Classification of Urticaria

**CHRONIC URTICARIA**

Charoen Choonhakarn, MD
Division of Dermatology
Khon Kaen University

**Spontaneous urticaria**
- Acute urticaria
- Chronic urticaria

**Physical urticaria**
- Cold contact urticaria
- Delayed pressure urticaria
- Heat contact urticaria
- Solar urticaria
- Urticaria factitia/dermographic urticaria
- Vibratory urticaria/angioedema

**Other urticaria disorders**
- Aquagenic urticaria
- Cholinergic urticaria
- Contact urticaria
- Exercise-induced anaphylaxis/urticaria

**Dermographism**
Overview
- Overview of Chronic Idiopathic Urticaria (CIU)
- How is its importance?
- Who needs investigation?
- Evolution of Therapy for CIU
- Clinical Efficacy of Antihistamines in CIU
- Summary and Conclusions

Definition of Chronic Urticaria
- Spontaneous wheals and/or angioedema
  - > 6 weeks; daily or almost daily or at least 2 times/week
- Pruritus can be severe and debilitating
- Significant negative impact on quality of life

Prevalence of Chronic Urticaria
- Urticaria affects 1/4 of population
  - Estimated 25% of cases are chronic (>6 weeks)
- Chronic spontaneous urticaria prevalence estimates range from 0.5%-1% of population
- Chronic urticaria: all age groups, more common among adults and women than among children and men
Clinical Impact and Burden

- Pruritus, the primary debilitating symptom of chronic urticaria, is associated with:
  - Severe discomfort
  - Sleep disturbance
  - Depression
- Productivity losses:
  - Adverse effects on work and classroom performance
  - 25%-30% reduction in work/school productivity
- Wheals and angioedema affect physical appearance
- The detrimental effect on QoL greater than that of other skin diseases and similar to that of coronary artery disease

Duration of chronic spontaneous urticaria

- Studies indicate that most patients suffer for >1 yr.
- A considerable number of patients seem to be affected >5 yrs.
- The overall duration likely to be longer in pts with:
  1. High disease severity (all pts with mild; symptom free after 2 yrs, 60% pts with moderate to severe symptom persist after 2 yrs and 30% symptom persist after 5 yrs).
  2. Angioedema (64-70% vs 43-48% suffer after 1 yr)
  3. Positivity of autologous serum skin test
  4. Combination with physical urticaria (dermographism, delayed pressure urticaria)

Mechanisms of Urticaria: Immune Effector Cells

- Mast cell is the central effector cell. Mast cells are the major source of mediators (histamine, cytokines, prostaglandins, leukotrienes).
- Basophils, monocytes, neutrophils, and eosinophils participate to a lesser extent.

Clinical Impact and Burden

- The Nottingham Health Profile (NHP)
  - Disease-specific questionnaire administered to 142 patients
  - Chronic urticaria associated with impairment or difficulty in:
    - Mobility
    - Sleep
    - Energy
    - Pain
    - Social isolation
    - Emotional reactions
    - Work
    - Home management
    - Social life
    - Home relationships
    - Sex life
    - Hobbies

Mast Cells Mediate Allergic Reactions

- Histamine → Allergic reaction
Inflammatory Reactions

- TNF
- IL-1β
- IL-8
- LTA
- LTB4
- LTC4
- LTD4
- LTB4
- Leukotrienes (LTEA-D)
- Prostaglandins (PGD2)
- Histamine
- Heparin
- Cathepsin G
- Chymase
- Serotonin
- VPF/VEGF
- MIP
- Tryptase
- Interleukin 1

Mast cells mediate allergic and inflammatory reactions.

Diagnostic tests may include:
- Physical examination
- Rigorous patient history (infection, occupational exposure, medications, foods)
- Stool for worm eggs/parasites
- Serum iron levels
- Autoantibodies
- Test for Helicobacter
- Diagnostic blood tests
- Antinuclear antibodies
- C-reactive protein (CRP)
- ESR
- Autologous serum skin test
- Stool for worm eggs/parasites
- Autoantibodies
- Test for infectious diseases
- Test for Helicobacter

In many patients, causes and/or triggers are not identified (0-45% successful identification)

Prevalence of Atopic Comorbidities in Patients With Urticaria

- Any atopic disease: 54.4%
- Hay fever: 44.0%
- Allergic asthma: 22.3%
- Atopic dermatitis: 18.2%

WHO NEEDS INVESTIGATION?

