Anaphylaxis

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Clinical vignette
Anaphylaxis

- 46 yo male from India eating at a Chinese restaurant with his family, on no meds, avoids seafood (fish allergy)
- Felt itchy and flushed after a bite of beef
- SOB within minutes, severe
- 911 called, patient collapse within 15 min
- 5 attempts at intubation: laryngeal edema
- Epi given, dead upon arrival ED (45 min)
Clinical Vignette Anaphylaxis

- What could have been done better?
- Could the death have been prevented?
- Are there risk factors for fatal anaphylaxis?
- How can the diagnosis be made?
Objectives

- Define anaphylaxis
- Identify the various types of anaphylaxis
- Review epidemiology
- Evaluate differential diagnosis
- Provide clinical/laboratory diagnosis
- Review treatment
Definition of anaphylaxis

- Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction.

- It is commonly, but not always, mediated by an allergic mechanism, usually by IgE.

- Allergic (immunologic) non-IgE-mediated anaphylaxis also occurs.

- Non-allergic anaphylactic reactions, formerly called anaphylactoid or pseudo-allergic reactions, may also occur.

[Source: Johnsson SGO et al. JACI 2004, 113:832-6]
Gell and Coombs classification of hypersensitivity

Type I  Immediate hypersensitivity
Type II  Cytotoxic reactions
Type III  Immune complex reactions
Type IV  Delayed hypersensitivity

Anaphylaxis can occur through Types I, II and III immunopathologic mechanisms

Kemp SF and Lorkey RF. J Allergy Clin Immunol 2002;110:341-8
Acutely released mediators of anaphylaxis

Degranulation of mast cells and basophils causes the release of:
- preformed granule-associated substances (eg: histamine, tryptase, chymase, carboxypeptidase, and cytokines)
- newly-generated lipid-derived mediators (eg: prostaglandin $D_2$, leukotriene (LT) $B_4$, $LTC_4$, $LTD_4$, $LTE_4$, and platelet activating factor)

Kemp SF and Lankey RF. J Allergy Clin Immunol 2002; 110:341-8
Primary symptoms of anaphylaxis

Skin:
flushing, itching, urticaria, angioedema

Gastrointestinal:
nausea, vomiting, bloating, cramping, diarrhea

Other:
feeling of impending doom, metallic taste

Respiratory:
dysphonia, cough, stridor, wheezing, dyspnea, chest tightness, asphyxiation, death

Cardiovascular:
tachycardia, hypotension, dizziness, collapse, death
Urticaria/Angioedema
Laryngeal Edema
Comments about anaphylaxis signs and symptoms

- Skin symptoms occur most commonly (> 90% of patients)
- Skin, oral, and throat symptoms are often the first ones noted
- Respiratory symptoms occur in 40% to 70% of patients
- Gastrointestinal symptoms occur in about 30% of patients
- Shock occurs in about 10% of patients
- Signs and symptoms are usually seen within 5 to 30 minutes
- The more rapid the onset, the more serious the reaction

Biphasic and protracted anaphylaxis

- Biphasic anaphylaxis is defined as return of symptoms after resolution of initial symptoms, without subsequent allergen exposure.
- Usually, symptoms return within 1 to 8 hours (sometimes longer).
- Up to 20% of anaphylactic reactions are biphasic.
- Patients with biphasic anaphylaxis may require more epinephrine to control initial symptoms.
- In protracted anaphylaxis, symptoms may be continuous for 5-32 hrs.

Biphasic/late-phase reaction

Cellular infiltrates: 3 to 6 hours (LPR)

- **Eosinophil**
  - CysLTs, GM-CSF, TNF-α, IL-1, IL-3, PAF, ECP, MBP

- **Basophils**
  - Histamine, CysLTs, TNF-α, IL-4, IL-5, IL-6

- **Monocytes**
  - CysLTs, TNF-α, PAF, IL-1

- **Lymphocytes**
  - IL-4, IL-13, IL-5, IL-3, GM-CSF

**Allergen**

- Histamine
- IL-4, IL-6

**3 to 6 hours**

- (CysLTs, PAF, IL-5)

**Proteases**

**Mast cell**

- PGs
- CysLTs

**EPR 15 min**

(Early-Phase Reaction)

**Return of Symptoms**
Bi-phasic Reaction

- Bi-phasic reactions noted in one-third of patients with (food induced) fatal or near fatal reactions
- Patients seem to have fully recovered when severe bronchospasm suddenly recurs
- Recurrence is typically more refractory to standard therapy and often requires intubation and mechanical ventilation

Incidence and prevalence of anaphylaxis

- “anaphylaxis in the US: an investigation into its epidemiology"
  - on the basis of a literature review, more than 1.21% of the population may be affected
  - 32 million have had 2 or more symptoms
  - 18 million diagnosed
  - 11 million have suffered a life-threatening reaction

Neugut AI et al. Arch Intern Med 2001;161:15-21
Incidence and prevalence of anaphylaxis (cont.)

