How To Diagnose And Manage A Potentially Fatal Angioedema

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Disclosure

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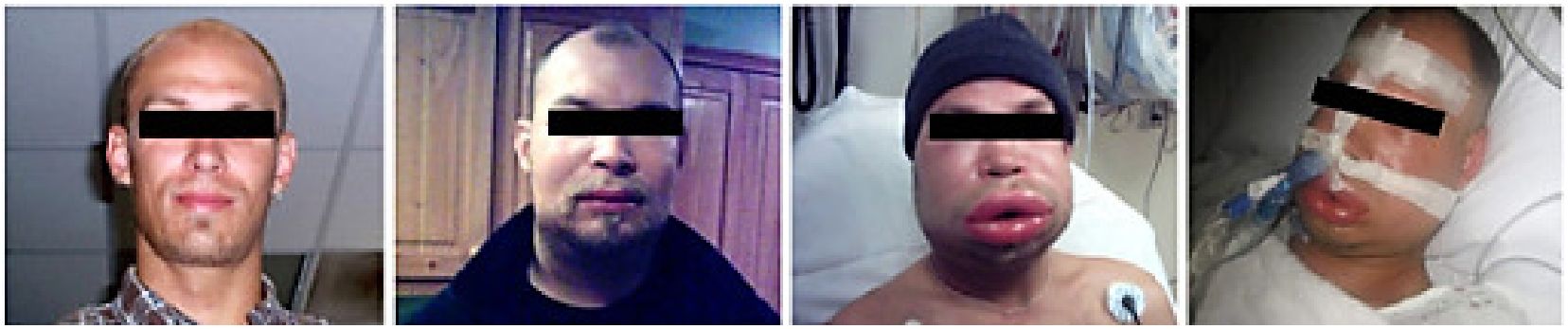
Speakers Bureau	CSL Behring, Dyax, Salix, Shire

Learning Objectives

- Recognize symptoms suggestive of hereditary angioedema (HAE)
- Differentiate HAE from other forms of angioedema
- Implement practice strategies to individualize treatment for patients with HAE

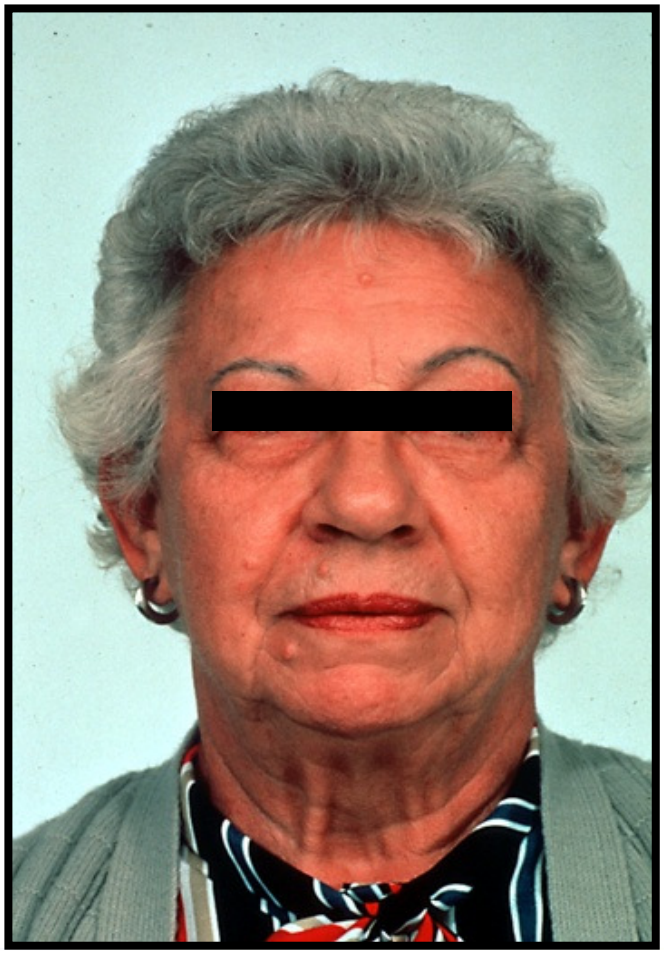
Clinical Presentation of Angioedema

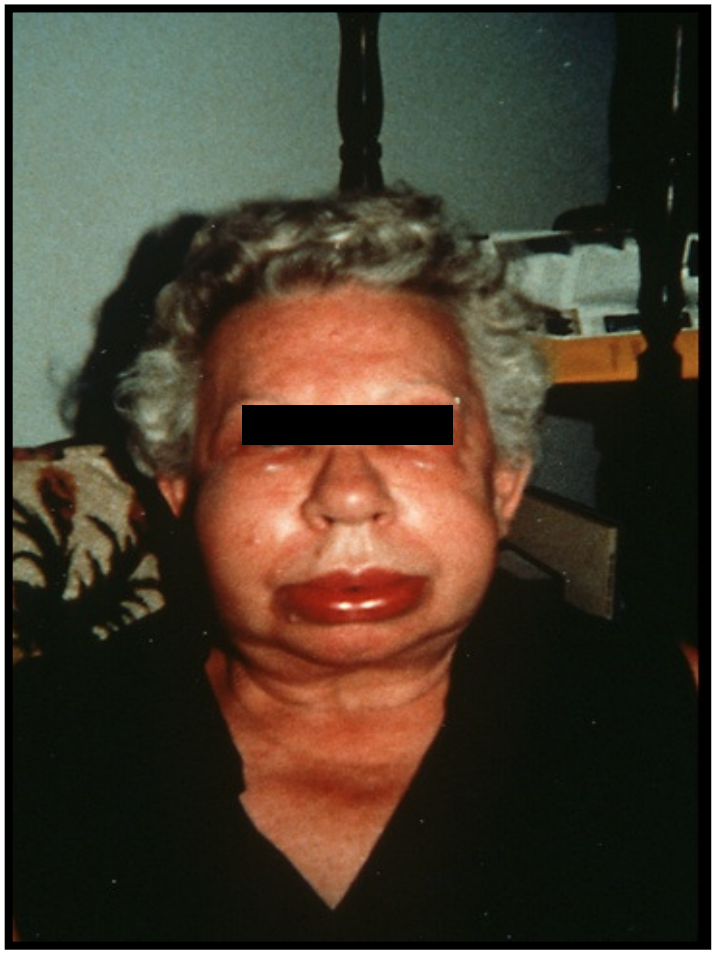
- Relatively rapid onset: minutes to hours
- Frequently asymmetric distribution
- Distribution not in dependent areas
- Among top 3 “allergic” conditions resulting in hospitalization



Source: Open*i*: HAE patient experiencing HAE attacks. Creative Commons Generic 2.0 License, https://creativecommons.org/licenses/by/2.0/. Originally from Bygum A, et al. *BMC Dermatol.* 2012;12:4.

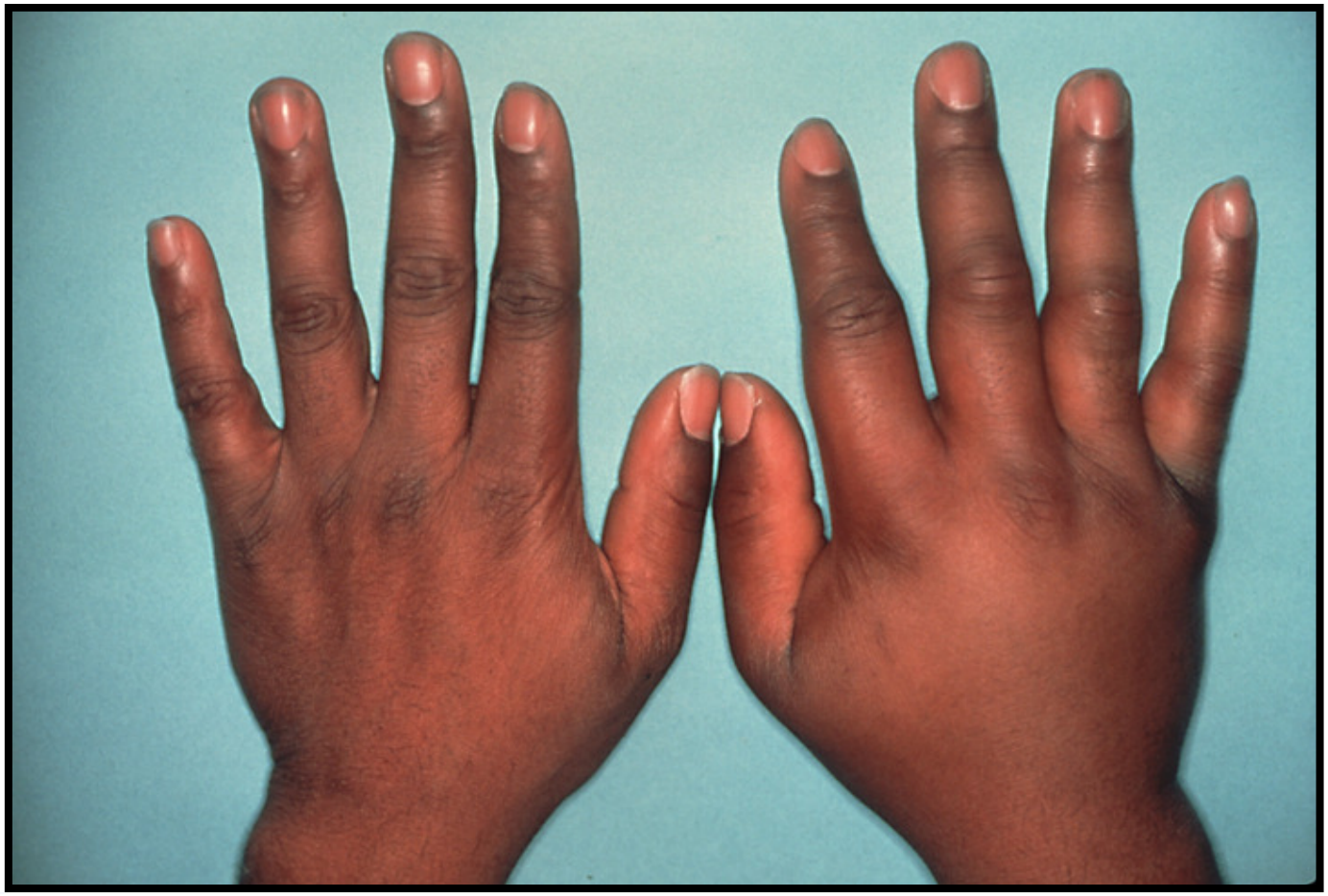
Facial Angioedema





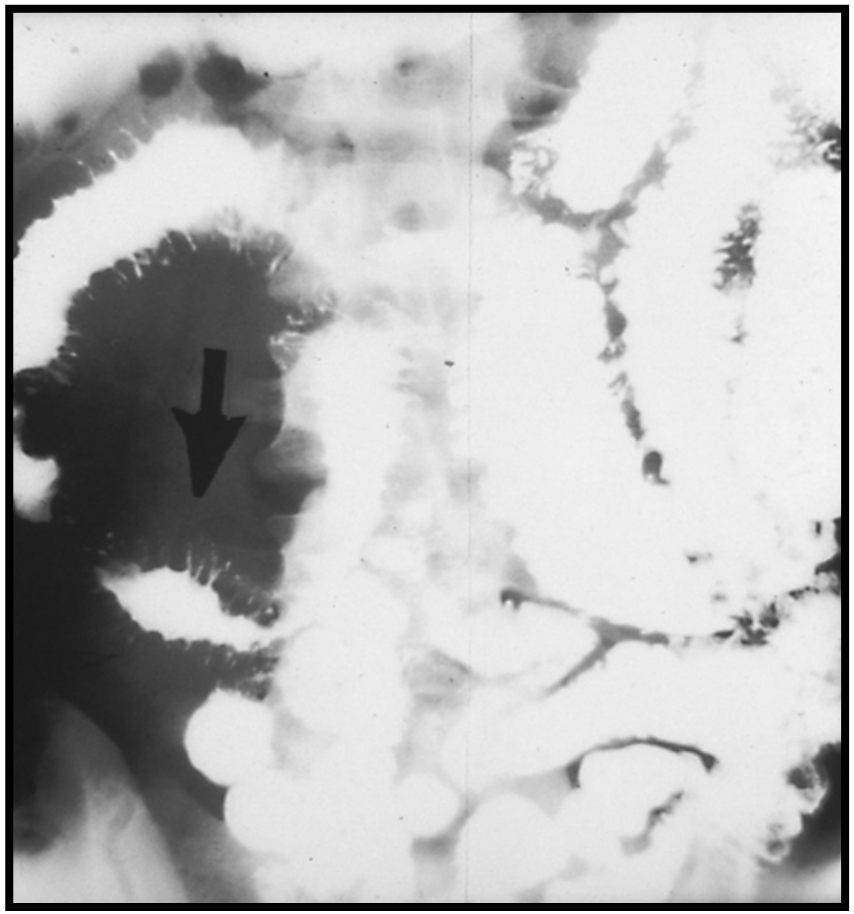
Courtesy of Michael M. Frank, MD.

