Disclosure

I have no relevant financial relationships with any companies related to the content of this course.
Educational Objectives

- Recognize and treat anaphylaxis
- List causes of urticaria and describe initial management
- Name 2 physiologic pathways for angioedema and state implications for treatment
- Identify situations where allergy testing is useful

A 24 year old woman presents to your office with hives for two weeks. She had a cold one week prior to the onset of hives. Diphenhydramine 25 mg provides relief, but hives return. Each hive lasts for < 24 hours and does not leave bruising. **What is the most likely cause of her hives?**

A. Detergent allergy  
B. Autoimmune disease (urticarial vasculitis)  
C. Shrimp allergy  
D. Viral infection  
> 80% of acute urticaria
What history is concerning for anaphylaxis?

- 2 or more of the following

- Acute onset after exposure to allergen

Allergen = substance that causes an allergic reaction

What can cause anaphylaxis?

During or within 1 hour after

- Food + Exercise (+/- ASA, EtOH cofactors)
  - Wheat, shrimp, legumes (peanut, soy), tree nuts, tomato
  - Exercise 2-3 hours after ingestion

*Simons FER et al. WAO anaphylaxis guidelines JACI 2011;127(3):587-593*
Prescribe auto-injectable epinephrine if history concerning for anaphylaxis

Only medication with mortality benefit

- **Timing**: As soon as possible
- **Location**: Anterolateral thigh
- **Route**: Intramuscular
- **Dose**: 0.3 mg (~0.01 mg/kg)

Causes of Hives:

- Kanani et al. Urticaria and angioedema. Allergy, Asthma and Clinical Immunology 2018
Which of the following tests are recommended for patients with chronic urticaria (CU)?

A. ANA
B. CBC/d, ESR/CRP, AST/ALT, TSH
C. Food allergy testing (specific IgE)
D. Thyroid autoantibodies (TPO, thyroglobulin)

Food Allergy Testing is not Recommended

- Many patients report food as a trigger of hives (> 30%)
- False positives common with food allergy testing (50-60%)
  - 17.5% CU patients had positive skin / blood allergy test to food
  - 0% had hives when they ate that food
Thyroid disease is seen more commonly in CU

- Hypothyroidism: 10% CU patients vs 0.6% controls
- Hyperthyroidism: 3% vs 0.5%
- Thyroid autoantibodies: 30% vs 5-10%
  - Don’t predict abnormal thyroid function
  - Severe / Persistent CU

Chronic Urticaria (CU) and Autoimmunity
Checking antibodies not routinely recommended

- Thyroid autoantibodies (30%)
- ANA: 30% CU patients have weakly positive speckled ANA in absence of SLE
- Fc epsilon receptor antibody (40% CU patients)
When to consider more testing for CU

<table>
<thead>
<tr>
<th>History</th>
<th>Possible dx</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hives last &gt; 24 hours</td>
<td>urticarial vasculitis</td>
<td>ANA, ESR, CRP C3, C4, C1q</td>
</tr>
<tr>
<td>Petechiae / Purpura Arthralgia / Arthritis Renal disease</td>
<td></td>
<td>Hepatitis B+C serology Cryoglobulin Skin biopsy</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Schnitzler</td>
<td>SPEP with IF Serum free light chains Skin biopsy</td>
</tr>
<tr>
<td>Fevers Arthralgia / Arthritis</td>
<td></td>
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</tbody>
</table>

Many patients with CU have physical triggers

- 76% report physical trigger
- 36% positive challenge
- 25% pressure-induced dermographism
  - Mastocytosis
  - Tryptase
- 13.4% cold-induced urticaria
Other ‘non-allergy’ triggers of hives

Patients may need to avoid one or more of these to prevent CU flares

<table>
<thead>
<tr>
<th>Radiocontrast media*</th>
<th>NSAIDs**</th>
<th>Dextran (e.g. HMW*** iron or other source)</th>
<th>Biologic agents* (e.g. some monoclonal antibodies)</th>
</tr>
</thead>
</table>

Physical factors (e.g. exercise, cold, heat, sunlight)

Ethanol

Medications* (e.g. opioids)

CU Management

Anti-histamines +/- Montelukast +/- omalizumab

~30% persist > 5 years despite tx

Fexofenadine 360 BID

Cetirizine 20 BID

Singulair

First line:
Second-generation antihistamines

Control inadequate after 2-4 weeks or earlier if symptoms are intolerable

Consider specialist referral

Second line:
↑ dose of second-generation antihistamines up to 4 fold

Control inadequate after 2-4 weeks or earlier if symptoms are intolerable

Third line:
Add on to second-generation antihistamine: omalizumab

Control inadequate within 6 months or earlier if symptoms are intolerable

Fourth line:
Add on to second-generation antihistamine: cyclosporine

Prednisone 40 mg/day 3 days
- Urticaria – mediated by **histamine** released by mast cells
  - Angioedema can co-exist → presence/absence of angioedema doesn’t change diagnostic considerations
- Angioedema –
  - Presence / Absence of hives is important diagnostic clue
  - **Histamine-mediated OR bradykinin-mediated**

