Treatment of Rashes and Hives

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Disclosures

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ALK
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Pharmacologic Management of All Things Wheezy and Itchy
**Chronic Idiopathic Urticaria (CIU)**

Urticaria is a common, mast cell–driven disease presenting with wheals or angioedema or both. Histamine and other mediators (platelet-activating factor (PAF) and cytokines) released from activated skin mast cells, result in:
- Sensory nerve activation
- Vasodilatation
- Plasma extravasation
- Cell recruitment to urticarial lesions

Histologically, wheals are characterized by:
- Edema of the upper and mid dermis
- Leakage of serum into the tissue

Chronic Idiopathic Urticaria (CIU)

- An estimated 80% to 90% of patients with chronic urticaria have no identifiable cause of the disease.
- CIU has significant detrimental effects on quality of life.
- In 10–20% of the cases, angioedema may be the first and often only manifestation of urticaria.
- Approximately 60% of the patients with CIU report on angioedema episodes.
- Pathogenesis is incompletely understood.


Associated Systemic Complaints During Active Wheal Flares

- Gastrointestinal symptoms
- Flushing
- Joint pain or swelling
- Cardiovascular manifestations
- Respiratory symptoms
- Other constitutional complaints

Note: similar symptoms are also reported by patients with mast cell activation disorders, and CIU is noted as one of the conditions that can be a mimicker.

Urticaria

Urticaria can be a sign of several other medical or autoimmune conditions:
- thyroid disease
- liver diseases
- chronic infections
- lupus

Most people with one of these conditions will have other symptoms apart from the hives.

Clinical Classification of Urticaria

**Acute Urticaria**
- Urticaria <6 weeks
- May be intermittent, with the skin returning to normal appearance in less than 24 hours
- Causes may include:
  - Drug reactions
  - Food allergy
  - Systemic disorders
  - Infection
- Underlying cause may be undetermined
- Most acute reactions resolve within days to weeks
- Therapy is symptomatic and attempts to suppress symptoms until urticaria abates

**Chronic Idiopathic Urticaria (CIU)**
- Urticaria > 6 weeks
- Generally unknown etiology → never found in most cases
- Consistent, reproducible trigger is often not identified
- Clinical pearl: Because chronic urticaria may stem from an underlying systemic illness, it is important to perform a complete history and physical examination and pursue basic laboratory testing and relevant diagnostic considerations

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Pathogenesis of type I hypersensitivity

Memory cell

Plasma cell

Endothelial cell

Blood vessel

Muscle cell

- Allergen
- IgE
- Fc receptor for IgE
- Smooth muscle
- Blood vessel
- Muscle cell
- Planes
- Nerve endings
- Mast cell
- Basophil

- Inflammation
- Eosinophil

**Context:**


Subtype-Classification of Chronic Urticaria

<table>
<thead>
<tr>
<th>Type</th>
<th>Subtype</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical urticaria</td>
<td>Acute spontaneous urticaria</td>
<td>Urticaria that resolves within 24 hours</td>
</tr>
<tr>
<td></td>
<td>Chronic spontaneous urticaria</td>
<td>Urticaria that resolves within 6 weeks</td>
</tr>
<tr>
<td></td>
<td>Induced urticaria</td>
<td>Urticaria induced by contact with a triggering substance.</td>
</tr>
<tr>
<td></td>
<td>Urticaria of unknown etiology</td>
<td>Urticaria that does not resolve in 6 weeks and lacks a triggering substance.</td>
</tr>
</tbody>
</table>

Other types of urticaria

- Angioedema urticaria
- Discoid urticaria
- Urticaria of unknown etiology

Urticaria Activity Score (UAS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Itch Severity</th>
<th>Number of Hives</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
<td>1-5</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>6-12</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>&gt;12</td>
</tr>
</tbody>
</table>

**Urticaria Activity Score (UAS)**

Daily scoring using the urticaria activity score (UAS)

Score: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe

Diagnostic work up has 3 major aims:

1. Exclude differential diagnoses
2. Assess disease activity, impact and control
3. Identify triggers of exacerbation or any underlying causes

