Urticaria: Diagnostic and Treatment Considerations

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Associate Professor of Dermatology
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Director of Translational Research
• Consulting/Ad board: Sanova works, Oakstone institute, Exeltis, Glossier, L'oreal, La Roche Posay, Galderma, Amgen, Aveeno, Valeant, Microcures, Nano Bio-Med, Biogen, Pfizer, Nerium, G&W Laboratories, Novartis, Oculus, Intraderm, Encore, Ferndale

• Speaker: Amgen, Valeant

• Grants: Valeant
• Affects 20% of population
• Occurs across the age spectrum
• Sometimes possible to identify a trigger such as food, drug, insect sting or infection
• More than 2/3 of cases are self-limiting
Chronic urticaria: an orphan disease for 125 years
Characteristics: The Basics

- **Pruritic**
  - Burning
- **Erythematous**
  - Often exhibit central pallor
- **Oval, round or irregular shape or plaques**
- **Plaques “move” to different locations over minutes to hours**
  - < 24 hours
- **Typically leaves no PIPA/scarring**
  - Other than from scratching
• Reaction mediated by activated mast cells and basophils in superficial dermis
  – When activated release histamine --> vasodilators

Histamine and Pruritus: A Simple Relationship

- Histamine receptors located on C-fiber neurons
- Histamine binding triggers an itch impulse
A bit more complicated...

ITAM: immunotyrosine activation motif
PKC: protein kinase C
GTP: guanosine triphosphate
MAC: membrane attack complex
Lyn, Syk: cytoplasmic tyrosine kinase

Extrinsic pathway of coagulation

smhs.gwu.edu
KERATINOCYTES AS ITCH RECEPTORS & NEUROTTRANSMITTERS

Acetyl choline
- Cell proliferation

Muscarinic

Nicotinic

Cell Differentiation

Exit

Ca++

Enter

EP1-4 receptor

Opioid receptor (MOR1)
(identical to the brain r)

Endorphins production

Histamine

Naltrexone inhibits

R- Neurotrophins
- NGF
- Tyrosine kinase
  - High affinity

Propio Melanocortine receptor
- Adrenocorticotropic hormone
- Melanostimulant hormone
- Endorphins
- Morphine
- Codeine
- Cannabinoids

So where are we?
Many mimics
Patients call everything “hives”
Diagnosis and Work up of Urticaria
Differential Diagnosis

- Insect Bites (papular urticaria)
- Atopic dermatitis
- Erythema multiforme
- Bullous pemphigoid
- Urticaria pigmentosa
- Vasculitis
- SLE
- Morbilliform drug eruptions
- PUPPP

- Erysipelas
- Cellulitis
- Contact dermatitis
- Dermatitis herpetiformis
- Photodermatitis
- Familial cold autoinflammatory syndrome
Pruritus: Itch without Rash

- Xerosis
- Uremia
- Cholestasis
- Malignancy
- Non-Hodgkins Lymphoma
- Polycythemia vera
- Thyrotoxicosis
- Multiple sclerosis (dysesthesias)
- Iron Deficiency Anemia
- Diabetes (autonomic dysfunction)
- Medications
- Psychiatric illness
Classification

• Acute versus Chronic Urticaria
  – Acute episodes < 6 weeks
    • More likely to have an identifiable trigger
  – Chronic episodes last > 6 weeks
    • “Chronic spontaneous vs inducible”
    • Less likely to have an identifiable trigger
      – ~70% cases have unknown etiology
      – Longer duration = lower chance of identifying cause

Ann Allergy 1965; 23:30
The Updated European Classification

Acute Urticaria: Common Causes

- Overall, identify cause in acute urticaria 20% - 90% cases
- Acute Urticaria - “infection, medication, food”
  - Foods/food products most commonly milk, egg, peanut, wheat and soy in kids
    - Tree nuts, peanuts and shellfish in adults
    - Yellow food dye annatto
    - Red food dye carmine
    - Contact with raw fruits or vegetables, animal saliva, certain detergents or perfumes
Common Causes (cont)

- Viral or bacterial infection especially in children
  - Mycoplasma
  - Adenovirus, enterovirus, rotavirus, respiratory syncytial virus, Epstein-Barr virus and CMV
- Parasitic infections
  - Blastocystis hominis, Plasmodium falciparum and Anisakis simplex
- Medications (especially antibiotics)
- Stinging insects
  - Bees, wasps, hornets, imported fire ants
- Latex products
  - Cross reacts with passion fruit, banana, avocado, chestnut, kiwi
And yes....

