Chronic Urticaria: Causes, Clinical Manifestations, and Treatment

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Disclosures
- Dr. Goldberg is a speaker for Merck, Mylan, Meda, Genetech and conducts research for Glaxo, Jeva, Merck, Genetech, Meda.
- Dr. Rance is a speaker for Merck and Genetech.

Objectives
- Upon completion of this session, participants should be able to:
  - Identify common causes of urticaria.
  - Discuss the clinical manifestations of urticaria.
  - Discuss urticaria treatment options.
Chronic Urticaria

- Defined as hives persisting for 6 weeks or longer.
- CU is an episodic and self-limited disorder in most patients.
- 80% - 90% will not have an identifiable cause.
- More prevalent in adults vs. children.
- 4:1 female to male ratio.
- Condition typically begins in the 3rd to 4th decades of life.
- The average duration of disease is two to five years.
- In patients in whom no trigger or underlying disorder is identified, there is a rate of spontaneous remission at 1 year of approximately 30-50%.

Prevalence

- CU affects between 0.5% – 5% of US population.
- CU impacts 15% – 25% of US population at some point in their lives.
- Thought to have the most impact on QOL of any allergic disease.

Symptoms of Urticaria

- Raised, distinct, erythematous, pruritic, blanching, transient lesions.
- Itching.
- Burning.
- Systemic symptoms.
  - Flushing.
  - Pharyngeal swelling, voice changes, stridor.
  - Bloating, diarrhoea (rare).
- May be associated with angioedema.
  - Swelling of the lips, face, and periorbital regions.
  - Occasional tongue swelling.
  - Rare: swelling of throat or true stridor.

References:

Cost/Utilization Pattern of CU Patients

- Study: 6,019 patients
- Although patients relatively young (average age = 36yrs), $1700 per year related directly to care and treatment of CU.
- AR diagnosed in 48%
- AS diagnosed in 21%
- Other allergy diagnosed in 19%
- 56% of CU patients managed by PCP
- Antihistamines are the most common treatment for CU
- OCS frequently prescribed (54% of patients)

Angioedema Clinical Presentations

- Angioedema
  - Deep dermal or subcutaneous swelling or edema of soft tissues resulting in periorbital, perioral, intraoral, or genital edema
- Presentation
  - approximately 40% patients: chronic urticaria + angioedema
  - approximately 40% patients: chronic urticaria - angioedema
  - approximately 20% patients with angioedema alone
**Diagnosis of Urticaria**

**“How long have you had urticaria?”**

- < 6 weeks
- 6 weeks

- **Acute**
  - ? Allergic
    - assess with skin-prick test, rast test, or rechallenge
  - ? Food or drug
    - assess with exclusion and/or rechallenge

- **Chronic**
  - ? Autoimmune
    - assess with autologous serum skin test, histamine discharge test
  - ? Latent infection
    - exclude parasitic infections, hepatitis

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**Diagnosis of Urticaria**

**“How long do your wheals last?”**

- < 1 hour
- 1-7 days

- **Contact urticaria** (may have a delayed phase)
  - confirm by rechallenge, skin-prick tests

- **Physical urticaria**
  - Except delayed-pressure urticaria
  - confirm by physical challenge

- **Ordinary urticaria** and delayed-pressure urticaria

- **Urticarial vasculitis**
  - confirm by skin biopsy

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Grattan & Charlesworth. *Allergy*. 2nd Ed. Grattan et al., Mosby London, 2001; p101 Fig. 6.18

Following a stimulus such as friction, mast-cell derived mediators initiate an axon reflex, which releases neuropeptides by antidromic stimulation, thereby propagating the flare and amplifying the response.


Mast Cell Activation

- **Classical**
  - IgG
  - IgM
  - C1
  - C4 C2
  - C3
  - C2a C4b C3a C5a

- **Alternate**
  - FcR D, B

- **Modulation via Activation of Receptors**
  - α andrenergic
  - β adrenergic
  - Cholinergic
  - Histamine
  - Hormones

- **Directly Activating**
  - Chemical Agents
  - Physical Agents

*Release threshold is decreased by:*
- Cytokines & chemokines in the cutaneous microenvironment
- Antigen exposure
- Histamine-releasing factors
- Autoantibody
- Psychological factors

*Release threshold increased by:*
- Corticosteroids
- Antihistamines
- Cromolyn (in vitro)

Role of Mast Cells in Chronic Urticaria: Threshold for Histamine Release Varies
Foods can cause hives in some people. Food-associated hives typically appear within 30 minutes of eating the food. Foods most likely to cause hives in children: milk, eggs, peanuts, other nuts, soy, and wheat. Foods most likely to cause hives in adults: fish, shellfish, peanuts, and tree nuts. Although food allergy is a less common cause of CU, some patients will report that variations in diet, particularly rich meals, or spicy foods will aggravate symptoms.

