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Exploring the Management of Urticaria: Discussion of Optimal Treatment Strategies

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Classification of urticarias

Acute Urticaria: < 6 weeks

Chronic Urticaria: > 6 weeks
Classification of chronic urticarias

Spontaneous Urticaria

Inducible Urticaria

Zuberbier et al., Allergy 2014: 69; 868-887
## Classification of chronic urticarias

<table>
<thead>
<tr>
<th>Spontaneous Urticaria</th>
<th>Due to known cause</th>
</tr>
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<tbody>
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Zuberbier et al., Allergy 2014: 69; 868-887
## Classification of chronic urticarias

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<tbody>
<tr>
<td></td>
<td>Symptomatic Dermographism</td>
<td></td>
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<tr>
<td></td>
<td>Cold Contact Urticaria</td>
<td></td>
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<tr>
<td></td>
<td>Solar Urticaria</td>
<td></td>
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<tr>
<td></td>
<td>Delayed Pressure Urticaria</td>
<td></td>
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<tr>
<td>Inducible Urticaria</td>
<td>Heat Contact Urticaria</td>
<td></td>
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<tr>
<td></td>
<td>Vibratory Urticaria</td>
<td></td>
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<tr>
<td></td>
<td>Contact Urticaria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aquagenic Urticaria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cholinergic Urticaria</td>
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Zuberbier et al., Allergy 2014: 69; 868-887
Chronic Inducible Urticaria (CIndU)
Classification of chronic urticarias

Spontaneous Urticaria
- Due to known cause
- Due to unknown cause

Inducible Urticaria
- Symptomatic Dermographism
- Cold Contact Urticaria
- Solar Urticaria
- Delayed Pressure Urticaria
- Heat Contact Urticaria
- Vibratory Urticaria
- Contact Urticaria
- Aquagenic Urticaria
- Cholinergic Urticaria

Zuberbier et al., Allergy 2014: 69; 868-887
Prevalence of chronic spontaneous urticaria

Prevalence: 0.5 – 1%
may be increasing
Prevalence of chronic spontaneous urticaria

Prevalence: 0.5 – 1%
may be increasing

Europe: 8 Million patients
World: 80 Million patients

Maurer et al., Allergy 2011: 66; 317-330
Chronic spontaneous urticaria is chronic…

> 6 weeks: 100%
> 6 months: 50%
> 10 years: 20%
Chronic spontaneous urticaria is chronic...

> 6 weeks: 100%
> 6 months: 50%
> 10 years: 20%

5-7 years on average
Chronic urticaria is a common, disabling, and complex disease.
Urticaria – Pathogenesis
Mast cells are the key effector cells in the induction of urticaria symptoms.

**CAUSE**
- IgE
- SCF
- FcεRI
- IgG
- FcεR
- LPS
- TLRs
- Complement
- Anaphylatoxins
- Neuropeptides
- Endothelin-1
- Bacteria
- Interleukins
- Chemokines
- Oxytocine
- Leukotriene
- POMCs
- Prostaglandins
- Cannabinoids
- Adenosine
- Urokinase
- Capsaicin
- ?
- PIRA/PIRB

**Recruitment**
- IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, TNF, MIPs, IFN-γ, GM-CSF, TGF-β, bFGF, VPF/VEGF, PGD₂, LTB₄, LTC₄, PAF, histamine, serotonin, heparin, chondroitin-sulfate, chymase, tryptase, CPA

**Vasodilation**
- Activation
- Extravasation
- Recruitment

**PRURITUS**
- ERYTHEMA
- WHEAL
- INFLTRATE

Urticaria and Angioedema. Zuberbier T, Grattan C, Maurer M (eds.). Springer 2010
Wheal and flare

Angioedema
Urticaria

Wheal and flare  Angioedema
Urticaria

Wheal and flare

Angioedema
Wheal and flare

Angioedema
Urticaria - Therapeutic strategies

- **Trigger**
- **Cause** → **Mast cell-activating signal** → **Mast cell activation** → **Mast cell mediators** → **Urticaria reaction**

**causal**

**symptomatic**
Urticaria - Therapeutic strategies

Trigger

Causal Pathway:
- Cause
- Mast cell-activating signal
- Mast cell activation
- Mast cell mediators

Symptomatic End:
- Angioedema
- Wheals

causal

symptomatic
Urticaria - Therapeutic strategies

Trigger

Cause

Mast cell-activating signal

Mast cell activation

Mast cell mediators

Wheals

Angioedema

causal

symptomatic

Urticaria and Angioedema. Zuberbier T, Grattan C, Maurer M (eds.). Springer 2010
Urticaria - Therapeutic strategies