Urticaria After Ingestion of Alcoholic Beverages

F Ribeiro, N Sousa, I Carrapatoso, A Segorbe Luís

Immuoallergology Department, Coimbra University Hospital, Coimbra, Portugal
Non-immunologic, Direct Mast Cell Activation

- “PROMS”
  - Polymyxin B
  - Radiocontrast media
  - Opiates
    - Codeine, morphine, meperidine
  - Muscle relaxants
  - Salicylates
- Other
  - **NSAIDS** (kids)
  - Vancomycin (remember “Red Man Syndrome”)
  - Dextran (in IVs and eye drops)
  - Neuromuscular blocking agents (D-tubocurarine)
  - Stinging nettle
  - Sympathomimetics (amphetamine, ephedrine, phenylephrine)
  - Tomatoes and strawberries
Contact Urticaria

- 30-60 mins after exposure
- Nonimmunologic
  - MC, no prior sensitization
    - Plants/nettles, animals/caterpillars, jellyfish, meds/DMSO, bacitracin
    - Others cobalt, chloride, benzoic acid, cinnamic aldehyde, cinnamic acid and sorbic acid
- Immunologic - IgE mediated rxn
  - Latex rubber, bacitracin, potato, apple, henna
- Dx: good hx, contactant test, prick test for food, RAST for immunologic contact urticaria
Chronic Urticaria: Physical aka Inducible Urticarias

- Reproducible by environmental factors
  - Physical stimuli
- Subtype of Chronic Urticaria: 20-30%
- Most frequently in young adults
- **DISTINGUISHING FEATURE** Attacks are brief, lasting only 30-60 mins versus few hours to days for typical urticaria
  - Exception=pressure urticaria, swelling lasts hours
- Episodic and often limited to areas of inciting stimulus
- Unresponsive to corticosteroids
- Less likely to spontaneously resolved
Examples of Physical Urticaria

- Dermatographism*
- Cholinergic
- Heat
- Exercise-induced
- Cold
- Aquagenic
- Solar Urticaria
- Vibratory
# Features of Physical Urticaria

<table>
<thead>
<tr>
<th>Type</th>
<th>Age (yrs)</th>
<th>Clinical Features</th>
<th>Angioedema</th>
<th>Diagnostic Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatographism</td>
<td>20-50</td>
<td>Linear lesions</td>
<td>No</td>
<td>Light stroking of skin; + transfer factor</td>
</tr>
<tr>
<td>Cold (primary vs. secondary)</td>
<td>10-40</td>
<td>Itchy, pale lesions (5% with cryos)</td>
<td>Yes</td>
<td>5-10 minute ice-cube test; + transfer factor</td>
</tr>
<tr>
<td>Cholinergic (heat bumps)</td>
<td>10-50</td>
<td>Itchy, monomorphic pale or pink lesions</td>
<td>Yes</td>
<td>Exercise or hot shower; + transfer factor</td>
</tr>
<tr>
<td>Pressure</td>
<td>20-50</td>
<td>Large painful or itchy lesions</td>
<td>No</td>
<td>Dermographometer; application of pressure to skin</td>
</tr>
<tr>
<td>Solar</td>
<td>20-50</td>
<td>Itchy pale or red swelling</td>
<td>Yes</td>
<td>Irradiation by a solar simulator; + transfer factor</td>
</tr>
</tbody>
</table>
Dermatographism Misnomers

• “Red Dermographism”
  – Response to *rubbing*, not stroking, the skin
• “White Dermographism”
  – Blanching response seen in patients with atopic dermatitis
  – Not a form of urticaria
• “Black Dermographism”
  – Black line associated with metal contact
• Chronic Urticaria:
  – 50% are free of lesions within 1 year
  – 20% continue to experience episodes for more than 10 years (not necessarily continuous)
The natural history of chronic urticaria in childhood: A prospective study

