

# Urticaria/Angioedema from the Allergist's Perspective

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# Disclosures

- Speakers Bureau
  - AstraZeneca
  - Merck
  - Novartis
  - PuraCap
  - Shire
  - Teva
- Clinical Study
  - Baxalta
- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation

# Objectives

- Differentiate acute versus chronic urticaria/angioedema
- Identify common underlying triggers for urticaria/angioedema
- Understand best therapy for treatment of urticaria/angioedema
- Recognize common types of physical urticaria/angioedema

# Background

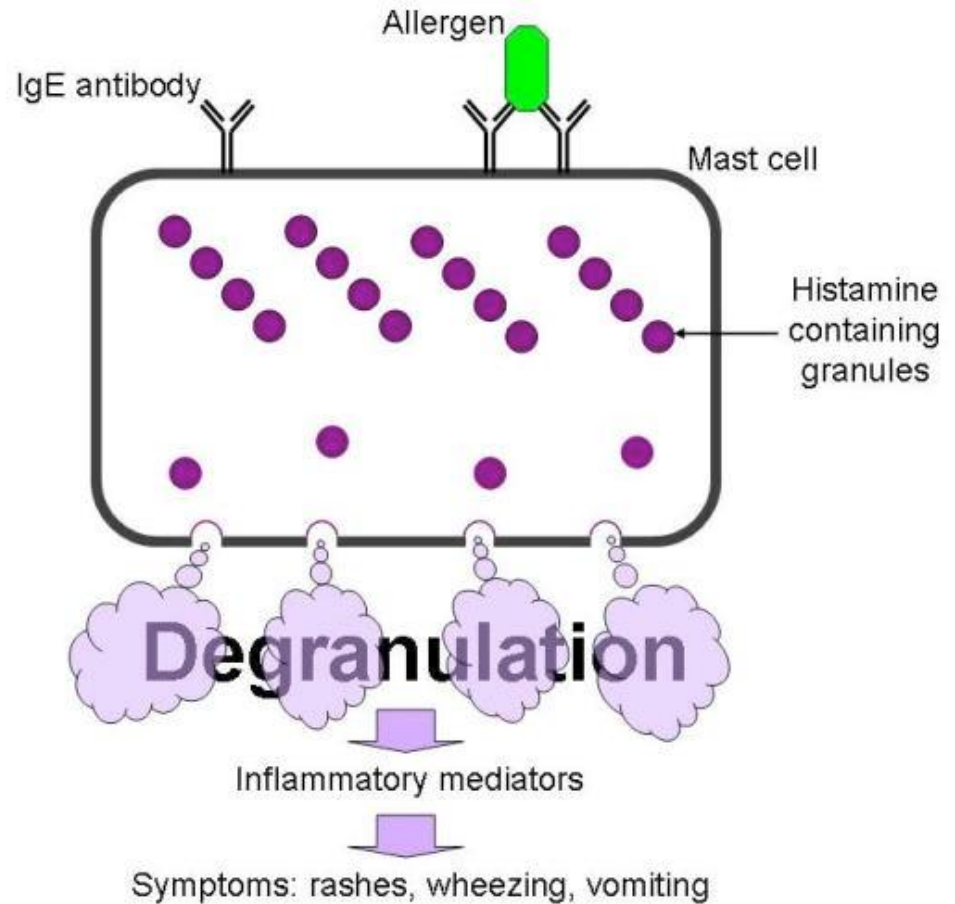
- Acute versus Chronic
  - Based on duration of disease with daily or almost daily symptoms
    - Acute <6 weeks duration
    - Chronic >6 weeks duration
- Distribution
  - Urticaria with angioedema 65%
  - Angioedema alone 20%
  - Urticaria alone 15%

# Acute

- Common, 10-20% of general population experience transient symptoms 1-2 times in lifetime
- Often related to mast cell and basophil activation from multiple triggers
- Both IgE and non-IgE-mediated mechanisms responsible
- Triggers
  - Medications
  - Foods
  - Illness
  - Inhalants
  - Insects

# Mechanism

- IgE-mediated process
  - Allergenic proteins cross-link IgE on mast cells/basophils leading to release of histamine/other mediators



