ANAPHYLAXIS
Workshop
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SPEAKER DISCLOSURE

• Consultant and/or Speakers Bureau for:

  Aerocrine
  Merck
  McNeil
  ISTA
  Sunovion
Anaphylaxis Defined

- A generalized or systemic hypersensitivity reaction, most commonly but not always IgE mediated, but where mast cell and basophil mediators play predominant role, which is
  - rapid in onset
  - potentially life-threatening
  - almost always unanticipated
- Initial mild symptoms may progress to a severe and irreversible outcome

Anaphylaxis is an acute, life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden release of mediators from mast cells and basophils.

- Anaphylactic reactions are not the sole result of immediate hypersensitivity mast cell/basophil derived mediators such as histamine, leukotrienes, and prostaglandins.
- Other mediator cascades are recruited (eg, clotting and complement) including non-mast cell derived mediators, which are also responsible for many of the symptoms that occur in anaphylactic reactions.

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):

a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise
c. Reduced BP or associated symptoms
d. Persistent gastrointestinal symptoms (eg, cramping, abdominal pain, vomiting

AND AT LEAST ONE OF THE FOLLOWING

Respiratory compromise (eg, dyspnea, wheeze-bronchospasm)

Reduced BP or associated symptoms of end-organ dysfunction

OR

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

a. Infants and children: Low SBP (age specific) or >30% decrease in SBP*
b. Adults: SBP of <90 mm Hg or >30% decrease from that person’s baseline

NIAID=National Institute of Allergy and Infectious Diseases; FAAN=Food Allergy and Anaphylaxis Network; BP=blood pressure; SBP=systolic blood pressure.

*Low 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.

PRIMARY SYMPTOMS OF ANAPHYLAXIS

- **SKIN:**
  - *flushing*, itching, urticaria, angioedema
- **Gastrointestinal:**
  - nausea, vomiting, bloating, cramping, diarrhea
- **Gynecologic**
  - Uterine Cramping
- **Other**
  - Feeling of impending doom
  - Metallic taste

- **RESPIRATORY:**
  - dysphonia, cough, stridor, wheezing, dyspnea, chest tightness, asphyxiation, death

- **CARDIOVASCULAR:**
  - *tachycardia*, hypotension, dizziness, syncope, death

(Skin oral and throat symptoms often noted first)

2. Phillip Korenblat, MD. Professor, Internal Medicine, Washington
ANAPHYLAXIS OBSERVATIONS

SIGNS AND SYMPTOMS

- Skin symptoms most common (> 90% of patients)
- Skin, oral, and throat symptoms often first noted
- Respiratory symptoms: 40% to 70% of patients
- Gastrointestinal symptoms: about 30% of patients
- Shock: about 10% of patients
- Signs and symptoms: usually within 5 to 30 minutes
- More rapid the onset, the more serious the reaction

Frequency and Occurrence of Signs and Symptoms of Anaphylaxis

If there is no cutaneous involvement, question the diagnosis 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><strong>Dizziness, syncope, hypotension</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30-35</td>
</tr>
<tr>
<td><strong>Abdominal</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhea, cramping</td>
<td>25-30</td>
</tr>
<tr>
<td>pain</td>
<td></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>

• Signs and symptoms: usually within 5 to 30 minutes
• More rapid onset, more serious the reaction

Anaphylaxis: Prevalence
Underestimated and Misdiagnosed

Underestimated:
- Negative autopsy findings in fatal reactions
- Rapid death may leave no characteristic macroscopic findings
- Myocardial ischemia is common in anaphylaxis - can be misclassified as death due to Myocardial Infarction

Misdiagnosis / Confusion with other conditions:
- Acute Asthma
- Airway obstruction with foreign body
- Diabetic, septic or other types of shock
- Panic attacks
- Urticaria

# Differential Diagnosis of Anaphylaxis

- **Common diagnostic dilemmas**
  - Acute asthma
  - Fainting/vasovagal episode (syncope)
  - Anxiety/panic attack
  - Acute generalized hives
  - Aspiration of a foreign body
  - Cardiovascular (myocardial infarction, pulmonary embolus)
  - Neurologic events (seizure, CVA)
- **Flush syndromes**
  - Peri-menopause
  - Carcinoid
  - Autonomic epilepsy
  - Medullary thyroid Ca
  - Vocal cord dysfunction
  - Psychosomatic episode, hyperventilation
- **Non-Organic Disease**
  - Psychosomatic episode, hyperventilation
  - Shock (other causes)
  - Hypoglycemic
- **Post-prandial syndromes**
  - Scombroidosis
- **Pollen food allergy syndrome**
  - Monosodium glutamate, Sulfites
  - Food poisoning
- **Excess Endogenous Histamine**
  - Mastocytosis/clonal mast cell disorders
  - Basophil leukemia
- **OTHER**
  - Non-allergic angioedema
  - C1-esterase deficiency
  - ACE inhibitor angioedema
  - Systemic capillary leak syndrome
  - Red man syndrome (vancomycin)
  - Pheochromocytoma

WAO guidelines 2011
Differential Diagnosis of Anaphylaxis

- Vasovagal reactions (syncope/faint)
- Myocardial infarction, Acute asthma
- Other forms of shock
  - Hemorrhagic, hypoglycemic, endotoxic,
- Reactions caused by excess endogenous production of histamine
- Flushing disorders (eg, rosacea, carcinoid, alcohol)
- Ingestant-related reactions mimicking anaphylaxis: restaurant syndromes (eg, monosodium L-glutamate [MSG], sulfites, scombroidosis), pollen food allergy syndrome (OAS)
- Miscellaneous (eg, acquired and hereditary angioedema, panic attacks, vocal cord dysfunction)

