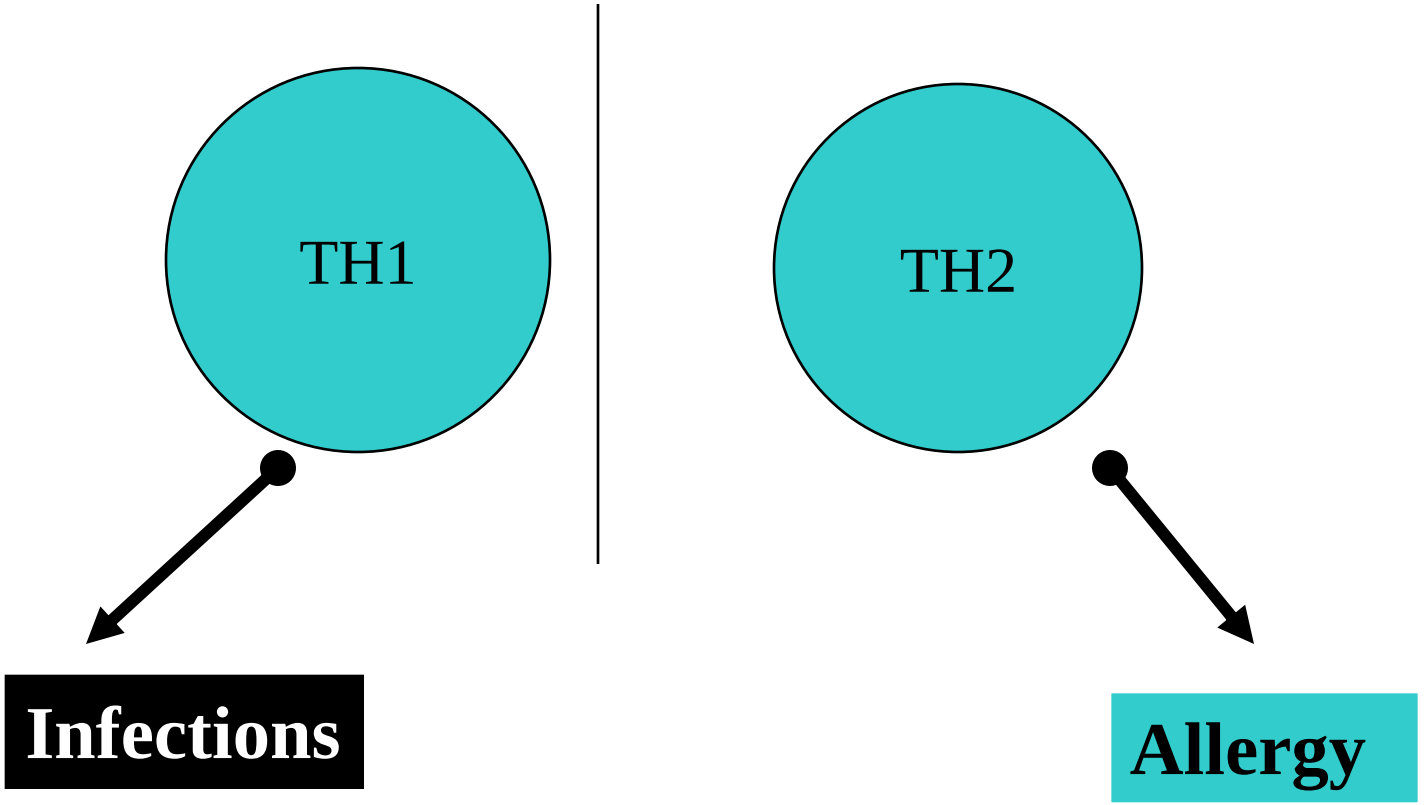
Urticaria & Angioedema

Julie Sterbank, DO
Robert Hostoffer, DO
Allergy Immunology Associates
(216) 381-3333

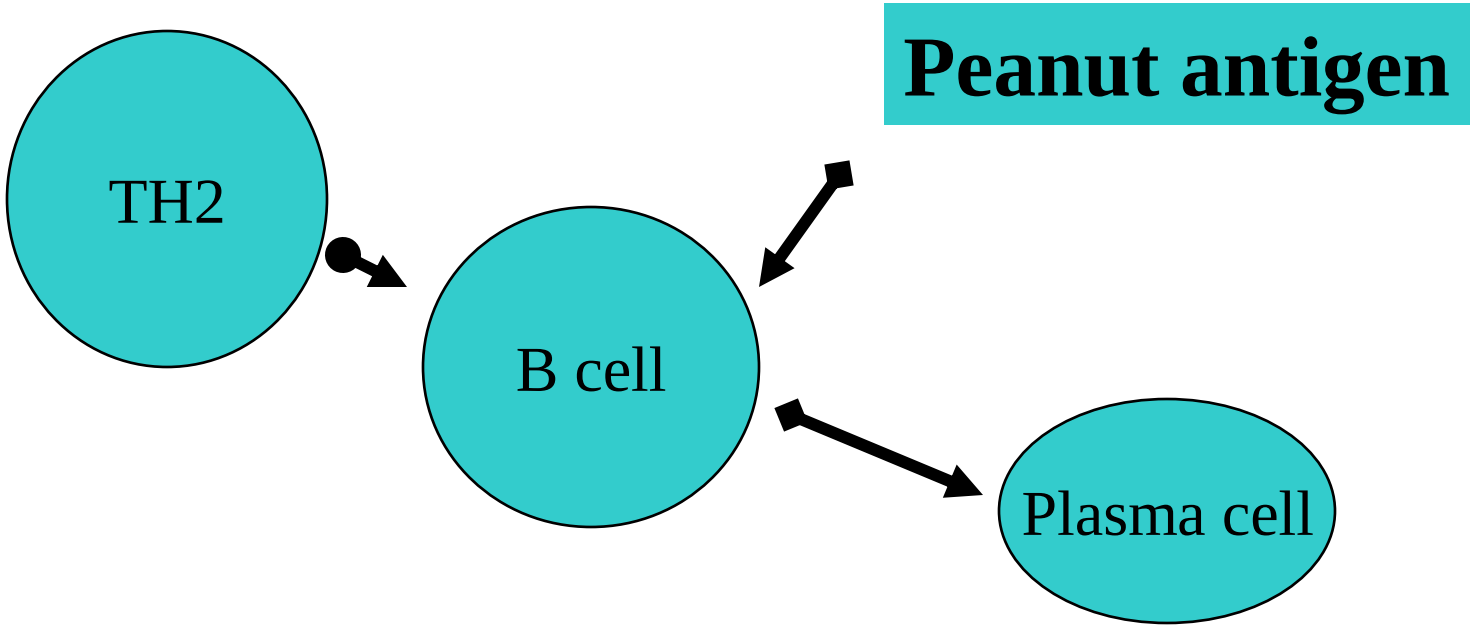
Outline

1. Review of Allergic Mechanism
2. Urticaria – Classification, Causes, Treatment
3. Angioedema – Classification, Causes and Treatment

