Anaphylaxis: Implementing Timely Diagnosis and Treatment Strategies to Optimize Care

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Faculty Disclosure

Consultant- Merck, Mylan, TEVA

Speakers Bureau- Aerocrine, Merck, Mylan, Genentech, Thermo Fisher Scientific, TEVA
In the absence of a known or likely allergen, anaphylaxis is likely when a reaction occurs suddenly and involves the skin and mucosal tissues and which of the following?

1. Respiratory symptoms
2. Gastrointestinal symptoms
3. Substernal pain
4. Headache

Use your keypad to vote now!
According to a recent consensus statement, how many doses of epinephrine should be provided to a patient at risk for anaphylaxis at discharge?

1. 1 dose
2. 2 doses
3. 3 doses
4. 4 doses

Use your keypad to vote now!
Most patients (85%-90%) experiencing an anaphylactic reaction will exhibit which of the following manifestations?

1. Cramping abdominal pain
2. Urticaria and angioedema
3. Dyspnea
4. Headache

Use your keypad to vote now!
Learning Objectives

• 1. Implement guideline-based strategies for the accurate diagnosis of anaphylaxis
• 2. Explain the rationale for the appropriate use of injectable epinephrine as first-line therapy for the treatment of anaphylaxis
• 3. Provide patients at risk for anaphylaxis with an emergency action plan that includes education on risk factors
Key Questions in Practice

• Is the prevalence of certain allergies and anaphylaxis changing?
• What causes anaphylaxis and what tests do you perform to confirm an allergy?
• What criteria do you use to determine whether a reaction should be treated with epinephrine?
  – What is the rationale for IM epinephrine?
  – Why are 2 doses of IM epinephrine sometimes necessary?
  – Why should auto-injectors not be substituted?
• Why should antihistamines or other adjunct therapies not be used as first-line therapy for an anaphylactic reaction?
• How do we ensure that patients are prepared to prevent a life-threatening reaction?

IM = intramuscular.
Allergy and Anaphylaxis Epidemiology
Definition of Anaphylaxis

• Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death\(^1\)

• Practical considerations:
  – Although “shock” may occur during anaphylaxis, it most often occurs in the absence of shock, hypoxia, or collapse
  – Anaphylaxis is defined by a wide spectrum of symptoms and severity
  – Quick recognition of anaphylaxis is critical for successful treatment

Anaphylaxis

• Anaphylaxis is likely underdiagnosed by patients and clinicians due to uncertainty and lack of universal clinical definition
• Overall, prevalence may be as high as 2%
• Appears to be increasing in children and adolescents
• Rates may be higher in northern US states
• ED visits, hospitalizations, and fatalities from anaphylaxis remain important issues

ED = emergency department.

Best Prevalence Data May Come From Epinephrine Auto-injector Prescriptions

Regional Differences in Epinephrine Auto-injector Usage

Number of EpiPen Prescriptions per 1,000 People (2004)

- Yellow: 2–3
- Orange: 4
- Blue: 5
- Purple: 6–7
- Light Purple: 8–12

Patterns of Anaphylaxis

• In adults$^{1,2}$
  – Most cases are idiopathic (~60%)
  – 22% are reported to be food related
  – Many end up being attributable to antibiotics and NSAIDs
  – Women predominate

• In children$^3$
  – Most cases are food related (>50%)
  – Males predominate
  – Episodes first occur at ~6 years of age

NSAIDs = nonsteroidal anti-inflammatory drugs.

