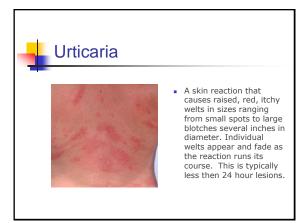
Pediatric Urticaria & Angioedema: A Practical Guide



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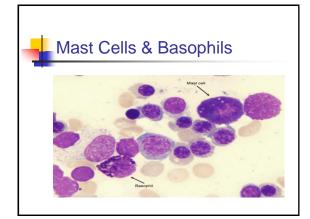
Urticarial Classification

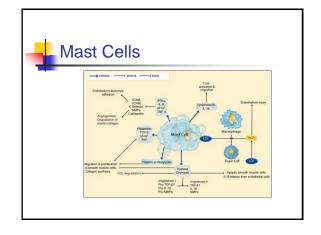
- Acute: Less than 6 weeks duration
- Chronic: More than 6 weeks duration
- How long does the hive remain?
- Any other symptoms or signs with the hives?





 A related type of swelling that affects deeper layers in the skin, often around eyes and lips. Many types don't itch. Duration is longer-1 or 2 days.







Mast Cell Activation/Degranulation

- IgE Immediate Hypersensitivity
- Classical Complement Pathway
- Alternative Complement Pathway
- Direct Activation of Mast Cell
- Plasma-kinin Generating System



IgE Immediate Hypersensitivity

- Causes
 - ALLERGENS
 - Modified IgE; IgG, Autoimmune anti-IgE or FcɛRI; or FcɛRII (CD23) on platelets or lymphocytes or eosinophils.
- Mediators
 - Histamine, leukotrienes PGD2, PAF, ECF-A, HRF



Activation of **Classical** Complement Pathway

- Causes:
 - Antigen-antibody complexes
 IgM, IgG1, IgG2, or IgG3
- Mediators:
 - C3a, C4a, C5a (anaphylatoxins) cause release of mast cell mediators



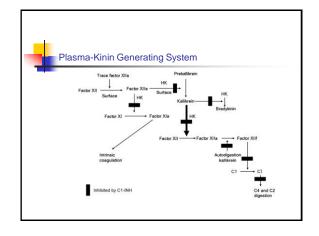
Activation of **Alternative** Complement Pathway

- Causes:
 - IgA-antigen complexes, complex polysaccharides, lipopolysaccharides
- Mediators:
 - C3a, C4a, C5a (anaphylatoxins) cause release of mast cell mediators



Direct Activation of Mast Cell Membrane

- Causes:
 - Morphine, Codeine, Polymyxin Antibiotics, Thiamine, Radiocontrast Media, Vancomycin, Certain Foods--strawberries
- Mediators:
 - Opiates act through specific receptors to release histamine
 - Others nonspecifically activate cell membrane to release or generate mast cell mediators





Plasma-Kinin Generating System

- Causes:
 - Activation by Negatively charged surfaces, collagen vascular basement membrane, or endotoxin.
- Mediators:
 - Bradykinin; thrombin activation; especially for HAE & some CIU





The Urticarial Spectrum

- IgE Mediated Episodic Hives
- Acute Consistent Urticaria
- Physical Urticarias
- Urticarial Vasculitis
- Chronic Idiopathic Urticaria



IgE Mediated Episodic Hives

- Acute Reactions—Often in minutes or hours
- Very common---Normally with other Symptoms
- Common With Foods—Within 2 hours
 - Nuts, Shellfish, kiwi, egg white, milk, soy, etc.
- Contact Urticaria--dog lick, laying in ragweed
- Hymenoptra--often with anaphylaxis
- Exercise plus specific food combination



IgE Mediated Episodic Hives Evaluation:

- HISTORY!!!
- Prick Skin Tests or ImmunoCaps help confirm cause and effect
- Exam: The lesions don't bruise, last less than 24 hours and can have itchy angioedema as well.



IgE Mediated Episodic Hives Therapy:

- Avoidance
- Antihistamines--remember they take 30 minutes to work.
- No effective/safe immunotherapy available for food allergy.
- If part of anaphylaxis: Epinephrine!



IgE mediated urticaria is most often caused by:

- A) Peanuts
- B) Ragweed
- C) Dust Mites
- D) ASA



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Ashley

- Ashley receives her allergy shot after school and has a granola bar and apple juice in your waiting room during her observation 30 minute wait. At 20 minutes she is at the nurses window complaining of itchy face, chest and legs.
- Many wheal and flare lesions are noted in those areas.