# Acute

- Diagnosis mostly based on history and physical exam
  - Skin testing or limited labs if indicated
- Biopsy findings
  - Dilation of small venules and capillaries in superficial dermis
  - Widening of dermal papillae, flattening of rete pegs, and swelling of collagen fibers

# Acute

- Treatment
  - Elimination of causative agent
  - First-line: Antihistamines
    - First-generation rapid onset and effective but sedative and can impair motor skills
    - Second-generation effective with minimal to no side effects
    - Oral corticosteroids use for poor response to A/H and for short duration



# Chronic

- Prevalence estimated 0.5-5% of general population, incidence estimated 1.4% yearly
- Cause
  - Idiopathic in majority of cases
  - Rarely allergic trigger
  - Autoimmune – increased association with thyroid disease
    - 30-50% produce IgG antibodies to the Fc epsilon component of the IgE receptor and 5-10% produce IgG antibodies to IgE itself
  - Infection –ie hepatitis, mononucleosis, parasitic (comorbid eos)
  - Vasculitides/connective tissue disease – ie SLE
  - Malignant neoplasm
  - Hormonal therapies - BCP

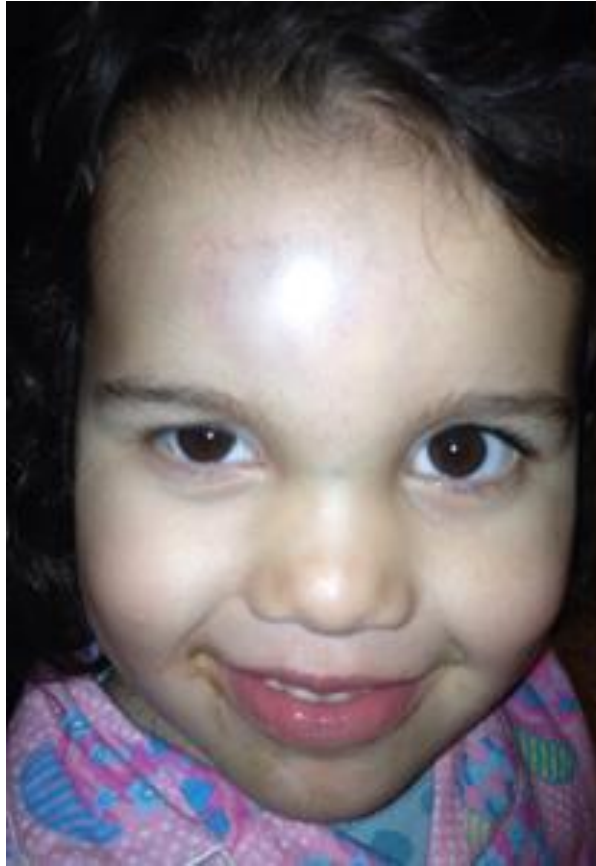
# Chronic

- Evaluation
  - Description
    - Edematous pink or red wheals of variable size and shape with surrounding erythema and generally pruritic
      - Painful or burning is not characteristic and suggests vasculitis
    - Individual lesions usually fade in 24-48 hours, new lesion may develop simultaneously at other sites
      - Vasculitis lesions are palpable and usually nonblanching, span several days and often have residual hyperpigmented changes
    - Angioedema typically is nonpruritic, brawny, nonpitting edema, without well defined margins and without erythema

# Urticaria versus Vasculitis



# Angioedema



# Chronic

- Evaluation
  - History
    - Relationship of episodes to the following:
      - Ingestion (medication or food)
      - Time of day
      - Menstrual cycle
      - Physical stimuli
      - Exertion
      - Occupational exposure
      - Stress
        - Physical
        - Emotional/Mental

# Chronic

- Evaluation
  - Testing
    - Most often not indicated for chronic cases
    - Targeted labs based on clinical suspicion may include:
      - CBC with differential, sedimentation rate and/or C-reactive protein, liver enzyme, and thyroid stimulating hormone level
    - Recurrent angioedema in absence of urticaria
      - Evaluate for hereditary angioedema, acquired C1 inhibitor deficiency, or ACE-I associated angioedema if clinically indicated

