Can be less severe, equally severe, or more severe than the initial reaction, ranging in degree from mild symptoms to fatal reactions
- The second response usually occurs within 10 hours after resolution of the initial response

>1 Dose of Epinephrine Often Required

Patients Requiring >1 Dose of Epinephrine

Availability and Knowledge Critical to Success With an Auto-injector

- 100 families of food-allergic children evaluated
  - Only 55% of the families had unexpired epinephrine on hand at the time of the survey
  - Only 32% of children and 18% of pediatricians able to use device correctly

- 100 physicians assessed for knowledge of an auto-injector
  - The majority of doctors did not know how to use an auto-injector
  - In 30% of cases, the demonstration would not have delivered epinephrine to a patient

Reasons Patients Report for Not Using an Auto-injector

- Used another medication to treat episode
- Previous reaction improved quickly
- Current reaction seemed mild or improved quickly
- Rapid progression of reaction

- Patient was unsure when to inject or injected too late
- Not accessible when reaction occurred
- Patient taking another medication that interfered
- Not prescribed by physician
- Not affordable
- Did not have auto-injector with them

Why Not an Antihistamine?

- Antihistamines
  - Antagonize only one of the multiple mediators in anaphylaxis
  - Take too long to work
Definition of Anaphylaxis

- Anaphylaxis is an acute, life-threatening systemic reaction resulting from the sudden release of mediators from mast cells and basophils.
- These mediators include:
  - Leukotrienes
  - Prostaglandins
  - Histamine
  - Platelet-activating factor
  - Interleukins
  - Others

Oral Diphenhydramine Takes Almost 80 Minutes for 50% Suppression

Suppression of Histamine-induced Flare

IM=intramuscular; PO=oral.

30 Minutes After Oral Diphenhydramine, Only 16% Suppression Observed

Flare Response

Percent Change From Baseline

*P=.01

Minutes Post Medication Administration

# Frequency and Occurrence of Signs and Symptoms of Anaphylaxis

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Percent*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cutaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Urticaria and angioedema</td>
<td>85-90</td>
</tr>
<tr>
<td>Flushing</td>
<td>45-55</td>
</tr>
<tr>
<td>Pruritus without rash</td>
<td>2-5</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea, wheeze</td>
<td>45-50</td>
</tr>
<tr>
<td>Upper airway angioedema</td>
<td>50-60</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>15-20</td>
</tr>
<tr>
<td>Dizziness, syncope, hypotension</td>
<td>30-35</td>
</tr>
<tr>
<td><strong>Abdominal</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhea, cramping pain</td>
<td>25-30</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>5-8</td>
</tr>
<tr>
<td>Substernal pain</td>
<td>4-6</td>
</tr>
<tr>
<td>Seizure</td>
<td>1-2</td>
</tr>
</tbody>
</table>

*Percentages are approximations.

Summary

- Immediate treatment with Epi is imperative
- No contraindications
- Delay = Fatalities
- Always available
- Self injector IM
- Emergency plan
Questions
References & Additional Slides
Anaphylaxis Treatment

No international consensus:
Epinephrine appears underutilized 20-60% use internationally. Corticosteroids are used in Canada, UK and Russia

Patient follow-up is lacking:
12-16% Referred for follow-up with Allergy Specialist
0-38% prescribed epi-pen following initial ER visit

Discussion focused on fatalities: what about morbidities and complications?

Comorbidities? Obesity?
Anaphylaxis is underreported
Incidence estimated to be 21 per 100,000 person-years
If this is projected as a national average, then approximately 63,000 new cases of anaphylaxis would be reported each year in the United States
Up to 41 M Americans


Seasonal Variation

FIG 1. Distribution of first episodes of anaphylaxis (n = 133) by suspected allergen and by month.