Ashley

Diagnosis:



Ashley

- Diagnosis: Allergic reaction from allergy shot
- Evaluation/Treatment:



Ashley

- Diagnosis: Allergic reaction from allergy shot (Keep food allergy in mind, too)
- Evaluation/Treatment: Epinephrine 1:1,000 IM, then antihistamine, prednisone dose and closely observe and treat as needed. Allergist gets notified later and next steps agreed upon.





Acute Consistent Urticaria

- Daily Hives--Aggressive, Waves of Hives
- Infections
 - Viral, Strep
- Drug Reactions
- (Think Serum Sickness Mechanism)
- Generally Not IgE
- Often Lasts 1 or 2 Weeks



Acute Consistent Urticaria **Evaluation**:

- HISTORY and EXAM
- Rapid strep/culture
- LFTs, Hepatitis Serology
- Drug Allergy Testing (only PCN)
 - 4+ Weeks Later
- Avoiding most allergy testing!!



Acute Consistent Urticaria Therapy

- Remove offending drug
- Treat infection
- Comfort:
 - Itch control: Antihistamines, Steroids
 - Explain what is happening and that it will pass. Many patients fear hives will go to anaphylaxis and death.
 - Try not to do harm!



Accurate allergy testing is available for:

- A) Sulfa
- B) Penicillin/Amoxicillin
- C) Cephalexin
- D) Azithromycin



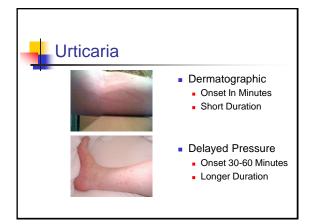
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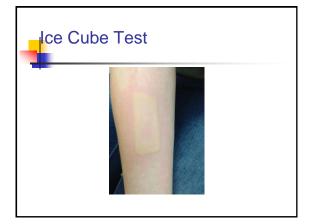
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Physical Urticaria

- Chronic, with problems often for years
- Heat--Cholinergic--small lesions
- Cold (+/- anaphylactic)
- Vibration
- Pressure (dermatographism vs. delayed)
- Aquagenic







Physical Urticaria Evaluation & Treatment:

- Challenge helps confirm but HISTORY is key.
- Heat, scratching, some meds worsen all types
- Avoidance is the main therapy
- Daily antihistamines
- At times more Rx is needed, but be cautious of side effects in the long term.
- These conditions often go on for years.





Angioedema

- Non-itchy swellings--' deeper' hives
- BRADYKININ, prostaglandins, leukotrienes, seratonin, etc. play a big role
- Usually have longer duration lesions
- Often found with hives--similar cause in those cases



Angioedema

- For Non-Itchy Think:
 - ACE Inhibitors
 - Familial Hereditary Angioedema
 - Acquired Angioedema
 - Idiopathic Angioedema



Hereditary Angioedema

- C1 Esterace Inhibitor 'Deficiency'
 - Type I: Low Amount
 - Type II: Non-functioning protein
 - Type III: Unknown, female only, nl C4 (very rare)
- Autosomal Dominant
 - But plenty of spontaneous mutations, too
- 1 in 100,000 population
- Typical onset as kid
- Not uncommon--GI, GU, airway, and posttraumatic symptoms



Hereditary Angioedema Diagnosis

- Screen: C4
- Actual:
 - C1 Esterace Inhibitor level quantitative
 - C1 Esterace Inhibitor level functional
- With Attack:
 - C2 is low or absent (types I & II)



Hereditary Angioedema Therapy

- ABCs, Pain Control, Fluids with attacks
- Replace C1 Esterace Inhibitor
 - Prevention (Cinryze)
 - Attacks (Berinert, Ruconest)
- Danazol, Stanazolol, Aminocaproic Acid
- Bradykinin Inhibitor (Firazyr)
- Kallikrein Inhibitor (Kalbitor)



Acquired Angioedema

- Type I (AAE-1): With other disorders, often has hives, at times purpura. Serum sickness/immune complex mechanism. Low C1q, C1-INH, C4, no FH.
 - B Cell Lymphoproliferative Disorders
- Type II (AAE-2): Auto-antibodies to the C1 Esterase Inhibitor. More common. Not associated with malignancy. Low C1q, C1-INH, C4, no FH.



A low C4 level is found in asymptomatic patients with:

- A) Peanut Allergy
- B) ACE inhibitor angioedema
- C) Hereditary Angioedema
- D) Allergic Asthma



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The non-itchy swelling of angioedema predominantly depends upon which substance?