Food as Triggers

- Fermented cheeses
- Fermented drinks
  (wine and beer)
- Fermented foods
- Sauerkraut
- Dry sausage
- Canned foods

Histamine Containing Foods

Histamine Rich

- Chocolate
- Egg White
- Strawberry
- Tomatoes
- Shell fish

Histamine Releasing

- Fermented cheeses
- Fermented drinks
  (wine and beer)
- Fermented foods
- Sauerkraut
- Dry sausage
- Canned foods

Additional Food Triggers

- Scombroid fish (improperly processed tuna, skipjack and mackerel) → histamine “poisoning”
- Non Scombroid fish, mahi-mahi, sardines, anchovies, and herring
- Red wines may contain high concentrations of vasoactive amines (tyramine, dopamine, histamine) that may cause headaches, but may also produce or worsen hives
- Old cheese, yeast, egg white, tomato, spinach - vasoactive amines
### Differential Diagnoses: Diseases with Classic Urticarial Lesions
- Cutaneous lupus erythematosus
- Urticarial vasculitis
- Cutaneous mastocytosis
- Urticaria pigmentosa
- Sweet syndrome
- Fixed drug eruption
- Bullous pemphigoid
- Reticular erythematosus mucinosis

### Differential Diagnosis: Physical Urticaria
- Dermographism
- Cold urticaria
- Cholinergic urticaria
- Pressure urticaria
- Solar urticaria
- Vibratory urticaria
- Aquagenic urticaria

*Fig. 22.17* Cold urticaria: a positive ice cube test. (Courtesy of Professor M Greaves, Institute of Dermatology, United Medical and Dental School, University of London.)
**Fig. 22.18** The eruption in solar urticaria is confined to the area exposed. (Courtesy of Dr J Hawke, Photobiology Department, St John's Dermatology Centre, London.)

**Fig. 22.13** Vibratory angioedema. Vibration induced swelling of the palm and forearm. (Courtesy of Professor M Greaves, Institute of Dermatology, United Medical and Dental School, University of London.)
Differential Diagnosis: Urticarial Vasculitis

- Long-lasting wheals (3-5 days)
- Foci of purpura
- Induration
- Residual hyperpigmentation

Wheals of urticarial vasculitis, lasting over 24 hours and resolving with bruises

Urticarial Vasculitis Extracutaneous Manifestations

- General features
  - Fever, malaise, myalgia
- Specific organ involvement
  - Lymphadenopathy, hepatosplenomegaly
  - Synovia (arthralgia, arthritis)
  - Kidneys (glomerulonephritis)
  - Gastrointestinal tract
  - Respiratory tract (laryngeal edema, COPD)
  - Eyes (conjunctivitis, episcleritis, uveitis)
  - CNS (benign intracranial hypertension)
Thyroid Autoimmunity

- Autoimmune mechanism underlying CU occurs in up to 50% of patients
- Screen for thyroid microsomal and thyroglobulin antibodies especially in:
  - Women
  - Family history of thyroid disease and autoimmune disease
- Consider a trial of Levothyroxine in cases of documented thyroid autoimmunity and a hypothyroid or euthyroid condition

Initial workup of Urticaria: Patient History

- Sinusitis
- Arthritis
- Thyroid disease
- Cutaneous fungal infections
- Urinary tract infections
- Upper respiratory tract infections (particularly important in children)
- Travel history (parasitic infection)
- Sore throat
- Epstein-Barr virus/infectious mononucleosis
- Insect stings
- Foods
- Recent transfusions with blood products
- Recent initiation of drugs

Figure 1. Six-month-old child with acute urticaria caused by latex, samples included have.

Initial Workup of Urticaria: Physical Exam

- Skin
- Eyes
- Ears
- Throat
- Lymph nodes
- Feet
- Lungs
- Joints
- Abdomen
Lab Assessment Options

- CBC
- ESR
- Test for specific IgE skin or serum
- Antinuclear antibody titer (ANA)
- UA
- Thyroid autoantibodies
- Thyroid stimulating hormone (TSH)
- Blood chemistry profile
- Hepatitis B and C
- Stool examination for ova and parasites
- Complement studies: CH50 (angioedema without urticaria: C4)
- Cryoproteins

Initial Management of Urticaria

- Nondrug therapy

  - Explanation and information

  - Avoid aspirin, codeine, morphine, ACE inhibitors

  - Minimize stress, over-heating, alcohol

- Exclusion diet when indicated by history:
  - E.g. food coloring and preservative avoidance

Management of Urticaria

**Pharmacologic Therapy**

- First Line
  - Non-sedating H1-receptor antihistamine:
    * If needed add sedating H1 antihistamine
    * If needed add H2 antihistamine and/or mast cell stabilizer

- Second Line
  - Corticosteroids

- Leukotriene Modifiers
**H₁-receptor Antihistamines**

**1st Generation**
- Diphenhydramine and Hydroxyzine
  - Advantages: rapid onset of action, relatively inexpensive, readily available; some may suppress urticaria to a greater degree than second-generation agents
  - Disadvantages: sedating, anticholinergic, short-acting, QID dosing, AM “hang-over” effect

