ANAPHYLAXIS AND ANGIOEDEMA

Edward Brooks, M.D.
Department of Pediatrics
Immunology and Infectious Disease
University of Texas Health Science Center at San Antonio

Anaphylaxis definition(s):

1) the acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue or both and at least one of the following: a) respiratory compromise or b) reduced blood pressure or symptoms of end-organ dysfunction

2) two or more of the following that occur rapidly after exposure to a likely allergen for that patient – involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms and/or persistent gastrointestinal symptoms

3) reduced blood pressure after exposure to a known allergen

Anaphylaxis and angioedema

Urticaria

- Therapy with antihistamines work best for most patients with acute-types of short-lasting urticaria.
- Combination therapy should be attempted if H1 antagonists do not suffice, H2 antagonists, montelukast
- Steroids and other immunosuppressants should be reserved for severe urticaria associated with angioedema of oropharynx or other systemic signs, moderate to severe drug reactions, urticarial vasculitis, and refractory cases of CIU

Angioedema

Laryngeal edema

Symptoms: dyspnea, chest pain, stridor, wheezing, throat tightness, dysphagia, drooling, anxiety

Usually responds to epinephrine (marginally in hereditary angioedema)
Gut angioedema

Symptoms: pain, swelling, nausea, vomiting
Often mistaken for acute abdomen
Chronic symptoms misdiagnosed as many conditions (celiac disease, GE, IBD, IBS)

Angioedema

Sx develop in seconds to 4 hours
Sense of “impending doom”
Respiratory compromise
Abdominal symptoms
Hypotension
Skin manifestations (in many but not all)
Reaction may be biphasic
Late sx may be worse than initial sx
Observe for 4 hours minimum (up to 24 hrs - rebound)
Increased risk for fatal anaphylaxis

Causes of anaphylaxis

- Food-induced anaphylaxis
  - Food allergy = #1 cause of anaphylaxis in the ED (30% of cases)
  - Rapid-onset, up to 30% biphasic
  - May be localized (single organ) or generalized
  - Any food:
    » peanut, tree nut, seafood (cow’s milk and egg in young children)
- Food-dependent, exercise-induced: 2 forms
  - Specific foods (wheat, celery most common)
  - Any food (post-prandial)
- Inhalational exposure may cause respiratory symptoms that can be severe – occupational, restaurants, home

Evaluation:
Interpretation of Laboratory Tests

- Positive prick test or specific IgE
  - Indicates presence of IgE antibody NOT clinical reactivity
  - ~90% sensitivity
  - ~50% specificity
  - ~50% false positives
  - Larger skin tests/higher IgE correlates with likelihood of reaction but not severity
- Negative prick test or specific IgE
  - Essentially excludes IgE antibody (>95% specific)
Specific IgE Levels Associated with 95% Risk of Reaction

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Food</th>
<th>Serum IgE (kU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 years</td>
<td>Egg</td>
<td>≥ 7</td>
</tr>
<tr>
<td>Child</td>
<td>Cow Milk</td>
<td>≥ 15</td>
</tr>
<tr>
<td>Child</td>
<td>Cow Milk</td>
<td>≥ 5</td>
</tr>
<tr>
<td>Child</td>
<td>Peanut</td>
<td>≥ 14</td>
</tr>
<tr>
<td>Child</td>
<td>Fish</td>
<td>≥ 20</td>
</tr>
</tbody>
</table>

Management of Food Allergy

- Complete avoidance of specific food trigger
- Ensure nutritional needs are being met
- Education
- Anaphylaxis Emergency Action Plan if applicable
  - most accidental exposures occur away from home

What You Should Know About Latex Allergy

- Latex allergy – public health health issue
- High-risk groups
  - Rubber industry workers
  - Healthcare workers (5-10%)
  - Children with spina bifida or multiple surgeries