Clinical Evaluation and Diagnosis:
- Rigorous patient history (infection, occupational exposure, medications, foods)
- Physical examination
- Diagnostic tests may include:
  - Differential blood count
  - ESR (to rule out severe systemic disease)
  - Autologous serum skin test
  - Gastroscopy
  - Specific IgE

Patients With Urticaria

Prevalence of atopic comorbidities in patients with urticaria.
Management

- Identification and elimination of underlying causes
- Avoidance or elimination of the eliciting stimulus
- Inhibition of mast cell mediators

Identification and elimination of underlying causes

- Removal of infectious agents and treatment of inflammatory processes
- Removal of FceRI autoantibodies: plasmapheresis, cyclosporin, IVIg, systemic corticosteroids
- Dietary management:
  - IgE-mediated food allergy
  - Avoid pseudoallergens in chronic urticaria for at least 3-6 months; beneficial effects observed after 2-3 wks

Avoidance eliciting stimulus

- Drugs: suspected drugs, pseudoallergic drugs eg. aspirin, NSAIDs, ACEI
- Physical stimuli: physical urticaria
- Stress: 50% of pts with chronic urticaria; stress is a trigger

Inhibition of mast cell mediators

- H1 antihistamines
- H2 antihistamines

Evolution of H1 Antihistamines: Timeline

First-generation
- Hydroxyzine
- Diphenhydramine
- Chlorpheniramine

Second-generation
- Terfenadine
- Cetirizine
- Acrivastine

Newer agents
- Desloratadine
- Levocetirizine
- Fexofenadine

Risk of first-generation H1-antihistamines generation

- Marked sedation/performance impairing
- Psychomotor and cognitive function
- Anticholinergic effects
- Drug interactions
- Short-acting duration
- Affects REM sleep
Evolution of Antihistamines

- Antihistamines are essential treatment for chronic idiopathic urticaria because of the dominant role of histamine in disease pathophysiology.
- Second-generation antihistamines, including newer agents, are less sedation (cetirizine, levocetirizine).
  - no sedation (desloratadine, fexofenadine, loratadine)
  - fewer anticholinergic effects
  - potentially less drug interactions vs the first-generation
  - anti-allergic and anti-inflammatory effects (chronic urticaria is a systemic disease)

First- and Second-Generation Antihistamines: Prodrugs and Metabolites

- Hydroxyzine
- Tripelididine
- Terfenadine
- Astemizole
- Loratadine
- Cetirizine
- Levocetirizine
- Desmethylastemizole
- Desloratadine

*Cetirizine is an R-enantiomer of cetirizine.

Management of Chronic Urticaria:

First-line

**Nonsedating second-generation H₁-antihistamine**

- Level of evidence 1++
- Grade of recommendation A

- Increase dose
- Symptoms not controlled

- Choose alternative therapy
- Symptoms not controlled

- Select another alternative treatment


- We recommend the use of the treatment algorithm as described for chronic urticaria.
- We recommend against the use of sedating antihistamines.
- We recommend against the use of astemizole and terfenadine.
- We recommend against the use of corticosteroids (except short term).
- We recommend aiming for complete symptom control.
- We suggest the same first-line treatment and updosing as described for children (weight adjusted) and pregnant or lactating women with chronic spontaneous urticaria.

New Guidelines EAACI/GA²LEN/EDF/WAO 2008

<table>
<thead>
<tr>
<th>Costs</th>
<th>Side Effects</th>
<th>Therapy</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>Very low</td>
<td>New generation (H₁-antihistamine)</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Low</td>
<td>Very low</td>
<td>New generation (H₁-antihistamine)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Low</td>
<td>Very low</td>
<td>Alternatives off-label (e.g., second generation)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Medium</td>
<td>Medium</td>
<td>Systemic comediment (not more than 2)</td>
<td>30 days</td>
</tr>
<tr>
<td>Very low</td>
<td>Very low</td>
<td>Allergen immunotherapy</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>Medium</td>
<td>Omalizumab A</td>
<td></td>
</tr>
<tr>
<td>Very low</td>
<td>Very low</td>
<td>Omalizumab</td>
<td></td>
</tr>
</tbody>
</table>

