Anaphylaxis
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Overview

• Definition
• Mechanisms
• Incidence
• Causes/ Differential Diagnosis
• Symptoms
• Diagnosis/ Lab findings
• Treatment
Definition: Anaphylaxis

• Serious allergic reaction that is rapid in onset and may cause death¹
• Systemic, immediate hypersensitivity reaction caused by immunoglobulin E (IgE)-mediated immunologic release of mediators from mast cells and basophils²
• Opposite of prophylaxis (protection), so it is referred to as anaphylaxis meaning against, or without protection
• Diagnosis is CLINICAL
  – based upon symptoms and signs
  – detailed history of acute episode

Definition: Anaphylactoid

- Non-IgE mediated degranulation of mast cells and basophils
- Reactions may produce the same clinical picture
  - i.e. Acute systemic reaction
- The World Allergy Organization suggested that term “anaphylactoid reaction” be eliminated
  - Suggest it be called “non immunologic” anaphylaxis
- Same initial management of each of these acute reactions
  - regardless of trigger or mechanism involved

Human Anaphylaxis

- Immunologic
  - IgE, FcεRI
    - foods, venoms, latex, drugs
  - Non-IgE, FcεRI
    - dextran, OSCS contaminants in heparin

- Idiopathic

- Non-Immunologic
  - Physical
    - exercise, cold
  - Other
    - drugs

From Simons E. JACI. 2010.
IgE-dependent Release of Inflammatory Mediators

Immediate Release
Granule contents: Histamine, TNF-α, Proteases, Heparin
Sneezing
Nasal congestion
Itchy, runny nose
Watery eyes

Over Minutes
Lipid mediators: Prostaglandins, Leukotrienes
Wheezing
Bronchoconstriction

Over Hours
Cytokine production: Specifically IL-4, IL-13
Mucus production
Eosinophil recruitment

Allergens
IgE
FcεRI
Biological Effects of Mast Cell Mediators

Fibroblasts
- Tryptase
- Chymase
- TNF-α
- IL-4
- IL-13
- SCF
- bFGF

IgE Production
- Histamine
- PGD₂
- LTC₄
- Kinins
- Chymase

Leukocyte Adhesion
- Histamine
- PGD₂
- LTC₄
- Kinins

Leukocyte Migration
- Histamine
- PGD₂
- LTC₄
- Kinins

Leukocyte Activation
- IL-5, IL-6
- TNF-α
- Tryptase
- PAF

Bronchoconstriction
Mucus Secretion
Edema Vasodilation
Nerve Stimulation

Church et al, JACI, 1997
Positive Feedback Model for IgE

Kawakami et al, Nature Reviews Immunology, 2002
Incidence

• True incidence unknown
• Most common causes = Drugs and foods
• Extremely wide ranging estimates
  – Affects 1.9 -27.2 million Americans\(^1\)
• Under-diagnosed and under-reported\(^2-4\)
  – UK (1992 – 1997): only 33 of 67 fatal reactions to drugs reported\(^5\)
• Biphasic anaphylaxis reported in 1- 20% \(^6\)
  – Initial sx's resolve then re-occur within 8 hrs
  – recurrences up to 72 hrs later have been reported

Incidence

• Drugs: Antibiotics and NSAIDS
  – Most common cause in adults
  – Penicillin responsible for 5,440 cases of fatal anaphylaxis per year (75% of U.S. anaphylaxis deaths)\(^1,2\)

• Foods: Peanuts and shellfish
  – Shellfish: most common culprit in adults
  – Peanut in children
  – Up to 125 deaths/year in US\(^3\)
  – 2001-2006: U.S. registry of food-induced anaphylaxis fatalities: 31 cases (17 from peanut)\(^4\)

