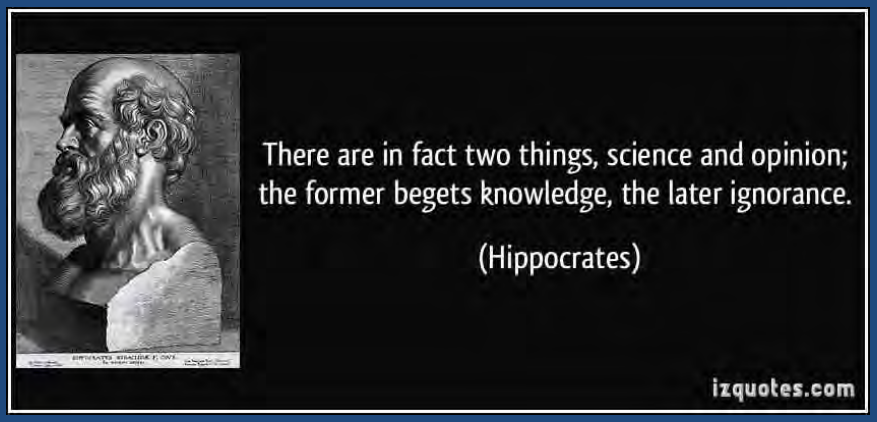
Disclosure of Conflicts of Interest

Marc Riedl, MD, MS

- **Research Support**: Biocryst, CSL Behring, Ionis, Pharming, Shire
- **Consultant**: Arrowhead, Biocryst, CSL Behring, Global Blood Therapeutics, Pharming, Salix, Shire
- **Speakers Bureau**: CSL Behring, Salix, Shire



Idiopathic Angioedema: Start at the beginning…..

- Defining Idiopathic
  - Arising spontaneously
  - From an obscure or unknown cause
  - Greek: *idios* (one's own), *pathos* (suffering) – "a disease of its own kind"
  - Isaac Asimov in The Human Body: "a high-flown term to conceal ignorance"
  - "The doctor is too big of an idiot to figure out the cause"
  - Diagnosis of exclusion
- **Absence of urticaria**
- **Recurrent**
- **3 or more episodes over a period of 6-12 months**

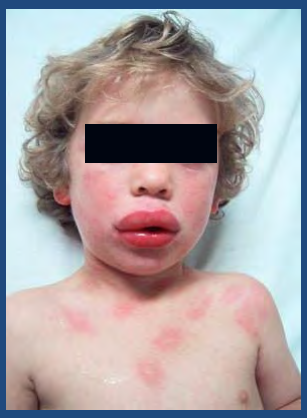
Frigas et al. Immunol Allergy Clin N Am 2006

Idiopathic Angioedema: Start at the beginning…..

- Is it angioedema?

Angioedema – General Features

- Non-pitting
- Localized swelling
- Involves skin or mucosa
- Result of fluid extravasation into deeper dermis and subcutaneous tissues
- Face, tongue, lips, periorbital region - most common sites
- Throat, larynx, extremities, genitalia, intestines
- May cause life-threatening respiratory distress



Angioedema vs Edema

Swelling	Angioedema	Edema
Symmetric	No	Yes
Dependent	No	Yes
Pitting	No	Yes
Mechanism	Increased permeability	Hydrostatic

Idiopathic Angioedema: Start at the beginning…..

- Is it angioedema?
  - Photographs critical
  - Episodic
    - Granulomatous chelitis (Melkersson-Rosenthal)
    - SVC syndrome
    - lymphedema
    - Capillary leak syndrome (Clarkson)
    - Contact dermatitis
    - Cellulitis
  - Other causes of dyspnea, “throat closing/choking”
    - VCD
    - Tracheomalacia
    - Exercise-induced asthma
  - Other causes of recurring abdominal pain
    - Gastritis
    - Esophagitis
    - Pancreatitis

Differential Diagnosis of Abdominal Pain

- Biliary disease
- Acute pancreatitis
- Dyspepsia
- Hiatus hernia
- Pneumonia
- Myocardial infarction
- Splenic abscess or infarction
- Appendicitis
- Diverticular disease
- Kidney stones
- Bladder distension
- Pelvic pain
- Mesenteric ischemia and infarction
- Ruptured aneurysm
- Peritonitis
- Intestinal obstruction
- Sickle cell disease
- Familial Mediterranean fever
- Women
- - Pelvic inflammatory disease
- - Adnexal pathology
- - Endometriosis
- - Ectopic pregnancy
- - Endometritis
- - Leiomyomas
- Celiac artery compression syndrome
- Painful rib syndrome
- Wandering spleen syndrome
- Abdominal wall pain
- Abdominal migraine
- Mesenteric lymphadenitis
- Eosinophilic gastroenteritis
- Epiploic appendagitis
- Abdominal compartment syndrome
- Fitz-Hugh-Curtis syndrome