- A) Histamine
- B) Bradykinin
- C) Tryptase
- D) IgG



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Urticarial Vasculitis

- Chronic Eruptions of erythematous wheals that resemble urticaria but histologically show changes of small vessel leukocytoclastic vasculitis.
- Type III Hypersensitivity Reaction
 - Ag-Ab complexes deposited in vascular lumina--complement activation & chemotaxis of neutrophils
- Very Rare In Pediatrics



Urticarial Vasculitis Clinical Presentation

- Urticarial Eruptions
 - Often burning or painful sensation rather than itch
- Duration over 24 hours
- Petechiae, ecchymoses, postinflammatory hyperpigmentation
- Angioedema of face or hands
- ??About 2% of Chronic Urticaria



Urticarial Vasculitis Clinical Presentation: Non-dermal

- Non-Dermal
 - Arthralgia or arthritis associated with onset of urticaria, Lymphadenopathy (40%)
 - Obstructive Lung Disease (21%)
 - Abdominal or Chest Pain (17%)
 - Photosensitivity
 - Fever (10%)
 - Raynaud's Phenomenon (6%)
 - Episcleritis or Uveitis (4%)



Urticarial Vasculitis Associated Conditions & Ddx

- Most Are Idiopathic
- Collagen Vascular Disease
 - esp. Lupus
 - Also Sjogren Syndrome, Monoclonal Gammopathies, Mixed Cryoglobulins, hematologic & solid malignancies
- Viral Infections
 - . i.e. Hepatitis B, C; Mononucleosis
- Serum Sickness
- Drugs:
 - ACE Inhibitors, PCN, Sulfas, Fluoxetine, cimetidine, diltiazem, thiazides, potassium iodide, NSAIDs, glatiramer acetate.



Urticarial Vasculitis Clinical Laboratory Tests

- CH50, C3, C4, C1q--Decreased in 1/3
 - Associated with purpuric resolution, sxs of arthralgias, abdominal pain, and obstructive lung disease
 - Associated with histologic findings--interstitial neutrophilic infiltrated of the dermis & IF of Igs or C3 deposited in the blood vessels & along the basement membrane zone
- Antibodies to C1q
- Other labs as indicated clinically
 - CXR, UA, PFT, Hepatitis studies, ANA, etc.



Urticarial Vasculitis

A Subset of Vasculitis

- Clinically
 - Urticarial Skin Lesions
- Histologically--
 - Necrotizing Vasculitis



Urticarial Vasculitis Therapy

- NSAID--Indomethacin (Indocin)
- Antihistamines
- Oral Steroids
- Antimalarial-hydroxychloroquine(Plaquenil)
- Azathioprine
- Cyclophosphamide
- Cyclosporine
- Dapsone



Urticarial Vasculitis Conclusions

- A Part Of The Urticaria Spectrum
- Hives That Last > 24 Hours, Leave Bruise, That Burn Or Are Painful
- Association With Arthralgia, Arthritis, Systemic Symptoms In Some Patients
- Biopsy Important
- Effective Therapy Is Available





Chronic Idiopathic Urticaria

- Over 6 Weeks Of Hives
- Lymphocytic, Neutrophilic, Mixed
 - Unknown significance
- Biopsy Without Vasculitis
- Dx When Everything Else Is Ruled Out
- Very Frustrating



Chronic Idiopathic Urticaria

- Possible Mechanisms
 - Autoimmune
 - Anti-IgE
 - Interleukins (IL-1, 3, 5)
 - HRF (histamine releasing factor)
 - Neuroimmunological



Chronic Idiopathic Urticaria Evaluation

- HISTORY and PHYSICAL
- A very frank discussion with the patient (and family if needed) about yield of tests.
 - 97%+ are "Normal"
- Can include cancer evaluation (colon, kidney, hematologic, lung), special diets without dyes or preservatives, hepatitis serology, chemistries, CBC, Tryptase, SPEP, thyroid function and antibodies, autoantibodies (ANA, RF, etc.), parasites, ETC.
- Allergy testing normally only gives some objective evidence that allergy isn't involved.



Chronic Idiopathic Urticaria Evaluation

- Antibody against the mast cell receptor for IgE (FCER1) (30-40%)
- Antibody against IgE (5-10%)
- Antibody against low affinity mast cell receptor for IgE (FCERII)



FcεRI: High-affinity receptor for IgE



Functional autoantibodies of CIU. IgG $^-$ anti-IgE antibodies combine with and cross-link adjacent receptor-bound IgE. IgG $^-$ anti-FcERI antibodies combine with and cross-link adjacent α -chains of FcERI. Black notched membrane structures represent α -chain of FcERI expressed on the surface of a dermal mast cell.