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Incidence

- Perioperative anaphylaxis: 1/10,000 to 1/20,000 \(^1,2\)
  - Neuromuscular blocking agents (50-75% cases)
  - Followed by latex and antibiotics
- Hymenoptera stings: 40 - 400 deaths/year \(^1,3\)
- ↑ Latex anaphylaxis\(^4\)
  - 6.5% of general population
  - 17% of cases of intraoperative anaphylaxis
- Allergen Immunotherapy: \(^4\)
  - Systemic reactions: 0.5%
  - Fatal reactions: 1 in 2.5 million injections

Idiopathic Anaphylaxis

- Diagnosis of exclusion
  - Up to 2/3 of pts presenting to a Allergy-Immunology clinic

- 1995: prevalence in US= 33,000 cases \(^1\)

- ED studies:
  - NYC: 6.1% pts \(^2\)
  - Australia: 27% \(^3\)
  - Pediatric study: 31.6% of pts \(^4\)

- 6% of Anaphylaxis hospitalizations in Italy (1985-1996) \(^5\)

- Outpatient studies
  - 59%: Private practice, university affiliated office in Memphis \(^6\)
  - 31.5% in Rochester, Minnesota \(^7\)

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2. Lin RY. JACI 2000;106.
4. Braganza SC. Arch Dis Child 2006;91.
Causes

- Any food, medication, biological substance, or insect sting or bite may trigger anaphylaxis
- Some triggers act through > 1 mechanism
  - insect venom
  - radiocontrast media
  - Medications
    - NSAIDS
- Novel medication causes:
  - Chemotherapy drugs: taxanes, platins, and others
  - Biologic agents (monoclonal Abs): Rituximab, omalizumab
## Causes

**TABLE III.** Mechanisms and triggers of anaphylaxis in the community

<table>
<thead>
<tr>
<th>Immunologic mechanisms (IgE dependent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foods, such as peanut, tree nut, shellfish, fish, milk, egg, sesame, and food additives*</td>
</tr>
<tr>
<td>Medications, such as β-lactam antibiotics and NSAIDs, and biological agents†</td>
</tr>
<tr>
<td>Venoms, such as stinging insects (Hymenoptera)</td>
</tr>
<tr>
<td>Natural rubber latex</td>
</tr>
<tr>
<td>Occupational allergens</td>
</tr>
<tr>
<td>Seminal fluid (prostate-specific antigen)</td>
</tr>
<tr>
<td>Inhalants, such as horse, hamster, and other animal danders and grass pollen (rare)</td>
</tr>
<tr>
<td>Radiocontrast media‡</td>
</tr>
<tr>
<td>Immunologic mechanisms (IgE independent, formerly classified as anaphylactoid reactions)</td>
</tr>
<tr>
<td>Dextran, such as high-molecular-weight iron dextran†</td>
</tr>
<tr>
<td>Infliximab†</td>
</tr>
<tr>
<td>Radiocontrast media‡</td>
</tr>
<tr>
<td>Nonimmunologic mechanisms</td>
</tr>
<tr>
<td>Physical factors, such as exercise,§ cold, heat, and sunlight/UV radiation</td>
</tr>
<tr>
<td>Ethanol</td>
</tr>
<tr>
<td>Medications, such as opioids†</td>
</tr>
<tr>
<td>Idiopathic anaphylaxis</td>
</tr>
<tr>
<td>Consider the possibility of hidden or previously unrecognized allergens</td>
</tr>
<tr>
<td>Consider the possibility of mastocytosis/clonal mast cell disorder</td>
</tr>
</tbody>
</table>

From Simons E. JACI. 2010.
Causes: Critically Ill

- Muscle relaxants
- Latex
- Antibiotics
  - esp. Beta-lactam antibiotics
- Induction agents or hypnotics
- Opioids
- Colloids
  - esp. Dextran, mannitol, hydroxymethyl starch
- Blood products
- Others
  - protamine, streptokinase, chlorhexidine
  - isosulfan blue dye, radiocontrast media
  - gelatin

From Practice Parameters. Lieberman P (ed) et al. JACI 2010.
Unusual Causes

• Foods:
  – vegetables, fruits
  – lupin flour
  – bird's nest soup
  – seal, whale, and kangaroo meats
  – storage mites in flour and baking mixes

