**Urticaria & Angioedema: idiopathic and difficult-to-manage no longer?**

Presentation at the 47th Annual Winter Refresher Course for Family Medicine

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**Conflicts of Interest**

Research Funding
- via Children’s Research Institute by Greater Milwaukee Foundation
- Associated with Fight Asthma Milwaukee Allies

Employment
- Veterans’ Affairs Hospital Milwaukee
- Medical College of Wisconsin
- Clinics at VA, Children’s Hospital of Wisconsin and Froedtert Hospital

Commercial
- No commercial conflicts of interest.

**Off-Label Disclosure**

Off-label uses and doses for generic medications WILL be reviewed.

Brand names will be avoided as best possible.

**Room survey regarding chronic urticaria**

For most consults, the referring provider...
- Prescribed diphenhydramine, prednisone
- Prescribed topical antihistamines and steroids
- Ordered food/aeroallergen tests
- Considered elimination diets or chemical exposure eliminations
- Screened for HAE with complement levels/C1INH
- Obtained blood testing for ANA, H pylori, CBC, LFT...

**Room survey regarding chronic urticaria**

None of the above are recommended by the present practice parameters for chronic urticaria

“Did we collectively miss the urticaria lecture?”

Disclaimer: I myself did not know this before fellowship

Today, I hope to provide that missing lecture and review that this condition, which strikes at any age, isn’t as idiopathic nor as difficult as first thought.
Learning Overview

1. Describe clinical and pathologic features
2. Understand known and unknown pathophysiology
3. Review physical urticarias
4. Review mimic disorders
5. Review treatment guidelines: from simple to difficult

Is it ‘hives’?

Clinical features

- noted pruritis
- wheal and flare
  - "white island with a red beach"
  - mono vs polymeric
  - round, geographic, linear
  - no fixed distribution pattern
- transient / evanescent
  - duration < 24-48 hrs/lesion
  - no residual pigmentation
- normal skin integrity
  - no blistering or desquamation
  - no scratching to bleeding

Dermatopathology

Mild dermal edema
Perivascular infiltrate:
- lymphocytes
- mast cells and eosinophils

Absence of...
- fibrinoid change
- hemorrhage
- leukocytoclasis

Frequency of Urticaria & Angioedema

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Hives (%)</th>
<th>Wheals (%)</th>
<th>Urticaria (%)</th>
<th>Angioedema (%)</th>
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<tbody>
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<td>Champion et al. (1989)*</td>
<td>UK</td>
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* A number of patients had angioedema. 44% not examined.
* Patients examined at all types of clinics.
* Most patients have both hives & angioedema

A small fraction ONLY develop angioedema

Mast cell degranulation: *urticaria's central pathogenic event*

Conventional Model of Mast Cell Activation

Images: L:http://www.bu.edu/histology
R: http://medcell.med.yale.edu/histology/connective_tissue_lab.php
"URTICARIAL CLOCK": Etiology associates with duration of disease

<table>
<thead>
<tr>
<th>Duration</th>
<th>Etiology</th>
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<tbody>
<tr>
<td>Short duration</td>
<td>contact urticaria, food/drug allergy</td>
</tr>
<tr>
<td>Intermediate</td>
<td>infectious (typically viral)</td>
</tr>
<tr>
<td>Chronic duration</td>
<td>autoimmune ~40%, idiopathic ~50%, physical only ~10%</td>
</tr>
</tbody>
</table>

ACUTE urticaria/angioedema (short duration): etiology

- Contact urticaria (with aeroallergen):
  - Dog licks the hand, hand wipes the eye, the eye swells.
  - Pollen sticks to the screen, face against the screen, face swells
- Food/Drug induced:
  - Infant eats peanut butter and develops hives only

Mechanism:
- classical mechanism of allergen-induced IgE crosslinking

ACUTE urticaria/angioedema (intermediate duration): etiology

- Viral mediated urticaria
  - School aged child develops URI with sinus drainage
  - Amoxicillin prescribed for 7 days, hives develop on last day but persist for 10 days following

Mechanism:
- presently unknown
- No known allergen triggering mast cell activation, thus the classical model fails to explain symptoms

Long term CHRONIC urticaria/angioedema etiology

- Typical history:
  - Spontaneous onset
  - No noted triggers except heat, pressure
  - recurrence more days than not per week
  - NSAIDs, narcotics & alcohol may worsen symptoms

Mechanism:
- No known allergen triggering mast cell activation, thus the classical model fails to explain symptoms
- Intrinsic in nearly all cases, about half autoimmune

Pathophysiology of chronic urticaria: autoimmune and intrinsic degranulation triggers

In a patient with chronic urticaria

Autoallergic IgE, anti-IgE, anti-FcεRI, other autoantibodies

Diagnosis:
Autoimmune suggestions

- ASST (autologous plasma skin test) intradermal challenge triggers wheals commonly in ~45% of CU patients
- 27% have thyroid autoantibodies
- OR of other autoimmunity within 10 years of diagnosis: 7.7–28.8
Diagnosis:
Autoimmune subtypes
40% have pathogenic IgG and 1 autoallergens:
- anti-FcεRIa
- anti-IgE

To date, there has been no clinical distinction between patient with autoimmune vs idiopathic CU.

