Allergy for the Dermatologist
Part I

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Disclosures

- Astra Zeneca
- Pfizer
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- Regeneron
Urticaria

Adapted from www.dermnetnz.org/topics/acute-urticaria/
Urticaria

Overview

- Pruritic, erythematous papules or plaques, with superficial swelling of the dermis
- 1 in 5 patients will experience urticaria in their lifetime
- Acute urticaria - lasts less than 6 weeks
Chronic urticaria

- Chronic urticaria (CU) - urticaria on most days of the week, for 6 weeks or longer
  - 40% of patients with CU have accompanying episodes of angioedema or deeper swelling of dermal or mucosal tissues\(^1,^2\)
  - 10% have angioedema as their main manifestation\(^1,^2\)

\(^1\)Kaplan AP. J Allergy Clin Immunol 2004.
Urticaria - incidence and recurrence (1/2)

- Estimated incidence in general population: 4.9% over 10 years
- In 10 years of follow up, 7.8% of those with urticaria developed CU
- Of those that developed CU, 52.6% achieved remission at 1 year and 88.9% at 5 years

Urticaria - incidence and recurrence (2/2)

- In patients attending an allergy clinic at an academic center:
  - 13% of patients with CU developed recurrent CU (return of CU >6 months after cessation of controller therapy)
  - Patients who developed recurrent CU were more likely to require treatment other than anti-histamines

1Kim JK, Har D et al. J Allergy and Clin Immunol In Practice 2018
Acute urticaria

- Occurs in up to 20 percent of the population
- Can be caused by medications, foods, infections
- Generally it is self-limited
Chronic urticaria

- 20% have a reversible physical trigger: Physical urticarias:
  - Dermographism
  - Cholinergic
  - Vibratory
  - Heat or cold induced contact urticaria
  - Aquagenic urticaria
  - Solar urticaria
  - Exercise induced urticaria
  - Delayed pressure urticaria
Dermographism

Chronic urticaria/chronic spontaneous urticaria (CSU)

- 80 percent: no external or allergic cause can be identified
  - Chronic idiopathic urticaria - some people classify 30-40% in this group as having an autoimmune etiology
  - The remaining 60% to 70% of patients with CIU (chronic idiopathic urticaria) are classified as having chronic spontaneous urticaria (CSU)
Chronic urticaria: Natural course of the disease

- CU is usually self-limited. Average duration is 2-5 years\textsuperscript{1,2}
- If no trigger is identified, rates of spontaneous remission at 1 year ~ approximately 30% to 50% have been reported\textsuperscript{3}
- In 1/5\textsuperscript{th} of patients symptoms have persisted beyond 5 years\textsuperscript{4}

CIU and autoimmunity

- 30% - 40% of patients with CIU have an autoimmune disease or CAU
- This is driven by IgG autoantibodies to either IgE or the α subunit of the high-affinity IgE receptor
- Leads to activation of mast cells and basophils
Mast cell activation by IgG anti-IgE receptor antibody

- Fc regions of the IgGs are in close proximity -> complement is activated

- release of C5a

- augmented histamine release upon binding to the C5a receptor

Mast Cells and CIU

- Mast cell number in patients with CU: not increased in either lesional or nonlesional skin compared to healthy controls\(^1\)

- Culture-derived mast cells grown from peripheral blood CD34+ cells from those with CU
  - \(\rightarrow\) elevated spontaneous histamine release over that observed in mast cells from healthy donors\(^2\)

\(^1\)Smith CH, Kepley C et al. J Allergy Clin Immunol 1995;96:360-4
\(^3\)Clinical & Experimental Allergy, Volume: 39, Issue: 6, Pages: 777-787.11 May 2009
Chronic urticaria and autoimmunity

- These antibodies cannot be used as diagnostic in identifying the source
- These antibodies may also be present in patients without CIU
- Although autoantibodies have been identified, the relationship of antibody titers to disease activity has not been clearly demonstrated\(^1,2\)