Extremity Angioedema

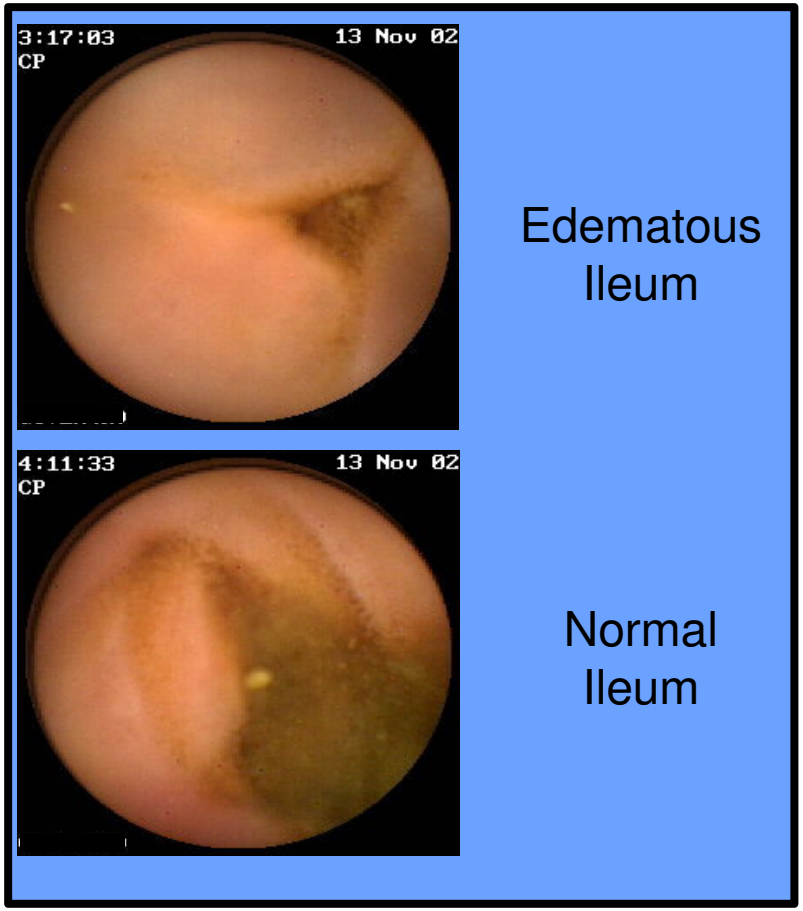


Courtesy of Michael M. Frank, MD.

Intestinal Angioedema



Frank MM, et al. *Annals Int Med*. 1976;84:580-593.



Courtesy of Marco Cicardi, MD, personal archive.

Sources:
Left: From *Annals of Internal Medicine*, Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. Volume 84, Issue 5, pages 580-93.Copyright © 1976 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.
Right: Courtesy of Marco Cicardi, MD, personal archive.

Causes of Angioedema

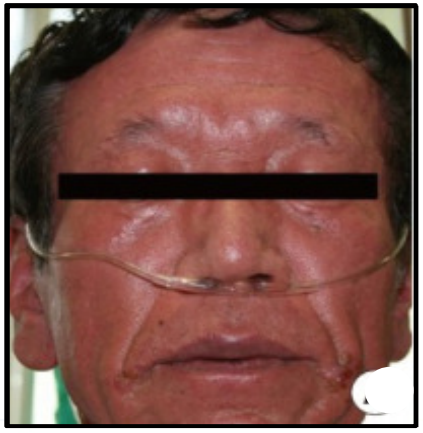
- Allergic: Foods, drugs, insect stings/bites
- Radiocontrast media
- Aspirin and other NSAIDs
- Autoimmune activity
- ACE inhibitor-induced
- Idiopathic
  - Histamine-induced/Mast cell-mediated
  - Bradykinin-induced
- C1 inhibitor (C1-INH) deficiency
  - Hereditary – Types I, II
  - Acquired
- Hereditary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

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

Etiology of Angioedema

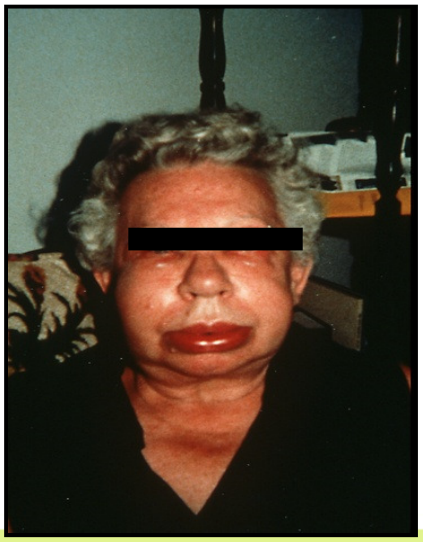
Mast-cell mediated

- Release of mast cell mediators
  - Histamine
  - Leukotriene C4
  - Prostaglandin D2
  - Heparin
- ≈90% associated with urticaria and/or pruritis



Kinin-related

- Generation of bradykinin and complement-derived mediators increase vascular permeability
- Absence of urticaria or pruritis



Sources:
Left: Open*i*; Creative Commons Attribution-Noncommercial 3.0 Unported License., https://creativecommons.org/licenses/by-nc/3.0. Modified from Lee JH, et al. *Allergy Asthma Immunol Res*. 2013;5:113-5.
Right: Courtesy of Michael M. Frank, MD.

Major Types of Angioedema

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

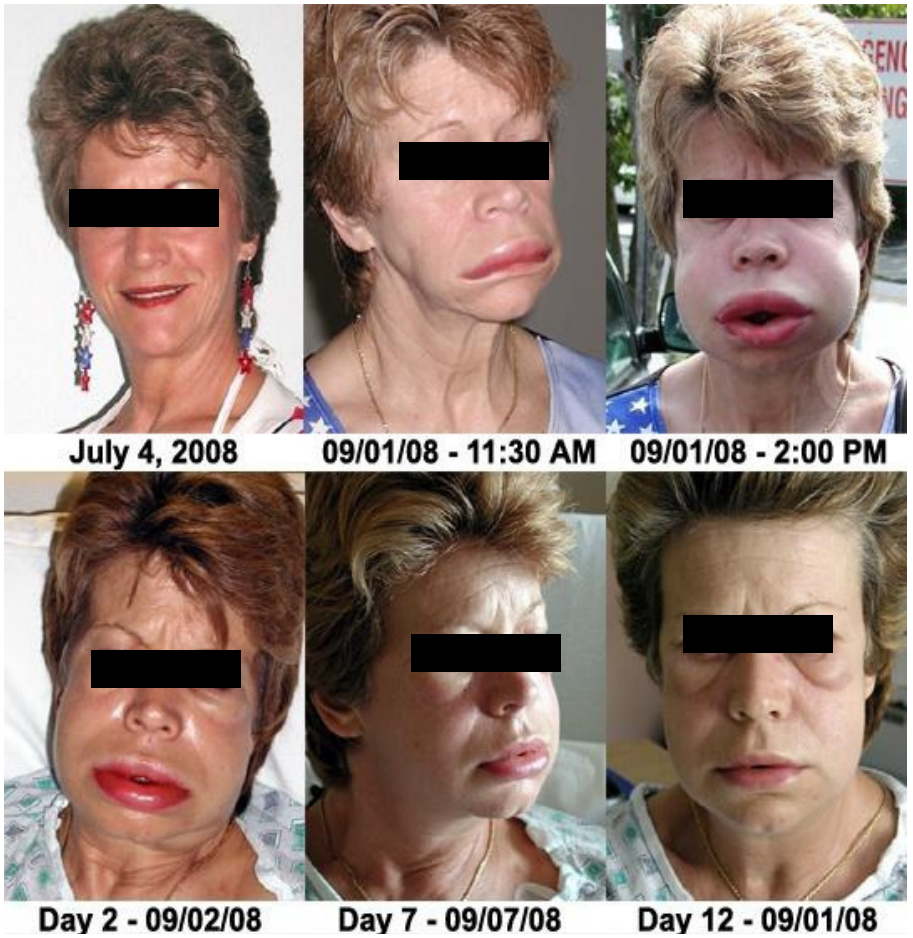
Causes of Isolated Angioedema: Study of 776 Patients

Cause*	No.	%	M:F Ratio	Age of onset	
				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-INH deficiency	197	25			
• Hereditary	183		0.88	8	1–34
• Acquired	14		1.8	56.5	42–76
Idiopathic	294	38			
• Histaminergic	254		0.56	40	7–86
• Nonhistaminergic	40		1.35	36	8–75
Peripheral/generalized edema	21	3	0.17	-	-

*Classification of angioedema without urticaria according to clinical or etiopathogenetic characteristics.
†Food, drug, insect bite, environmental allergen, or other physical stimulus.
Zingale LC, *CMAJ*. 2006;175:1065-1070.

HAE

- Potentially fatal genetic disorder associated with deficiency or dysfunction of C1-INH
- Characterized by swelling involving the deep dermis; generally localized; mildly pruritic and/or burning or painful; lasts hours to several days



Source: Hereditary Angioedema Association

Osler: Hereditary Angio-Neurotic Edema

HEREDITARY ANGIO-NEUROTIC ŒDEMA.

WILLIAM OSLER.

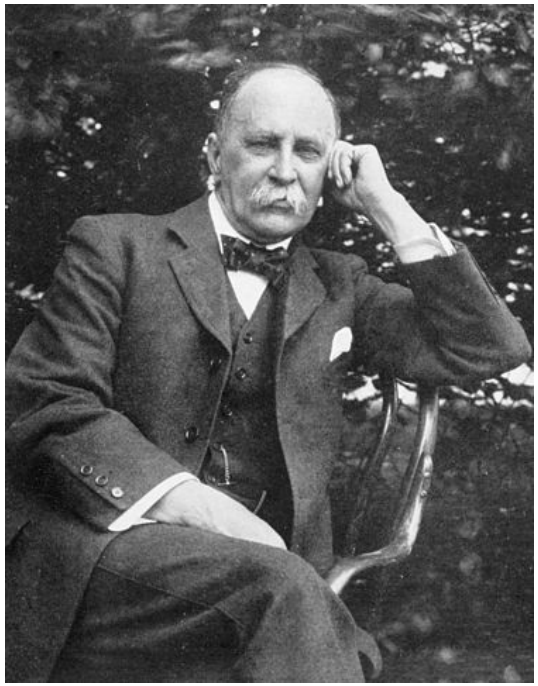
The American Journal of the Medical Sciences (1827-1924): Apr 1888: 95, 4; American Periodicals Series Online pg 362.

HEREDITARY ANGIO-NEUROTIC ŒDEMA

BY WILLIAM OSLER, M.D.,

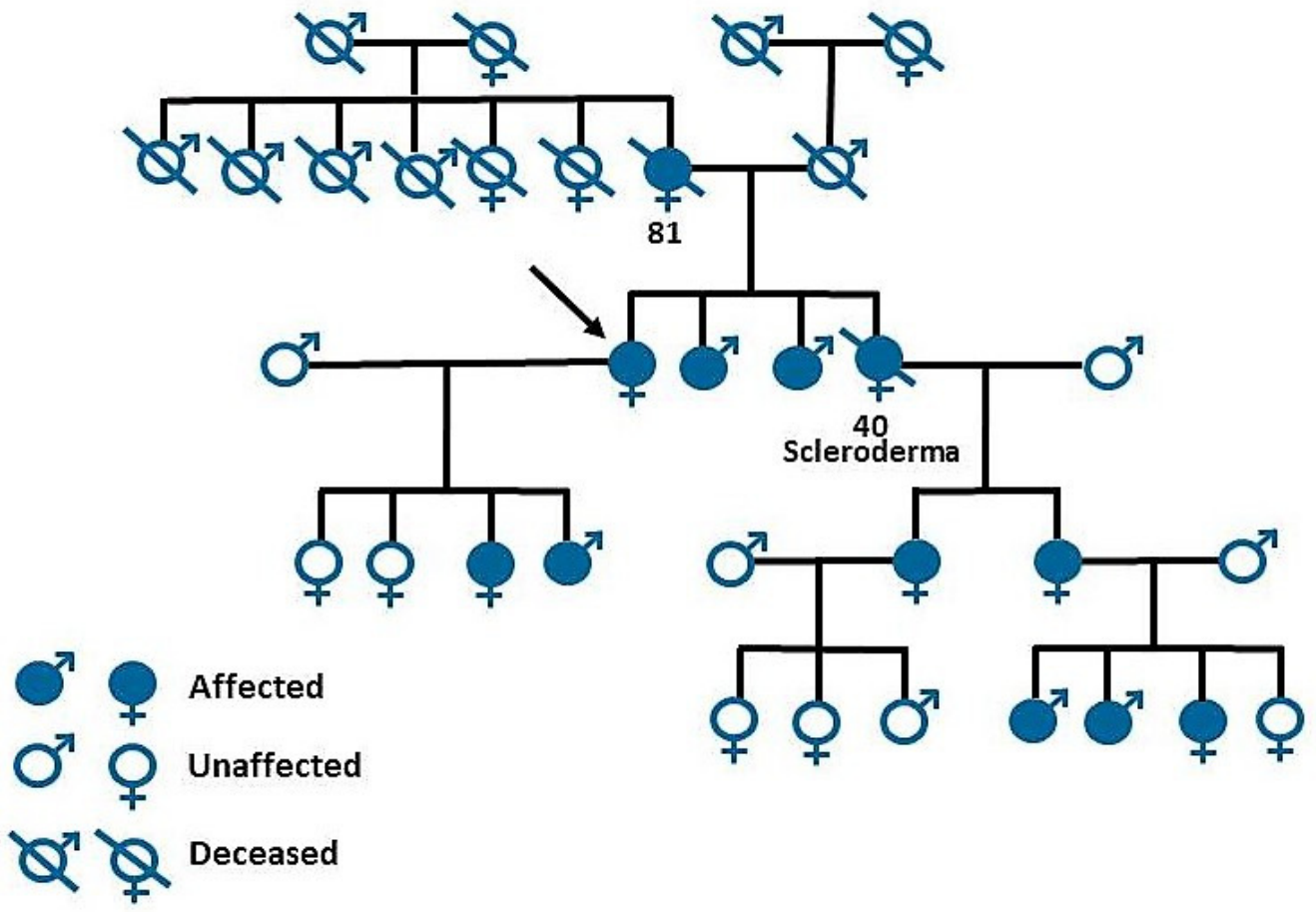
Briefly summarized, the affection in the family which I have studied has the following characteristics:

