Itch and Swelling update:

Practical Approach to Urticaria & Angioedema

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Disclosure Information

- I have no financial relationships to disclose

Objectives

- Recognize urticaria & angioedema
- Develop an appropriate differential for urticaria & angioedema, respectively
- Understand the diagnostic approach & treatment of urticaria & angioedema

Urticaria

- Derived from 18th century Latin from “urtica” which refers to nettle
- Related to Latin verb “urere”
- “Urere” translates “to burn”
- Nettle is any plant from the Genus Urtica

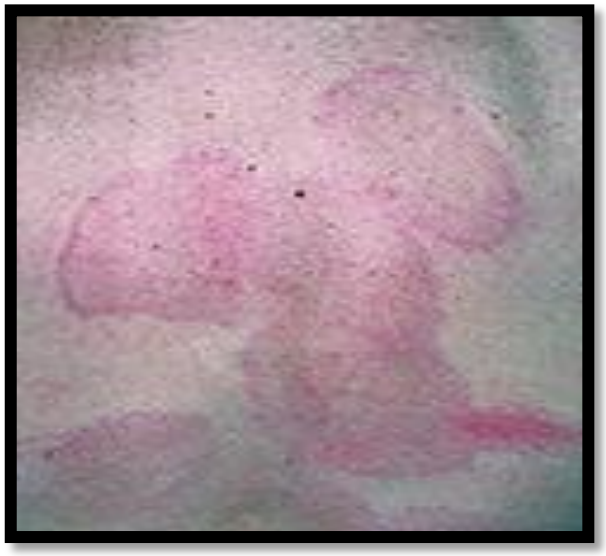
- Nettle plants:
  - ✧ have toothed leaves covered with secretory hairs
  - ✧ secretion of a stinging fluid leads to a burning sensation on skin

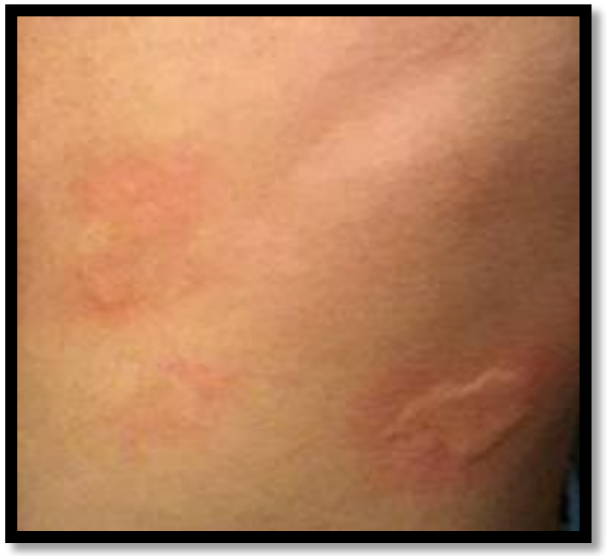
Epidemiology: urticaria

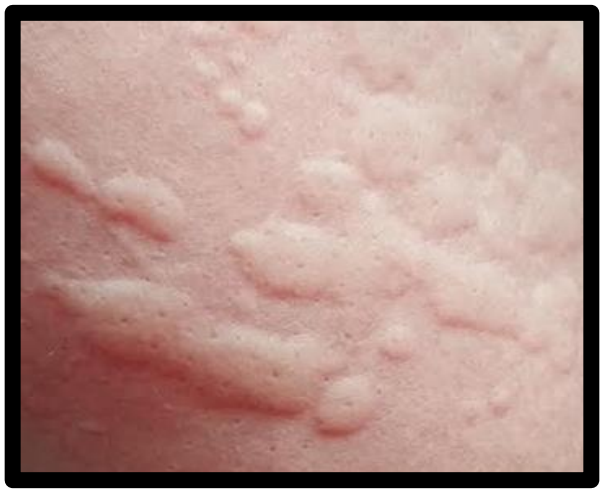
- Urticaria has been observed to occur more commonly in the adult population as compared to among children
- Acute urticaria is more common in children
- Chronic urticaria is more common in adults
- In a lifetime, **15-20%** of patients will experience urticaria

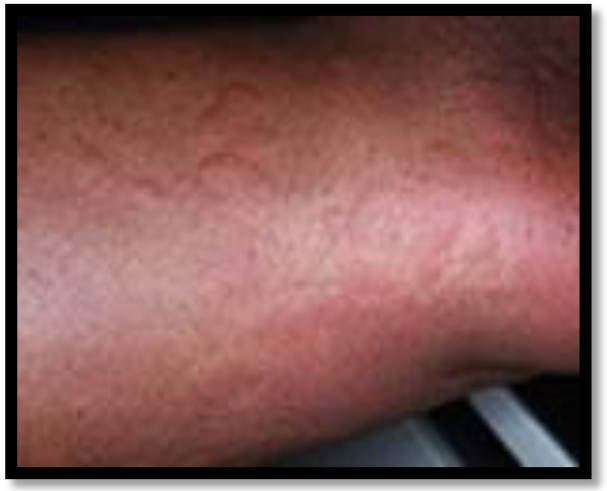
Urticarial lesions

- Pruritic, raised, circumscribed
- Shape varies: serpiginous, round, oval
- Lesions may have central pallor