Causes of Isolated Angioedema

Table 1 *Types of recurrent angioedema diagnosed in 1058 patients examined between 1993 and 2012*

	Patients, *n* (%)	Male, *n* (%)	Female, *n* (%)	Male : female ratio
Hereditary angioedema	377 (36)			
C1-INH-HAE	353 (94)	151 (43)	202 (57)	0.75
FXII-HAE	6 (1)	1 (17)	5 (83)	0.2
U-HAE	18 (5)	12 (67)	6 (33)	2
AAE	681 (64)			
C1-INH-AAE	49 (7)		31 (63)	0.58
ACEI-AAE	183 (27)	42%	76 (42)	1.4
IH-AAE	379 (56)	155 (41)	224 (59)	0.69
InH-AAE	70 (10)	36 (51)	34 (49)	1.06
Total	1058 (100)	480 (45)	578 (55)	0.83

C1-INH-HAE, hereditary angioedema (HAE) with C1-inhibitor deficiency; FXII-HAE, HAE with factor XII mutation; U-HAE, HAE of unknown origin; ACEI-AAE, acquired angioedema (AAE) related to angiotensin-converting enzyme inhibitor therapy; IH-AAE, idiopathic histaminergic AAE; InH-AAE, idiopathic nonhistaminergic AAE.

Mansi M, J Intern Med. 2014

Causes of Angioedema in Children

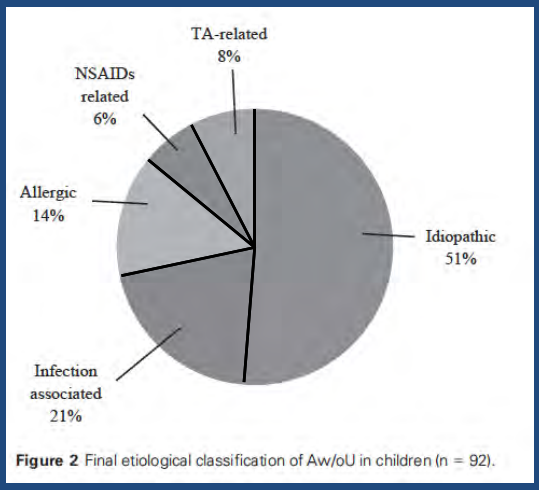


Figure 2 Final etiological classification of Aw/oU in children (n = 92).

Karagol et al. Pediatr Allergy Immunol 2013

Exclusion of Known Causes

- Personal medical history
  - Allergic: Food, latex, insect sting, medication
  - Medication-induced: ASA/NSAID, ACE-I, ARBs, estrogen
  - Physical: cold, vibratory, pressure, UV
  - Systemic conditions: gammopathy, malignancy, thyroid disease, chronic viral infection, vasculitis, hypereosinophilic syndrome, episodic angioedema with eosinophilia (Gleich syndrome)
- **Family medical history** – positive c/w HAE
  - 25% of C1INH def patients without family history

Sher J, et al. Curr Allergy Asthma Rep. 2013

Medications Known to Cause Angioedema

- **ASA/NSAIDs**
- **ACE-I**
- **ARBs**
- **Narcotics**
- **Antibiotics**
- **Estrogens**
- proton pump inhibitors
- statins
- diuretics
- calcium channel blockers
- beta- blockers
- psychotropic drugs (paroxetine, risperidone)
- Monoclonal antibodies
- DPP-IV inhibitors

Looking for Evidence of Known Causes

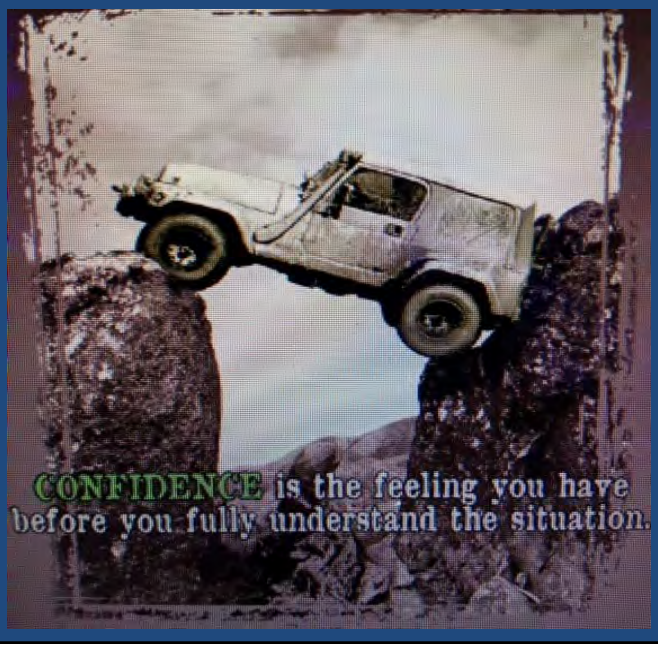
- Physical Exam (photos) – is it angioedema?
  - Abdominal pain: CT, ultrasound
  - Airway symptoms: direct laryngoscopy
- Signs/Symptoms of mast cell activation
  - Urticaria, flushing, pruritus, bronchospasm
- Diagnostic tests – based on clinical history to exclude reasonable underlying causes