EPIDEMIOLOGY OF ANAPHYLAXIS

- **At Risk:** 1% to 15% of the population (US data\(^1\))
  - **Prevalence:** Estimated that up to 2% of population BUT UNDERDIAGNOSED!
- Up to 1% of patients with anaphylaxis may die
- **Fatalities** per year in the US:
  - Food-induced: 150
  - Antibiotic-induced: 600
  - Venom-induced: 50
- **Food allergy** affects up to 6%-8% of children younger than 4 years of age and 2% of the US population beyond the 1\(^{st}\) decade of life\(^3,4\)
- **Incidence** of anaphylaxis is increasing\(^5\)

Modest Increase in Annual Incidence Rates of Anaphylaxis: Rochester, Minnesota, 1990-2000

- Best prevalence data come from the number of prescriptions for epinephrine auto-injectors
- Prevalence may be as high as 2% and rising more so in the younger age group
- Data suggest hospitalizations and fatalities from anaphylaxis are increasing

Angioedema Urticaria Anaphylaxis (any)

Increasing Anaphylaxis Hospitalizations: Australia, 1993-2005


Hospitalizations Per 100,000 Population

ICD-10-AM introduced

Year

Anaphylaxis Epidemiology

- No racial or ethnic differences
- Anaphylaxis more common in children and adolescents but anaphylactic DEATHS more common in adults
- Anaphylaxis: M>F to age 15 Then F>M for > 15
- Males: Hymenoptera stings
- Females: Latex, ASA/NSAIDS, Muscle relaxants
- Atopy: for Foods, RCM, Latex, EIA, Idiopathic
  But not for Hymenoptera, PCN, Insulin
- Oral less likely/severe than systemic (Drugs)
- Gaps in administration predispose to reactions but longer interval⇒less likely recurrence
Mechanisms of Human Anaphylaxis

Human Anaphylaxis

Immunologic

Idiopathic

IgE, FcεRI
Foods, venoms, latex, drugs (penicillin), biologic therapies, immunotherapy

Non-IgE, FcεRI
Blood products, immune aggregates, drugs

Non-Immunologic

Other Drugs (opioids)

Physical Exercise, cold

IgE=immunoglobulin E; FcεRI=high-affinity IgE receptor;

GELL AND COOMBS CLASSIFICATION OF HYPERSENSITIVITY REACTIONS

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>IMMEDIATE HYPERSENSITIVITY</td>
</tr>
<tr>
<td>Type II</td>
<td>CYTOXIC REACTIONS (Incompatible blood transfusions: complement fixing Abs to formed elements of blood)</td>
</tr>
<tr>
<td>Type III</td>
<td>IMMUNE COMPLEX REACTIONS (Complement activated by Ag/Ab or molecular aggregates: IVIG if IgA↓, protamine, dextran)</td>
</tr>
<tr>
<td>Type IV</td>
<td>DELAYED HYPERSENSITIVITY</td>
</tr>
</tbody>
</table>

Anaphylaxis can occur through Types I, II and III
Causes of Anaphylaxis

- Food: 35%
- Idiopathic: 24%
- Insect sting: 14%
- Medication: 13%
- Exercise: 7%
- Other: 7%
Anaphylactic Triggers

Based on summary of published studies:
In many reactions, anaphylactic triggers are unknown.
Fatal Reactions Etiology


- Sting: 47
- Anesthetic: 35
- Nuts: 32
- Antibiotics: 27
- Possible Food: 18
- Other Drug: 15
- Food: 13
- Contrast Media: 11
- Other: 3

Pumphrey RSH. Anaphylaxis 2004
Main findings

- ~20 recorded deaths/year i.e. ~1:2.8 million
- 50% iatrogenic; 25% food and 25% venom
- ~50% died from asphyxia (food) and 50% from shock (iatrogenic and venom)
- Median time to death:
  5 mins if iatrogenic; 15 mins venom; and 30 mins food
- **Adrenalin rarely used before cardiac arrest**

AGENTS THAT CAUSE ANAPHYLAXIS: IgE-DEPENDENT TRIGGERS

- Foods (eg peanut, tree nuts, seafood, soy, sesame, peach)
- Medications (eg β-lactam antibiotics)
- Venoms
- Natural rubber latex
- Allergen immunotherapy
- Biologic therapies (eg, monoclonal antibodies)
- Diagnostics

- Seminal fluid
- Hormones
- Animal or human proteins
- colorants (insect-derived, eg. carmine)
- enzymes
- Alpha-1,3 galactose in red meat (Alpha Gal)
- aspirin and NSAIDs (rarely through IgE)

Kemp SF and Lockey RF, J Allergy Clin Immunol 2002;110:341-8
Known Mechanisms and Triggers of Anaphylaxis in the Community

- Immunologic mechanisms
  - IgE dependent
    - Foods (eg, peanut, tree nut, shellfish, fish, milk, egg, soy, sesame, peach, chick pea)
    - Insect stings
    - Natural rubber latex
    - Biologic therapies (eg, monoclonal antibodies)
    - Allergen Immunotherapy
    - Medications (eg, Beta lactam antibiotics)
    - Seminal fluid

Known Mechanisms and Triggers of Anaphylaxis in the Community (cont’d)

• Non-immunologic mechanisms
  – Physical factors (eg, exercise, cold)
  – Ethanol
  – Medications (eg, opioids)
  – Radiocontrast Media
  – NSAIDS (most commonly)

• Idiopathic anaphylaxis
  – Consider the possibility of:
    • Hidden or previously unrecognized allergens
    • Mastocytosis/clonal mast cell disorder
Triggers of Anaphylaxis: Food

- Peanuts
- Shellfish
- Tree nuts (eg, walnuts, pecans)
- Milk
- Eggs
- Fish
- Wheat
- Soybean