- 92 children 4 to 15 years of age with CU
  - Median duration of 4.3 years (range 2.5-5.8 years).
  - Remission rates at 1, 3, and 5 years after the onset of CU symptoms were 18.5%, 54%, and 67.7%
A Cohort Study of the Relationship Between Anger and Chronic Spontaneous Urticaria

Table 1 The results of one way variance analysis for between group differences with regards to obtained variables

<table>
<thead>
<tr>
<th>Values</th>
<th>$df$</th>
<th>$F$</th>
<th>$p$</th>
<th>Post hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>HADS depression</td>
<td>(2.96)</td>
<td>6.372</td>
<td>0.003</td>
<td>CSU &gt; healthy ($p = 0.007$) AA &gt; healthy ($p = 0.011$)</td>
</tr>
<tr>
<td>HADS anxiety</td>
<td>(2.96)</td>
<td>8.673</td>
<td>0.000</td>
<td>CSU &gt; healthy ($p = 0.005$) AA &gt; healthy ($p = 0.001$)</td>
</tr>
<tr>
<td>Multidimension of anger</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Anger symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger symptoms</td>
<td>(2.96)</td>
<td>14.923</td>
<td>0.000</td>
<td>CSU &gt; healthy ($p = 0.000$) AA &gt; healthy ($p = 0.005$)</td>
</tr>
<tr>
<td>2. Anger related behaviors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggressive</td>
<td>(2.94)</td>
<td>4.251</td>
<td>0.017</td>
<td>–</td>
</tr>
<tr>
<td>Calm</td>
<td>(2.94)</td>
<td>2.144</td>
<td>0.123</td>
<td>–</td>
</tr>
<tr>
<td>Anxious</td>
<td>(2.94)</td>
<td>11.273</td>
<td>0.000</td>
<td>CSU &gt; AA ($p = 0.029$) CSU &gt; healthy ($p = 0.000$)</td>
</tr>
</tbody>
</table>

21 OF 30 WERE MARRIED
History and Physical Examination

1. Onset (e.g. timing of symptoms with any change in medication or other exposures).
2. Frequency, duration, severity, and localization of wheals and itching.
3. Dependence of symptoms on the time of day, day of the week, season, menstrual cycle, or other pattern.
4. Known precipitating factors of urticaria (e.g. physical stimuli, exertion, stress, food, medications).
5. Relation of Urticaria to occupation and leisure activities.
6. Associated angioedema, systemic manifestations (headache, joint pain, gastrointestinal symptoms, etc.).
7. Known allergies, intolerances, infections, systemic illnesses or other possible causes.
8. Family history of urticaria and atopy.
11. General physical examination.
Urticaria Diagnostic Evaluation

• History & Physical Exam Short Cut
  – Diary*
    • Any unusual exposures immediately prior to the episode
  – Does the patient have pictures?
    • Iphone, galaxy, etc
  – Family hx
    • HLA-DR4, HLA-DRB4 53, HLA-DQ8
  – Provocative tests for physical causes
## Provocative Testing

<table>
<thead>
<tr>
<th>Physical Urticaria</th>
<th>Testing Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold</td>
<td>Ice cube test</td>
</tr>
<tr>
<td>Localized heat</td>
<td>Test tube of water at 44°C</td>
</tr>
<tr>
<td>Cholinergic</td>
<td>Exercise for 15-20 min or leg immersion in 44°C bath</td>
</tr>
<tr>
<td><strong>Delayed pressure</strong></td>
<td>Sand bag test: 15 lb weight for 15 min</td>
</tr>
<tr>
<td>Dermatographism</td>
<td>Stroking the skin firmly</td>
</tr>
<tr>
<td>Solar</td>
<td>Specific wavelength of light exposure</td>
</tr>
<tr>
<td>Aquagenic</td>
<td>Water compress</td>
</tr>
<tr>
<td>Vibratory</td>
<td>Vortex for 4 min</td>
</tr>
</tbody>
</table>
Laboratory tests:
  - No routine labs
    - ** New European guidelines for chronic spontaneous urticaria: ESR/CRP and blood differential
    - Other potential labs: LFTs, HepB, ANA, Stool, U/A, Thyroid function, anti-thyroid antibodies
  - Complements (if + angioedema)
    - Screen with C3 and C4 levels → C4 low, C3 normal in angioedema
    - C1q level low in acquired, but normal in hereditary
  - Skin tests
    - Allergy testing if specific trigger can be implicated
Laboratory Diagnosis of Chronic Urticaria