Carr TF, et al. Allergy Asthma Proc. 2012

For Consideration: Diagnostic Evaluation

- CBC with diff
- Chemistry Panel
- ESR
- C4, C1INH level and function
- Thyroid function and autoantibodies
- Protein electrophoresis
- Tryptase
- Allergy evaluation
  - Food
  - Drug
  - Environmental
  - Venom
  - Latex
- Urinalysis
- Cultures (throat, urine)
- CH50, C3, immune complex assays

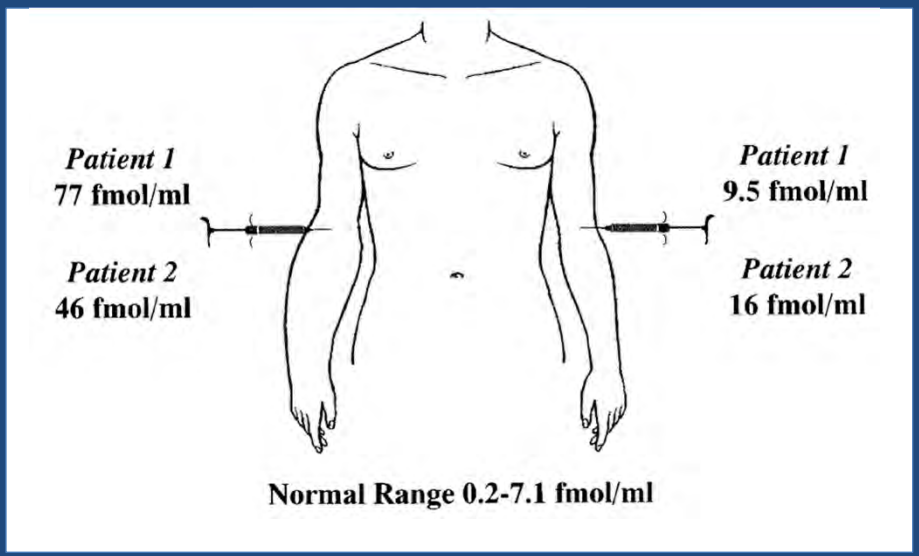
All Systems Normal: Now What?



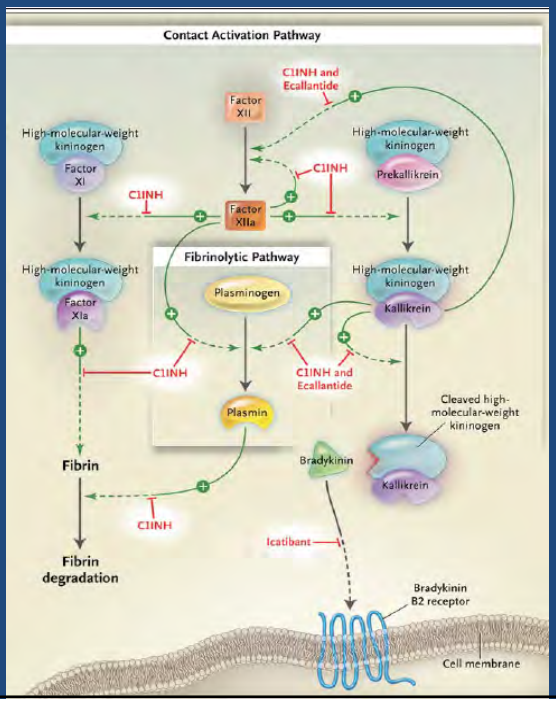
Idiopathic Angioedema: Pathophysiology

- Mast-cell mediated vs. Kallikrein-Bradykinin pathway
  - Pattern of clinical symptoms
    - Duration, anatomical location, severity
  - Lack of validated laboratory tests to differentiate

In Vivo Generation of Kinins in HAE

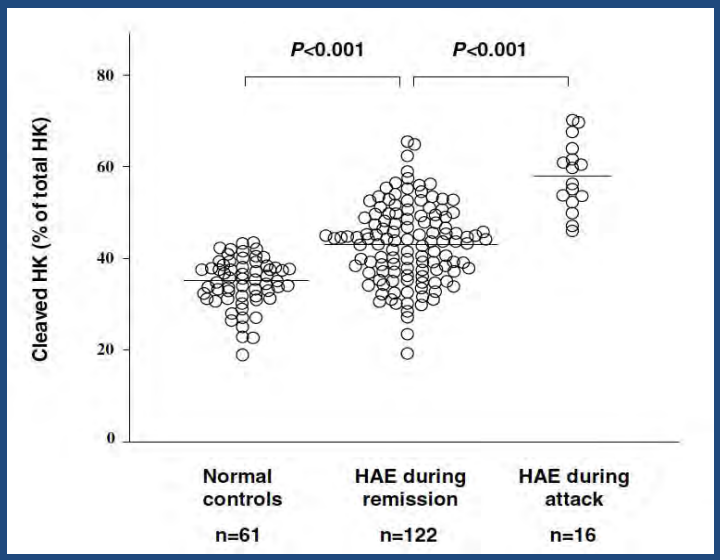


Nussberger J, et al. *J Allergy Clin Immunol*. 1999;104:1321-1322; with permission.