- Food allergy affects up to 6%-8% of children younger than 4 years of age and 2% of the US population beyond the 1st decade of life

- Incidence of anaphylaxis is increasing
FATAL FOOD-INDUCED ANAPHYLAXIS

A clinical review of anaphylactic fatalities (N=32)

- in a retrospective analysis of 32 deaths in patients age 2-33 years
  - peanut and tree nuts caused >90% of reactions
  - prevalence of peanut allergy has doubled in children <5 years of age in the last 5 years
  - most patients had a history of asthma
  - most did not have injectable epinephrine available at the time of their reaction and death

IATROGENIC ANAPHYLAXIS

- Estimated 550,000 serious allergic reactions to drugs/year in US hospitals
- Most common drug triggers
  - Penicillin (highest number of deaths from anaphylaxis)
  - Sulfa drugs
  - Non-steroidal anti-inflammatory drugs
  - Muscle relaxants
- Most common biologic triggers
  - Monoclonal antibodies (i.e. omalizumzb)
  - Anti-lymphocyte globulin
  - Vaccines
  - Allergens

Neugut AI et al. Arch Intern Med 2001;161:15-21
Iatrogenic Anaphylactic Triggers:

> half million serious allergic reactions to drugs/year in US hospitals

• Medications
  - Antibiotics: PCN (most deaths), Sulfa drugs
  - Aspirin and other NSAIDs
  - Cancer chemotherapeutic agents (carboplatin, doxorubicin)
  - Anesthetics (suxamethonium, veroconium)

• Diagnostic Agents
  - Iodinated contrast media
  - Fluorescein

• Blood transfusions

• Allergen immunotherapy

• Vaccinations
  - Anti-venoms
  - Monoclonal antibodies (rituximab, infliximab, and rarely, omalizumab)
PERI-OPERATIVE ANAPHYLAXIS

- Neuromuscular blocking drugs (muscle relaxants), eg suxamethonium, rocuronium, alcuronium, atracurium
- Induction agents, eg thiopentone, propofol, alfathesin
- Other: including local anesthetics, antibiotics, protamine, and latex
- Predisposing factors: atopy, asthma; previous exposure

Fisher M. In: Anaphylaxis, John Wiley & Sons Ltd., Chichester, UK, 2004:193-206
ALLERGEN IMMUNOTHERAPY – INDUCED ANAPHYLAXIS

- Fatal reactions uncommon: 1 per 2,000,000 injections
- Risk factors for fatality include:
  - Dosing errors
  - Poorly controlled asthma (FEV$_1$ < 70%)
  - Concomitant β-blocker use
  - Lack of proper equipment and trained personnel
  - Inadequate epinephrine treatment

Stewart GE and Lockey RF. J Allergy Clin Immunol 1992;90:567-78
Triggers of Anaphylaxis:
Insect Stings and Bites

- Bees
- Vespids
  - Wasps
  - Yellow Jackets
  - Hornets
- Fire ants

- At least 50 deaths per year in US (0.5% - 5% Allergic)-- Rising
- ↑ numbers of fire ants and Africanized bees and ↑ outdoor activity
Hymenoptera insects

- wasp
- fireant
- Honey bee
- Yellow jacket
Natural Rubber Latex and Anaphylaxis

• Some groups are at increased risk
  – Healthcare workers (11-15%)
  – Children with spina bifida (up to 50%)
  – Persons having 3 or more surgeries
  – Otherwise < 1% population

• Sources of Natural Rubber Latex
  a) In hospitals: gloves, catheters, adhesives, and vials with NRL closures.
  b) In community settings: gloves, condoms, balloons, toys, and shoes

• Incidence has decreased since powder-free latex gloves and non-latex gloves have become available

• Cross reacting foods: avocado, kiwi, banana, potato, chestnut and papaya may be triggers

FOOD-DEPENDENT EXERCISE-INDUCED ANAPHYLAXIS

- Most common in females, and from late teens to mid-30’s
- Triggered by exercise 2-4 hours after ingesting offending food
- Foods implicated: wheat, seafood, fruit, milk, celery, and fish.
- Associations: asthma, positive skin prick tests to foods
- Mechanism: two signals required

Aunhachoke K et al. J Med Assoc Thai 2002;85:1014-8
ANAPHYLAXIS FROM IMMUNE CAUSES OTHER THAN IgE

• Cytotoxic (Type II)
  - transfusion reactions to cellular elements (IgG, IgM)

• Immune aggregates (Type III)
  - intravenous immunoglobulin
  - Dextran (possibly)

Kemp SF and Lockey RF, J Allergy Clin Immunol 2002;110:341-8
ANAPHYLAXIS: NON-IMMUNOLOGIC CAUSES

MULTIMEDIATOR COMPLEMENT ACTIVATION/ACTIVATION OF CONTACT SYSTEM

- Radio-contrast media
- Over-sulfated chondroitin sulfate (OSCS) in heparin
- Renal dialysis with sulphonated polyacrylonitrile, cuprophane, or polymethylmethacrylate dialysis membranes
- Ethylene oxide gas on dialysis tubing (possibly through IgE)
- Protamine

Kemp SF and Lockey RF, J Allergy Clin Immunol 2002;110:341-8
ANAPHYLAXIS: NON-IMMUNOLOGIC CAUSES

NONSPECIFIC DEGRANULATION OF MAST CELLS AND BASOPHILS

- Opiates
- Physical factors:
  - exercise (no food or medication co-trigger)
  - temperature (cold, heat)

Kemp SF and Lockey RF, J Allergy Clin Immunol 2002;110:341-8
IDIOPATHIC ANAPHYLAXIS