Clinical diagnosis

 Currently the clinical diagnosis depends on autologous serum skin testing.



Autologous serum-plasma skin test. PBS, Saline solution negative control; serum and plasma are injected in a volume of 0.05 mL and the reaction read at 30 minutes. Both serum and plasma have given positive responses. The reaction at the injected site is examined 30 minutes later. A wheal with a diameter at least 1.5 mm greater than a control saline solution wheal is deemed positive



Chronic Idiopathic Urticaria Evaluation



- So What Do We Do???
- H&P
- Basic Labs-try not to miss cures/major issues
 - CBC with diff
 - Sed Rate
 - Metabolic panel
 - Autoimmune
- Diet Trials (or some allergy testing)
- Remove Medications



Chronic Idiopathic Urticaria Treatment

- Education: Average duration 2+ years (14% > 5 yrs), non-fatal disease, not food or drug related, etc.
- Comfort: Daily non-sedating antihistamines, etc.
- DO NO HARM!
- Consider 'anti-inflammatories'



Chronic Idiopathic Urticaria Treatment

- Nonspecific Factor Avoidances If Applicable
 - Fever, illness
 - Heat, exercise
 - Alcohol ingestion
 - Emotional Stress
 - Menstrual Cycle, hyperthyroidism
 - ASA



Chronic Idiopathic Urticaria Treatment: Antihistamines

- Comfort: Daily non-sedating
 - OK to push the dose: 2-4 times allergic rhinitis dosing
 - Loratadine<fexophenadine/cetirizine< xyzal or clarinex
- If still symptoms--add an older, 1st generation
 - Hydroxyzine, Doxepin, Chlortrimeton
 - These do effect performance
- Try adding H2 blockers and leukotriene blockers
- DO NO HARM!
 - ** Response Rate 45% of Patients (Kaplan 2014)



Jennifer

Jennifer is a 17 year old with 2 years of hives. The itchy lesions last 4 to 8 hours, don't bruise, hit anywhere and anytime. Despite zyrtec twice daily, zantac, and singulair she often has to cancel events with family and friends due to the hives and can't sleep well. She is tired and frustrated. Otherwise, she is healthy.



Chronic Idiopathic Urticaria Treatment

- Anti-inflammatories--Think as a Rheumatologist
 - Omalizumab (Xolair)
 - Cyclosporine
 - Dapsone
 - colchicine, hydroxychloroquine, tricyclic antidepressants, SSRIs, plasmaphoresis, stanozolol, indocin



Chronic Idiopathic Urticaria Treatment: Xolair (omalizumab)

- Monoclonal Anti-IgE (human & murine)
- 65% of refractory patients respond well
- 35% are hive free
- Onset in days. Very well tolerated!
- 150 or 300 mg every 4 weeks. No need to get an IgE level for dosing.
- Rare anaphylaxis, question of coronary artery issues, with main side effect being cost.



Chronic Idiopathic Urticaria Treatment: Cyclosporine

- Immunosuppressive
 - Also inhibits histamine release from human basophils and skin mast cells
- 60 to 80% response rate in CIU patients failing high dose H1 blockade
- Help starts within a week
- Find lowest effective dose
- Toxicity issues: Hypertension, Decrease Renal Function



Chronic Idiopathic Urticaria Treatment: Dapsone

- About 2/3rds respond
- For leprosy, anti-inflammatory
- Be sure they have G6PD
- Follow Hg, liver function, fatigue



Chronic Idiopathic Urticaria Treatment

- This is long term treatment!
 - Recheck periodically
 - When better, cut back on meds starting with most toxic one
 - May need to increase Rx during illnesses
- Keep vigilant for other issues
- 25% have thyroid antibodies
- After disease 'Quits', it recurs in 1/3



Jennifer

- We added Xolair 300 mg every 4 weeks
- Better at day 3
- No hives after 2 weeks
- Likely try the 150 mg dose in future



Antibody mediated autoimmune chronic urticaria can be caused by all of the following except:

- A) Antibody against the high affinity mast cell receptor for IgE (FCER1)
- B) Antibody against IgE
- C) Antibody against low affinity mast cell receptor for IgE (FCERII)
- D) Antibody against condrointin



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Hives Conclusions

- Recognize The Spectrum
 - Acute IgE Reactions
 - Acute Consistent
 - Physical
 - Urticarial Vasculitis
 - Chronic "Idiopathic"



Hives Conclusions

- Testing For IgE In Specific Types Only
- Seek Underlying Cause & Correct If Possible
- Control Symptoms
- DO NO HARM!