1. The occurrence of local swellings in various parts of the body, face, hands, legs, genitals, buttock, and throat. In one instance, possibly two, death resulted from a sudden *œdema glottidis*.
2. Associated with the œdema, there is almost invariably gastro-intestinal disturbance: colic, nausea, vomiting, and sometimes diarrhœa.
3. A strongly marked hereditary disposition, the disease having affected members of the family in five generations.



Osler W. *Am J Med Sci.* 1888;95:362-367.

Autosomal Dominant Disease



Frank MM, et al. *Ann Int Med*. 1976;84:580-593.

Deficiency of C1 Esterase Inhibition

VOL. 35, JULY 1963 37 AMERICAN JOURNAL OF MEDICINE

A Biochemical Abnormality in Hereditary Angioneurotic Edema*

Absence of Serum Inhibitor of C'1-Esterase

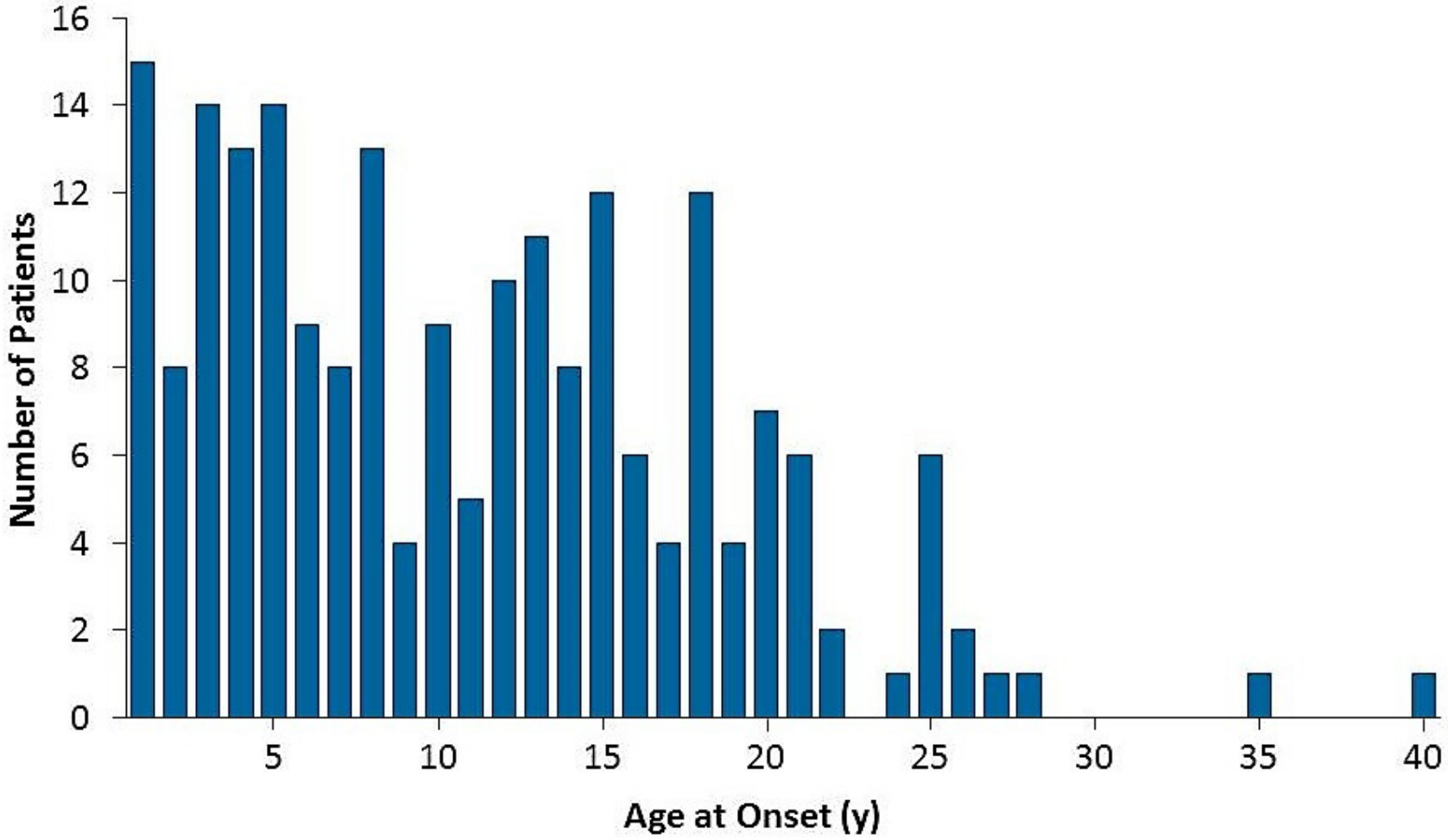
VIRGINIA H. DONALDSON, M.D.† *and* RICHARD R. EVANS, M.D.

Epidemiology of HAE

- Estimated prevalence is difficult to ascertain
  - Autosomal dominant inheritance
  - Varying estimates from 1 in 30,000 to 1 in 80,000
  - No known ethnic or gender differences
- Average attack frequency in untreated patients
  - Approximately 1 episode per 2-week period
- Disease severity is highly variable
  - Between patients and within families
  - No simple relationship between disease severity and C1-INH level

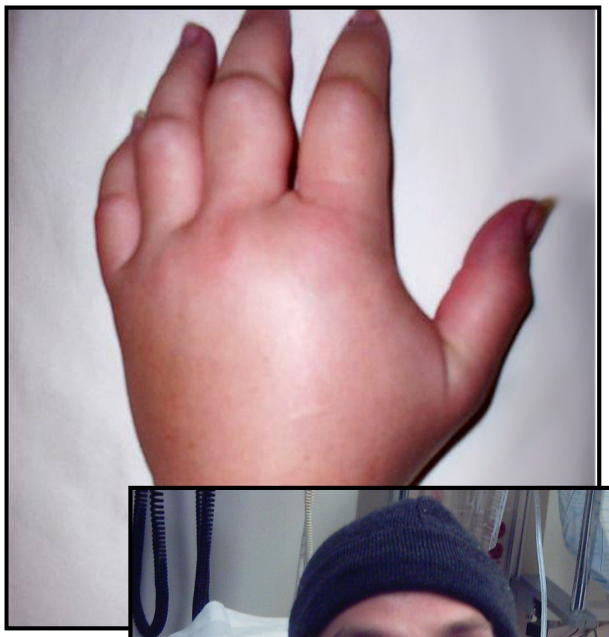
Frank MM, et al. *Annals Int Med*. 1976;84:580-593; Agostoni A, et al. *J Allergy Clin Immunol.* 2004;114:S51-S131.

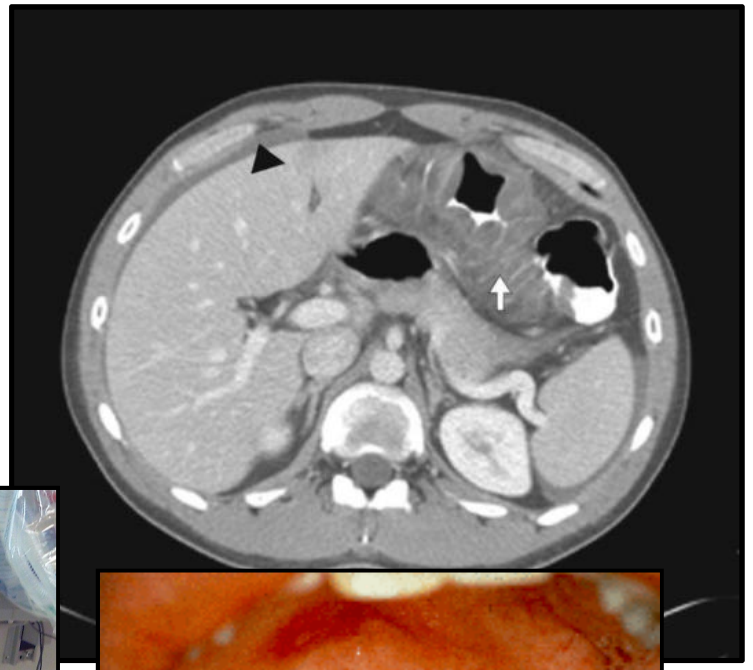
Age at Onset of HAE Attacks

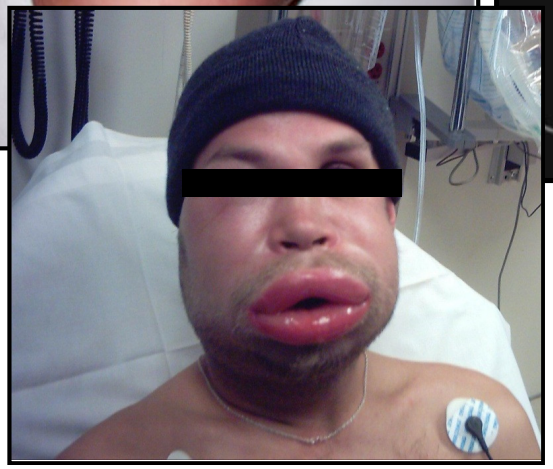


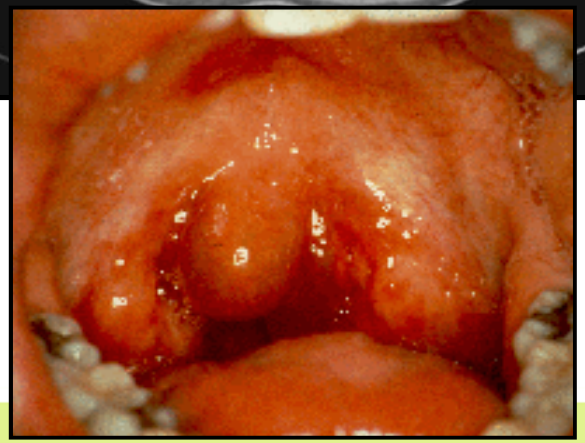
Bork K, et al. *Am J Med*. 2006;119:267-274.