Current Prevalence of Food Allergies in the United States

• 8 major foods are responsible for >90% of serious allergic reactions in the United States (fish, shellfish, peanut, tree nuts, milk, egg, wheat, soy)\(^1\)

• In adults aged >18 years\(^2,3\)
  – Prevalence of tree nut, peanut, sesame allergy was 1.3%
  – Reported rise in seafood allergy

• In children aged <18 years\(^2,4\)
  – Recent survey suggests prevalence is 8.0% (↑ from previous reports)
  – Prevalence highest for peanut followed by milk and shellfish
  – Reported rises in tree nut allergy in children
  – ~30% had multiple food allergies
  – ~38% had severe allergies

Food-related Visits to the ED

• From 2001-2005, there were 1,015,000 total ED visits (203,000/y) for food-related acute allergic reactions
  – An ED visit in the United States for a food-related acute allergic reaction occurred every 3 minutes

• 448,000 visits (90,000/y) classified as probable food anaphylaxis
  – An ED visit in the United States for food-related anaphylaxis occurred every 6 minutes

Anaphylaxis in the Pediatric ED

- 213 anaphylactic reactions representing 0.18% of all patient encounters in a pediatric ED (4 months-18 years of age)
- Trigger identified as foods in 71% of cases
  - Seafood (fish/shellfish) 26%
  - Peanut 20%
  - Tree nuts 20%
  - Fruits/vegetables 11%
  - Cow’s milk 7%
  - Chicken egg/wheat 5%
- >90% characterized as mild-moderate reactions
- Anaphylaxis code underused with 151 reactions coded as “allergic reactions,” but met criteria for anaphylaxis
- Hospitalization rate was 14%

Classification, Risk Factors, and Signs and Symptoms of Anaphylaxis
**Classification of Human Anaphylaxis**

<table>
<thead>
<tr>
<th>Immunologic</th>
<th>Nonimmunologic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Idiopathic</strong></td>
<td><strong>Other</strong></td>
</tr>
<tr>
<td><em>IgE, FcεRI</em></td>
<td></td>
</tr>
<tr>
<td>Foods, venoms, latex, drugs</td>
<td>Dextran, OSCS (contaminant in heparin)</td>
</tr>
<tr>
<td><em>Non-IgE, FcεRI</em></td>
<td></td>
</tr>
<tr>
<td>Drugs such as NSAIDs, opioids, neuromuscular blocking agents, radiopaque contrast media</td>
<td>Physical</td>
</tr>
<tr>
<td>Exercise, cold</td>
<td></td>
</tr>
</tbody>
</table>

**ANAPHYLACTOID**

IgE = immunoglobulin E; FcεRI = high-affinity IgE receptor; OSCS = over-sulfated chondroitin sulfate.

Factors That Increase Risk of an Event or Potentiate Its Severity

**Infants**
Cannot describe their symptoms

**Adolescents and young adults**
Increased risk-taking behaviors

**Surgery, labor and delivery**
Risk from medications (e.g., antibiotic to prevent neonatal group B strep infection)

**Elderly**
Increased risk of fatality from medication or venom-triggered anaphylaxis

Factors That Increase Risk of an Event or Potentiate Its Severity (cont’d)

**Comorbid Diseases**

- Asthma and other respiratory diseases
- Cardiovascular diseases
- Allergic rhinitis and eczema
- Psychiatric illness (e.g., depression)

**Concurrent Medications/Ethanol/Recreational Drug Use**

- β-adrenergic blockers and ACE inhibitors (may result in more severe reaction, may reduce effectiveness of epinephrine)
- Ethanol/sedatives/hypnotics/antidepressants/recreational drugs (potentially affect recognition of anaphylaxis triggers and symptoms)

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*a* Atopic diseases are a risk factor for anaphylaxis triggered by food, exercise, and latex, but not for insect stings, β-lactam antibiotics, or insulin. ACE = angiotensin converting enzyme.

## Frequency and Occurrence of Signs and Symptoms of Anaphylaxis

### Signs and Symptoms

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Percent&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cutaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Urticaria or 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>Hypotension, dizziness, or syncope</td>
<td>30-35</td>
</tr>
<tr>
<td>Abdominal</td>
<td></td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhea, or cramping pain</td>
<td>25-30</td>
</tr>
</tbody>
</table>

### ACTION ITEM:

Recognize that cutaneous symptoms are present in as many as 90% of anaphylaxis cases, and in the absence of a known allergen, involvement of ≥2 systems is indicative of anaphylaxis.

