Do My Patient’s Hives Always = Allergy?

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Objectives

1. Review the pathophysiology and key features of urticaria

2. Compare & contrast the definitions of causes for acute urticaria versus chronic urticaria

3. Review common causes for allergic etiologies of urticaria as well as non-allergic etiologies of urticaria

4. Discuss in detail characteristics leading to a diagnosis of chronic idiopathic urticaria and angioedema

5. Discuss treatment options for patient that suffer from chronic urticaria and/or angioedema
What is Urticaria?
Urticaria defined

- Vascular reaction of the skin (involves histamine, kinin, vasoreactive mediators to main a few)
- Transient - each individual lesion lasting about 4 to 6 hours
- Raised erythematous plaques (wheals) varying in size
- Usually accompanied by intense itching
- Often will have central pallor
- Can merge into large plaques
Why Should I Care?

- Estimates suggest this problem will affect 20% of the population at some point in their lives \(^{(1,2)}\)
- This statistic appears similar in both the US and other countries
- It is a common problem found throughout a patient’s lifetime (infants to adults in their 90s)
- Without an obvious diagnosis, can be difficult for even experienced clinicians to understand & treat
- We receive referrals for this from all specialties including primary care, pain management, surgery, dentistry to name a few
Why Should I Care (continued)

- Quality of life data comparing chronic urticaria and chronically pruritic patients suggests that they have significantly decreased quality of life

- Attributed to lack of sleep & inability to concentrate

- Zuberbier et al *Allergy* (2014)(1)
Pathophysiology Behind Urticaria
Food antigen

IgE antibody

IgE receptor

Multivalent food antigen binds and cross-links two or more IgE antibodies

Mast cell

Degranulation (minutes)

Release of proinflammatory mediators following fusion of lysosomes with cell wall
Antigen

IgE

IgE Fc receptor

Signals for activation of phospholipase A₂

Signals for cytokine gene activation

Nucleus

Membrane phospholipids

Degranulation

Granule contents
  • Histamine
  • Proteases
  • Chemotactic factors (ECF, NCF)

Secreted cytokines

Arachidonic acid

Leukotrienes B₄, C₄, D₄

Prostaglandin D₂

PAF

Primary mediators

Secondary mediators

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Production and release of lipid mediators, e.g. Prostaglandins, leukotrienes, platelet-activating factor

Release of preformed mediators, e.g.
- Histamine
- Heparin
- Proteases
- Chondroitin sulfates
- TNF
- Antimicrobial peptides

- Recruitment and activation of monocytes and macrophages
- Migration and activation of dendritic cells
- Recruitment and activation of T cells
- Recruitment and activation of neutrophils, basophils and eosinophils
- Phagocytosis and/or antimicrobial activity
- Effects on epithelial cells, tight junction proteins, etc.
- Degradation of endogenous toxic mediators
Resting mast cell shows granules containing serotonin and histamine.

Activated mast cell: Multivalent antigen crosslinks bound IgE antibody causing release of granule contents.
"It's hives."
Mimickers of Urticaria

- Drug rashes
- Viral exanthems
- Inflamed atopic dermatitis
- Keratosis pilaris
Keratosis Pilaris
"I must say, Mr. Jennings, you have the worst case of Hives I've ever seen."
Most common causes of allergic urticaria (2)

- **New food** - something unusual that patient does not typically have

- **New medication** - antibiotic are most frequently implicated

- **Venom allergy** - stings with honeybee, wasp or yellow jackets (In southern states also fire ants)
Most Common Food Allergies in Children (3)

- Milk
- Egg
- Peanut
- Tree nuts
- Soy
- Wheat
Most Common Food Allergies in Adults$^{(3)}$

- Fish
- Shellfish
- Tree nuts
- Peanut
Allergies to Food Dyes

Allergy to food dyes are extremely rare except in cases of yellow food dye from annatto and red food dye from carmine (Wang & Sampson 2011)(4)
CARMINE

Carmine is a red food coloring that comes from boiled cochineal bugs, which are a type of beetle.

There have been reports that the bug based coloring can cause severe allergic reactions in some people.

Carmine can be found in Skittles, Good n Plenty, Dannon strawberry yogurt, Ocean Spray grapefruit juice & often times strawberry or raspberry ice cream.
Annatto
Don’t believe everything you find on the internet…

**Health Benefits of Annatto**

- Improves digestion
- Helps to manage diabetes
- Aids in prevention of cancer
- Helps in treatment of gonorrhea
- Aids in maintaining healthy bones
- Beneficial in reducing signs of aging
- Prevents macular degeneration and cataracts
- Reduces risk of neural tube defects in newborn infants

*Source: Green health trend and microbiome gut flora conservation*
Please note….as you are taking your history

It would be rare to see widespread urticaria caused by inhalant allergies such as pollens or pet dander
Other Causes of Urticaria

**Blood products** - transfusion reactions

- **Contact allergens** - animal saliva, raw foods – typically in isolated areas of skin

- **Physical urticaria** - pressure induced, cold, heat, exercise and in very rare cases water

- **Medications** - narcotics, NSAIDs, contrast dye (mast cell degranulators as part of MOA)
Frequently Overlooked…

Infectious Causes - including viral, bacterial and parasitic causes

(although parasitic causes are rare in the US)
Infection as a Cause

The etiology of different forms of urticaria in childhood: Salkesen D et al. Pediatric Dermatology (2004)(5)

