

Update on Chronic Urticaria: *more than skin deep*

AMANDA JAGDIS
CLINICAL IMMUNOLOGY & ALLERGY, INTERNAL MEDICINE
ISLAND HEALTH AUTHORITY, VICTORIA BC
CLINICAL INSTRUCTOR, UBC

Faculty/Presenter Disclosure

- **Faculty:** Amanda Jagdis
- **Relationships with commercial interests:**
 - **Speakers Bureau/Honoraria: Aralez Pharmaceuticals.**

Mitigating Potential Bias

The presentation will be a guidelines-based approach to management and will include discussion of all the currently available guidelines-based treatment options.

What's new in Chronic Urticaria?

- Updated terminology and classification
- Epidemiology & Pathophysiology
- Quality of life impact
- Evidence-based guidelines
 - Diagnostic work-up
 - Management of chronic urticaria

Urticaria

- Characterized by the sudden appearance of wheals, angioedema or both

Zuberbier T. et al. Allergy 2014; 69(7):868-887

Wheals

- Central swelling of variable size surrounded by erythema (flare)
- Itching or sometimes burning sensation
- Transient: skin returns to normal in 1-24 hours

Zuberbier T. et al. Allergy 2014; 69(7):868-887

Angioedema

- Sudden, pronounced swelling of the lower dermis and subcutaneous tissue
 - frequently below mucous membranes
- Itchy or painful
- Up to 72 hours to resolve

Zuberbier T. et al. Allergy 2014; 69(7):868-887

Symptoms due to Mast Cell mediator release

- Mast cell degranulation in the skin
- Release of mediators (histamine & others)
- Sensory nerve activation → pruritus
- Increased vascular permeability → plasma extravasation and tissue edema

Sussman et al. Allergy, Asthma & Clinical Immunology (2015) 11:7

Terminology and Definitions

- **Acute Urticaria:**
 - Urticaria for < 6 weeks
- Allergic reaction to foods, drugs, or insect stings
- Acute viral infections
- Spontaneous

Zuberbier T. et al. Allergy 2014; 69(7):868-887

Terminology and Definitions

- **Chronic Urticaria**
 - Intermittent wheals, angioedema, or both, for ≥ 6 weeks

Zuberbier T. et al. Allergy 2014; 69(7):868-887

Terminology and Definitions

- Chronic urticaria is further classified as
 - **Spontaneous**
 - **Inducible:** Urticaria occurs in response to known stimulus, eg.
 - Physical urticaria
 - Cholinergic urticaria
 - Contact urticaria
 - Aquagenic urticaria

Zuberbier T. et al. Allergy 2014; 69(7):868-887

Terminology and Definitions

Chronic idiopathic urticaria is now called
Chronic Spontaneous Urticaria

Zuberbier T. et al. Allergy 2014; 69(7):868-887

Chronic spontaneous urticaria: Epidemiology

- Prevalence 0.5-1%
- Peak onset 20-40 years of age
- More common in women
- Associated spontaneous angioedema in 1/3 – 2/3 of cases
- Average duration is about 3-5 years
- Longer duration associated with severe disease

Sussman et al. Allergy, Asthma & Clinical Immunology (2015) 11:7

Chronic spontaneous urticaria: Pathophysiology

- 45% have autoimmune component
- Antibodies to IgE receptor subunit, or to IgE on mast cell surface
- 25% of cases have thyroid auto-antibodies

Sussman et al. Allergy, Asthma & Clinical Immunology (2015) 11:7

Chronic spontaneous urticaria: Quality of life impact

- Significant morbidity
- Associated with substantial impairment in health-related quality of life
- Negative impact on all areas of life
 - Work, school, social activities, diet and sleep

Sussman et al. Allergy, Asthma & Clinical Immunology (2015) 11:7

Chronic spontaneous urticaria: Quality of life impact

- Psychiatric comorbidity
- Mood, anxiety and personality disorders reported
- 48% of patients with CSU met criteria for psychiatric diagnosis

Staubach et al. Acta Derm Venereol 2011; 91: 557-561.

“Intensive and costly general screening programs for causes of urticaria are strongly advised against.”

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Limited initial testing recommended in current guidelines

1. Exclude severe inflammation:
 - CBC differential
 - ESR or CRP
2. Omission of suspected drugs
 - Eg. NSAIDs
3. Rule out differential diagnoses

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What is not useful?

- Food-specific IgG testing
 - Carr et al. Allergy, Asthma & Clinical Immunology 2012, 8:12
<http://www.aacijournal.com/content/8/1/12>
- Routine extensive testing of serologies etc.
 - Guided by patient history

Differential Diagnosis

- Urticarial vasculitis
- Hereditary angioedema
- ACE inhibitor-induced angioedema
- Cryopyrin associated periodic syndromes
- Exercise-induced anaphylaxis
- PUPPP
- Urticaria pigmentosa

Red Flags

- Burning, painful hives lasting >24 hours with residual hyperpigmentation

Urticarial Vasculitis

- Atypical urticaria, lesions last >24hrs
- Skin biopsy showing vasculitis

Red Flags

- Angioedema *without* urticaria

Hereditary Angioedema, Acquired Angioedema

- Recurrent angioedema, *without* urticaria or pruritus, affecting skin, upper respiratory, and GI tracts
- Laryngeal involvement may cause fatal asphyxiation
- C4; C1 inhibitor level

ACE-inhibitor induced angioedema

- Angioedema while on ACE-inhibitor

Red Flags

- Urticaria accompanied by constitutional, systemic symptoms

Hereditary/Acquired Autoinflammatory Disease

- Recurrent, unexplained fever
- Bone/joint pain
- Malaise
- Eg. Cryopyrin associated periodic syndromes; Schnitzler's syndrome; Adult Onset Still's Disease; TNF Receptor Associated Periodic Syndrome (TRAPS).