### Diagnostic Test

<table>
<thead>
<tr>
<th>Types</th>
<th>Subtypes</th>
<th>Recommended Routine Tests</th>
<th>Extended diagnostic (based on history)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Urticaria</td>
<td>Acute Spontaneous Urticaria</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Inducible Urticaria</td>
<td>Cold urticaria</td>
<td>Cold provocation test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delayed pressure</td>
<td>Pressure test and threshold test</td>
</tr>
<tr>
<td></td>
<td>Solar Urticaria</td>
<td>Heat urticia</td>
<td>Heat provocation and threshold test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solar urticaria (UV and visible light of different wavelengths and threshold test)</td>
<td>Different blood count, ESR or CRP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic demographren</td>
<td>Cold demographren and threshold test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vibratory angioedema</td>
<td>Test with vibration, for example roller or mixer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aquagenic urticaria</td>
<td>Provocation testing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cholinergic urticaria</td>
<td>Provocation and threshold testing</td>
</tr>
</tbody>
</table>


### Pharmacological Therapy

Step 1: Add an antihistamine agent
- First choice: 2nd generation H1-antihistamines
  - Add leukotriene receptor antagonist
  - Add for general antipruritic treatment
- Add for general antipruritic treatment
- Add for general antipruritic treatment

Step 2: Oral or naso-pulmonary antihistaminergic antihistamines
- 2nd generation H1-antihistamines
  - Add leukotriene receptor antagonist
  - Add for general antipruritic treatment

Step 1: Add leukotriene receptor antagonist
- Availabilities of drugs (e.g. RONISO) and relevant physical factors if antihistamines are deemed ineffective.

Step 4: Add step 3 or 4 medication or step 3 antihistamines + leukotriene receptor antagonist
- Add for general antipruritic treatment

Step 5: Add step 3 or 4 medication or step 3 antihistamines + leukotriene receptor antagonist
Pharmacologic Therapy: First Line Therapy

<table>
<thead>
<tr>
<th>NON-SEDATING ANTIHISTAMINE</th>
<th>SEDATING ANTIHISTAMINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Name</td>
<td>Brand Name</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>2nd Generation</td>
<td>Cetirizine</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>Allegra®</td>
</tr>
<tr>
<td>3rd Generation</td>
<td>Fexofenadine</td>
</tr>
<tr>
<td>Desloratadine</td>
<td>Clarinex®</td>
</tr>
<tr>
<td>SEDATING ANTIHISTAMINE</td>
<td>Generic Name</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>Polaramine®</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Atarax®</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Benadryl®</td>
</tr>
</tbody>
</table>

Leukotriene Receptor Antagonists

- Leukotrienes may have a role in the pathogenesis of chronic urticaria as suggested by the fact that cysteinyl leukotrienes when injected into the skin cause a wheal and flare response.
- Results of several clinical trials show mixed results with some showing benefit and others no benefit, either compared with placebo or less efficacy than second-generation antihistamines.
- Large proportion of patients with angioedema-predominant CSU noted a significant improvement in disease severity and frequency.
- AAAAI update on the diagnosis and management of acute and chronic urticaria recommends montelukast as one of the optional add-on therapies for patients without adequate response to antihistamines.
- Because montelukast is generic, a short (few week) trial may be considered for patients with refractory chronic urticaria.

Treatment: Immunomodulatory Agent

Omalizumab (Xolair) was FDA approved March 21, 2014

Omalizumab is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to IgE.

By inhibiting binding of IgE to the receptor, the release of inflammatory mediators such as histamine, leukotrienes, and prostaglandins is limited, thus blunting the inflammatory response.

Reference:
CIU

- Elevated serum total tryptase level has also been demonstrated in patients with CIU relative to healthy controls.
- Corticosteroids are not recommended for long-term use as the steroid side effects are proportional to dose and duration and over time cause more disability than the CIU.
- Epinephrine should be prescribed if the diagnosis of anaphylaxis has not been excluded.
- Acute urticaria and angioedema is often, but not always related to mast cell and basophil activation from multiple triggers, which include IgE-mediated and non-IgE-mediated mechanisms.

Management of Urticaria

- Refractory CIU should be referred to allergy or dermatology for consideration of advanced therapies.
- Goal of treatment is to treat the disease until resolved.
- Therapeutic approach:
  - Identification and elimination of underlying causes
  - Avoidance of eliciting factors
  - Use of pharmacological treatment
  - Treatment should follow principles of stepping up or stepping down in the treatment based on symptomatology.


Mimicker of Urticaria: Urticarial Vasculitis and Autoinflammatory Diseases

- Urticarial vasculitis is a variant of cutaneous small vessel vasculitis.
- Characterized by inflamed and reddened patches or wheals on the skin that appears to resemble urticaria, but when the skin is examined closely under a microscope, a vasculitis is found (inflamed blood vessels).
- Inflammation of the small blood vessels in the skin.
- Signs and symptoms:
  - Itching and burning sensation in the affected skin
  - Lesions (wheals) caused by urticarial vasculitis may also cause bruising.