**2nd Generation**
- Cetrizine, Desloratidine, Fexofenadine, Levocetirizine, and Loratadine
  - Advantages: less sedating, no adverse anticholinergic effects; BID and QD dosing
  - More expensive than 1st generations

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**Stepwise Treatment Approach**

**First line therapy:**
H₁ antihistamines may not control 5% to 50% of pts
- Dose may be increased as high as 4X
  - Cetrizine
  - Desloratidine
  - Fexofenadine
  - Levocetirizine
  - Loratadine
  - Desloratadine
  - 20 mg > 5 mg in cold urticaria
  - Levocetirizine and desloratadine
  - Higher doses better

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**Strategy for Antihistamine Therapy**

- Antihistamines are NOT PRN drugs!
- Start with a long-acting, non-sedating Rx in the morning
- Combination of classes can be helpful
- To non-sedating antihistamine, add a sedating antihistamine
- Increase dose of antihistamine to tolerance

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Evidence that cutaneous blood vessels possess \( H_2 \) receptors as well as the commonly recognized \( H_1 \) receptors, and that these receptors are involved in the mediation of cutaneous vasodilatation and vascular permeability.

- 85/15 ratio of skin \( H_1/H_2 \) receptors
- Combination of anti \( H_{1,2} \) provides additional treatment benefit
- Doxepin blocks both receptors and is a more potent anti-\( H_1 \) blocker than diphenhydramine or hydroxyzine
- Sedation may limit usefulness of Doxepin

**Combined \( H_1-H_2 \) Receptor Antagonists**

**Alternative Therapies: 2nd Line Agents**

- Leukotriene Modifiers
  - Montelukast
  - Zafirlukast
  - Favorable for CU w ASA or NSAID hypersensitivity
  - The best studied group of alternative agents
  - Excellent safety
  - Time to response: several days to 1 week
  - Time to relapse: several days

**Number of Antihistamine Tabs/Week per Patient: Placebo vs. Montelucast**

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Colchicine
- 0.6mg BID. In some patients, may decrease dose to QD.*
- Possible mechanism: suppression of leukotriene generation and decrease leukocyte adhesiveness and migration
- Favorable safety profile
- Low cost
- Time to response: several days to 1 month
- Time to relapse: several days

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Chloroquine
- Multiple potential anurticarial mechanisms include suppression of T-lymphocyte activation
- First reported effective 40 years ago
- Comparable safety profile
- Low cost
- Time to response: 1-3 months
- Time to relapse: Unknown
- Dose: 200mg-400mg QD. Need to monitor for retinal side effects.*

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Additional treatment options:
- Sulfone (Dapsone)
- 5-Aminosalicyclic acid:
  - Sulfasalazine: 500mg QD, up to 2g QD. Monitor G6PD.
  - Olsalazine: up to 1.5g QD. Monitor G6PD.
- Cyclosporine
  - 2.5-5mg/kg QD in divided doses. Titrate to lowest effective dose. Response time: 2 days to several weeks.
2nd Line Agents with Limited Data

- Tacrolimus: 0.025 – 0.2 mg/kg QD orally divided; titrate to lowest effective dose.
- Mycophenolate: 1-2g QD orally divided.

Use of Prednisone in Urticaria

- Used for patients with severe disease after other treatments have been tried
- 40 to 60 mg QD in tapered doses over 2-3 weeks until symptoms significantly improve
- Taper dose to QOD when tolerable
- Use lowest effective dose
- Continue baseline antihistamine treatment

3rd Line Agents

- Methotrexate
  - 7.5-15mg/week. Give with folic acid.
  - Mechanism of action: anti-inflammatory, antiproliferative, and potentially immunomodulatory
  - Time to response: several days to 2 weeks
  - Time to relapse: within 2-3 weeks
3rd Line Agents

- Androgens:
  - Danazol
    - 400-600mg QD in divided doses
  - Stanozolol
    - 1-5mg QD, orally divided

  Mechanism of action: stimulation of hepatic synthesis of various proteases
  - Time to response: 1 day to 2 weeks
  - Time to relapse: Several days

3rd Line Agents, contd’

- IVIG
  - Theoretically the most immunomodulatory potential in urticaria
  - May modulate cell adhesion, immunoregulatory molecules, complement function, cytokine levels, autoantibodies, and anti-idiotypic networks
  - Time to response: several days to several weeks after starting
  - Time to relapse: several days to several months?

3rd Line Agents, contd’

- Additional treatment options:
  - Phototherapy
  - Warfarin
  - Nitrogen mustard
  - Dihydropyridine calcium channel blocker
  - Gold salts
  - Plasmapheresis

Summary of Recommendations

- Antihistamines mainstay of therapy (H₁ and H₂)
- Nonsedating at low/high doses effective for mild/moderate disease
- Sedating antihistamines at HS may be of benefit
- LTRAs worth trying
- Minimize systemic corticosteroids (alternate day)
- Refer to specialist for refractory cases and those requiring prolonged steroid therapy.

Questions??

Thank you.