Diagnosis and Treatment of Acute and Chronic Urticaria/Angioedema

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Objectives

1. Describe and identify urticaria and angioedema
2. Identify causes of both acute and chronic urticaria
3. Be able to initiate workup and understand treatment of acute and chronic urticaria
Case 1

- 15 year old female presents with a 3 day history of generalized itchy rash
- Describes lesions as “welts/hives”
- No other features of anaphylaxis
- Sore throat 2 days preceding rash
- Ate almonds in a salad 6pm evening before and woke up with rash next morning
- No history of atopy, not on any meds
Case 1- Questions

1. What are the features of urticaria and angioedema?
2. What could explain/cause her symptoms?
3. Could this be related to food allergy?
4. How should this patient be managed?
What are the features of urticaria (hives)?
What are the features of urticaria?

- Raised, pink/red, central pallor lesions of varying sizes
- **Transient**
  - Lesions last <24 hours
- Itchy, not painful
- Blanchable/non purpuric
- Lesions leave no scarring or hyperpigmentation
What are the features of urticaria?

- Lesions >24 hours
  - Contact dermatitis
  - Atopic dermatitis
  - Papular urticaria
  - Morbilliform or exanthematous drug eruptions
  - Vasculitis
  - Erythema multiforme
    - Dusky/dark red center, pale pink ring, bright/darker red outer ring
Angioedema

- Angioedema – involving deeper dermal and subcutaneous layers
  - May be pruritic, often characterized as a deeper and dull discomfort – burning quality
- Transient lasting up to 2-4 days
- Asymmetric
- Involvement of face, oral cavity/throat, bowel, extremities and genitals
Urticaria

- Urticaria very common
  - Up to 20% of population affected\(^1\)
- Urticaria manifestation of a variety of diverse clinical entities
- Acute Urticaria \(< 6\) weeks
- Chronic urticaria \(>6\) weeks
  - Prevalence, poorly studied, up to 1.8%\(^2\)
- Angioedema often occurs with urticaria

1. Saini Middleton’s Allergy 2013
2. Zuberbier Clin Exp Dermat 2010
Causes of acute urticaria

- Infections
  - Bacterial, viral or parasites
- Food allergy IgE mediated
- Food reactions (non IgE mediated)
- Insect stings
- Latex
- Medication (antibiotics, NSAIDs, narcotics)
- Contact reactions (IgE or non IgE mediated)
- Unknown up to 46% \(^1\)
- Serum sickness
  - Fever, joint symptoms and lymphadenopathy
Acute urticaria

- History is critical
  - Signs of anaphylaxis
  - Other signs and symptoms
  - Recent infection
  - Travel history
  - History of urticaria
  - Current or new medications, esp NSAIDs
Acute urticaria

- **Infectious**
  - Most common cause of acute urticaria esp. in children
  - Estimates range between 49-81%\(^1,2\)
  - Often present in association with antibiotics
    - Of 88 children presenting with cutaneous symptoms and on B-lactams, only 6 had +OC\(^3\)

1. Saicksen Ped Dermaolo 2004
2. Montureux Arch Dermatolo 1998
3. Caubet JACI 2011
Acute urticaria

- Infectious
  - Viral infections most common cause of infectious urticaria
  - Mechanism unknown
    - IgE antibodies have been detected to influenza\(^1\), rhinovirus\(^2\), HIV\(^3\), RSV\(^4\)
    - Complement activation?
Acute urticaria

- IgE mediated (immediate hypersensitivity reactions)
  - IgE mediated reactions (food, medications, stings, latex) start within 2 hours of exposure
  - Most IgE mediated reactions tend to have short duration
IgE mediated reactions

Acute urticaria

- **Investigations**
  - No specific tests recommended
  - Dictated by history and physical
  - For suspected allergic trigger: skin tests, RAST or challenge testing
Acute urticaria

Management

- Removal of offending trigger
- Treat with 2\textsuperscript{nd} generation antihistamines
  - Cetirizine 10mg for >6 years
    - Up to 20 mg for adults
  - Loratidine 10mg for >6 years
    - 5mg for ages 2-6
Acute urticaria

Management

1st generation antihistamines

- **Hydroxyzine** 25-50mg qid
  - **Children**
    - <40kg 2mg/kg/day divided qid max 25mg/dose
    - >40kg 25-50mg daily or bid