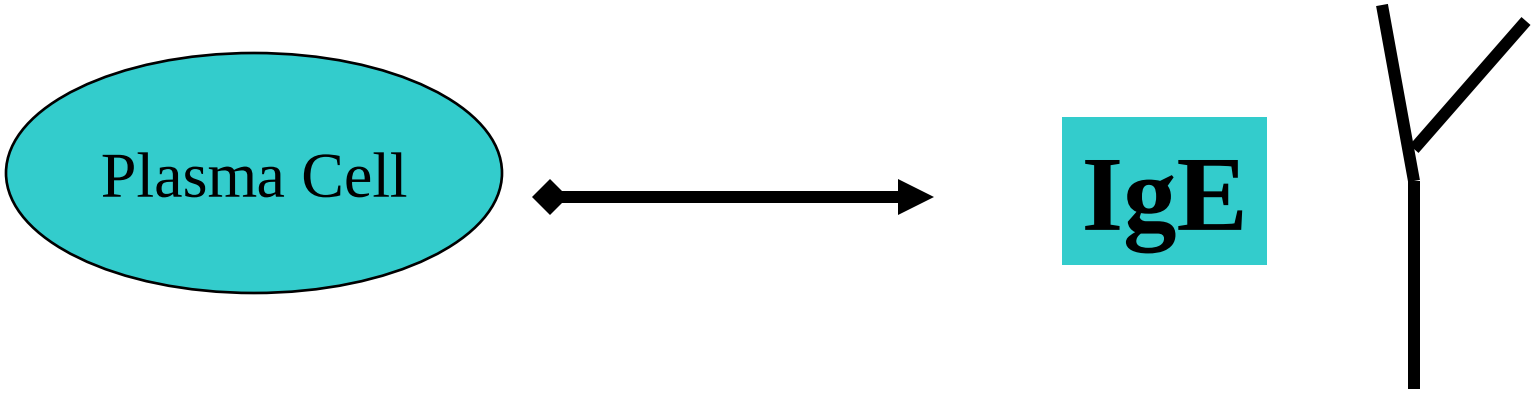
Mechanism of Allergy



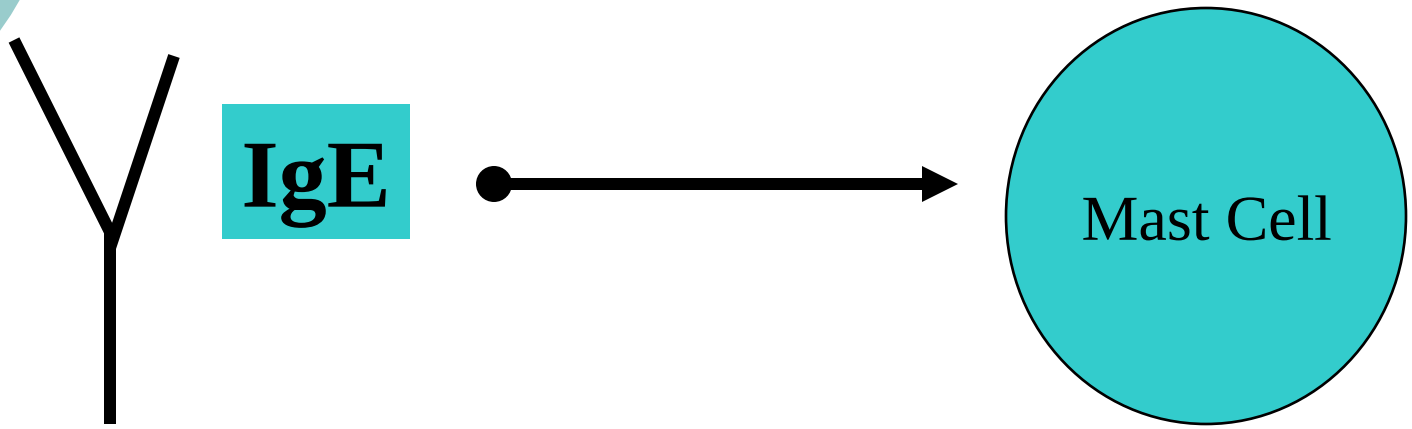
Mechanism of Allergy II



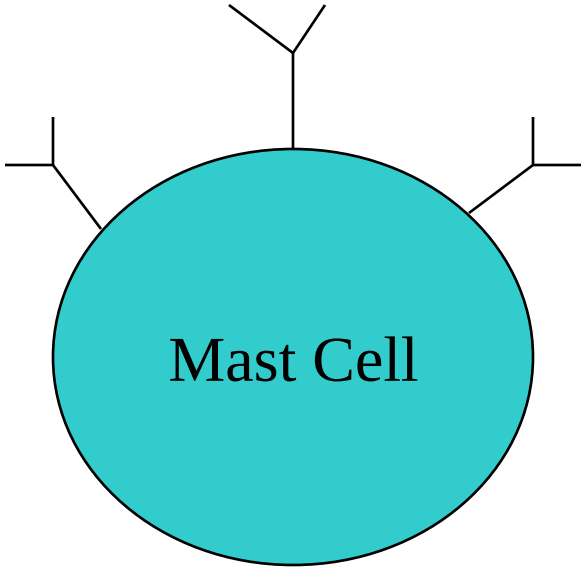
Mechanism of Allergy III



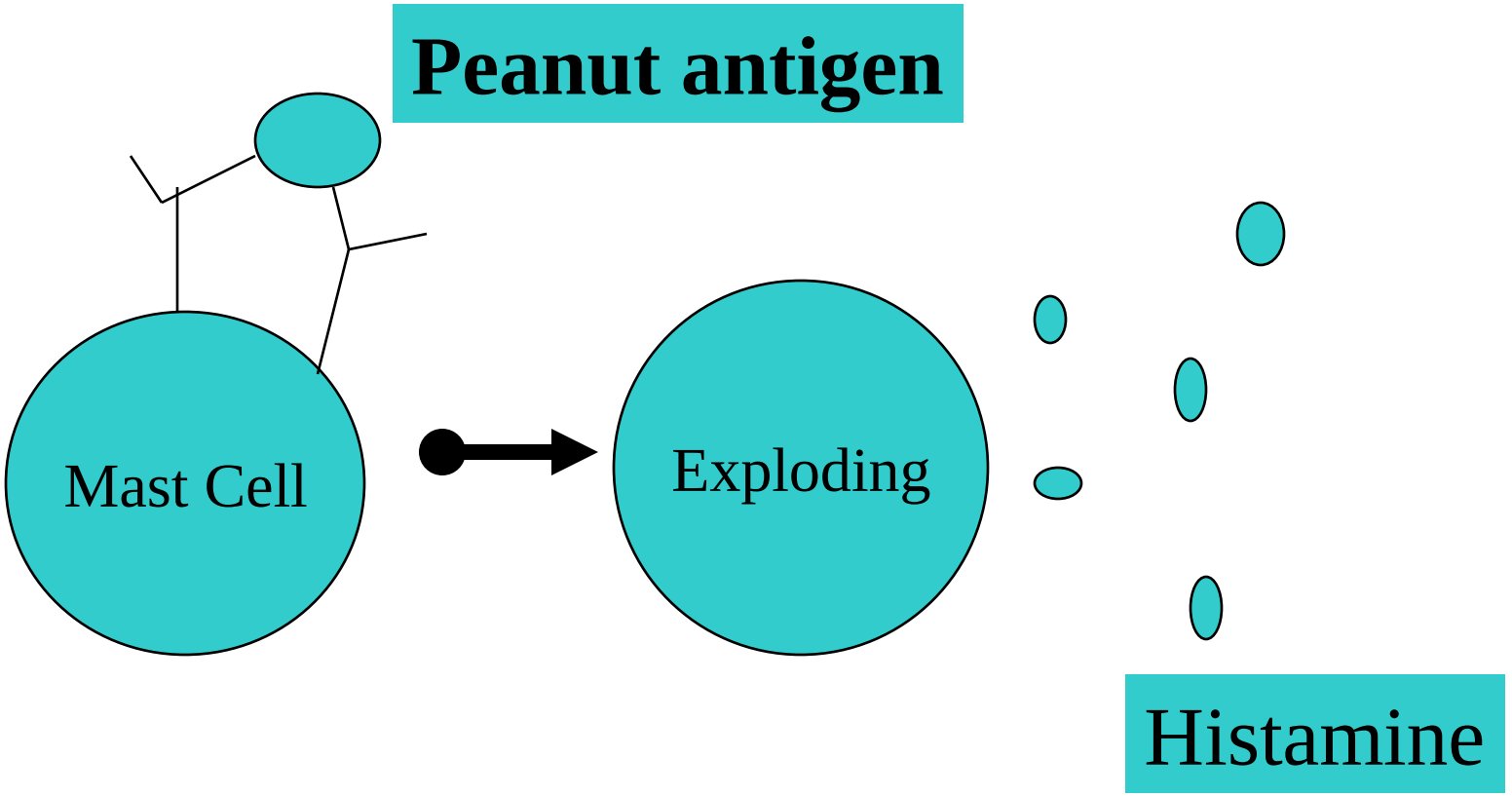
Mechanism of Allergy IV



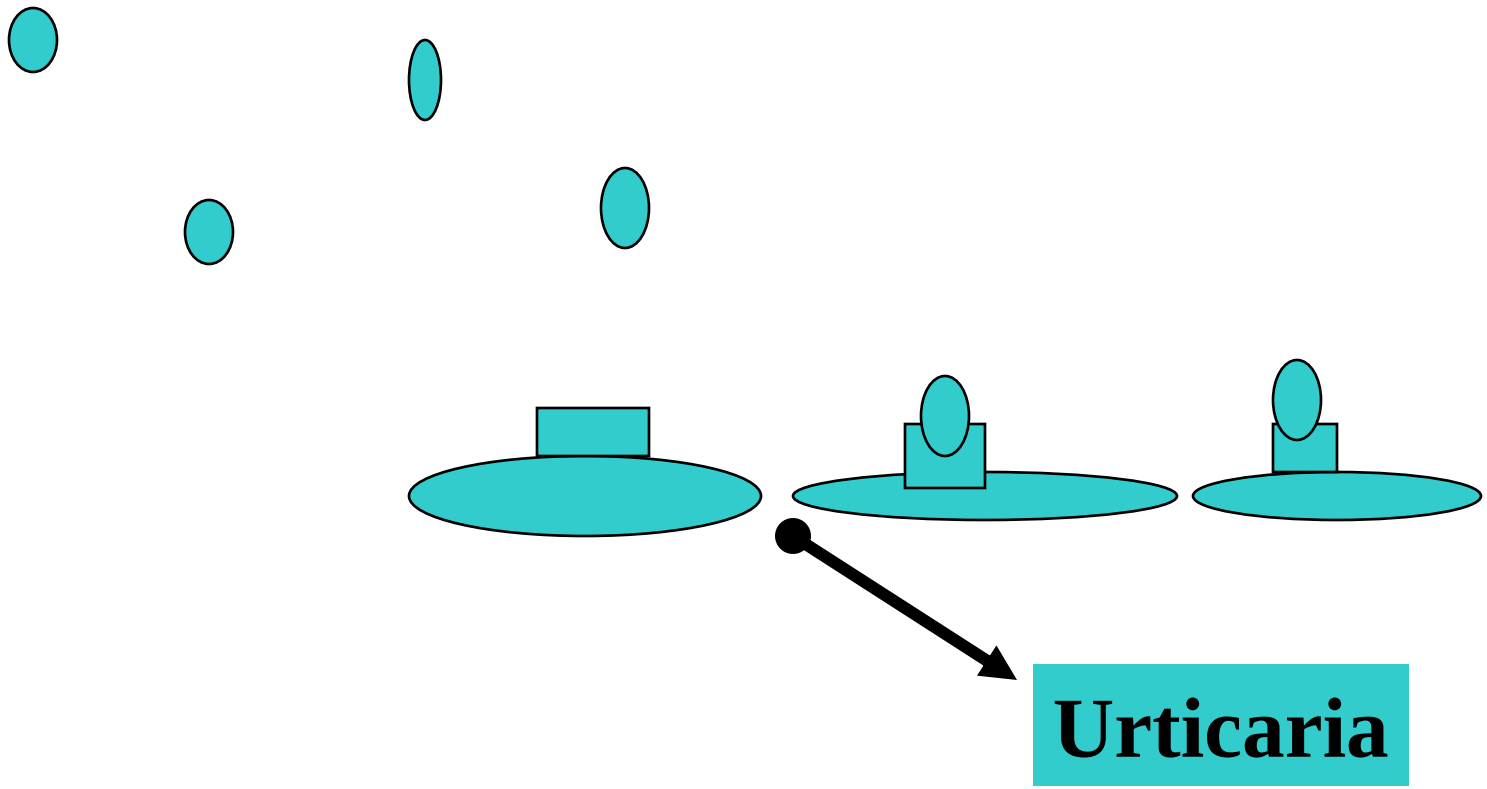
Mechanism of Allergy V



Mechanism of Allergy VI



Mechanism of Allergy VII

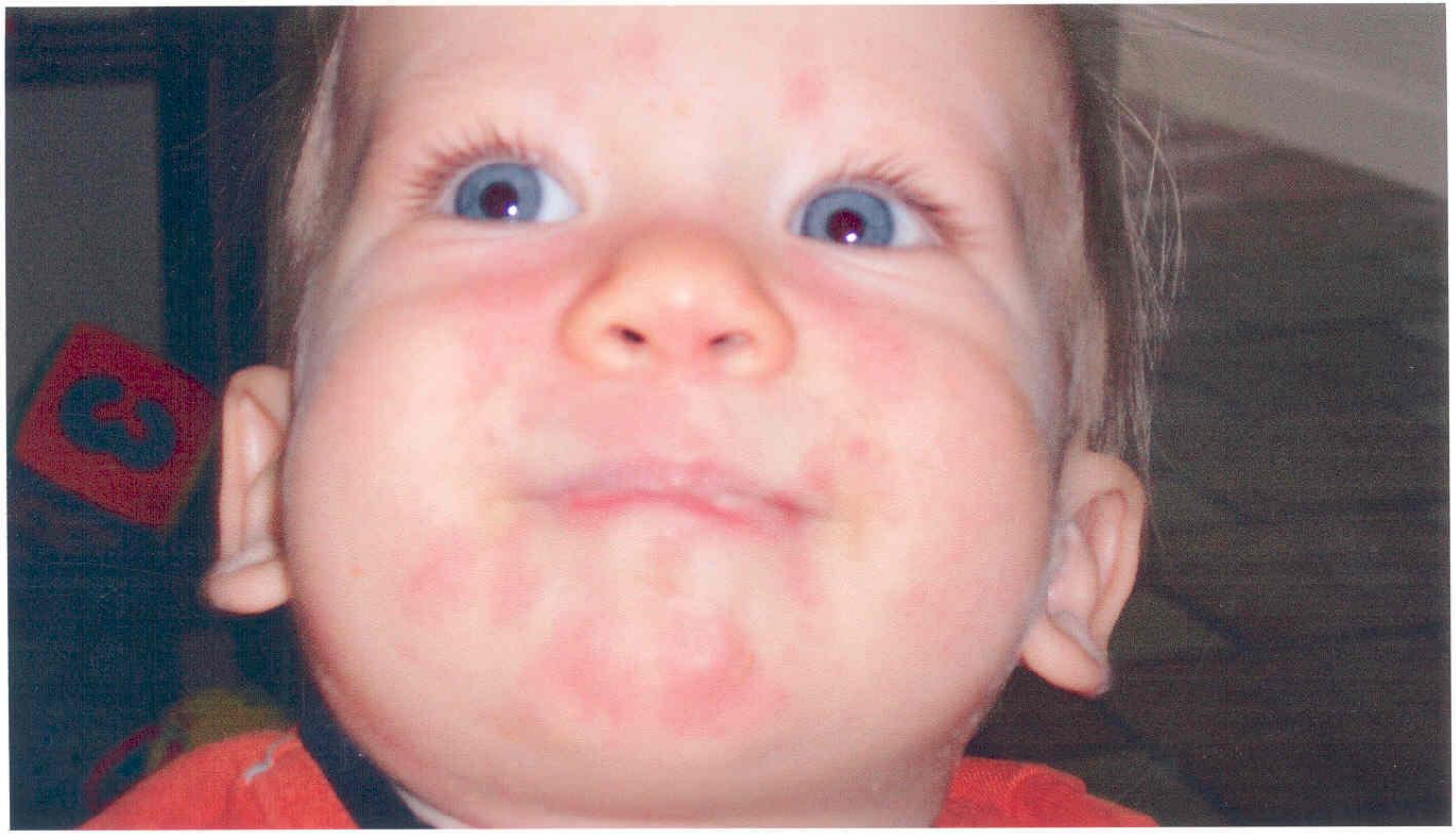


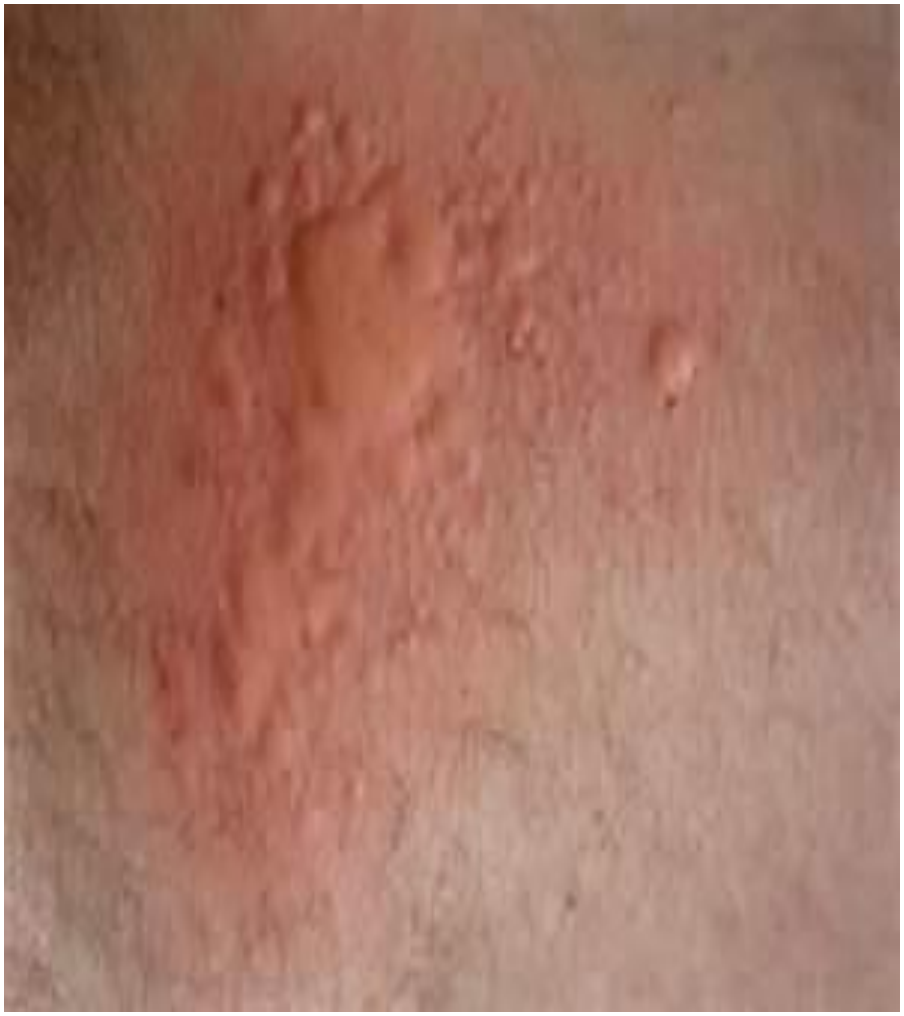
Urticaria

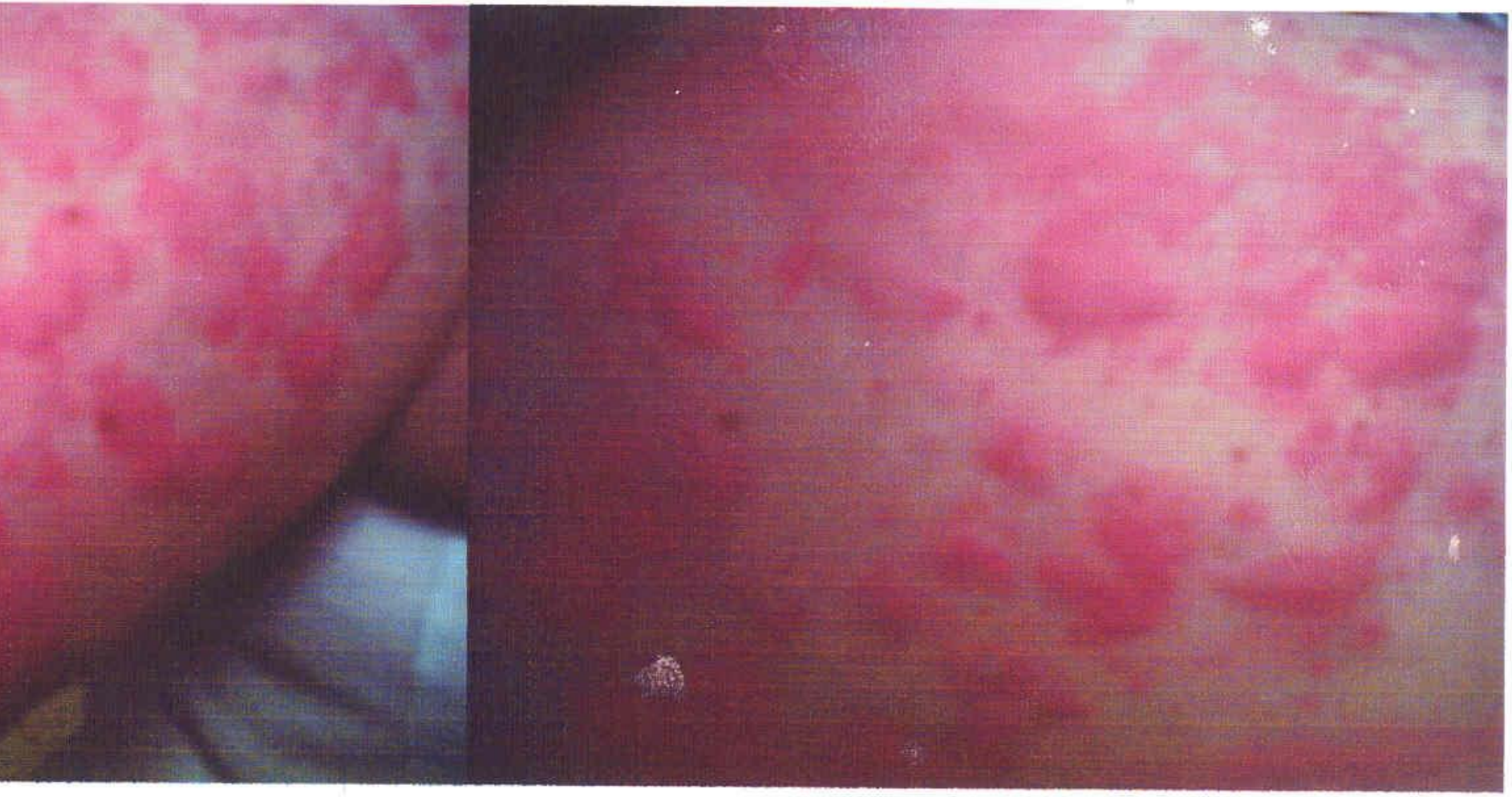
- Affects 20% of population
- Occurs across the age spectrum[1]
- Sometimes possible to identify a trigger such as food, drug, insect sting or infection
- More than 2/3 of cases are self-limiting

Characteristics

- Pruritic (most severely at night)
- Erythematous
- Often exhibit central pallor
- Blanches
- Oval, round or irregular shape or plaques
- Plaques “move” to different locations over minutes to hours
- Last less than 24 hours
- Leave no residual marks (other than those created by scratching)







Pathophysiology

- Reaction mediated by activated mast cells and basophils in superficial dermis[2]
- When activated, mast cells release histamine causing itching and vasodilators which cause swelling