First-Line Management of Chronic Urticaria:
EAACI/GA²LEN/EDF Guidelines’ Recommendations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Methodologic Quality</th>
<th>Level of Evidence</th>
<th>Grade of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desloratadine</td>
<td>1++</td>
<td>1--</td>
<td>A</td>
</tr>
<tr>
<td>Acrivastine</td>
<td>++</td>
<td>1+</td>
<td></td>
</tr>
<tr>
<td>Desmethylastemizole</td>
<td>++</td>
<td>1+</td>
<td></td>
</tr>
<tr>
<td>Omalizumab</td>
<td>++</td>
<td>1+</td>
<td></td>
</tr>
<tr>
<td>Terfenadine</td>
<td>++</td>
<td>1+</td>
<td></td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>++</td>
<td>1+</td>
<td></td>
</tr>
<tr>
<td>Etor definit</td>
<td>++</td>
<td>1+</td>
<td></td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>++</td>
<td>1+</td>
<td></td>
</tr>
<tr>
<td>Increase dosage if necessary</td>
<td>3</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>
**Antihistamine Indications and Formulations:**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Chronic Inflammation</th>
<th>Urticaria</th>
<th>Tablet</th>
<th>Syrup</th>
<th>Drops</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desloratadine</td>
<td>6 y (O/K)</td>
<td>√</td>
<td>√</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Loratadine</td>
<td>6 y</td>
<td>√</td>
<td>√</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>6 y</td>
<td>√</td>
<td>√</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>6 y</td>
<td>√</td>
<td>√</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>6 month (Oty)</td>
<td>√</td>
<td>√</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Mizolastine</td>
<td>6 y</td>
<td>√</td>
<td>√</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Ebastine</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = not available.

**Antihistamine Recommended Doses:**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Recommended Dose (mg)</th>
<th>Adjustment for Impaired Renal Function</th>
<th>Adjustment for Impaired Liver Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desloratadine</td>
<td>5-10</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Loratadine</td>
<td>5-10</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>5-10</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>5</td>
<td>√ (elderly)</td>
<td>√</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>120-180</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Mizolastine</td>
<td>10</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>Ebastine</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Antacid administration reduces fexofenadine bioavailability.

**Desloratadine: Highest H1-Receptor Affinity**

Receptor-binding affinity of histamine antagonists on recombinant human H1 receptor

<table>
<thead>
<tr>
<th>Anti-H1</th>
<th>Ki (nM)</th>
<th>Relative Affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desloratadine</td>
<td>0.9</td>
<td>194.4</td>
</tr>
<tr>
<td>Carbazoline</td>
<td>10</td>
<td>17.5</td>
</tr>
<tr>
<td>Mizolastine</td>
<td>22</td>
<td>8.0</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>40</td>
<td>4.4</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>47</td>
<td>3.7</td>
</tr>
<tr>
<td>Ebastine</td>
<td>52</td>
<td>3.4</td>
</tr>
<tr>
<td>Loratadine</td>
<td>138</td>
<td>1.2</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>175</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Desloratadine: Slow Dissociation from H1-Receptor**

Human H1-Receptor in CHO Cells: Kinetic of Dissociation [H] pyrilamine vs [H] desloratadine

Long Duration of Action

**Antihistamine Pharmacokinetics: Role of Cytochrome and Efflux/Influx Transporter Families**

Blood and tissue concentrations variability

**Second-Generation Antihistamines: Potential Drug/Food Interactions**

<table>
<thead>
<tr>
<th>Potential Interaction</th>
<th>Desloratadine</th>
<th>Levocetirizine</th>
<th>Fexofenadine</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp</td>
<td>–</td>
<td>NR</td>
<td>+++</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>+</td>
<td>NR</td>
<td>++</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>+</td>
<td>NR</td>
<td>++</td>
</tr>
<tr>
<td>QTc interval</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Alcohol</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Food</td>
<td>–</td>
<td>–</td>
<td>+*</td>
</tr>
</tbody>
</table>

P-gp = P-glycoprotein, NR = not reported.