Prevalence of generalized allergic reaction

- Epidemiologic surveys have reported systemic reactions to insect stings in 1% of children and 3% of adults.
- Food-induced anaphylaxis is estimated to occur in 1-3% of children.
- Drug reactions are also common with anaphylaxis occurring in approximately 1% of adults.
- Radiocontrast media cause anaphylaxis in 0.1% of procedures performed.
Prevalence of generalized allergic reaction

- Allergen immunotherapy injections cause systemic symptoms in 10-15% of treated patients but anaphylaxis is estimated to occur in 3% of cases.
- Increasing reports of latex anaphylaxis over the past 10 years approaching 1% of adults.
- Estimates suggest that 5% of adults may have a history of anaphylaxis.
Clinical Manifestations

- Cutaneous
  - Pruritus, urticaria, angioedema, flushing
- Gastrointestinal
  - Nausea, emesis, cramps, diarrhea
- Ocular
  - Pruritus, tearing, redness
- Genitourinary
  - Urinary urgency, uterine cramp
Clinical Manifestations

- **Cardiovascular**
  - Tachycardia then hypotension
  - Shock: ≤ 50% intravascular volume loss
  - Bradycardia (4%) (transient or persistent)
  - Myocardial ischemia

- **Lower respiratory** - bronchoconstriction wheeze, cough, shortness of breath

- **Upper respiratory**
  - Laryngeal/pharyngeal edema
  - Rhinitis symptoms
### Frequency of Signs and Symptoms

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria, angioedema</td>
<td>88</td>
</tr>
<tr>
<td>Dyspnea, wheeze</td>
<td>47</td>
</tr>
<tr>
<td>Dizziness, syncope, hypotension</td>
<td>33</td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhea, cramping abdominal pain</td>
<td>30</td>
</tr>
<tr>
<td>Flush</td>
<td>46</td>
</tr>
<tr>
<td>Upper airway edema</td>
<td>56</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
</tr>
<tr>
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</table>

Temporal Pattern

- Uniphasic
- Biphasic
  - Same manifestations as at presentation recur up to 8 hours later
  - Reported in up to 20% of cases
- Protracted
  - Up to 32 hours
  - May not be prevented by glucocorticoid
Mechanisms

- Type I hypersensitivity - IgE (Anaphylaxis)
- Allergen exposure
- Production of allergen-specific IgE
- IgE-sensitized mast cells
- IgE-mediated mast cell degranulation upon re-exposure to allergen
Complement activation (Anaphylactoid)
- Type II hypersensitivity
- Type III hypersensitivity
- Aggregated Ig
- Non-immunologic (iodinated dye)

Direct mast cell activation
- Drugs (e.g. ASA, vancomycin), exercise, cold, idiopathic
Mediators

- **Histamine**
  - H₁: smooth muscle contraction
  - vascular permeability
  - H₂: vascular permeability
  - H₁+H₂: vasodilatation, pruritus

- **Leukotrienes**
  - Smooth muscle contraction
  - vascular permeability and dilatation

- **Nitric Oxide**
  - Smooth muscle relaxation
  - vascular permeability and dilatation
Anaphylaxis Differential Diagnosis

- Vasovagal syncope
- Systemic mastocytosis
- Scromboid poisoning
- Other causes of shock (hypovolemic, cardiogenic, septic)
Causes of IgE-Mediated Anaphylaxis

- Antibiotics and other medications
  - Beta lactams, tetracyclines, sulfas
- Foreign proteins
  - Latex, hymenoptera venoms, seminal plasma
- Foods
  - Shellfish, legumes, nuts and others
Food-Related Anaphylaxis

- Food-induced anaphylaxis
  - Rapid-onset
  - Multi-organ system involvement
  - Potentially fatal
  - Any food, highest risk:
    - peanut, nut, seafood, sesame
- Food-associated, exercise-induced
  - Associated with a particular food
  - Associated with eating any food
Fatal Food Anaphylaxis

- Frequency: ~150 deaths/year
- Risk:
  - Underlying asthma – Delayed epinephrine
  - Symptom denial – Previous severe reaction
- History: known allergic food
- Key foods: peanut / nuts / shellfish
- Biphasic reaction
- Lack of cutaneous symptoms in 80%
Prevalence of Venom Sensitization

