Wheals in Motion: Urticaria Assessment and Management

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No conflicts of interest to disclose
Urticaria

• Moderate to severe impact on quality of life
  – Comparable to severe atopic dermatitis
  – Comparable to coronary artery disease
  – Higher prevalence of depression, anxiety, and sleep difficulties
  – Patients missed 14% of the prior week’s work hrs
  – Health care use greatly elevated among those with chronic hives: extra 6 visits per patient in 6 months - approx double the rate of controls
Pathogenesis

IgE dependent degranulation

IgE independent degranulation
Vasodilation, leakage of plasma, pruritus
Urticaria Diagnosis

• Acute onset
• Wheals:
  – Swelling & erythema
  – Pruritus/burning sensation
  – Transient (1-24hrs)
• Angioedema (40%)
• Often prominent in dependent areas or in areas of pressure/constriction
Angioedema: nonpitting edema without associated erythema, often NOT in dependent areas
URTICARIA DIAGNOSIS

Individual wheals last ≤ 24 hours
Acute Urticaria

- <6 weeks - Incidence: 15-25%
Chronic Urticaria

- Chronic > 6 weeks - ~30% become chronic

CAUSES OF CHRONIC URTICARIA

- 35% Idiopathic
- 5% Pseudoallergic
- 5% Infection-related
- 5% Autoimmune
- 5% 'Ordinary' (non-physical, non-vasculitic)
- 35% Physical
- 5% Vasculitic
Chronic Urticaria - Prognosis

- Spontaneous resolution in ~20-50% within 1 yr

- Divided into inducible/physical urticarias and spontaneous chronic urticaria
  - Inducible/Physical urticaria and autoimmune urticaria have a more prolonged course
Inducible/Physical Urticarias ~ 20-35%

- **Dermatographism**: wheal arises moments after scratching skin
  - 2-5% general population, usually asymptomatic
Inducible/Physical Urticarias

– **Cholinergic**: follows exercise/increased temp, hot water, stress
  - 30% of physical urticarias
  - Distinct morphology – small 2-5 mm macules
  - Teens young adults
Inducible/Physical Urticarias

- **Cold** - 5-30% of physical urticarias
  - Rare reports of hypotension, death after swimming in cold water reported

Apply ice cube for 5 min – hives develop upon rewarming
Inducible/Physical Urticarias

- **Delayed Pressure** – angioedema 4-6 hrs post pressure, may last up to 48 hrs
- **Solar** (immediate with UV exposure)
- **Vibratory urticaria**
- **Aquagenic**
Spontaneous Chronic Urticaria – Idiopathic/Autoimmune ~75%

- Many have IgG antibodies that crosslink FcεR1
- Rare patients have anti-IgE antibodies

Presence of antibodies has no predictive effect on response to treatment
Spontaneous Chronic Urticaria - Others $\sim \leq 5\%$

- Ingestants
- Contactants
- Infections
- Hormonal changes
- Systemic illness
- Occult malignancy

Food allergy testing not indicated

Age-appropriate malignancy screening only
Diagnostic Evaluation of Chronic Urticaria

• Thorough history and physical
• Targeted laboratory testing based upon findings
  – Routine lab screening is controversial but generally not recommended. If performed, limit to
    – CBC with differential
    – Basic metabolic panel
    – CRP, ESR
Treatment

• EDUCATION

• Prevention
  – Avoidance of physical triggers (tight clothing, heat)
  – Avoidance of drugs capable of exacerbating urticaria (NSAIDS, opiate analgesics, etc) when possible
  – Emollients
Treatment - 1st Line

- H1 Antihistamines (large placebo-ctrl’d RCTs)
  - 2nd+ generation (cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine, etc)
    - Daily or bid for two weeks, then increase to 4 times standard dose if no response
    - May be combined with 1st generation antihistamines
  - 1st generation (diphenhydramine, hydroxyzine)
    - Must be taken 3-4 times daily
    - Sedating, hangover effect
Treatment – 1st line

- Doxepin (tricyclic antidepressant)
  - H1 and H2 antihistamine activity
  - Sedation, anticholinergic effects, increased appetite, QT prolongation
  - Start at 10 mg QHS and slowly increase to max of 75-125 mg QHS
Treatment – 1st line

- H2 antihistamines (cimetidine, ranitidine, famotidine)
  - 15% of histamine receptors in skin are H2 type
  - Inhibits cytochrome p450 enzymes that metabolize 1st generation antihistamines and consequently increase their plasma concentration
  - Not recommended as monotherapy, may provide modest benefit when added to H1-blockers
Treatment – 1st Line

• Systemic corticosteroids
  – Brief use for severe symptoms only
  – Highly effective but no long-term remittive effect

• Epinephrine (0.3mL of 1:1000 IM)
  – Rapidly reverses urticaria and angioedema
  – Patients at risk for life-threatening angioedema or anaphylaxis should have an Epipen
Treatment – 2nd Line

• Leukotriene inhibitors (small placebo-ctrlId RCTs)
  – Block leukotriene receptors (which are potent inflammatory mediators)
  – (montelukast, zafirlukast, etc)
  – Not as effective as H1 blockers alone
  – May enhance response when combined with H1 blockers
Treatment – 2nd Line