- 5-year review of 1.15 million persons in Manitoba, Canada
- dispensing patterns of epinephrine for out-of-hospital treatment
- 0.95% of the general population had epinephrine dispensed
- dispensing rates in the general population varied with age:
  - 1.44% for individuals <17 years of age
  - 0.9% for those 17-64 years of age
  - 0.32% for those >65 years of age
- interpretation: anaphylaxis from all triggers, occurring out of hospital, appears to peak in childhood, and then gradually decline

Risk Factors for Anaphylaxis

- Asthma (Sampson H, NEJM, 1992)
- Prior Severe reactions
- Atopy (food, hymenoptera)
- Occupational (latex)
- Systemic mastocytosis
- Once Sensitized Atopic (Asthma) higher risk for fatal anaphylaxis (Lockley et al, JACI, 1987)
Effect of Gender on Incidence of Anaphylaxis

Causes of Anaphylaxis Adults

- Idiopathic: 70%
- Medications
- Foods
- Other

Children May Be Different

- 46 children
- Median age first episode 5.8 years
- Males > Females
- Only small proportion idiopathic
- Atopic derm, urticaria/angiodema, sensitivity predictive of recurrence

International collaborative study of severe anaphylaxis

● Objective
  • To quantify the risk of anaphylaxis due to drugs and other exposures in hospital patients

● Methods
  • Hospitals in Sweden, Hungary, India and Spain
  • Incident cases 1992-1995
  • Clinical diagnosis using a priori agreed criteria, independent of presumed trigger

Epidemiology 1998;9:141-46
International collaborative study of severe anaphylaxis (cont.)

- Main findings
  - 123/481,752 i.e. risk of 15-20/100,000 admissions
  - 33% males
  - Median age ~53
  - 79% respiratory symptoms; 70% cardiovascular symptoms; 49% both
  - Death in 2% of cases
UK anaphylaxis death registry

- **Objective**
  - To understand the circumstances leading to fatal anaphylaxis

- **Methods**
  - Running since 1992; ONS mortality data coded for anaphylaxis since 1993
  - Detailed information obtained from medical records, medical staff, coroners officers and mast cell serum tryptase

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
- Adrenaline rarely used before cardiac arrest
Agents that cause anaphylaxis:
IgE-dependent triggers

- foods (eg: peanut, tree nuts, seafood)
- medications (eg: β-lactam antibiotics)
- venoms
- latex
- allergen immunotherapy
- diagnostic allergens
- exercise (with food or medication co-trigger)
- hormones
- animal or human proteins
- colorants (insect-derived, eg: carmine)
- enzymes
- polysaccharides
- aspirin and NSAIDs (possibly through IgE)

Kemp SF and Lorkey RF, J Allergy Clin Immunol 2002;110:341-8
Risk of anaphylaxis

• estimated risk in US: 1-3%
• fatalities per year in the US:
  - food-induced: 150
  - antibiotic-induced: 600
  - venom-induced: 50

Kemp SF and Lockey RF, J Allergy Clin Immunol 2002;110:341-8
Food-induced anaphylaxis

- many anaphylactic reactions are caused by food
  - accidental food exposures are common and unpredictable
  - anaphylaxis from food can occur at any age, but children, teens and young adults are at highest risk
- prevalence of peanut allergy has doubled in children <5 years of age in the last 5 years
- seafood allergy is reported by 2.3% of the US population, and is more common in adults than in children

Most common food allergies

- peanut
- tree nut
- shellfish
- fin fish
- milk
- egg
- soy
- wheat
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
  - most patients had a history of asthma
  - most did not have injectable epinephrine available at the time of their reaction and death

Latex Allergy Risk Groups

- Health Care Workers (5-10%)
- Rubber Industry Workers
- Spina Bifida (18-28%)
- Urogenital Abnormalities
Latex-Induced Anaphylaxis: Common Triggers

- Proteins in natural rubber latex
- Component of ~40,000 commonly used items
  - Rubber bands
  - Elastic (eg, undergarments)
  - Hospital and dental equipment
- Latex-dipped products are biggest culprits
  - Balloons, gloves, bandages, hot water bottles
- Patients undergoing surgery especially vulnerable
  - Latex is common in medical supplies: disposable gloves, airway and intravenous tubing, syringes, stethoscopes, catheters, dressings, bandages