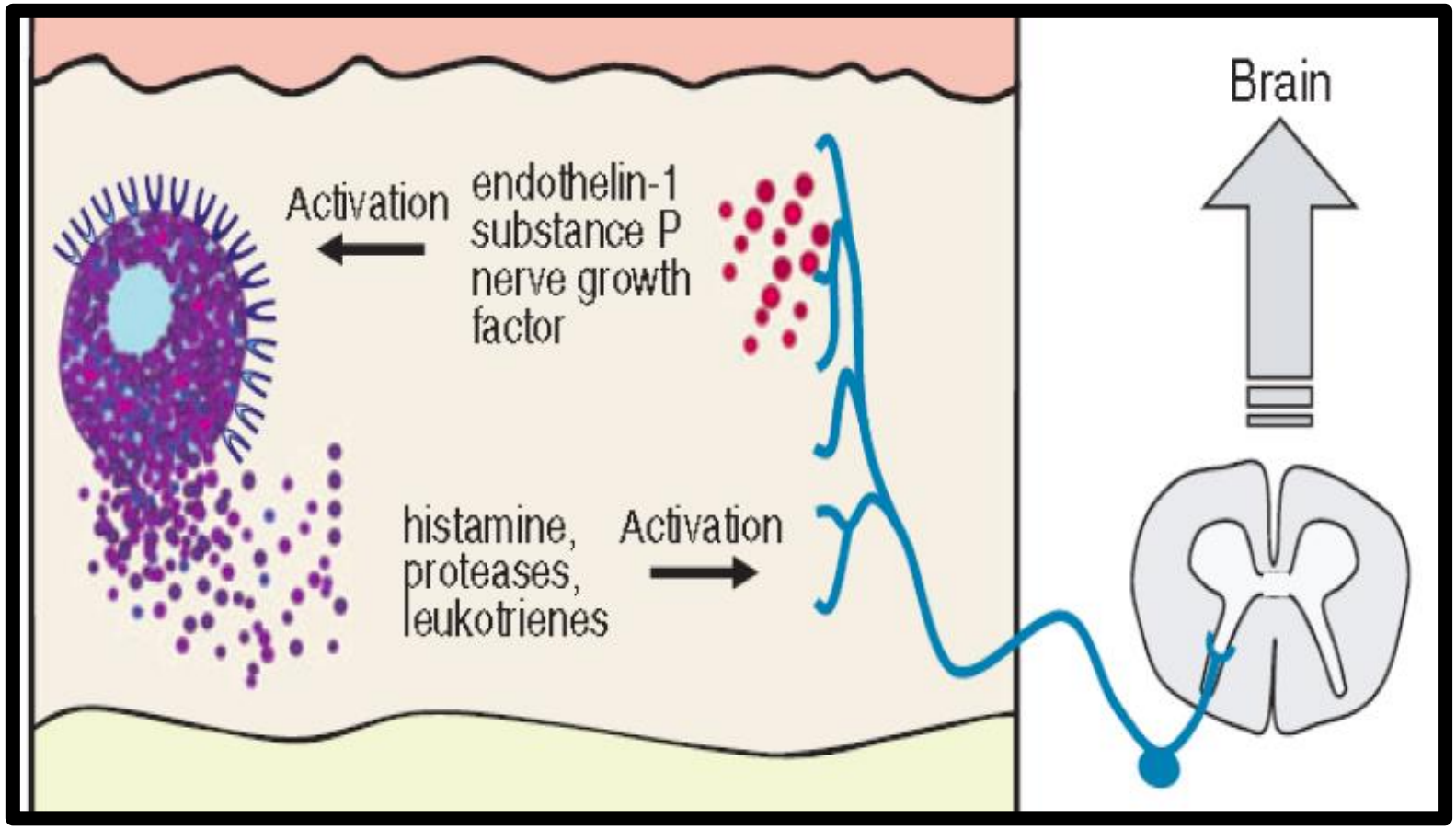




Pathophysiology

Pathogenesis

- Mediated primarily by mast cells & basophils in the superficial dermis.
- Release of many molecules: histamine, leukotriene, prostaglandin, and several other mediators
- Leads to erythema, flare, edema & pruritus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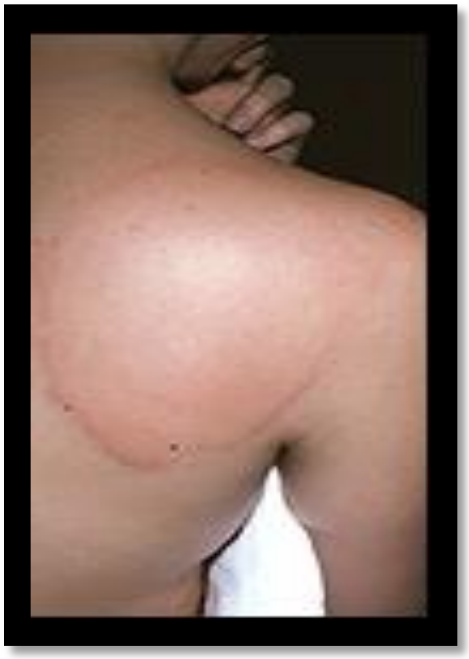
Activation
endothelin-1
substance P
nerve growth
factor
histamine,
proteases,
leukotrienes
Activation

Urticaria: duration

- **Acute:** Lesions occur for less than 6 weeks
- **Chronic**: Recurrent symptoms for greater than 6 weeks
- Atopic individuals are more at risk for developing acute urticaria
- Chronic urticaria is generally not associated with atopy