- **Diphenhydramine** 25-50mg qid
  - **Children**
    - 2-6 years 6.25mg q4-6hours max 37.5mg/day
    - 6-12 12.5-25mg q4-6 hours max 150mg/day
Acute urticaria

Management

- Steroids
  - Prednisone 30-60mg/day for 3-7 days
  - Children 0.5mg-1mg/kg/day for 3-7 days
- Consider epinephrine autoinjector (food, venom, angioedema)
Acute urticaria

Referral for:

- Food
- Venom
- Drugs (especially if common/frequently used)
- Resistant or severe symptoms/angioedema
- Symptoms >2-3 weeks
Case 2

- 31 year old female
- 10 week itchy raised lesions, generalized
- Angioedema of lip
- No constitutional symptoms
- No joint pain
- Past medical history: Hashimoto’s, vitiligo
Case 2

Questions

1. What are the causes of chronic urticaria and angioedema?
2. What investigations should be ordered?
3. How do we manage chronic urticaria and angioedema?
Chronic Urticaria/Angioedema
(Mast cell driven)

Cooper, KD. J. Am. Acad. Derm 1991; 25:166
Etiology

- Idiopathic or autoimmune
- Physical
- Hormonal
- Infections
  - Viral (Hep B, C, EBV, HIV)
  - Bacterial (H. pylori)
  - Parasitic
- Associated with other autoimmune disease
  - SLE, Stills, JRA, dermatomyositis, celiac
- Urticarial Vasculitis
- Neoplastic
  - Esp. hematologic, mastocytosis
- Hypereosinophilic Syndrome
- Cytopyrin associated periodic syndromes
Autoimmune Urticaria

- Patients with chronic urticaria have a higher incidence of antithyroid antibodies
  - Seen in 15% of patients

Leznoff and Sussman JACI 1989
Autologous serum skin test

- Significance of a negative ASST: essentially rules out autoimmune urticaria

- Significance of a positive ASST: indicates the presence of autoreactivity in the serum, but in-vitro confirmation is required before this can be identified as due to functional autoantibodies
Autoimmune urticaria
Physical Urticaria
Dermatographism
# Physical urticarias

<table>
<thead>
<tr>
<th>Urticaria</th>
<th>Precipitant</th>
<th>Time of onset</th>
<th>Duration</th>
<th>Local symptoms</th>
<th>Systemic symptoms</th>
<th>Tests</th>
<th>Mechanism</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic dermographism</td>
<td>Stroking skin</td>
<td>Minutes</td>
<td>2-3 hr</td>
<td>Irregular, pruritic wheals</td>
<td>None</td>
<td>Scratch skin</td>
<td>Passive transfer; IgE; histamine; possible role of adenosine triphosphate; substance P; possible direct pharmacologic mechanism</td>
<td>Continual hydroxyzine regimen or nonsedating antihistamines; combined H&lt;sub&gt;1&lt;/sub&gt; and H&lt;sub&gt;2&lt;/sub&gt; blockers</td>
</tr>
<tr>
<td>Delayed dermographism</td>
<td>Stroking skin</td>
<td>30 min-8 hr</td>
<td>≤48 hr</td>
<td>Irregular, pruritic wheals</td>
<td>None</td>
<td>Scratch skin; observe early and late</td>
<td>Unknown</td>
<td>Avoidance of precipitants</td>
</tr>
<tr>
<td>Pressure urticaria</td>
<td>Pressure</td>
<td>3-12 hr</td>
<td>8-24 hr</td>
<td>Diffuse, tender swelling</td>
<td>Flu-like symptoms</td>
<td>Apply weight</td>
<td>Unknown</td>
<td>Trial of antihistamines, middle- to low-dose glucocorticosteroids, dapsone</td>
</tr>
<tr>
<td>Solar urticaria</td>
<td>Various wave-lengths of light</td>
<td>2-5 min</td>
<td>15 min-3 hr</td>
<td>Pruritic wheals</td>
<td>Wheezing; dizziness; syncope</td>
<td>Phototest</td>
<td>Passive transfer; reverse passive transfer; IgE; possible histamine</td>
<td>Avoidance of precipitants; antihistamines; sunscreens, hydroxychloroquine</td>
</tr>
<tr>
<td>Familial cold urticaria</td>
<td>Change in skin temperature from cold air</td>
<td>30 min-3 hr</td>
<td>≤48 hr</td>
<td>burning wheals</td>
<td>Tremor; headache; arthralgia; fever</td>
<td>Expose skin to cold air</td>
<td>Unknown</td>
<td>Avoidance of precipitants</td>
</tr>
<tr>
<td>Essential acquired cold urticaria</td>
<td>Cold contact</td>
<td>2-5 min</td>
<td>1-2 hr</td>
<td>Pruritic wheals</td>
<td>Wheezing; syncope; drowning</td>
<td>Apply ice-filled copper beaker to arm; immerse arm in cold water</td>
<td>Passive transfer; reverse passive transfer; IgE (IgM); histamine; vasculitis can be induced</td>
<td>Cyproheptadine or other antihistamines; desensitization; avoidance of precipitants, oral doxycycline, or penicillin</td>
</tr>
</tbody>
</table>
## Physical urticarias