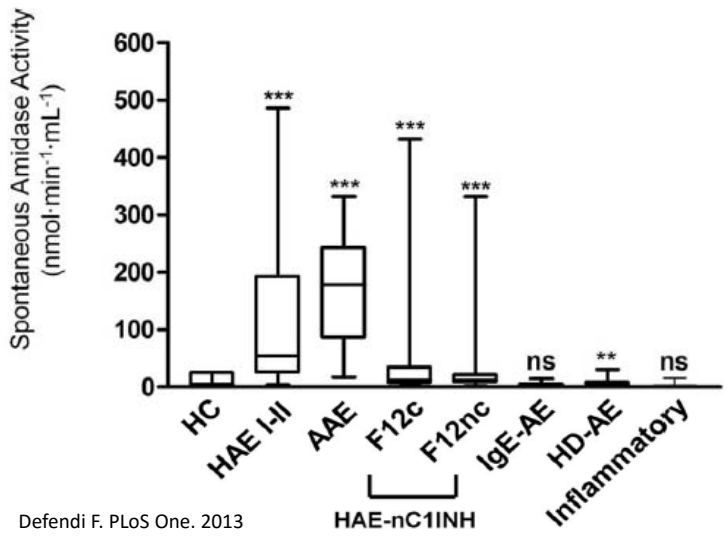
Zuraw NEJM 2008

Cleaved HMWK in C1INH Deficiency



Suffritti C. Clin Exp Allergy 2014

Amidase Activity in Bradykinin-Mediated Angioedema



Defendi F. PLoS One. 2013

Table 1
Components of the kallikrein-kinin system

Current Name	Synonym	Abbreviation	Gene	Plasma Concentration
Kinin-forming proteases				
Factor XII	Hageman factor	FXII	*F12*	30–35 mg/L
Plasma prekalikrein	Fletcher factor	pKK	*KLKB1*	35–50 mg/L
Prolylcarboxypeptidase	—	PCP	—	—
Tissue kallikreins	—	tKK	*KLK1-15*	—
Kininogens				
High-molecular-weight kininogen	Fitzgerald trait (HK) and	HK	*KNG1*	70–90 mg/L
Low-molecular-weight kininogen	Flaugeac trait (HK + LK)	LK	*KNG1*	170–220 mg/L
Kinins				
Bradykinin	—	BK	—	—
$desArg^{9}$-bradykinin	—	$desArg^{9}$-BK	—	—
Lys-bradykinin	Kallidin	Lys-BK, KD	—	—
$desArg^{10}$-kallidin	—	$desArg^{10}$-KD	—	—
Kallikrein inhibitors				
C1 Inhibitor	—	C1INH	*SERPING1*	—
α_2-Macroglobulin	—	α_2-M	*A2M*	—
Kallistatin	—	—	*SERPINA4*	—
Kininases				
Angiotensin I–converting enzyme	Kininase II	ACE	*ACE*	—
Carboxypeptidase N	Kininase I	CPN	*CPN1, CPN2*	—
Carboxypeptidase M	—	CPM	*CPM*	—
Aminopeptidase P	—	APP	*XPNPEP2*	—
Dipeptidylpeptidase IV	CD26	DPPIV	*DPP4*	—
Neutral endopeptidase 24.11	CD10	NEP, CALLA, CD10	*MME*	—
Accessory participants				
u-Plasminogen activator receptor	—	u-PAR	*PLAUR*	—
Plasminogen	—	—	*PLG*	—
C1 proteases	—	C1r, C1s	*C1R, C1S*	—
Prolylcarboxypeptidase	—	PCP	*PRCP*	—
Kinin receptors				
B_1-receptor	—	B1R	*BDKRB1*	—
B_2-receptor	—	B2R	*BDKRB2*	—

Ghannam A, et al. Immunol Allergy Clin North Am. 2013

Causes of Isolated Angioedema

Table 1: Classification of angioedema without urticaria according to clinical or etiopathogenetic characteristics, *n* = 776

	Patients		M:F ratio	Age at onset, yr	
	No.	%		Median	Range
Related to a specific factor*	124	16	0.51	39	13-76
Autoimmune disease/infection	55	7	0.62	49	3-78
ACE inhibitor-related	85	11	0.93	61	32-84
C1-inhibitor deficiency	197	25			
Hereditary	183		0.88	8	1-34
Acquired	14		1.8	56.5	42-76
Unknown (idiopathic) etiology	294	38			
Histaminergic	254		0.56	40	7-86
Nonhistaminergic	40		1.35	36	8-75
Peripheral/generalized edema	21	3	0.17	—	

Note: M = male, F = female, ACE = angiotensin-converting enzyme.
*A food, drug, insect bite, environmental allergen or other physical stimulus.