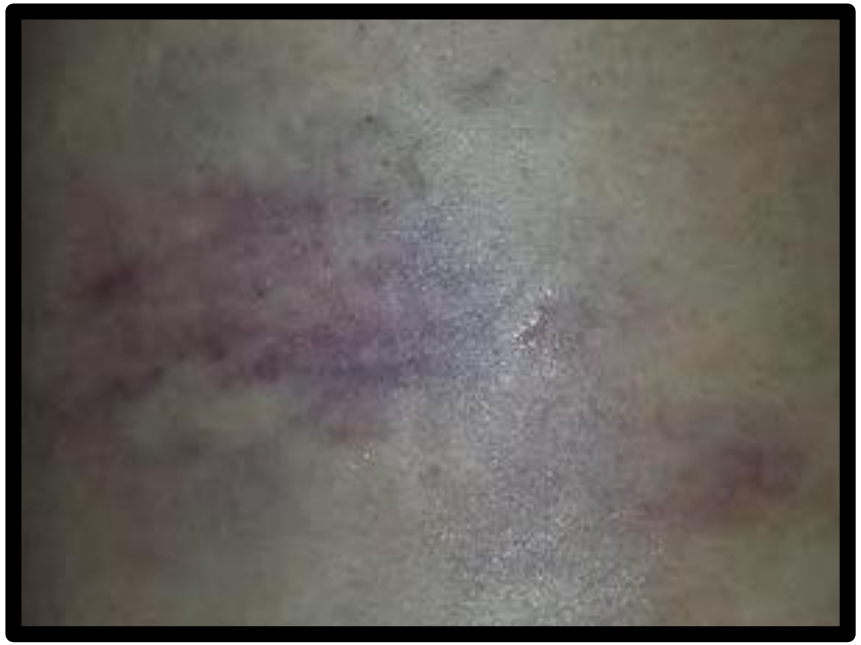
Clinical phenotype

- Size varies: less than one centimeter to several centimeters
- Lesions are pruritic & raised
- Can present with **OR** without angioedema

Clinical phenotype

- Symptoms occur **throughout the day**
  - ✧ Often times, pruritus is most severe at night
- **Transient** lesions
  - ✧ Develop within seconds to minutes resolving within 24 hours
- Lesions are generally **not** painful
  - ✧ If lesions are painful, consider vasculitis on the differential

Clinical phenotype



Urticaria

- **Versatile etiologies**

  ✧ Infections

  ✧ IgE Mediated Allergic Cases

  ✧ Direct Mast Cell Activation

  ✧ Physical stimuli

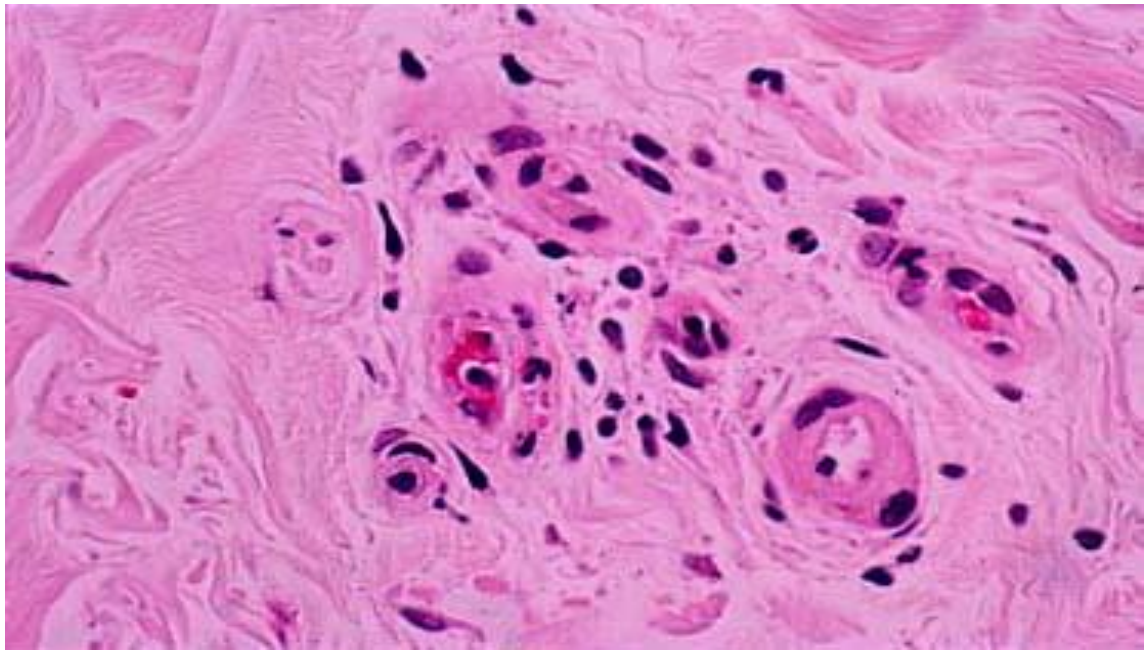
  ✧ Undetermined mechanism(s) constitute an estimated 80% of acute & chronic spontaneous urticarial cases

Chronic urticaria

- Defined as duration of lesions lasting 6 weeks or greater
- Chronic urticaria is further divided into **2 subtypes:**
  - ✧**Chronic spontaneous urticaria**
    - ✧Formerly known as chronic idiopathic urticaria
  - ✧**Chronic inducible urticaria**
    - ✧Otherwise known as physical urticaria

Chronic urticaria: histopathology

- Universal feature of biopsy: presence of mixed cellular perivascular infiltrate surrounding the dermal post-capillary venule



Chronic urticaria: genetics

- Genetic polymorphisms in histamine-related genes are implicated in mast cell activation & histamine metabolism
  - ✧ FcεRI and HNMT
- Genetic polymorphisms of leukotriene-related genes. These genes may be involved in leukotriene overproduction.
  - ✧ ALOX5, LTC4S, PGE2 receptor gene PTGER4