- History of systemic reaction in 0.5% - 3.0% of the population
- Positive venom skin test or RAST in 15% - 25% of the population
- Transient positive skin test or RAST may occur after uneventful sting
- Presence of IgE venom antibody not necessarily predictive of clinical sensitivity
Natural History of Insect Sting Allergy

- Spontaneous loss of clinical venom sensitivity
- Adults differ from children
- Evolution of systemic reactions
  - frequency and severity
  - large local into systemic
  - no predictive markers
Drug Hypersensitivity

- Clinical presentation: urticaria/angioedema/anaphylaxis
- Caused by many drugs and biologics
- Most often due to β-lactam antibiotics
- Less common with many non-β-lactam antibiotics
Pseudoallergic Reactions

- Opiates
- Radiocontrast media
- Colloid volume expanders
- Dextran
- Mannitol
- ASA / NSAIDs
Atopy and Risk of Anaphylaxis

Risk Factor
- Idiopathic
- Exercise
- Latex
- Radiocontrast media

Not Risk Factor
- Penicillin
- Insulin
- Muscle relaxants
- Hymenoptera venoms
Risk Factors for Severity of Anaphylaxis

- Age: Most fatalities > 45 yo
- Gender: Worse in males
- Constancy of antigen administration
- Time elapsed since last reaction
10-15% during initial immunotherapy, 1-3% during maintenance

Most in < 20 minutes, but severity worse with later onset

Systemic not preceded or predicted by large local reactions
Allergen Immunotherapy - Systemic Reactions

- Related to: dose/vial errors, unstable asthma, seasonal flare, extreme sensitivity, ß blockers, new vial/new extract, rush schedule

- Fatal reactions: 58 observed over 25 years:
  - 90% in < 30 minutes
  - 30% due to errors
  - 50% delayed use of epinephrine
  - 50% with acute asthma
  - 25% prior systemic reactions
  - 25% peak pollen season

Lockey 1987, 1992; Reid 1990, 1992
Adults versus children

- Canadian Pediatric Surveillance: 81% of events in children were due to food allergies.
- Fatal anaphylaxis:
  - Young children: Cow’s milk
  - Adolescent: Peanut allergy
  - Adults: Tree nut; venom, drug
- Children are more likely to have respiratory symptoms; adults more likely to have CV compromise.

  Clinical and Experimental Allergy 32: 651-660
Anaphylaxis Fatalities
Post-Mortem Findings

- Airway (laryngeal) and tissue (visceral) edema
- Pulmonary hyperinflation
- Tissue eosinophilia
- Elevated serum tryptase
- Myocardial injury
Anaphylaxis Fatalities

- Fatalities \( \approx 4\% \)
- Increased Risk
  - Beta Blockade, severe hypotension, bradycardia, sustained bronchospasm, poor response to epinephrine
  - Adrenal Insufficiency
  - Asthma
  - Coronary Artery Disease
Anaphylaxis Diagnosis

- Clinical Features
- Serum Tryptase
- Serum or urine histamine
Positive prick test or RAST
- Indicates presence of IgE antibody NOT clinical reactivity (~50% false positive)

Negative prick test or RAST
- Essentially excludes IgE antibody (>95%)

ID skin test with food
- Risk of systemic reaction & not predictive
- Contraindicated
Differential Diagnosis

- Acute or chronic urticaria or angiodema
- Asthma attack
- Foreign body aspiration
- Food poisoning
- Vasovagal reaction
- Anxiety attack
- Mastocytosis
- Carcinoid syndrome
- Pheochromocytoma
- Serum Sickness
- Anaphylactoid
- Scromboid fish
- Pseudoallergic medication response
Diagnostic Approach: IgE-Mediated Food Allergy

- Test for specific-IgE antibody
  - Negative: reintroduce food
  - Positive: start elimination diet

