Urticaria and Hives: What’s the Buzz?

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Urticaria

Characteristics
- Transient (lasting less than 24 hours)
  - Often rapidly fluctuates
  - Need to ask the question of duration carefully as the whole attack lasts longer than 24 hours but the individual lesions do not
- Pruritic
  - NOTE: individuals with urticarial tend to rub rather than scratch
- Pink papules and plaques with a pale center
- No skin color change (i.e. brown or purple)
- No epidermal disruption on primary lesions
- If no lesions currently, ask for photos

Prevalence
- 1/5 of individuals will experience urticaria in their lifetime
- Women are 2 times as likely to have urticaria
- The peak incidence is between 20 and 40 years of age
- Urticaria can have a significant impact on one’s quality of life

Definitions:
- Depth of involvement
  - Urticaria is a whealing of the skin affecting the dermis
    - Tends to be more pink
    - Can affect any area of the body
  - Angioedema is a whealing of the skin affecting the subcutis
    - Tends to be dull colored
    - Affects the face and eyes
  - Urticaria and angioedema can occur together
- Acute urticarial lasts less than 6 weeks(1)
- Chronic urticarial lasts longer than 6 weeks
  - Most cases of chronic urticarial become asymptomatic by 2 years
  - 10-50% may have symptoms for greater than 5 years
  - Physical urticarias are less likely to remit
- Urticaria can occur with angioedema
- Hereditary angioedema does NOT have associated urticaria

Pathogenesis
Mast cells, basophils, and Immunoglobulin E (IgE) are the major players in urticaria.

Urticaria can occur as part of a type I hypersensitivity reaction as well as an anaphylactic reaction.

- Clinical history will help differentiate

Basophils

- Often low in active disease and increase with remission
  - Likely related to movement from the blood into the tissue

Mast cells

- Unknown function in humans
- Stimuli to lead to degranulation
  - Allergens
  - Antibodies to Fc-epsilon R1 and IgE
  - Substance P
  - Stem cell factor
  - C5a
  - Opiates, NSAIDs, ASA, ACEi (angioedema)
- Mast cells release histamine which leads to vasodilation and increased vessel permeability

IgE binding to mast cells and basophils leads to degranulation

- Leads to itchy, red, raised wheals with minimal epidermal change

Common causative and exacerbating factors include:

- Aspirin
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Angiotensin converting enzymes (ACE) inhibitors
- IgE mediated allergies to things such as food occur RARELY

**Diagnosis**

- **THERE IS NO NEED FOR ROUTINE TESTING IN URTICARIA**
  - Unlikely to find an underlying cause
  - A good clinical history will often pick up common culprits
    - Drugs, foods, H Pylori, etc

Clinical History

- Duration of lesion
  - Less than 24 hours
    - Typical urticaria
  - Greater than 24 hours
    - More typical for urticarial vasculitis
      - Vasculitis accounts for 5% of chronic urticaria
    - Note that angioedema often lasts longer than 24 hours
- Duration of flare
  - 6 weeks or less of 2 times per week of symptoms
- Timing of flare
  - Urticaria is often worse at night
- Associated symptoms
Fevers and arthritis should be a warning sign
- Possible syndromes include
  - Urticarial vasculitis
  - Schnitzler’s syndrome
    - Urticaria, fevers, bone pain, elevated ESR, IgM monoclonal gammopathy
  - Cryopyrin-associated periodic fevers
- Abdominal pain and back pain
  - If angioedema may have bowel swelling
  - If vasculitis may have renal involvement
- Drugs
  - Up to 9% of acute urticaria
- Physical stimuli
  - Accounts for roughly 20-35% of chronic urticaria
  - Types
    - Cold
    - Heat
    - Vibration
    - Exercise
- Recent infections
  - Upper respiratory tract infections are a precipitant of approximately 40% of acute urticaria
  - Rare in chronic urticaria
- Autoimmunity
  - Approximately 30-40% of chronic urticaria have autoantibodies
- Food
  - Less than 1% of acute urticarial
- Idiopathic
  - 50% of acute urticaria
  - 30-40% of chronic urticaria
- Pseudoallergic
  - Some food preservatives and salicylates have been associated with urticaria
  - Not considered a true allergy