Autoimmunity testing available but
- uncertain clinical utility
- inter-test inconsistency

Prognosis:
eventual spontaneous auto-resolution
- 50% within 6 mo of onset
- 20% within 36 mo of onset
- 20% within 60 mo of onset
- <2% within 25 yr

- 50+% have ≥ 1 recurrence after apparent spontaneous resolution

Mimic Disorders
Overview
- Cutaneous mastocytosis (urticaria pigmentosa)
- Urticarial vasculitis
- Bullous Pemphigoid (urticarial phase)
- Bradykinin-mediated angioedema syndromes
- Serum (like) Sickness
- Papular urticaria (arthropod bites)
- Familial Cold Urticaria
- Schnitzler’s Syndrome

Mimic Disorders: Urticarial Vasculitis
- Burns more than itches
- Dependent areas more common
- Ecchymosis noted
- Duration > 24-36 hrs per lesion
- Systemic symptoms possible
  - Hypocomplementemic variant (HUVS)

Mimic Disorders:
Cutaneous mastocytosis (urticaria pigmentosa)
- Pressure urticating pigmented lesions (Darier’s sign)
- Children: polymorphic, limited to skin, auto-resolving
- Adults: monomorphic, associated with systemic mastocytosis

Mimic Disorders:
Bullous Pemphigoid (urticarial phase)
- Pruritic with plaque-like urticarial components
- Prodrome lasting months may precede blistering
- Linear IgG and C3 on dermal-epidermal junction
- Eosinophilic spongiosis
Mimic Disorders:

- bradykinin-mediated angioedema
  - ACE-inhibitor induced
  - Hereditary Angioedema
    - Type I
    - Type II
    - With normal C1INH (type III)
  - Acquired Angioedema
    - Functional antibody against C1INH
    - Frequently paraneoplastic
    - Idiopathic
  - Clinical Pearls:
    - No concomitant urticaria, just angioedema
    - No response to antihistamines, corticosteroids, epinephrine
    - Delayed post-physical trauma or idiopathic commonly
    - Angioedema crescendos for ~24 hours, resolution over DAYS

Diagnosis:

Laboratory Studies

If unremarkable history/exam findings (low concern for mimic disorders), allergy testing is not recommended not cost-effective no improved patient care outcomes

Limited testing may be indicated for “reassurance value”

CBC with differential, ESR and/or CRP, liver enzymes, TSH...

However...

Management: Step 1

First Line Agents

- Second generation oral antihistamines
- Avoidance of triggers if sensitive
  - physical triggers
  - alcohol
  - narcotics
  - NSAIDs

Diagnosis: Laboratory Studies Rarely Change Management

1.6% altered management, 0.28% improved based on change in management


Diagnosis: Physical Triggers

- cold-induced urticaria (ice-cube challenge)
- cholinergic urticaria (warm water bath, autologous sweat)
- vibratory urticaria (vortex testing)
- solar/aquagenic

Images: https://www.aaaai.org/about-aaaai/newsroom/photo-gallery/photos—urticaria—and-angioedema

Management: Step 1

First Line Agents

- Choice of second gen AH
  - Potency per usual dosing:
    - fexofenadine ≅ cetirizine > loratadine*
  - Loratadine is nearly never used by our subspecialty
  - desloratadine, levocetirizine (enantiomeric formats) without demonstrated superiority vs racemic form
    - fexofenadine: no sedation, $$$
    - cetirizine: sedation, $*
    - loratadine: sedation*, $
Management: Step 2
Initial Treatment Failure
• Dose advancement of second gen H1
  • up to 4x usual prescribed daily dose/day
• Add H2 antihistamines
• Add leukotriene receptor antagonists
• Add first gen antihistamines (H1) before bedtime
  • doxepin
  • hydroxyzine
• NOTE: NOT FDA approved at higher dose for urticaria
  • Fexofenadine at high dose studied in 6000 participants at 600-800mg/day
  • No cardiotoxicity
  • No potassium channel blockade
  • No change of heart rate or QT interval
  • Psychomotor and cognitive function (at 360mg dose)

Management: Step 2
High Dose Second-Gen Antihistamine
• NOTE: NOT FDA approved at higher dose for urticaria
  • Fexofenadine at high dose studied in 6000 participants at 600-800mg/day
  • No cardiotoxicity
  • No potassium channel blockade
  • No change of heart rate or QT interval
  • No psychomotor and cognitive function (at 360mg dose)