Zingale LC, CMAJ. 2006

All Systems Normal: Now What?

- Our next "best" diagnostic…..
  - Empiric trial of targeted therapy with close monitoring of response: goal of identifying underlying mediator
  - "High-dose" antihistamines to prevent episodes
    - What's an adequate dose?
    - For how long?
    - How to determine response or lack thereof
  - Trial of corticosteroids
    - Same questions as above

Please try to suffer from the disease for which I am treating you"

Failure of Empiric Histamine-directed Treatment

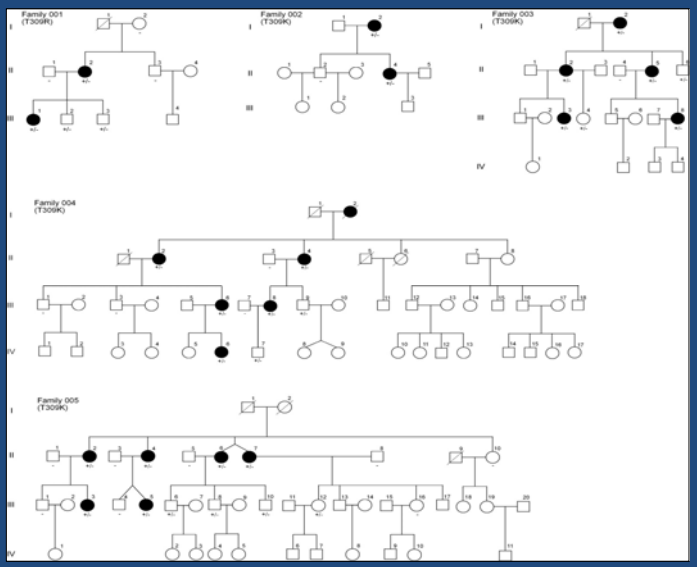
- ? Trial of kallikrein-bradykinin targeted drugs acutely
  - Icatibant: specific to B2-receptor
  - Ecallantide: specific to plasma kallikrein activity
  - C1INH: most non-specific in absence of C1INH-deficiency
- ? Trial of prophylactic therapy
  - Tranexamic Acid
  - Progestin

Montinaro, Am J Emerg Med. 2013
Berry A, J Allergy Clin Immunol Pract. 2013
Colás C. J Investig Allergol Clin Immunol. 2012
Saule C. Clin Exp Allergy. 2013
Wintenberger C. Clin Exp Immunol. 2014

Differentiating Histaminergic from Non-histaminergic Angioedema

Differentiating HAE-nml C1INH from Idiopathic Angioedema

Hereditary Angioedema with Normal C1-INH (Type III) is FAMILIAL



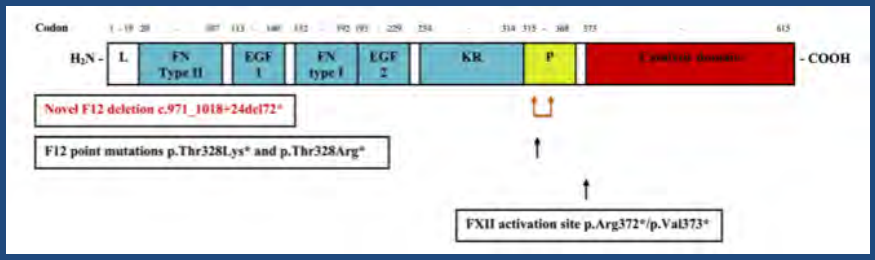
Dewald, G. & Bork, K. *Biochem. Biophys. Res. Commun*. 2006;343:1286-1289.

Diagnosis: Hereditary Angioedema with normal C1-INH (Type III)

- **Familial condition**
- Clinical diagnosis + exclusion of other causes
- Pathophysiology poorly defined
- **Appears kinin-mediated**
- Striking predominance in women
  - Estrogen role in regulating phenotypic expression
- Facial and lip swelling frequent
- **Recurrent tongue swelling a cardinal symptom**
- Many patients have only skin swelling, with **infrequent GI angioedema**
- **Asphyxiation due to airway involvement occurs**

Bork K. *AJM* 2007;120:987-92.

