# Angioedema

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## Disclosures

- None

## Objectives

- Differentiate the various angioedema subtypes
- Identify patients who are C1 inhibitor replacement candidates
- Understand laboratory workup of angioedema

## Question #1

35-year-old woman presents to your clinic with a 3 month history of persistent, classic appearing hives associated with angioedema of the lips or tongue and eyelids. She otherwise feels well. The most likely diagnosis is:

A. Food allergy
B. Lymphoma
C. Idiopathic urticaria and angioedema
D. Dust mite allergy
E. Antibiotic allergy

## Question #2

76-year-old man with a history of non-Hodgkin's lymphoma treated successfully with R-CHOP chemotherapy 3 years ago presents with a two-month history of severe, painless swelling of his lips and scrotum. Which of the following test results would support a diagnosis of acquired angioedema?

A. Normal C1 esterase inhibitor
B. Elevated tryptase level
C. Undetectable C1q
D. Normal C4 level

## Question #3

62-year-old African-American man with a history of stage III CKD as well as CAD status post MI with LV dysfunction presents to the ER acutely with tongue and lip swelling associated with airway compromise that began 2 hours after his morning medications. Which medication is most likely to blame?

A. Lisinopril
B. Hydrochlorothiazide
C. Oral nitrate
D. Simvastatin
E. Metoprolol

## Question #4

The single most cost-effective, readily-available screening test for hereditary angioedema is which of the following?

A. C3 level
B. C4 level
C. CH 50, AH 50, mannose binding lectin, C1q, C1 esterase inhibitor protein, C1 esterase inhibitor functional assay
D. Autoantibodies to C1 inhibitor complex

## Question #5

Idiopathic angioedema, by far the most common subtype of angioedema in general clinical practice, is largely a histamine mediated process and may respond well to regularly scheduled antihistamines.

A. True
B. False

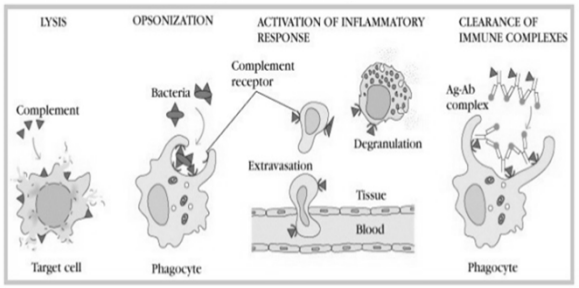
## Angioedema Classifications

- Hereditary
- Acquired
- Angiotensin Converting Enzyme Inhibitor- Associated
- Idiopathic
- "Allergic"

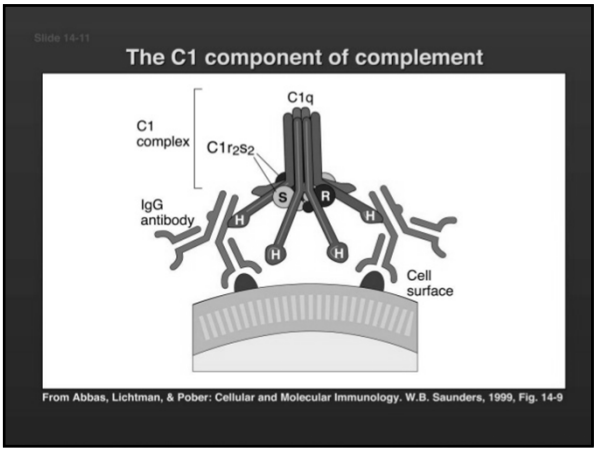
## What is Angioedema?

Asymmetric, non-pitting, non-dependent, non-pruritic… swelling!

