What is angioedema? As Supreme Court justice John Paul Stevens once quipped about another more controversial topic, “I can’t define it, but I know it when I see it.”

Loosely defined as “the localized, transient, episodic edema of the deeper skin or mucosa of the GI or GU tracts, caused by extravasation of plasma but NOT inflammatory cells into affected areas.”

Features of Angioedema
- Usually occurs on face/extremities, can be associated w/ burning sensation and or warmth, although pruritis is uncommon (a feature that helps distinguish it from urticaria)
- GI involvement
  - Edema/swelling of GI tract related to angioedema can cause severe abdominal pain, nausea/vomiting/diarrhea, even bowel obstruction/ischemia, bad enough to mimic severe gastroenteritis/colitis
  - Can occur in the absence of skin findings
  - Therefore, patients with recurrent abdominal pain +/- enteritis-like symptoms of otherwise unknown origin should include a workup for angioedema.
- Either type usually abates in 24-48 hours
- Occasionally “migraine” presentation of rare cerebral angioedema
- Fever/leukocytosis very unusual unless other concomitant process

Types of Angioedema
- Idiopathic (by far most common)
- Medication-induced (in order: ACE-inhibitor, ARBs, fibrinolytics, estrogen, NSAIDs, penicillins (including synthetic penicillins), narcotics, and every other class of antihypertensive medications)
- Allergen-induced
- Physically induced (i.e., by mechanical, chemical, electromagnetic, or thermal trauma)
- C1 esterase (C1INH) inhibitor of complement and kallikrein/kinin systems
  - Hereditary C1INH deficiency, occurring as variants both as quantitative (more common) or qualitative (less common) deficiencies of C1INH
  - Acquired C1INH deficiency (one of which is mediated by IgG specific for C1INH).

ACE-induced Angioedema—A Big Puzzle
- The cutaneous, abdominal, and laryngeal manifestations are the same as in C1INH-deficiency-induced angioedema, except that the angioedema is often limited to face/neck and is less likely to involve the GI/GU tracts.
- Likely linked to decreased degradation of bradykinin, but only partially the story.
- Possibly ACE-inhibitors potentiate the action of BK in people who are predisposed to angioedema from other reasons that would otherwise be innocuous (i.e., cold, physical stimuli, etc.)
- Age/gender seem to have no effect on freq/severity of ACE-angioedema, but African Americans seem to be more susceptible to it. Interestingly, Nigerians and other groups of West Africans given ACE-inhibitors have a lower freq/severity of angioedema than similarly-dosed African Americans.
- The appearance of ACE-induced angioedema is NOT dependent upon size or timing of dose, nor does the length of therapy appear to affect the frequency of ACE-angioedema.
- In some patients, there appears to be a Type I-hypersensitivity allergic angioedema, but not common (more common in older, sulfhydryl-based ACEs, like captopril.)

Joe, if someone has angioedema, how do you diagnose and manage them?
Well, if someone has ACE-angioedema, that person should never be challenged again with ACE-inhibitors. This prohibition includes ARBs, and ostensibly, and of the meds previously mentioned.
Management of angioedema pretty much is limited to the side effects of the angioedema, especially when head and neck angioedema compromise the airway. Early, and if necessary, surgical security of the airway is preferred. Otherwise, we give these patients high-dose steroids, epinephrine, H1 and H2 blockers, although there are no randomized control trials to support the use of these agents and, from a pharmacological perspective, likely offer no specific benefit since the angioedema is usually not an IgE-mediated allergic reaction.

So, what is this C1INH I keep talking about?
- C1INH is the inhibitor of C1q. What is C1q?
- C1q is one-third of a very important complex in the complement cascade. What is the complement cascade?

**The Complement Cascade**, or aka, Rounds w/ Dr. Ohman
Three different pathways for activation of a whole passel of plasma proteins manufactured by the liver that help immunoglobulin, cellular immunity, and the reticuloendothelial system defend the body from invaders.

*Classical Complement Pathway*—ah, there’s nothing like the classics to make you nostalgic… C1r+C1s form a heterodimer, but can’t do their job until C1q can link the two and expose their combined active site. Together C1q+C1r+C1s is an active dude

\[ C4 \rightarrow C4a + C4b \] (C4a is a weak mediator of inflammation and a neutrophil chemotactic agent.)
\[ C2 \rightarrow C2a + C2b \] (I can’t find that C2a does anything?)

C4b+C2b join together in noncovalent fashion and together expose their mutual activity as a C3 convertase.

\[ C4b+C2b \rightarrow C3 \rightarrow C4b+C2b + C3a + C3b \] (C3a is too a weak mediator of inflammation and a NCA.)

C3b binds to the microorganism OR C4b+C2b joins with C3b to form an active C5 convertase.

\[ C4b+C2b+C3b + C5 \rightarrow C4b+C2b+C3b + C5a + C5b \] (C5a is the strongest complement anaphylatoxin)

C5b binds C6 and C7 to expose a site on C7 that allows the complex to stick to the lipid membrane. C5b+C6+C7 bind C8, which inserts through the lipid membrane and provides a binding site for C9. The complex, once C9 binds, allows for fast polymerization of more C9, which eventually forms a MAC.

*Alternative Complement Pathway*—the spirit of ’92 lives on…
Constitutively there is activation of the classical pathway, leading to a small amt of C3b being formed. C3b can bind Factor B, which then is joined by factor D to cleave B into Ba and Bb.

C3b+Bb is a VERY VERY active C3 convertase, leading to large amounts of C3b production. This then allows classical complement pathway to do its work more efficiently.

*Where does C1INH come in?*
C1INH binds the C1r-C1s heterodimer, causing it to be stabilized and whisked away from C1q, thus preventing the formation of C4-C2 convertase. Therefore, deficiency of the inhibitor can cause C1q to proceed unchecked, leading to excessive C4 conversion. C4 conversion is often the rate-limiting step in the classical pathway, given the C4 concentrations are lower than C3 by approximately a magnitude.

See the provided illustrations for better, more concise explanations of the above. It’s not especially important for the case in the patient, but it’s a good review.