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<sup>a</sup>Percentages are approximations.

Anaphylaxis Is Likely When 1 of the Following Criteria Is Met

1. Sudden onset of an illness, with involvement of the skin, mucosal tissue, or both (minutes to several hours):
   
   **AND at least 1 of these:**
   
   1. Sudden respiratory symptoms
   2. Sudden reduced BP or symptoms of end-organ dysfunction

2. OR

2. 2 or more of the following that occur suddenly after exposure to a likely allergen or other trigger for that patient (minutes to several hours):

   1. Sudden skin or mucosal symptoms
   2. Sudden respiratory symptoms
   3. Sudden reduced BP or symptoms of end-organ dysfunction
   4. Sudden gastrointestinal symptoms

3. OR

3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours)

BP = blood pressure; GI = gastrointestinal.

Which of the following is the ideal route of delivery for epinephrine?

1. Inhaled
2. Intravenous
3. Intramuscular
4. Subcutaneous

Use your keypad to vote now!
A second dose of epinephrine can be administered after the first dose in as little as:

1. 5 minutes
2. 10 minutes
3. 20 minutes
4. 40 minutes

Use your keypad to vote now!
Case Study:
John, 7-Year-Old Boy
Case Study: John, 7-Year-Old Boy

Today’s workup:
• Current medications: none
• Height: 44”
• Weight: 40 lb
• BP: 98/58 mm Hg
• Heart rate: 85 bpm
• Skin exam normal, no eczema
• HEENT exam normal
• Respiratory exam normal
• No other complaints or conditions of note

HEENT = head, eyes, ears, nose, throat.
Case Study: John, 7-Year-Old Boy (cont’d)

• Review of allergic history:
  – No history of anaphylaxis before recent event
  – Developed localized hives on neck after drinking milk at 1 year of age
Pharmacologic Management of Anaphylaxis
Acute Management When Anaphylaxis Is Suspected

- Administer IM epinephrine quickly
  - Repeat every 5 to 10 minutes if necessary
- Place patient in supine position with legs elevated
- Consider oxygen for patients who:
  - Have prolonged reactions

ACTION ITEM:
Intramuscular epinephrine can be administered every 5 to 10 minutes if necessary for the treatment of patients with anaphylaxis

IM epinephrine (to lateral aspect of thigh) from 1:1,000 dilution (0.1 mg/mL) injected as 0.2 to 0.5 mL (0.01 mg/kg in children, maximum dose 0.3 mg) to control symptoms and increase blood pressure
Additional Measures When Anaphylaxis Is Suspected

• Evaluate hypotension and need for IV fluids

<table>
<thead>
<tr>
<th>In general</th>
<th>Persistent hypotension &lt;90/60 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children &gt;1 to 10 years</td>
<td>Systolic &lt;70 mm Hg + (2x age in years)</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>Systolic &lt;90 mm Hg</td>
</tr>
</tbody>
</table>

• Individualize observation

Other Factors to Consider When Treating an Anaphylactic Episode

• Types of supportive treatments
  – IV fluids for hypotension
  – Antihistamines, corticosteroids, vasopressors, or glucagon

• Severity and rate of progression of the episode

• Onset of action and method of administration of the drug(s) administered
Rationale for Epinephrine
Fatal Events Can Rapidly Progress

• Failure to administer epinephrine promptly is the most important factor contributing to death in children and adolescents with anaphylaxis\(^1\)

• Median time to respiratory or cardiac arrest was\(^2\):
  – 5 minutes for iatrogenic reactions
  – 15 minutes for venom
  – 30 minutes for foods

• \(~50\%\) (13/25) of deaths occurred within the first 60 minutes after onset of anaphylaxis\(^3\)

Therapies Other Than Epinephrine Frequently Given in the ED

- In a retrospective, multicenter chart review, only 20% of pediatric patients with food-related anaphylaxis received epinephrine.
- They frequently received other medications, including:
  - Antihistamines (59%)
  - Corticosteroids (56%)
  - IV fluids (23%)
  - Inhaled β-agonists (13%)
- When epinephrine was given, it was most frequently given subcutaneously (74%).

