Chronic Urticaria
Evaluation and Therapy

Not Too Much, Not Too Little

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Focus Points

- Chronic Urticaria
  - Etiologies and Associations
  - Evidence-based Investigations
  - Evidence-based Treatment

Parents concerned that certain foods are causative.

Moderate response to standard dose antihistamines.

Past medical history and ROS is negative.

Diagnosis, Evaluation & Treatment?

Urticaria
(Urtica dioica, stinging nettle)
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
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

Available literature suggests that a cause is documented in only ~25% of cases despite exhaustive investigations

Remainder designated as "chronic idiopathic urticaria"

In Contrast to Acute Urticaria

1. Infection (~50-90%)
   - Viral & bacterial URI; UTI
2. Medications (~5%)
   - Antibiotics, antipyretics
3. Food (~3%)
   - W/in 2 hrs of ingestion; usually atopic
   - Egg, milk, soy, peanut, wheat, fish

Chronic 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>Precipitants</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Chronic idiopathic urticaria</td>
<td>48%</td>
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<tr>
<td>Chronic Autoimmune Urticaria (30-50%)</td>
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<tr>
<td>Physical urticaria</td>
<td>40%</td>
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<tr>
<td>Urticarial Vasculitis (neutrophilic urticaria)</td>
<td>6%</td>
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<tr>
<td>Other - Infection, allergens, food additives/dyes, drugs, Autoinflammatory syndromes</td>
<td>6%</td>
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</tbody>
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Clinical and Experimental Allergy 2007:37:631–650

In contrast to Bailey and Shaker. Current Opinion in Pediatrics, 2008; 20:425–430

MaR-Apr;21(2):102-8

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Chronic Autoimmune Urticaria
the presence of histamine-releasing antibodies in the serum

IgG autoantibodies against the high affinity IgE receptor (FcεRI) 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 ↑LT
    • Aggravates, rather than causes, urticaria in a subset of patients

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 ATU
    • Typically euthyroid

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)
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
- Juvenile RA
- IDDM

Treat associated diseases ≠ resolution of urticaria

Infections

- H. pylori
- Parasites (endemic regions or history of travel)
- Silent or symptomatic UTI -> abx confounding?

Treat associated diseases may eliminate CU in a subset of patients

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)

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

Dietary pseudoallergens
- Salicylates, dyes and food preservatives

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 utility of history-based investigations is supported by well done studies...
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 EAACI 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 (WBC, eos)
  - ESR/CRP
  - Thyroid Autoantibodies/Thyroid Function
  - Urinalysis

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

**Antihistamines:**
Remain the Cornerstone of Treatment

- **Long acting 2nd gen H1 antihistamines- 1st 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)**

**Case Wrap-up**

- 8 year-old well female
- 4 month history of daily, generalized, markedly pruritic hives

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**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

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**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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**1st gen H1 sedating antihistamines**

- **Anti-H1/H2 (doxepin)**

**Other Drugs**

- Leukotriene Antagonists- role to be defined
- H2 blockers- marginal benefit, diminish wheals

**Immunomodulators, Immunosuppressants- severe, refractory cases**

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Case Wrap-Up
Dx: Chronic urticaria

- Given the duration of symptoms, moderate response to antihistamines and parental anxiety regarding foods:
  - CBC/diff, TSH/anti-thyroid Ab, ESR, UA
  - Specific IgE to candidate foods only
  - Basophil histamine release assay

- Rx
  - Combination max-dose antihistamines +/- immunomodulators pending response and results of antibody testing for CAI

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

Thank You