Clinical classification

Types of urticarial (2)
- Acute urticaria
- Chronic spontaneous urticarial
  - Autoimmune urticaria
- Chronic inducible urticaria
  - Physical Urticaria
  - Cholinergic
  - Contact
Any of the above with angioedema
  ➢ Not a distinct category but can occur with any of the above entities

Additional important types
  ➢ Urticarial vasculitis
  ➢ Urticarial syndromes

Laboratory Evaluation
  ➢ No routine laboratory work is necessary
  ➢ For chronic disease
    ➢ There is an increased incidence of thyroid antibodies and celiac disease
    ➢ 30-40% of patients have positive autologous serum skin testing or a chronic urticarial index indicating autoimmunity
      ▪ Note that there is no need to routinely test for this
    ➢ Consider celiac screening in children
  ➢ For hereditary angioedema without urticaria
    ➢ C4 and C1 esterase inhibitor level and function is warranted
  ➢ For lesions lasting longer than 24 hours urticarial vasculitis should be ruled out
    ➢ Should refer patient to dermatology
    ➢ Initial workup
      ▪ Skin biopsy
      ▪ Renal functions (BUN, Cr, Urinalysis)
    ➢ If evidence of vasculitis, further workup

Mimickers
  ➢ Clues to alternative diagnosis
    ➢ Age
      ▪ Elderly individuals (especially over the age of 80) with new onset of urticaria may have urticarial bullous pemphigoid
    ➢ Associated symptoms
      ▪ Fevers and arthralgias may be seen with vasculitis as well as auto-inflammatory diseases
      ▪ Abdominal pain, hearing loss, and muscle pain may be more common in auto-inflammatory diseases
    ➢ Bruising
      ▪ More common in vasculitis
    ➢ Duration of lesions
      ▪ Longer than 24 hours should be concerning for vasculitis
  ➢ Urticarial vasculitis
    ➢ More common in middle aged women
    ➢ Lasts longer than 24 hours
    ➢ Leave behind bruising or brown patches
    ➢ Tends to have more symptoms of burning
- Associated joint pain, abdominal pain, and kidney disease
- May have underlying systemic diseases
  - Autoimmune
    - SLE
    - Sjogrens
  - Infectious
    - Hepatitis B or C, EBV
- Unique dermoscopy showing purpuric dots and globules

**Acute urticaria**

- Affects approximately 20% of the populations
- By definition acute urticarial lasts less than 6 weeks; however, it often resolves in 2-3 weeks
- Associated angioedema can occur in up to 30% and is more common in children
- Approximately 25% of individuals have systemic symptoms
  - Wheezing, upset stomach, cough, runny nose, flushing, headache, fever, tachycardia, joint pain, and conjunctivitis
    - These symptoms may indicate the possibility of anaphylaxis
- Most commonly is idiopathic (50%) or follows an upper respiratory tract infection (40%)
- Less common causes are
  - Drugs (9%)
    - Antibiotics (most common)
    - NSAIDs and Aspirin (most common)
    - ACE inhibitors
    - Iodine-based contrast
    - Proton pump inhibitors
    - Opiates
  - Food
    - Cow’s milk (important in children under 6 months)
    - Egg
    - Fish and seafood
    - Fruits
    - Nuts
    - Tomato
    - Wheat
    - Yeast
- Antihistamines are often adequate for treatment
- Recurrent bouts of urticarial may occur in about 12% of individuals

**Acute Urticaria:**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Idiopathic</td>
<td>30-50%</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>Up to 40%</td>
</tr>
<tr>
<td>Drugs</td>
<td>Up to 9%</td>
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Chronic Urticaria (4)

- Affects approximately 1% of the population
- More common in individuals 30-50 years of age
- Most common causes are physical triggers, autoimmune, and idiopathic
- 30-50% go into spontaneous remission by 1 year
- 20% have persistent disease beyond 5 years
  - Autoimmunity, severe disease, and angioedema are associated with longer disease duration
- Autoimmune versus idiopathic
  - Individuals with autoimmune urticarial do not differ clinically or histologically from those without autoimmune disease

Physical urticarias (5)