- Elimination diet
  - No resolution: reintroduce food
  - Resolution
    - Open / single-blind challenges to “screen”
    - DBPCFC
Prevention of Anaphylaxis

- History: drug, venom, food, latex reactions
  - Avoidance, Medic-Alert and ID card
- Penicillin skin tests & prn desensitization
- Hymenoptera avoidance & immunotherapy
- Iodinated Dye Pretreatment
- Avoid
  - β blockade in those on immunotherapy or at risk of Hymenoptera anaphylaxis
  - Immunotherapy in those on β blockers
  - ACE inhibitors in food / Hymenoptera anaphylaxis
Clinical Manifestations

<table>
<thead>
<tr>
<th>Clinical features of anaphylaxis</th>
<th>Frequency of Signs and Symptoms</th>
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</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td>Urticaria, angioedema, pruritus, flushing, morbilliform rash</td>
</tr>
<tr>
<td>Urticaria, angioedema</td>
<td>88</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Upper airway – rhinorrhea, congestion, sneezing, stridor, hoarseness</td>
</tr>
<tr>
<td>Lower airway – cough, wheeze, dyspnea, chest tightness, cyanosis</td>
<td>Dizziness, syncope, hypotension</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia, arrhythmia, syncope, hypotension, shock</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Pruritus or edema of the lips/tongue/palate, metallic taste in the mouth, nausea, vomiting, abdominal cramps, diarrhea</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Anxiety, headache, seizure, syncope, loss of consciousness</td>
</tr>
<tr>
<td>Ocular</td>
<td>Pruritus, conjunctival injection, lacrimation</td>
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## Mediators

<table>
<thead>
<tr>
<th>Class of product</th>
<th>Examples</th>
<th>Biological effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme</td>
<td>Tryptase, chymase, cathepsin G, carboxypeptidase</td>
<td>Remodel connective tissue matrix</td>
</tr>
<tr>
<td>Toxic mediator</td>
<td>Histamine, heparin</td>
<td>Toxic to parasites&lt;br&gt;Increase vascular permeability&lt;br&gt;Cause smooth muscle contraction</td>
</tr>
<tr>
<td>Cytokine</td>
<td>IL-4, IL-13</td>
<td>Stimulate and amplify T&lt;sub&gt;H&lt;/sub&gt;2 cell response</td>
</tr>
<tr>
<td></td>
<td>IL-3, IL-5, GM-CSF</td>
<td>Promote eosinophil production and activation</td>
</tr>
<tr>
<td></td>
<td>TNF-α (some stored preformed in granules)</td>
<td>Promotes inflammation, stimulates cytokine production by many cell types, activates endothelium</td>
</tr>
<tr>
<td>Chemokine</td>
<td>CCL3 (MIP-1α)</td>
<td>Attracts monocytes, macrophages, and neutrophils</td>
</tr>
<tr>
<td>Lipid mediator</td>
<td>Leukotrienes C4, D4, E4</td>
<td>Cause smooth muscle contraction&lt;br&gt;Increase vascular permeability&lt;br&gt;Stimulate mucus secretion</td>
</tr>
<tr>
<td></td>
<td>Platelet-activating factor</td>
<td>Attracts leukocytes&lt;br&gt;Amplifies production of lipid mediators&lt;br&gt;Activates neutrophils, eosinophils, and platelets</td>
</tr>
</tbody>
</table>

*Figure 12-12 Immunobiology, 6/e. (© Garland Science 2005)*
Pathophysiology: Mouse Models
Anaphylaxis Exercise-Induced Syndrome

- Prodrome - flushing, pruritus, fatigue
- Early - urticaria, angioedema
- Established - stridor, GI symptoms, collapse
- Late - headache
- Precipitating Events: isometric and isotonic exercise; hot environment
- Temporally unpredictable
Anaphylaxis Exercise-Induced Syndrome

- Avoidance of exercise, especially in heat
- Avoidance of allergenic foods before exercise
- Buddy system-epinephrine
Pumphrey RS. *Clin Exp Allergy*. 2000;30(8):1144-1150