\(^1\)Eckman JA, Hamilton RG et al. J Invest Dermatol 2008
\(^2\)Kaplan AP, Joseph K et al. J Allergy Clin Immunol 2008
Chronic Urticaria: Patient History

- Urticarial skin lesions typically last less than 24 hours without residual change to the skin area.
- Scratching and rubbing skin -> development of ecchymosis
- Multiple ecchymotic lesions or painful lesions should alert to possible urticarial vasculitis
- Pruritus of CU - often noticeable at night
- Severe symptoms during periods of stress can occur

Chronic urticaria - ? Triggers

- Foods are extremely rare triggers
- Food elimination may help in some patients
- Exacerbating factors: NSAIDs, hormones etc
- Patients may suspect food allergies, but it is rarely proven
- Pseudoallergens, or chemicals in foods, have occasionally been linked to urticaria - restricted diets may assist patients these particular patients

- Exacerbating factors: aspirin or other NSAIDs, hormones, or particular drugs, should be sought and eliminated

1 Magerl M, Pisarevskaja D et al. Allergy 2010
Urticaria: Physical appearance

- Urticaria are pruritic, raised, and erythematous and they can have central pallor
- Shape can be round, oval, or serpiginous, and can be confluent
- H1 blocker antihistamines, can cause the appearance to be flat
- Size may range from < 1 cm to several centimeters
Chronic idiopathic urticaria

Urticaria and angioedema: Physical appearance

- It can be deeper tissue swelling which is what occurs more with angioedema.

- Angioedema involving the face, lips, tongue, extremities, or genitalia may occur in conjunction with hives or as a separate entity.
Angioedema

Lab evaluation and testing in chronic urticaria (1/3)

- Diagnosis is usually made clinically
- In 80-90% of cases a source is not identified
- Consensus statements recommend limited testing:
  - A complete blood count with differential to assess for eosinophilia
  - C-reactive protein or erythrocyte sedimentation rate to identify the risk of underlying rheumatic disease
  - TSH level
- Results of these laboratory studies are normal in most patients who lack signs and symptoms of systemic disease

¹Tarbox JA, Gutta RC et al. Ann Allergy Asthma Immunol 2011
Lab evaluation and testing in chronic urticaria (2/3)

- Value of testing for thyroid autoantibodies is thought to be linked to the idea of identifying an underlying association with possible chronic autoimmune urticaria (CAU)

- Allergen skin testing is of little value in CU except in rare cases. A high rate of false positive results may be expected, owing to the higher rate of dermographism
Lab evaluation and testing (3/3)

- A meta-analysis involving 29 clinical studies and more than 6000 cases found no association between # of tests ordered and diagnosis reached\(^1\)

- An underlying disease was found in 1.6% of cases tested (105 of 6462):
  - Cutaneous vasculitis (60 cases)
  - Thyroid disease (17 cases)
  - SLE (7 cases)
  - Connective tissue disease (16 cases)
  - Paraproteinemia (3 cases)

\(^1\)Kozel MM, Bossuyt PM et al. J Am Acad Dermatol 2003
When to do a skin biopsy?

- Uncertain diagnosis
- No response to standard
- Therapies that involve significant toxic effects are to be used

Differential diagnosis

- Systemic lupus erythematosus (SLE)
- Urticarial vasculitis: Hives are more painful and not so much pruritic. In addition:
  - Lesion last longer than 48 hours
  - Lesions leave residual pigmentation changes
  - Lesions recur whenever glucocorticoids are tapered
Typical findings with skin biopsies

- Histopathology of urticarial lesion:
  - Skin mast cells that have degranulated in the dermis
  - Perivascular leukocyte infiltrate:
    - Lymphocytes
    - Eosinophils
    - Neutrophils
    - Basophils
    - All migrate to skin lesion
Findings on skin biopsies