HAE Symptoms









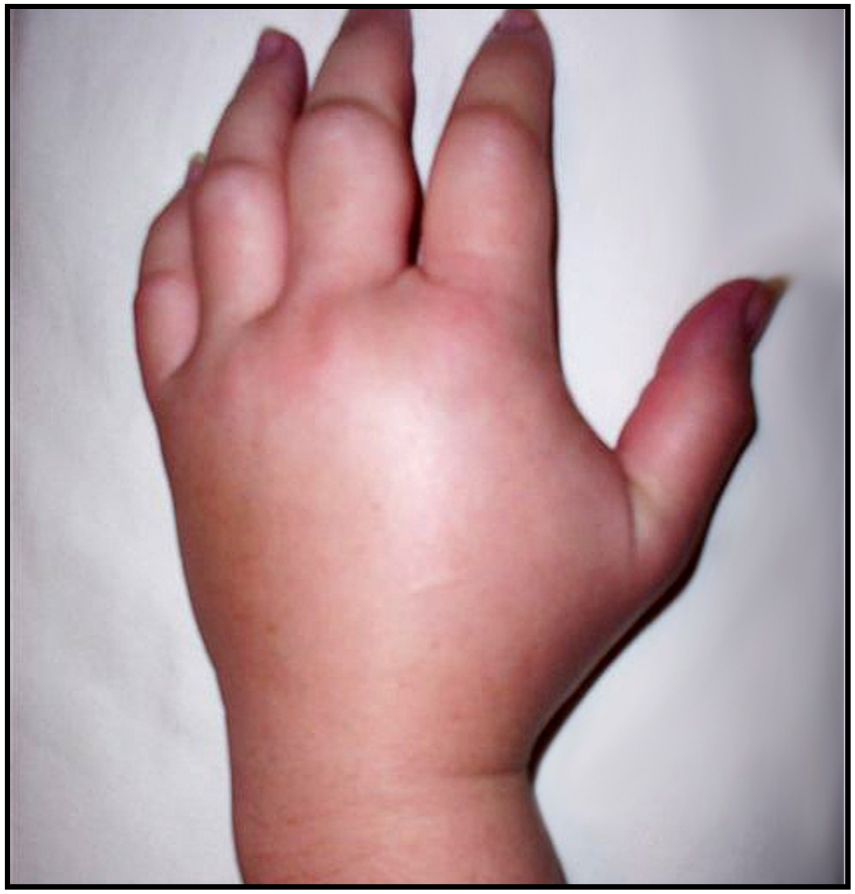
Sources:
Top left: Hereditary Angioedema Association. Commercial License purchased from HAEA Image Repository.
Bottom left: Creative Commons: HAE patient experiencing HAE attacks. Attribution Generic 2.0 License: https://creativecommons.org/licenses/by/2.0/. Modified from Bygum A, et al . *BMC Dermatol.* 2012;12:4.

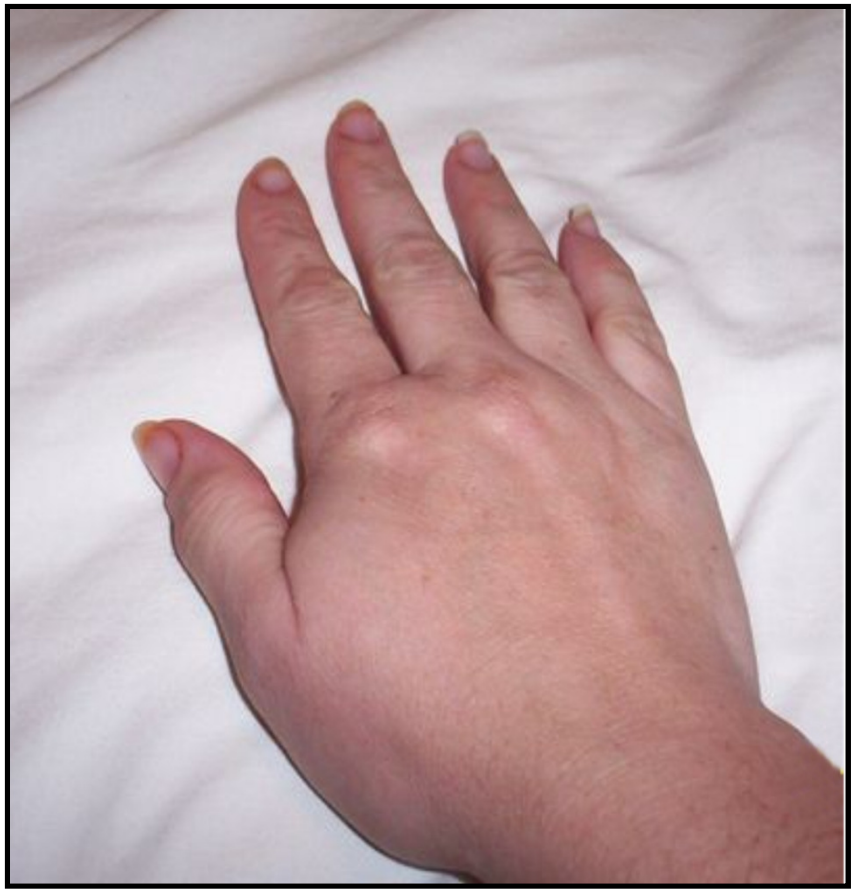
Delay in HAE Diagnosis

- Documented failure to recognize and diagnose HAE
  - 1976 survey by Frank et al. found a mean delay in diagnosis of 22 years[1]
- Delay still observed in recent survey[2]
  - Mean age at diagnosis: 16.8 years (range, 1–42 years)
  - Mean age when symptoms began: 7.8 years (range, 1–18 years)
  - Mean delay in diagnosis: 9.1 years (range, 0–32 years)
- Delay still observed in recent surveys (mean delays)
  - Denmark: 16.3 years
  - Spain: 13.1 years[4]
  - Argentina: 15.3 years[5]

1. Frank MM, et al. *Ann Intern Med*. 1976;84:580-593; 2. Zuraw BL, unpublished data;
3. Bygum A. *Br J Dermatol*. 2009;161:1153-1158; 4. Roche O, et al. *Ann Allergy Asthma Immunol.* 2005:4:498-503;
5. Romero DS, et al. *Medicina*. 2009;69:601-606.

Extremity Attacks





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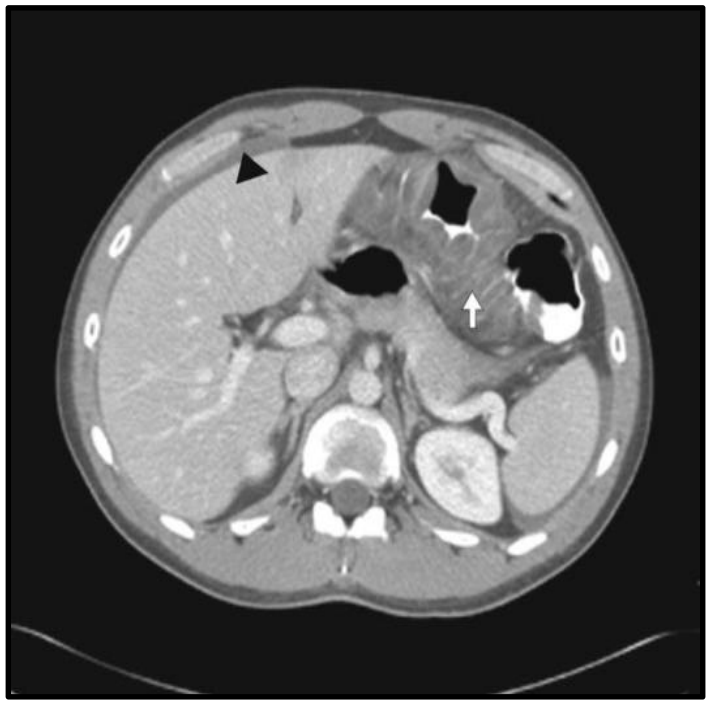
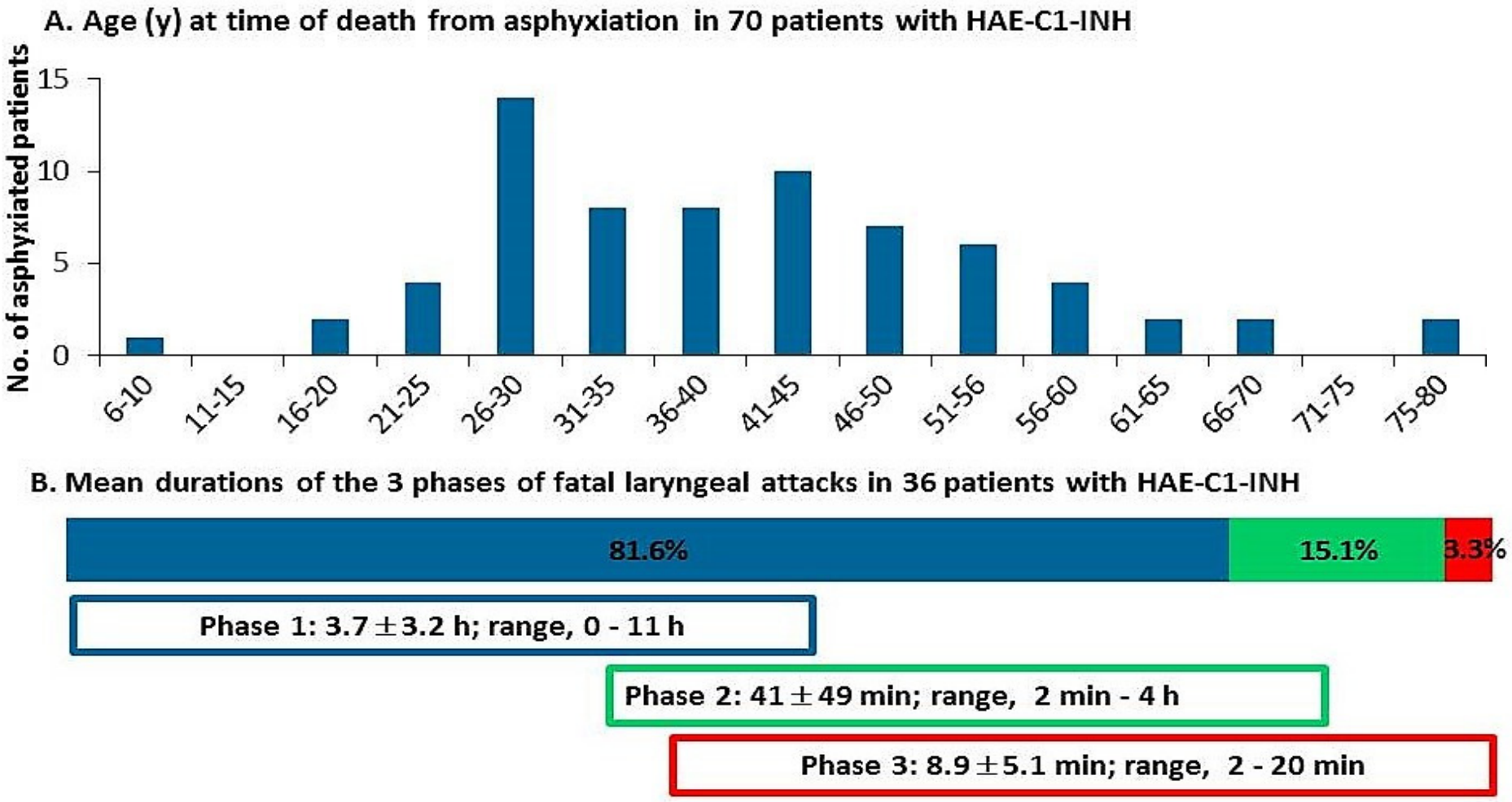
Abdominal Attacks

- Occur in 93% of patients with HAE
- Mild to severe intractable pain
- Vomiting common; constipation/diarrhea may occur
- Intestinal obstruction
- Fluid loss may lead to hypovolemic shock
- Protuberant abdomen, tenderness and rebound possible
- Symptoms mimic surgical emergencies, resulting in misdiagnosis and unnecessary surgery



Frank MM, et al. *Ann Intern Med*. 1976;84:580-593.
Agostoni A, et al. *J Allergy Clin Immunol*. 2004:114:S51-S131.
Frank MM. *Immunol Allergy Clin N Am*. 2006;26:653-668.
Agostoni A, Cicardi M. *Medicine*. 1992;71:206-215.