*Antacid administration reduces fexofenadine bioavailability.
Pharmacologic Properties of Second-Generation Antihistamines*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Sedation</th>
<th>Drug/Food Interaction Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desloratadine</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Loratadine</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Ebastine</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mizolastine</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

* At clinically recommended doses.

How to prescribe antihistamines?

- Once control of CIU symptoms is obtained with daily treatment, **continuous therapy** (whether or not the patient is showing symptoms) preserves patient QoL better over the long term as compared with than PRN treatment only given only at symptom flare-up.

EAACI/GA²LEN/EDF/WAO Guidelines for Treatment

- Nonsedating, second generation H₁-antihistamine
- Not controlled
- Increase dosage

Where Are The Data?
**The AUDACU Trial**

** Parameters assessed**
- Critical Temperature Threshold (Temp Test 2.0)
- Hyperthermic skin area (Thermography)
- Wheal volume (Volumetry)

---

**Updosing of Desloratadine Improves Urticaria Skin Symptoms**

- Standard dose of AERIUS works in ACU
- UPDOSING (using 4x the standard dose) results in even better total symptom control in patients with ACU
- UPDOSING is safe
Nonresponsive Chronic Urticaria: EAC/GA/LEN/EDF Guidelines’ Recommendations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Methodologic Quality</th>
<th>Level of Evidence</th>
<th>Grade of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination NS 2nd-Generation AH</td>
<td>++</td>
<td>2+</td>
<td>C</td>
</tr>
<tr>
<td>+ Cyclosporin A</td>
<td>+</td>
<td>2-</td>
<td>D</td>
</tr>
<tr>
<td>+ Metolazone</td>
<td>+</td>
<td>2-</td>
<td>D</td>
</tr>
<tr>
<td>+ H1-AH</td>
<td>+</td>
<td>2-</td>
<td>D</td>
</tr>
<tr>
<td>+ Another agent</td>
<td>+</td>
<td>2-</td>
<td>D</td>
</tr>
<tr>
<td>TRH/Tryptophan</td>
<td>-</td>
<td>3-</td>
<td>D</td>
</tr>
<tr>
<td>Ketotifen</td>
<td>++</td>
<td>2+</td>
<td>C</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>No RCT</td>
<td>3</td>
<td>D</td>
</tr>
<tr>
<td>Dapsone</td>
<td>No RCT</td>
<td>3</td>
<td>D</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>No RCT</td>
<td>3</td>
<td>D</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>No RCT</td>
<td>4</td>
<td>D</td>
</tr>
</tbody>
</table>

Non responsive Chronic Urticaria: NSAIDs - nsAH up dosing (up to 4x)

- nsAH up dosing (up to 4x) to symptom persist after 2 weeks.

- Exacerbation: Systemic Steroid (for 3–7 days) if symptoms persist after 1–4 weeks.

Desloratadine

- Highest H1-receptor affinity among second-generation.
- Slow dissociation from H1-receptor.
- Greater in vitro and in vivo antihistaminic potency than loratadine.
- No anticholinergic effects at clinical doses.
- Unlike loratadine, not metabolized by liver cytochrome P450 3A4 pathway.
- Unlike fexofenadine, no interaction with intestinal P-gp and OATP 9-11.
- No interaction with food.
- Unlike levocetirizine, no sedation.

Chronic Urticaria: Conclusions

- Common systemic disease with a significant impact on work productivity and quality of life.
- Idiopathic nature, mostly.
- Non-sedating 2nd generation AH (newer agents) recommended first-line therapy.
- Continuous treatment is recommended.
- Regular dose non-sedating 2nd generation AH: absence of symptoms<50% of pts.
- Updosing to 4x if no response: 1/3-1/4 pts remain symptomatic.

- Maurer M et al. Allergy, 2011.

Desloratadine

- Highest H1-receptor affinity among second-generation.
- Slow dissociation from H1-receptor.
- Greater in vitro and in vivo antihistaminic potency than loratadine.
- No anticholinergic effects at clinical doses.
- Unlike loratadine, not metabolized by liver cytochrome P450 3A4 pathway.
- Unlike fexofenadine, no interaction with intestinal P-gp and OATP 9-11.
- No interaction with food.
- Unlike levocetirizine, no sedation.
THANK YOU