• Bee products

• Herbal formulations

• Injectants
  • Botox

• Insect saliva
  – mosquitoes
  – pigeon ticks
  – triatomid bugs
  – green ants, pharaoh ants

• Venoms
  – jellyfish
  – scorpions
  – snakes
Differential Diagnosis

• At least 40 other conditions should be considered in differential diagnosis of anaphylaxis

• Divided by age group:
  – Infants
  – Children and adults
  – Pregnant women
**TABLE E2. Differential diagnosis of anaphylaxis**

<table>
<thead>
<tr>
<th>Reactions caused by the excess endogenous production of histamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic mastocytosis</td>
</tr>
<tr>
<td>Urticaria pigmentosa</td>
</tr>
<tr>
<td>Basophilic leukemia</td>
</tr>
<tr>
<td>Acute promyelocytic leukemia with retinoic acid treatment</td>
</tr>
<tr>
<td>Hydatid cyst</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vasodepressor (vasovagal) reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingestant-related reactions mimicking anaphylaxis (restaurant syndromes)</td>
</tr>
<tr>
<td>Monosodium glutamate</td>
</tr>
<tr>
<td>Sulfites</td>
</tr>
<tr>
<td>Scombroidosis</td>
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</tbody>
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<table>
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<tr>
<th>Other forms of shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic</td>
</tr>
<tr>
<td>Hypoglycemic</td>
</tr>
<tr>
<td>Cardiogenic</td>
</tr>
<tr>
<td>Endotoxic</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Flushing disorders</th>
</tr>
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<tbody>
<tr>
<td>Rosacea</td>
</tr>
<tr>
<td>Carcinoid</td>
</tr>
<tr>
<td>Red man syndrome as a result of vancomycin</td>
</tr>
<tr>
<td>Postmenopausal</td>
</tr>
<tr>
<td>Alcohol-induced</td>
</tr>
<tr>
<td>Unrelated to drug ingestion</td>
</tr>
<tr>
<td>Related to drug ingestion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medullary carcinoma thyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic epilepsy</td>
</tr>
<tr>
<td>Vasointestinal peptide and other vasoactive peptide–secreting gastrointestinal tumors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 esterase deficiency syndromes (acquired and hereditary angioedema)</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Neurologic (seizure, stroke)</td>
</tr>
<tr>
<td>Capillary leak syndrome</td>
</tr>
<tr>
<td>Panic attacks</td>
</tr>
<tr>
<td>Vocal cord dysfunction syndrome</td>
</tr>
</tbody>
</table>
### TABLE E1. Frequency of 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><strong>Dizziness, syncope, hypotension</strong></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>

*On the basis of a compilation of 1865 patients reported in references 1 through 14.†Percentages are approximations.‡Children may have a lower frequency of cutaneous symptoms in anaphylaxis.

From Practice Parameters. Lieberman P (ed) et al. JACI 2010.
Symptoms: Cutaneous

• Criterion most frequently used to make the diagnosis
  – Seen in ≈90% of anaphylactic reactions
• Generalized hives/urticaria (85-90%)
• Flushing & Pruritis (45-55%)
• Pruritis without rash (2-5%)
• Angioedema:
  – periorbital edema and conjunctival swelling
  – swollen lips-tongue-uvula
Urticaria
Flushing & Pruritis
Angioedema

- Swollen lips, tongue, uvula

www.amazonaws.com; www.ispub.com/
Periorbital edema & Conjunctival swelling

Symptoms: Respiratory

• Up to 60% of cases
• Sensation of throat closure or choking
  – Upper airway angioedema in 50-60%
• cough, wheeze, and dyspnea (45-50%)
• change in voice quality
• nasal discharge and congestion (15-20%)
Symptoms: GI & CVS

• Gastrointestinal sxs. in 30%
  – Nausea/ vomiting
  – Diarrhea
  – Crampy abdominal pain

