Chronic Urticaria

Jason Knuffman, M.D.
Allergy and Clinical Immunology
Quincy Medical Group – Unity Point Health System
Quincy, IL

Disclosures

- None

Objectives

- Identify various external urticaria triggers
- Explained the various on label treatments for urticaria
- Recognize signs and symptoms suggestive of underlying, causative conditions associated with urticaria

Outline

- Urticaria Overview
- Histamine and Dermatographism
- Histology
- Autoimmunity
- Differential and Diagnostic Workup
- Treatment
- Prognosis

Question #1

- Of all cases of chronic hives, which of the following is the most commonly identified cause (not a trigger) ?
  - A. Cold weather
  - B. Food allergy
  - C. Co-workers
  - D. Stress
  - E. Unknown

Question #2

- Which of the following are considered "on-label" treatments for chronic hives?
  - A. Prednisone
  - B. Cetirizine (Zyrtec) and Omalizumab (anti-IgE)
  - C. Cyclosporin
  - D. Singulair
  - E. None of the Above

Question #3

- All of the following are consistent with chronic idiopathic hives, except:
  - A. Intensely pruritic, raised lesions
  - B. Occasional swelling of the upper lip
  - C. Lesions last several hours, then disappear
  - D. Lesions appear without an identifiable trigger
  - E. Lesions last several days, leave behind ecchymoses and are associated with unintentional weight loss

Urticaria – General Facts

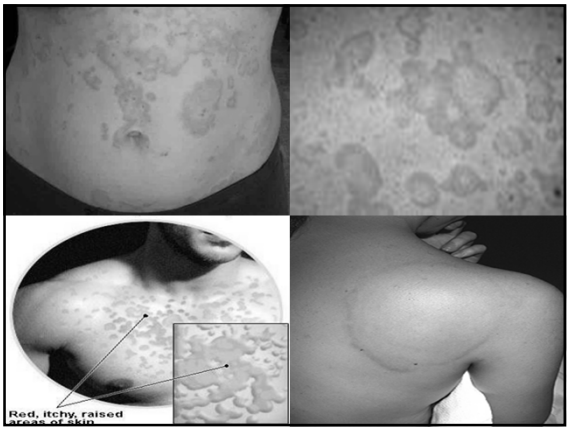
- Affects 25% of population, lifetime incidence
- Intensely pruritic “welts”
- Occur anywhere on the body
- Mast cell degranulation - histamine
- Lesion is circumscribed, raised and erythematous with central pallor
- Often associated with angioedema
- Can be presenting symptom in SLE, cryoglobulinemia, autoimmune thyroid disease, urticarial vasculitis etc.

Urticaria – General Facts

- Prevalence: about 0.5-5% of U.S. population
- Incidence: per year is about 1.4%
- Associated with angioedema in about 60% of cases
- Hives can be constantly present or episodically present
- Variable course, sometimes waxing and waning response to the same therapies

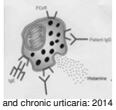
Acute vs. Chronic Urticaria

- Acute
  - < 6 weeks duration
  - Can be associated with identifiable cause (stinging insects, foods, drugs etc)
  - Think about drugs: B-lactams, salicylates, opiates, vancomycin, radiocontrast media, IV iron etc
  - Allergy testing can be useful
- Chronic
  - > 6 weeks (continuously or intermittently present)
  - Rarely associated with identifiable cause
  - Allergy testing rarely useful as the process involves direct mast cell irritation (not an allergic antibody mediator)