- 54 children (23 girls, 31 boys, ages 1 to 19 years)
- Various forms of urticaria
- Infection was most frequent cause (48.6%)
- Drugs second most common (5.4%)
- Food allergy least common (2.7%)
Infection as a cause (continued)

Acute Urticaria in infancy and early childhood: A prospective study -

Mortureux et al. *Archives of Dermatology* 1998

- 57 Infants (ages 1 to 36 months)
- Infection with/without drugs (mainly antibiotics) - 81%
- Foods in 6 patients (11%)
- There was an association with family history of atopy in 33 patients (58%)
Infection as a cause (continued)

Association of acute urticaria with Mycoplasma pneumoniae infection in hospitalized children -

Wu, CC et al. Annals of Allergy, Asthma and Immunology (2009)(7)

• Association with mycoplasma in children with **acute urticaria** that did not respond to oral antihistamines

• Did have benefit when treated with azithromycin
Infection as a Cause (continued)

Can be associated with Hepatitis A, B, C -

- Criber (2006) - *Clinical Review of Allergy & Immunology*(8)

Can be associated with HIV infection -

Infections Implicated but Unproven\textsuperscript{(1,10)}

- H. pylori
- Streptococci
- Staph
- Giardia
- Norovirus
- Parvovirus
What’s a clinician to do?
Acute versus Chronic Urticaria
Acute versus Chronic Urticaria\(^{(2)}\)

**Acute Urticaria** = Less than 6 weeks duration

**Chronic Urticaria** = Greater than 6 weeks duration
Acute Urticaria

Look for an obvious trigger in the history that would suggest an allergic cause:

- New food
- New drug
- New sting
Acute Urticaria (continued)

Remember in true food allergy, patient should have history of a “reaction” each time he or she ingests the particular food.

Rarely is it something “hidden” or I would find on widespread
Testing Related to Acute Urticaria

Typically **NOT RECOMMENDED** without a history of an obvious trigger

- May resolve and not return

- Typically in over 80% of cases or greater, we never identify a specific trigger

- So recommendation is to treat the urticaria and observe
Treatment for Acute Urticaria

- Can use prednisone in severe cases or in cases affecting the face or eyes.
- Often you can start H1/H2 histamine blockade.
- Recommendation is to use second generation H1 antihistamines (cetirizine, fexofenadine, loratadine) because they allow for titration to significantly higher doses if needed unlike the sedating H1 antihistamines.
Treatment for Acute Urticaria

- H2 blockade usually use famotidine or ranitidine

- You can use first generation antihistamines for breakthrough even when using second generation antihistamines (still caution patient about sedation)
Chronic Urticaria\(^{(2,11)}\)

- Most often NOT ALLERGIC
  - Must think of other causes such as autoimmune problems, small vessel vasculitis, malignancies especially lymphoma, thyroid dysfunction, kidney and liver dysfunction
  - Guidelines again recommend against exhaustive testing and against allergy testing due to very low yield
  - However, most specialists will test at least baseline labs to look for a cause
Second-generation, H1-receptor antihistamines

Updosing of antihistamine

± First-generation (sedating), H1-receptor antihistamines
± H2-receptor antihistamines, ± Leukotriene receptor antagonist

Oral corticosteroids

For chronic urticaria:
Immunosuppressive/immunomodulatory agents
- Cyclosporine
- Sulfasalazine
- Dapsone
- IVIG
- Omalizumab
Labs the Immunologist will consider

- CBCD
- BMP
- LFTs
- TSH
- ANA
- Immunoglobulins (A, G, E, M)
- Specific antibodies
Most often, we are still left with...
Good news! Your lab results look great. Everything is normal; you are the picture of health.
Treat the Symptoms\(^2\)

- Don’t forget that these patients are often quite miserable because the disorder can be quite disruptive to sleep, work, school\(^1\)

- Typically start with H1/H2 blockade and potentially titrate doses up to four times the usual daily dose in the second generation H1 antihistamines

- May add montelukast and sometimes beneficial although the data is not strong
Treat the Symptoms (continued)

- May use first generation H1 antihistamines cautiously for breakthrough episodes or itching (diphenhydramine, hydroxyzine) but these often do not allow for easy titration to higher doses due to sedation

- More attention now on adverse effects in the older patient including the use of doxepin

- I also caution parents about paradoxical reactions to diphenhydramine
When Antihistamamines Fail…

- Consider omalizumab (monclonal antibody) which binds to IgE - labeled for patients 12 years and older

- Cost is substantial!!! - $2500 to $3000 per month for drug alone

- There is a black box warning for late anaphylaxis (4 to 6 hours after administration)

- Patients must carry a current epinephrine auto injector

- Initiation in the office requires first three injections to have a 2 hour observation
If Omaluzimab Fails…

Consider other immunomodulators:

- Colchicine
- Sulfasalazine
- Dapsone
- Hydroxychloroquine
- Cyclosporin (direct mast cell inhibitor)
Urticaria

- > 48 hours
  - Urticarial vasculitis
- < 48 hours
  - > 6 weeks
    - Chronic urticaria
    - Other
    - Physical
    - Chronic autoimmune urticaria
    - Chronic idiopathic urticaria
  - < 6 weeks
    - Acute urticaria
      - Idiopathic
      - Infection
      - Food
      - Medication
      - Venom
      - Latex
      - Contact
      - Dermatographism
      - Cholinergic
      - Cold induced
      - Solar
      - Aquagenic
Questions?

Do you know where Noah kept the bees?  
In the ark hives?
References