# Physical Urticaria

- Subgroup of patients with tendency to have flares from environmental stimuli on inflammatory cells
  - Mechanism of mast cell activation uncertain
- Estimated 0.5% of population is affected
  - Lifetime prevalence 4-6%
- Comprises 20-30% of all cases of CU
- Variable resolution of disease
  - 13-16% at 1 year, 50% after 5 years
  - Dependant on subtype, age of onset, and severity

# Physical Urticaria

- Aquagenic
  - Rare condition, 0.3% of CU
  - Trigger is direct contact with any water source independent of temperature
  - Confirmed with 35°C water applied to skin for 30 minutes
- Cholinergic
  - 11% of young adults, 2-5% of CU
  - “pinpoint” (1-3mm) hives surrounded by larger flares associated with increased core body temperature
  - Common factors: exercise, sweating, emotion, hot baths/showers, saunas
  - Severity ranges from mild pruritus to serious life-threatening reactions





# Physical Urticaria

- Cold
  - 2% of CU
  - Pruritis and swelling with cold stimulus exposure
  - Systemic reaction associated with systemic cold exposure (aquatic activities)
  - Confirmed by applying cold stimulus to skin with wheal-and-flare appearing during skin re-warming
  - Treatment is avoidance, pharmacotherapy in some case (ie: epinephrine for systemic reaction history)
- Delayed-pressure
  - 1-2% of CU
  - Swelling, that can be painful, delayed onset 4-6 hours (occasionally 12-24 hours) after pressure exposure
  - Common factors: working with tools, sitting on a bench, constricting garments
  - Confirmed by 15# weight suspended over shoulder for 15 minutes
  - Often very difficult to treat, conventional antihistamine dosing frequently not efficacious



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# Physical Urticaria

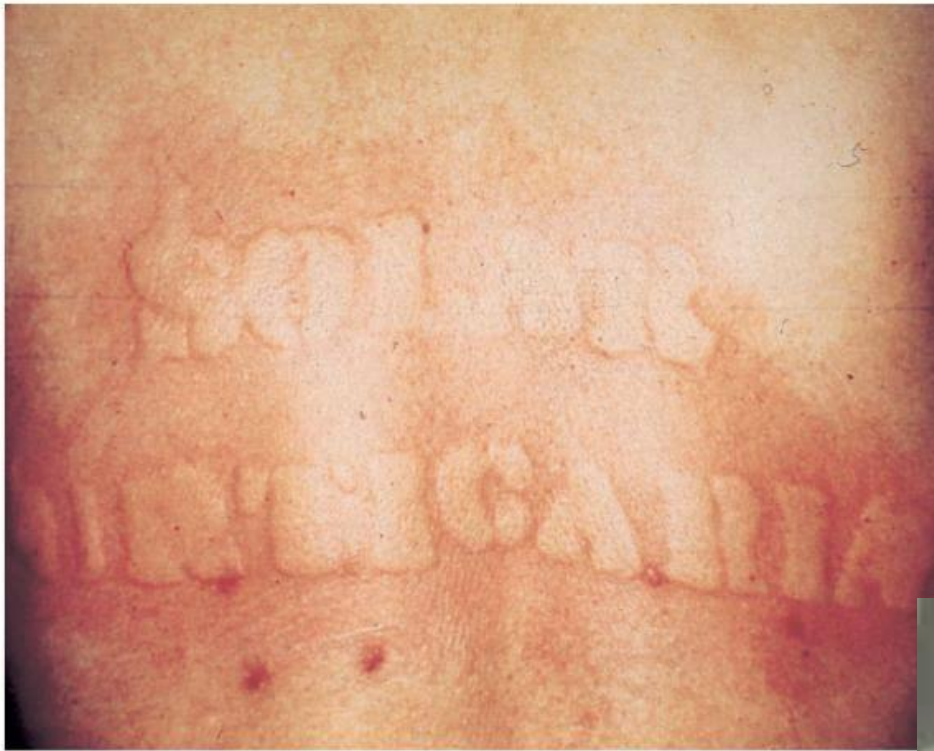
- Dermatographia
  - Most common physical urticaria, 2-5% of general population, 10% of CU
  - Wheal-and-flare quickly with pressure applied to skin
  - Confirmed by stroking skin with firm object
- Exercise-provoked
  - Occur in two conditions
    - Cholinergic
    - Exercise-induced anaphylaxis – 2 types
      - Provoked by exercise
      - Exercise temporally related to food or medication (ASA) ingestion
        - Two subgroups – specific food trigger and non-specific
          - Wheat & celery most common
      - Management includes – avoiding exercise several hours after eating, carry injectable epinephrine, exercise with partner, and wearing medical ID jewelry
        - If symptoms begin, immediate cessation of activity