Latex - Containing Products

<table>
<thead>
<tr>
<th>Reactions Rare</th>
<th>Reactions Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubber bands, erasers</td>
<td>Gloves (especially powdered)</td>
</tr>
<tr>
<td>Toy rubber parts</td>
<td>Balloons</td>
</tr>
<tr>
<td>Crepe paper rubber products</td>
<td>Condoms</td>
</tr>
<tr>
<td>Shoe soles, latex (elastic) on clothing</td>
<td>Dental dams</td>
</tr>
<tr>
<td>Feeding nipples and pacifiers</td>
<td></td>
</tr>
<tr>
<td>NOTE -- latex paint does not contain latex</td>
<td></td>
</tr>
</tbody>
</table>

Latex and Food Allergy Connection

Many Fruits and Vegetables Especially

- Banana
- Chestnut
- Passion fruit
- Avocado
- Kiwi
- Celery
- Melon
What You Should Know About Insect Stings
- Anaphylaxis in 1% of children stung
  - Symptoms usually occur within minutes
  - Systemic reaction in 5-10% of children stung
  - Reactions can vary from mild to life-threatening

Managing Insect Allergy
- Refer to allergist for testing
- Self-injectable epinephrine
- Patients with a history of a systemic reaction and documented insect sensitivity at testing
- Immunotherapy highly effective (>90%)

Drug-induced anaphylaxis
- Penicillin most common
  - Cross reactivity with cephalosporins is low (~14% of PCN skin test positive subjects)
  - Adverse events may cross-react with sulfadiazine
- Chemotherapy
  - Platinum agent every high (6-77%)
  - Radiographic contrast material (non-IgE mediated)

Drug allergy - anesthesia
- Anaphylaxis during anesthesia: 1 in 4000 to 1 in 25,000
- Can present as cardiovascular collapse, airway obstruction, and/or skin manifestation
- Difficult to differentiate between immune and nonimmune mast cell-mediated reactions and pharmacologic effects
- Neuromuscular blocking agents such as succinylcholine can cause nonimmunologic histamine release
- Reactions to opioid analgesics are usually caused by direct mast cell mediator release rather than IgE-mediated
- Antibiotics that are administered perioperatively
- Protamine can cause severe systemic reactions through IgE-mediated or nonimmunologic mechanisms
- Methylmethacrylate (bone cement) has been associated with hypotension and various systemic reactions

Drug allergy - desensitization

<table>
<thead>
<tr>
<th>Drug Allergy</th>
<th>Desensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>Desensitization</td>
</tr>
<tr>
<td>Reaction Type</td>
<td>Desensitization</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>Desensitization</td>
</tr>
<tr>
<td>Reaction Duration</td>
<td>Desensitization</td>
</tr>
<tr>
<td>Reaction Severity</td>
<td>Desensitization</td>
</tr>
</tbody>
</table>

Table 1: Drug desensitization test or desensitization

<table>
<thead>
<tr>
<th>Drug Desensitization Test</th>
<th>Desensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>Desensitization</td>
</tr>
<tr>
<td>Reaction Type</td>
<td>Desensitization</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>Desensitization</td>
</tr>
<tr>
<td>Reaction Duration</td>
<td>Desensitization</td>
</tr>
<tr>
<td>Reaction Severity</td>
<td>Desensitization</td>
</tr>
</tbody>
</table>

100% success rate
All subsequent reactions were less severe than initial reaction, epinephrine used only once

HSRs were classified as mild (absence of chest pain, changes in blood pressure, dyspnea, oxygen desaturation, or facial swelling or swelling of a lower extremity) or severe (including at least 1 of these).

Diagnostic testing
- Serum tryptase – within 1 hour ideal, up to 24 hours may be elevated, special handling
- Urinary histamine
- Skin testing
- In vitro IgE testing
- Challenge testing

Treatment of anaphylaxis
- Epinephrine
- Anti-histamines – primarily short acting H1 antagonists (diphenhydramine)
- Corticosteroids – beneficial in asthma sx, and to prevent late-phase reactions
- Observe for 4-8 hours
- Indications for Extended Observation
  - Severe reaction of slow onset
  - History of previous biphasic reaction
  - Marked asthmatic component
  - Ingested antigen (continuous absorption)
- Discharge
  - Autoinjectable epinephrine
  - Anti-histamines for 24-48 hours
  - Education: avoidance of suspected causative agents

Respond Quickly!
- Administer epinephrine quickly
- Activate EMS – 911
- Then, call emergency contacts

Emergency Department Management of Food Allergy

Patients with severe food allergy may not receive education on avoidance, self-injectable epinephrine or referral to an allergist at emergency department visits. It is imperative for primary care doctors and allergists to recognize the risks and help patients avoid a future accident.