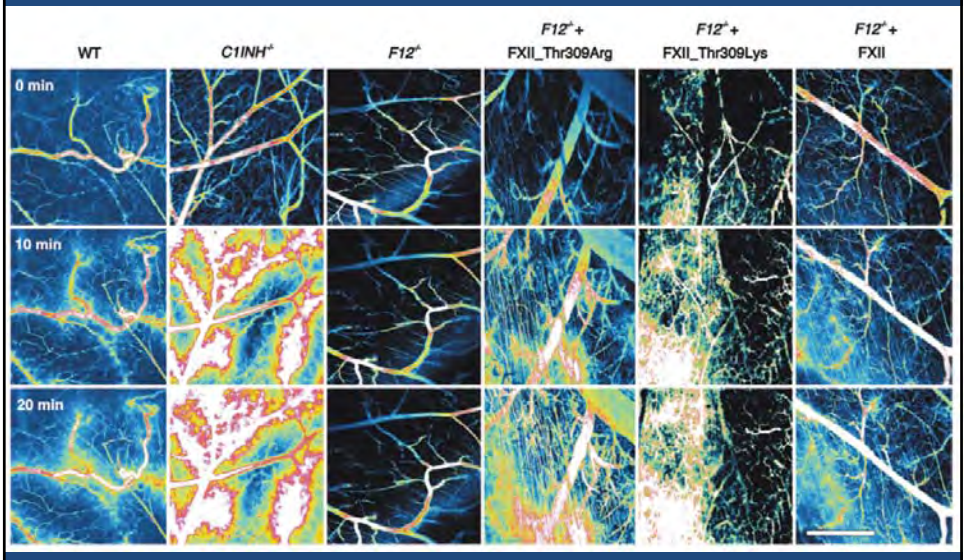
Novel Mutation: Factor XII Deletion



- Point mutations and deletion affect proline-rich region with uncertain function
- Some evidence for role in Factor XII binding to negatively charged surfaces ➡ Factor XII autoactivation, contact system activity

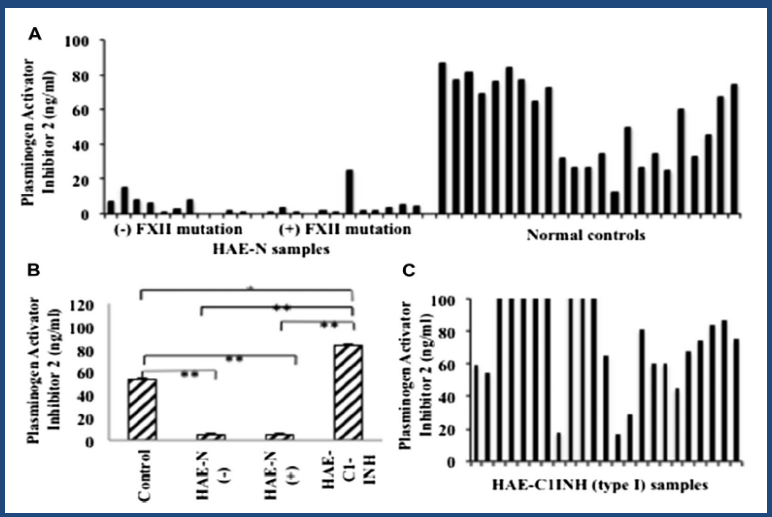
Bork K, et al. *Clin Immunol*. 2011;141:31-35.

Mechanism for HAE-Factor XII



Bjorkqvist et al. J Clin Invest. 2015

HAE with Nml C1INH - Unknown



Kaplan A. JACI, In Press

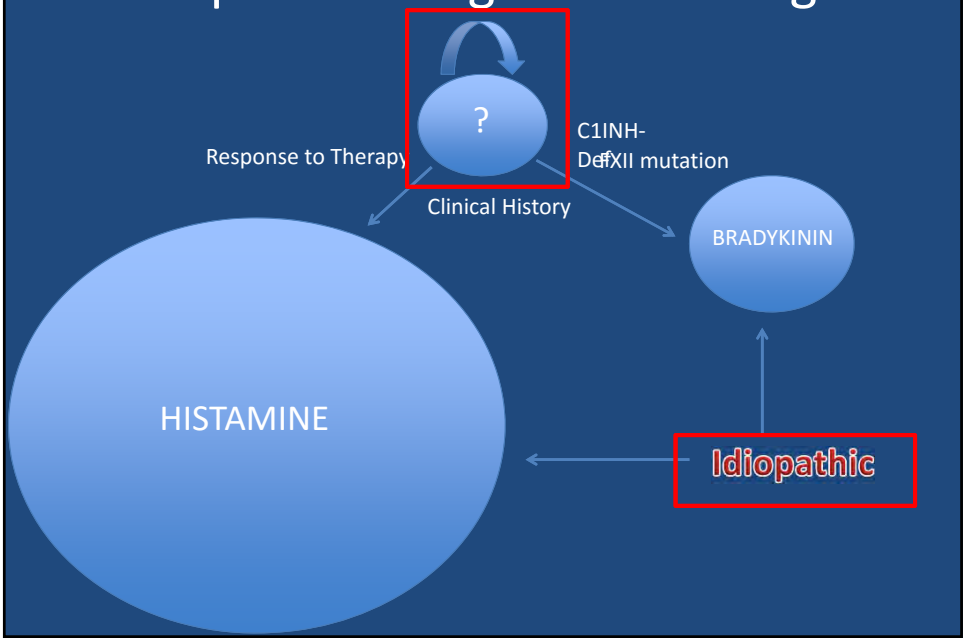
HAE Normal C1INH: Diagnosis

TABLE II. Recommended diagnostic criteria for HAE with normal C1-INH[46]