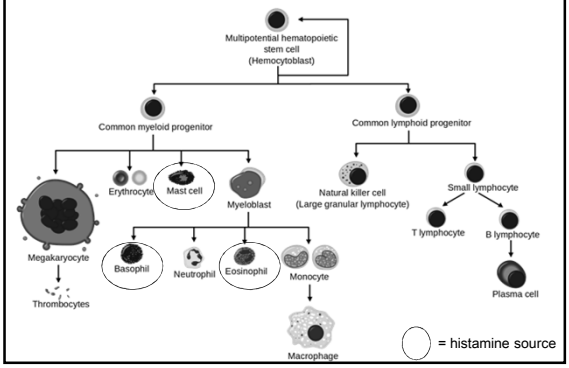
CU – Secondary Causes

- Allergy
  - Rarely, IgE-mediated reactions from foods, drugs, or other allergens
- Infection
  - Viral: hepatitis B and C, EBV, HSV, others
  - Helicobacter pylori infections
  - Helminthic parasitic infections.
- Systemic conditions
  - Specific complement component deficiencies;
  - Cryoglobulinemia (eg, with hepatitis C and chronic lymphocytic leukemia);
  - Serum sickness
  - Connective tissue diseases
    - SLE, juvenile rheumatoid arthritis;
  - Thyroid disease (both hypothyroidism and hyperthyroidism)
  - Neoplasms (particularly lymphoreticular malignancy and lymphoproliferative disorders);
  - Other endocrine disorders (eg, ovarian tumors), OC use
- Autoantibody-associated urticaria
  - Presence of autoantibodies
    - thyroid autoantibodies
    - IgE receptor autoantibodies



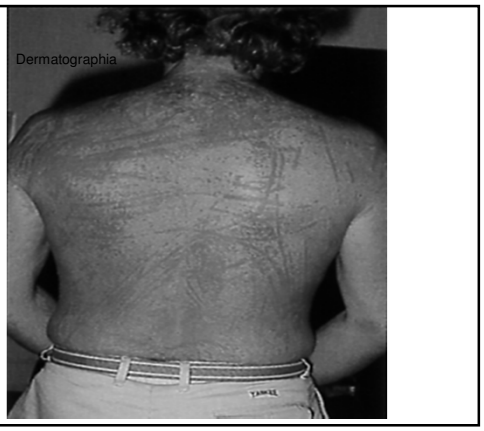
Practice parameter: The diagnosis and management of acute and chronic urticaria: 2014 update (J Allergy Clin Immunol 2014;133:1270-7.

Immune Cell Sources of Histamine



Dermatographism

- "Skin writing"
- Traumatically-induced urticaria
- When scratched, skin turns white (reflex vasoconstriction) followed by pruritus, erythema and swelling (hive)
- 2-5 % of population, young adults
- No antigen identified, histamine is mediator
- Biopsy: edematous tissue, no increased cellularity
- Hives appear rapidly, gone within 1-2 hours



Urticaria Triggers

- Physical Triggers: (pressure, cold, heat, perspiration, solar, aquagenic, vibratory)
- Viral illnesses
- Drugs (antibiotics, NSAIDs…)
- Stress/anxiety
- Plant or animal exposure
- Travel or unusual setting (hotel, spa, vacation)
- Inhaled, irritant exposures
- Foods (strawberries, sulfites in wines, alcoholic beverages, others)
- Others as identified by the patient
- Cause vs. trigger commentary in patient care

Autoantibodies

- ~40% of patients with CU have autoantibodies, or chronic autoimmune urticaria (CAU)
  - Most antibodies are IgG auto-antibody directed to the high-affinity IgE receptor (alpha subunit)
  - Some are IgG auto-antibodies directed at IgE
- Autoantibodies shown by:
  - Autologous serum intradermal skin test, which demonstrates the triggering of cutaneous mast cells in the dermis by the autoantibody found in the patient's serum
  - Basophil histamine release assay – aka the "Chronic Urticaria Index" test

CU - Histology

- Mixed cellular, perivascular infiltration
- The infiltration is mainly mononuclear cells
- Neutrophils and eosinophils present in both short and long duration wheals
- Mast cell counts can increase in upwards of 10-fold in the dermis
- Skin biopsy NOT normally required to make diagnosis of chronic urticaria

G. Edward Stewart II 2002

Urticarial Vasculitis

- Histopathology consistent with *leukocytoclastic vasculitis, predominantly neutrophils*
- Characterized by hives lasting >24hr, painful, burning lesions > pruritic, palpable purpura, residual hyperpigmentation
- Extracutaneous disease is common - associated with paraneoplastic syndromes, drug reactions, infections, autoimmune disorders…
- Look for increased ESR, complement consumption
- Relatively emergent steroid therapy often warranted
- Up to 5% of CU patients!!!