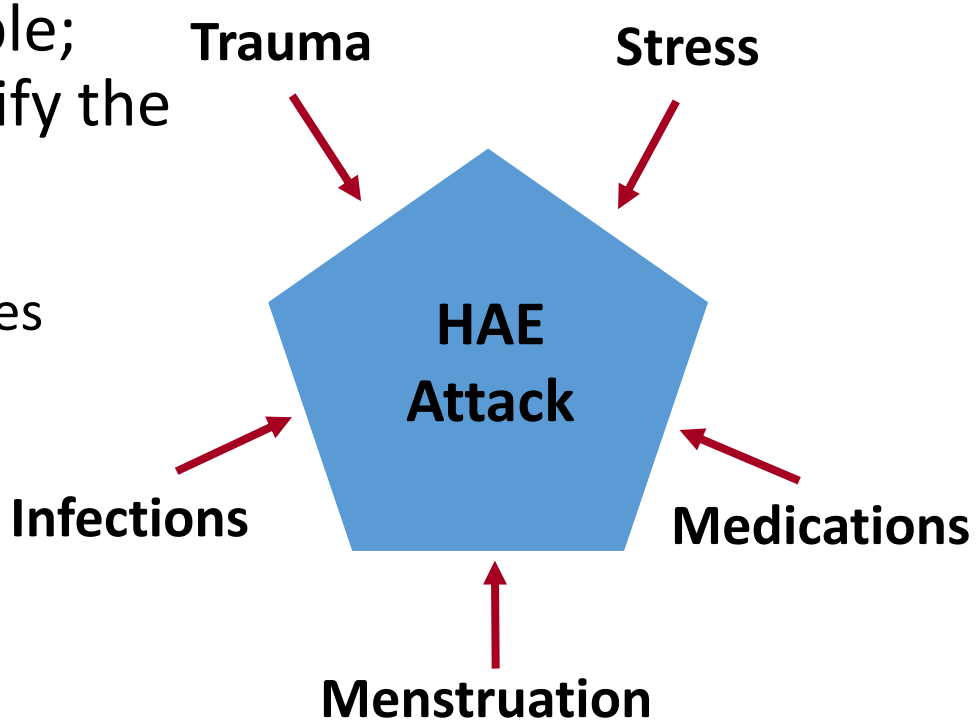
Bork et al: Laryngeal Edema Data



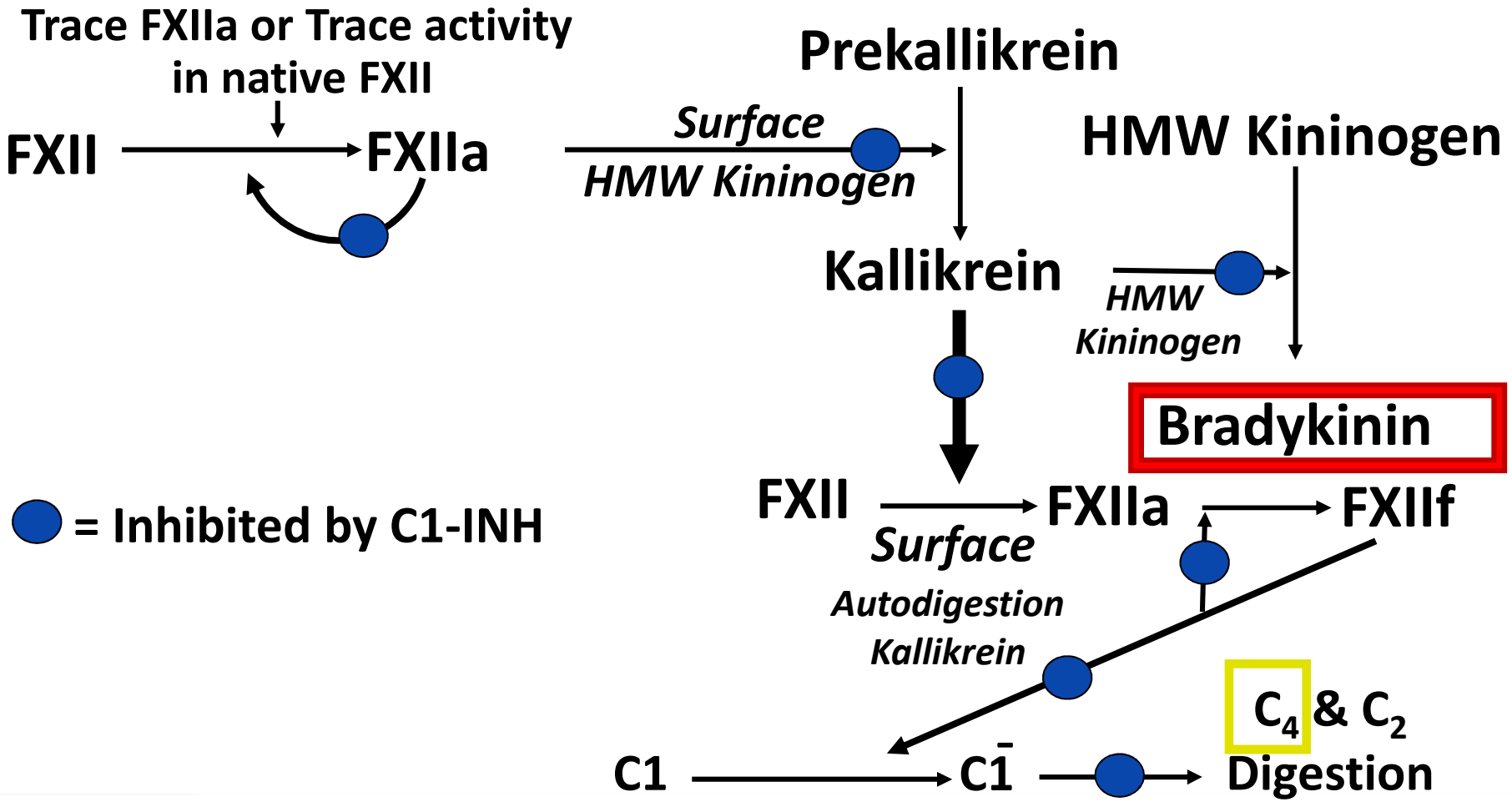
Bork K, et al. *J Allergy Clin Immunol.* 2012;130:692-697.

Triggers of HAE Attacks

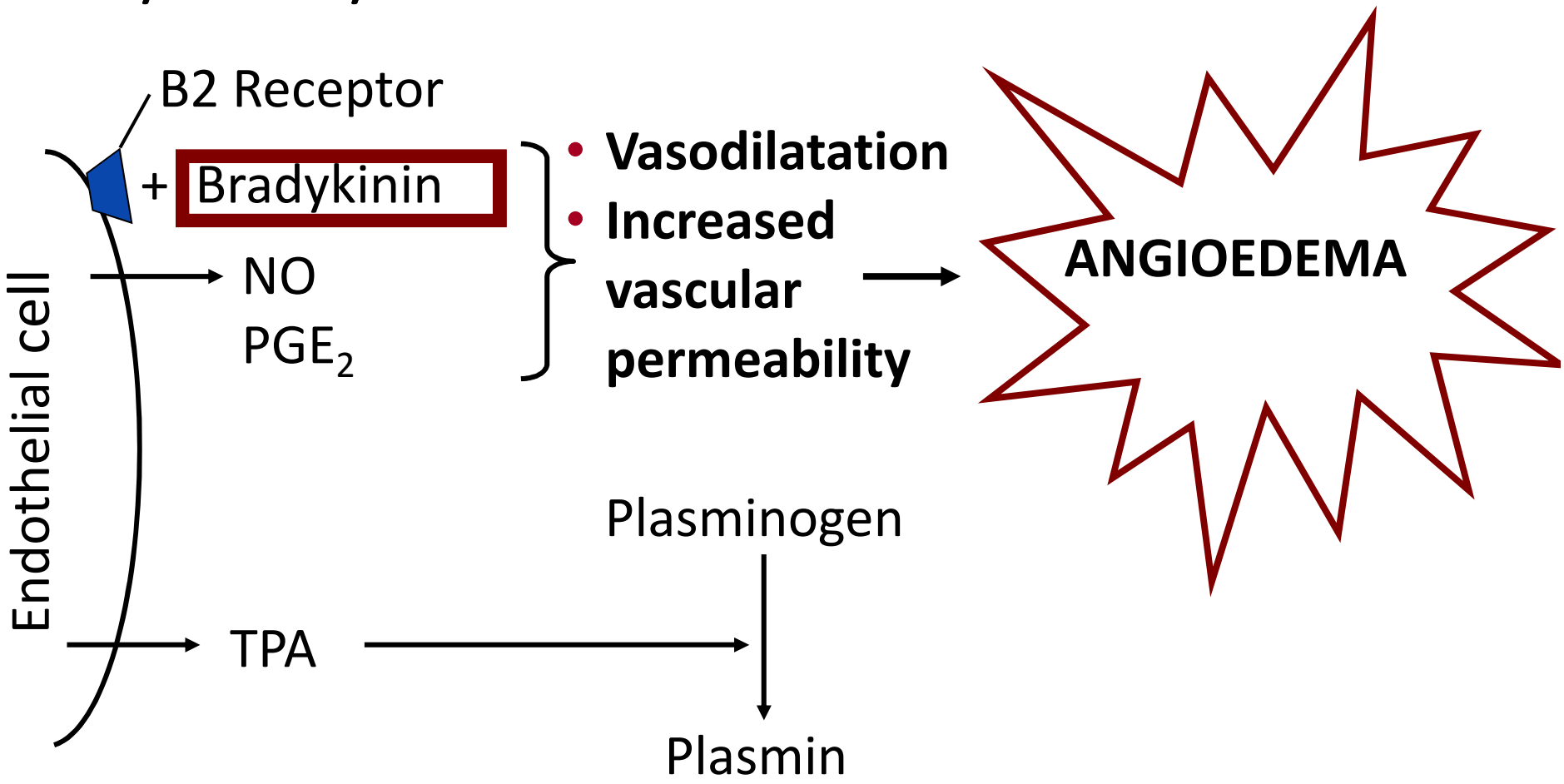
- Attacks often unpredictable; 40% of patients can identify the cause of an episode
  - Physical trauma
  - Surgical/Medical procedures
  - Infection
  - Emotional stress
  - Some medications (ACE inhibitors, oral contraceptives)
- Hormonal influence
  - Estrogens increase attack severity/frequency



Function of C1-INH



Activation of Endothelial Cells by Bradykinin



B2, Bradikinin-2 receptor; NO, nitric oxide; PGE_2, prostaglandin E_2; TPA, tissue plasminogen activator.

Zhao Y, et al. *Am J Physiol Heart Circ Physiol.* 2001;280:1821-1829.

Three Documented Types of HAE

	Type I	Type II	Type III
Percent of all HAE	~85%	~15%	Rare
C4 level	Low	Low	Normal
C1-INH antigenic level	Low	Normal	Normal
C1-INH antigenic function	Low	Low	Normal

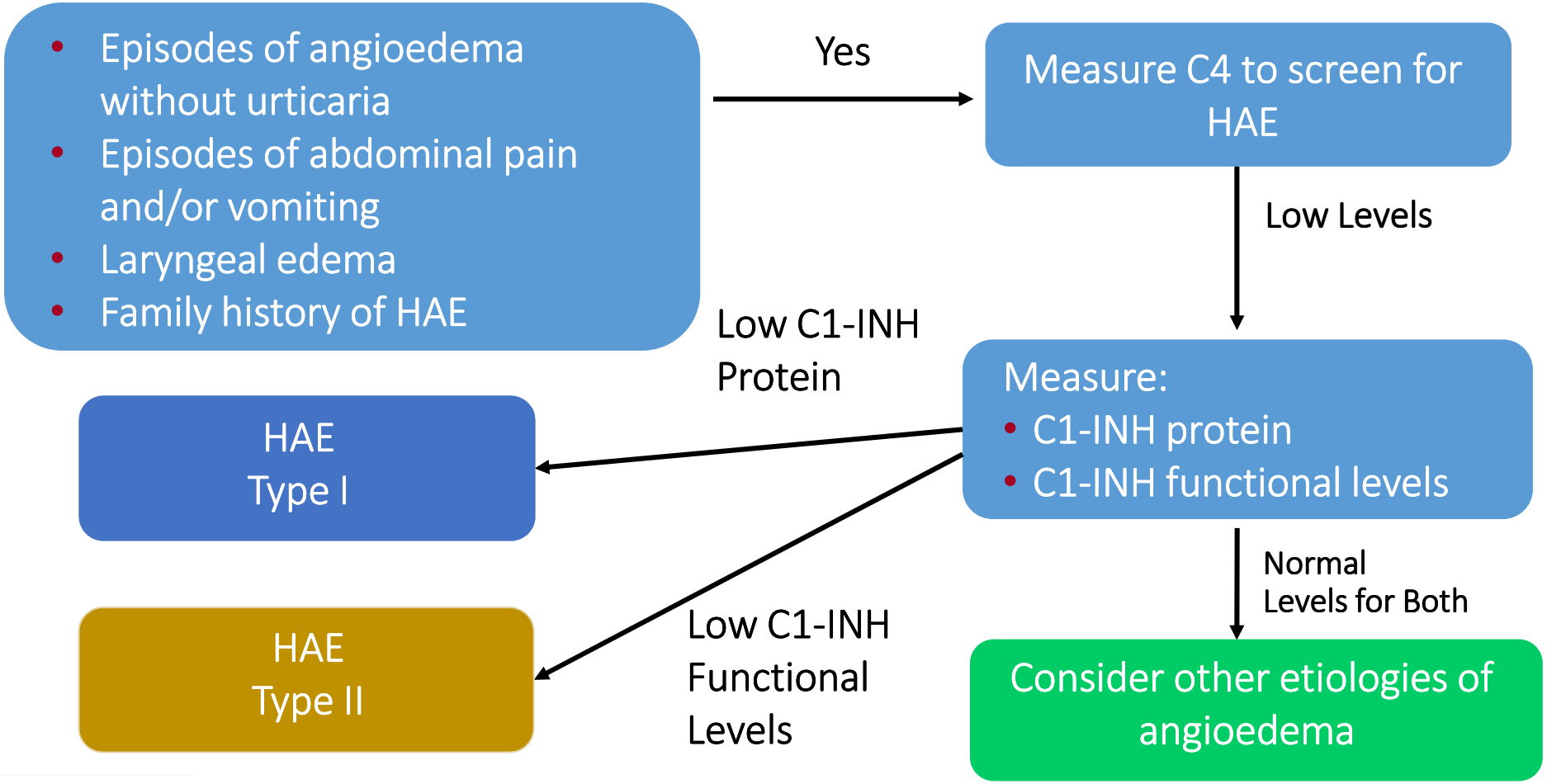
Complement Profile in Recurrent Angioedema

Type	C1-INH Function	C1-INH Level	C4 Level	C3 Level	C1q Level
HAE Type I	L	L	L	N	N
HAE Type II	L	N-H	L	N	N
HAE with normal C1-INH	N	N	N	N	N
Acquired C1-INH I/II	L	L	L	L-N	L
ACE-I associated angioedema	N	N	N	N	N
Idiopathic angioedema	N	N	N	N	N

L = Low; N = Normal; H = High

Zuraw BL, et al. *J Allergy Clin Immunol*. 2013;131:1491-1493.