## The Multiple Activities of Complement System




http://www.slideshare.net/MMASSY/complement-its-biological-role



## C1 Inhibitor protein (C1 INH)

- C1 INH protein:
  - Inhibits complement cascade
    - Binds C1r and C1s, leading to disassembly of C1 complex, thereby blocking ***anaphylatoxin formation (C3a, C4a and C5a)***
  - Inhibits mannose binding lection pathway
  - Inhibits the contact system of coagulation
    - Inhibits activated factor XII and subsequent formation of ***bradykinin***
      - ***Bradykinin is the major mediator of swelling in HAE***

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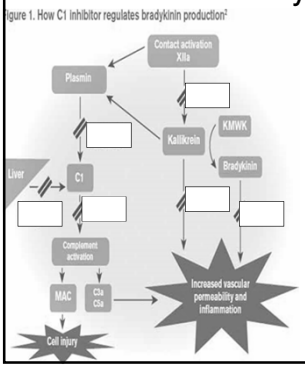
## C1 INH Regulates the Production of Bradykinin




- Blocks kallikrein's conversion of factor XII into XIIa
- Blocks pre-kallikrein conversion to kallikrein
- Blocks cleavage of high-molecular-weight kininogen by activated kallikrein (which would form *more* bradykinin)

www.thehospitalist.org June 1, 2013 • Moises Auron, MD, FAAP, FACP, and David M. Lang, MD, FAAAAI, FACAAI, FACP, Cleveland Clinic

*Practice parameter*

**A focused parameter update: Hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor–associated angioedema**

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## Hereditary Angioedema

- Mutation in the C1 inhibitor gene (~250 mutations described)
- Incidence: 1/30,000 - 1/80,000
- Males=females, no racial differences
- Two modes of inheritance leading to absence of C1 INH:
  - Autosomal dominant (75%)
    - C1 INH gene mutations, chromosome 11q
  - Spontaneous mutations (25%) – proband may start mutational line

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## Hereditary Angioedema

- Swelling onset: Childhood (75%), may worsen in puberty
- Presents with:
  - Abdominal pain – bowel-wall edema
  - Swelling of extremities, genitals, tongue, face, trunk and larynx
  - Laryngeal compromise as cause of death
- Prodrome of an erythematous nonurticarial rash (erythema marginatum), localized tingling, or a sense of skin tightness.
- Triggers:
  - Drugs (ACE-I, estrogens, others), pregnancy, stress, trauma, dental procedures – usually spontaneous

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## Hereditary Angioedema: Subtypes

- 3 Types of HAE
  - Type I HAE (85%), C1-INH protein is low
  - Type II HAE (10-15%), C1 INH protein normal, but not *functional*
    - *Need C1 INH functional assay*
  - Type III HAE (<5%), autoantibodies to C1 protein – both C1-INH and functional can be normal!
    - Diagnosis of exclusion

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## Hereditary Angioedema

- C4 levels are *always low*
- C2 level is *low during an attack*, normal otherwise
- C1 and C3 levels are normal or near-normal

## Management of Hereditary Angioedema

- Education!
- Supportive
- C1 inhibitor replacement
  - Acute attack vs. long-term (twice weekly) prophylaxis
- Antihistamines, corticosteroids and epinephrine have negligible effects on symptoms (i.e. bradykinin)
- Attenuated androgens were previously used (eg. Stanozolol, Danazol)
  - reverse the gene dysregulation and allows expression of functional C1 inhibitor protein
  - Safety concerns such as anxiety, virilization, change in libido, abnormal LFTs, hepatic adenomas/carcinoma, hepatic failure
  - No longer treatment of choice
- Ace inhibitors contraindicated

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## A Word on Short Term Prophylaxis

- "Predictable" Triggers
  - Dental/medical/surgical procedures
- Best: 1000-2000 U (20 U/kg for children) of plasma-derived C1INH
- Alternative: 2 U (10 mL/kg forchildren) of FFP given 2-12 hours before expected procedure.
- Plasma-derived C1INH provides a *more standardized dose* of C1INH protein and has undergone *more rigorous viral inactivation steps.*