# Physical Urticaria

- Solar
  - 0.4-0.5% of CU
  - Quick appearance (generally 1-3 minutes) with sunlight exposure
  - Confirmed with phototesting with different wavelengths
- Vibratory
  - 0.1% of CU
  - Pruritis and swelling to vibratory stimulus
  - Can be familial
  - Confirmed by exaggerated response with skin exposure to a vortex mixer





# Chronic

- Management
  - Non-pharmacologic
    - Avoidance of exacerbating triggers
      - NSAIDs, heat, tight-fitting clothing, and physical factors if indicated
      - Pseudoallergens- substances that induce intolerance reactions
        - Additives, vasoactive substances, spices
  - Pharmacologic
    - Potent topical corticosteroids possibly effective for delayed-pressure urticaria
    - Step-care approach is mainstay



# Chronic

- Management
  - Step-care Approach
    - Step 1- Monotherapy with 2<sup>nd</sup> generation antihistamine
    - Step 2- One of more of following
      - Increased dose of Step 1 2<sup>nd</sup> generation antihistamine
      - Add another 2<sup>nd</sup> generation antihistamine
      - Add H2 antagonist
      - Add leukotriene receptor antagonist
      - Add 1<sup>st</sup> generation antihistamine at bedtime
    - Step 3- Dose advancement of potent antihistamine
    - Step 4- Add an alternative agent

# Chronic

- Management
  - Alternative agents used for refractory cases
    - Omalizumab
      - Efficacy supported by large double-blind randomized controlled trials
      - Low rate of adverse effects
      - FDA-approved for ages 12 and older
      - Rarely induces remission without maintenance treatment
    - Cyclosporine
      - Greatest published experience for efficacy of other alternative agents
      - Requires frequent lab monitoring and follow-up visits
    - Other anti-inflammatory agents, immunosuppressants or biologics
      - Dapsone, sulfasalazine, hydroxychloroquine, and colchicine

# Urticaria Differential Diagnosis

- Vasculitis
  - Overall low prevalence
  - Systemic symptoms may be present such as fever, arthralgia, arthritis
  - Lesions
    - >24 hours duration in same location
    - Less pruritic, more painful
    - Palpable purpura or petechiae
    - More prominent on lower extremities
    - Can leave residual pigmented changes
  - Obtain skin biopsy with any unusual presentation

# Urticaria Differential Diagnosis

- Cutaneous T-cell Lymphoma (CTCL)
  - Heterogeneous group of lymphoproliferative disorders
  - Characterized by accumulation of malignant clonal T-lymphocytes in skin
  - Incidence 12.7/1,000,000 M>F and AA>other races
  - Frequent, severe pruritis normally not relieved by emollients, topical steroids or oral antihistamines
  - Sezary syndrome
    - More aggressive form, generalized erythroderma and lymphadenopathy
  - Mycosis fungoides
    - Most common variant, mostly diagnosed 5<sup>th</sup> & 6<sup>th</sup> decades
    - Typically present as erythematous patches which may progress to plaques and tumors
    - Indolent course, progression over years to decades
- Diagnosis confirmed by skin biopsy



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# Angioedema Differential Diagnosis

- Hereditary angioedema
- Acquired C1 inhibitor deficiency
- ACE-I associated angioedema

<b>Mast cell mediator-mediated</b> (With wheals <sup>1</sup> )	<b>Bradykinin-mediated</b> (Without wheals <sup>2</sup> )
Chronic spontaneous urticaria Autoreactive Infection Intolerance Other causes Unidentified cause  Physical urticaria Other urticaria	Hereditary angioedema Type 1 (C1-Inhibitor <i>concentration</i> low) Type 2 (C1-Inhibitor <i>activity</i> low) Type 3 (related to factor XII mutation)  Non-hereditary angioedema Acquired angioedema Drug induced (e.g. ACE inhibitor) Idiopathic angioedema

