ANAPHYLAXIS, URTICARIA AND ANGIOEDEMA

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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 mechanisms
- Eliminate the term “anaphylactoid”
- Categorize into immune and non-immune mediated
- Mast cell activation, IgE/non-IgE mediated histamine, leukotrienes, and prostaglandins, PAF

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/epinephrine 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

Urticaria – involving the superficial dermis
Most often characterized by intense pruritis due to histamine effect

Angioedema – involving deeper dermal and subcutaneous layers
May be pruritic but often characterized as a deeper and dull discomfort – burning quality

Laryngeal edema

Symptoms: dysnea, chest pain, stridor, wheezing, throat tightness, dysphagia, drooling, anxiety
Usually responds to epinephrine (marginally in hereditary angioedema)

Angioedema - Gut

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

Angioedema - extremities

Diagnostic testing

**TABLE E2**: Laboratory tests to be considered in the differential diagnosis of anaphylaxis

<table>
<thead>
<tr>
<th>Test measured</th>
<th>Overview</th>
</tr>
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<tbody>
<tr>
<td>Serum eosinophils</td>
<td>Serum eosinophil levels peak 48-96 hours after the onset of symptoms and persist for 5-7 days.</td>
</tr>
<tr>
<td>Plasma histamine</td>
<td>Plasma histamine levels begin to rise within 5-15 minutes and remain elevated for 30-60 minutes. They are of little help if the patient is seen more than an hour or even after the onset of the event.</td>
</tr>
<tr>
<td>Urinary histamine and metanephrines</td>
<td>Elevated histamine and metanephrines are elevated for a longer period</td>
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<tr>
<td>Plasmatic histamine levels</td>
<td>Useful for evaluation of patients with a history of histamine-induced reactions.</td>
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<tr>
<td>Urea nitrogen</td>
<td>Serum urea nitrogen is usually elevated in cases of severe anaphylaxis.</td>
</tr>
<tr>
<td>Uric acid</td>
<td>Serum uric acid levels are often increased in cases of severe anaphylaxis.</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Elevated thyroid-stimulating hormone levels may be seen in patients with severe anaphylaxis.</td>
</tr>
<tr>
<td>Total serum histamine</td>
<td>Useful in the diagnosis of anaphylaxis.</td>
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<tr>
<td>Baseline tryptase</td>
<td>Useful in the diagnosis of anaphylaxis.</td>
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<tr>
<td>Tryptase by immunofluorescence</td>
<td>Useful in the diagnosis of anaphylaxis.</td>
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<tr>
<td>Carboxypeptidase</td>
<td>Useful in the diagnosis of anaphylaxis.</td>
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<tr>
<td>Skin testing</td>
<td>Useful in the diagnosis of anaphylaxis.</td>
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<tr>
<td>In vitro IgE testing</td>
<td>Useful in the diagnosis of anaphylaxis.</td>
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<tr>
<td>Challenge testing</td>
<td>Useful in the diagnosis of anaphylaxis.</td>
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Anaphylaxis

With laryngeal edema, wheezing or hypotension

- Epinephrine 0.3 mg IM
  - Repeat x 2; prepare for intubation
- Diphenhydramine 25-50 mg IV/PO
- Corticosteroids (prednisone) 60 mg IV/IM

Urticaria only

- (no h/o wheezing, laryngeal edema or hypotension)
- Epinephrine 0.3 mg IM
  - Repeat x 2
- Corticosteroids (prednisone) 60 mg IV/IM/PO

Treatment of anaphylaxis

- Epinephrine
  - More rapidly anaphylaxis develops, the more likely the reaction is to be severe
- Anti-histamines – primarily short acting H1 antagonists (diphenhydramine)
- Corticosteroids – beneficial in asthma sx, and to prevent late-phase reactions
- Remain recumbent if hypotension present
- 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

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.

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.

Angioedema

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

Chronic Urticaria

Autoimmune
  - Isolated urticaria (no systemic illness)
  - Due to IgG Ab to FceRI
  - Autoologous skin test/basophil activation
  - Feature of systemic autoimmunity
  - SLE, JIA, IBD
  - Screening: CBC, CMP, UA, ANA, TPO, RF
  - Skin biopsy: leukocytoclastic vasculitis
Chronic Urticaria - treatment

Anti-histamine, anti-histamine, anti-histamine
- H1 blockers: cetirizine, prn
diphenhydramine/hydroxyzine, doxepin
- H2 blockers: cimetidine
- montelukast
- Immunosuppression: corticosteroids, CsA, dapsone
- omalizumab

Bradykinin-mediated Angioedema

Hereditary Angioedema (HAE)

1:10,000-1:50,000
- Angioedema: face, extremities, gut, larynx, genitals/bladder/urethra
- Rash: serpiginous non-pruritic redness (erythema marginatum?)
- NO URTICARIA
- Bradykinin mediated, not histamine/mast cell
- C1 esterase inhibitor deficiency
- Serine pro tease family (SERPING1)
- 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

Treatment of Hereditary Angioedema
Pharmacologic therapy for HAE with Acute Episode

**Known diagnosis of HAE**

- **Type I or II**
  - pdC1INH (Berinert) 1500 units IV
  - ecullitide (Kalbitor) 30 mg SQ or icatibant (Firazyr) 30 mg SQ

- **Unknown type (Type III - HAE with normal C1 esterase)**
  - pdC1eINH (Berinert) 1500 units IV, may repeat in 4 hours
  - ecullitide (Kalbitor) 30 mg SQ or icatibant (Firazyr) 30 mg SQ

*If unavailable consider solvent detergent-treated plasma or FFP
 Patients on anabolic steroids may respond to additional doses*

**Additional therapy for HAE with Acute Episode**

**HAE with H/O laryngeal attacks with intubation**

- Follow pharmacologic intervention algorithm
- Consider epinephrine 0.3 ml IM
- Prepare for intubation

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**Biochemical cascade leading to bradykinin**

![Diagram of Biochemical cascade leading to bradykinin](image)