Basic screening tests
- CBC/D
- CMP
- ESR
- UA
- Thyroid function tests (TFTs) - TSH, T4, and thyroid autoantibodies (antimicrosomal and antithyroglobulin antibody)
- H. pylori IgG

Comprehensive workup
- Total IgE
- Anti-FcεRI antibody (or Chronic urticaria index)
- Skin prick test and/or serum IgEs (low yield)
- ANA
- RF
- Vitamin D 25 (OH)

In specific situations:
- Hepatitis B and C workup (if LFTs elevation)
- Cryoglobulin (if cold urticaria)
- Stool analysis for ova and parasites (O&P)
- Tryptase, if anaphylaxis
- Skin biopsy

If angioedema with or without urticaria, consider the following:
- C4, C3 levels
- C1-esterase inhibitor - qualitative and quantitative
- CH50 (total hemolytic complement)
- C1q

Patients with HAE do not usually have urticaria
Chronic urticaria as a systemic disease

Razvigor Darlenzki, MD, PhD\textsuperscript{a,\text独具}, Jana Kazandjieva, MD\textsuperscript{b}, Torsten Zuberbier, MD\textsuperscript{c}, Nikolai Tsankov, MD, PhD, MSc\textsuperscript{a}

- Assoc w/:
  - Autoimmune diseases
  - Atopy
  - Infections
  - Metabolic conditions
  - Neoplastic disorders
• Skin biopsy?
  – Generally, not helpful

• Indications:
  – Lesions lasting more than 24 to 48 hours
  – Atypical?
  – Scarring
  – Purpura
  – Suspicion of Urticaria pigmentosa
  – Refractoriness to therapy
Therapeutic Approach: An Overview

- **Avoiding triggers**
  - Known antigens
  - Potentiating factors
    - Alcohol, narcotics, non-steroidal anti-inflammatory drugs/asa, "pseudoallergens"
    - Loose fitting clothing, temperature control, photoprotection
  - Underlying conditions: *Thyroid, H.pylori, dental abscess*

- **Inhibiting mast cell mediators/release**
  - H1 antihistamines
    - Prefer 2nd gen, non-sedating, long-acting antihistamines
  - Combination of therapies

- **Treating the inflammatory response**
  - Ex: *Omalizumab*, cyclosporin, dapsone, methotrexate, colchicine, mycophenolate mofetil, hydroxychloroquine
Table I. Key concepts in urticaria management in children

- Avoidance/elimination of underlying causes and/or eliciting triggers is important.
- Second-generation H1-antihistamines are the mainstay of pharmacological treatment aimed at providing symptom relief. Up-dosing has not been validated in children. First-generation H1-antihistamines should be avoided, mostly due to relevant side-effects.
- Difficult cases may require other therapeutic interventions, the risk–benefit ratio being carefully analysed as there is hardly any evidence supporting it in children.
- Corticosteroids should be avoided whenever possible and strictly used for short periods only (3–7 days), given the unacceptable side-effects from long-term use.
1st Line: H1 Antihistamines

- H1 antihistamines
  - First generation:
    - Diphenhydramine, Chlorpheniramine, Hydroxyzine
      - **Hydroxyzine only one specifically contraindicated in pregnancy**
        » PEDS considerations
  - **Second generation** (non-sedating):
    - Cetirizine, Loratadine
  - Second generation derivatives:
    - Desloratadine, Levocetirizine, Fexofenadine
- Go with non-sedating
  - NO Cetirizine and Levocetirizine in severe renal impairment (CC <10ml/min)
    • Loratadine and Desloratadine with caution
### GO UP TO 4-FOLD DOSE