# Hereditary Angioedema

**Table 2 Phenotypes of HAE due to C1INH deficiency and HAE with normal C1INH**

Finding	HAE Due to C1INH Deficiency	HAE with Normal C1INH
Average age of symptom onset	11.7 ± 7.7 yr	26.8 ± 14.9 yr
Gender	Female = Male	Female > Male
Attack location		
Abdominal	Almost all patients experience	50% of Patients experience
Facial	Occasional	Common
Tongue	Not common	Common
Erythema marginatum	Common	Not seen
Multiorgan attacks	Common	Uncommon
Disease-free intervals	Generally short	May be considerable
Penetrance	Generally high; rare asymptomatic carrier	Generally low; may see obligate asymptomatic carrier

*C1INH = C1 inhibitor; HAE = hereditary angioedema.*



**Table 1. New Products Approved for Hereditary Angioedema**

Generic (Brand)/Manufacturer	Drug Class	Dosage	Year	Self-dosing	Adverse Effects	Cost per Treatment (AWP)	Pregnancy Category	Dispensing Pharmacies <sup>a</sup>
<b>PROPHYLAXIS</b>								
PdC1-INH (Cinryze)/Shire	C1-INH	1,000 U IV every 3-4 days	2008	Yes	Headache, nausea, anaphylaxis (rare), arterial and VTE events (rare), viral transmission (theoretical)	\$6,181	C	Accredo, Caremark, CuraScript
<b>TREATMENT</b>								
PdC1-INH (Berinert)/CSL Behring	C1-INH	20 U/kg IV	2009	Yes	GI upset, headache, anaphylaxis (rare), thrombosis (rare), viral transmission (theoretical)	\$8,517	C	Accredo, BioRx, BioScrip, Caremark, Coram, Crescent, CuraScript, Humana, Walgreens
RhC1-INH (Ruconest)/Pharming Group N.V.	C1-INH	50 U/kg IV or 4,200 U IV if ≥84 kg	2014	Yes	Headache, abdominal and oropharyngeal pain, anaphylaxis (rare)	\$9,500	B	Accredo, Caremark, CuraScript, Walgreens
Ecallantide (Kalbitor)/Dyax Corp.	Kallikrein inhibitor	30 mg SC given as three 10 mg/mL injections	2009	No	Headache, fatigue, nausea, diarrhea, fever, prolonged PTT, anaphylaxis (rare)	\$14,292	C	Accredo, Caremark, US Bioservices, Walgreens
Icatibant (Firazyr)/Shire	Selective bradykinin B <sub>2</sub> receptor antagonist	30 mg SC	2011	Yes	Injection-site reactions (erythema, swelling, pruritus [common]), risk of exacerbating coronary artery disease (theoretical)	\$10,374	C	Accredo, Aetna, BioRx, Caremark, Cigna Tel-Drug, Coram, Humana, ICORE, OptumRx, Orsini, Walgreens

<sup>a</sup> List may not be comprehensive.

AWP: average wholesale price; C1-INH: C1 esterase inhibitor; GI: gastrointestinal; pd: plasma-derived; PTT: partial thromboplastin time; rh: recombinant human; VTE: venous thromboembolism. Source: References 3, 4, 15, 37.



Questions, Comments, Clarifications...



Urticaria & Angioedema

# Resources

- Advances in the Pharmacotherapy of Hereditary Angioedema, U.S. Pharmacist. 2015; 40(10):HS17-21.
- Evidence-based diagnosis and treatment of chronic urticaria/angioedema, Allergy & Asthma Proceedings. 2014; 35(1):10-16.
- The diagnosis and management of acute and chronic urticaria: 2014 update, J Allergy Clin Immunol. 2014; 133(5):1270-77.
- Dissociation Between History and Challenge in Patients with Physical Urticaria, J Allergy Clin Immunol Pract. 2014; 2(6):786-90.
- Not all that itches is urticaria, Ann Allergy, Asthma, & Immunol. 2012; 109:10-13

# Course Description

- Urticaria and angioedema are common medical conditions seen by primary care providers as well specialists. Diagnosis and management can be challenging for the medical provider. Optimal management involves identifying possible underlying triggers as well as ruling out other diseases presenting in a similar fashion. This lecture is intended to help providers identify and optimally management urticaria and angioedema.