Current Approaches to the Diagnosis and Management of Urticaria

Cardiovascular & Medicine Symposium

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DISCLAIMERS AND DISCLOSURES

- Aerocrine Speakers Bureau
- Executive Board Member-- Florida Allergy, Asthma & Immunology Society
DISCLAIMERS AND DISCLOSURES

- Many urticaria treatments not FDA approved
CONFLICTS OF INTEREST

None
OBJECTIVES

- Discuss the various clinical features of urticaria and angioedema
- Describe appropriate and effective treatment strategies to deal with urticaria
- Understand the pathophysiology underlying acute and chronic urticaria.
CLASSIC FEATURES OF HISTAMINERGIC URTICARIA

- Pruritic, erythematous, cutaneous elevations
- Blanchable
- Annular, or serpiginous--variable size.
- Macules (H1 antihistamines)
- Migratory
- Resolve within 24 hours without marks, bruises or scars

Middleton’s Allergy 7th ed. Principles & Practice 2009
Fifty Shades of Hives

- Traditional pruritic, migratory, blanching rash
- Small papules of cholinergic urticaria
- Dermatographism


http://www.usc.edu/student-affairs/Health_Center/adolehealth/images/b4derm5_clip_image020.jpg

URTICARIA VS ANGIOEDEMA

- **Urticaria** – involving the superficial dermis
  - Most often characterized by intense pruritis due to histamine effect

- **Angioedema** – involving deeper dermal and subcutaneous layers
  - Deeper and dull discomfort – burning quality
    - Fewer mast cells and sensory nerve fibers
  - 40% of CU patients*
  - Eyelids, lips, genitals, palms, soles

*Kaplan A. JACI 2004 114(3):465*
CLASSIFICATION

- **Acute urticaria**: Less than 6 weeks
  - 2/3 of cases. Up to 20% of population
  - Rapid onset and course
  - Likely infectious (81%)\(^1\) food, drug, contact

- **Chronic urticaria**: Greater than 6 weeks
  - 30% of urticarial cases, 0.5% of population
  - Spontaneous or autoimmune.
  - Active most days
  - About 50% have symptoms beyond 1 year \(^2\)

Causes of Urticaria

- Drug reaction
- Food reaction
- Ingestion of allergens
- Infections
- Transfusion reactions
- Insects (papular)
- Collagen vascular Dz
- Malignancy

Physical urticarias:
- Cold
- Cholinergic
- Dermatographism
- Pressure
- Vibratory
- Solar
- Aquagenic

- Chronic spontaneous
- Chronic autoimmune
GENERAL CONSIDERATIONS

- Always need to differentiate urticaria from anaphylaxis
  - Ingested or injected allergens prior to reaction?
  - Oropharyngeal, respiratory, gastrointestinal, hypotension suggests anaphylaxis

- Inhaled allergens cause respiratory and ocular symptoms but not urticaria
Drug induced urticaria

- Most commonly manifests within 1-24h post-ingestion
- Elimination should show gradual resolution
- Repeat offenders: Opioid analgesics & NSAIDS
ASA/NSAID ASSOCIATED URTICARIA-ANGIOEDEMA

- Common cause of acute urticaria and regular contributor to chronic urticaria

- Acute mechanisms:
  - IgE mediated
  - COX-1 inhibition (type 3 NSAID pseudoallergy)
ASA/NSAID ASSOCIATED URTICARIA-ANGIOEDEMA

- Chronic urticaria:
  - NSAIDs lower threshold for urticarial flares
  - Thought COX-1 inhibition involved

- 35% of chronic urticaria patients will experience flares after ingestion of NSAIDs/ASA*

*Middleton’s Allergy. 2013. p1304-1306.
**Food Induced Urticaria**

- Commonly seen with *acute* urticaria
  - Expect immediate reaction within 2h
  - Consistent response

- Rarely cause of chronic urticaria

- Skin prick test vs. specific IgE

- Elimination diets
  - Elimination of salicylates and food additives
  - Food diaries
INFECTIOUS URTICARIA

- Likely cause of 80% of pediatric acute urticaria
  - immune complex deposition
  - complement activation

- Viral and bacterial infections\(^1\)
  - Benign viral infections (URIs, gastroenteritis)
  - UTIs
  - Dental infections

2. Middleton’s Allergy. 2013; p581
INFECTIOUS VS BETA-LACTAM USE AND ACUTE URTICARIA\textsuperscript{1,2}

- Of 88 children on beta-lactams presented to the ER with a delayed presentation of urticaria

  - 66% were found to have evidence of a viral infection
  - Only 6 had antibiotic sensitivity as indicated by oral challenge testing with the same antibiotic.