• Common in adults referred to allergists for anaphylaxis
• Uncommon in children
• Negative skin tests, negative dietary history, no associated diseases eg. mastocytosis
• Preventive medication: oral corticosteroids, H₁ & H₂ antihistamines, anti-leukotrienes
• Deaths rare
• May gradually improve over time

Anaphylactic Reaction

**Mast Cell**

- **Allergen**
- **IgE antibody**
- **Mast cell granules**

**Immediate reaction**
- Wheeze
- Urticaria
- Hypotension
- Abdominal cramping

**Late-phase reaction**

**Phil Lieberman: Anaphylaxis, a clinician's manual**
ACUTELY RELEASED MEDIATORS OF ANAPHYLAXIS

- Degranulation of mast cells and basophils causes the release of:
  - preformed granule-associated substances
    - histamine
    - heparin
    - tryptase
    - chondroitin sulfate
    - chymase
    - carboxypeptidase
  - cytokines
  - newly-generated lipid-derived mediators
    - prostaglandin D$_2$,
    - leukotriene (LT) B$_4$, LTC$_4$, LTD$_4$, LTE$_4$,
    - platelet activating factor.

\[ \downarrow \text{PAF acetylhydrolase and/or} \downarrow \text{histamine deaminase} \Rightarrow \uparrow \text{RISK} \]

Kemp SF and Lockey RF. J Allergy Clin Immunol 2002; 110:341-8
Mediator Recruitment

Mast Cell

- Activation of factor XII
- Clot lysis Platelet Activation
- Complement activation
- Contact system With kinin formation

Clotting
# Mast Cell and Basophil Mediators

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Pathophysiology</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kininogenase (kallikrein)</td>
<td>Activate contact system</td>
<td>Hypotension angioedema</td>
</tr>
<tr>
<td>Tryptase</td>
<td>Activate contact system, complement, clotting</td>
<td>Hypotension angioedema, DIC</td>
</tr>
<tr>
<td>Heparin</td>
<td>Inhibits clotting, anticomplementary</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Chymase</td>
<td>Formation angiotensin II</td>
<td>Modulates hypotension</td>
</tr>
</tbody>
</table>
Pathophysiology

• Signs and symptoms due primarily to\textsuperscript{1}
  – Smooth muscle contraction
  – Increased vascular permeability
  – Vasodilation

• Respiratory compromise and cardiovascular collapse cause most fatalities\textsuperscript{2}

• Urticaria and angioedema: most common manifestations
  – Might be delayed or absent in rapidly progressive anaphylaxis\textsuperscript{2}
  – The more rapid the occurrence, the more likely a severe and life-threatening reaction

• Symptoms generally appear within minutes but can occur as late as several hours\textsuperscript{2}

\textsuperscript{1} Lieberman P. Clinician’s Manual on Anaphylaxis 2005
\textsuperscript{2} Lieberman et al. J Allergy Clin Immunol 2005
Endogenous Compensatory Mechanisms for Hypotension

ACE

Phil Lieberman: Anaphylaxis, a clinician’s manual
Drugs That May Complicate Rx

• Beta blockers
• Ace inhibitors
• Ace blockers
• Tricyclics
• MAO inhibitors
Multimediator Recruitment in Anaphylaxis

- Complement
  - Decreased $C_4, C_3$
  - Formation $C_{3a}$

- Contact system
  - Decreased high molecular weight kininogen
  - Formation of activation complexes

- Coagulation pathway
  - Decreased factor V, VII
  - Decreased fibrinogen
**BIPHASIC/LATE-PHASE REACTION**

**Cellular infiltrates: 3 to 6 hours (LPR)**

- **Allergen**
  - Histamine
  - IL-4, IL-6
  
- **Mast cell**
  - EPR 15 min (Early-Phase Reaction)
  - Eosinophil
    - CysLTs, GM-CSF, TNF-α, IL-1, IL-3, PAF, ECP, MBP
  - Basophil
    - Histamine, CysLTs, TNF-α, IL-4, IL-5, IL-6
  - Monocyte
    - CysLTs, TNF-α, PAF, IL-1
  - Lymphocyte
    - IL-4, IL-13, IL-5, IL-3, GM-CSF

**Return of Symptoms**
Patterns of Anaphylaxis

• **Uniphasic**
  – Event that occurs then subsides within 1 to 2 hours after onset of symptoms either with or without therapy

• **Biphasic**
  – Symptoms resolve after treatment but return between 30 minutes and 72 hours later

• **Protracted**
  – Symptoms do not resolve with treatment and may last up to 32 hours despite aggressive treatment

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Uniphasic Anaphylaxis

- Antigen Exposure
- Initial Symptoms
- Treatment
- Time

Antigen Exposure

Initial Symptoms

Treatment
Biphasic Anaphylaxis

**Initial Symptoms**
- Treatment
- 0

**Second-Phase Symptoms**
- Treatment
- 8 to 12 hours

Biphasic Reactions

- Up to 20% of attacks\(^1\)
- In up to **one third of patients** with (food induced) fatal or near fatal reactions\(^2\)
- Usually, initial symptomatic period followed by an asymptomatic period of 1 to 8 hours, but the asymptomatic phase may last longer than 24 hours\(^3\)
- No predictive characteristics (age, gender)\(^4\)

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3. Lieberman P. *Ann Allergy Asthma Immunol* 2005
Protracted Anaphylaxis

Initial Symptoms

Antigen Exposure

Up to 32 hours¹

BIPHASIC AND PROTRACTED ANAPHYLAXIS

- **Biphasic anaphylaxis**: Return of symptoms after resolution of initial symptoms, without subsequent allergen exposure
  - Symptoms return within 1 to 8 hours (sometimes longer)
  - Up to 20% of anaphylactic reactions are biphasic
  - Patients often require additional epinephrine
- **Protracted anaphylaxis**: symptoms may be continuous for 5-32 hrs (Requires additional epinephrine)