• Cardiovascular symptoms (35%)
  – Dizziness
  – Syncope
  – Tachycardia
  – Hypotension
  – Collapse
Symptoms: Timing

• Depends on mode of antigen exposure
  – if injected → within 5-30 minutes
  – if ingested → within first 2 hours
  – Symptoms can be delayed by several hours
• More rapid the onset, more rapid severe the episode
• Biphasic anaphylaxis: symptoms may reappear several hours after symptoms have disappeared
• Protracted anaphylaxis: lasting for several days
  – Not suppressed by corticosteroid therapy
# Diagnostic criteria for Anaphylaxis

## TABLE I. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)  
   **AND AT LEAST ONE OF THE FOLLOWING**
   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

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*PEF, Peak expiratory flow; BP, blood pressure.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

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Laboratory workup

- ↑ concentrations of plasma histamine or serum or plasma total tryptase
- Obtain blood samples as soon as possible after onset of sx(s).
  - elevations are transient
- Plasma histamine
  - Peak within 5 to 15 minutes
  - Decline to baseline by 60 min
- Plasma tryptase
  - Peaks within 0.5-1.5 hrs
  - Normal range 1 -11.4 ng/mL
  - some use 1 - 15 ng/mL

From Practice Parameters. Lieberman P (ed) et al. JACI 2010
Laboratory workup: Tryptase

- Tryptase = selective marker of mast cells
- Beta-tryptase (mature) is stored in secretory granules
  - Actively released when mast cell degranulates

↑ Total tryptase level supports diagnosis

NL tryptase does NOT rule out

From Figure 1. Schwartz LB. Immunol Allergy Clin NA 2006
Initial Treatment

- Early recognition
- Removal of the suspect inciting antigen
- Place patient in supine position
- Assess ABCs
  - Cardiovascular monitoring in ED or ICU
- Supplemental oxygen
- Volume resuscitation
- Intramuscular injection of epinephrine
Treatment: Epinephrine

- Treatment of choice for anaphylaxis
- Guidelines based on the consensus of expert opinion
- Rationale for use based on its pharmacology
- Alpha-1 adrenergic agonist effects:
  - $\uparrow$ vasoconstriction, peripheral vascular resistance
  - $\downarrow$ mucosal edema
- Beta-1 adrenergic agonist effects:
  - $\uparrow$ inotropy and chronotropy
- Beta-2 adrenergic agonist effects:
  - $\uparrow$ bronchodilation
  - $\downarrow$ release of mediators of inflammation from mast cells and basophils
Treatment: IM Epinephrine

- IM injection recommended over SQ injection
  - more rapid ↑ in plasma and tissue concentration
- Epinephrine dilution for IM injection
  - 1 mg/mL, 1:1000 or 0.1%
  - dose drawn up using 1 mL syringe
- Adults= 0.3 to 0.5 mg single dose
  - injected IM into mid-anterolateral thigh (vastus lateralis muscle)
  - may repeat at 5 to 15 minute intervals
- Overweight pts: as deep an injection as possible into the muscle
Treatment: IM Epinephrine

- Can be administered by an auto-injector
- Adult dose: 0.3mg EpiPen®, Twinject®, or Auvi-Q™
- Pediatric dose: 0.15mg EpiPen Jr®, Twinject®, or Auvi-Q™
  - Weight < 25-30kg

- Early use of epinephrine = crucial for success
- A few reactions will be fatal no matter what treatment is given
Treatment: IV Epinephrine

- IV infusion (0.1mg/mL; 1:10,000)
  - Adults: 0.5mg IV x1, then q 5 minutes prn
- If continuous infusion (Slow rate)
  - Adults: initial dose = 2 - 10 micrograms per minute
  - Infants and children: initial dose = 0.1 - 1 microgram/kg per minute
- Rate titrated according to response and the presence of continuous hemodynamic monitoring
- IV bolus dose associated with more dosing errors and more adverse effects
Side Effects: Epinephrine

- Transient pharmacologic effects
  - anxiety/fear
  - restlessness
  - headache
  - dizziness
  - palpitations
  - pallor
  - tremor