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**Bradykinin**

- **C1 INH**
- Kallikrein
- High Molecular Weight Kininogen
- Bradykinin
- ACE
- Inactive BK
- Endothelial Cell
- Vasodilation, Edema
A 56-year-old woman presents to your clinic with chief complaint of lip swelling / angioedema. She denies any associated hives. She does not have a family history of angioedema. She does not have dermatographism on physical examination. Which of the following is the next best step?

A. Review medications to see if patient takes ACE inhibitor
B. Check C1 inhibitor level
C. Check tryptase
D. Check food allergy testing

ACE inhibitor induced angioedema

- Most common cause of angioedema in emergency department and hospital
- 0.1-0.2% incidence among patients on ACE inhibitors

55% during first 90 days
What about ACE inhibitor cough? Are ARBs ok?

ARBs are ok

(but recommend not starting for ~1 year since last angioedema episode)

ACE inhibitor induced cough is a risk factor for angioedema

Lab tests for bradykinin-mediated angioedema

<table>
<thead>
<tr>
<th>Hereditary Angioedema</th>
<th>Acquired Angioedema</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autosomal Dominant</strong></td>
<td>Acquired</td>
</tr>
<tr>
<td>(+) family history of angioedema</td>
<td>- Lymphoproliferative malignancy</td>
</tr>
<tr>
<td>Onset ~11 years of age</td>
<td>- Autoimmune disease</td>
</tr>
<tr>
<td></td>
<td>No family history of angioedema</td>
</tr>
<tr>
<td></td>
<td>Onset after 40 years of age</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>C1inh level</th>
<th>C1inh function</th>
<th>C4</th>
<th>C1q</th>
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</thead>
<tbody>
<tr>
<td>HAE Type I</td>
<td>&lt;30%</td>
<td>&lt;30%</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>HAE Type II</td>
<td>Normal</td>
<td>&lt;30%</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>Acquired</td>
<td>Normal Low</td>
<td>Low</td>
<td>&lt;30%</td>
<td>Low</td>
</tr>
</tbody>
</table>
Identifying bradykinin-mediated angioedema important for next management steps

- Doesn’t respond to anti-histamines, steroids, epinephrine
- Laryngeal edema
- Targeted medications available

![Diagram of kallikrein pathway]

Allergy Testing …
Allergen = substance that causes an allergic reaction

Allergy Testing is reliable for –

- outdoor seasonal allergens:
  - trees
  - grass
  - weed

- indoor perennial allergens:
  - dust mites
  - animals
  - cockroach

85~90% sensitivity and specificity
(Skin Test > specific IgE)
**Allergy Shots**  
(allergic rhinitis, allergic asthma, atopic dermatitis)

**Average duration is 3-5 years**

**Build-up phase:**  
Injections 1-2/week

**Maintenance phase:**  
1x/month

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**Can be problematic**

Value of testing depends on clinical history

Skin testing helpful  
Specific IgE not helpful

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Adapted from American Academy of Allergy, Asthma & Immunology.  
AIT Practice Parameter 3rd update JACI 2010
Adverse Reactions to Food

IgE-mediated
- Classic Food Allergy
- Oral Allergy Syndrome

Non-IgE-mediated
- Celiac disease

Mixed
- Atopic Dermatitis
- Eosinophilic Esophagitis

Which history is consistent with food allergy?

A. 45 year old presents with hives 30-60 minutes after eating peanut. Patient does not have a history of seasonal allergies.

B. 25 year old presents with mouth itching and no other symptoms immediately when eating peanut. Patient has a history of severe seasonal allergies.

C. 36 year old presents with fatigue, malaise, abdominal bloating, and distention. Patient notes occasional joint swelling that worsens after meals although not with any particular food.

D. 27 year old presents with long-standing difficulty swallowing that is worse when eating red meat. The patient reports that some other members of his family have had similar difficulty with swallowing. The patient has a history of atopic dermatitis and seasonal allergies.
Food Allergy Testing

**Sensitization**
Detection of IgE specific to foods through skin prick or blood tests (specific IgE)

**Allergy Clinical History!!**
& Sensitization

**Negative Predictive Value > 95%**
**Positive Predictive Value < 50%**

Unnecessary food elimination

Ordering food allergy testing for patients without history of classic food allergy can have significant negative consequences

