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Angioedema without Urticaria: Evaluation and Management

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MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

Disclosures

- Consultant: Shire, CSL Behring, Pharming, Biocryst
- Research Grant: Shire, Biocryst

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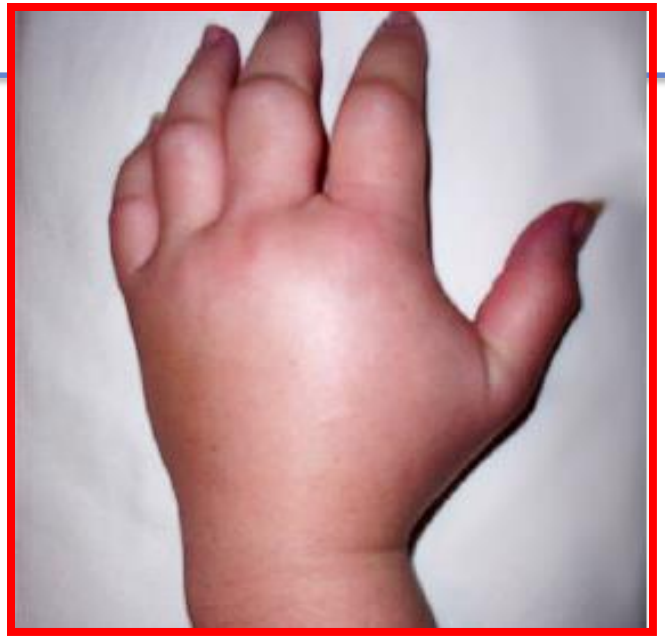
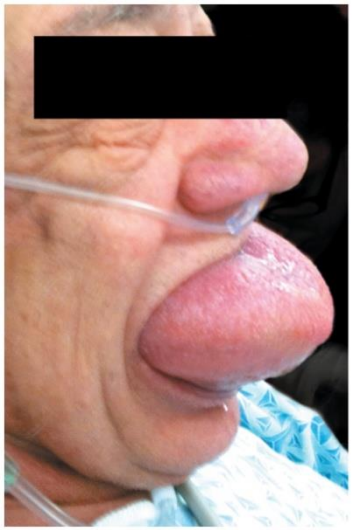
Objectives

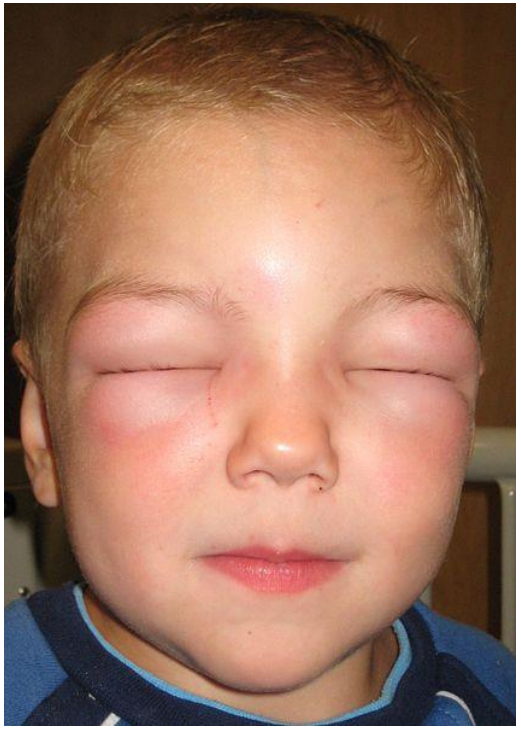
- Differentiate the role of histamine and bradykinin in angioedema
- Contrast histaminergic and nonhistaminergic types of angioedema
- Discuss treatment options for patients with angioedema

Angioedema

- Rapid swelling below the surface of the skin
- Self-limited and localized
- Results from extravasation of fluid into interstitial tissues