1. Middleton’s Allergy. 2013; p581
ENVIRONMENTAL EXPOSURES

- **Aeroallergens**
  - Very rare causes of urticaria
    - aeroallergen testing is not necessary
  - Exceptions--immediate contact to animal saliva or foods

- **Stinging insects**
  - Hymenoptera venom (IgE)
  - Fire ants (IgE)
  - Triatoma (kissing bugs) – nocturnal bites, SW USA
  - Papular urticaria – bedbugs, fleas, mites, chiggers, moquitos
Papular Urticaria

- Crops of itchy, red bumps, exposed parts
- 0.2 - 2 cm in diameter
- Lasting days!
- May leave marks or scars due to scratching

https://dermnetnz.org/arthropods/papular-urticaria.html
Physical Urticarias
COLD URTICARIA

- Rapid onset of pruritus, erythema, and swelling after cold exposure
  - Can have hypotension from full-body immersion as in cold pools
  - Lip swelling with cold foods
  - Dx: ice cube on arm for 4 min with 10 min observation
  - Can be associated with cryoglobulinemia, cold agglutinin, cryofibrinogenemia, and PNH
  - Tx: underlying disease and antihistamines
  - Pathogenesis: largely by histamine, also eotaxin, NCF, PAF, PGD2, TNFα
**Cholinergic Urticaria**

- Small punctuate wheals and prominent flares
  - Upper body/neck first, then generalized spread

- Associated with exercise, hot showers, **sweating**, and anxiety

- Some can have lacrimation, salivation, and diarrhea (increased cholinergic/parasympathetic activity)
CHOLINERGIC URTICARIA

From: Middleton, 7th edition
GENERALIZED CHOLINERGIC URTICARIA

Dx:

A. Intradermal methacholine
- 0.01mg of methacholine (Mecholyl) in 0.1mL of saline → characteristic hive surrounded by smaller satellite lesions

B. Non-exertional elevation of the patient's core body temperature.
- arms submerged in a 40°C hot water bath until the core body temperature has increased at least 0.7°C
Exercise-induced Anaphylaxis

Confused with cholinergic urticaria!

Differs from generalized cholinergic urticaria:
- Larger lesions (10-15mm) than cholinergic urticaria
- Associated with wheezing and PFT changes
- ? response to antihistamine prophylaxis
- Tx: avoidance of exercise after certain foods
- Few reported fatalities
  - Cessation of exercise results in immediate improvement/resolution of symptoms.
DELAYED PRESSURE URTICARIA (ANGIOEDEMA)

- Delayed until 4-6 hours after sustained pressure
- Usually more painful or burning as opposed to pruritus
- Can occur with tight clothing, hammering, walking, or sitting for hours
- Dx: sling with 5-15lb weight attached to forearm or shoulder for 10-15 minutes
- Tx: Variable response to antihistamines
  - Desoloratadine + Montelukast may be helpful*

**Solar Urticaria**

- Rare

- 1-3 minutes of exposure

- Pruritus within 30 sec, then erythema and edema to exposed area

- Resolve within 1-3 hours

- Dx: fluorescent light appropriate wavelength

- Tx: antihistamines, sun avoidance, protective clothes, and topical blocks
AQUAGENIC URTICARIA*

- Rare, less 100 cases reported
- First described in 1964
- Small wheals with water, not dependent on temperature
- Dx: direct application of a tap water compress or distilled water compress to the skin x 30 min

AQUAGENIC URTICARIA

Pin-head to match-head sized wheal surrounded by erythema on the upper trunk after the water provocation test.

DERMATOGRAPHISM

- 2-5% of population

- With scratched skin: white line of vasoconstriction, then pruritus, erythema, and swelling

- ? IgE mediated without obvious antigen

- Pts have an abnormal circulating IgE that bestow a physical sensitivity to dermal mast cells

- Tx: H1 antihistamines
  - Severe cases seen with systemic mastocytosis and urticaria pigmentosa

Illustration from: http://www.tbeeb.com/ph/files/1/health_topics/Dermatographism.jpg
CHRONIC URTICARIA
Autoimmune vs Spontaneous
CHRONIC URTICARIA (HIVES > 6 WEEKS)

- Subdivided into:

  1. **Chronic spontaneous histaminergic urticaria (55–60%).**

  2. **Chronic autoimmune urticaria (40–45%)**
     - Autoantibodies found in 40-50% of CU pts
     - Antithyroid antibodies seen in 15-24%
     - 35-40% have IgG reactive to α subunit of FcεRI
     - 5-10% with functional anti-IgE antibody
     - Usually IgG1 and IgG3, possible IgG4
CHRONIC SPONTANEOUS HISTAMINERGIC URTICARIA

- Formerly “chronic idiopathic urticaria”
- Waxing and waning
- Usually non-atopic individuals with normal IgE
- Exhaustive laboratory investigation is not useful or recommended
  - Systematic review, 29 studies (6462 patients)\(^1\)
    - cause identified in only \textbf{1.6}\% of patients
    - \underline{no association} between the number of tests ordered and identification of the underlying disorder.

Urticarial Vasculitis

- Usually manifestation of underlying systemic disease
  - Fever, elevated ESR, arthralgias, myalgias, and leukocytosis common clues
  - Longer lasting individual lesions (> 36-48 hrs)
  - Scarring on healing not due to excessive scratching
  - Refractory and painful

- Bx: necrotizing vasculitis around small venules, with Ig and complement deposition
URTICARIAL VASCULITIS

- **Drug induced**
  - ACE inhibitors, penicillin, sulfonamides, fluoxetine, and thiazides

- **Systemic Diseases**
  - SLE and Sjögren syndrome
  - Monoclonal gammopathies (IgA and IgM)
  - Mixed cryoglobulins, hematologic and solid malignancies.