- Rare effects
  - ventricular arrhythmias
  - angina
  - myocardial infarction
  - pulmonary edema
  - ↑ BP
  - intracranial hemorrhage
Systemic Steroids:
  – Methylprednisolone 60mg IV
H1 antagonists
  – Diphenhydramine 50mg IV
H2 antagonists
  – Famotidine 20mg IV
Short acting Beta-agonists
  – Albuterol (0.083%) 2.5mg nebulized
Leukotriene modifiers
Drug desensitization
FIG E2. Algorithm for the treatment of an anaphylactic event in the outpatient setting. IV, Intravenous.

1. Anaphylaxis preparedness

2. Patient presents with possible/probable acute anaphylaxis

3. Initial assessment supports potential anaphylaxis? eg, nonlocalized urticaria after immunotherapy

   YES

   Immediate intervention:
   - Assess airway, breathing, circulation, mentation
   - Inject epinephrine and reevaluate for repeat injection if necessary
   - Supine position (if cardiovascular involvement suspected)

   NO

   Consider other diagnosis

4. Subsequent emergency care that may be necessary depending on response to epinephrine:

   Consider:
   - Call 911 and request assistance
   - Recumbent position with elevation of lower extremity
   - Establish airway
   - O₂
   - Repeat epinephrine injection if indicated
   - IV fluids if hypotensive; rapid volume expansion
   - Consider inhaled bronchodilators if wheezing
   - H₁ and H₂ Antihistamines
   - Corticosteroids

5. Good clinical response?

   NO

   Observation
   - Length and setting of observation must be individualized
   - Autoinjectible epinephrine

   YES

   Consultation with allergist-immunologist

6. GOOD CLINICAL RESPONSE?

   NO

   Observation
   - Length and setting of observation must be individualized
   - Autoinjectible epinephrine

   YES

   Consultation with allergist-immunologist

7. Call 911 if not already done

   Consider:
   - Epinephrine intravenous infusion
   - Other intravenous vasopressors
   - Consider Glucagon

8. Cardiopulmonary arrest during anaphylaxis:

   - CPR and ACLS measures
   - Prolonged resuscitation efforts encouraged (if necessary)
   - Consider:
     - High-dose epinephrine
     - Rapid volume expansion
     - Atropine for asystole or pulseless electric activity
     - Transport to emergency dept or ICU

From Practice Parameters. Lieberman P (ed) et al. JACI 2010
Cardiovascular disease = important risk factor for death from anaphylaxis\textsuperscript{1}  
  – middle-aged and older individuals

Pts on β-blockers: Epinephrine resistant anaphylaxis  
  – Glucagon (1mg/mL) 1-5 mg IV over 5 minutes  
  – Followed by 5-15 ug/min infusion titrated to response

Persistent asthma: not optimally controlled  
  – important risk factor for death from anaphylaxis\textsuperscript{2,3}  
  – especially in adolescents and young adults

Depression:  
  – Tricyclic antidepressants and MAO inhibitors  
  – may potentiate the effect of epinephrine

\textsuperscript{1} Greenberger, PA. Ann Allergy Asthma Immunol 2007; 98:252.  \textsuperscript{2} Pumphrey, R. Curr Opin Allergy Clin Immunol 2004; 4:285.  \textsuperscript{3} Pumphrey, RSH. JACI. 007; 119:1018
Anaphylaxis: Important points

- Potentially fatal disorder
- Rate of occurrence ↑ in industrialized countries
- Underrecognized b/c it can mimic other conditions
- Symptoms may be variable in presentation
  - Skin symptoms present in up to 90%
- Greatest # of fatalities
  - adolescents and young adults
- Hx. of anaphylaxis seems to indicate ↑ risk of future anaphylaxis
- Early recognition and use of Epinephrine is critical for patient survival
- Long-term management: finding cause and avoidance
References


• Lieberman P (ed.) Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol. 2005 Mar;115(3 Suppl 2):S483-523.