Mayo Clinic
Case 1: Jen

Jen is a 43-year-old female patient who presents to your office today complaining of hives with episodic angioedema over a 3-month period. She has been prescribed a standard dose of antihistamines by her primary care provider, but reported inadequate response of treatment. Jen had previously taken several courses of oral prednisone with marked relief, but her hives recurred immediately each time after completion of therapy.

What questions do you want to include in the history of present illness?
Case 1

• Jen’s hives are of unknown etiology and typically resolved within 24 hours, but return 2 to 3 weeks later.
• Lesions are pruritic and often disrupted her sleep
• Lesions did not leave residual bruising or hyperpigmentation
• She denied symptoms of angioedema
• Other than mild fatigue, she also denied other symptoms suggestive of systemic illness

Case 1

Physical exam

Notable for urticarial lesions involving the forearms and posterior chest

Physical exam is otherwise, unremarkable

Case 1

What medical treatment regimen are you going to prescribe?

The patient was ultimately treated with omalizumab 300 mg subcutaneously every 4 weeks with rapid and complete resolution of her urticaria.
At her 6-month follow-up, her symptoms were still controlled while continuing omalizumab therapy.
Case 1

A thorough clinical history and physical examination are imperative to make a diagnosis of urticaria. Guidelines do not recommend extended testing to identify possible allergies or other causes (e.g., for food allergies, bacterial or parasitic infection or malignancies.

Use of validated disease severity assessment tools and quality of life (QoL) instruments is important to monitor disease severity and impact and to guide therapy adjustments.


Rashes

Common Rashes in Adults

Measles
Shingles
Rickettsial infection,
Toxic shock syndrome

Drug reactions and connective tissue diseases are the most common noninfectious causes.
### Common Rashes in Children

<table>
<thead>
<tr>
<th>Condition</th>
<th>Location</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic dermatitis</td>
<td>Extensor surfaces of extremities, cheeks, and younger children; flexor surfaces in older children</td>
<td>Erythematous plaques, excoriation, severely dry skin, scaling, vesicular lesions</td>
</tr>
<tr>
<td>Molluscum contagiosum</td>
<td>Anywhere; rarely on oral mucosa</td>
<td>Flesh-colored or pearly white, small papules with central umbilication</td>
</tr>
<tr>
<td>Erythema infectiosum (fifth disease)</td>
<td>Face and thighs</td>
<td>Erythematous, &quot;slapped cheek,&quot; rash followed by petechial papules and macules in a lacy, reticular pattern</td>
</tr>
<tr>
<td>Impetigo</td>
<td>Anywhere</td>
<td>Face and abdomen are most common</td>
</tr>
</tbody>
</table>

### Common Rashes in Children

<table>
<thead>
<tr>
<th>Condition</th>
<th>Location</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pityriasis rosea</td>
<td>Trunk, bilateral and symmetrical; Christmas tree distribution</td>
<td>Scaly patches on the trunk, usually present first, followed by number similar patches; oral papules, nose colored patches with white crusts</td>
</tr>
<tr>
<td>Roseola infantum (exanthema subitum)</td>
<td>Trunk, spreads peripherally</td>
<td>Macular to maculopapular</td>
</tr>
<tr>
<td>Scarlet fever</td>
<td>Upper trunk, spreads throughout body; cheeks, palms, and soles</td>
<td>Erythematous, blanching, fine macules, resembling a sunburn, sandpaper-like papules</td>
</tr>
<tr>
<td>Tinea infection</td>
<td>Anywhere</td>
<td>Alopecia or broken hair follicles on the scalp, erythematous annular patch or plaque with a raised border and central clearing on the body (tinea corporis)</td>
</tr>
</tbody>
</table>

### Measles

Highly contagious viral illness that occurs worldwide.

Clinical manifestations: fever, malaise, cough, coryza, and conjunctivitis, followed by exanthem

Following exposure, approximately 90 percent of susceptible individuals will develop measles.

Period of contagiousness is estimated to be from five days before the appearance of the rash to four days afterward.

Illness may be transmitted in public spaces, even in the absence of person-to-person contact.

Patients being evaluated for measles should be isolated.
Molluscum Contagiosum

Strong evidence for the efficacy of any treatment for molluscum contagiosum is lacking. Inflammation of molluscum is common and can be a sign of impending regression. Inflammation should not be mistaken for bacterial infection. Immunocompromised patients are at risk for extensive and persistent disease. Children with molluscum contagiosum should not be excluded from daycare or school. Lesions should be covered with clothing or a bandage to reduce the risk of transmission to others.