  - Same process occurs in angioedema but in deeper layers of the skin and subcutaneous tissues

Classification

- Acute versus Chronic Urticaria
  - Acute episodes < 6 weeks
    - more likely to have an identifiable trigger
  - Chronic episodes last > 6 weeks
    - less likely to have an identifiable trigger

Common Causes

- Acute Urticaria
  - Foods/food products most commonly milk, egg, peanut, wheat and soy in kids
  - Tree nuts, peanuts and shellfish in adults
  - Yellow food dye annatto
  - Red food dye carmine
  - Contact with raw fruits or vegetables, animal saliva, certain detergents or perfumes

Common Causes (cont)

- Acute Urticaria
  - Viral or bacterial infection especially in children
  - Parasitic infections usually in combination with impressive eosinophilia
  - Medications especially antibiotics
  - Stinging insects including bees, wasps, hornets, imported fire ants
  - Latex products

Common Causes (cont)

- Certain foods or drugs that cause direct mast cell activation
  - Narcotics, muscle relaxants, vancomycin, radiocontrast media, stinging nettle
  - Tomatoes and strawberries
  - NSAIDS (although patients can also have IgE allergy to NSAIDS as well)

Uncommon Causes of Urticaria

- Physical Stimuli
  - Cold temperatures, sunlight, pressure, vibration, exercise
- Serum sickness reactions
  - Reactions to exogenous proteins, can be associated with fever, arthralgia, lymphadenopathy
- Progesterone-associated
  - Rare reports in progesterone OCP and HRT

Systemic Causes of Urticaria*

- Urticarial vasculitis (cutaneous or systemic)
- Mastocytosis
- SLE, RA, celiac & other autoimmune diseases
- Cutaneous small vessel vasculitis
- Malignancy

- *warning signs:*

  lesions lasting >24 hours, appear ecchymotic, purpuric, or are painful and/or occur in association with lymphadenopathy, fever, weight loss, joint or muscle pain

Diagnosis

- Detailed history
  - including has pt ever had urticaria before
  - were there any unusual exposures immediately prior to the episode
  - Does the patient have pictures?
- Physical Exam
  - If the patient does not have lesions at time of exam, consider showing them photos of urticaria as an example

Diagnosis (cont)

- Laboratory testing – Acute Urticaria
  - Allergy testing if specific trigger can be implicated (would possibly include skin prick testing or immunocap testing for IgE to specific food or drug)

- Laboratory testing – Chronic Urticaria*
  - CBCD
  - UA
  - ESR
  - LFTs

**These results are often normal so there is no clear consensus that these must be done*

Treatment of Urticaria

- H1 antihistamines

  First generation:

  diphenhydramine, chlorpheniramine, hydroxyzine

  Second generation:

  cetirizine, loratadine, fexofenadine

Treatment of Urticaria (cont)

- First generation antihistamines:
  - more sedating, require more frequent dosing
- Second generation antihistamines:
  - higher dosing than standard dosing to obtain positive effects
  - Can be sedating at higher dosages

Treatment of Urticaria (cont)

- Pregnant women or those breastfeeding may use loratidine or cetirizine

Treatment of Urticaria (cont)

- Consider use of H2 blocker as well although data is not particularly supportive
  - ranitidine, nizatidine, famotidine and cimetidine

    (note cimetidine can increase drug levels in other medications taken concurrently)

Treatment of Urticaria (cont)

- Consider use of oral prednisone, but weigh risks and benefits and recognize medications with less side effects are available
- Consider referral to an allergy/immunology specialist for episodes with clear trigger or those which don’t respond to your treatment