<table>
<thead>
<tr>
<th>Type</th>
<th>Cause/Description</th>
<th>Onset</th>
<th>Duration</th>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat urticaria</td>
<td>Heat contact</td>
<td>2-5 min (rarely delayed)</td>
<td>1 hr</td>
<td>Pruritic wheals</td>
<td>Apply hot water-filled cylinder to arm</td>
</tr>
<tr>
<td></td>
<td>Cholinergic urticaria</td>
<td>General overheating of body</td>
<td>2-20 min</td>
<td>Papular, pruritic wheals</td>
<td>Possible histamine, possible complement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 min - 1 hr</td>
<td></td>
<td>Syncope; diarrhea; vomiting; salivation; headaches</td>
<td>Bathe in hot water; exercise until perspiring; inject methacholine chloride</td>
</tr>
<tr>
<td>Aquagenic urticaria</td>
<td>Water contact</td>
<td>Several min - 30 min</td>
<td>30-45 min</td>
<td>Papular, pruritic wheals</td>
<td>Passive transfer; possible immunoglobulin; product of sweat gland stimulation; histamine; reduced protease inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None Reported</td>
<td>Apply water compresses to skin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Avoidance of precipitants; antihistamine; application of inert oil</td>
</tr>
<tr>
<td>Vibratory angioedema</td>
<td>Vibrating against skin</td>
<td>2-5 min</td>
<td>1 hr</td>
<td>Angioedema</td>
<td>Apply body or vibrating mixer to forearm</td>
</tr>
<tr>
<td>Exercise induced anaphylaxis</td>
<td>Exercise; some cases of ingestion of certain foods</td>
<td>During or after exercise</td>
<td>Minutes to hours</td>
<td>Pruritic wheals</td>
<td>Exercise testing; immersion tests</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Respiratory distress; hypotension</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

From: **Cancer Risk in Patients With Chronic Urticaria: A Population-Based Cohort Study**


### Table 3. Standardized Incidence Ratios (SIRs) of Hematologic Cancers in Chronic Urticaria

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Observed</th>
<th>Expected</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. with cancer</td>
<td>58</td>
<td>14&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.1 (3.1-5.4)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37</td>
<td>9</td>
<td>4.1 (2.9-5.7)</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
<td>5</td>
<td>4.2 (2.6-6.4)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>7</td>
<td>1</td>
<td>7.0 (2.8-14.4)</td>
</tr>
<tr>
<td>20-39</td>
<td>6</td>
<td>1</td>
<td>6.0 (2.2-13.1)</td>
</tr>
<tr>
<td>40-59</td>
<td>12</td>
<td>2</td>
<td>6.0 (3.1-10.5)</td>
</tr>
<tr>
<td>60-79</td>
<td>30</td>
<td>8</td>
<td>3.8 (2.5-5.4)</td>
</tr>
<tr>
<td>≥80</td>
<td>3</td>
<td>2</td>
<td>1.5 (0.3-4.4)</td>
</tr>
<tr>
<td>Time from diagnosis to detection, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>33</td>
<td>2</td>
<td>16.5 (11.4-23.2)</td>
</tr>
<tr>
<td>1-&lt;2</td>
<td>4</td>
<td>2</td>
<td>2.0 (0.5-5.1)</td>
</tr>
<tr>
<td>2-&lt;4</td>
<td>10</td>
<td>4</td>
<td>2.5 (1.2-4.6)</td>
</tr>
<tr>
<td>4-&lt;6</td>
<td>11</td>
<td>3</td>
<td>3.7 (1.8-6.6)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Based on the 2003 Cancer Registry Report of Taiwan.