H1 Antihistamines in Peds

#### Table III. Oral second-generation H1-antihistamines licensed for paediatric use (alphabetical order)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Drug</th>
<th>Form</th>
<th>Daily dose for children</th>
<th>Daily dose for adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilastine\textsuperscript{b}</td>
<td>T</td>
<td>≥12 years: 20 mg once a day</td>
<td>20 mg once a day</td>
</tr>
<tr>
<td>Cetirizine\textsuperscript{c}</td>
<td>S, T</td>
<td>2–5 year: 2.5 mg twice a day</td>
<td>10 mg once a day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–11 years: 5 mg twice a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥12 years: 10 mg once a day</td>
<td></td>
</tr>
<tr>
<td>Desloratadine\textsuperscript{c}</td>
<td>S, LYO, T</td>
<td>1–5 years: 1.25 mg once a day</td>
<td>5 mg once a day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–11 years: 2.5 mg once a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥12 years: 5 mg once a day</td>
<td></td>
</tr>
<tr>
<td>Ebastine</td>
<td>S, LYO, T</td>
<td>2–5 years: 2.5 mg once a day</td>
<td>10 mg once a day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–11 years: 5 mg once a day</td>
<td>20 mg once a day</td>
</tr>
<tr>
<td>Fexofenadine\textsuperscript{c}</td>
<td>T</td>
<td>6–11 years: 30 mg twice a day\textsuperscript{d}</td>
<td>120 mg\textsuperscript{d} or 180 mg once a day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥12 years: 120 mg\textsuperscript{e} or 180 mg once a day</td>
<td></td>
</tr>
<tr>
<td>Levocetirizine\textsuperscript{c}</td>
<td>S, T</td>
<td>2–5 years: 1.25 mg twice a day\textsuperscript{d}</td>
<td>5 mg once a day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥6 years: 5 mg once a day</td>
<td></td>
</tr>
<tr>
<td>Loratadine</td>
<td>S, T</td>
<td>2–11 years: 5 mg once a day</td>
<td>10 mg once a day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥12 years: 10 mg once a day</td>
<td></td>
</tr>
<tr>
<td>Mizolastine</td>
<td>T</td>
<td>≥12 years: 10 mg once a day</td>
<td>10 mg once a day</td>
</tr>
<tr>
<td>Rupatadine\textsuperscript{b}</td>
<td>T</td>
<td>≥12 years: 10 mg once a day</td>
<td>10 mg once a day</td>
</tr>
</tbody>
</table>

\textsuperscript{a} This table provides the oral second-generation H1-antihistamines licensed for pediatric use (alphabetical order).

\textsuperscript{b} Bilastine is available in a 20 mg film-coated tablet.

\textsuperscript{c} Cetirizine, Desloratadine, Ebastine, Levocetirizine, and Rupatadine are available in syrup (S), liquid oral extension (LYO), and tablet (T) forms.

\textsuperscript{d} Maximum daily dose: 20 mg for children and 60 mg for adults.

\textsuperscript{e} Maximum daily dose: 60 mg for children and 120 mg for adults.

\textsuperscript{f} Maximum daily dose: 120 mg for children and 180 mg for adults.

Acta Derm Venereol 2013; 93: 500-508
At standard doses, several antihistamines are effective and safe in complete suppression of chronic spontaneous urticaria. Research on long-term treatment using standardized outcome measures and quality of life scores is needed."
• No H₁ antihistamines are class A
  – Loratidine and cetirizine are B
  – Diphenhydramine long track record of safety
• Tx for nausea!
• Current data indicates that administration during lactation has no detrimental effect on breast-fed infant
H2 Histamine Antagonists

- Basophils have H2 receptors that mediate histamine release.
- Safe toxicity profile
  - Paucity of clinical data
- Cimetidine, Ranitidine, Famotidine
- Famotidine ~ diphenhydramine
  - Twenty-five patients an emergency department setting.
- Off-label indication
- Dosing
  - Ranitidtine: 1-2 mg/kg q 12h
  - Cimetidine: 20-40 mg/kg/d split q6h

Vitamin D supplementation: a potential booster for urticaria therapy


- 42 adult subjects
  - High-dose (4000 IU) vs low-dose (600 IU) x daily for 12 weeks.
    - All triple drug therapy of ranitidine, montelukast and a high dose of cetirizine.
  - 33 % reduction in total urticaria severity score (USS) at 1 week post-enrollment in both treatment groups
  - ~40% reduction in total USS in subjects treated with high-dose
Vitamin D as a Marker for Disease Severity in Chronic Urticaria and Its Possible Role in Pathogenesis

Yu Ri Woo, Kyung Eun Jung, Dae Won Koo, Joong Sun Lee

Department of Dermatology, Eulji University School of Medicine, Daejeon, Korea
2nd line: Leukotriene Receptor Antagonists

