Evidenced Based Work-up & Treatment Chronic Urticaria in Children

Not Too Much, Not Too Little

Kelly M. Cordoro, M.D.
Associate Professor, Dermatology and Pediatrics
University of California, San Francisco

I have no conflicts of interest

Focus Points

- Chronic Urticaria
  - Etiologies/Associations
  - Evidence-based investigation of patients
  - Evidence-based treatment (summary statements)
Urticaria: a reaction pattern that reflects the activation of mast cells and basophils

- Many types and classification systems
- Common Urticaria
  - Acute (< 6 weeks)
  - Chronic (> 6* weeks)
  - Episodic/recurrent
- All forms of urticaria occur in children

Immunologic and non-immunologic stimuli can trigger mast cell degranulation

Vasoactive & Inflammatory Mediators → Histamine, Eicosanoids, Cytokines

Courtesy Elsevier Inc, 2008
A Word on Acute Urticaria

1. Infection (~50-90%)
   - Viral & bacterial URI
   - UTI

2. Medications (~5%)
   - Antibiotics, antipyretics (ASA, acetaminophen)

3. Food (~3%)
   - W/in 2 hrs of ingestion; usually atopic
   - Egg, milk, soy, peanut, wheat, fish

Management of Acute Urticaria

- Avoid exhaustive diagnostic evaluations for an infectious etiology
- Focus testing on specifics from the H&P
- If lesions last > 24 hr, pain, purpura, blisters → skin biopsy
- Education/reassurance
- Remove the inciting agent / treat infection
- Symptomatic Care
  - H1 antihistamines
  - Soaks/emollients
  - Oral corticosteroids-
    very severe cases only
Chronic Urticaria in Children

- Wheals +/- angioedema for > 6 weeks
- Negatively affects quality of life
- Natural history data is lacking but only ~25% of children will remit within 3 years of presentation

Clinical and Experimental Allergy 2007;37:631–650
Available literature suggests that a cause is documented in only ~25% of cases despite exhaustive investigations

Remainder designated as “chronic idiopathic urticaria”

3 Subsets of Associations

1. Clearly documented precipitants (causal)

2. Clearly documented associations (? causal)

3. Poorly documented but proposed etiologies (little to no evidence of causality)
### Subsets/Frequency of Documented Precipitants

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic idiopathic urticaria</td>
<td>48%</td>
</tr>
<tr>
<td>Chronic Autoimmune Urticaria (30-50%)</td>
<td></td>
</tr>
<tr>
<td>Physical urticaria</td>
<td>40%</td>
</tr>
<tr>
<td>Urticarial vasculitis</td>
<td>6%</td>
</tr>
<tr>
<td>Large % of these cases likely represent neutrophilic urticaria</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>6%</td>
</tr>
<tr>
<td>- Infection, allergen exposure, drugs</td>
<td></td>
</tr>
<tr>
<td>- Food; dietary pseudoallergens (dyes/preservatives)</td>
<td></td>
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<tr>
<td>- Autoinflammatory syndromes</td>
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</table>


### Chronic Autoimmune Urticaria

the presence of histamine-releasing antibodies in the serum

IgG autoantibodies against the high affinity IgE receptor (FceRI) on mast cells and basophils or against IgE

Physical Urticaria

Physical stimuli are the most commonly identified precipitants of CU in kids.

- Reliably reproduced by challenge testing
- Identification limits search for other causes
- Prolonged duration
  - Remission: 12% after 1 year; 38% after 5 years


Non-immunologic Precipitants

- Direct mast cell degranulation
  - Opioids
  - Radiocontrast media

- Sensitivity to COX Inhibition
  - Aspirin, NSAID
  - Divert AA metabolism to \( \uparrow \)LT
    - Aggravates, rather than causes, urticaria in a subset of patients

Clinical and Experimental Immunology, 2008. **153**: 151–161
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Autoimmune Disease: higher rates in CU pts vs. healthy controls

- Thyroid autoimmunity
  - More frequent than in the general population
    - kids: 4% in CU vs. 0.35-1.6% in healthy controls
  - Anti-thyroglobulin and anti-microsomal Ab
    - Not pathogenic; reflect underlying autoreactivity
    - This subset more likely to have AIU

Autoimmune Disease:
higher rates in CU pts vs. healthy controls

- Small case-control studies or single case reports

- Celiac disease: 5% vs. 0.67% in controls\(^1\)
- Juvenile RA (JIA/JCA)
- IDDM

Treating associated diseases ≠ resolution of urticaria

\(^1\) Bailey and Shaker. Current Opinion in Pediatrics, 2008; 20:425–430

Infections

- H. pylori (indirect immune triggers- mimicry?)
- Parasites (endemic regions or history of travel)
- Silent or symptomatic UTI

Treating associated diseases may eliminate CU in a subset of patients

3 Subsets of Associations

1. Clearly documented precipitants (causal)

2. Clearly documented associations (? causal)

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No Evidence for...