Biphasic Reactions
Factors signaling a potential 2nd reaction

- A delay of 30 minutes or more between antigen and onset of symptoms\(^1\)
- Ingested antigen\(^2\)
- Severity of first phase\(^2\)
- Hypotension in first phase\(^4\)
- Delay in administration of epinephrine\(^2,3\)
- Failure to give epinephrine or insufficient dose\(^3\)
- Failure to administer or diminished doses of corticosteroid\(^1\)

1. Lieberman P. Ann Allergy Asthma Immunol 2005
2. Lee and Greenes, Pediatrics 2000
3. Lieberman P. Allergy Clin Immunol Int 2004
Subsequent Reactions May Increase in Severity with Time

Severity of previous reaction is not predictive of fatality

* p<0.001

Modified from Simons et al, J Allergy Clin Immunol 2004
LABORATORY TESTS IN THE DIAGNOSIS OF ANAPHYLAXIS

Tryptase is non specific. (Elevated in acute MI trauma, amniotic fluid embolism, sudden infant death syndrome, scombroid poisoning). If WNL does not rule out anaphylaxis.
Plasma Histamine and Tryptase Levels Following Bee Sting Challenge

SERUM TRYPTASE

- Histamine and tryptase levels may not correlate
- Tryptase higher if allergen administered parenterally (hymenoptera or injections) than orally (foods)
- Tryptase: Connective tissue mast cells > Mucosal mast cells (MC degranulation \( \implies \beta \) tryptase)
- Ratio Total Tryptase(\( \alpha + \beta \)) / \( \beta \) <10: Anaphylaxis
- If > 20 indicates systemic mastocytosis
- In ideal conditions, positive predictive value of serum tryptase can be 92.6%, but negative predictive value is only 52%

Tryptase Dynamics

• Optimally, obtain blood sample for total serum tryptase from 15 minutes to 3 hours of symptom onset
• Total serum tryptase peaks 60-90 minutes after symptom onset may remain elevated acutely for 6+ hours
• Total serum tryptase is not elevated in most patients with food anaphylaxis
• Serial measurement of tryptase levels during an anaphylaxis episode, and measurement of a baseline level after recovery might be more useful than measurement at one single point in time
• Tryptase levels that are within normal limits cannot be used to refute the clinical diagnosis

Histamine and other Biomarkers

- Plasma histamine begins to rise in 5 minutes but remains elevated for only 30 to 60 minutes.

- Draw blood with large bore needle, keep at 4°C and centrifuge promptly and freeze plasma.

- Urinary histamine metabolites may remain elevated as long as 24 hours. (24 hour urinary histamine and N-methylhistamine).

- Blood tests for other biomarkers, such as carboxypeptidase A3 and platelet-activating factor are reported but remain experimental.

Simons E et al. JACI 2007;120:S2-24
### Additional Objective Tests to Consider in the Differential Diagnosis of Anaphylaxis

<table>
<thead>
<tr>
<th>To Be Measured</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma histamine</td>
<td>Plasma histamine levels begin to rise within 5-10 min and remain elevated only for 30-60 min. They are of little help if the patient is seen as long as an hour or more after the onset of the event.</td>
</tr>
<tr>
<td>24-Hour urinary histamine metabolite (methyl histamine) of time</td>
<td>Urinary histamine and its metabolites are elevated for longer period; up to 24 hours</td>
</tr>
<tr>
<td>Plasma-free metanephrine</td>
<td>To rule out a paradoxical response to a pheochromocytoma</td>
</tr>
<tr>
<td>Serum serotonin</td>
<td>To rule out carcinoid syndrome</td>
</tr>
<tr>
<td>Urinary 5-hydroxyindoleacetic acid</td>
<td>Also to rule out carcinoid syndrome</td>
</tr>
<tr>
<td>Serum vasointestinal hormonal polypeptide panel including pancreatic hormone,</td>
<td>Useful to rule out the presence of a vasoactive polypeptide-secreting gastrointestinal tumor or a medullary carcinoma of the thyroid, which also can secrete vasoactive peptides</td>
</tr>
<tr>
<td>vasointestinal polypeptide, and substance P</td>
<td></td>
</tr>
</tbody>
</table>

Patient Factors that Increase Risk of Anaphylaxis Severity and Fatality

- Age
  - Infants
  - Adolescents and young adults
  - Elderly
- Pre-menstrual women and girls
- Comorbidities
  - Asthma: especially if severe or uncontrolled
  - Cardiovascular (CV) disorders including hypertension
  - Mastocytosis and clonal mast cell disorders

Adolescents/Young Adults at Risk\(^1\)

- A Web-based questionnaire of 174 participants sought to identify why adolescents are at high risk for fatal food anaphylaxis

- Risk-taking involved
  - Only 74% always carried epinephrine
  - 75% always read labels
    - 42% of these would eat a food labeled “may contain” an allergen

- 29 participants (17%) were designated as “high risk” because they did not always carry epinephrine and ate food that may have contained an allergen

- The education of teens and their peers during social activities may reduce risk-taking and its consequences

Patient Factors that Increase Risk of Anaphylaxis Severity and Fatality

- Concurrent medication/chemical use
  - β-blockers
  - Angiotensin-converting enzyme (ACE) inhibitors
- Other
  - Exercise
  - Acute infection, such as upper respiratory tract infection
  - Additional factors include stress, occupation (eg, beekeeping)
  - Recent previous anaphylactic reaction
- Rapid onset of anaphylaxis increases the risk of a more severe or life-threatening episode