<sup>b</sup>The sum may not equal to the overall expected number because of the different observation times in each stratification.
<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Observed</th>
<th>Expected</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>646</td>
<td>310(^b)</td>
<td>2.1 (1.9-2.3)</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>49</td>
<td>24</td>
<td>2.0 (1.5-2.7)</td>
</tr>
<tr>
<td>Tongue, gingiva</td>
<td>25</td>
<td>11</td>
<td>2.3 (1.5-3.4)</td>
</tr>
<tr>
<td>Oropharynx, hypopharynx, and others</td>
<td>8</td>
<td>4</td>
<td>2.0 (0.9-3.9)</td>
</tr>
<tr>
<td>Larynx</td>
<td>4</td>
<td>3</td>
<td>1.3 (0.4-3.4)</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>10</td>
<td>5</td>
<td>2.0 (1.0-3.7)</td>
</tr>
<tr>
<td>Nose, sinus, and ear</td>
<td>2</td>
<td>1</td>
<td>2.0 (0.2-7.2)</td>
</tr>
<tr>
<td>Hepatogastroenterologic system</td>
<td>303</td>
<td>135</td>
<td>2.2 (2.0-2.5)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>19</td>
<td>7</td>
<td>2.7 (1.6-4.2)</td>
</tr>
<tr>
<td>Stomach</td>
<td>42</td>
<td>20</td>
<td>2.1 (1.5-2.8)</td>
</tr>
<tr>
<td>Small intestine</td>
<td>1</td>
<td>2</td>
<td>0.5 (0.0-2.8)</td>
</tr>
<tr>
<td>Colonrectum, cecum, and anus</td>
<td>78</td>
<td>46</td>
<td>1.7 (1.3-2.1)</td>
</tr>
<tr>
<td>Liver and gallbladder</td>
<td>146</td>
<td>53</td>
<td>2.8 (2.3-3.2)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>12</td>
<td>7</td>
<td>1.7 (0.9-3.0)</td>
</tr>
<tr>
<td>Retroperitoneum and others</td>
<td>5</td>
<td>1</td>
<td>5.0 (1.6-11.7)</td>
</tr>
<tr>
<td>Lungs and mediastinum</td>
<td>105</td>
<td>46</td>
<td>2.3 (1.9-2.8)</td>
</tr>
<tr>
<td>Lungs and trachea</td>
<td>102</td>
<td>45</td>
<td>2.3 (1.8-2.8)</td>
</tr>
<tr>
<td>Mediastinum including heart, thymus</td>
<td>3</td>
<td>1</td>
<td>3.0 (0.6-8.8)</td>
</tr>
<tr>
<td>Skin</td>
<td>14</td>
<td>10</td>
<td>1.4 (0.8-2.3)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1</td>
<td>1</td>
<td>1.0 (0.0-5.5)</td>
</tr>
<tr>
<td>Nonmelanoma</td>
<td>13</td>
<td>9</td>
<td>1.4 (0.8-2.5)</td>
</tr>
<tr>
<td>Female genitalia</td>
<td>33</td>
<td>16</td>
<td>2.2 (1.5-3.1)</td>
</tr>
<tr>
<td>Uterus</td>
<td>5</td>
<td>3</td>
<td>1.7 (0.5-3.9)</td>
</tr>
<tr>
<td>Cervix including ovary</td>
<td>24</td>
<td>12</td>
<td>2.0 (1.3-3.0)</td>
</tr>
<tr>
<td>Vulva, placenta, and others</td>
<td>4</td>
<td>1</td>
<td>4.0 (1.1-10.2)</td>
</tr>
<tr>
<td>Female breast</td>
<td>32</td>
<td>19</td>
<td>1.7 (1.2-2.4)</td>
</tr>
<tr>
<td>Male genitalia</td>
<td>29</td>
<td>17</td>
<td>1.7 (1.1-2.4)</td>
</tr>
<tr>
<td>Prostate</td>
<td>26</td>
<td>16</td>
<td>1.6 (1.1-2.4)</td>
</tr>
<tr>
<td>Testis, penis, and others</td>
<td>3</td>
<td>1</td>
<td>3.0 (0.6-8.8)</td>
</tr>
<tr>
<td>Genitourinary system</td>
<td>45</td>
<td>20</td>
<td>2.3 (1.6-3.0)</td>
</tr>
<tr>
<td>Bladder</td>
<td>15</td>
<td>11</td>
<td>1.4 (0.8-2.2)</td>
</tr>
<tr>
<td>Kidney, urinary system, and others</td>
<td>30</td>
<td>9</td>
<td>3.3 (2.2-4.8)</td>
</tr>
<tr>
<td>Others</td>
<td>28</td>
<td>8</td>
<td>3.1 (2.1-4.5)</td>
</tr>
<tr>
<td>Brain</td>
<td>10</td>
<td>2</td>
<td>5.0 (2.4-9.2)</td>
</tr>
<tr>
<td>Other neural systems</td>
<td>1</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Bone, joint, and soft tissue</td>
<td>4</td>
<td>2</td>
<td>2.0 (0.5-5.1)</td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>11</td>
<td>4</td>
<td>2.6 (1.4-4.9)</td>
</tr>
<tr>
<td>Endocrine system other than thyroid</td>
<td>2</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Ill-defined sites</td>
<td>2</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Unknown origin</td>
<td>6</td>
<td>6</td>
<td>1.0 (0.4-2.2)</td>
</tr>
</tbody>
</table>