- Leukotrienes are signaling molecules from the arachidonic acid inflammatory pathway
  - Receptors on mast cells
- Dosing is daily; low AE rate
  - Response 30 to 50 percent
- All the same?
  - Most not effective as monotherapy
  - Zileuton 600 mg four times daily for one week > Zafirlukast 20 mg twice daily for one week
- Synergy with H1 antihistamines
  - Loratidine 5mg + Montelukast 10 mg daily
2nd line: Doxepin

- Very potent H-1 and H-2 antihistaminic properties
- Small studies: N = 16-50 pts
- Dosing: 10-25 mg BID to TID
  - Largest study: 10 mg TID vs diphenhydramine 25 mg TID
    - 43% vs 5% total and 74% vs 10% partial clearance
- AE: sedation, xerostomia
- Not in pts with recent MI or hepatic dysfunction
- Start 10 mg qhs and increase slowly

Goldsobel AB et al: J Allergy Clin Immunol 1986; 78: 867
2nd line: Nifedipine

- Mast cell stabilizing properties
- Doses range:
  - 5 to 10 mg three times daily
  - 30-60 mg daily in extended-release form
  - Can titrate up 5 mg based on clinical response and appearance of side effects.
- Study example: 10 patients; Nifedipine 10 mg three times daily
  - 7/10 patients reports + improvement
- Dizziness and reflex tachycardia
- Clinical pearl: Grapefruit juice increases serum levels of nifedipine
3rd line: Omalizumab

- Humanized monoclonal antibody of IgG1k type that binds free IgE in the blood
- 150-375 mg SQ q2-4 weeks
- Initial dosing is based on pre-treatment serum IgE levels and weight for maximum of 150 mg per injection site
  - Multiple injections may be required for each administration.
- The most significant AE is anaphylaxis*.  
  - Blackbox warning
  - Administration in a medical facility, followed by patient observation for a period of time.
    - ~ two hours after initial injection and 30 minutes for subsequent injections.
  - Less likely: serum sickness-like reaction

Kaplan AP et al: J Allergy Clin Immunol 2008; 122:569  
Magerl M et al: J Allergy Clin Immunol 2010;126:665
Omalizumab

- MOA unknown
- May work by:
  - Down-regulating IgE receptors on mast cells
  - Rapid reduction of plasma IgE might down-regulate mast cells independent of IgE receptor density
  - Prevention of FcεRI dependent-secretion of mast cell cytokines by unknown method

*Nature Reviews Drug Discovery* 2004 March; 3, 199-200
*J Allergy Clin Immunol.* 2011 May;127(5):1300
Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria

- Phase 3, multicenter, randomized, double-blind study,
  - Moderate-to-severe chronic idiopathic urticaria recalcitrant to H1 blockers
- 323 patients; 3 SQ injections (4 weeks apart)
  - Doses of 75 mg, 150 mg, or 300 mg or placebo,
  - 16-week observation symptomatic
- Reduction of sx: $-8.1 \pm 6.4$ in the 150-mg group ($P=0.001$), and $-9.8 \pm 6.0$ in the 300-mg group ($P<0.001$)
### Q4-WEEK DOSING TABLE

<table>
<thead>
<tr>
<th>Pretreatment serum IgE (IU/mL)</th>
<th>Body Weight</th>
<th>Pounds</th>
<th>≥ 30-100</th>
<th>&gt;132-154</th>
<th>&gt;154-198</th>
<th>&gt;198-330</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 30-100</td>
<td>150 mg</td>
<td>150 mg</td>
<td>150 mg</td>
<td>300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 100-100</td>
<td>300 mg</td>
<td>300 mg</td>
<td>300 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 200-300</td>
<td>300 mg</td>
<td>See adjacent table</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Q2-WEEK DOSING TABLE

<table>
<thead>
<tr>
<th>Pretreatment serum IgE (IU/mL)</th>
<th>Body Weight</th>
<th>Kilograms</th>
<th>≥ 30-100</th>
<th>&gt;132-154</th>
<th>&gt;154-198</th>
<th>&gt;198-330</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 30-100</td>
<td>225 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 100-200</td>
<td>225 mg</td>
<td>225 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 200-300</td>
<td>225 mg</td>
<td>225 mg</td>
<td>300 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 300-400</td>
<td>300 mg</td>
<td>225 mg</td>
<td>225 mg</td>
<td>300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 400-500</td>
<td>300 mg</td>
<td>300 mg</td>
<td>375 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 500-600</td>
<td>300 mg</td>
<td>375 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 600-700</td>
<td>375 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DO NOT DOSE</td>
</tr>
</tbody>
</table>
Feeling lazy?