Algorithm for Diagnosis of HAE



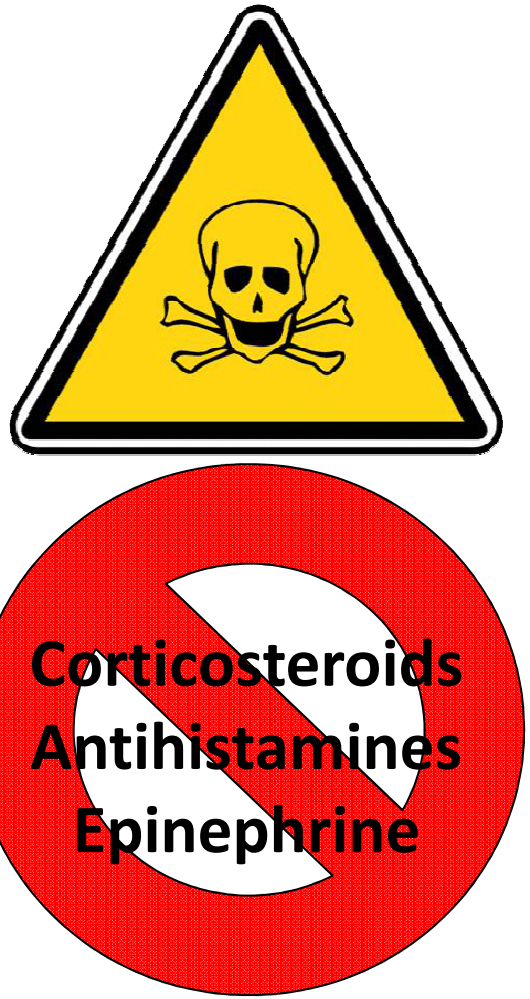
Bowen T, et al. *Allergy Asthma Clin Immunol*. 2010;6:24.

Treatment of HAE: Two Conceptual Approaches

- Treatment of acute attacks
  - Terminate ongoing attack
  - Prevent morbidity and mortality
- Prophylactic therapy
  - Minimize attack frequency and severity
  - Prevent hospitalizations and emergency room visits

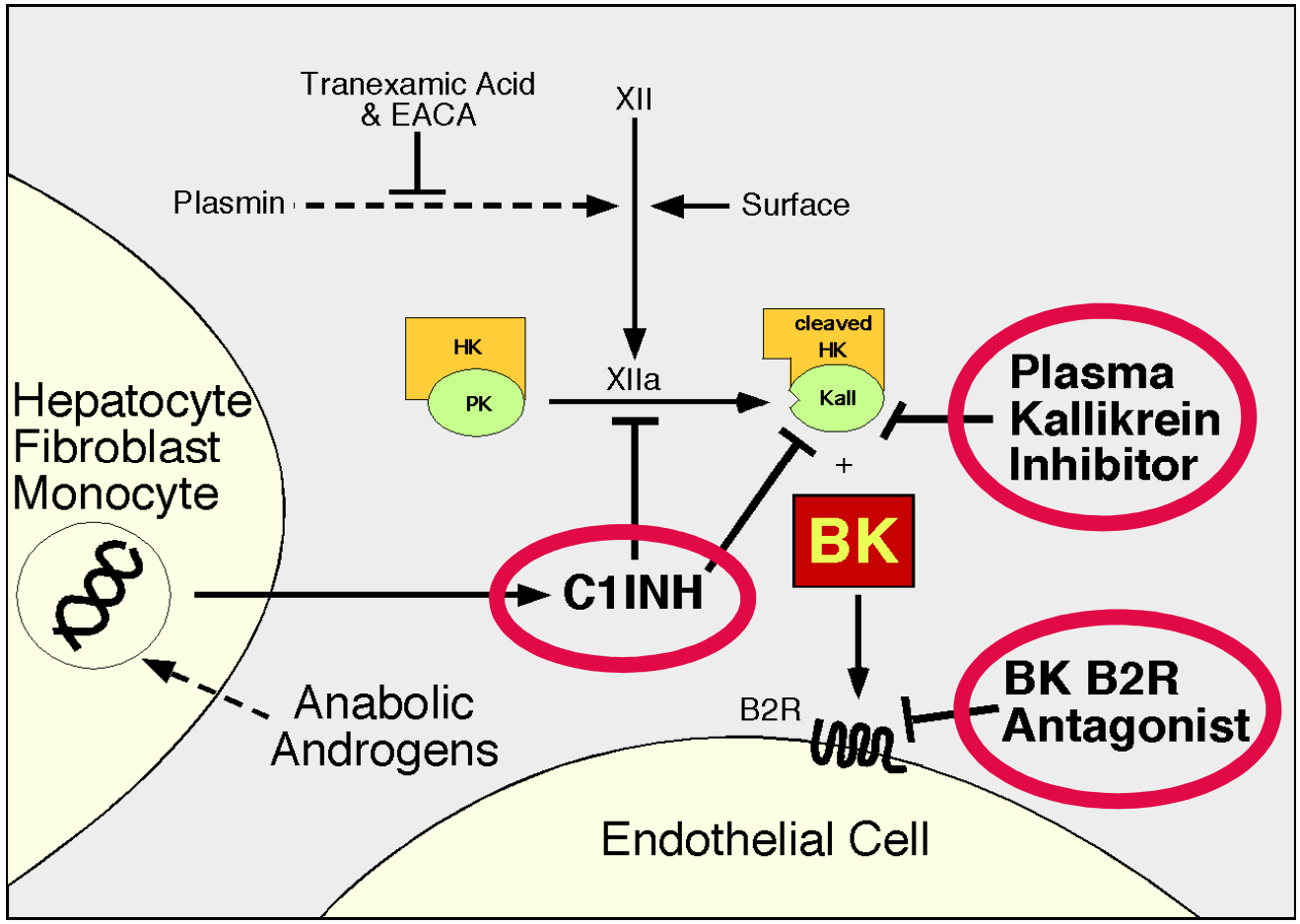
Historical Treatment of HAE Attacks

- Until late 2009, no effective FDA-approved therapy for acute attacks
  - Supportive therapy only
- Extremity attacks
  - No effective treatment available
- Gastrointestinal attacks
  - Relief of pain and nausea
  - Aggressive fluid replacement hydration
- Oropharyngeal attacks
  - Hospitalize with careful observation
  - Timely intubation, if necessary
  - Be prepared for tracheostomy
- Fresh-frozen plasma: ***Caveat lector***



Zuraw BL. *N Engl J Med*. 2008;359:1027-1036.

Newer Therapies for HAE

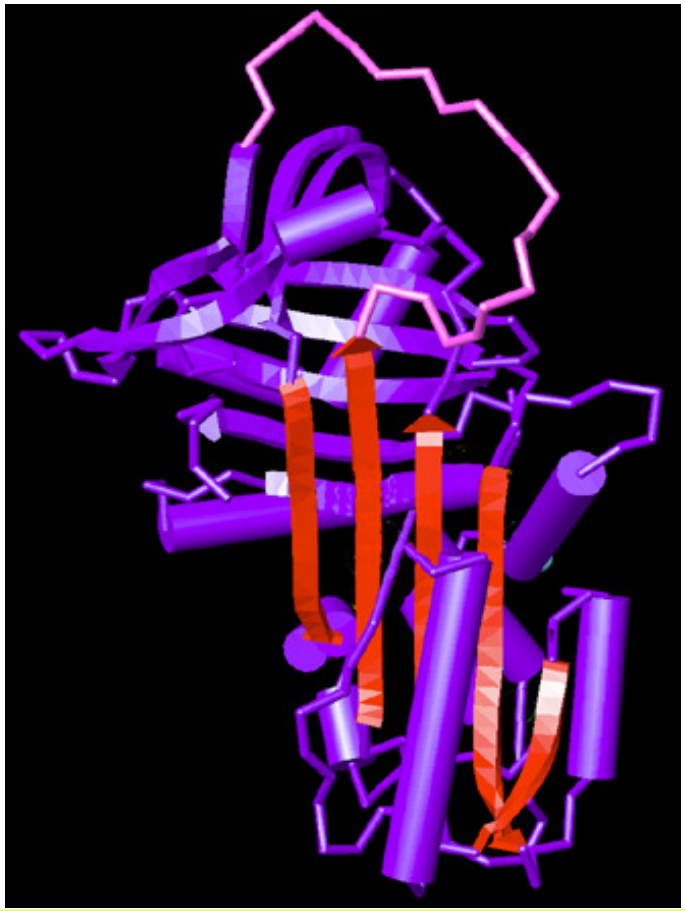


B2R, B_2-receptor; BK, bradykinin; EACA, epsilon-aminocaproic acid; HK, high-molecular-weight kininogen; PK, prekallikrein.
Zuraw BL. *Immunol Allergy Clin North Am*. 2006;26:691-708.

C1-INH Replacement Therapy

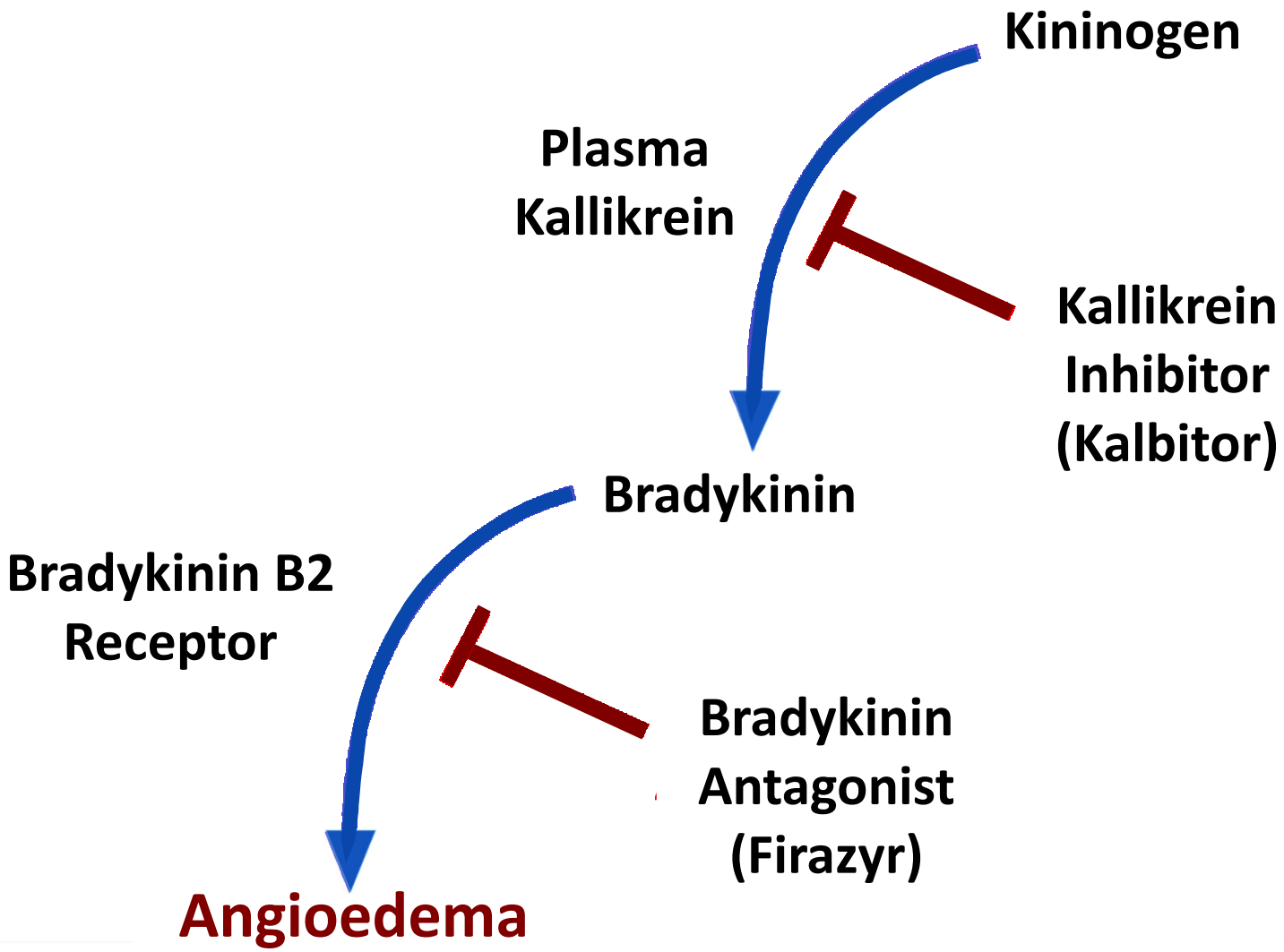
Three C1-INH products investigated for acute attacks and long-term prophylaxis in HAE

- Plasma-derived C1-INH (Cinryze®)
- Plasma-derived C1-INH (Berinert®)
- Recombinant human C1-INH (Ruconest®)



Adapted from Zuraw BL, Herschbach J. *J Allergy Clin Immunol*. 2000;105:541-546.