\(^a\) Based on the 2003 Cancer Registry Report of Taiwan. All data were rounded to a whole number.

\(^b\) The sum may not equal to the overall expected number because of the different cancer registration systems in different regions.
Concerning presenting features

- Recurrent fever
- Constitutional symptoms
- Joint involvement
- Family History
- Poor response to antihistamines
Investigations

- Through history and physical exam
- No consensus on which tests should be routinely performed
- Suggestion:
  - CBC
  - CRP/ESR
  - TSH
  - U/A
Investigations

- Complement system: e.g. C3, C4, and CH$_{50}$
- Thyroid antibodies
- LFTS
- Antinuclear antibody (ANA)
- Stool analysis for ova and parasites
- Rheumatoid factor
- Hepatitis B and C workup
- Cryoglobulin levels
- Anti-TTG Ab
- Serum protein electrophoresis
- Urinalysis
- H. pylori workup (limited experimental evidence to recommend this)
- Chest radiograph and/or other imaging studies
- Skin biopsy
- Physical challenge testing
## Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Quality of Evidence</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-generation antihistamines (at licensed doses)</td>
<td>High</td>
<td>Strong (+)</td>
</tr>
<tr>
<td>First-generation antihistamines</td>
<td>High</td>
<td>Strong (−)</td>
</tr>
<tr>
<td>Second-generation antihistamines (at higher than licensed doses)</td>
<td>Moderate</td>
<td>Weak (+)</td>
</tr>
<tr>
<td>Anti-H2-antihistamines as add-on therapy</td>
<td>Moderate</td>
<td>Weak (+)</td>
</tr>
<tr>
<td>Oral corticosteroids (short course)</td>
<td>Low</td>
<td>Weak (+)</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>Very low</td>
<td>Strong (−)</td>
</tr>
<tr>
<td>Leukotriene receptor antagonists (as add-on therapy)</td>
<td>Low</td>
<td>Weak (+)</td>
</tr>
<tr>
<td>Anti-inflammatory agents (dapsone, sulfasalazine, hydroxychloroquine, colchicines, mycophenolate mofetil)</td>
<td>Low-very low</td>
<td>Weak (+)</td>
</tr>
<tr>
<td>Immunosuppressive agents</td>
<td>Moderate</td>
<td>Weak (+)*</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Very low</td>
<td>Weak (+)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Very low</td>
<td>Weak (+)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Very low</td>
<td>Weak (+)</td>
</tr>
<tr>
<td>Biologic agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Moderate</td>
<td>Weak (+)*</td>
</tr>
<tr>
<td>IVIG</td>
<td>Low</td>
<td>Weak (+)</td>
</tr>
</tbody>
</table>

(+) recommendation for medication; (−), recommendation against medication.