For patients with IgE levels between 30 and 700 IU/mL and body weight between 66 and 330 lb.

http://www.xolair.com/hcp/determining-the-dose.html
• “After reconstituting and swirling for 1 minute, gently swirl the vial for 5 to 10 seconds approximately every 5 minutes in order to dissolve any remaining solids. The lyophilized product takes 15 to 20 minutes to dissolve. If it takes longer than 20 minutes to dissolve completely, gently swirl the vial for 5 to 10 seconds approximately every 5 minutes until there are no visible gel-like particles in the solution. Do not use if the contents of the vial do not dissolve completely by 40 minutes.”
3rd Line: Cyclosporin A

- 3-5mg/kg/day benefit about 2/3 of patients with antihistamine recalcitrant CU
- Example of studies:
  - Cyclosporin 5mg/kg/day for 8 weeks, then 4mg/kg/day for 8 weeks
    - 82.5% controlled week 1
    - 50% relapse rate by month 9 but short lived/easily controlled
  - Double-blind RCT; N = 99
    - 16 weeks, varying dosages (3mg/kg not as effective) + ceterizine
  - Long term cyclosporin
    - 3 mg/kg for 3 months, 1 to 2 mg/kg for 8 to 14 months, then 1 to 1.5 mg/kg for 60 to 120 months
      - 25% resolution, 22.5% improvement
      - No malignancy or abnormal renal function; 16% drop out due to AE

Toubi E et al: Allergy 1997; 52: 312
Kessel A et al. Allergy 2010; 65:1478
3rd line: Dapsone

- Inhibits PMN chemotaxis/ Anti-MPO
- Dapsone 25mg daily + cetirizine 10mg daily
  - 9 urticaria controlled within 3 months and maintained for 1 further month. 2 improved with dapsone 50mg daily. No flare when dapsone was discontinued.
- Dapsone 50 mg + desloratadine 10 mg
  - Dapsone + desloratadine > desloratadine (p<0.001)
    - Three-months follow-up
      - 9/38 complete response, 27/38 partial response, 2/38 no response
- Titrate slowly: check g6pd, CBC/retic

Colchicine

- Inhibits PMN chemotaxis
- Biopsy specimens with neutrophils and eosinophils
- Study example:
  - N=7
  - Prednisone 20 to 40 mg daily for 5 days, H1 antihistamines plus colchicine 0.6 mg. twice daily
  - 5/6 controlled
3rd Line: Methotrexate

- More effective in patients with functional auto-antibodies to FcεRIα and/or IgE?
- Study example:
  - N=10
  - Methotrexate 5 to 15 mg weekly (cumulative dose 15 to 60 mg)
    - 1 clear (no symptoms, off glucocorticoids, on antihistamines)
    - 4 considerable benefit (improvement with glucocorticoid reduction)
    - 3 some benefit (fewer wheals but no glucocorticoid reduction)
    - 2 no benefit
  - Relapse within weeks of d/c
- Clinical pearls: X Trimethoprim, the sulfonamides, and dapsone
  - Tetracyclines increase serum [ ].
- AE: Bone marrow suppression, teratogenicity, hepatic toxicity, gastrointestinal intolerance, interstitial pneumonitis, pulmonary fibrosis
3rd Line: Mycophenolate Mofetil

- inhibiting the production of autoantibodies to the high-affinity IgE receptor and/or IgE
- Studies:
  - N=9; patients on prednisone and antihistamines
    - 1 gm BID x 12 weeks
    - By week 4 prednisone decreased
    - All patients off prednisone by week 12
    - No rebound after 6 months
  - Retrospective chart review; n=19
    - Autoimmune and idiopathic CU
    - Dose: 1000 to 6000 mg divided twice daily
    - Improved both types of CU (91% vs. 88%)
      - Complete control higher in the autoimmune group (70% vs. 41%)
- AE: GI and hematologic.

