The Patient with Allergic Diseases: Urticaria & Angioedema

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Disclosures

- None
Objectives

- Differentiate Urticaria and Angioedema
- Recognize and treat anaphylaxis and anaphylactic reactions
- Recognize and treat mastocytosis
- Recognize the variety of manifestations of latex sensitivity
Topics
- Urticaria/Angioedema
- Anaphylaxis
- Latex Allergy
- Anaphylactoid Reactions
Incidence

- 15% of population
- F > M (~2.5:1)
- Peak incidence 2\textsuperscript{nd} - 4\textsuperscript{th} decades
- 50% both urticaria and angioedema
- 40% urticaria alone
- 10% angioedema alone
Urticaria/Angioedema

- **Urticaria**
  - Pruritic, erythematous, cutaneous elevations that blanch with pressure, indicating the presence of dilated blood vessels and edema

- **Angioedema**
  - Similar pathologic alterations in deep dermis and subcutaneous tissue; swelling is predominant manifestation, little or no pruritis; may be painful or burning
Angioedema

- Unlike other forms of edema
  - Not characteristically in dependent areas
  - asymmetrically distributed
  - transient

- Often seen with urticaria
Urticaria

- **Acute vs chronic**
  - Urticaria that exceeds 6 weeks is arbitrarily designated chronic

- **Dermagaphism**
  - Ability to write on skin: 2-5% of population
  - Only small fraction warrant chronic treatment with antihistamines
CASE 1: MJ

- 42 y/o w/m with CC: “whelps” x 2 months
  - Itching
  - 1st episode: No lifestyle changes
  - Doctors didn’t help
    - Benadryl, Claritin, Tavist w/o relief
    - Lab work, x-rays normal
- PE: 0.5-5 cm urticarial lesions
Urticaria
Urticaria

- Papules and plaques:
  - pruritic
  - erythematous
  - edematous
  - blanchable
  - 1mm to several cm in diameter
  - last < 24 hours
Urticaria Evaluation

History

- Duration - < or > 6 weeks
- Triggers – identifiable cause more likely in acute but < 5% in chronic
  - ingestants, contactants, physical stimuli, infections
- Lesional hx
  - duration, purpura, pain
  - refer to Dermatology if suspected vasculitis for Bx
- PMH/ROS suggestive of systemic disease
Urticaria Evaluation

- **Acute urticaria**
  - systemic disease
  - acute infections
  - dermatographism

- **Chronic urticaria**
  - systemic disease
  - usually idiopathic/autoimmune
Physical Urticaria

- Dermatographism
- Cholinergic
- Cold
- Delayed pressure urticaria/angioedema
- Solar
- Vibratory
- Aquagenic
Ice cube test

- Cold Urticaria
What’s this?
Causes of Urticaria

- Infections
  - URI virus, HBV, EBV, β-Strep, Mycoplasma
- Drugs (NSAIDS, Aspirin)
- Foods or other ingestants (rare)
- Contactants
  - soaps, perfumes, deodorants, insects
- Systemic disease
  - thyroid, CTD, malignancy
- Autoimmune
- Idiopathic (>80% in chronic urticaria)
Urticaria Evaluation

Labs

- Skin tests
  - Seldom indicated
  - Of questionable value
    - can’t get the patient off antihistamines
    - many patients have dermatographism
  - Most urticaria is not triggered by food or aeroallergens
- Labs as indicated by Hx/PE
  - TSH, CBC, LFT’s, ESR, ANA, C4
- Skin Bx as indicated by Hx
Urticaria Differential Diagnosis
Other pruritic skin conditions

- Urticarial vasculitis
- Viral exanthema
- Contact dermatitis
- Parasites
- Liver disease
- SLE
- Malignancy
Urticaria Pigmentosa

- Persistent pigmented macular lesions
- Darier’s sign
- Adult cases more likely to progress to systemic disease
Mastocytosis

- Excessive Mast cells
- Four classifications
  - indolent
  - with hematologic abnormalities
  - aggressive
  - mast cell leukemia
- Multiple organ involvement
  - BM, GI, liver, skin, long bones
Mastocytosis

- Pruritis, flushing, urticaria, hypotension,
- Idiopathic anaphylaxis
- May progress to malignancy
- Anemia is a poor prognosis
- Treat with:
  - antihistamines, oral cromolyn, NSAID’s
  - possible use of LTRA
Urticarial Vasculitis

- Necrotizing vasculitis
  - endothelial cell edema
  - perivascular PMN infiltrate
  - fibrinoid deposits in venules
  - leukocytoclasia - nuclear debris
- Last > 24 hours
- Painful and leave purpura/bruising with resolution
Urticaria:
Treatment

- Eliminate trigger factors
- H-1 Antihistamines
- combination H-1 & H-2 Antihistamines
- Corticosteroids
- Avoid ETOH, ASA, Tobacco
- Avoid hot showers, hot tubs
Case 2: CW