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Chronic urticaria

Chronic Spontaneous Urticaria	Chronic Inducible Urticaria
• **Lesions occur independent of stimulus** • 40% of patients will have concomitant angioedema • 10% of patients will present with only angioedema	• **Consistent stimulus that triggers lesions** • Lesions are short lived: may last up to two hours • Challenge test to confirm suspected stimulus • Biopsy shows no cellular infiltrate*

*Delayed pressure urticaria is an exception

Chronic urticaria

- Autoimmune diseases are more prevalent in **chronic spontaneous urticaria** patients
- Literature postulates that functional autoantibodies to IgE or IgE receptors may exist in 30-40% of individuals
- The remaining group of patients are without a known pathogenic mechanism

Differential diagnosis for urticaria

- Pruritic skin conditions that are confused for urticaria

  - ✧ Atopic Dermatitis
  - ✧ Allergic Contact Dermatitis
  - ✧ Drug Eruptions
  - ✧ Insect Bites
  - ✧ Bullous Pemphigoid in the initial stages prior to vesicle development
  - ✧ Erythema Multiforme Minor

Workup for urticaria

- Detailed history of present illness
- Physical examination

Workup for urticaria

- Limited lab testing is recommended for acute & chronic urticaria

  Consider:

  ✧ CBC with differential

  ✧ Stool for ova & parasites

  ✧ ESR & CRP

- ANA is generally not recommended given high rate of false positives

- Allergy/immunology referral

Case study

Contemplating the etiology of chronic urticaria and the implications of current guidelines

- 44 year old female with Hashimoto's thyroiditis
- Daily urticaria & pruritus
- Recurrent symptoms despite antihistamine & methylprednisone therapy

Case study

- Initial lab work up including CBC with Differential, ESR, Hepatic panel & Basophil histamine release assay were unremarkable
- CRP was within normal range at .69 mg/dL
- Thyroid peroxidase antibody level elevated at 306 IU/mL
- Anti-nuclear antibody titer mildly positive at 1:40 & Anti-mitochondrial antibody titer result was positive 1:640
- Given positive anti-nuclear & anti-mitochondrial antibody titers → liver biopsy was conducted

Case study

- Liver biopsy showed pathology consistent with primary biliary sclerosis
- Workup for urticaria may reveal underlying organic disease
- Case suggests clinicians can broaden their lab assessment when evaluating chronic urticaria in absence of other signs & symptoms

General guidelines for treatment

- Management strategies **vary depending on the type of urticaria**

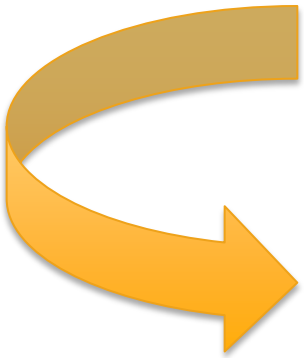
- **General guidelines:**
  - ✧ Avoidance measures
  - ✧ Antihistamines
  - ✧ Corticosteroids
  - ✧ **For refractory & severe cases:**

    Immunomodulatory & Immunosuppressive therapies

Chronic spontaneous urticaria

Start 2nd generation H1 Antihistamine

Double to Quadruple the standard dose if tolerated by patient



Omalizumab

Cyclosporine

Chronic spontaneous urticaria

- Cyclosporine is a **high alert** medication
  - ✧ requires frequent monitoring of blood pressure & kidney function
- Estimated rate of failure to the three recommended drugs is 7%
  - ✧ 1st generation antihistamine, omalizumab, and cyclosporine
- Leukotriene receptor antagonist & H2 antihistamine are no longer part of the updated treatment recommendations

Chronic spontaneous urticaria

Alternative Therapies to Consider

- Dapsone
- Sulfasalazine
- Hydroxychloroquine
- Methotrexate
- IVIG

✧ Clinical practice as per literature favors use of dapsone or sulfasalazine

Chronic inducible urticaria

Physical

- Symptomatic dermographism
- Cold urticaria
- Delayed pressure urticaria
- Solar urticaria

Non-physical

- Cholinergic urticaria
- Contact urticaria
- Aquagenic urticaria

Treatment

- Partial or full avoidance of the physical stimuli that induce symptoms
- Avoidance may not be practical based on the patient's history
- Pharmacologic therapy is the next step in management
  - ✧ Displays varying degrees of success

Treatment

- Individualized therapy approach may have increased efficacy
    - ✧Trial & error approach
- Various types of physical urticaria may demonstrate differing responses to antihistamine trials
    - ✧Dermographism has clinically been shown to be responsive
    - ✧Heat induced urticaria is typically resistant

Treatment

- Second-generation H1 antihistamine:
  - ✧ Start at standard doses and can titrate up to double or quadruple the standard dose
- H2 antihistamine:
  - ✧ Add at standard dose (example: Ranitidine 150 mg twice a day)
  - ✧ If patient is not improving, discontinue
- Hydroxyzine: given at bedtime as it has sedating effects
- Doxepin: antidepressant with anti-histaminergic properties

Treatment

- If standard therapies are not adequate, consider biological therapy
  - ✧ **Omalizumab** can be used in a variety of inducible urticaria
  - ✧ Non-responders to omalizumab may arise

- Other options for therapy for refractory disease
  - ✧ Glucocorticoids
  - ✧ Phototherapy
  - ✧ Immunomodulatory agents: cyclosporine & dapsone

Omalizumab

- FDA approved for Chronic Spontaneous Urticaria
- Off Label Use for Chronic Inducible Urticaria

Omalizumab: a miracle biologic?