- Occult (asymptomatic) infection
  - Dental and sinus abscesses
  - GI or vaginal candidiasis

- Diet and dietary pseudoallergens
  - Salicylates, dyes and food preservatives → often suspected but very rarely confirmed and not reproducible

- Malignancy

Clinical and Experimental Allergy, 2007; 37: 631–650
Children presenting with chronic urticaria are frequently over-investigated.

Clinical history and physical examination are the best tools to establish the diagnosis, identify precipitants and define the necessity of further evaluation.

Investigations: How Much is Enough?

The EBM Approach

- A diagnostic test is only useful if its outcome changes the pretest probability of an underlying disease or causative factor
- Only a few specific lab tests in CU are valuable in this respect
- Consider historical items as diagnostic tests that either ↑ or ↓ the probability of finding an underlying disease or cause

The evidence...

- Numerous well done studies document the lack of diagnostic utility of lab investigations in kids with CU

- Systematic review of 29 studies involving 6462 patients; authors concluded:
  - history is most important
  - routine lab tests are of little value and only useful if based on the history

Clinical and Experimental Allergy, 2008; 38, 1061–62.

Rational Stepwise Approach

- No investigations are required for patients with mild, antihistamine responsive disease and negative history

Rational Stepwise Approach: History-Directed Investigations

- Provocation testing for physical inducers
  - Avoids or limits further testing and directs interventions

- Skin Prick Tests or Specific IgE Tests
  - Focus the testing to *candidate allergens only*
  - Avoid indiscriminant panel testing; high false + rate
  - Negative tests reassure parents and liberalize diets/activities

BSACI and the EAECI recommendations for the investigation of CU.
Clinical and Experimental Allergy, 2007; 37: 631–650

1st Tier Screening Investigations

antihistamine non-responders; more severe disease

- CBC/diff
- ESR/CRP
- Thyroid Autoantibodies/Thyroid Function
- Urinalysis
Potential 2nd Tier Investigations

- guided by the initial H&P and screening labs
  - Infectious disease screen (viral, bacterial, parasitic)
  - ANA / other specific antibodies
  - Celiac disease screen
    (total IgA & TG IgA Ab + intestinal bx if +)
  - Serum cryoproteins (select cases of cold urticaria)
  - LFT/viral hepatitis serologies
  - Skin biopsy

Functional Autoantibody Testing: Too Much?

- *in vitro* basophil histamine release assay -> gold standard, commercially available (IBT Laboratories)

Some authorities advocate testing as part of the diagnostic work-up in all children presenting with chronic or recurrent urticaria

- May mark patients with more severe, refractory disease
- May limit the search for other causes

Sabroe and Greaves. BJD 2006; 154: 813–819
Too Much

- Elimination/re-challenge diets (food additives)
- Comprehensive allergy panels (high false + rate)
- Complement studies (limit to suspected UV)
- C1 esterase inhibitor assays (HAE does not p/w urticaria)
- Exhaustive searches for occult infection/malignancy

The primary treatment of urticaria is education/reassurance for the parents, removal of the inciting agent (when identifiable, if possible), and symptomatic relief.
The efficacy of antihistamines in urticaria is attributed to:

* H1 action on afferent C nerve fibers of the skin: reduces itching
* H1 action on the axon reflexes of the skin: reduces erythema
* H1/H2 action on the endothelial cells: reduces extravasation/edema
* H1 inhibition of cytoplasmic transcription factors (NF-kB): reduces inflammation

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**Antihistamines:**

*Remain the Cornerstone of Treatment*

- Long acting 2\(^{nd}\) gen H1 antihistamines- 1\(^{st}\) line
  - Class 1 evidence and Grade A recommendation
  - Comparative clinical data in CU show similar efficacy overall

- Dose escalation (off label) and combination therapy

- Always dose on a schedule (not prn)
Conclusions: Chronic Urticaria

- Well controlled studies are required to delineate the clinical significance of asymptomatic infections and other associations in patients with CU

- The H&P is the “MVP” in defining the work-up

- Antihistamines alone or in combo remain the mainstay of Rx... targeted therapy is on the horizon
Select References

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