- Mast cells and basophils release histamine and other mediators (prostaglandins, leukotrienes, cytokines) on activation
- Result: local vasodilation, itch, and swelling in the skin.
- Histamine: central mediator, as suggested by the prominent clinical symptom of pruritus and response to antihistamines
Urticaria - H and E staining

- Skin mast cells that have degranulated in the dermis

- Perivascular infiltrate: lymphocytes, eosinophils, neutrophils, and basophils

Differential diagnosis and other causes (1/2)

- Drug- or food-based reaction
- Unrecognized infections such as hepatitis or mononucleosis
- Contact urticaria
- Insect bites leading to papular urticaria
- Urticaria pigmentosa
- Urticarial vasculitis
- Familial cold urticaria, Muckle-Wells syndrome, Schnitzler syndrome, Gleich syndrome (eosinophilic dermatitis).
- Cryoglobulinemia causing cold-induced urticarial or vasculitic lesions can be seen in hepatitis B or C infection
Differential diagnosis and other causes (2/2)

- Acute urticaria/anaphylaxis to foods, drugs, and other agents frequently demonstrate skin symptoms within 2 hours

- Bacterial/viral infections are common causes of acute urticaria in children
  - Of 88 children at an emergency department with delayed presentation of cutaneous eruption including urticaria, 66% were found to have evidence of a viral infection¹

Differential - urticarial vasculitis

NSAIDS in urticaria

- NSAIDs - aspirin, naproxen and ibuprofen can trigger urticaria
  - Reaction is related to inhibition of cyclooxygenase by these agents
  - Reported frequency of NSAID-induced exacerbations of skin disease ranges from 25% to 50%\(^1\)
- In some patients, period of aspirin sensitivity ends when the urticarial disease resolves
- Up to 35% of patients with chronic spontaneous urticaria (CSU) experience exacerbation of skin symptoms when exposed to ASA/NSAIDs\(^2\)

\(^1\)Grattan CE. Clin Exp Dermatol 2003
Recent evidence-based guidelines support that the most effective, first-line therapy for CU is the use of the nonsedating second generation antihistamines:

- fexofenadine, loratadine, desloratadine, cetirizine, and levocetirizine

In up to 50 percent of patients, this may only be partially effective and other therapies can be considered in addition.

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2 Maurer M, Weller K et al. Allergy 2011.
Treatment (2/4)

- When nonsedating 2\textsuperscript{nd} generation antihistamines are not enough consider:
  - Increasing the dose of the nonsedating antihistamine\textsuperscript{1,2}
  - Combine nonsedating antihistamine with:
    - A sedating older-generation antihistamine (diphenhydramine, hydroxyzine)
    - Or a tricyclic antidepressant such as doxepin, which blocks both H\textsubscript{1} and H\textsubscript{2} receptors\textsuperscript{3,4}
    - Or cyproheptadine taken at bedtime
  - Addition of an H\textsubscript{2} blocker\textsuperscript{5}
  - Consideration of a trial of a leukotriene pathway inhibitor\textsuperscript{6}

Although systemic corticosteroids work, the optimal dose and course has not been studied and repeated use can raise concerns regarding adverse reactions.

Alternatives to corticosteroids in antihistamine-refractory cases of CU:

- Omalizumab$^{1,2,3}$

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$^2$Maurer M, Rosén K et al. N Engl J Med 2013
$^3$Saini S, Rosen KE et al.. J Allergy Clin Immunol 2011
Treatment (4/4)

- Sulfasalazine\(^1\)
- Dapsone, hydroxychloroquine\(^2\)
- Calcineurin inhibitors such as cyclosporine and tacrolimus\(^3\)
- Mycophenolate\(^4,5\)

\(^3\)Trojan TD, Khan DA. Curr Opin Allergy Clin Immunol Immunol 2012. 
Chronic urticaria and Omalizumab (1/3)

In a study done by A. Kaplan et al. timing and duration of omalizumab response was assessed\(^1\)

- 975 patients in the study: received either: placebo, omalizumab 75 mg, 150 mg or 300 mg