- Administered in clinical setting
- SubQ: 150 or 300 mg every 4 weeks
- Dosing is not dependent on serum IgE level (free or total)
- Dosing is not dependent on body weight

Omalizumab adverse effects

- US Boxed Warning: Anaphylaxis
  - ✧ **immediate & delayed-onset anaphylaxis** has been reported following administration

- Anaphylaxis may present as bronchospasm, abdominal pain, hypotension, syncope, urticaria, and/or angioedema of the tongue or throat

- Common adverse effects:

  - ✧ CNS (headache), pain, dizziness, fatigue
  - ✧ Local injection site reaction

Omalizumab adverse effects

- Anaphylaxis has occurred after the first dose and in some cases one year after initiation of regular treatment
- Due to the risk, patients need to be observed closely for an appropriate time period after administration
- Patients will receive treatment under direct medical supervision

Potential future therapy

Other therapies under investigation currently:

- TNF-alpha inhibitor
- Rituximab: Monoclonal Antibody to CD20 marker
- Anakinra: IL-1 antagonist
- Intravenous immune globulin

Angioedema

- an·gio·ede·ma
- called also angioneurotic edema, giant urticaria, quincke's disease
- angioedema is poorly defined, pronounced swelling that occurs in the deep dermal layer, subcutaneous, or sub-mucosal tissue

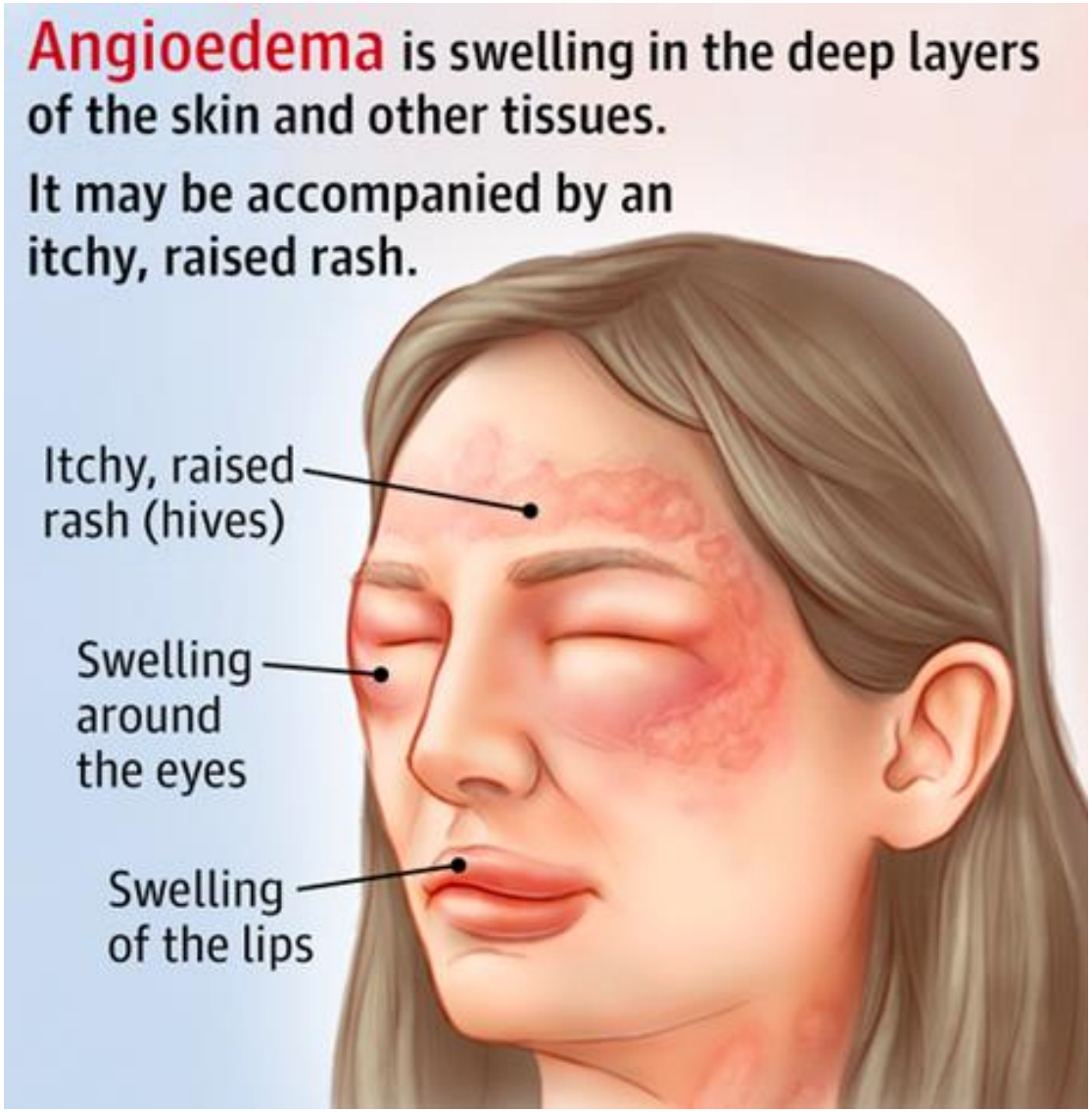
Epidemiology: angioedema

- Affects both children & adults
- Angioedema occurs in an estimated 50% of cases of chronic urticaria

