Hereditary Angioedema: Diagnosis and Management

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Mechanisms of angioedema

TYPE	CAUSE/ MECHANISM	MAIN MEDIATOR
Allergic	IgE to food, antibiotics	Histamine
Pseudoallergic	NSAIDs, arachidonic acid metabolism	Leukotrienes
ACE Inhibitor	ACE-Inhibitor	Bradykinin
Hereditary (HAE)	Hereditary C1-INH deficiency	Bradykinin
Acquired C1-INH deficiency	from CTD, B-Lymphoma	Bradykinin

Consider investigations for HAE if[1,2]:

- Angioedema (recurrent, non-pruritic, non-responsive to antihistamine)
- No urticaria, may have serpiginous rash
- Unexplained abdominal pain
- A family history

[1]Gompels et al, 2005; [2]Bowen et al, 2004; [3]Temino et al, 2008

◆**Three types of HAE[3]**:

Parameter	I	II	III
Percent of all HAE	85	15	? Rare
C1INH Antigenic Level	Low	Normal	Normal
C1INH Functional Level	Low	Low	Normal

Acquired C1-INH Deficiency (ACID): 2 Types

1. Consumption of C1 inhibitor
   - Connective tissue disease
     - SLE or cryoglobulinemia
   - Complement activation from immune complexes
     - in B-cell lymphomas
     - anti-idiotypic antibodies to monoclonal Ig
2. Autoantibodies to C1-INH

   Circulating IgG antibody to C1-INH itself

Low C1q levels in ACID, normal C1q in HAE

C1 Inhibitor (C1-INH)

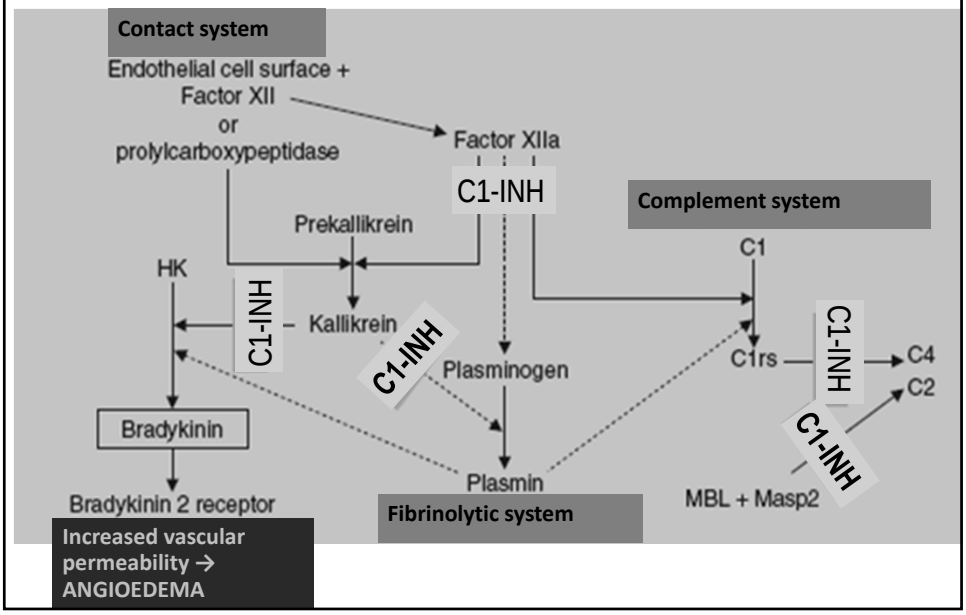
- Inactivates C1 esterase (C1r, C1s) complex

C1(C1r,C1s) —C1-INH→ C4 → C2 → C3 …

- Lack of C1-INH leads to abnormal activation of classical complement pathway, ↓ C4 (and C2) levels

Agostoni A. JACI. 2004:114:S51-S131. Davis AE. *Clin Immunol*. 2005;114:3-9.

C1 INH: "suicide" enzyme depleted in 3 systems



Laboratory Evaluation of Possible C1INH Deficiency:

Begin with C4

	C4	C3	C1 INH Quant	C1 INH Function	C1q
Allergic IgE	Nl	Nl	Nl	Nl	Nl
Idiopathic	Nl	Nl	Nl	Nl	Nl
HAE Type 1	Low	Nl	Low	Low	Nl
HAE Type 2	Low	Nl	Nl/High	Low	Nl
HAE Type 3	Nl	Nl	Nl	Nl	Nl
Acquired Type 1	Low	Nl	Low	Low	Low
Acquired Type 2	Low	Nl	Nl/Low	Low	Low

Clinical treatment of HAE may include:

- Long-term (routine) prophylaxis
- Short-term prophylaxis
- Treatment of acute attacks

When is prophylaxis for HAE necessary?

Consideration Criteria	Episodic Therapy	Prophylactic Therapy
Description of HAE Attacks		
Frequency of Attacks	<1/Month	≥1/Month
Rapid progression of attacks	No	Yes
Timely access to care	Yes	No
Nature of HAE Attacks		
History of laryngeal attacks	No	Yes
Emergency visit to physician/hospital	≤ 3/year	> 3/year
Intubation due to HAE	No	Yes
Hospitalization due to HAE	≤ 1/year	> 1/year
ICU due to HAE	No	Yes
Burden On Activities of Daily Living		
Missed days of school or work	≤10 days/year	>10 days/year
Significant anxiety or compromise in quality of life	possible	consider
Impacts lifestyle (vacation, family, sports)	No	Yes
Analgesic dependency	No	Yes

Hereditary angioedema (HAE) therapy considerations for prophylaxis with the goal of therapy to enable each patient with HAE to live as normal a life as possible. These therapy considerations are proposed for guidance only. Therapy decisions should be based on close consultation between physician and patient on what the best course of therapy should be for a patient's particular needs, problems, and concerns. Pregnant women and children younger than puberty are best managed without androgens. ICU indicates intensive care unit.

Modified from Craig T, Riedl M, Dykewicz MS, et al. Ann Allergy Asthma Imm 2009;102: 366-372

Approved FDA Treatments for HAE

	Acute treatment		
Generic	C1 esterase inhibitor (human)	Ecallantide	Icatibant
Brand name	Berinert®	Kalbitor®	Firazyr®
Mechanism	C1 INH replacement	Blocks kallikrein binding site, inhibits conversion of HMWK to bradykinin	Bradykinin 2 receptor antagonist
FDA Indication	Treatment of acute abdominal and facial attacks in adults and adolescents	Treatment of acute attacks of HAE in patients ≥16 years age	Treatment of acute attacks of HAE in adults ≥18 years age
Administration	Intravenous	Subcutaneous three 1ml injections	Subcutaneous one 3ml injection
Safety	Potential viral, CJD transmission	Anaphylaxis 2.7%. 7.4% seroconvert to anti-ecallantide antibodies (all classes)	Injection site swelling, pain

Approved FDA Treatments for HAE		
	Prophylaxis	
Generic	C1 esterase inhibitor (human)	Attenuated androgens: danazol, stanozolol
Brand name	Cinryze®	
Mechanism	C1 INH replacement	Increase C1 INH synthesis
FDA Indication	Route prophylaxis against HAE attacks in adults and adolescents	Prevention of attacks of angioedema of all types (cutaneous, abdominal, laryngeal) in males and females
Administration	intravenous	oral
Safety	Potential viral, CJD transmission	Multiple issues