Risk factors for Anaphylaxis

• *Defects in mediator degradation pathways:*
  a) Elevated baseline serum tryptase
  b) Elevated plasma histamine levels,
  c) Elevated baseline serum bradykinin levels due to low serum ACE activity,
  d) Elevated baseline platelet-activating factor (PAF) levels due to reduced PAF acetylhydrolase activity
## Factors Associated With Risk of Potentially Life-threatening Reactions

<table>
<thead>
<tr>
<th>Variable</th>
<th>$P$ value</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at the time of the index sting (per year)</td>
<td>&lt;0.001</td>
<td>1.029</td>
<td>1.018</td>
</tr>
<tr>
<td>Female gender</td>
<td>&lt;0.001</td>
<td>0.553</td>
<td>0.387</td>
</tr>
<tr>
<td>≥1 preceding, less severe systemic sting reaction before the index sting</td>
<td>&lt;0.001</td>
<td>4.687</td>
<td>2.913</td>
</tr>
<tr>
<td>Index sting by vespid species</td>
<td>0.008</td>
<td>1.730</td>
<td>1.147</td>
</tr>
<tr>
<td>ACE inhibitor medication at the time of the index sting</td>
<td>0.019</td>
<td>2.269</td>
<td>1.129</td>
</tr>
</tbody>
</table>

- For patients with venom allergy, increased baseline serum tryptase concentrations are associated with risk for severe anaphylactic reactions.
- Preventive measures should include substitution of ACE inhibitors.

Fatal Anaphylactic Reactions

Fatal anaphylactic reactions are often associated with:
- Delay between time of symptom onset and administration of treatment\(^1\)
- History of asthma\(^1,2\)
- Adverse events due to medication\(^2\)

However, most fatal reactions are unpredictable
- Appropriate management after recovery from a severe reaction may be protective against a fatal recurrence\(^2\)
- Epinephrine is used in treatment of 62% of fatal reactions, but given before cardiac arrest in only 14% of reactions\(^3\)

Risk of Systemic Reactions in Patients Taking β-blockers Receiving Immunotherapy

• “It is unclear whether patients taking β-blockers are at increased risk of having a serious systemic reaction to allergen immunotherapy injections”
• In one study, β-blockers did not increase the frequency of systemic reactions in patients who were receiving immunotherapy ($P > .95$)
  – However, patients taking β-blockers may still be at increased risk for more severe systemic reactions or for reactions that may be more refractory to therapy
• “Anaphylaxis in patients taking β-blockers may be more difficult to treat”
• The “contraindication should be relative not absolute”

## FACTORS AFFECTING PROGNOSIS

<table>
<thead>
<tr>
<th>Factor</th>
<th>Poor Prognosis</th>
<th>Good Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of symptoms</td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td>Initiation of treatment</td>
<td>Late</td>
<td>Early</td>
</tr>
<tr>
<td>Route of exposure</td>
<td>Injection</td>
<td>Oral*</td>
</tr>
<tr>
<td>β-adrenergic blocker use</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Presence of underlying disease</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* true for drugs, not foods
Treatment

- **Epinephrine** is the drug of choice for all anaphylactic episodes
- Early and aggressive use to maintain airway, blood pressure, and cardiac output
- Flexibility in dosing needed to treat effectively
  - 25% to 35% of patients require more than a single injection
  - Different doses for pediatrics and adults

Lieberman et al. *J Allergy Clin Immunol* 2005
Epinephrine Action

Epinephrine

- Vasoconstriction
- Peripheral vascular resistance
- Mucosal edema
- Insulin release
- Norepinephrine release
- Inotropy
- Chronotropy
- Bronchodilation
- Vasodilation
- Glycogenolysis
- Mediator release

a1-adrenergic receptor

a2-adrenergic receptor

b1-adrenergic receptor

b2-adrenergic receptor

Epinephrine Dosing

- Intramuscular injection in lateral thigh produces most rapid rise in blood level
  - 0.01 mg/kg in children
  - 0.3 to 0.5 mg in adults

Epinephrine Auto-Injector

- **Drug of choice**
  - Best location is IM in the thigh
    - EpiPen IM thigh 12,222* pg/mL vs Epi IM deltoid 1821 and Saline IM deltoid 1458
- **Used at 1st sign of systemic reaction**
  - The earlier in the allergic process the better the prognosis; delayed use associated with fatal reactions
- **Dose**
  - 0.15mg (33 lbs to 66 lbs); 0.3mg (>66 lbs) of a 1:1,000 dilution IM in lateral thigh prn q 5-15 min.
Expired Epinephrine Content
Percent of Labeled dose

Simons FER et al. JACI 2000;105:1025
Epinephrine Administration
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

http://www.adrenaclick.com/about-adrenaclick/
Epinephrine Use: not available in all countries

A WAO House of Delegates survey (2003 to 2005) in 35 countries

Simons FER. Ann Allergy Asthma Immunol 2005
Epinephrine
Ampule/Needle/Syringe

- EpiPen not available in many countries
- Fixed dose, expensive cost of EpiPen
- Unstable chemical, degrades rapidly by air and light

Needle length 1.27-1.3 cm (No26,27)
EpiPen is 1.43 cm

Comparison of Two Auto-injectors

Adult

- EpiPen (Dey Laboratories) auto-injector for adults available with single 0.3-mg (1:1,000 v/v) dose
- Adrenaclick (Shionogi Pharmaceuticals) auto-injector of epinephrine available with a single 0.3-mg dose of epinephrine

Pediatric

- EpiPen Jr. with 0.15-mg (1:2,000 v/v) dose is available for children <30 kg; EpiPen may be used for larger children
- Adrenaclick auto-injector of epinephrine available with a single 0.15-mg dose for patients who weigh 33-66 pounds
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.