- 37 y/o b/m with CC: “swelling, typically of 1 or both hands every 3-4 months x 18 yrs
- Frightened by recent episode involving face/throat
- Seen by a number of physicians, no definitive diagnosis, no treatment plan has helped. No current medications
- PE: normal
Angioedema

- 10-20% of the population
- 94% of cases are drug induced
  - ACEI
  - NSAIDS
  - Others
- IgE mediated
  - Associated with urticaria
- Hereditary
- Autoimmune acquired
  - very rare, < 50 case reports
Angioedema

- Non-pitting edema
- Occurs deeper than urticaria
- Overlying skin is usually normal
- Usually burns and is not pruritic
ACEI Induced Angioedema

- 1-2 cases per 1000 persons
- >70% symptomatic within first week of therapy
- Likely precipitated by increased bradykinin
  - Angiotensin II inhibits bradykinin
    - ACEI blocks conversion of angiotensin I → II
    - Vasodilatation, increased vascular permeability
- Can lead to life-threatening upper airway obstruction
  - 22% require intubation with 11% mortality
- Rare in Angiotensin II receptor blockers
Hereditary Angioedema

- Rare (1/150,000)
- Autosomal dominant
- Onset in adolescence
- Angioedema is
  - painless and non-pruritic
  - lasts 3-5 days
  - unresponsive to Epi, antihistamines, pred.
  - triggered by mild trauma
Hereditary Angioedema

- C1 Inhibitor (C1-INH) deficiency
  - Type I (85%)
    - Quantitative deficiency (5-30% normal)
  - Type II (15%)
    - Qualitative deficiency
    - Quantity is normal or elevated
    - Functional activity is markedly reduced
- Type III
  - Unknown cause
  - C1q, C1-INH, C4 normal with suggestive history
  - C4, C1-INH normal during attack
Hereditary Angioedema

- C4 and C2 markedly low
  - both between and during attacks
  - C4 is screening test
- Autosomal dominant inheritance
- Symptoms related to subcutaneous and/or submucosal edema
- C1 normal
  - Low C1 consider acquired form
    - Lymphoma
    - Low C4, C2 and C3
Hereditary Angioedema

- **Onset of symptoms**
  - Before adolescence in over half
  - First attack may occur well into adult life

- **Attacks**
  - Progress for 1-2 days, resolve over 1-2 days
  - Skin, respiratory tract, GI tract
  - Respiratory attacks can be serious threat
Hereditary Angioedema: Treatments

- **C1 Inhibitor**
  - Cinryze: approved for long term prophylaxis
  - Berinert: approved for treating attacks

- **Plasma Kallikrein inhibitor**
  - Ecallantide (Kalbitor): approved for treating attacks

- **Bradykinin receptor antagonist**
  - Icatibant (Firazyr): approved for treating attacks
Acquired Angioedema

- Very rare
- Present in adults
- CLL, NHL, cryoglobulinemia, Waldenstrom macroglobulinemia, myeloma
- Decreased C4 like in HAE
- Decreased C1q which distinguishes HAE from AAE
## HAE vs AAE

<table>
<thead>
<tr>
<th>DZ</th>
<th>C1 INH Quant</th>
<th>C1 INH Activity</th>
<th>C1q</th>
<th>C4</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAE I</td>
<td>Low</td>
<td>Low</td>
<td>NL</td>
<td>Low</td>
</tr>
<tr>
<td>HAE II</td>
<td>NL</td>
<td>Low</td>
<td>NL</td>
<td>Low</td>
</tr>
<tr>
<td>AAE I</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>AAE II</td>
<td>Low/NL</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
Universal Precautions & Latex

- Between 5.5 and 6.4 million health care workers in the U.S. don latex gloves on a routine basis

- Between 1988 and 1992:
  - 11.8 billion latex examination gloves
  - 1.8 billion surgical latex gloves
Latex Reactions

- Irritant
- Allergic CONTACT Dermatitis
- Type I IgE mediated allergic reaction: systemic reaction
Latex **Irritant** Reaction

- Non allergic cutaneous response
- Erythema, chapping, cracking, dryness, rarely vesicles
- Only latex exposed areas
- Prolonged and repeated Latex exposure
- Age: older skin is more easily irritated and heals more slowly
Allergic Contact Dermatitis

- Type IV Gel & Coombs
- Multiple exposures: weeks to months
- Reaction to chemical additives in gloves
- Reaction 12-24 hrs after exposure
  - may be 6-96 hours after exposure
- Vesicular skin lesions
- Hypoallergenic gloves appropriate
- Patch test to ID culprit additive
Systemic Latex Reaction

- Gel & Coombs type I
- Anti-latex IgE
- Occurs in minutes: rarely > 2 hours
- Contact urticaria, rhinoconjunctivitis, anaphylaxis
- Mucosal exposure > cutaneous exposure
- Modest correlation between IgE concentration and severity
Reaction Severity

