U023 - Urticaria Management

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Columbus KL

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Conflict of interest: None
Urticaria is a dermatological disorder characterized by the sudden appearance of itchy hives (wheals), angioedema or both.

A **hive** consists of three typical features:

1. Central **swelling** of variable size, usually surrounded by a reflex erythema
2. Associated **itching** (pruritus), or sometimes a **burning** sensation
3. Usually resolves within a few hours and always by 24 hours

**Angioedema** is typically characterized by:

1. Sudden, pronounced **swelling** of the lower dermis and subcutis
2. Sometimes **pain** rather than itching
3. Frequent involvement below mucous membranes
4. Up to 72 hours for resolution

The terms ‘itch/pruritus’, and ‘hive/wheal’ are interchangeable. For the purpose of this training tool, itch and hive will be used to describe these key symptoms of urticaria

Chronic urticaria (CU)
Urticaria is characterized by the sudden appearance of hives (wheals), angioedema or both lasting for ≥6 weeks

Chronic spontaneous urticaria (CSU)
- Spontaneous development of symptoms (no external specific trigger)
- Includes patients with known (autoimmune, infection, etc.) and unknown causes for urticaria

Chronic inducible urticaria (CINDU)
- Symptoms induced by a specific trigger

Physical
- Cold
- Delayed pressure
- Heat
- Solar
- Dermographic
- Vibratory

Other
- Aquagenic
- Cholinergic
- Contact

CSU is a chronic disease whose duration is estimated to be 1–5 years\(^1,2\)

Of the diagnosed CSU patient population:

- 50% will resolve within 6 months of onset\(^2\)
- 20% will resolve within 3 years\(^2\)
- 20% will resolve within 5–10 years\(^2\)
- <2% will resolve within 25 years\(^2\)

![Years since diagnosis](image)

- In very rare cases, CSU can persist for up to 50 years\(^1\)

CSU = chronic spontaneous urticaria.

Recent revisions to the EAACI/GA²LEN/EDF/WAO guidelines have updated the CSU diagnosis steps¹

1. **Take a thorough history** Patients should be questioned regarding: *Time-of-onset* of disease *Frequency/duration* of and provoking factors* for hives and/or angioedema

2. **Physical examination** of the patient
   - This should include a diagnostic provocation test including drug, food and physical tests only where it is indicated by history

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EAACI/GA\textsuperscript{2}LEN/EDF/WAO urticaria guidelines: paths to diagnosis of CSU\textsuperscript{1}


AAE = acquired angioedema due to C1-inhibitor deficiency; ACE = angiotensin converting enzyme; AE = angioedema; AH = antihistamine; AID = auto-inflammatory disease; HAE = hereditary angioedema. EAACI = European Academy of Allergy and Clinical Immunology; GA\textsuperscript{2}LEN = Global Allergy and Asthma European Network; EDF = European Dermatology Forum; WAO = World Allergy Organization.
Chronic spontaneous urticaria

diagnostic workup

• Exclude differential diagnoses

• Rule out severe inflammation

• Measure disease activity and impact
Rule out severe inflammatory process

• CRP/ ESR

• COMPLETE BLOOD COUNT
Management plan

• Removal of any identified cause
• Avoidance of aggravating factors
• Advice and information
• Lotions for symptomatic relief
• First line drugs (Non sedating Antihistamines)
• Second line interventions as per clinical situation
• Third line immunosuppressive therapies
Basic treatment: Avoidance of triggers and relevant physical factors if physical urticaria/angioedema is present

<table>
<thead>
<tr>
<th>STEP 1</th>
<th>Monotherapy with sgAH</th>
<th>Monotherapy with sgAH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>if adequate control: After 2-4 weeks or earlier, if symptoms are intolerable</td>
<td>assess for patient’s tolerance and efficacy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 2</th>
<th>Increase sgAH dose (upto4x)</th>
<th>One or more of the following:</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>- Dose advancement of sgAH used in step 1</td>
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<tr>
<td></td>
<td></td>
<td>- Add another sgAH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Add H2 antagonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Add LTRA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Add fgAH, to be taken at bed time</td>
</tr>
</tbody>
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<thead>
<tr>
<th>STEP 3</th>
<th>Add on to sgAH : Omalizumab</th>
<th>Dose advancement of potent antihistamine (e.g. Hydroxyzine or doxepin) as tolerated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If adequate control: within 6 months or earlier, if symptoms are intolerable</td>
<td>assess for patient’s tolerance and efficacy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STEP 4</th>
<th>Add on sgAH : Cyclosporine</th>
<th>Add an alternative agent:</th>
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<tr>
<td></td>
<td></td>
<td>- Omalizumab or cyclosporine</td>
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<tr>
<td></td>
<td></td>
<td>- other anti-inflammatory agents,</td>
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<td></td>
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<td>immunosuppressants or biologics</td>
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TWO SUBGROUPS OF RESPONDERS to Omalizumab

The heat map of individual patient-level UAS7 and ISS data confirmed two subgroups of responders to omalizumab in CSU:

• **Subgroup one**: early treatment responders – patients who responded after one dose of omalizumab (<4 weeks)

• **Subgroup two**: late treatment responders – patients who need additional time to respond (up to 24 weeks)

**Increased IgE levels** linked to faster relapse in omalizumab discontinued CU patients
Table X

- Dapsone
- Methotrexate
- Autoserum therapy
- Azathiopurine
- Tranexamic acid
- Colchicine
- H2 antihistamines
- Montelukast
- Phototherapy
- Sulfasalazine
- IVIg

Only trials of low quality or case series have been published
Recommended treatment for CSU (1)

• Second generation H\textsubscript{1}-antihistamines are recommended first-line treatment for CSU\textsuperscript{1,2}
  
  – However, standard therapy with licensed doses of H\textsubscript{1}-antihistamines is often ineffective; up to 50% of patients have an inadequate response to approved doses of H\textsubscript{1}-antihistamines\textsuperscript{1}

• Guidelines recommend an up to 4-fold dose increase* in H\textsubscript{1}-antihistamine second-line, in patients with an inadequate response to H\textsubscript{1}-antihistamines at licensed doses\textsuperscript{2}
  
  – This results in a higher degree of efficacy in some, but not all, patients, with up to one third of patients remaining unresponsive\textsuperscript{1–4}

\*Not licensed.

• Treatment options for patients refractory to second generation H₁-antihistamines, even at higher doses, are limited
• Guidelines recommend third-line addition of omalizumab, cyclosporin A to existing H₁-antihistamine treatment¹
  – Omalizumab 300 mg is approved in the EU/the US for the treatment of CSU/CIU in adult and adolescent (12 years and above) patients with inadequate response to H₁-antihistamine treatment/who remain symptomatic despite H₁-antihistamine treatment²,³
  – The level of evidence for the efficacy of montelukast in urticaria is low¹
  – Efficacy of ciclosporin A in combination with a second-generation H₁-antihistamine has been demonstrated in clinical trials, but it is associated with a high incidence of adverse effects¹

2. Xolair® SmPC 2014;