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**TABLE E2.** HAE-specific agents

| Generic name (trade name, manufacturer) | FDA indications | Dosage | Mechanism | Anticipated potential side effects |
|---|---|---|---|---|
| Plasma-derived nanofiltered C1INH (Cinryze, ViroPharma) | Long-term prophylaxis | 1000 U administered intravenously every 3-4 d | Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin | Rare: risk of anaphylaxis Theoretical: transmission of infectious agent |
| Plasma-derived nanofiltered C1INH (Berinert-P, CSL Behring) | Acute attacks | 20 U/kg administered intravenously | Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin | Rare: risk of anaphylaxis Theoretical: transmission of infectious agent |
| Ecallantide (Kalbitor, Dyax) | Acute attacks | 30 mg administered subcutaneously (administered as 3 injections of 1 mL each) | Inhibits plasma kallikrein | Uncommon: anti-drug antibodies, risk of anaphylaxis |
| Icatibant (Firazyr, Shire) | Acute attacks | 30 mg administered subcutaneously | Bradykinin B2 receptor antagonist | Common: injection-site reactions |
| Recombinant human C1INH (Rhucin, Pharming) | Acute attacks (pending) | 50-100 U/kg administered intravenously | Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin | Uncommon: risk of anaphylaxis in rabbit-sensitized subjects |

Adapted from Zanw.[68]
*FDA*, US Food and Drug Administration; *MASP*, mannan-binding lectin serine protease.

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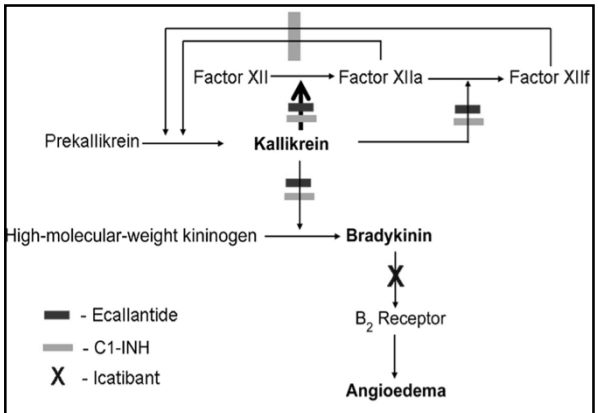


*Ann Allergy Asthma Immunol.* 2010;104:193–204.

## Acquired Angioedema

- Absence of family history!
- Middle age or older patients
- Associated with malignancy or lymphoproliferative disorder, rarely SLE
- Unlike hereditary form of angioedema, acquired will respond to epinephrine within minutes
- Can involve laryngeal edema

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## Acquired Angioedema

- All of the following are decreased:
  - *C1q*
  - C4
  - Functional C1 INH
- C1 INH is degraded faster than it can be produced
- Treatment of underlying disease will resolve the swelling

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## ACE Inhibitor-Associated Angioedema

- African Americans, smokers at higher risk
- Face, lips and tongue, classically
- 0.1-0.7% incidence
  - Highest incidence during 1st month of treatment
  - 27% may occur greater than 6 months after starting therapy
- Inhibiting ACE leads to unopposed bradykinin formation, causing angioedema
  - So, a *class effect* and not a hypersensitivity reaction

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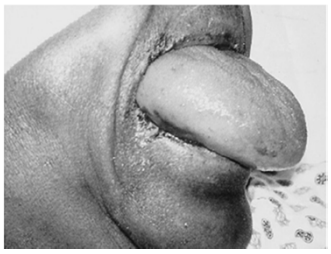
## ACE Inhibitor Induced Angioedema



Intensive Care Med 1997;23(7):795;

## If no ACE-I, what about other anti-hypertensive agents?

- Meta-analysis: Modest risk of recurrent angioedema exists (0 - 9.2%) in patients who experienced angioedema in response to ACE-I therapy and then are switched to ARB therapy (1)
- Piller et al (2) reviewing the incidence of angioedema in 42,418 patients on anti-hypertensives
  - 0.12% with angioedema
    - 70% ACE-Is, 15% to diuretics, 9% to -blockers, and 6% to calcium channel blockers


1. *Ann Allergy Asthma Immunol.* 2008;101:495–499
2. Piller LB et al (ALLHAT). *J Clin Hypertens.* 2006;8:649–656.