Red Flags

- Urticaria pigmentosa
- "Darier's sign": Lesions urticate when scratched

Chronic Spontaneous Urticaria: Management

- Goal of therapy:
 - Complete symptom control and disease remission
- Nonpharmacologic:
 - Avoid exacerbating factors
 - NSAIDs, stress
 - Physical triggers

1st generation antihistamines are *no longer* indicated for use in urticaria

Sussman G. et al. Asthma, Allergy and Clinical Immunology. 2015; 11: 1-7

First generation antihistamines are not indicated

- Potentially interfere with restful (REM) sleep
- Cause hangover or “morning-after” effects
- Impair learning and memory, and reduce work efficiency

Impairment is not necessarily accompanied by sedation

Church et al. Allergy. 2010; 65: 459-66.
Sussman G. et al. Asthma, Allergy and Clinical Immunology. 2015; 11: 1-7

First generation antihistamines are not indicated

- First generation H1-antihistamines have been implicated in
 - Civil aviation accidents involving pilot fatalities
 - Motor vehicle accident fatalities
 - Overdoses
- Diphenhydramine 50 mg resulted in poorer driving performance than alcohol sufficient to produce a blood concentration of 0.1%

Weiler JM, et al. Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. A randomized, placebo-controlled trial in the Iowa driving simulator. Ann Intern Med 2000;132:354-363.
Church et al. Allergy. 2010; 65: 459-66.

EAACI/GA²LEN/EDF/WAO
Chronic Spontaneous Urticaria Treatment Guideline

First line:

- Modern second-generation antihistamine at standard dose
- Should be taken on a daily basis rather than PRN
- No advantage to combining or “rotating” antihistamines

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Sussman G. et al. Asthma, Allergy and Clinical Immunology. 2015; 11: 1-7

Chronic Spontaneous Urticaria Treatment Guideline

- *If symptoms persist after 2 weeks*

Second Line:

- Increase dosage up to 4-fold of modern second generation antihistamine
- Eg. Cetirizine up to 40mg daily or desloratadine up to 20mg daily

Zuberbier T. et al. Allergy 2014; 69(7):868-887

Chronic Spontaneous Urticaria Treatment Guideline

- *If symptoms persist after 1-4 further weeks*

Third line therapy under specialist supervision:

- Add on to second line, options include:
 - Omalizumab
 - or Ciclosporin A
 - or Montelukast

Zuberbier T. et al. Allergy 2014; 69(7):868-887

Role of oral corticosteroids

- A short course of systemic corticosteroids can be used for acute exacerbations
- Eg. 0.3-0.5 mg/kg of prednisone for up to 10 days
- Avoid using corticosteroids for long-term control of chronic urticaria

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Role of antileukotriene and H2 antihistamine therapy

- A trial of montelukast can be used for H1-antihistamine refractory chronic urticaria
- Level of evidence is low
- H2 antihistamines are no longer recommended for first, second or third-line therapy

Zuberbier T, et al. Allergy 2014; 69(7):868-887

Omalizumab

- Omalizumab: anti-IgE humanized monoclonal antibody
- Prescribed and overseen by specialist
- Given by subcu injection
- Side effects: injection site reactions, anaphylaxis, unclear association with cardiovascular disease

Chronic Spontaneous Urticaria: Omalizumab

- Approved in 2014 by Health Canada
- Third-line treatment for:
 - Chronic Spontaneous Urticaria refractory to treatment with non-sedating second generation H1 antihistamines
 - Approved for patients ≥ 12 years of age
- Large, well-designed, randomized double-blind, placebo-controlled trials demonstrating safety and efficacy

Summary & Take Home Principles

- Chronic Spontaneous Urticaria replaces the term Chronic Idiopathic Urticaria
- Evidence-based guidelines for Chronic Spontaneous Urticaria
 - Limited routine diagnostic testing advised
 - First line: Non-sedating, non-impairing second generation H1 antihistamines
 - Second line: Up-dosing to 2, 3, or 4 times the licensed dose of second generation H1 antihistamines
 - Third line: Omalizumab has emerged as an effective option for refractory disease

Who should be referred:

- Acute Urticaria
 - Without an obvious or previously defined trigger
 - Suspicion of allergy (Ex. food/drug/latex/venom) for confirmatory testing and management
- Chronic Urticaria
- Patients with Red Flags

Reading List

Guidelines:

- The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Zurbier et al. [Allergy](#). 2014 Jul;69(7):868-87.

Articles:

- Insights and advances in chronic urticaria: a Canadian perspective. Sussman G et al. [Allergy Asthma Clin Immunol](#). 2015 Feb 11;11(1):7.

References

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- Insights and advances in chronic urticaria: a Canadian perspective. Sussman G et al. [Allergy Asthma Clin Immunol](#). 2015 Feb 11;11(1):7.
- High Prevalence of Mental Disorders and Emotional Distress in Patients with Chronic Spontaneous Urticaria. Staubach et al. *Acta Derm Venereol* 2011; 91: 557-561.
- CSACI Position statement on the testing of food-specific IgG. Carr, et al. *Allergy, Asthma & Clinical Immunology*, 2012, 8:12.
- Histamine and H1-antihistamines: celebrating a century of progress. Simons FE & Simons K. *J Allergy Clin Immunol* 2011;128:1139-50.
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- Omalizumab for the treatment of chronic spontaneous or autoimmune urticaria. Maurer et al. *NEJM* 2013. Mar 7;368(10):924-35.
- Autoimmune chronic spontaneous urticaria: what we know and what we do not know. Kolkhir et al. *J Allergy Clin Immunol* June 2017. 139;6: 1772-81