Urticaria Activity score (UAS) (range, 0-6):

- Comprises a sum of daily ratings for itch severity and number of hives (0-3 points for each).
- The weekly Urticaria Activity Score (UAS7) sums UAS scores during a 7-day period, and possible values for the UAS7 range from 0 to 42

\(^1\)Kaplan et al. Journal of Allergy and Clinical Immunology. 2016
The following definitions of response to treatment were based on the UAS7:

- Either complete response (itch and hive free, UAS7=0)
- Or well-controlled urticaria (UAS7 ≤ 6)

19 percent of patients achieved complete response (UAS7 = 0) in the 300 mg dose of omalizumab by week 4, and 37 percent achieved well controlled (UAS7 ≤ 6) urticaria in this group by week 4.
The timing of well-controlled and complete response suggests that there might be 2 categories of responders to omalizumab:

- Those who respond early (before week 4) and those who require more than 3 monthly doses to respond.
- The median time to complete response was observed between 8 and 10 weeks for 300 mg of omalizumab.
Response to omalizumab in chronic urticaria

Kaplan et al. Journal of Allergy and Clinical Immunology, February 2016, Volume 137, Issue 2, pages 474-481

P < 0.05, ** p<0.001, Reference 44
Omaluzimab’s effectiveness

- Meta-analysis of 67 studies and over 1000 patients treated with omalizumab:
  - Reported a complete response rate of 72.2%
  - Partial response rate of 17.8%
  - This confirms that outside of clinical trials omalizumab appears highly effective in treating CSU\textsuperscript{1,2}

\textsuperscript{1}Tharp MD, Bernstein JA et al. JAMA Dermatology 2018
\textsuperscript{2}Miller RL, Shtessel M et al. J Allergy Clin Immunology. 2019
Omaluzimab resistance

- Omalizumab resistance is poorly understood
- In a retrospective observation study done based on chart review: Resistance to omalizumab in severe CSU appeared to be associated with the following factors:¹
  - Obesity
  - Arterial hypertension
  - High plasma C3 level
  - High-CRP level

¹Magen E, Chikovani Tet al. Allergy Asthma Proc. 2019
Cyclosporine and urticaria (1/2)

- A meta-analysis of 18 studies investigated the efficacy and safety of cyclosporine in 332 treatment of CSU refractory to anti-histamines
  
  - Though limited by quality and quantity of prior studies, the authors reported response rates for cyclosporine:
    
    - Up 73% with moderate dose therapy (4-5 mg/kg/day) for 12 weeks

^1Kulthanan K, Chawekulrat P et al. J Allergy Clin Immunology In Practice 2018
Cyclosporine and urticaria (1/2)

Adverse event rates occurred in 23% in the low dose group (2 to ≤ 4 mg/kg/day) and 57% in the moderate dose group.

The number of adverse events increased with increasing dosage.

However, rates of major adverse events (hypertension and elevated creatinine) did not significantly differ between the very low-dose group (6%) and the moderate dose group (10%)\(^1,2\)

\(^1\)Kulthanan K, Chaweekulrat P et al. The J Allergy Clin Immunology In Practice 2018
\(^2\)Miller RL; Shtessel M; Robinson LB; Banerji A. J Allergy Clin Immunology. 2019
Urticaria - summary

- Typical urticaria are very pruritic, erythematous and raised
- Urticaria can be acute or chronic
- In acute urticaria, causes can be foods, medications, infections or other processes
- In chronic urticaria 80-90 percent of time causes are not identified
- Consensus regarding lab testing is limited to a few tests
Chronic urticaria summary

- Many patients will spontaneously remit, typically may last 2-5 years, with 1/5th of patients persisting beyond 5 years.
- Treatment is focused initially on:
  - Second generation antihistamines, sometimes in multiple doses
    - Next moving on to 1st generation antihistamines
    - H2 blockers and LTRA.
- Other agents for treatment have been used more in limited cases.
- Omalizumab has been FDA approved since 2014.