Venzor et al 2002

Table 4
Histopathologic Features of Urticarial Vasculitis

	Urticarial vasculitis	Chronic urticaria	Acute urticaria
Leukocytes	Neutrophils dominate	T cells, macrophages, and eosinophils	Few cells
Location	Vessell wall and perivascular	Perivascular	Perivascular
Endothelial Cell swelling	Yes	Minimal	No
Leukocytoclasis	Yes	No	No
Red blood cell extravasation	Yes	No	No

UV

CU

AU

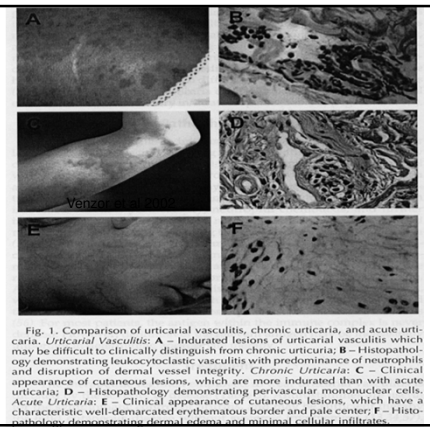


Fig. 1. Comparison of urticarial vasculitis, chronic urticaria, and acute urticaria. *Urticarial Vasculitis*: **A** – Indurated lesions of urticarial vasculitis which may be difficult to clinically distinguish from chronic urticuria; **B** – Histopathology demonstrating leukocytoclastic vasculitis with predominance of neutrophils and disruption of dermal vessel integrity. *Chronic Urticaria*: **C** – Clinical appearance of cutaneous lesions, which are more indurated than with acute urticaria; **D** – Histopathology demonstrating perivascular mononuclear cells. *Acute Urticaria*: **E** – Clinical appearance of cutaneous lesions, which have a characteristic well-demarcated erythematous border and pale center; **F** – Histopathology demonstrating dermal edema and minimal cellular infiltrates.

Diagnostic Evaluation

- The diagnosis of chronic urticaria made *almost solely* on the basis of H&P
- Pursue laboratory investigations, ONLY IF CLINICAL SUSPICION EXISTS FOR A SECONDARY ETIOLOGY
  - CBC, ESR, ANA, complement levels, thyroid auto-antibodies, hepatitis B surface antigen, hepatitis C Ab, SPEP
- One series* showed that 1 out of 356 cases (1,872 total lab tests) benefited from a "laboratory workup" for chronic urticaria
- Routine testing to foods and/or food additives NOT indicated
- Consider skin biopsy if urticarial vasculitis a concern

* Tarbox et al Ann Allergy Asthma Immunol. 2011;107:239-243

Therapy – Antihistamines – Mainstay for Relief of Pruritus

- First generation H1 receptor blockers:
  - H1 blockers are limited by sedation and anticholinergic side effects (dry mouth, diplopia, blurred vision, urinary retention, vaginal dryness)
    - Hydroxyzine 25-200mg, four times per day, scheduled!
    - Cyproheptadine 2-4mg 3 times per day (esp. cold urticaria)
    - Doxepin 10-75 mg, taken 30 minutes before bedtime to prevent nocturnal itching, promote sleep
  - Gradual up-titration can be useful

Stanaland 2002

Therapy – Antihistamines – Mainstay for Relief of Pruritus

- Second generation H1 receptor blockers:
  - Loratadine 10mg QD-BID
  - Cetirizine 10-40 mg per day
  - Fexofenadine 60-180mg BID
  - Levocetirizine 5mg QD-QID*
  - Desloratadine 5mg QD-QID*
- Advantages over first generation H1 blockers:
  - Less frequent dosing
  - Non- or low sedating

* Staevska et al in J Allergy Clin Immunol 2010;125:676-82

Therapy – H2 Blockers

- Usually *added to* H1 blocker therapy
- Ranitidine 150mg BID, nizatidine 150mg BID, cimetidine up to 800mg BID, famotidine 40mg QD
- Cimetidine can increase levels of doxepin…

Stanaland 2002

Therapy – Leukotriene Modifiers

- Besides histamine mediating the immediate urticarial response, a late phase reaction occurs
- Leukotrienes play a partial role in mediating this late phase reaction, especially in chronic forms of urticaria
  - Others include PGD2, proteases, proteoglycans etc..
- Also used in treatment of asthma, rhinitis and atopic dermatitis
- Thought of as an add-on therapy to antihistamines and/or steroid sparing agents

Erbagci 2002

Therapy – Thyroid Replacement

- Hashimoto's disease is the only chronic condition with a common association to CIU and angioedema
- A handful of studies on thyroid replacement in euthyroid patients with thyroid antibodies, no consensus
- No tests (including thyroid antibodies) with predictive value regarding the value of thyroid replacement
- If hypothyroid, then replete thyroid hormone