- Retrospective review of all hospital admissions in New York state over 13 years:
  - ✧ Angioedema was the 2nd most common “allergic” disease to facilitate hospitalization
  - ✧ 42% of admissions for angioedema were ethnically described African Americans
  - ✧ African Americans appeared to be disproportionately affected since they make up 16% of New York state’s total population

Angioedema

- Sudden, pronounced swelling of lower dermis & subcutis
- More commonly painful rather than pruritic
- Angioedema **without** urticaria: occurs in 10-20% of patients
- Resolution can take up to three days or longer, depending on sub type


Angioedema is swelling in the deep layers of the skin and other tissues.
It may be accompanied by an itchy, raised rash.
Itchy, raised rash (hives)
Swelling around the eyes
Swelling of the lips

Angioedema classification

- **Non C1 esterase inhibitor deficiency**

- **Normal C1 esterase inhibitor protein level & normal function**
  - ✧ Allergic
  - ✧ Pharmacologic
  - ✧ Infectious
  - ✧ Physical
  - ✧ Idiopathic

Non C1 inhibitor deficiency

- **Allergic:** IgE Mediated & Mast Cell Mediated
  - ✧ frequently seen with urticaria
- **Pharmacologic:** ACE-Inhibitor induced angioedema
  - ✧ Mechanism: bradykinin induced angioedema
- **Pseudo-Allergic:**
  - ✧ NSAIDS
  - ✧ often accompanied by urticaria

Non C1 inhibitor deficiency

- **Infectious**
  - ✧ Associated with H. Pylori infection most commonly
- **Physical**
  - ✧ Examples: exposed to cold, vibration, pressure
- **Idiopathic**
  - ✧ No identifiable cause as per clinical & diagnostic work up

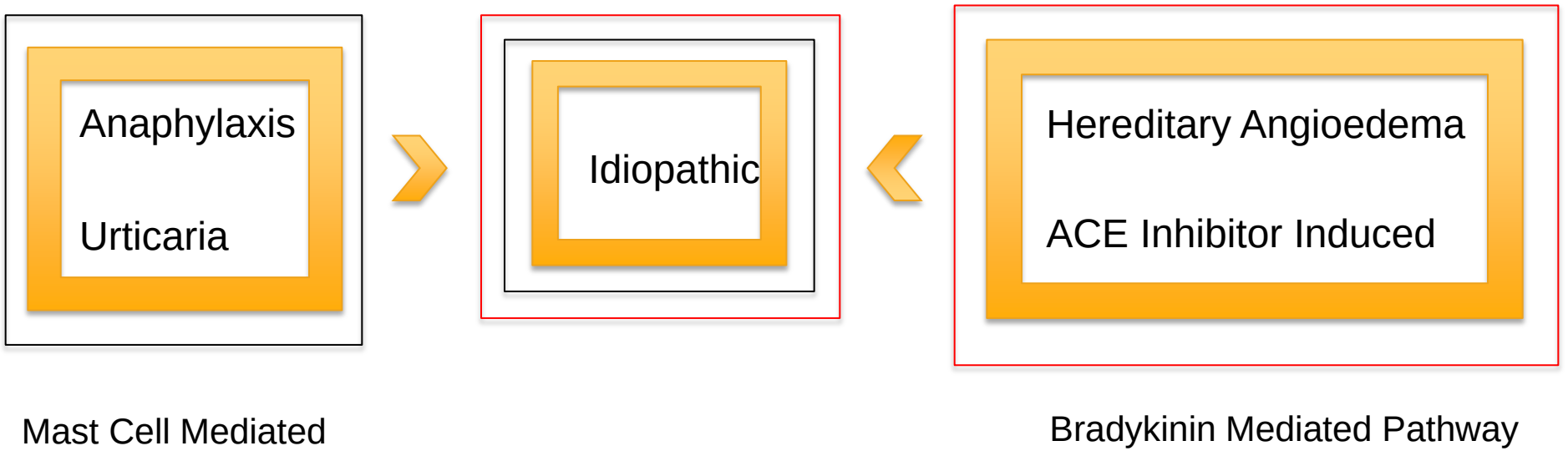
Angioedema classification

- **C1 Inhibitor Deficient : Hereditary Type**

  ✧ **Deficient C1 esterase inhibitor protein**
  ✧ Hereditary Type 1, Type 2, Type 3

- **C1 Inhibitor Deficient: Acquired Type**

  ✧ **Normal C1 esterase inhibitor protein**
  ✧ **Decreased C1 esterase inhibitor protein function**
  ✧ Acquired Type 1, Type 2



Mast Cell Mediated

Bradykinin Mediated Pathway

Pathogenesis of mast cell mediated angioedema

- Swelling of the subcutaneous tissues due to increased vascular permeability & extravasation of intravascular fluid
- Mast cell derived mediators: histamine, leukotriene, prostaglandin
- Mast cell mediators affect layers of superficial to subQ tissues including dermal-epidermal junction → leads to urticaria & pruritus
- **Allergic** angioedema is the most common type and includes reactions to foods such as **peanuts and shellfish, medications including antibiotics, insect bites and stings, and latex.**

Mast cell mediated angioedema

- Patient may experience urticaria, flushing, generalized pruritus, bronchospasm, hypotension.

