Frequently raised complaints by patients with urticaria and angioedema

1. Intolerable symptoms in spite of treatments

Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.

(Definition of health in the WHO constitution)

2. What is the cause of my urticaria?
   Food?, Sick of internal organs?, etc.
   Please treat at causative level, not symptomatically.

3. How long does it take for cure?
   Do I suffer from urticaria for life long?

4. I don’t like drugs just for symptoms.
   I don’t want to be dependent on drugs.

Principle of the management of urticaria

In general,

- Urticaria inducible by certain stimuli are resistant for medications.
  whereas

- Urticaria characterized by spontaneously appearing wheals are subject to medications, especially antihistamines.

The efficacy of systemic steroid on urticaria depends on subtypes urticaria

<table>
<thead>
<tr>
<th>Subtypes of urticaria</th>
<th>Expectable</th>
<th>Not expectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous urticaria</td>
<td>Acute and chronic spontaneous urticaria (including autoimmune urticaria)</td>
<td>—</td>
</tr>
<tr>
<td>Inducible type urticarias</td>
<td>Delayed pressure urticaria (DPU)</td>
<td>Urticarias due to type I allergy and NSAIDs intolerance, the other physical urticarias, etc.</td>
</tr>
<tr>
<td>Angioedema</td>
<td>Spontaneous/idiopathic urticaria (histaminergic)</td>
<td>Other types of angioedema, HAE-ACEI induced angioedema, etc.</td>
</tr>
<tr>
<td>Diseases related to urticaria</td>
<td>Urticarial vasculitis</td>
<td>Urticaria pigmentosa, Schnitzler syndrome, CAPS</td>
</tr>
</tbody>
</table>
It is important to distinguish acute and chronic spontaneous urticaria (CSU) from the other types of urticaria, not only because the absence of direct trigger for exciting wheal formation, but also because responsiveness to treatments, especially steroids.

Management of chronic spontaneous urticaria (CSU)

Algorithm for the treatment of CSU suggested by guidelines: **BSACI, 2007**

1. Non sedating H1-antihistamine (nsAH)
   - If symptoms persist after 2 weeks
   - nsAH up dosing (up to 4x)
2. Add Leukotriene antagonist or change nsAH
   - If symptoms persist after 1 - 4 weeks
3. Add Ciclosporin A, H2-antihistamine, Dapsone, Oxaliplatin
   - If symptoms persist after 1 - 4 weeks
   - Exacerbation: Systemic Steroid (for 3-7 days)
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Algorithm for the treatment of CSU suggested by guidelines: **EAACI, 2009**

1. Anti-histamines
   - 1) standard doses, 2) change drugs, 3) increase doses
2. Supplementary medications
   - e.g. H1-blockers*, anti-leukotrienes*, extracts of inflammatory rabbit skin inoculated with vaccinia virus, glycyrrhizinic acid, dapsone, anti-anxiety drugs, tranexamic acid
   - *Off label use
3. Steroids
   - Corticosteroids, equivalent to 5-15 mg/day prednisolone
4. Experimental trials
   - Immunological treatments (e.g. CisA*, corticosteroids, equivalent >20 mg/day)

Algorithm for the treatment of CSU suggested by guidelines: **JDS, 2011**

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Stages of the refractory urticaria and angioedema

1. Intolerable symptoms in spite of vigorous treatments
2. No or mild symptoms on heavy load of treatments (adverse effects, cost, cumbersomeness)
3. No or mild symptoms on treatments with mild or moderately heavy load of treatments
4. No or mild symptoms on safe and readily available treatments, such as antihistamines, but recur if stop medication

Three points to be taken for the management of refractory urticaria and angioedema

1. How to suppress apparent symptoms?
2. How to control underlying disease activities towards remission/cure?
3. Balance for the effect and burdens
4. Time course towards the remission/cure

Immunosuppressivess/modulative treatments for urticaria

<table>
<thead>
<tr>
<th>Chronic</th>
<th>Other type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid (Pred&gt;20mg/d)</td>
<td><strong>Anaphylaxis</strong></td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>* —</td>
</tr>
<tr>
<td>CisA</td>
<td><strong>(RCT) solar</strong></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>* —</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>* —</td>
</tr>
<tr>
<td>IVIG</td>
<td>* —</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>* —</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>** —</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>**(RCT) cholinergic, cold, etc</td>
</tr>
</tbody>
</table>

* For autoimmune urticaria  ** For non autoimmune urticaria

The effectiveness is for reducing/suppressing symptoms, not necessarily for cure. They may also applied for non-autoimmune urticaria
Algorism for treatment of chronic idiopathic (spontaneous) urticaria

- **Symptoms disappeared or improved**: Continue the same treatment for 1-2 months. Take into account the time to symptoms free, kinds and natures of medications, etc.