Why Not an Antihistamine?

- Antihistamines antagonize histamine only and have a much slower onset of action than epinephrine
- Anaphylaxis is not mediated by histamine alone\(^a\)
- Evidence-based guidelines state that antihistamines are considered supportive therapy and do not replace epinephrine
  - No direct outcome data regarding effectiveness of antihistamines in anaphylaxis
  - Should never be used alone in the treatment of anaphylaxis
  - Can be given after epinephrine administration since they may be useful for control of cutaneous and cardiovascular manifestations

\(^a\)Other mediators include leukotrienes, prostaglandins, kinins, platelet-activating factor, interleukins, tumor necrosis factor.

Oral Diphenhydramine Takes 80 Minutes for 50% Suppression

Time to 50% Suppression of Histamine-induced Flare

PO = by mouth.

Action of Epinephrine

Epinephrine

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

$\alpha_2$-adrenergic receptor
- ↓ Insulin release

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

$\beta_2$-adrenergic receptor
- ↑ Bronchodilation
- ↑ Vasodilation
- ↓ Mediator release

IM Epinephrine: Onset of Effect

Maximum pharmacodynamic effect occurs before 10 minutes
- Systolic pressure
- Diastolic pressure
- Heart rate

Epinephrine absorption was delayed in the children receiving SQ injection vs IM injection

SQ = subcutaneous.
Key Points to Consider

- Anaphylactic events can progress rapidly
- Antihistamines antagonize only the effects of histamine and do not act fast enough to prevent fatalities
- The use of either antihistamines or corticosteroids as first-line therapy for anaphylaxis is inappropriate
- The vasopressive effects of epinephrine, along with its effects in preventing and relieving laryngeal edema and bronchoconstriction, may be lifesaving
- Absorption by IM injection faster than SQ injection
Practice Parameter Summary: Use of Epinephrine

- Epinephrine should be administered at an appropriate dose without delay at the onset of evident anaphylaxis.
- Treatment in order of importance is: epinephrine, patient position, oxygen, IV fluids, nebulized therapy, vasopressors, antihistamines, corticosteroids, and other agents.
- Epinephrine is:
  - First-line therapy.
  - Rapid acting and antagonizes the pathophysiologic.

ACTION ITEM:
Epinephrine should be administered at an appropriate dose without delay at the onset of evident anaphylaxis.

Case Study:
Sheri, 45-Year-Old Woman
Case Study: Sheri, 45-Year-Old Woman

Today’s workup:
• Height: 66”
• Weight: 145 lb
• BP: 117/82 mm Hg
• Heart rate: 98 bpm
• Respiratory exam: normal
• HEENT exam: normal
• GI exam: normal
Case Study: Sheri, 45-Year-Old Woman (cont’d)

• Allergic history:
  – Documented allergy to yellow jackets and hornets
    • Confirmed via skin testing

• Current medications:
  – Epinephrine auto-injector for self-management
2 Doses of Epinephrine Are Needed in Many Cases
Patterns of Anaphylaxis

- **Uniphasic**
  - Isolated reaction producing signs and symptoms within minutes (typically within 30 minutes) of exposure to an offending stimulus

- **Biphasic**
  - Late-phase reactions that can occur 1 to 72 hours (most within 10 hours) after the initial attack (1%-23%)

- **Protracted**
  - Severe anaphylactic reaction that may last between 24 and 36 hours despite aggressive treatment
There Are 4 Basic Reasons to Supply 2 Doses

1. Because of its severity, an episode may require ≥2 doses to control
2. An episode may be biphasic
3. An episode may be protracted
4. A mistake may be made with the first dose
It is important to provide $\geq 2$ auto-injectors to patients at risk for anaphylaxis, as $\geq 2$ dose of epinephrine are needed in what percentage of anaphylaxis cases?