*Although the recommendation is “weak” according to the GRADE approach, it is stronger than in other cases based on the quality of existing evidence.
Treatment

- Step 1
  - Monotherapy with second generation antihistamine
    - Cetirizine, fexofenadine, loratidine, desloratidine
  - Avoidance of triggers (NSAIDS, physical stimuli)

Bernstein JACI 2014
Comparative Efficacy of H1 Antihistamines

- Cetirizine versus loratidine$^1$
  - Loratidine greater improvement in symptom scores, but similar rates of resolution
- Cetirizine versus fexofenadine$^2$
  - Cetirizine superior
- Levocetirizine versus desloratidine$^3$
  - Levocetirizine superior

2. Handa J Dermatolog Treat 2004
3. Staevska JACI 2010
Treatment

- Step 2
  - Dose advancement¹ of 2nd generation antihistamine used in Step 1
    - Cetirizine 20mg
    - Desloratidine 20mg
    - Fexofendine 240mg bid
    - Loratidine 10 mg
  - Add another 2nd generation antihistamine
  - Add LRTA
  - Add 1st generation antihistamine at bedtime
  - Add H2 antagonist

Kavosh Am J Clin Derm 2011
Treatment

- **Step 3**
  - Dose advancement of potent antihistamine
    - Hydroxyzine 10-25mg daily max 50 mg qid
    - Doxepin 10mg daily max 150 mg daily
Treatment

Step 4

- Omalizumab or cyclosporine
- Other anti-inflammatory agents
Omalizumab

- Recombinant humanized IgG1 monoclonal antibody against IgE
- Prevents binding of IgE to IgE receptors on mast cells, basophils and dendritic cells
- Used to treat severe and inadequately controlled asthma in adults and children with relevant allergies
Omalizumab
Treatment

- Epinephrine
  - Not generally needed, patients with CU don’t develop laryngeal swelling
Case 2

- Patient remains convinced that her symptoms related to foods or additives.
  - Is there any evidence that diet can help?
  - Is there any evidence that food additives contribute to CU?
Pseudoallergens

Box 1 Explicitly prohibited foodstuffs

Chewing gum, candy, and similar products
Spices and herbs (except salt and chives)
Additives: E100-E1518, preservatives or artificial colors, gelling agents, thickening matter, humectants, emulsifiers, flavor potentiators, antioxidants, separating agents, sweeteners, baking agents, modified starches, foaming agents, stabilizers, flavoring agents
Breads with additional grains, herbs, or other such added ingredients
Packaged bread is preferable to bakery bread, because the ingredients are on the label
Alcohol
Sesame
Pasta with eggs, cake, biscuits, potato chips
Margarine and mayonnaise
Eggs
Smoked meats
Seafood
Tomatoes, artichokes, peas, mushrooms, spinach, rhubarb, olives
sweet peppers
Fruit, dried fruits, and fruit juices
Herbal tea
Any substitutions not listed as acceptable in the clinical diary's guidelines
Any substance that the patient remains unsure if it is allowed or not
Use only fresh foods; no preserved foods, except deep-frozen foods without any additives
Food additives and CU

- 100 patients with active CU
- Single blinded challenge with 11 additives most commonly associated
- Doses based on max amount/24 hours
- Simultaneously gave all 11 additives in 15 capsules

Rajan JACI In Practice 2014
**Food additives and CU**

<table>
<thead>
<tr>
<th>Additives tested</th>
<th>Doses (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FD&amp;C yellow 5</td>
<td>50</td>
</tr>
<tr>
<td>FD&amp;C yellow 6</td>
<td>50</td>
</tr>
<tr>
<td>K+ metabisulfite</td>
<td>100</td>
</tr>
<tr>
<td>MSG</td>
<td>2500</td>
</tr>
<tr>
<td>Aspartame</td>
<td>150</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>100</td>
</tr>
<tr>
<td>Methyl paraben</td>
<td>100</td>
</tr>
<tr>
<td>Butylated hydroxyanisole</td>
<td>250</td>
</tr>
<tr>
<td>Butylated hydroxytoluene</td>
<td>250</td>
</tr>
<tr>
<td>Sodium nitrate</td>
<td>50</td>
</tr>
<tr>
<td>Sodium nitrite</td>
<td>50</td>
</tr>
</tbody>
</table>
Food additives and CU

- **Results**
  - Only 2 patients had increased urticaria during single blind challenge
  - These 2 patients rechallenged double blinded and had no reactions

- **Conclusion**
  - Food additive avoidance not recommended
  - Do single and double blinded challenges if suspicious
Prognosis