Therapy - Steroids

- Effective, typically
- Can be used in extreme exacerbations with good control of symptoms
- Patients can be very reluctant to stop steroids due to tremendous efficacy
  - Lowest effective dose
  - Alternate day dosing
- Constant monitoring for SE's and reassessment

Anti-IgE Therapy - Omalizumab

- Recombinant humanized mAb that binds to free IgE and inhibits binding of IgE to FcεRI, the high-affinity IgE receptor.
- Omalizumab reduces the number of FcεRI receptors on the surfaces of mast cells and basophils
- Approved for poorly-controlled, persistent allergic asthma in 2003
- FDA-approved for anti-histamine resistant CIU in 2014

Omalizumab

- Dose and administration (hives):
  - 150-300 mg SC once every 4 weeks (not at home)
- Even though it is an anti-IgE antibody, no baseline IgE level is needed prior to therapy
- No available biomarkers to predict efficacy
- Side effects include injection site redness and atypical anaphylaxis (black box warning)
- Cost and access to omalizumab is an obstacle to therapy
- Typically given in allergy or pulmonary offices, infusion centers, occasional some primary care as well

-Practice parameter: The diagnosis and management of acute and chronic urticaria: 2014 update (J Allergy Clin Immunol 2014;133:1270-7.
-Xolair PI.

CU: What Do I Do?

- History and Physical
- Allergy testing ? for reassurance
- If patient is antihistamine naïve:
  - Cetirizine 10 mg AM, 10 mg bedtime
  - Ranitidine 150 mg AM, 150 mg bedtime
  - Singulair 10 mg bedtime
- Trigger avoidance
- Directed secondary workup
- Follow up 2-4 weeks

CU: What do I do?

- If second generation antihistamines not working, then:
  - Short course (or 2) of oral steroids
    - Kenalog 80 mg IM or prednisone 30 mg per day for 5 days, then 10 mg for 5 days
  - Hydroxyzine 100 mg AM/Noon/PM/Bedtime
  - Plaquenil 200 mg twice daily
  - Cyclosporin 100 mg once-twice daily
  - Sulfasalazine 500 mg daily-twice daily
  - Dapsone 50 mg daily
  - Colchicine 0.6 mg once-twice daily
  - Omalizumab

Unproven Therapies

- Steroid – sparing agents:
  - Dapsone – check for G6PD deficiency first given the association with hemolytic anemia
  - Cyclosporin – hypertension, hirsutism
  - Hydroxychloroquine – check G6PD level, periodic eye exams to evaluate for defects in accomodation or convergence, corneal deposits or retinal toxicity
  - Mycophenlate mofetil - immunosuppression
  - Sulfasalazine – rare agranulocytosis
  - Methotrexate – multiple, potential toxicities
  - Warfarin

Stanaland 2002
Ruddy 2001

Prognosis

- No indication thus far in literature that suggests that the natural history of CU is influenced by treatment modalities
  - Symptom-based “treatment” only
- Prognosis (+/- treatment) summed up as follows (from a review of several authors reporting a course for CU):
  - 50% will resolve within 6 months
  - 20% will resolve within 36 months
  - 20% will resolve within 60 months
  - <2% will resolve within 25 YEARS
- Caveat: ~50% will experience at LEAST one recurrence of CU after apparent spontaneous resolution

Beltrani 2002

Question #1

- Of all cases of chronic hives, which of the following is the most commonly identified cause (not a trigger) ?
  - A. Cold weather
  - B. Food allergy
  - C. Co-workers
  - D. Stress
  - E. Unknown

Question #2

- Which of the following are considered "on-label" treatments for chronic hives?
  - A. Prednisone
  - B. Cetirizine (Zyrtec) and Omalizumab (anti-IgE)
  - C. Cyclosporin
  - D. Singulair
  - E. None of the Above

Question #3

- All of the following are consistent with chronic, idiopathic hives, *except*:
  - A. Intensely pruritic, raised lesions
  - B. Occasional swelling of the upper lip
  - C. Lesions last several hours, then disappear
  - D. Lesions appear without an identifiable trigger
  - E. Lesions last several days, leave behind ecchymoses and are associated with unintentional weight loss

Urticaria Summary

- "Twitchy/leaky mast cell" syndrome, histamine is main mediator
- 90+% of all chronic urticaria is either autoimmune or idiopathic
- Urticaria as a herald of underlying and consequential systemic disease process
- Foods/food additives are *NOT* causative (but can serve as triggers) as a rule
- Essentially unknown and unalterable course with present – day therapies

Thank You!