- **Step up to Tx in Fig. 3**: Benefits overcome disadvantages, such as adverse effects, costs

- **Change to other drugs, or consider to increase the level of treatment (Fig. 3)**: Continue present treatment

- **Oral anti-histamines (1-2 wks)**: Continue present treatment

- **Supplementary medications**

- **Steroids**

- **Experimental trials**

CQ12: Should idiopathic urticaria continued to be treated for a certain period after a disappearance of symptoms?

**Comments**: Idiopathic urticaria should continued to be treated for a while after disappearance or decrease of the symptoms.

**Recommendation level**: B, Evidence level II

**References**:


Management of inducible type urticaria

**Physical urticaria**
- Mechanical urticaria (Symptomatic Dermographism)
- Cold urticaria
- Solar urticaria**
- Heat urticaria
- Delayed pressure urticaria (DPU)

**Other urticaria types**
- Cholinergic urticaria**
- Aquagenic urticaria
- Contact urticaria*
- Allergic urticaria*

**Angioedema** (except for bradykinin mediated angioedema)

Reported treatments for inducible type urticarias

<table>
<thead>
<tr>
<th>Urticaria Type</th>
<th>Avoid Triggers</th>
<th>Hardening / Tolerance</th>
<th>Steroids</th>
<th>Omalizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical urticaria</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Cold urticaria</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Solar urticaria</td>
<td>✔️</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
</tr>
<tr>
<td>Heat urticaria</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Aquagenic urticaria</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>DPU</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Cholinergic urticaria</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Contact urticaria</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Allergic urticaria</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Angioedema</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>

Mechanical urticaria (especially with severe itching)
Effects of Ciclosporin on refractory mechanical urticaria

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Duration (yr)</th>
<th>Duration of CsA, (month)</th>
<th>Previous medications</th>
<th>Outcome</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>M</td>
<td>4</td>
<td>21</td>
<td>H1-antagonists in 3-fold doses, corticosteroids (5mg/day, 2 weeks)</td>
<td>Cure</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>F</td>
<td>5</td>
<td>16, continue</td>
<td>H1-antagonists in 3-fold doses, leukotriene antagonists, corticosteroids (2.5-20mg/day, 2 years)</td>
<td>Improvement</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>F</td>
<td>12</td>
<td>32, continue</td>
<td>H1-antagonists in 3-fold doses, leukotriene antagonists, corticosteroids (2.5-20mg/day, 2 years)</td>
<td>Improvement</td>
<td>Upper respiratory distress</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>F</td>
<td>0.5</td>
<td>8, continue</td>
<td>H1-antagonists in 3-fold doses, leukotriene antagonists, corticosteroids (10-30mg/day, 2 weeks)</td>
<td>Improvement</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>F</td>
<td>15</td>
<td>0.5</td>
<td>H1-antagonists in 4-fold doses, corticosteroids (5mg/day, 2 weeks)</td>
<td>Inefficiency</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>43</td>
<td>M</td>
<td>5</td>
<td>0.25</td>
<td>H1-antagonists in 3-fold doses, leukotriene antagonists</td>
<td>Inefficiency</td>
<td>Headache, nausea</td>
</tr>
</tbody>
</table>

Taxonomy of the treatment for urticaria and view points for practice

- **Short time, temporary actions**
  - Adrenalin injection
  - Antihistamine (i.v, i.m, p.o)
  - Steroid infusion
  - Plasmapheresis, IVIG, etc

- **Long time control**
  - Antihistamine
  - Auxiliary medications
  - Oral steroids, etc

- **Long time remission, cure**
  - Desensitization
  - Prophylactic use of antihistamines, etc

Principle of the management of urticaria

- **Diagnosis of disease subtype**
  - Inducible urticaria
  - Spontaneous urticaria

- **Make clear the aim and options of treatments**
  - Drug therapies for symptoms (anti-histamines, etc)

- **Remove or avoid Causes/aggravating factors**
  - No symptoms under treatments (Remittance of disease activities)
  - No symptoms without treatments

Thank you for your listening