Instruction to use EpiPen
ANAPHYLAXIS IN THE EMERGENCY DEPARTMENT

- Chart review in 21 North American Emergency Departments
- Random sample 678 charts of patients with food allergy
- **Management:**
  - 72% received antihistamines
  - 48% received systemic corticosteroids
  - 16% received epinephrine (24% of those with severe reactions)
  - 33% received inhaled albuterol
  - only 16% received Rx for self-injectable epinephrine
  - only 12% referred to an allergist

Clark S et al. J Allergy Clin Immunol 2004;347-52
OFFICE MANAGEMENT OF ANAPHYLAXIS

CHECKLIST

• Have a posted, printed detailed emergency protocol for recognition and treatment of anaphylaxis
• Practice regularly
• stethoscope and sphygmomanometer
• tourniquets, syringes, needles (including large bore 14-gauge)
• injectable epinephrine (adrenaline) 1:1000
• oral airway and endotracheal tubes
• oxygen, and equipment to administer it
• diphenhydramine (or similar) injectable antihistamine
• corticosteroids for IV injection
• vasopressor (eg dopamine, noradrenaline)
• glucagon
• automatic defibrillator
MANAGEMENT OF ANAPHYLAXIS

Have a posted, printed detailed emergency protocol for recognition and treatment of anaphylaxis

Practice regularly!!

I. Speed is critical:
   a) assess airway, breathing, circulation, and mentation
   b) EPINEPHRINE, IM into the muscle of the anterolateral thigh;
      1:1000 dilution, 0.3 - 0.5 mL (0.01 mg/kg in children); repeat, every 5-15 minutes as necessary.

MANAGEMENT OF ANAPHYLAXIS

II. Secondary measures:
   a) place patient in recumbent position and elevate his/her legs
   b) maintain airway (endotracheal tube or cricothyrotomy)
   c) oxygen, 6 - 8 liters/minute
   d) normal saline IV; volume expanders (colloid solution) for severe hypotension

Kemp SF and Lockey RF. J Allergy Clin Immunol 2002;110:341-8
III. Other measures:

a) epinephrine 1:1000, ½ dose (0.1- 0.2 mg) into reaction site
diphenhydramine, 50 mg IV or orally (1.25 mg/kg, up to 50 mg dose for children); maximum daily dose: adults 400 mg; children 200 mg

b) ranitidine, 50 mg in adults and 12.5 - 50 mg (1 mg/kg) in children, dilute in 5% D/W, total 20 ml, inject slowly IV, over 5 minutes (cimetidine 4 mg/kg OK for adults, dose not established for children)

Kemp SF and Lockey RF. J Allergy Clin Immunol 2002;110:341-8
MANAGEMENT OF ANAPHYLAXIS

- for Bronchospasm
  - nebulized albuterol (salbutamol) 2.5 - 5 mg in 3 ml normal saline
- for Refractory Hypotension
  - Dopamine, 400 mg in 500 ml normal saline IV 2 - 20 µg/kg/min
  - Glucagon, 1- 5 mg (20 - 30 µg/kg, max 1 mg in children), IV over 5 minutes followed with continuous IV infusion 5-15 µg/min
  - Methylprednisolone, 1- 2 mg/kg per 24 hr

Kemp SF and Lockey RF. J Allergy Clin Immunol 2002;110:341-8
Discharge Management and Prevention of Future Anaphylaxis

- Anaphylaxis action plan
- Epinephrine Prescription and Education
- Medical alert identification (i.e. bracelet)
- Referral to allergy specialist for diagnostic studies to determine triggers for anaphylaxis
- Identification and avoidance of known triggers
- Immunotherapy (venom)
- Drug desensitization if and when necessary

WAO Anaphylaxis Guidelines 2011
Evaluation of Patient with History of “Anaphylaxis”

• History is most important tool to determine whether a patient has had anaphylaxis and its cause
  – A thorough differential diagnosis should be performed

• Laboratory tests may or may not be helpful to confirm a diagnosis of anaphylaxis

• In the management of a patient with a previous episode of anaphylaxis, education is necessary
  – Patients should always be educated on prevention strategies and instructed in self-management of anaphylaxis
  – Avoidance management should be individualized, taking into consideration factors such as age, activity, occupation, hobbies, residential conditions, comorbidities, and current medications
  – Patients should have an emergency action plan
Barriers to Auto-injector Use

- Not prescribed by physician
- Not available or affordable
- Not accessible/not used when reaction occurred
- Patient-related
  - Used another medication
  - Reaction seemed mild or improved quickly
  - Patient was unsure when to inject
  - Previous systemic allergic reaction improved quickly

Causes of Epinephrine failure

• Delayed administration
• Rapid progression of anaphylaxis
• Empty ventricle syndrome
• Inadequate doses
• Inappropriate site, poor technique
• Use of expired epinephrine
• Underlying disease eg. asthma, CVD
• Patient taking a beta-blocker

Evaluation (cont’d)

• Epinephrine is the drug of choice, and the appropriate dose should be administered promptly at the onset of apparent anaphylaxis
  – Emphasis on early treatment, specifically the self-administration of epinephrine, is essential
  – Healthcare professionals should be familiar with the various available auto-injectors
  – Both the healthcare professional and the patient should be very familiar with the technique of administration
Conclusions

• Anaphylaxis is a life-threatening acute reaction which, although increasing in prevalence is frequently misdiagnosed, under-reported and under-treated.

• Physician and patient awareness must be increased to properly prevent, diagnose, and treat anaphylaxis and improve patient outcomes.

• Rapid and proper administration of epinephrine is the standard of treatment.

• Patients who self administer should be directed to the ER for follow-up care after the first dose of epinephrine.