- The exact mechanism of stimulation of mast cell release of mediators as well as trigging of basophils is unknown
  - Possibly unknown channels stimulated to allow calcium influx
- In general, often poorly respond to prednisone and respond better to anti-histamines (2)
- Dermatographism
  - Most common physical urticaria (approximately 50%)
  - Provoked by scratching, stroking, or pressure
- Delayed pressure urticarial
  - Provoked by pressure 30min to 12 hours prior
- Cholinergic
  - Second most common urticarial (approximately 10%)
  - Provoked by elevated body temperature, spicy food, emotion, and hot water
  - Pinpoint size lesions
  - Often involves the limb and trunk with a few minutes after exercise
- Cold-contact
  - Exposure to cold
- Heat-contact
  - Exposure to hot
- Aquagenic
  - Exposure to water
- Solar
  - Exposure to light at a specific wavelength
- Vibratory
  - Exposure to vibration
  - More often is angioedema
    - Vibratory machinery
    - Lawn mower
    - Riding a bike
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<td>Physical</td>
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<tr>
<td>Vasculitis</td>
<td>5%</td>
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Treatments

First line
- Reassurance that this is something that will likely resolve
- Topical 1-2% menthol cream or 1% pramoxine
- Non-sedating antihistamines (H1 blockers) (6)
  - Certirizine, levocertirizine, fexofenadine, loratadine, desloratadine
  - Take 1-2 tablets twice daily
  - Pearls
    - Doses of 2-4 times the over the counter dose are more effective
      - One study found that up to 4-fold increase in dosing improved symptoms in ¾ of individuals with difficult to treat chronic urticaria(7)
    - Acts as a negative agonist which can only bind an INACTIVE receptor
      - Therefore, must be given PROPHYLACTICALLY
    - Tachyphylaxis can occur so changing between non-sedating antihistamines can increase efficacy
      - Some patients taking certirizine will be sedated
- Sedating antihistamines (H1 blockers)
  - Diphenhydramine or hydroxyzine
    - Useful at night time to help with sleep

Second line
- Non-sedating antihistamines (H2 blockers)
  - Some mast cells have H2 receptors
  - H1 blockers are more effective in combination with H2 blockers(8)
  - The medications are safe
  - Ranitidine, famotidine
    - 1 tablet 2 twice daily
- Leukotriene antagonists (LTA)
  - Montelukast
    - 10mg daily in combination with oral antihistamines showed improved quality of life but no reduction in the number and frequency of urticarial episodes(9)
- Doxepin
  - A tricyclic antidepressant with strong H1 and H2 properties
Caution with use due to strong sedation effects as well as QT prolongation
10mg TID was found to be effective in 74% of patients with urticarial compared to diphenhydramine at 25mg TID (10)

Note
- Doxepin is too sedating to use in the daytime
- CAUTION in elderly as there is a risk of falls and a black box warning
- Urinary retention is common in the elderly population
- Typically, I dose at night time starting with 10mg and increasing as tolerated up to 30mg nightly

Third line (11)
- In most cases, first and second line therapies as well as time will lead to resolution of disease
- Stacking therapies is ideal
- CAUTION with prednisone as they are often effective with urticarial but are difficult to withdraw
  - A short course of prednisone may be considered in refractory cases to high dose H1, H2, & LTA
  - 0.3-0.5mg/kg trial
  - Relapse rate as high as 50%
- Omalizumab(12)
  - FDA approved for refractory chronic urticarial
  - High expense
  - Subjects included in most trials had disease for a minimum of 6 months and greater than 8 weeks of constant itching
  - The IgE levels were between 30 and 700
    - Additional studies found that Omalizumab is effective in individuals with IgE greater than 700
  - Response rates
    - 38.1% complete responses
    - 55.1% partial responses
  - Best used in combination with other treatments
  - Anaphylaxis has been reported and is estimated at a 1/1000 injection risk
    - Pooled studies have round the risk to be lower
  - Should be considered 3rd line at 300mg per month for up to 6 months
  - Should be reserved for specialists
- Immunosuppressive therapy
  - Cyclosporine, mycophenolate mofetil, plaquenil, dapsone, and azathioprine
  - Should be reserved for specialists

General therapeutic approach
- First step
  - Initiate non-sedating antihistamines at the normal dose
  - If sleep is disrupted use sedating antihistamines at night
Second step
- Increase the dose of non-sedating antihistamine to 2-4X the normal dose
- Consider
  - Adding montelukast daily
  - Adding H2 blocker

Third step
- Likely referral
- Consider a trial of oral corticosteroids
- In refractory cases consider omalizumab versus immunosuppressive therapy (cyclosporine)

References: