Update in the Pathogenesis of Chronic Urticaria in Adults

Chair: Dr Chei-Soo (South Korea), Dr Jonathan Bernstein (US)

COI Disclosure
In relation to this presentation, I declare the following, real or perceived conflicts of interest:

<table>
<thead>
<tr>
<th>Consultancy fees from</th>
<th>Research support and Speaker's Bureau from</th>
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<tbody>
<tr>
<td>MSD</td>
<td>GlaxoSmithKline</td>
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<tr>
<td>Novartis</td>
<td>Tanabe-Mitsubishi</td>
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<td>Kyouwahakkou-Kirin</td>
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</table>
Urticaria is a disease that develops wheals.

Extravasation of plasma (wheal)

Vasodilatation (flare)

- Histamine, etc.
- Bradykinin
- IgE

In the dermis, these substances cause:
- Vasodilation
- Increased permeability
- Extravasation of plasma (wheal)
- Flare (redness and swelling)
In spite of relatively simple clinical features, the shape and size of the eruptions and the etiology of urticaria is largely various and heterogeneous.
Urticaria is a disease that develops wheals

- **Direct stimuli (specific)**
  - Exogenous antigens, physical stimuli, certain foods/drugs, insect toxins, chemical substance, etc.

- **Indirect stimuli (mostly not specific)**
  - Infection, fatigue, stress, diets, anti-IgE/FcεRI autoantibodies, drugs, internal organ failure, urticaria related syndromes, etc.

- Not identified in many cases
### Classification of chronic urticaria subtypes (presenting with wheals, angioedema, or both)

<table>
<thead>
<tr>
<th>Chronic Urticaria Subtypes</th>
<th>Inducible Urticaria</th>
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<tbody>
<tr>
<td><strong>Chronic Spontaneous Urticaria (CSU)</strong></td>
<td>Symptomatic dermographism(^1)</td>
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<td>Spontaneous appearance of wheals, angioedema, or both (\geq 6) weeks due to known or unknown causes</td>
<td>Cold urticaria(^2)</td>
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<td>Delayed pressure urticaria(^3)</td>
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<td></td>
<td>Solar urticaria</td>
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<td>Heat urticaria(^4)</td>
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<td>Vibratory angioedema</td>
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<td></td>
<td>Cholinergic urticaria</td>
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<td>Contact urticaria</td>
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<td>Aquagenic urticaria</td>
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</table>

\(^1\)also called urticaria factitia, dermographic urticaria; \(^2\)also called cold contact urticaria, \(^3\)also called pressure urticaria; \(^4\)also called heat contact urticaria;

*Urticaria needs to be differentiated from other medical conditions where wheals, angioedema, or both can occur as a symptom, for example skin prick test, anaphylaxis, auto-inflammatory syndromes, or hereditary angioedema (bradykinin-mediated angioedema).

Factors that may be associated with the pathogenesis of urticaria

1. Direct triggers (mainly exogenous and transient)
   1) Exogenous antigens
   2) Physical stimuli
   3) Sweating
   4) Foods*
      food antigens, food histamine, pseudo-allergens (pork, bamboo shoot, rice cake, spices, etc), food additives (preservatives, artificial pigment), salicylic acids*
   5) Drugs
      antigens, contrast media, NSAIDs*, preservatives, succinic acid esters, vancomycin (red man syndrome), etc
   6) Exercises

2. Background factors (mainly endogenous and continuous)
   1) Sensitization (specific IgE)
   2) Infections
   3) Tiredness/stress
   4) Foods*, except for antigens
   5) Drugs: Aspirin*, other NSAIDs* (for FDEIA), angiotensin converting enzymes (ACE) inhibitors (for angioedema), etc
   6) Autoantibodies against IgE or the high affinity IgE receptors
   7) Underlying disease
      Collagen and related disease (SLE, Sjögren's syndrome, etc), lymphoproliferating diseases, hereditary disorders (e.g. C1-INH deficiency), serum sickness, other organ dysfunctions, circadian rhythm (idiopathic urticaria tends to aggravate from evening toward morning)

Any one is not sufficient to cause urticaria by itself

*: May act as either direct triggers or background factors.

A histamine releasing antigen in sweat for basophils and skin test of patients with cholinergic urticaria has been identified as MGL_1304 released from *M. globosa* on the skin.