Angioedema

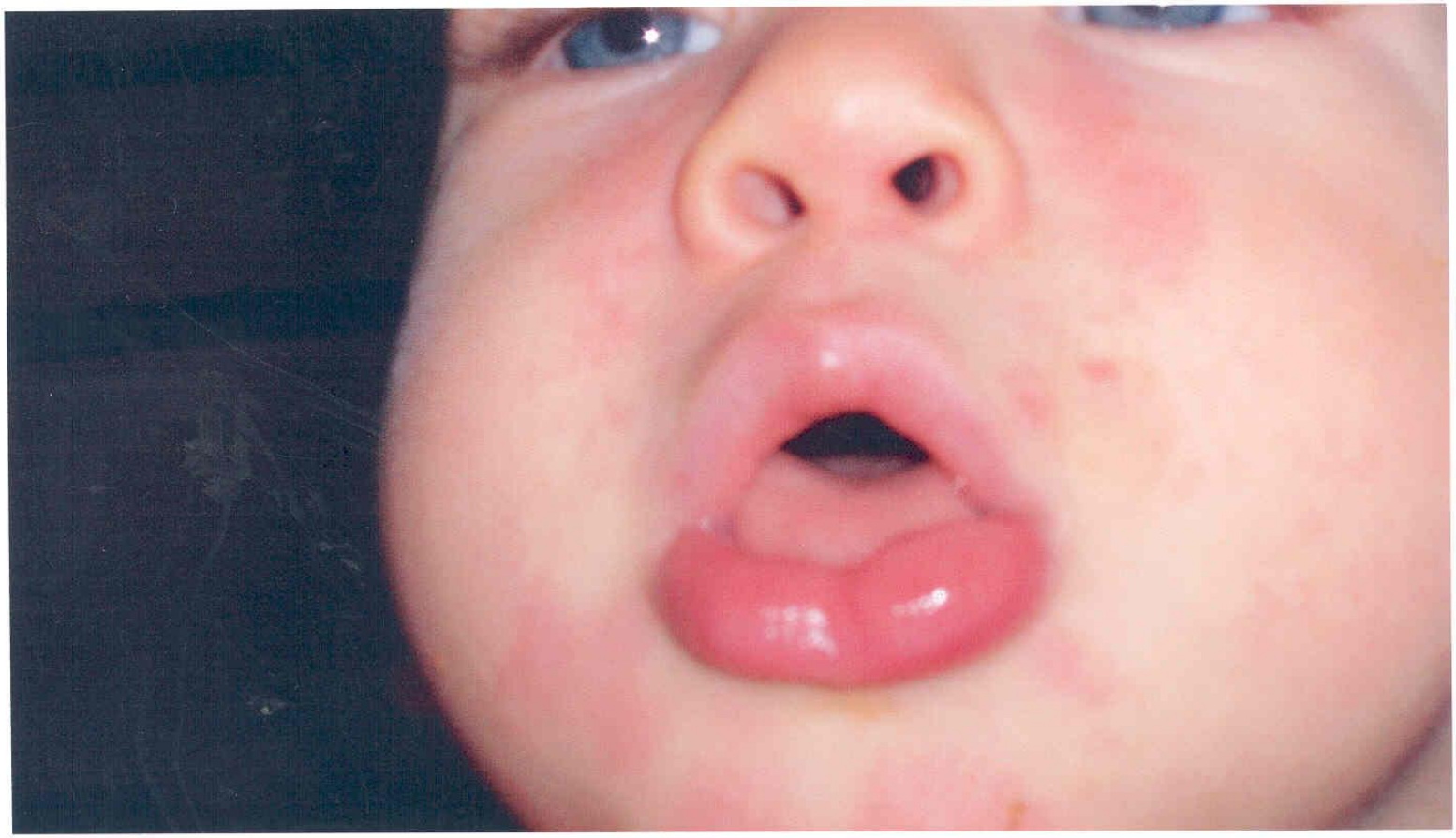
Characteristics

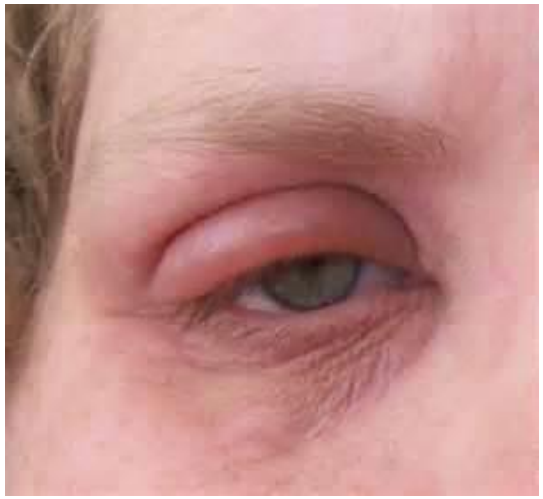
- Similar process to urticaria
- Occurs deeper in subcutaneous tissue
- “Swelling” due to extravastation of fluid into tissues from vasodilators
- Typically seen in areas with little connective tissue such as lips, face, mouth, uvula and genitalia
- Can occur in bowel wall which manifests as colicky abdominal pain

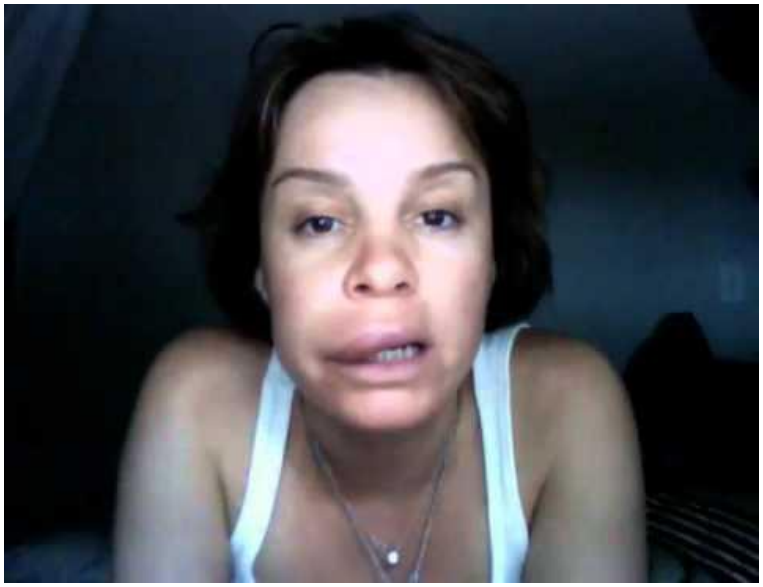
Characteristics (cont)

- Rapid onset (typically minutes to hours)
- Often asymmetric in distribution
- Often in non-gravitationally dependent areas such as lips, mouth, face, tongue
- Can be associated with urticaria, sometimes with allergic reaction or part of anaphylaxis, or may occur in isolation

**Can be life-threatening if associated with airway compromise*







Classification of Angioedema

- Mast cell-related angioedema
  - Can begin within minutes of exposure of trigger like food, drug, sting
  - May occur with other allergic type symptoms such as urticaria
  - Usually resolves within 24-48 hours
- Bradykinin-induced angioedema
  - Develops more gradually
  - Often longer to resolve 2-4 days
  - Example: ACE induced angioedema