Atopic Dermatitis (AD)

Most common inflammatory skin disease in the industrialized world\(^1\)

Affects 25% of children and 2% to 3% of adults\(^2\)

Chronic and pruritic inflammatory skin disorder with multiple etiologies

Patients with loss of function mutation in the FLG gene may have:

- earlier onset of AD
- more severe, persistent AD
- more likely to wheeze and have allergic sensitization

Key symptoms → pruritus and sleep disturbances

\(^1\) [Egawa G, Kabashima K, Multifactorial skin barrier deficiency and atopic dermatitis: Essential topics to prevent the atopic march. Journal of Allergy and Clinical Immunology (2016), doi: 10.1016/j.jaci.2016.06.00.]


Atopic Dermatitis: Pathophysiology

\(\rightarrow\) Filaggrin (FLG): structural protein required for epidermal barrier function major component of the stratum corneum

\(\rightarrow\) Reduced FLG: transepidermal water loss, allergen penetration, skin bacterial colonization
Atopic Dermatitis: Pathophysiology

- Dysfunction of skin barrier
- Dysregulation of the immune system
- Environmental triggers

Complex interaction between various susceptibility genes, host environments, infectious agents, defects in skin barrier function, and immunologic responses.

Increase susceptibility to infection or colonization with a variety of organisms:
- herpes simplex virus (HSV)
- staphylococcus aureus

Medical History Must Address

- Age of onset
- Family history
- Psychosocial impact
- Frequency of skin infections
- Frequency of days off school/work/activities
- Sleep disruptions
Atopic Dermatitis: Management

- Elimination of exacerbating factors
- Restoration of the skin barrier function
- Hydration of the skin
- Pharmacologic treatment of skin inflammation
- Patient education


Atopic Dermatitis: Treatment

Treatment options must address skin barrier repair, barrier protection, or inflammatory or immunomodulatory components

- Moisturizers - emollient therapy
- Control pruritus
- Topical corticosteroids
- Non pharmacological

Atopic Dermatitis: Step-care Management


Case 2

Lilly is a 14-month-old girl who presents to clinic with a "rash" that will not go away. The rash started on her arms, wrists, and behind her knees at the age of 4 to 5 months old and has progressively worsened. The areas now affected were the popliteal and antecubital fossae, arms and abdomen. She constantly scratches her skin with worsening symptoms at night, like her a strong family history of atopic disease.

Her mother treats symptoms with OTC Neosporin, which is not helpful.

Lilly is bathed daily using a homemade fragrant soap. Sometimes Lilly's mother uses baby lotion to moisturize Lilly's skin most everyday. The family uses various laundry detergents.

Case 2

Physical examination
Vital signs are within normal limits
Lilly is attentive and appropriately interactive
Cutaneous examination reveals symmetric, ill-defined, brightly erythematous, scaling, pink patches on her cheeks and similar patches anecubital fossa and lichenification erythematous plaques popliteal area bilaterally
Skin-prick testing was not considered in the presence of widespread eczema

What questions and concerns do you have about Lilly at this point?
Case 2

Lilly is a 14-month-old girl who presents to clinic with a "rash" that will not go away. The rash started on her arms, wrist, and behind her knees at the age of 4 to 5 months old and has progressively worsened. The areas now affected were the popliteal and antecubital fossae, arms and abdomen. She constantly scratches her skin with worsening symptoms at night. Her mother treats symptoms with OTC Neosporin, which is not helpful.

Lilly is bathed daily using a homemade fragrant soap. Sometimes Lilly's mother uses baby lotion to moisturize Lilly's skin most everyday. The family uses various laundry detergents.

Case 1

What is your diagnosis?

What medical treatment regimen are you going to prescribe for Lilly?

What non-pharmacological interventions are you going to prescribe for Lilly?

What patient education objectives will you include in Lilly's care?

What are reasons for nonadherence?

Case 1

Follow-up visit 4 weeks later....
Case 1 Atopic Dermatitis

What are critical components the medical treatment regimen for Lilly?
In constructing a medical treatment regimen, we must appreciate of chronic nature of AD, exacerbating factors, and appropriate treatment options
Control or break the scratch—itch cycle

What patient education interventions are needed?
Teach how to control or break the scratch—itch cycle
Moisturize
Infection avoidance

Summary

Exact mechanisms by which CU occurs remains poorly elucidated.
Since 50% or more of cases have an identifiable autoantibody, it is still believed by many that autoimmunity plays an important role.
Early identification and aggressive treatment of AD is a critical first step to improving outcomes.

Thank you!

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