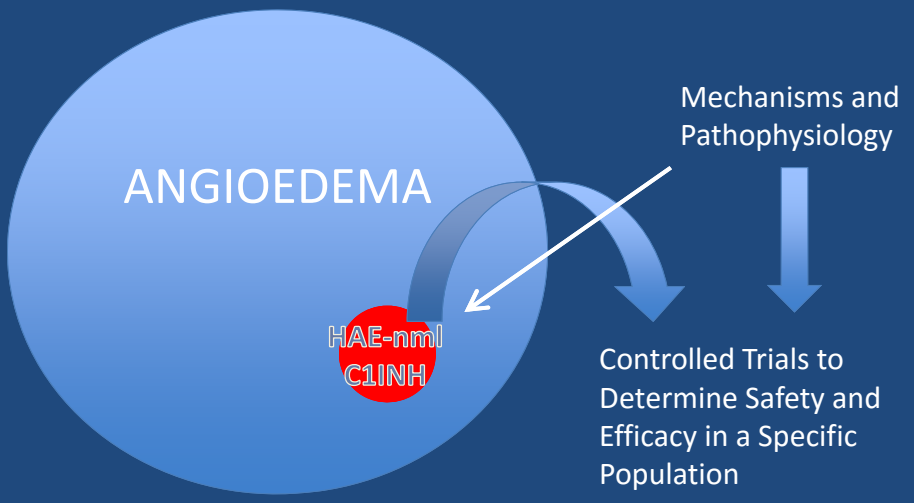
- A history of recurrent angioedema in the absence of concomitant hives or concomitant use of a medication known to cause angioedema
- Documented normal or near normal C4, C1-INH antigen, and C1-INH function
- *Plus one* of the following:
  - Demonstration of a factor XII mutation associated with the disease
  - A positive family history of angioedema *and* documented evidence of lack of efficacy of chronic high-dose antihistamine therapy (cetirizine at 40 mg/d or the equivalent, for at least 1 month and an interval expected to be associated with three or more attacks of angioedema)

Zuraw BL et al., Allergy Asthma Proceedings 2012
Riedl MA. J Allergy Clin Immunol: In Practice, 2013

Improved Diagnostic Testing



Clinical Studies



Differentiating HAE Normal C1INH from Idiopathic AE

- Idiopathic Angioedema
  - Family history +/-
  - Histamine (majority) OR Bradykinin (minority)
    - Clinical symptom pattern
      - Shorter duration
      - GI symptoms and airway compromise rare in absence of anaphylaxis
    - Response to therapeutic trials
      - Histaminergic
      - Refractory to antihistamines: idiopathic BK
- HAE normal C1INH
  - Family history +
  - Bradykinin-mediated
    - Clinical symptom pattern suggestive but not definitive
      - Longer duration
      - Tongue and GI involvement
      - Airway compromise
    - Response to therapeutic trials
      - Refractory to antihistamines/corticosteroids

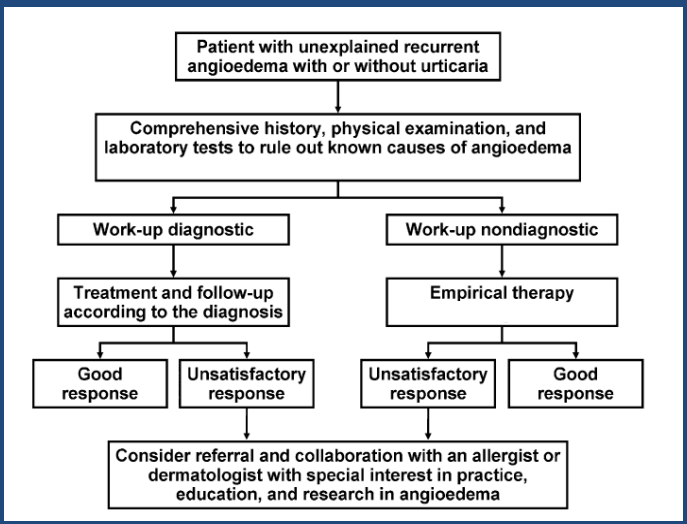
*Factor XII Mutation Analysis?