Latex Allergy Diagnosis

- Risk Group
- Latex Associated Reactions
- Cross-reactive foods: avocado, mango, chestnut, banana, kiwi

Testing
1. RAST (38-82%)
2. Skin Test (100%)
Anaphylaxis: Idiopathic

1. Recurrent, often severe
2. No Identifiable Precipitant
3. 50% Atopic
4. Refractory to Therapy
Idiopathic Anaphylaxis


Age 25 –71 (mean 48)
43% Atopic
Frequency: > 5/Year 31%
Follow-up: 2.5 year (mean)
- 21 Patients (60%) resolved
- 9 Decreased Frequency
- 2 Increased Frequency
- 3 Same
- 3 Frequent Episodes
- 2 Chronic Glucocorticoids

Exercise-Induced Anaphylaxis:

- Flushing, pruritus, wheezing, syncope
- Running, jogging, dancing, skating
- Food ingestion 4 hours prior >50% cases (wheat 60% cases)

Recommendations:
- Discontinue Exercise if notice earliest Symptom,
- Limit Exercise on Hot, Humid Days,
- Avoid Exercise 4-6 hrs Post Prandial,
- Avoid Exercise Post Allergy Immunotherapy,
- Avoid Beta-Blockers and ACE Inhibitors
- Medi-Alert Bracelet

Shadick et al JACI 1999
A BEE NEST!
I HATE BEES!

WHAP.
ZZZZZZZ

AEE!

I DON'T SEE THE "HARPOON" THAT "GORED" YOU, BUT THIS WILL HELP THE STING.

CALL THE NATIONAL GUARD. I'M SURE THEY CAN TRACK THE BEE ON RADAR.
Venom-Induced Anaphylaxis: Incidence

- 0.5% to 5% or 1.36 million to 13 million Americans are sensitive to 1 or more insect venoms
  - Hymenoptera order of insects
    - Bees
    - Wasps
    - Yellow jackets
    - Hornets
    - Fire ants
- At least 40 to 100 deaths per year
- Incidence increasing due to
  - Rise in the number of fire ants and Africanized bees
  - Increase in people engaging in outdoor activities
- Immunotherapy 98-99% effective to prevent reactions

Hymenoptera Sting

- Natural History:
  - 60% Re-sting reaction rate
  - The more severe the initial anaphylactic symptoms, the more likely there will be a re-sting reaction
  - The severity of the sting reaction is not related to the degree of skin test sensitivity or titer of serum venom-specific IgE
Risk of Systemic Reaction to Sting for VIT-Treated and Untreated Patients

Golden, et al. JACI 2000
Frequency of Systemic Reactions to Stings after Discontinuing VIT

Golden, et al. JACI 2000
Allergen immunotherapy-induced anaphylaxis

- Fatal reactions are uncommon: 1 per 62,000,000 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
Iatrogenic anaphylaxis

- estimated 550,000 serious allergic reactions to drugs/year in US hospitals
- most common drug triggers
  - penicillin (highest number of documented deaths from anaphylaxis)
  - sulfa drugs
  - non-steroidal anti-inflammatory drugs
  - muscle relaxants
- most common biologic triggers
  - anti-sera for snakebite
  - anti-lymphocyte globulin
  - vaccines
  - allergens

Neugut AI et al. Arch Intern Med 2001;161:15-21
Anaphylaxis: non-immunologic causes

MULTIMEDIATOR COMPLEMENT ACTIVATION/ACTIVATION OF CONTACT SYSTEM

- radiocontrast media
- ethylene oxide gas on dialysis tubing (possibly through IgE)
- protamine (possibly)
- ACE-inhibitor administered during renal dialysis with sulfonated polyacrylonitrile, cuprophane, or polymethylmethacrylate dialysis membranes