- Symptoms begin within minutes of exposure to allergen, resolves in 24-48 hours

NSAIDS: pseudo-allergic angioedema

Common NSAIDS implicated in pseudo-allergic angioedema & urticaria

- ASA
- Ibuprofen
- Diclonfenac
- Naproxen
- Metamizole

Bradykinin induced angioedema

- **NOT** associated with urticaria, bronchospasm, or other symptoms of allergic reactions
- Prolonged time course
- Onset occurs in 24-36 hours and resolves within 4-5 days
- Relationship between trigger and onset of symptoms is not always clear

Hereditary Angioedema

Hereditary angioedema	C1 Inhibitor Level	C1 Inhibitor Function	C4
HAE Type 1	Low	Normal	Low
HAE Type 2	Normal	Low	Low
HAE Type 3*	Normal	Normal	Normal

HAE Type 3 displays enhanced plasma factor 12 activity (Hageman factor)

Genetics

- C1 Inhibitor protein encoded gene is on chromosome 11

- Type 1 Hereditary Angioedema
  - ✧ **Autosomal Dominant Inheritance**

- Type 2 Hereditary Angioedema
  - ✧ **Autosomal Dominant Inheritance**

Acquired angioedema

- **Acquired Type 1**

  ✧ Secondary to malignancy
  ✧ Commonly: B cell lymphoma, multiple myeloma
  ✧ Immune-complex-mediated depletion of C1 inhibitor protein

- **Acquired Type 2**

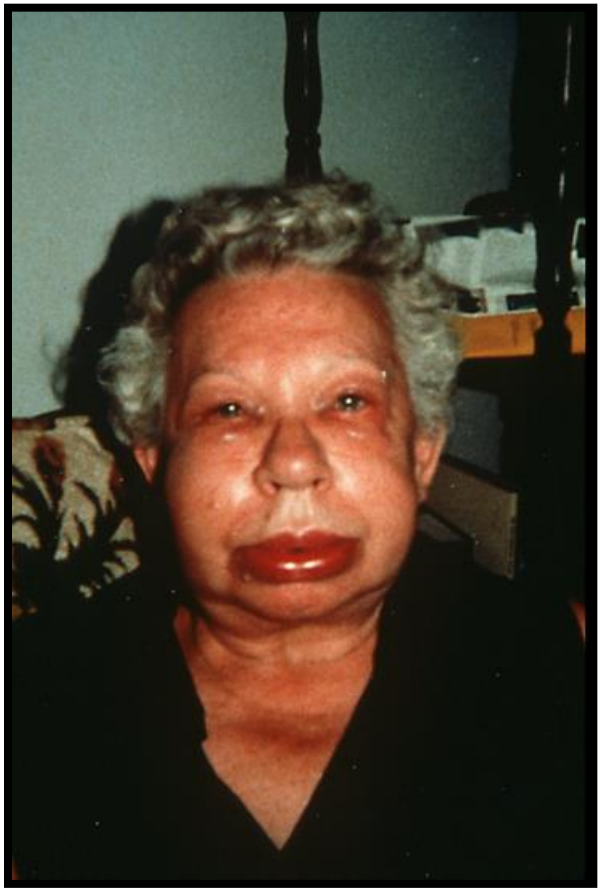
  ✧ Autoimmune process
  ✧ Auto-antibodies against C1 Inhibitor protein