- 139 patients with CU followed prospectively over 5 years
- Only 14% symptomatic at 5 years
- Longer duration associated with
  - + ASST
  - Severe symptoms
  - ATA
  - Angioedema
Prognosis

Table I. Autoimmune diseases in patients with CU and control subjects

<table>
<thead>
<tr>
<th>Disease</th>
<th>Total population (n = 12,778 patients with CU and 10,714 control subjects)</th>
<th>Female subjects (n = 8,472 patients with CU and 9,188 control subjects)</th>
<th>Male subjects (n = 4,306 patients with CU and 1,526 control subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P value</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>17.338</td>
<td>13.51-22.2</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>28.81</td>
<td>15.40-54.25</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>RA</td>
<td>13.25</td>
<td>7.39-23.76</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Type I diabetes mellitus</td>
<td>7.703</td>
<td>4.78-12.65</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>15.17</td>
<td>5.54-14.54</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>26.96</td>
<td>6.6-110.17</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>SLE</td>
<td>14.59</td>
<td>4.56-46.73</td>
<td>&lt;.0005</td>
</tr>
</tbody>
</table>

Confino Cohen JACI 2012
Case 3

- 56 year old male presents with intermittent swelling of top or bottom lip
- Has had swelling of left side of tongue
- Swelling lasts up to 1 day
- No urticaria
- Tried cetirizine 20mg and wasn’t sure if effective
- WIC tried epinephrine and it took 6 hours before swelling came down
Case 3

- No family history of angioedema
- No obvious triggers
- Hypertensive
  - Meds ramipril and ASA both taken for 3 years
Case 3

1. What is the cause of his angioedema?
2. Why was there minimal or no response to cetirizine and epinephrine?
3. How should this patient be managed?
Angioedema

- **Histamine mediated**
  - Responds to antihistamine, steroids, epinephrine

- **Bradykinin mediated**
  - Poor to no response to antihistamine, steroids, epinephrine
  - More prolonged time course lasting up to 2-4 days
  - Never associated with urticaria
ACEI Angioedema

- Angioedema only; no urticaria
- Incidence 0.30%\(^1\)
  - 5X increase in African-Americans\(^2\)
- Most common cause of acute angioedema
- Up to 20% life threatening\(^3\)

1. Makani Am J Cardio 2012
2. Brown Clin Pharm Ther 1996
ACEI Angioedema

- Tends to involve face
- Usually starts within 3 months of treatment\(^1\)
  - may present years later\(^2\)
- Bradykinin mediated
  - Poor response to antihistamines, steroids, epinephrine

1. Toh Arch Inter Med 2012
ACEI Angioedema

Treatment

- Removal of ACEI - 88% of patients will still have symptoms within 1st month\(^1\)
- Admission to hospital
- ARB up to 1.5-10% risk of angioedema\(^2,3\) (patients who have had ACEI angioedema)
  - Don’t start least 4 weeks after discontinuing ACEI
- Avoid renin inhibitors (Rasilez)
- Consider Referral
  - C4 levels and C1INH measurement recommended

1. Beltrami J Hypertens 2011
Case 4

- 24 year female
- History of severe AD, currently controlled
- History mild asthma
- 1 year history of typical urticaria starting 1 week prior to periods and ends 1-2 days after menstrual flow
- ?diagnosis
Autoimmune Progesterone Dermatitis
Autoimmune Progesterone Dermatitis

- Very rare – cyclical eruptions 3-10 days prior to menstruation
- Stops within 2 days of flow
- Intradermal testing with progesterone positive
- Intramuscular challenge with progesterone positive
Take home messages

- **Urticaria**
  - Transient <24 hours, no pain, blanching, no scarring or hyperpigmentation

- **Angioedema**
  - Transient up to 2-4 days
  - Response to therapy differentiates histamine vs bradykinin mediated
    - Bradykinin mediated angioedema – always no urticaria
Take home messages

- **Acute urticaria/angioedema < 6 weeks**
  - History is critical in establishing cause
  - Most allergic reactions occur within 2 hours of exposure and are short lived

- **Chronic urticaria/angioedema >6 weeks**
  - Mostly idiopathic or autoimmune
  - Physical urticaria
  - CBC, TSH, ESR/CRP and U/A as initial investigations
Questions?