Management: Step 3
Initiation of sedating antihistamine
• advancement of potent antihistamine as tolerated
  • Doxepin
    • Potency ~500 times that of diphenhydramine
    • H1 and H2 blockade properties
    • Risks of QTc prolongation, sedation, weight gain, SSRI interaction
    • Hydroxyzine
      • sedating

Management: Step 4
alternative agents
• omalizumab
• cyclosporine
• oral corticosteroids
• hydroxychloroquine
• dapsone
• sulfasalazine
• mycophenolate
• tacrolimus

Management: Step 4
omalizumab
• FDA approved 2014 for CIU
• refractory to antihistamines
• dose response effect noted
  • age: >12 yrs
• Response rate ~70%
• Concerns:
  • No natural history modifying properties.
  • Risk of anaphylaxis 0.09-0.2%

Management: Third Line: Cyclosporine
• Only treatment with potential to alter natural history
• Dosing typically 1-3mg/kg/day
• Risk of secondary malignancy, HTN, liver issues, immunosuppression
Management: Third Line: other medications

- Sulfasalazine
  - PRO: Rapid onset
  - CON: response rate, sulfonamide allergy, kidney/renal, gametogenesis
- Dapsone
  - PRO: neutrophilic inflammation
  - CON: G6PD risk, anemia risk
- Hydroxychloroquine
  - PRO: favorable tolerance
  - CON: retinal exam, slow onset
- Mycophenolate
  - PRO: negligible data
- Tacrolimus
  - PRO: safer than cyclosporine
  - CON: negligible data
- Cyproheptadine
  - PRO: cold urticaria data
  - CON: sedation, weight gain

Typical Case (Sliding Doors)
18 yo female with itchy welts on her skin and lip swelling suddenly, lasting for 8 weeks before presentation. Ate peanuts a few times at outset of symptoms.

Usual Care
- ED visit:
  - Rx diphenhydramine 50mg 4 times daily for 1 week, ranitidine 150mg BID for a week and a taper course of oral corticosteroids.
  - Advise to stop using any peanuts, avoid fabric softener.
- PCP follow-up:
  - Reassess control on symptoms off medication. Restarted prednisone and benadryl.
  - IgE testing for peanut ordered.

Improved Guideline Based Care
- ED visit:
  - Rx cetirizine 10mg once daily.
  - No labs ordered.
- PCP follow-up:
  - Partial control on cetirizine.
  - Screening for physical triggers negative.
  - Screening for mimic disorders negative.
  - Patient told this is unlikely an allergic disorder.
  - Increase of dose of cetirizine up to 20mg twice daily with control achieved.

Take Home Pearls:

Workup

Most urticaria/angioedema can be managed well in primary care! *

* My strongly held personal belief.

Diagnosis

**Primum urticaria? (Before all, is it hives?)**

- Confirm your patient is having hives
  - Itchy, transient wheal/flare reactions
  - without excoriation
  - without residual pigmentary changes/blistering
- If hives are present, there is no need for HAE workup

Evaluation

- Acute urticaria, if no suggestion of food/drug/aeroallergen trigger, does not require laboratory evaluation
- Chronic urticaria, without suggestion of mimic disorder symptoms, does not require laboratory or biopsy

Etiology is related to duration of disease

- Quick onset/resolution → consider food/drug allergy
  - Workup may be indicated
- Days to 6 weeks → viral-mediated urticaria
  - No workup needed
- More than 6 weeks → idiopathic/autoimmune
  - Exclude mimic disorders
- Single lesion lasting ≥ 2 days → refer to dermatology
  - worry about mimic disorders
Take Home Pearls:
Management

• Start with second generation oral antihistamines
• Avoid first generation antihistamines, topicals, prednisone
• Titrate dose to achieve control (up to 4x usual doses/day)

• if treatment failure,
  • add-on LTRA and/or H2 blocker
  • add on a first-gen antihistamine
  • refer to allergist for omalizumab or alternative medications
  • use oral corticosteroids sparingly if uncontrolled

Resources

• Allergy Practice Parameters: allergyparameters.org
  • Joint Task Force on Practice Parameters (JTFPP)
  • American Academy of Asthma, Allergy and Immunology* www.aaaai.org
  • American College of Asthma, Allergy and Immunology* www.acaai.org

• Specialist Advice:
  • Call your local or hospital’s allergist on-call
  • CHW’s Consultation Line: (414) 266-2460
  • UW-Madison’s Consultation Line: (800) 472-0111

• Questions:
  • jsteinberg@mcw.edu

* AAAAI and WAO headquarters are in Milwaukee; ACAAI HQ in suburban Illinois