## Idiopathic Angioedema

- Most likely subtype!
- An “extension” of idiopathic urticaria
- Responds to antihistamines for prevention and treatment of symptoms
- Injectable epinephrine can be prescribed for a history of laryngeal swelling
- Similar to urticaria in terms of pathophysiology – simply occurs in the deeper skin and tissue structures

## Allergic Angioedema

- Histamine-related swelling resulting from antibody mediated process (i.e. IgE)
- Mast cells release histamine & other preformed mediators >>> hives, angioedema and other signs and symptoms of anaphylaxis (multiple organ systems)
- Foods, meds, stinging insects, inhalants, etc.
- Skin testing and/or serum testing for an allergic process is warranted to confirm a strong history
- Angioedema in this case is an *extension* of urticaria

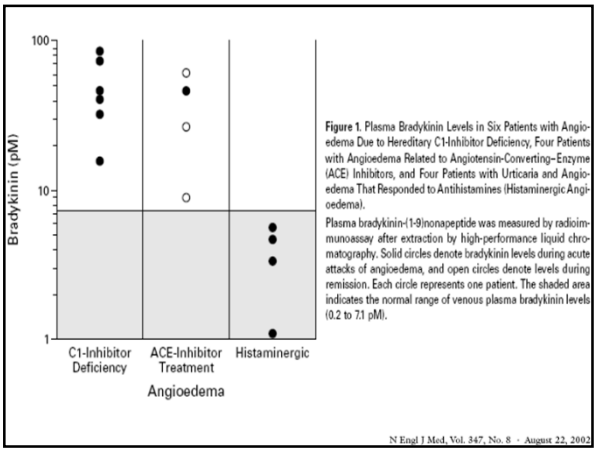



**Figure 1.** Plasma Bradykinin Levels in Six Patients with Angioedema Due to Hereditary C1-Inhibitor Deficiency, Four Patients with Angioedema Related to Angiotensin-Converting–Enzyme (ACE) Inhibitors, and Four Patients with Urticaria and Angioedema That Responded to Antihistamines (Histaminergic Angioedema).

Plasma bradykinin-(1-9)nonapeptide was measured by radioimmunoassay after extraction by high-performance liquid chromatography. Solid circles denote bradykinin levels during acute attacks of angioedema, and open circles denote levels during remission. Each circle represents one patient. The shaded area indicates the normal range of venous plasma bradykinin levels (0.2 to 7.1 pM).

N Engl J Med, Vol. 347, No. 8 · August 22, 2002

## Complement Labs: Bottom Line

- C4 level is the best screening test (cost effective and highly sensitive) for any angioedema situation, especially without hives
- For a child or teenager with angioedema, obtain C4, C1 INH protein *and* C1 INH functional assay
- "C1q level" (not "C1q binding") to evaluate for acquired angioedema in middle age or older adults – in addition to C4, C1 INH protein and C1 INH functional assay

| | C1INH level | C1INH function | C4 level | C3 level | C1Q level |
|---|---|---|---|---|---|
| HAE type I | Low | Low | Low | Normal | Normal |
| HAE type II | Normal-High | Low | Low | Normal | Normal |
| HAE with normal C1INH levels | Normal | Normal | Normal | Normal | Normal |
| Acquired C1INH deficiency | Low | Low | Low | Low-Normal | Low |
| ACE-I | Normal | Normal | Normal | Normal | Normal |
| Idiopathic angioedema | Normal | Normal | Normal | Normal | Normal |

## Question #1

35-year-old woman presents to your clinic with a 3 month history of persistent, classic appearing hives associated with angioedema of the lips or tongue and eyelids. She otherwise feels well. The most likely diagnosis is:

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A 76-year-old man with a history of non-Hodgkin's lymphoma treated with R-CHOP chemotherapy presents with a two-week history of severe swelling of his lips and scrotum. Which of the following test results would support a diagnosis of acquired angioedema?

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## Question #5

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A. True
B. False

## Angioedema: Summary

- Idiopathic angioedema by *far* most common!
- HAE = childhood, Acquired angioedema = older adults
- Angioedema *in the absence of urticaria* warrants a more detailed investigation of the complement system
- Ace inhibitors need to be considered the cause of mid-facial angioedema until proven otherwise
- Newer agents have emerged on the market to assist in management of patients/families with hereditary angioedema

## Thank You!

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