- Future experience is NOT predicted by prior reactions
- Severe anaphylactic reactions may occur following any type of exposure
- In general, mucosal exposure results in more severe reactions than cutaneous exposure
Treatment: Latex Anaphylaxis

- Avoid further exposure
  - Non Latex gloves
  - Hypoallergenic latex gloves are NOT APPROPRIATE
- Medic Alert Bracelet
- Carry epi and antihistamines
- Pretreatment for necessary exposure
Latex Crossreactivity:
PLANT PRODUCT

- banana
- avocado
- kiwi
- chestnut
- apricot
- grapes
- passion fruit
- pineapple
- peaches
- cherry
- potato
- tomato
Most Frequent Signs and Symptoms of Anaphylaxis

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria/Angioedema</td>
<td>88</td>
</tr>
<tr>
<td>Upper Airway Edema</td>
<td>56</td>
</tr>
<tr>
<td>Dyspnea/Wheeze</td>
<td>47</td>
</tr>
<tr>
<td>Flush</td>
<td>46</td>
</tr>
<tr>
<td>Hypotension</td>
<td>33</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>30</td>
</tr>
</tbody>
</table>
Vasovagal Reaction

- Stress or fright
- Slow pulse
- Maintain blood pressure
- Pale, cold clammy skin
- Recumbancy alleviates symptoms
- No urticaria or pruritis
# DDX Anaphylaxis

<table>
<thead>
<tr>
<th>System</th>
<th>Anaphylaxis</th>
<th>Vaso-Vagal Rxn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td>Urticaria, erythema</td>
<td>Pale, clammy</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Globus, SOB wheezing, SPO2</td>
<td>Hyperventilation SPO2:</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia, hypotension</td>
<td>Bradycardia, normotensive</td>
</tr>
<tr>
<td>G.I.</td>
<td>N, V, D</td>
<td>N, V, D</td>
</tr>
<tr>
<td>C.N.S.</td>
<td>“Feeling of impending doom”</td>
<td>Light headed, confused</td>
</tr>
</tbody>
</table>
Anaphylaxis: Treatment

- Stabilize airway
- **Epinephrine**
- O2
- Large gauge IV
- Benadryl 50-100 mg IV or IM
- Cimetidine 300 mg IV
- Methyprednisolone 125mg IV
Anaphylaxis Management
After Initial Assessment

- Antihistamine
- Corticosteroids
- Beta-Agonists for wheezing
- Fluids, Vasopressors
- Glucagon
  - Used for nonresponsive anaphylaxis in patients on beta-blockers
- Atropine
Anaphylactoid Reaction

- Resemble anaphylaxis but not immunologically mediated
  - Not IgE mediated
- Does not require prior sensitization
  - Reaction may occur on first exposure
- Symptoms = anaphylaxis
- Treatment = anaphylaxis
Anaphylactoid Reactions
Non IgE mediated causes

- Complement-mediated
- Direct activation of mast cell-mediator release
- Arachidonic acid metabolism
- Unknown
Complement Mediated Anaphylactoid Reactions

- Human plasma and blood products
- Dialysis membranes
Direct activation of Mast Cell mediator release

- Opiates
- Vancomycin
- Muscle-depolarizing drugs
- Aminoglycosides
- Radiocontrast media
Direct activation of Mast Cell mediator release

- Radiocontrast media
  - Increased risk with IV administration and high osmolality
  - Sensitization not required
  - Previous reaction increases probability of reaction on rechallenge
  - Anaphylaxis in 1-10% of initial exposures
  - Pretreatment can be given to decrease risk
Modulators of Arachidonic Acid Metabolism

- Aspirin and Nonsteroidal drugs
  - Generally progresses more slowly
  - Less often hypotension
  - Bronchoconstriction, wheezing often begin within 30 minutes and progress for several hours
Anaphylaxis While Receiving Beta-blocker Therapy

- Unusual severity
- Bradycardia during profound hypotension
- Severe sustained bronchospasm
- Total body angioedema
- Refractory to usual treatment
  - Glucagon is used for refractory cases
Treatment of Anaphylaxis:
in presence of Beta-blockade

- Aggressive and prompt support
- Epinephrine
- Large volume IV
- Glucagon
- Atropine
- Increased dopamine or beta-agonist
- Antishock trousers
Prevention of Anaphylaxis
Radiocontrast Media (RCM)

- Use non-ionic media
- History
- Premedicate before RCM
  - Prednisone 50 mg PO 13, 7 and 1 hour before procedure
  - Benadryl 1mg/kg 1 hour before procedure
Anaphylaxis:
Differential Diagnosis

- Vasodepressor Reaction
- Flush syndrome
- Restaurant Syndrome
- Other forms of shock
- Endogenous overproduction of histamine
- Red-man syndrome
- Pseudoanaphylaxis
Questions?