Efficacy and safety of sulfasalazine in patients with chronic idiopathic urticaria

Roy Anthony Orden, MD*; Hersha Timble†; and Sarbjit S. Saini, MD†

- Retrospective chart review 39 patients with sulfasalazine-treated CIU
  - Initiated at a dosage of 500 mg/d and increased by 500 mg each week based on clinical tolerance/labs.
    - Titrated up weekly until a dose of 2,000 mg/d was achieved
    - Weekly labs until stable on 2g/d (cbc, lfts)
- 83.9% improvement in symptoms within the first 3 months,
  - 51.6% of patients asymptomatic within the first 6 months of starting sulfasalazine
- Serious AE leading to drug discontinuation occurred in 6.5% of patients
  - Drug-induced leukopenia; one with rhabdomyolysis.
  - AE rates ~ cyclosporin and omalizumab (high dose)

Ann Allergy Asthma Immunol 2014;112: 64e70
• Unclear mechanism - decrease the release of histamine from either mast cells and/or basophils
• Example of Studies (small; 14-88 patients)
  – 3 treatments weekly (median number 22)
    • 9 week
    • 30% resolved, 20% moderate improvement, 29% marked improvement
  – 3 treatments weekly (median number 31.4)
    • Clearance in 10 patients (45%), marked improvement in five (22%), and moderate improvement in seven (31%) patients
  – Relapses controlled with antihistamines
Revisions to the international guidelines on the therapy of chronic urticaria

**Second-generation H₁-Antihistamine (sgAH)**

- If symptoms persist after 2 weeks
- Increase sgAH dose (up to 4x)
- If symptoms persist after 1-4 weeks
- Add Omalizumab, Cyclosporine A, or Leukotrieneantagonist
- Short course systemic corticosteroid may be tried for exacerbations

PREVENTIVE TX!

JDDG: Journal der Deutschen Dermatologischen Gesellschaft  2013; 11(10).971-978,
The diagnosis and management of acute and chronic urticaria: 2014 update

Chief Editors: Jonathan A. Bernstein, MD, David M. Lang, MD, and David A. Khan, MD
STEP 1

- Monotherapy with second generation antihistamine
- Avoidance of triggers (e.g., NSAIDs) and relevant physical factors if physical urticaria/angioedema syndrome is present.
STEP 2
One or more of the following:

- Dose advancement of 2\textsuperscript{nd} generation antihistamine used in Step 1
- Add another second generation antihistamine
- Add H\textsubscript{2}- antagonist
- Add leukotriene receptor antagonist
- Add 1\textsuperscript{st} generation antihistamine to be taken at bedtime
STEP 3
Dose advancement of potent antihistamine (e.g. hydroxyzine or doxepin) as tolerated
STEP 4
Add an alternative agent

- Omalizumab or cyclosporine
- Other anti-inflammatory agents, immunosuppressants, or biologics
Not so simple - Treatment of Physical Urticarias

- **Dermatographism:** nifedipine, broad-band UVB phototherapy, narrow-band UVB phototherapy, PUVA photochemotherapy, omalizumab
- **Delayed-pressure urticaria:** NSAIDs, montelukast, colchicine, dapsone, sulfasalazine, systemic glucocorticoids, danazol, stanozolol, chloroquine, tranexamic acid, intravenous immunoglobulin, etanercept, infliximab, omalizumab
- **Cold urticaria:** zafirlukast, montelukast, cyclosporin, mizolastine, stanozolol, omalizumab, anakinra
- **Cholinergic urticaria:** danazol, stanozolol, scopolamine butylbromide, omalizumab
- **Solar urticaria:** β-carotene, hydroxychloroquine, cyclosporin, phasmapheresis, photopheresis, broad-band UVB phototherapy, ultraviolet A phototherapy, PUVA photochemotherapy, intravenous immunoglobulin, omalizumab
- **Aquagenic urticaria:** stanozolol, PUVA photochemotherapy
- **Adrenergic urticaria:** propranolol
• It’s all in the history...sometimes
  – Should guide w/u
• Climb the (therapeutic) ladder
  – High ceiling on antihistamines
  – Combo is King
"I must say, Mr. Jennings, you have the worst case of Hives I've ever seen."