- Trigger
  - Cause
    - Mast cell-activating signal
    - Mast cell activation
    - Mast cell mediators
    - Wheals
      - Angioedema

causal
symptomatic

Urticaria and Angioedema. Zuberbier T, Grattan C, Maurer M (eds.). Springer 2010
Urticaria - Therapeutic strategies

- **Trigger**
  - **Cause**
  - Mast cell-activating signal
  - Mast cell activation
  - Mast cell mediators
  - Wheals Angioedema

**Urticaria and Angioedema. Zuberbier T, Grattan C, Maurer M (eds.). Springer 2010**

**causal**

**symptomatic**
What is the goal of treating patients with chronic urticaria?

Absence of symptoms
„Treat the disease until it is gone“
Urticaria Control Test (UCT)

Is your urticaria under control?
Urticaria Control Test (UCT)

1. How much have you suffered from the **physical symptoms of the urticaria** (itch, hives (welts) and/or swelling) in the last four weeks?
   - O very much
   - O much
   - O somewhat
   - O a little
   - O not at all

2. How much was your **quality of life** affected by the urticaria in the last 4 weeks?
   - O very much
   - O much
   - O somewhat
   - O a little
   - O not at all

3. How often was the **treatment** for your urticaria in the last 4 weeks **not enough** to control your urticaria symptoms?
   - O very often
   - O often
   - O sometimes
   - O seldom
   - O not at all

4. **Overall**, how well have you had your urticaria **under control** in the last 4 weeks?
   - O not at all
   - O a little
   - O somewhat
   - O well
   - O very well
Urticaria Control Test (UCT)

1. How much have you suffered from the physical symptoms of the urticaria (itch, hives (welts) and/or swelling) in the last four weeks?
- Very much
- Much
- Somewhat
- A little
- Not at all

0 points - 1 point - 2 points - 3 points - 4 points

2. How much was your quality of life affected by the urticaria in the last 4 weeks?
- Very much
- Much
- Somewhat
- A little
- Not at all

0 points - 1 point - 2 points - 3 points - 4 points

3. How often was the treatment for your urticaria in the last 4 weeks not enough to control your urticaria symptoms?
- Very often
- Often
- Sometimes
- Seldom
- Not at all

0 points - 1 point - 2 points - 3 points - 4 points

4. Overall, how well have you had your urticaria under control in the last 4 weeks?
- Not at all
- A little
- Somewhat
- Well
- Very well

0 points - 1 point - 2 points - 3 points - 4 points
Urticaria Control Test (UCT)

1. How much have you suffered from the **physical symptoms of the urticaria** (itch, hives (welts) **and/or swelling**) in the last four weeks?
   - O very much
   - O much
   - O somewhat
   - O a little
   - O not at all

2. How much was your **quality of life** affected by the urticaria in the last four weeks?
   - O very much
   - O much
   - O somewhat
   - O a little
   - O not at all

3. How often was the treatment for your urticaria in the last 4 weeks **needed to control urticaria symptoms**?
   - O very often
   - O often
   - O sometimes
   - O seldom
   - O not at all

4. **Overall**, how well have you had your urticaria **under control** in the last 4 weeks?
   - O not at all
   - O a little
   - O somewhat
   - O well
   - O very well

≥12 = ✓
Validity, reliability and interpretability of the Thai version of the urticaria control test (UCT)

Kanokvalai Kulthanan¹, Leena Chularojanamontri¹*, Papapit Tuchinda¹, Chuda Rujitharanawong¹, Marcus Maurer² and Karsten Weller²
Urticaria Control Test

www.moxie-gmbh.de

karsten.weller@charite.de
Treatment of chronic urticaria

How do we help our patients to get their urticaria under control?
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

Zuberbier et al., Allergy 2014: 69; 868-887
Second-generation H₁-Antihistamine (sgAH)
Second-generation $H_1$-Antihistamine (sgAH)

If symptoms persist after 2 weeks

Increase sgAH dose (up to 4x)
Effects of sedating antihistamines

First Generation Antihistamine

REM Sleep delay and reduced

Church, Maurer, ..., Zuberbier. Allergy 2010; 65: 459-66
Combination vs. Updosing

**Pruritus reduction (in %)**

- **Combination**
  - 2 x 2: 16
  - 3 x 2: 38
- **Updosing**
  - 4 x 1: 13

Schulz et al., *Hautarzt* 2009
Second-generation H₁-Antihistamine (sgAH)

If symptoms persist after 2 weeks

Increase sgAH dose (up to 4x)
Patients sufficiently treated with antihistamines

- ns-AH (regular dose): 45%
- ns-AH (high dose): 65%
Increasing the dose of antihistamines

Weller et al., PLoS ONE 2011
Non sedating, modern, second generation antihistamines are the first line treatment!

Which one should I use? How do I choose?
Updosed AHs work better!

EXAMPLE: Cold urticaria
Cold Urticaria
Trigger Threshold Assessment in Cold Urticaria
Trigger Threshold Assessment in Cold Urticaria
Updosing of Bilastine improves protection from cold in patients with cold urticaria!
Updosing of Bilastine improves protection from cold in patients with cold urticaria!

Krause et al., Allergy 2013: 68; 921-928.
Updosing of Bilastine improves protection from cold in patients with cold urticaria!

Krause et al., Allergy 2013: 68; 921-928.
Updosing of Bilastine improves protection from cold in patients with cold urticaria!

Krause et al., Allergy 2013: 68; 921-928.
Updosing of Bilastine in cold urticaria patients increases the number of complete responders!

<table>
<thead>
<tr>
<th></th>
<th>Complete response*</th>
<th>Partial response**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Placebo</td>
<td>1 (5%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>BL 20 mg</td>
<td>7 (35%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>BL 40 mg</td>
<td>11 (55%)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>BL 80 mg</td>
<td>12 (60%)</td>
<td>7 (35%)</td>
</tr>
</tbody>
</table>

*No wheal-and flare reaction at lowest temperature (4°C)
**Reduction in temperature threshold >5°C

Krause et al., Allergy 2013: 68; 921-928.
Updosed AHs work better!

EXAMPLE:
Chronic spontaneous urticaria
Updosing of Bilastine in CSU

- **No therapy**
- **Bilastine 20mg**
  - if no CR
  - **Bilastine 40mg**
  - if no CR
  - **Bilastine 80mg**

*Rescue medication (bilastine 20mg)

**Daily documentation of the UAS (wheal number / pruritus intensity)**

**CU-Q2oL completion**

Weller et al., Unpublished data
Updosing of Bilastine improves chronic spontaneous urticaria!

Weller et al., Unpublished data
Updosing of Bilastine improves chronic spontaneous urticaria!

Patients with minimal urticaria activity and minimal pruritus (in %)

- UAS7 ≤ 6
  - 1
  - 2
  - 8

- Pruritus7 ≤ 3
  - 1
  - 5
  - 10

Weller et al., Unpublished data
Second-generation H\textsubscript{1}-Antihistamine (sgAH)

Increase sgAH dose (up to 4x)

If symptoms persist after 2 weeks

Add Omalizumab, Cyclosporine A, or Leukotrieneantagonist

If symptoms persist after 1-4 weeks

Short course systemic corticosteroid may be tried for exacerbations

EAACI / GA\textsuperscript{2}LEN / EDF / WAO

Urticaria Guidelines: 2013 Revision and Update
Omalizumab works in CSU

Maurer et al., N. Engl. J. Med. 2013: 368; 924-935
Omalizumab works in CSU

**Change in UAS7**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Omalizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75 mg</td>
</tr>
</tbody>
</table>

- Placebo: -10
- Omalizumab 75 mg: -14
- Omalizumab 150 mg: -16
- Omalizumab 300 mg: -18

***Maurer et al., N. Engl. J. Med. 2013: 368; 924-935***
Omalizumab works in CSU

Responders (in %) UAS7≤6 at Week 12

- Placebo: 19.0%
- 75 mg: 26.8%
- 150 mg: 42.7%
- 300 mg: 65.8%

***

Maurer et al., N. Engl. J. Med. 2013, in press
Omalizumab works in CSU

Improvement in QoL (DLQI score)

- Omalizumab 300 mg
- Omalizumab 150 mg
- Omalizumab 75 mg
- Placebo

Maurer et al., N. Engl. J. Med. 2013: 368; 924-935
Second-generation H$_1$-Antihistamine (sgAH)

Increase sgAH dose (up to 4x)

If symptoms persist after 2 weeks

Add Omalizumab, Cyclosporine A, or Leukotrieneantagonist

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GA²LEN Global Urticaria Forum

URTICARIA 2016: Guideline Consensus Conference

GA²LEN Global Urticaria Forum

GUF 2016

5th Consensus Conference on the Update and Revision of the EAACI/GA²LEN/WAO/EDF Guideline for Urticaria

URTICARIA 2016

BERLIN
LANGENBECK-VIRCHOW-HAUS
29 November – 1 December 2016

globalurticariaforum.org; urticariaguideline.org
Bilastine reduces proinflammatory cytokine levels *in vivo*!