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
Differential Diagnosis of Anaphylaxis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Differentiation from Anaphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scombroid Syndrome</td>
<td>History of Antecedent Ingestion of Suspect Fish</td>
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<tr>
<td></td>
<td>Oral Burning, Tingling, Blistering, or Peppery Taste after Ingestion</td>
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<tr>
<td></td>
<td>Emesis Common</td>
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<td></td>
<td>Episode May Last Days (Though More Commonly Hours)</td>
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<th>Condition</th>
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<tr>
<td>Vasovagal Syndrome</td>
<td>Bradycardia, not tachycardia</td>
</tr>
<tr>
<td></td>
<td>Pallor rather than Flushing</td>
</tr>
<tr>
<td></td>
<td>No Pruritus, Urticaria, Angioedema,</td>
</tr>
<tr>
<td></td>
<td>Upper Respiratory Obstruction, or</td>
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<tr>
<td></td>
<td>Bronchospasm</td>
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<tr>
<td></td>
<td>Nausea, but no abdominal pain</td>
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<tr>
<td>Globus Hystericus</td>
<td>No Clinical or Radiological Evidence of</td>
</tr>
<tr>
<td></td>
<td>Upper Respiratory Obstruction</td>
</tr>
<tr>
<td></td>
<td>No Flushing, Pruritis, Urticaria,</td>
</tr>
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<td>Bronchospasm, Abdominal Pain or</td>
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<td></td>
<td>Hypotension</td>
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<th>Condition</th>
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<tr>
<td>Mastocytosis</td>
<td>No Upper Respiratory Obstruction, Bronchospasm Uncommon</td>
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<tr>
<td></td>
<td>Urticaria Pigmentosa Often Present</td>
</tr>
<tr>
<td></td>
<td>Slower Onset of Attacks; Chronic Low-Grade Symptomatology between Attacks</td>
</tr>
<tr>
<td>Carcinoid Syndrome</td>
<td>No Upper Respiratory Obstruction, Urticaria, or Angioedema</td>
</tr>
<tr>
<td></td>
<td>Slower Onset of Attacks</td>
</tr>
<tr>
<td></td>
<td>May have Cutaneous Stigmata, Including Telangiectases on trunk</td>
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</tbody>
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Diagnosing anaphylaxis

Allergists can identify specific causes by:

- complete and accurate medical/allergy history
- skin tests/specific IgE levels
  - foods
  - insect venoms
  - drugs (some)
- challenge tests: (selected patients, physician-monitored, preferably in hospital)
  - foods
  - NSAIDs
  - exercise

Simons FER. J Allergy Clin Immunol 2006;117:367-77
Anaphylaxis: Diagnosis

1. Histamine Levels Increased
   A. Plasma
   B. 24 Hour Urine
2. Tryptase, carboxypeptidase A
3. Complement Activation
4. Antigen-Specific IgE
   A. RAST
   B. Skin Testing
Laboratory tests in the diagnosis of anaphylaxis
Problems with laboratory tests

- histamine and tryptase levels may not correlate with each other

- histamine level was elevated in 42 of 97 patients in the Emergency Department, but only 20 of 97 had an elevated tryptase level

- histamine levels correlated better with symptoms and signs

- plasma histamine levels only remain elevated for one hour after symptom onset; therefore, this test is usually not practical

Tryptase Levels in Anaphylaxis and Systemic Mastocytosis
Schwartz, NEJM1987
Anaphylaxis in the emergency department

- Chart review study in 21 North American Emergency Departments
- Random sample of 678 charts of patients presenting with food allergy
- Management:
  - 72% received antihistamines
  - 48% received systemic corticosteroids
  - 16% received epinephrine (24% of those with severe reactions)
  - 33% received respiratory medication (e.g., inhaled albuterol)
  - Only 16% received Rx for self-injectable epinephrine at discharge
  - Only 12% referred to an allergist

Clark S et al. J Allergy Clin Immunol 2004;347-52
Acute Management of Anaphylaxis

Castells al et Allergy 2005
ACLS guideline 2005
AAAAAI Practice parameters 2005

1. Administer 0.3-0.5 mL 1/1000 epinephrine IM while patient is recumbent
   no supine or sitting position (empty heart)
   repeat X 2 at 5 to 10 min intervals if SBP < 90
2. Anti-histamines, steroids, bronchodilators
3. If β blockade is present use glucagon
   5-15 μ/min i.v. continuous infusion
4. Observation for a minimum of 4-5 hours
5. At discharge, educate patient to avoid future episodes
6. Assess whether patient needs EpiPen prescription
7. Assess whether patient needs Allergy referral
Use of Anti-IgE Antibody to Reduce Responsiveness to Allergens: Xolair
Clinical Vignette Anaphylaxis

- What could have done better?
  Repeated epi and trachestomy
- Could the death be prevented?
  Diagnosis and education
- What were the risk factors for fatal anaphylaxis?
  Asthma and a prior severe reaction
- How can the diagnosis be made?
  Tryptase, carboxypeptidase A (2006), ST/CAP
State Statutes Protecting Students’ Rights to Carry and Use Asthma and Anaphylaxis Medications

Anaphylaxis Medication

* Legislation pending.
Questions?