• Recognition that many patients will require a second dose of epinephrine is essential.
THANK YOU
• OPTIONAL SLIDES
Clinicians and Patients Need to Improve Action/Treatment Plans

- 29 patients interviewed to identify physician advice related to implementation of action plans for severe food allergies
- 85% of patients said that doctors told them to include antihistamines in the treatment of future reactions:
  - 9/21 (43%) have used their epinephrine auto-injector subsequently
  - 7/29 (24%) were told to use antihistamines as the sole treatment, and 6/29 (21%) before using epinephrine

Clinicians and Patients Need to Improve Action/Treatment Plans

• Out of 20 patients with a reported plan of action for future severe reactions, only 45% would use epinephrine, 55% would go to an emergency department, and 70% would take antihistamines.

• Patients report a lack of training regarding the use of EAIs by their doctors, in addition to an emphasis on antihistamine use, which may be reflected in the low planned use of EAIs in future severe allergic reactions.

Patients and Clinicians Must Increase Awareness of Anaphylaxis and Its Treatment

- 25 patients identified through a 4-year retrospective chart review were surveyed
- Healthcare providers also queried
- Only 18% of patients would seek emergency assistance after using epinephrine
- 59% of patients carried an injector at all times
- 20% would administer epinephrine after an asymptomatic exposure

Adolescents/Young Adults at Risk\textsuperscript{1}

- A Web-based questionnaire of 174 participants sought to identify why adolescents are at high risk for fatal food anaphylaxis
- Risk-taking involved
  - Only 74\% always carried epinephrine
  - 75\% always read labels
    - 42\% of these would eat a food labeled “may contain” an allergen
- 29 participants (17\%) were designated as “high risk” because they did not always carry epinephrine and ate food that may have contained an allergen
- The education of teens and their peers during social activities may reduce risk-taking and its consequences

\textsuperscript{1} Sicherer et al. FAAN. 2006.
Patients Carrying Epinephrine: By Age

1. Phil Lieberman, MD. Chief Editor, Joint Task Force on Practice Parameters.
Patients Carrying Epinephrine

• A study by Lieberman found that caregivers of children age 0-9 and people 60-70 years of age are more likely to keep their injector with them\(^1\)
• Teenagers and young adults often do not carry their injectors\(^1\)
• A separate study found that only 16% of EpiPen\(^\circledR\) patients always carry 2 injectors\(^2\)

1. Phil Lieberman, MD. Chief Editor, Joint Task Force on Practice Parameters.
Awareness Must Increase

- Anaphylaxis is a life-threatening acute reaction which is underreported, frequently misdiagnosed, and undertreated
  - Food allergy affects up to 6%-8% of children younger than 4 years of age and 2% of the US population beyond the 1st decade of life\(^1,2\)
- Rapid and proper administration of epinephrine is the standard of treatment\(^2\)
  - Many patients require a second epinephrine injection to treat anaphylaxis\(^3\)

Patients Must Be Educated

• Many patients fail to correctly recognize and treat anaphylaxis
  – Inadequate treatment (often carry 0 or 1 dose of epinephrine)\(^1\)
  – Delay in treatment
  – Failure to use auto-injector properly
  – Outdated epinephrine

Physicians Must Respond

- Many physicians often fail to correctly recognize and treat anaphylaxis
  - Failure to look for biphasic reaction and provide appropriate treatment\(^1\)
  - Delayed treatment\(^1\)
  - Many patients sent home without a referral to an allergist/immunologist or instructions to avoid the allergen\(^2\)
  - Many patients sent home without an epinephrine auto-injector for future reactions or for potential biphasic reaction\(^2\)

---

Epinephrine is Underutilized for acute treatment

• Only about 30% of individuals requiring epinephrine during a reaction actually received it\(^1\)

• In fatal food-induced reactions, failure to use, delayed use, or inappropriate dose are contributing factors to death\(^2\)

• Used in treatment of 62% of fatal reactions but given before cardiac arrest in only 14% of reactions\(^3\)

Patients requiring a 2nd dose

- 35% (Korenblat et al. Allergy Asthma Proc 1999)
- 35% (Varghese et al. AAAAI 2006)
- 25% (Haymore et al. Allergy Asthma Proc 2005)
- 16% (Kelso JM. J Allergy Clin Immunol 2006)
Anaphylaxis Is a Growing Public Health Issue

• Measures must be put in place to reduce the risk of accidental exposure and to respond appropriately in an emergency
  – Comprehensive school board policies
  – Standardized school anaphylaxis plans
  – Greater community support and involvement

• All those in regular contact with children at risk should participate in training sessions
Epinephrine Use: growing in developed countries

- Awareness is increasing
  - Due largely to increase in awareness of childhood food allergies

- Increased population at risk as number of children with food allergies increases

- Second dose of epinephrine may be required more often than previously suspected
Final Thoughts

• Awareness levels are key to properly preventing, diagnosing, and treating anaphylaxis

• Improved treatment is needed:
  - Flexibility of dosage (0.1, 0.15, 0.3, 0.5) to allow smaller dose for very young and larger dose for bigger adults
  - Flexibility in needle size to assure IM delivery
  - Longer shelf/storage life
  - Smaller device
  - Better labeling

• Patient should be directed to the ER for follow-up care after the first dose of epinephrine for the treatment of anaphylaxis

Epinephrine for the Treatment of Anaphylaxis

These recommendations are also reflected in previous position statements/guidelines from the World Allergy Organization (2008) and the Canadian Pediatric Society Allergy Section (1998).

Apparent Lack of Response to Epinephrine (Uncommon)

- Delay in injection
- Rapid progression of reaction
- Empty ventricle syndrome
- Patient taking another medication that interfered
- Dose too low
  - On a mg/kg basis for body weight of patient
  - Auto-injector past expiry date
- Delayed absorption (route, site, poor technique)