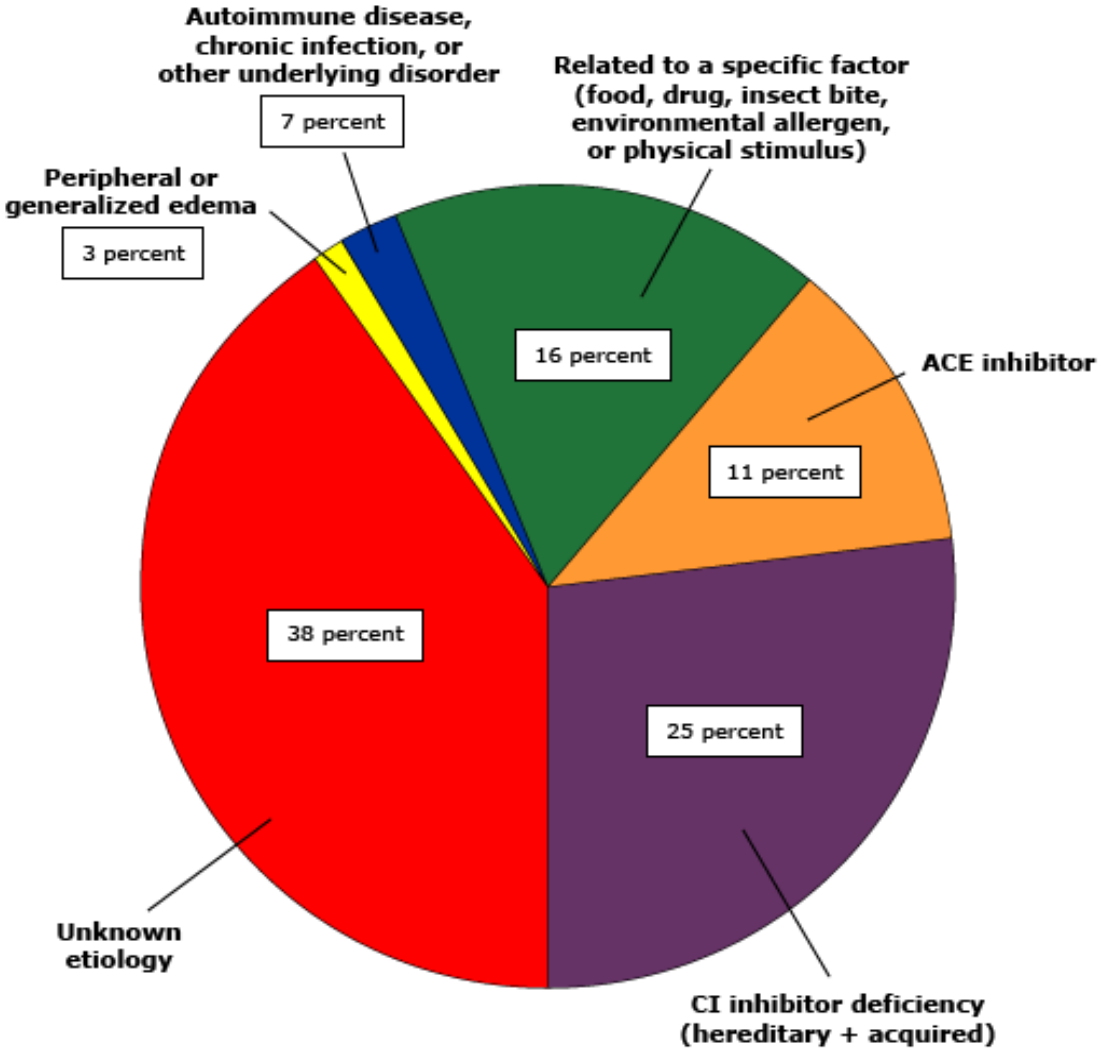
Medications Associated with Angioedema

- ACE Inhibitors
- ARBs
- Ca^{2+} Channel Blockers
- Estrogens
- Fibrinolytics

Diagnosis

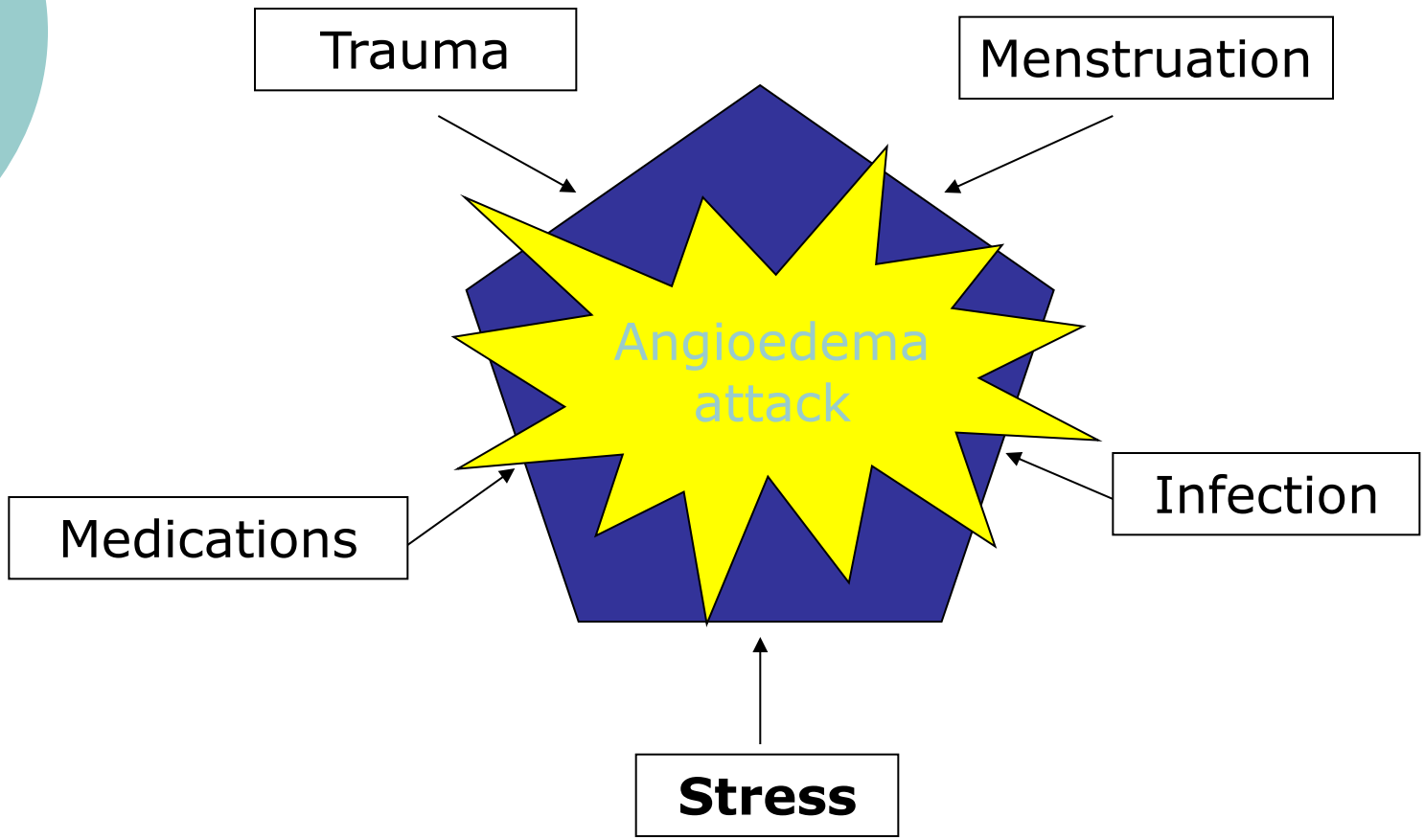
- History is key!
  - Are there allergic symptoms such as urticaria?
  - Are there new exposures?
  - What happened immediately preceeding the episode?
  - Are there other family members that have experienced similar episodes?