- **Viral**
  - hepatitis B, hepatitis C, and infectious mono.

- **Most cases are idiopathic**
Exacerbating Factors for Urticaria

- Mechanical
  - Scratching/Rubbing
  - Friction (tight clothing)
  - Vibration
  - Pressure

- Heat
  - Showers, occlusive clothes

- Dietary
  - EtOH
  - ?Salicylate rich foods (tomatoes)
    - Limited evidence
  - ?Spicy foods

- Drugs
  - ASA/ NSAIDS!!
  - Opioids
**Urticaria: Laboratory Evaluation**

**Acute:**
- unlikely to have any useful labs
- Consider common foods
  - self limited viral infections

**Chronic Intractable:**
- CBC
- LFT's
- Thyroid studies
  - TSH, free T4, antibodies
- Basophil histamine release assay
- Anti-IgE IgG Ab
TREATMENT

Antihistamines, antihistamines, antihistamines
H1 ANTIHISTAMINES

- **Main stay** and cornerstone of pharmacotherapy for histaminergic urticaria

- Responsiveness varies
  - 50 to 95% of patients achieve satisfactory control with one or a combination of antihistamines*  

- Ceterizine > fexofenadine > loratadine > placebo

ANTI-HISTAMINE HEAD-TO-HEAD TRIAL FOR HISTAMINE WHEAL AND FLARE

Onset of Pharmacodynamic Activity in Wheal / Flare Study – Results

Randomized, double-blind, single-dose, crossover comparison trial in 20 healthy male adults

- 50% of cetirizine subjects responded by 20 minutes*
- 70% of cetirizine subjects responded by 40 minutes**
- 95% of cetirizine subjects responded by 60 minutes

Wheal inhibition greater than 95%

**ADDITIONAL TREATMENT OPTIONS**

- **H2 blockers** may enhance symptom relief???
  - Cutaneous vasculature also have H2 receptors
  - Ranitidine, Cimetidine, Famotidine

- **Leukotriene inhibitors** (Zileuton, Zafirlukast, Montelukast)
  - Reasonably low adverse effect profile
  - reasonable add-on therapy
**ADDITIONAL TREATMENT OPTIONS**

- **Steroids**: can help late-phase infiltration
  - Maximize anti-histamine therapy first

- **Doxepin** – antidepressant and antihistamine
  - Blocks H1 and H2, 7 times more potent than hydroxyzine
  - Significant sedation as well as QT prolongation
  - Generally avoided in children <12 years of age

- **Ketotifen** – mast cell stabilizer for physical sx’s
  - AE: sedation and weight gain
**THE ALLERGIST/IMMUNOLOGIST APPROACH**

1. **Reassurance**
   - Good news/bad news talk
   - Begin, self limited, 2/3 cases resolve in 6 weeks, 50% by 1 year

2. Optimize *non-sedating antihistamines* first (cetirizine, levocetirizine, fexofenadine, desloratadine)
   - Begin at FDA age-approved doses.
     - Double, triple, quadruple daily dose if needed (“off label”)

3. Add *sedating antihistamine* for “breakthrough” symptoms
   - Diphenhydramine or hydroxyzine

4. Add montelukast and/or H2 at FDA- age approved doses

5. Epinephrine for oropharyngeal involvement (rare)
Refractory Chronic Urticaria Further Treatment Options (Off-label):

- **Cyclosporine**: effective but significant AE’s
  - Mast cell and basophil stabilization
  - Immunosuppression
  - Risk of HTN and renal failure
  - If steroid-resistant or comorbidities

- **Dapsone** - screen for G6PD

- **Plaquenil** - needs Ophthalmology eval

- **Sulfasalazine** - needs CBC and LFTs

- **IVIG, thyroxine?**
OMALIZUMAB (ANTI-IGE MONOCLONAL AB)

- FDA approved for CU (3/21/2014)
  - For CU ≥12 years of age who remain symptomatic despite H1-antihistamine treatment
- Benefit in several days
- Well tolerated, less potential for harm compared (eg, calcineurin inhibitors)
- Not everyone will benefit (NNT= 2.6 for becoming hive free and itch free at 12 weeks)*
- ? mechanism of action in CU
  - Stabilization of mast cells, basophils
  - Anti-IgE properties
- Anaphylaxis 1 : 1000 doses

Lang. Annals of Allergy, Asthma & Immunology. 112 (4). April 2014
OMALIZUMAB AND URTICARIAL ITCH SCORE
OMALIZUMAB AND HIVE SCORE
SUMMARY

- Common, affecting migratory, lesions < 24h
- No bruising, marks or scars after resolution
- Beware of mimickers (anaphylaxis, urticarial vasculitis, papular urticaria, mast cell disorders)
- Non-sedating antihistamines first
- Sedating antihistamines on standby
- No cure, but good prognosis
THANKS! QUESTIONS???

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