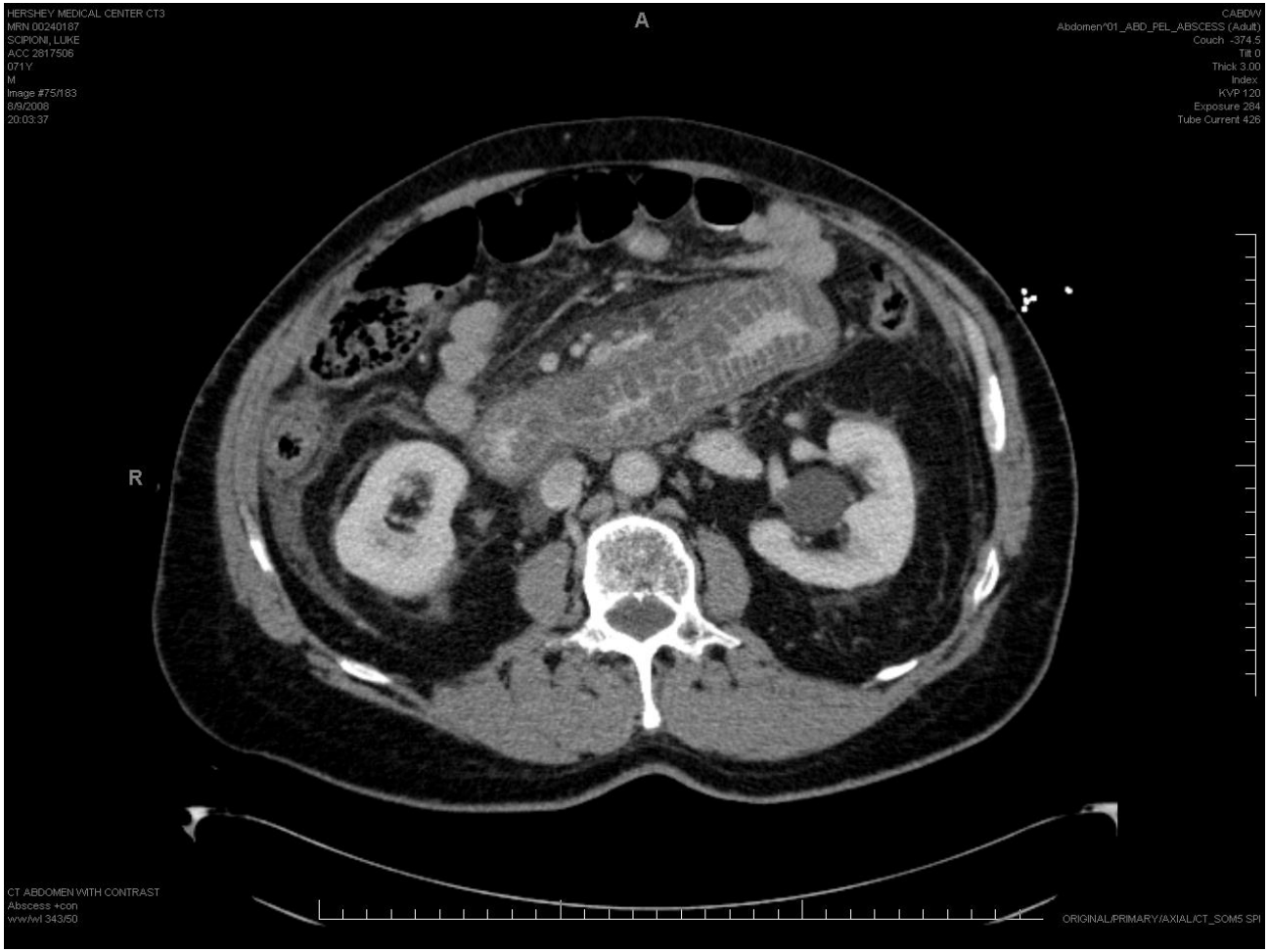
Hereditary angioedema

- Develops more slowly compared to mast cell mediated angioedema
- Develops spontaneously or after trauma, commonly with dental maneuvers
- Main sites of involvement: face, hands, arms, legs, genitalia, buttocks
- Begins with a **prodrome** and is associated with colicky abdominal pain
- Laryngeal involvement = life threatening

Hereditary angioedema triggers

- Trauma & surgery
- Mechanical pressure
- Emotional stress
- Menstruation
- Oral contraceptive use
- Infection

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Differential diagnosis

- Contact Dermatitis
- Cellulitis & Erysipelas
- Facial Lymphedema
- Autoimmune Conditions
  - ✧ SLE, Polymyositis, Dermatomyositis
- Hypothyroidism
- SVC syndrome

Evaluation

- History of present illness is **critical to obtain**
- Diagnostic work up:
- CBC with Differential, ESR, CRP, BMP, Liver function tests, TSH
- C1 Inhibitor protein level & C1 inhibitor protein function
- C4 and C1q levels

Angioedema mechanism

- Allergic Angioedema: Mast cell mediated pathway
- ACE-I Induced Angioedema: Bradykinin mediated pathway
- Hereditary Angioedema: Complement mediated pathway
- Idiopathic Angioedema: unknown

Allergic angioedema: treatment

- Mainstay therapies for allergic angioedema WITH anaphylaxis:
  - ✧ Intravenous fluids, oxygen, IM epinephrine

- Main therapies for allergic angioedema WITHOUT anaphylaxis:
  - ✧ Antihistamines & Glucocorticoids
  - ✧ Methylprednisone or prednisone taper can be trialed
  - ✧ Specific dosing has not been studied in acute allergic angioedema cases

ACE inhibitor induced angioedema: treatment

- Mechanism: bradykinin mediated pathway

- Treatment:
  - ✧ Protect Airway if indicated
  - ✧ Discontinue the drug & monitor for resolution

- Swelling will resolve generally in 48 to 72 hours

- Other therapies can be considered if angioedema is refractory to above
  - ✧ Efficacy of various therapies is currently being studied

ACE inhibitor induced angioedema: treatment

- Following therapies are also being used for hereditary angioedema treatment:

  ✧ Icatibant: bradykinin B_2-receptor antagonist

  ✧ C1 inhibitor concentrate

  ✧ Ecallantide: recombinant protein inhibits conversion of HMWK to bradykinin

  ✧ FFP contains ACE enzyme

Hereditary angioedema treatment

Treatment Options

- Purified C1 Inhibitor Concentrate (Cinryze, Berinert, or Ruconest)
- Ecallantide: Kallikrein inhibitor (Kalbitor)
- Icatibant: Braykinin B2 receptor antagonist (Firazyr)

Hereditary angioedema treatment

FFP or solvent detergent treated plasma

- ✧ this therapy is no longer recommended and should be used if other agents are not available
- ✧ FFP may have paradoxical effect and can worsen angioedema acutely

Hereditary angioedema prophylaxis

Prophylactic treatment: prior to procedures, post trauma

- ✧ C1 Inhibitor Concentrate:
  - Cinryze: FDA Approved
  - Bernert: Off Label Use
- ✧ Recombinant C1 Inhibitor Concentrate: Ruconest
- ✧ Subcutaneous C1 Inhibitor
- ✧ Danazol: Anabolic Androgen
  - Mechanism: increase levels of C1 inhibitor protein
  - Adverse effects: hepatotoxicity, HCC, hirsuitism

Idiopathic angioedema treatment

- Trial non-sedating antihistamine (2nd generation H1 antihistamine)
  - ✧ Dosing can increase up to 4 times the standard dose
  - ✧ If infrequent attacks: consider prednisone & diphenhydramine at the sign of first swelling
- Severe, refractory cases
  - ✧ Consider dapsone, icatibant, rituximab

Summary

- Urticarial lesion description & duration is important information to acquire in the history
- Obtain a diagnostic workup & consider the various therapies used to manage urticaria depending on the type of urticaria
- Angioedema can be life threatening: obtain a work up if clinical suspicion present
- Consider angioedema mechanism as a way to approach treatment once life threatening conditions have resolved

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Thank you!