• Omalizumab (large placebo-ctrlld RCTs)
  – Humanized IgG anti-IgE antibody (binds IgE and inhibits its binding to FcεRI)
  – 150-300 mg subq Q4weeks
  – Complete/almost complete resolution of symptoms ~66-70%
  – High cost
Treatment – 2nd Line

• Cyclosporine A (small placebo-ctrlld RCTs)
  – Inhibits calcineurin --> reduced transcription of inflammatory cytokines
  – 150-300 mg subq Q4weeks
  – Complete/almost complete resolution of symptoms ≥53-70%
  – Toxicities: close hematologic, renal.hepatic monitoring
### 3<sup>rd</sup> Line Treatments

<table>
<thead>
<tr>
<th>DRUG</th>
<th>LEVEL OF EVIDENCE</th>
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<tbody>
<tr>
<td>H2 Blockers (with H1 antihistamine)*</td>
<td>III</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Ib</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Ib</td>
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<tr>
<td>Sulfasalazine</td>
<td>III</td>
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<tr>
<td>Colchicine</td>
<td>III</td>
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<tr>
<td>Mycophenolate mofetil</td>
<td>IIb</td>
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<tr>
<td>IVIG</td>
<td>III</td>
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<tr>
<td>Rituximab</td>
<td>IV</td>
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<tr>
<td>Chronic/frequent corticosteroids</td>
<td>IV</td>
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</tbody>
</table>

* Pharmacokinetic effect of H2 blocker + 1<sup>st</sup> generation antihistamines
# Urticaria Treatment Approach

## 1st
- Prevention via elimination of known triggers
- *2nd*+ generation antihistamine

## 2nd
- 4X dose of *2nd* generation histamine divided bid
- Add Bedtime *1st* generation antihistamine or doxepin

## 3rd
- If ≥6weeks, perform thorough H&P with ROS, targeted studies, and CBC, ESR, CRP
- If urticaria have atypical appearance/symptoms, consider skin biopsy/alternative Dx
- Add leukotriene inhibitor vs. omalizumab vs. cyclosporine

## 4th
- Consider 3rd line agent based on severity of symptoms & comorbidities
Chronic Urticaria Differential Dx

• Generalized pruritus – excoriations, but no primary skin lesions
• Flushing – macular erythema, no wheals
• Urticarial vasculitis
  – Lesions typically last >24 hr and resolve with purpura or hyperpigmentation, often tender/painful
  – Biopsy demonstrates leukocytoclastic vasculitis
Urticarial vasculitis
Chronic Urticaria Differential Dx

- Urticarial phase of autoimmune bullous disease
Chronic Urticaria Differential Dx

- Urticaria pigmentosa
Chronic Urticaria Differential Dx

- Hereditary or acquired angioedema – angioedema without urticaria
Chronic Urticaria Differential Dx

• Autoinflammatory/periodic fever syndromes – atypical urticaria, systemic symptoms, family history
  – Familial Mediterranean fever
  – Hyper-IgD syndrome
  – Blau syndrome
  – Familial cold autoinflammatory syndrome
  – Muckle-Wells syndrome
  – Neonatal onset multisystem inflammatory disorder
Urticaria – KEY POINTS

• Major impact on quality of life
• Wheals that last ≤ 24 hours
• Acute urticaria < 6 weeks, Chronic > 6 weeks
• Antihistamines are first line treatment
• Thorough H&P with ROS is most critical diagnostic step
• Exhaustive lab testing is typically unnecessary
• Chronic urticaria typically lasts for years
References

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- ABIM and AAAAI Choosing Wisely Guidelines http://www.chossingwisely.org
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<thead>
<tr>
<th>Level</th>
<th>Therapy/Prevention, Aetiology/Harm</th>
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<tbody>
<tr>
<td>1a</td>
<td>Systematic review (with homogeneity) of RCTs</td>
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<tr>
<td>1b</td>
<td>Individual RCT (with narrow Confidence Interval)</td>
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<td>1c</td>
<td>All or none (i.e., all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it)</td>
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<tr>
<td>2a</td>
<td>Systematic review (with homogeneity) of cohort studies</td>
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<td>2b</td>
<td>Individual cohort study (including low quality RCT; e.g., &lt;80% follow-up)</td>
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<td>2c</td>
<td>&quot;Outcomes&quot; Research or ecologic studies (studies of group changes)</td>
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<tr>
<td>3a</td>
<td>Systematic review (with homogeneity) of case-control studies</td>
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<td>3b</td>
<td>Individual Case-Control Study</td>
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<td>4</td>
<td>Case-series (and poor quality cohort and case-control studies)</td>
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<tr>
<td>5</td>
<td>Expert opinion or based on physiology, bench research or &quot;first principles&quot;</td>
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Oxford Centre for Evidence Based Medicine
Herbs associated with urticaria

- Cranberry
- Echinacea
- Hypericum
- Willow
- Garlic
- Ginger
- Glucosamine
- Horseradish
- Phytoestrogen
- Propolis
- Royal jelly
- Valerian