Epidemiology of Angioedema



Uptodate. Angioedema

Common Triggers of HAE Attacks



Aleena Banerji, MD. Overview of Hereditary and Acquired Angioedema. 2010.

Hereditary Angioedema

- Usually presents in second decade of life
  - May be seen in younger children or even into 30's
- Edema can be present in different organs and can alter presentation:
  - **Tongue** – most serious as can cause obstruction
    - Face
    - Trunk
    - Genitals
  - **GI track** – can resemble SBO and have pt go for emergent surgery
  - **Extremities**
- Attacks usually last 2-5 days

Recurrent Angioedema - Familial

HAE due to ↓ C1 inhibitor def	Type I	Functional def – bradykinin mediated
	Type II	Functional def – Bradykinin mediated
HAE w/normal C1 inhibitor	Factor XII Mutation (prev Type III)	Assoc w/Factor XII mutation, likely bradykinin mediated
	Unknown cause	Mutation unknown, likely bradykinin mediated

Recurrent Angioedema - Sporadic

Acquired C1 inhibitor def		Assoc w/underlying malignancy or anti C1 inhibitor antibodies likely bradykinin mediated
ACE - I Related		Decreased catabolism of bradykinin – likely bradykinin mediated
Allergic		Mast Cell degranulation

Laboratory Evaluation

- Consider basic lab work-up
  - CBCD
  - BMP
  - LFTs
  - ESR
  - UA
- Also some more specific labs
  - C3 and C4

Laboratory Evaluation (cont)

- When you refer, we may order
  - Tryptase where anaphylaxis might be present
  - Immunocap testing to particular trigger
  - C1 inhibitor antigen and function

Complement Values in Angioedema

Type	Subtype	C4	C1INH antigen	C1INH funct	C1q
C1INH def	Type I	↓	↓	↓	wnl
	Type II	↓	wnl	↓	wnl
Norm C1INH	Factor XII	wnl	wnl	wnl	wnl
Acq C1INH Def		↓	↓	↓	↓
Allergic		wnl	wnl	wnl	wnl

Hospital Treatments – Acute Episode

What treatments should be given?

- C-1-esterase inhibitor if available
  - FFP – should be second line treatment today
    - Carries same risk as blood transfusion
- Intubation precautions
- Volume support
- On discharge
  - Start prophylaxis ideally with C-1-esterase inhibitor
  - Refer to allergy/immunology for care
    - Confirm with repeat C-4, C-1-esterase inhibitor level and functional assay.

Medical Management

- Use of androgens has fallen out of favor given the number of C1 inhibitors and the increased risk of hepatocellular carcinoma with androgren use in excess of 10 years

Medical Management Cont.

- C1 inhibitor concentrates - direct C1-esterase inhibitors that decrease bradykinin production
  - Berinert
    - 20 units/kg intravenous infusion
    - Half life Berinert: 22 hours
    - Time to peak: ~4 hours
      - FDA approved 2009
  - Cinryze
    - 1000 units/patient BID weekly dosing for prophylaxis
    - Half life Cinryze: 56 hours
    - Time to peak: ~4 hours
      - FDA approved 2008

Medical Management Cont

- C1 inhibitor concentrates
  - Adverse Reactions:
    - 12%: Head Aches
    - 1-10%: Dermatological: Pruritus, rash; Gastrointestinal: Abdominal pain, abnormal taste; Neuromuscular & skeletal: Back pain, extremity pain; Respiratory: Sinusitis, URI, Bronchitis
    - <1%: Anaphylaxis
  - Pregnancy category: C

Medical Management of HAE

- Firazyr (Icatibant)
  - 30mg SC q6h for max of 3 doses
  - Bradykinin B2 receptor antagonist therefore stopping bradykinin action
  - Adverse Reactions:
    - >10%: Local: Injection site reaction
    - 1% to 10%: Central nervous system: Pyrexia, dizziness Hepatic: Transaminase increased
    - <1% Anti-icatibant antibody production, headache, nausea, rash
  - Pregnancy Class: C

Medical Management of HAE

- Kalbitor (Ecallantide)
  - 30mg SC
  - Reversibly inhibits plasma kallikrein therefore decreasing bradykinin levels
  - Adverse Reactions:
    - >10%: Central nervous system: Headache, fatigue; Gastrointestinal: Nausea, diarrhea
    - 1% to 10%: Central nervous system: Fever; Dermatologic: Pruritus, rash, urticaria; Gastrointestinal: Vomiting, upper abdominal pain; Local: Injection site reactions; Respiratory: Upper respiratory infection, nasopharyngitis; Miscellaneous: Antibody formation, anaphylaxis
    - <1% Hypersensitivity

Medical Management of HAE

- Lysteda (Tranexamic acid)
  - Oral, I.V.: 25 mg/kg/dose every 3-4 hours (maximum: 75 mg/kg/day)
  - 1000 mg 4 times/day for 48 hours
  - Displaces plasminogen from fibrin irreversibly to cause a decrease in fibrinolysis; also inhibits proteolytic activity of plasmin
  - Pregnancy category: B
  - Adverse Reactions:
    - IV Form: Cardiovascular: Hypotension (with rapid I.V. injection) Central nervous system: Giddiness; Dermatologic: Allergic dermatitis; Endocrine & metabolic: Unusual menstrual discomfort; Gastrointestinal: Diarrhea, nausea, vomiting; Ocular: Blurred vision
    - OralForm: >10%: Central nervous system: Headache; Gastrointestinal: Abdominal pain; Neuromuscular & skeletal: Back pain, muscle pain; Respiratory: Nasal/sinus symptoms; 1% to 10%

Thank You! Questions?

References

1. Kaplan AP. Urticaria and angioedema. In: Middleton's Allergy: Principles and practice, 7th, Adkinson NF, Bochner BS, Busse WW, et al. (Eds), Mosby, St Louis, MO 2009. Vol 2, p.1063.
2. Ying S, Kikuchi Y, Meng Q, Kay AB, Kaplan AP TH1/TH2 cytokines and inflammatory cells in skin biopsy specimens from patients with chronic idiopathic urticaria: comparison with the allergen-induced late-phase cutaneous reactions

References Cont

3.Histamine H2-receptor antagonists for urticaria.Fedorowicz Z, van Zuuren EJ, Hu NCochrane Database Syst Rev. 2012;3:CD008596.

4. Källén B. Use of antihistamine drugs in early pregnancy and delivery outcome. J Matern Fetal Neonatal Med. 2002;11(3):146