Genetics and Genomics

- Familial implications of angioedema condition
- Uneasy lies the head that wears a “genetic crown”
- Informed and appropriate counseling
- Preventing unnecessary anxiety and guilt for patients

- Scientific Registries - Collaborative efforts to collect genetic, clinical, laboratory data
- Identification and confirmation of underlying genetic causes
- Gene therapy, genomic editing as therapeutic strategies

“The Road to Nowhere”



Frigas et al. Immunol Allergy Clin N Am 2006

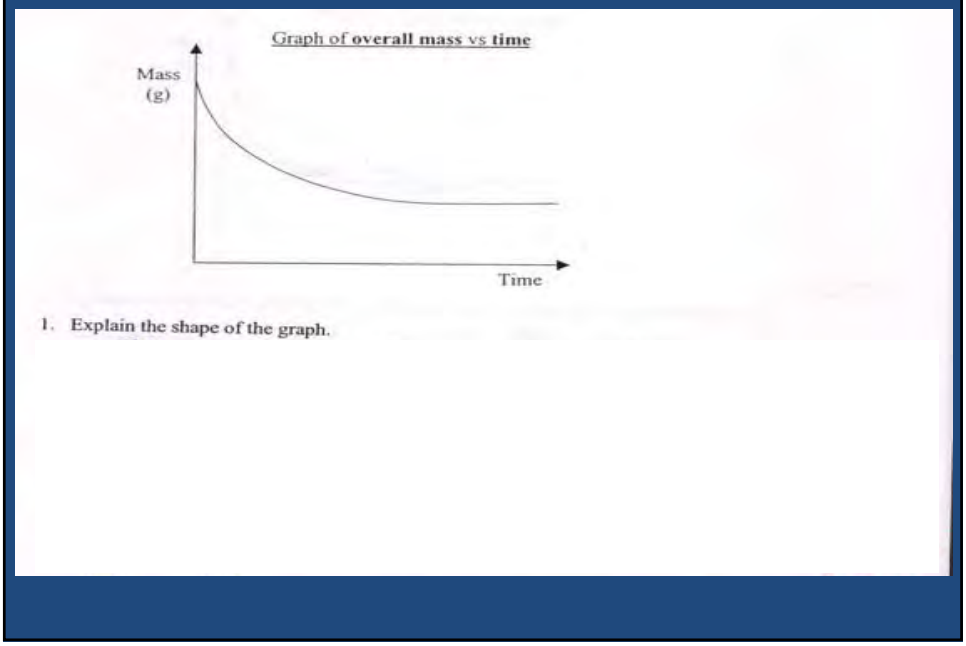
Causes of Angioedema

- Allergic: Foods, drugs, insect stings/bites
- Radiocontrast media
- ASA and other NSAIDs
- Autoimmune
- ACE inhibitor-induced
- C1 inhibitor deficiency
  - Hereditary – Types I, II
  - Acquired
    - Hereditary with normal C1 inhibitor
- Idiopathic
  - Histamine-induced/Mast cell-mediated
  - Bradykinin-induced

Agostoni A. *J Allergy Clin Immunol*. 2004;114:S51-S131.
Cichon S. *Am J Hum Genet*. 2006;79:1098-1104.

Major Types of Angioedema

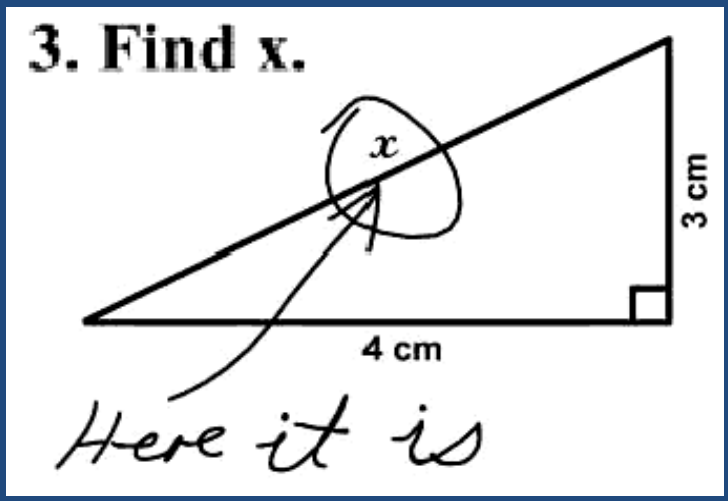
	Mast-cell mediated *or* allergic	Bradykinin mediated *or* non-allergic
Onset	Minutes to hours	Days
Urticaria	+	-
Pruritis	+	-
Pain/burning	-	May be present
Response to antihistamine	+	-
Response to steroids	+	-



Our Patients' Perspective

- Recurring troubling symptoms
- Disfiguring
- Disabling
- Frightening – fear of asphyxiation
- Secondary depression and anxiety

- SYSTEMATIC APPROACH – Enables gradual move from "searching for cure" to focus on effective management plan



US HAEA Angioedema Center at UCSD