Treatment of anaphylaxis
Complicating factors
- Beta-blockers
- Beta-adrenergic blocking agents can interfere with the activity of epinephrine.
- ACE inhibitors
- Angiotensin-converting enzyme inhibitors can block the endogenous compensatory response to angiotensin II.
- prevent the destruction of bradykinin
- Angiotensin II receptor blockers (ARB)
- Angiotensin II blocking agents can interfere with the compensatory response of angiotensin II.
- Tricyclic antidepressants
- Tricyclics can prevent the re-uptake of catecholamines at nerve endings, and therefore exaggerate the response to epinephrine, thus making judgment of the dose difficult.
- MAO inhibitors
- Monoamine oxidase inhibitors prevent the degradation of epinephrine, again making the judgment of the correct dose difficult.
Anaphylaxis management

- The more rapidly anaphylaxis develops, the more likely the reaction is to be severe and potentially life-threatening.
- Prompt recognition of signs and symptoms of anaphylaxis is crucial. If there is any doubt, it is generally better to administer epinephrine. Epinephrine and oxygen are the most important therapeutic agents administered in anaphylaxis.
- Appropriate volume replacement either with colloid or crystalloids and rapid transport to the hospital are essential for patients who are unstable or refractory to initial therapy for anaphylaxis in the office setting.

Risk Management

- Pediatrician and allergist found liable in 2002 verdict: $10 million settlement
- 13 y.o. boy in vegetative state after anaphylaxis to peanut at age 8. His previous reaction at age 6 was a generalized rash with wheezing.
- Both physicians failed to prescribe self-injectable epinephrine
- Both failed to warn parents of potential severity of the boy’s peanut allergy

Angioedema

- Allergic
- Hereditary (HAE)
- Acquired
- Autoimmune
- Chronic Idiopathic

Hereditary Angioedema (HAE)

- 1:10,000-1:50,000
- Angioedema: extremities, gut, larynx, face
- rash: serpiginous non-pruritic erythema (erythema marginatum?)
- NO URTICARIA
- female predominance
- Autosomal dominant, 25% spontaneous mutation, 11q12-q13.1

Kaplan Enzymatic pathways in the pathogenesis of hereditary angioedema: The role of C1 inhibitor therapy. J ALLERGY CLIN IMMUNOL VOLUME 126, NUMBER 5
Kaplan Enzymatic pathways in the pathogenesis of hereditary angioedema: The role of C1 inhibitor therapy.


Bowen et al. Allergy, Asthma & Clinical Immunology 2010, 6:24
Bowen et al. Allergy, Asthma & Clinical Immunology 2010, 6:24

Bowen et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy, Asthma & Clinical Immunology. 2010, 6:24

Table 1: Treatment of acute angioedema

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>Fexofenadine 180 mg</td>
</tr>
<tr>
<td>Moderate</td>
<td>Montelukast 10 mg 4 times daily</td>
</tr>
<tr>
<td>Severe</td>
<td>EMLA 10% cream 3 times daily</td>
</tr>
</tbody>
</table>

Table 2: Long-term prophylaxis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma-derived C1 inhibitor (pC1INH)</td>
<td>300 mg/daily</td>
</tr>
<tr>
<td>Antihistaminic Agents</td>
<td>2-4 mg/daily</td>
</tr>
</tbody>
</table>

Table 3: Short-term prophylaxis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma-derived C1 inhibitor (pC1INH)</td>
<td>300 mg/daily</td>
</tr>
<tr>
<td>Antihistaminic Agents</td>
<td>2-4 mg/daily</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>40-60 mEq/day</td>
</tr>
</tbody>
</table>

Figure 1: Schematic diagram of prophylaxis.

Figure 2: Graphical representation of the proposed algorithm.

Figure 3: Flowchart diagram for diagnosis and management of hereditary angioedema.