Symptoms of Classic Food Allergy

- **Sudden skin or mucosal symptoms and signs**
  - (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)
- **Sudden respiratory symptoms and signs**
  - (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)
- **Sudden reduced BP or symptoms of end-organ dysfunction**
  - (e.g. hypotonia [collapse], incontinence)
- **Sudden gastrointestinal symptoms**
  - (e.g. crampy abdominal pain, vomiting)

Minutes to 2 hours after ingesting food
Symptoms are reproducible after specific food

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Stukus DR and Mikhail I. Curr Allergy Asthma Rep 2016;16(5):34.
Oral Allergy Syndrome

<table>
<thead>
<tr>
<th>Food Allergy</th>
<th>OAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peanut</td>
<td>Ara h 2</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>Cor a 9 / 14</td>
</tr>
<tr>
<td>Walnut</td>
<td>Jug r 1</td>
</tr>
</tbody>
</table>
Patient C: 36 year old presents with fatigue, malaise, abdominal bloating, and distention. Patient notes occasional joint swelling that worsens after meals although not with any particular food.

**Learn How Your Body Responds to 96 Different Foods**

This at-home test measures your body's immune response to 96 foods to help provide guidance on what foods may be the best to choose for an elimination diet.

- **Measures**: IgG Reactivity to 96 Foods
- **Collection Method**: Finger Prick Blood

**Test Over 450 Items**

Test over 450 individual foods, additives, colorings, molds, functional foods, medicinal herbs and chemical substances (such as environmental, chemical, pharmaceutical substances) can be tested.

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**Eosinophilic Esophagitis (EoE)**

- 27 year old presents with long-standing difficulty swallowing that is worse when eating red meat. The patient reports that some other members of his family have had similar difficulty with swallowing. The patient has a history of atopic dermatitis and seasonal allergies.
EoE and Food

- Skin testing not helpful to identify which foods trigger EoE
- Food allergy patients on oral food immunotherapy → EoE (2.72%)
- Food elimination → food allergy

Venom / Stinging Insects

20% have positive testing

Anaphylaxis → Skin Testing, Epinephrine

- 50% risk for anaphylaxis
- < 5% risk for anaphylaxis
- Same as general population
Which patient would benefit from mold skin testing?

A. 54 year old man presents with a recent diagnosis of severe persistent asthma that is not responding to increasing doses of inhaled and oral steroids. A total IgE level is 1343. Chest CT shows bronchiectasis.

B. 46 year old man with headaches and generalized fatigue over the last several months. A total IgE level is 40. He is concerned about a possible allergy to the black mold in his bathroom.

C. 32 year old woman with eye irritation and rhinorrhea at work in a damp office where there was water leakage last year. Her symptoms resolve when she is out of the office.

Established Effects
- IgE-mediated mold sensitization worsens asthma, allergic bronchopulmonary aspergillosis (ABPA), allergic fungal rhinosinusitis (AFRS)
- Hypersensitivity Pneumonitis

Toxic Effects
- Mycotoxins
- Volatile organic compounds
- Particulates (spores, hyphae)

Irritant Effects
- Irritant effects involve the mucus membranes of the eyes and upper and lower respiratory tracts and are transient
- Symptoms or signs persisting weeks after exposure should not be ascribed to irritant exposure

No credible evidence that exposure to molds induces a state of immune dysregulation (eg, immunodeficiency or autoimmunity).
Educational Objective 1
Recognize and treat anaphylaxis

- 2 or more of the following
- Acute onset after exposure to allergen

Sudden skin or mucosal symptoms and signs
(e.g. generalized hives, itch, flush, swollen lips-tongue-uvula)

Sudden respiratory symptoms and signs
(e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)

Sudden reduced BP or symptoms of end-organ dysfunction
(e.g. hypotonia (collapse), incontinence)

Sudden gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)

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Educational Objective 2
List causes of urticaria and describe initial management

- > 48 hours*
  - Urticarial vasculitis
  - > 6 weeks*
    - Chronic urticaria
    - Chronic spontaneous urticaria (CSU)
    - Other
    - Inducible

- < 48 hours*
  - Acute urticaria

High dose antihistamines
Omalizumab

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Kanani et al. Urticaria and angioedema. Allergy, Asthma and Immunology 2018
Educational Objective 3
Name 2 physiologic pathways for angioedema and state implications for treatment

Angioedema + Urticaria

- IgG anti-IgE
- Omalizumab

Angioedema w/o Urticaria

- High Molecular Weight Kininogen
- Kallikrein
- Bradykinin
- Endothelial Cell
- B2R antagonist
- C1 INH
- Kallikrein inhibitor

Educational Objective 4
Identify situations where allergy testing is useful

- Seasonal outdoor allergen
- Perennial indoor allergen
- Skin testing best
- Specific IgE helpful

- Food, Venom, Mold
  Value of testing depends on clinical history

- Medication
  Skin testing helpful
  Specific IgE not helpful
Questions?