1. Up to 15%
2. Up to 25%
3. Up to 36%
4. Up to 45%

Use your keypad to vote now!
Frequency of Need for 2 Doses of Epinephrine Regardless of Cause

Patients Requiring >1 Dose of Epinephrine

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 second dose can be administered within the first 5 minutes of the previous dose
  - *There is no way to predict who will require ≥2*

**ACTION ITEM:**
Ensure that all patients at risk for anaphylaxis have at least 2 doses of epinephrine at their disposal in convenient, safe places

Why Should Patients at Risk Be Given an Epinephrine Auto-injector?
A Higher Proportion of Subsequent Reactions Are Severe and Require Epinephrine

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

Data from the first 5,149 patients in a voluntary registry for peanut and tree nut allergy.

Locations Outside the Home Are Common Sites for Subsequent Reactions


2nd and 3rd reactions commonly occur away from home.
Difficulty Drawing Epinephrine From an Ampule in the Real World

![Graph showing time in seconds for Parents, Physicians, General Duty Nurses, and ED Nurses. The graph indicates that the Physicians group took significantly more time compared to the other groups.](image)

*P* < .05 vs all control groups
Absorption of Epinephrine Faster With IM vs SQ Injection

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

- SQ epinephrine: 34 ±14 min
- IM epinephrine: 8 ± 2 min

$P < .05$

Comparison of Auto-injectors: EpiPen

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

- Clearly labeled end caps to guide you through administration
- Easy-to-follow Instructions, printed on the side of the auto-injector, to remind you how to use it
- A red injector tip to show which end to inject

Available at: http://www.adrenaclick.com/about-adrenaclick
Reasons Patients Report Not Using an Auto-injector

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

When prescribing an epinephrine auto-injector, how often do you ensure the patient receives the device they were trained on?

1. Always
2. Most of the time
3. Sometimes
4. Never

Use your keypad to vote now!
Implementing an Emergency Action Plan
Identifying Risk Factors

• Assess a patient’s environment and their risk
  – Has the allergen been confirmed?
  – Has the patient had previous reactions to trace exposures?
  – Does the patient have an allergy to foods that are potential risk factors for fatal anaphylaxis?
  – Does the patient have asthma?
  – Is the patient in an environment where they are required to actively avoid the allergen(s)? Do they require assistance or special attention?
  – Does the patient have an emergency action plan?
  – If in school, does the school have an emergency action plan?
Food Allergy Action Plan

ACTION ITEM:
Ensure that all patients at risk for anaphylaxis have an emergency action plan

Universal Recommendations for Patients at Risk for Anaphylaxis

• Following a reaction at hospital discharge or when risk is perceived based on patient history and allergen testing:
  – Epinephrine auto-injector prescription (2 doses)
  – Auto-injector training
  – Education on avoidance of allergen
  – Emergency action plan
  – Follow-up with primary care clinician
  – Referral to allergist if first presentation or cause is unknown

**Action Plan**

- Recognize that cutaneous symptoms are present in as many as 90% of anaphylaxis cases and, in the absence of a known allergen, involvement of ≥2 systems is indicative of anaphylaxis.
- Intramuscular epinephrine can be administered every 5 to 10 minutes if necessary for the treatment of anaphylaxis.
- Epinephrine should be administered at an appropriate dose without delay at the onset of evident anaphylaxis.
- Ensure that all patients at risk for anaphylaxis have at least 2 doses of epinephrine at their disposal in convenient, safe places.
- Ensure that all patients at risk for anaphylaxis have an emergency action plan in place.
In the absence of a known or likely allergen, anaphylaxis is likely when a reaction occurs suddenly and involves the skin and mucosal tissues and which of the following?

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Q & A