Control (n=14)

Cholinergic urticaria (n=35)

Histamine release (net %)

Positive (Histamine release >5%)

23/35 (66%)

0/14 (0%)

*M. globosa* is synthesized as 29kDa protein, processed and released as a 17kDa protein.


Factors and possible underlying causes of CSU

**Food**: allergens, and psuedallergens (spices, salicyclic acid and other additives)

**NSAIDs**

**ACI inhibitor** *

(for Angioedema)

**Fatigue**

**Stress**

**Infections**

**Autoimmunity**: against IgE/FcεRIα*, thyroid tissues

*: May explain mast cell activation and/or vascular reactions
Clinical features of patients with chronic urticaria with or without autoantibodies

Evidences of ASST for association with clinical features


Evidences of ASST against association with clinical features

Causes and exacerbating factors of CSU

A variety of factors may be associated with exacerbation and improvement of the symptoms of CSU to various degrees. However, none of them explains the whole pathogenesis of CSU in most patients.
The pathogenesis urticaria has been studied in view points of

- Mechanism of mast cell activation
  - IgE mediated:
    - exogenous/endogenous antigen, anti-IgE, anti-FcεRIα
  - Serum factors:
    - Complements, histamine release factors (identified and unidentified)
    - Neuropeptides, proteases, etc

- Mediators released from mast cell
  - histamine, prostaglandins, PAF, bradykinin, cytokines, etc

- Histopathology
  - Mast cells, lymphocytes, eosinophils, neutrophils, basophils

- Trigger/underlying causes
  - Exogenous antigens
  - Physical stimuli
  - Infections *H. Pylori* infection)
  - Diet (pseudoantigens, etc)
  - Biomarkers

- Treatments
  - antihistamines
  - Omalizumab
  - Targeting histamine, inflammation/immune system, IgE, coagulation system, etc.
Algorithm in the practice parameters of urticaria published by AAAAI, ACAAI and JCAAI (2014)


EAACI global guideline (2014)

Allergy 2014; 69: 868-887

**First line:**
Modern second generation antihistamines

**Second line:**
Increase dosage up to fourfold of modern second generation antihistamines

**Third Line:**
Add on to second line*: Omalizumab or Ciclosporin A or Montelukast

Short course (max 10 days) of corticosteroids may also be used at all times if exacerbations demand this

*the order of third line treatments does not reflect preference.

**STEP 1**
- Monotherapy with second generation antihistamine
- Avoidance of triggers (e.g., NSAIDs) and relevant physical factors if physical urticaria/angioedema syndrome is present.

**STEP 2**
One or more of the following:
- Dose advancement of 2nd generation antihistamine used in Step 1
- Add another second generation antihistamine
- Add H₂- antagonist
- Add leukotriene receptor antagonist
- Add 1st generation antihistamine to be taken at bedtime

**STEP 3**
Dose advancement of potent antihistamine (e.g. hydroxyzine or doxepin) as tolerated

**STEP 4**
Add an alternative agent
- Omalizumab or cyclosporine
- Other anti-inflammatory agents, immunosuppressants, or biologics

*the order of third line treatments does not reflect preference.
The pathogenesis urticaria has been studied in view points of:

- **Mechanism of mast cell activation**
  - IgE mediated:
    - exogenous/endogenous antigen, anti-IgE, anti-FcεRIα
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- **Mediators released from mast cell**
  - histamine, prostaglandins, PAF, bradykinin, cytokines, etc

- **Histopathology**
  - Mast cells, lymphocytes, eosinophils, neutrophils, basophils

- **Trigger/underlying causes**
  - Exogenous antigens
  - Physical stimuli
  - Infections (*H. Pylori* infection, virus, etc)
  - Diet (pseudoantigens, etc)
  - Biomarkers

- **Targets of treatments**
  - Targeting histamine, inflammation/immune system, IgE, coagulation system, etc.

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= translationally controlled tumor protein (Kawakami, 2014)

antihistamines

Omalizumab
sparse lymphocytic

perivascular eosinophilic

diffuse intradermal neutrophilic

perivascular neutrophilic
Involvement of basophils in CSU

- Basophils are observed in skin lesion of CSU.

- Number of peripheral blood basophils are decreased (Basopenia) in patients with CSU in correlation to the severity of CSU.

- Basophils of many patients with CSU are low- or non-responsive to anti-IgE antibody.

- Both decreases in number and in response to anti-IgE antibody of basophils recover either by natural course or the treatments of CSU.


Levels of plasma FDP, D-dimer and serum CRP are both elevated in correlation to disease activities.