Targeting Bradykinin



Comparison of Acute HAE Therapies

Drug	Potential Safety Concerns	Disadvantages	Advantages	Status
Plasma-derived C1-INH	• Infectious risk • Potential infusion reactions	• Needs IV access • Dependent on plasma supply	• Extensive clinical experience • Relatively long half-life	• Berinert®: Approved in the US and many other countries for HAE acute treatment[1] • Cinryze®: Approved in the US for HAE long-term prophylactic therapy; in Europe for acute and prophylactic treatment[2,3]
Recombinant C1-INH	• Potential hypersen-sitivity	• Needs IV access	• No human virus risk • Scalable supply	• Rhucin®/Ruconest®: Approved in the US and Europe for HAE acute treatment[4]

1. Berinert [package insert]. Kankakee, IL: CSL Behring LLC; 2015; 2. Cinryze [package insert]. Lexington, MA: Shire ViroPharma Incorporated; 2014; 3. Cinryze [Summary of Product Characteristics]. Brussels, Belgum: Shire Services BVBA; 2015; 4. Ruconest [package insert]. Leiden, The Netherlands; Pharming Technologies: 2015.

Comparison of Acute HAE Therapies

Drug	Potential Safety Concerns	Disadvantages	Advantages	Status
Ecallantide[1]	• Allergic reactions • Antibody formation	• Requires administration by a healthcare provider	• No infectious risk • Subcutaneous administration	• Kalbitor®: Approved in the US for acute HAE therapy[1]; currently not approved in Europe
Icatibant[2]	• Local injection reactions		• No infectious risk • Stable at room temperature • Subcutaneous administration	• Firazyr®: Approved in the US and many other countries for acute HAE therapy[2]

1. Kalbitor [package insert]. Burlington, MA: Dyax Corp; 2015; 2. Firazyr [package insert]. Lexington, MA: Shire; 2015.

Long-Term Prophylactic Treatment for HAE

- Does the patient require long-term prophylaxis?
  - Not all HAE patients
  - Need varies by individual
    - Frequency, severity, and type of attacks
    - Availability of care
    - Failure of on-demand therapy
- Modalities
  - Anabolic androgens (attenuated or impeded)
  - C1-INH replacement
  - Antifibrinolytics
  - Progestin

Acute treatment should be available for ALL patients on prophylaxis

Comparison of Prophylactic Therapies: Attenuated Androgens and C1-INH

Drug	Potential Side Effects	Disadvantages	Advantages	Contraindicated Populations
Attenuated androgens[1]	• Weight gain • Liver damage • Hyperlipidemia • Hepatocellular carcinoma • Mood changes	• Adverse effects	• Low cost • Oral administration	• Pregnant women • Children
C1-INH[2]	• Potential for blood-borne pathogens • Port thrombosis and infection	• Intravenous access • High cost	• Replaces missing (Type I HAE) or abnormally functioning (Type II HAE) C1-INH	• Hypersensitivity to blood products

1. Danazol [package insert]. North Wales, PA: Teva Pharmaceuticals; 2015; 2. Cinryze [package insert]. Lexington, MA: Shire ViroPharma Incorporated; 2014.

Guidelines on Management of HAE

- International Consensus Algorithm for the Diagnosis, Therapy and Management of Hereditary Angioedema[1]
- Hereditary Angioedema International Working Group (HAWK): Evidence-based treatment consensus publication[2]
- WAO Guideline for the Management of Hereditary Angioedema[3]
  International Consensus on Hereditary and Acquired Angioedema[4]
- US Hereditary Angioedema Association Medical Advisory Board Consensus Document[5]

1. Bowen T, et al. *Allergy Asthma Clin Immunol* 2010;6:24; 2. Cicardi M, et al. *Allergy* 2012;67:147–57; 3. Craig T, et al. *World Allergy Organis J.* 2012;5:182–199; 4. Lang DM, et al. *Ann Allergy Asthma Immunol.* 2012;109:395–402; 5. Zuraw BL, et al. *J Allergy Clin Immunol Pract.* 2013;1:458–467.

HAE Guidelines

- Consensus documents
  - Efforts to move from expert opinion to evidence-based recommendations
- High-quality evidence lacking in some areas
- Provide guidance for management, not rigorous rules or protocols

HAE Guidelines: Areas of Agreement

- On-demand treatment necessary for every HAE patient
  - Must be reliably and efficiently accessible
  - Includes patients receiving long-term prophylaxis
- All or nearly all attacks eligible for treatment
- Laryngeal attacks uniquely life-threatening and require special attention
- Early treatment of attacks beneficial in reducing morbidity and complications
- Prophylactic therapy indicated for patients in whom on-demand treatment alone is unsatisfactory

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HAE Guidelines: Areas Lacking Clarity

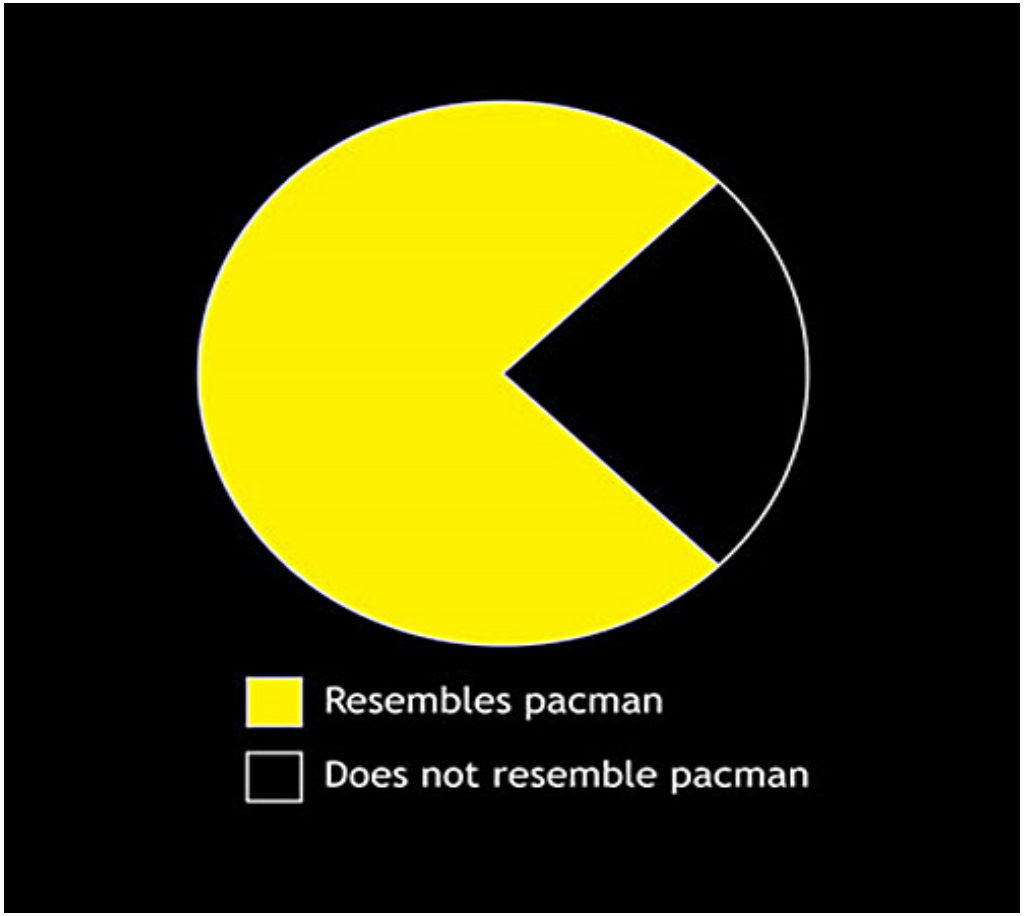
- Specific indications for prophylaxis
- "Preferred" agents for prophylactic or acute HAE treatment
  - Exception is special populations: pediatrics, pregnancy

Considerations for Routine Prophylaxis vs Acute Treatment Alone

- Nature of HAE symptoms
  - Frequency
  - Severity
  - Rapidity of onset and progression
  - Anatomical location
  - Level of functional impairment
  - Degree of psychological impact
- Availability of a rapid, efficient acute treatment plan
- Impact of HAE on work or school
- Restoring “normalcy” to daily life

Craig T, et al. *World Allergy Organ J.* 2012;5:182–199; Cicardi M, et al. *Allergy* 2012;67:147–157.

The Science and the Art of Medicine



Individualization of HAE Therapy

Patient factors

- Attack frequency
- Rapidity of progression
- Laryngeal attacks
- Access to medical care
- History of frequent hospitalization
- Treatment complications

Medication factors

- Efficacy
- Safety
- Administration route
- Patient preference/ tolerability
- Administration location
- Source
- Cost

Components of a Comprehensive Treatment Plan: Essentials of Modern HAE Therapy

1. Acute treatment plan for every patient
2. Routine prophylaxis for some patients
3. Logistics of treatment plan
4. Monitoring for efficacy and side effects

Acute Treatment Plan

- Essential for every person/family with HAE
- Tailored to individual circumstances
- Rapidly and efficiently accessible
- Choices
  - Medication
  - Administration location(s)
  - Self-administration
- Develop a “back-up” plan
- Equip patient to navigate the health care system

Riedl MA. *Immunol Allergy Clin N Am.* 2013;33:471–485.

Acute Treatment Plan Logistics

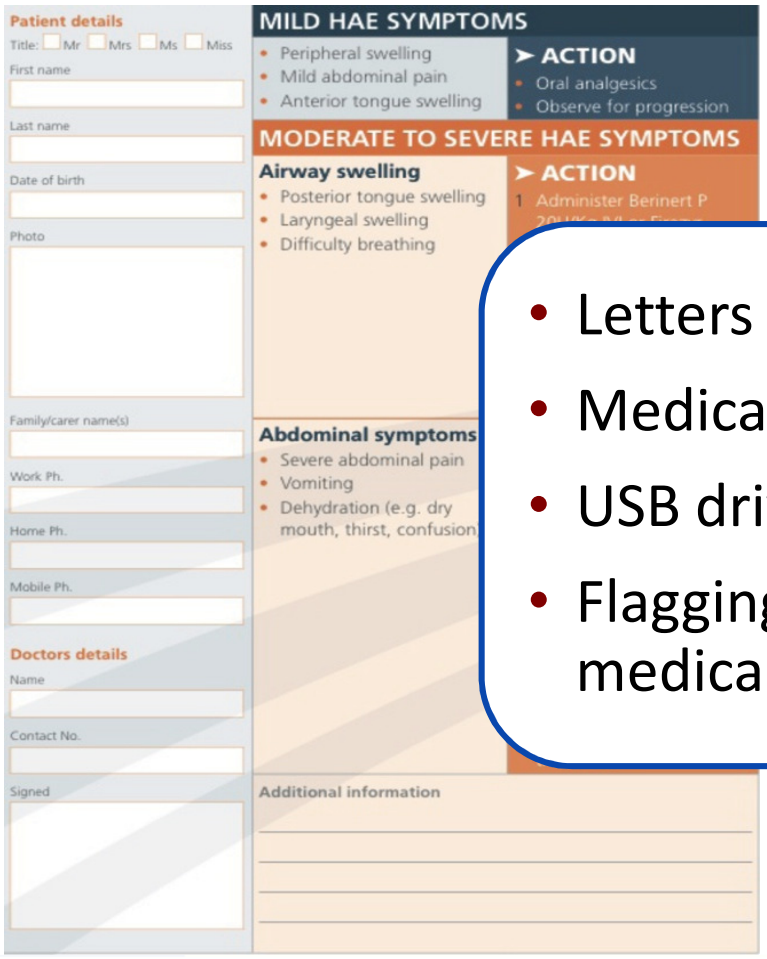
Reliable, accessible and efficient

- Self-administration
- Intravenous infusions
- Subcutaneous injections
- Personal comfort level
- Education/technical instruction
- Family or friend assistance
- Medication labeling

- Home health nursing “on call”
- Hospital-based acute care
  - “Brown-bagging” medication

What works best for the patient?
Is the plan reliable?