Blood coagulation potential is increased in CSU

Coagulation factor concentration

APTT clot waveform analysis (represents coagulation potential *in vitro*)

Calibrated automated thrombography (CAT) (Thrombin produce potential *in vitro*)


Sakukrai, et al. (submitted)
## Cases treated by medications with anti-coagulation/fibrinolysis activities

<table>
<thead>
<tr>
<th>Authors and subjects</th>
<th>Preceding treatments</th>
<th>Medications</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Chua SL, Gibbs S (2005), 1 case</td>
<td>Resistant for anti-histamines and immune-suppressants</td>
<td>Heparin subcutaneous injections (5000 units × 2/day)</td>
<td>A case report. Remission, and recurrent on stop medication.</td>
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<tr>
<td>Asero et al. (2010), 8 cases</td>
<td>Resistant to anti-histamines and steroids. Increase of coagulation markers.</td>
<td>Heparin subcutaneous injections (11,400 units/day) + tranexamic acid 1g × 3/day (oral)</td>
<td>Very effective for 5 out of 8 cases</td>
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<tr>
<td>Parslew et al. (2000), 8 cases</td>
<td>Resistant for anti-histamines</td>
<td>Warfarin (PT-INR: 2-2.5)</td>
<td>Effective for 6 out of 8 cases</td>
</tr>
<tr>
<td>Mahesh et al. (2009), 5 cases</td>
<td>Resistant for anti-histamines and steroids. APST positive</td>
<td>Warfarin (PT-INR: 1.1-1.8)</td>
<td>Effective for 4 out of 5 cases</td>
</tr>
<tr>
<td>Takahagi et al. (2010), 2 cases</td>
<td>Resistant for anti-histamines and immune-suppressants.</td>
<td>Protease inhibitor (Nafamostat mesilate; NM, div, and camostat mesilate; CM, oral).</td>
<td>Eruptions disappeared during NM div, and recurred when stopped div. Symptoms of one case were effectively suppressed by oral CM.</td>
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Prothrombin (II) → Thrombin → Fibrinogen (I) → Fibrin

Potential of the intrinsic pathway is elevated in CSU

Heparin

Blood coagulation pathways

Potential of the intrinsic pathway is elevated in CSU

Intrinsic pathway measured by APTT (activated partial thromboplastin time)

Extrinsic pathway measured by PT (prothrombin time)

What does trigger the extrinsic pathway?

Tissue factor (III) (tissue damage, etc)

Prothrombin fragment F1+2

FDP & D-dimer

Thrombin stabilizes (exposure of endothelial cell collagen, etc)

Tissue factor (III)

The coagulation process is initiated by the extrinsic pathway with an exposure to tissue factor, followed and enhanced by the activation of the intrinsic pathway and results in fibrin formation.
What is the mechanism of coagulation/fibrinolysis in chronic urticaria?


Activated Factor XII

Activated FVII

- Asero, et al reported the increase of FVIIa (initiator of the extrinsic pathway), but not FXIIa (initiator of the intrinsic pathway) in CSU.


- They also revealed the expression of TF in eosinophiles in the site of wheal formation.
TF expression by endothelia cells is induced by histamine and basophils via H1-receptor

(Y. Yanase, et al. unpublished data)
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

1st step aim: No symptoms under treatments (Remittance of disease activities)

2nd step aim: No symptoms without treatments

Continuous vs on demand use of antihistamine

**Desloratadine**


**Epinastine**

Time course of itching in day time: Number of days when itch score was >3


**Ebastine**


All three studies endorse proactive use of antihistamine after the diminishment of symptoms. The effect of them on "cure" remains as uncertain.
Long term effect of omalizumab on chronic urticaria

Chronic spontaneous urticaria

Solar urticaria
Cold urticaria
Heat urticaria
Cholinergic urticaria
Delayed pressure urticaria
Mechanical urticaria
Urticarial vasculitis

Omalizumab has been reported to be effective for subtypes of chronic urticaria, regardless of the autoimmunity, suggesting the important role of IgE in the common mechanism of urticaria.

It does not appear to bring "cure" of urticaria.
Effect of 1 month proactive treatment with oral anti-histamine on recurrence over 3 month

1 month proactive treatment reduced the recurrence in 3 months.

Even if no Sx for 1 month, 40% recurred in a month after stopping anti-histamine.

(Hide, unpublished data)
Thank you for your attention