Hereditary Angioedema Action Plan



Patient details

Title: Mr Mrs Ms Miss

First name

Last name

Date of birth

Photo

Family/carer name(s)

Work Ph.

Home Ph.

Mobile Ph.

Doctors details

Name

Contact No.

Signed

MILD HAE SYMPTOMS

- Peripheral swelling
- Mild abdominal pain
- Anterior tongue swelling

➤ **ACTION**

- Oral analgesics
- Observe for progression

MODERATE TO SEVERE HAE SYMPTOMS

Airway swelling

- Posterior tongue swelling
- Laryngeal swelling
- Difficulty breathing

➤ **ACTION**

1 Administer Berinert P

Abdominal symptoms

- Severe abdominal pain
- Vomiting
- Dehydration (e.g. dry mouth, thirst, confusion

Additional information

- Letters
- Medical ID bracelets
- USB drives
- Flagging the electronic medical record

Date

To Whom It May Concern:

Ms./Mr. _____ has been diagnosed with Hereditary Angioedema (HAE) and is under my care to treat her/his condition. This genetic condition leads to sporadic episodes of cutaneous, intestinal, and/or a that may be severely disabling and life-

HAE attacks requires one of the following stered as quickly as possible to abort

1000-2000 units intravenously tor) 30 mg subcutaneously 30 mg subcutaneously

medications may be necessary in the event ecurring angioedema symptoms.

tion, management of acute attacks may with airway monitoring, analgesic and nd intravenous fluids as appropriate. **rticosteroids are not effective in treating ed form of angioedema.** Epinephrine may ng measure for significant laryngeal edema, mise requires immediate dosing of the sted above and careful monitoring.

It is medically necessary that the patient carry the listed HAE medications and related treatment supplies while traveling.

I may be reached with any questions regarding this condition at XXX-XXX-XXXX.

Sincerely,

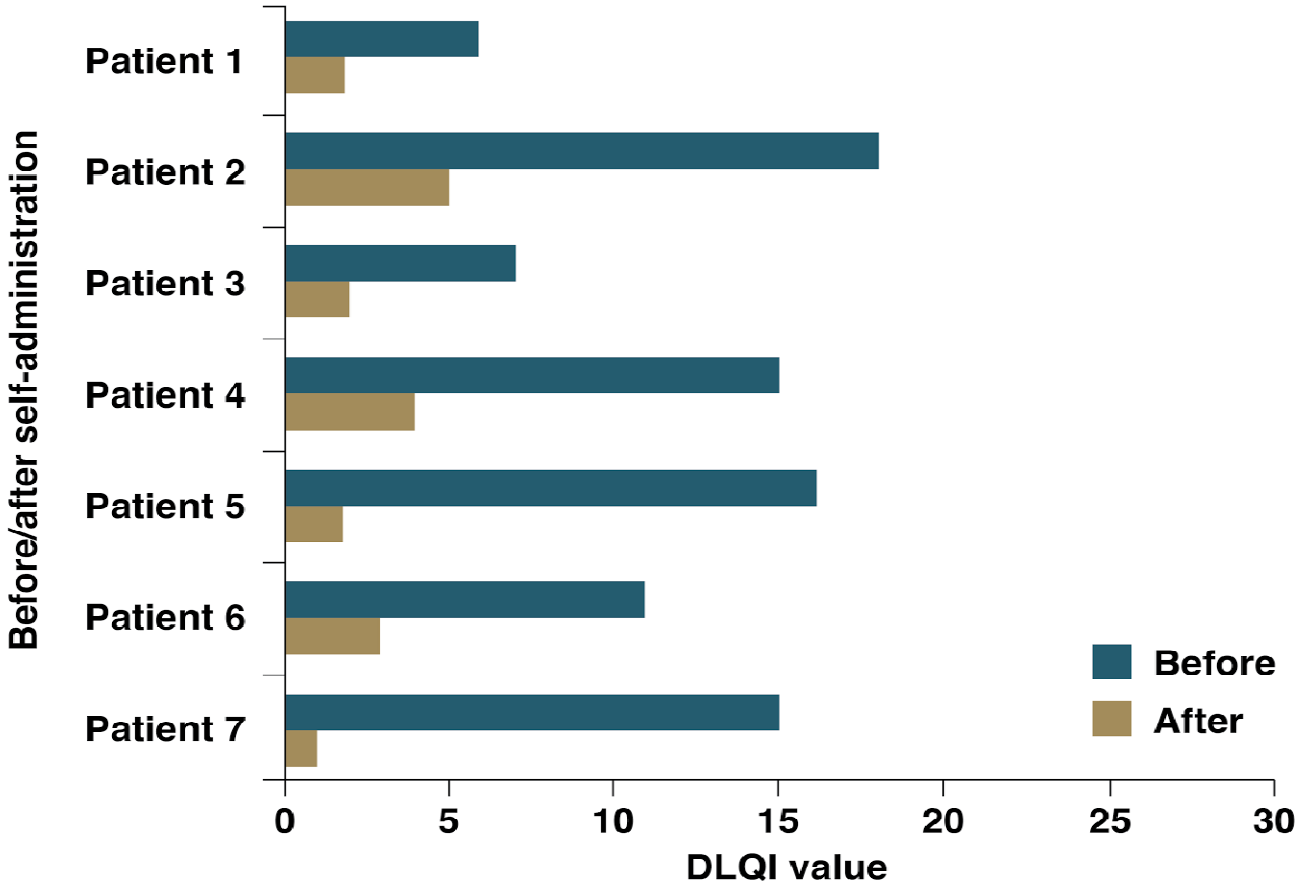
Courtesy of Dr. Connie Katelaris.

Home Administration of HAE Therapy

- Demonstrated benefits with proper implementation:
  - Increased QoL, flexibility & convenience
  - Decreased time to treatment, severity/duration of attacks
- Considerations:
  - Individual patient
  - Route of administration
  - Training programs
  - Counseling/consent

Longhurst H, et al. *Allergy Asthma Clin Immunol*. 2010;6:22; Levi M, et al. *J Allergy Clin Immunol*. 2007;117:904–908; Dagen C, Craig T. *Allergy Asthma Clin Immunol.* 2010;6:11; Bygum A, et al. *Eur J Dermatol*. 2009;19:147–151; Kreuz W, et al. *Transfusion*. 2009; 49;1987–1995.

Improved QoL with Self-Administered Therapy



Bygum A, et al. *Eur J Dermatol.* 2009;19(2):147–151.

Monitoring for Efficacy and Side Effects

- Known and unknown risks of medications
  - Androgens
  - Plasma products
  - Local and systemic treatment reactions
  - IV access issues
- Individual patient variability in response to therapies
- HAE is a complex, highly-variable, chronic condition
  - Benefits of periodic monitoring

Challenges in Practice with the Treatment of Acute Attacks of HAE

- Patient not understanding risks associated with acute attacks (in particular laryngeal attacks)
- Not having treatment for an acute attack available
  - Hospital
  - At home
- Not knowing when to treat
- Lacking training on self-administration
- Costs of medication/administration
  - Local reimbursement policies

Benefits of Involving an HAE Specialist

- National referral centers or networks
- Collaborative care with local physicians
- Optimal patient education regarding condition and treatment options
- Iterative process to adjust/adapt treatment plan over time

Creating a Comprehensive Treatment Plan for Hereditary Angioedema

- Evaluation/diagnosis
- Optimization of management plans
- Collaboration with local MDs and specialists
- Telemedicine presence

Box 1
Suggested steps in developing a comprehensive HAE treatment plan

Initial Evaluation of Confirmed HAE

- Assess current features of angioedema (frequency, severity, anatomic location, treatment, impact on activities/quality of life)
- Educate patient and family on HAE symptoms, triggers, prodromes, risks, genetics, screening
- Discuss treatment goals for patient
- Discuss required acute treatment plan, comparative medication options
- Discuss option of routine prophylaxis, comparative medication options
- Discuss benefits of early acute treatment
- Discuss unique risks of airway angioedema warranting medical evaluation
- Discuss indications for short-term prophylaxis (surgical, medical, or dental procedures)

Following Selection of Therapeutic Agent(s)

- Determine if candidate for self-administration based on patient and medication factors
- Determine site of treatment (self-administration vs home health provider vs medical facility)
- Provide patient-specific prescription and clinical documentation for processing/payor authorization
- Arrange self-administration training (in office or via home health) as applicable
- Determine plan for reporting use of medication: scheduled office visit, phone, e-communication, home health reports
- Determine plan for communication of treatment plan to local health care providers, integration of care as applicable
- Provide tools for navigating health system: written treatment plan, letter, USB drive, medical alert bracelet
- Provide resources for ongoing education

Periodic Follow-Up Evaluations

- Assess current features of angioedema (triggers, frequency, severity, anatomic location, treatment impact on activities/quality of life)
- Review medication use: frequency and efficacy
- Review medication adverse effects; safety laboratory tests if indicated (androgens: semiannual liver function tests, lipid profile, complete blood count, urinalysis, annual liver ultrasonography; plasma-derived C1INH: consider annual hepatitis B/C, human immunodeficiency virus testing)
- Discuss obstacles to treatment; identify reasons for untreated symptoms that interfered with activity
- Review interactions/communication with other health care providers; integration of care
- Review whether patient goals are achieved with current treatment plan
- Consider treatment adjustments if goals are not achieved (change acute medication or plan logistics, add/remove/titrate prophylactic therapy as clinically indicated)
- Ensure medication refills are provided
- Review benefits of early acute treatment
- Review unique risks of airway angioedema
- Review anticipated indications for short-term prophylaxis

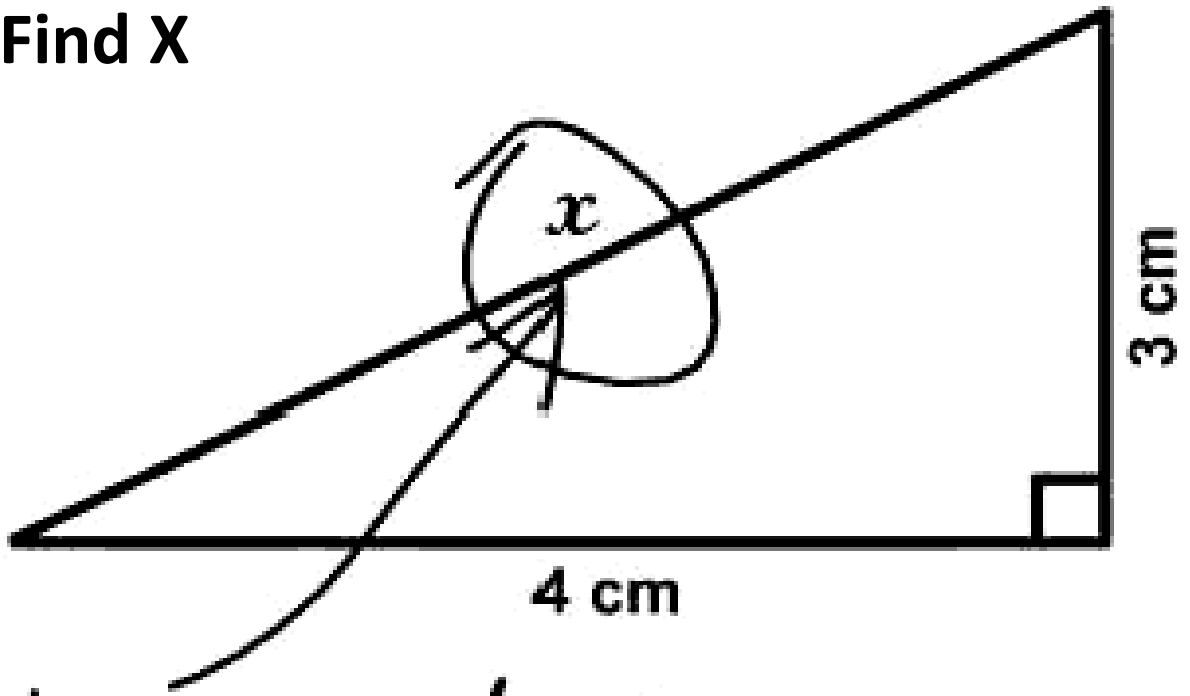
Riedl MA. *Immunol Allergy N America.* 2013;33:471-485.

Summary

- Key to diagnosis of HAE is a high index of suspicion
- Diagnosis of C1-INH Deficiency (HAE Type I and II) requires laboratory confirmation
- All HAE patients should have an effective plan in place for on-demand treatment of acute attacks
- Prophylactic treatment beneficial in selected patient based on individual factors
- Treatment plans including self-administered medication improve patient quality of life

Thank You

3. Find X



Here it is