Angioedema: Bradykinin vs. Histamine

	Bradykinin	Histamine
Severity of swelling	Greater	Lesser
Duration of swelling	Longer	Shorter
Risk for fatal airway obstruction	Appreciable	Exceedingly low
Abdominal attacks	Very common	Rare
Response to antihistamines, corticosteroids, epinephrine	Poor	Excellent

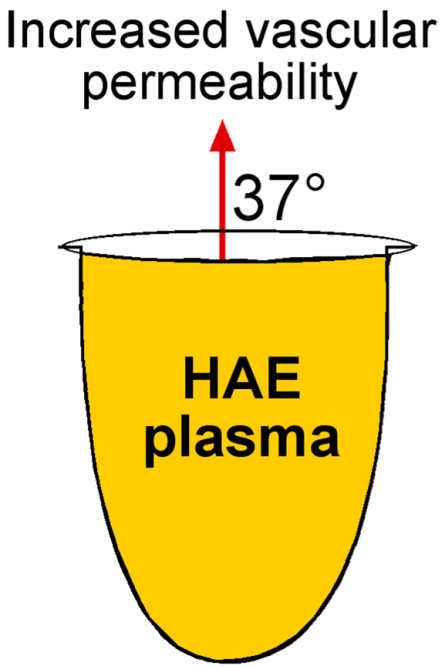
What is Hereditary Angioedema?

Debilitating and potentially life-threatening autosomal dominant disease

- Caused by an inherited deficiency in C1 esterase inhibitor
- Recurrent attacks of angioedema
- Swelling of extremities, face, abdomen, larynx
- If untreated, up to 40% mortality rate from asphyxiation

Bork K, et al. *Mayo Clin Proc*. 2000

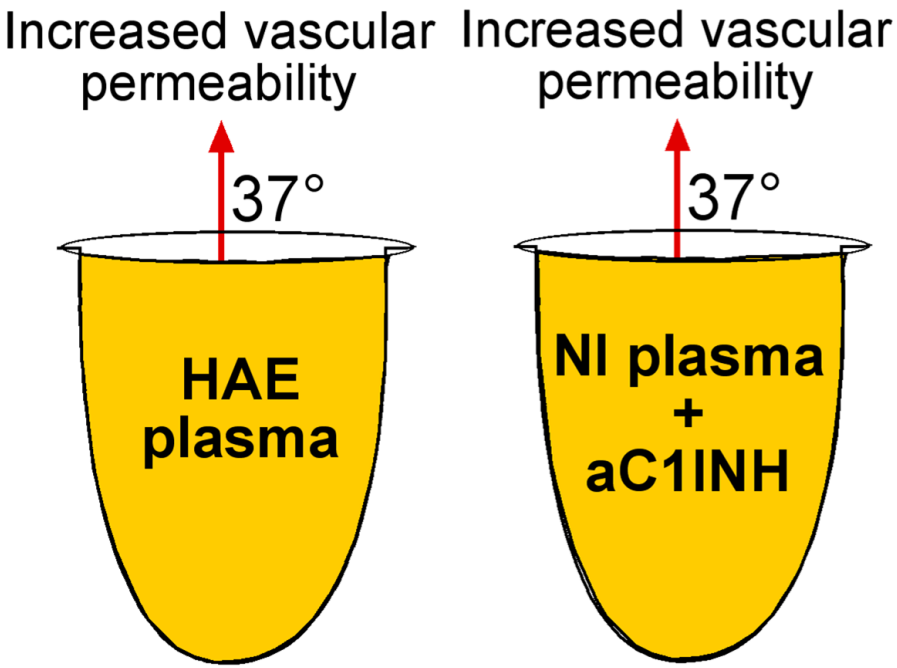
Generation of Vascular Permeability–Enhancing Activity



Incubation of HAE plasma *ex vivo* resulted in generation of a factor that enhanced vascular permeability

Shoemaker LR, et al. *Clin Exp Immunol*. 1994;95:22-28.

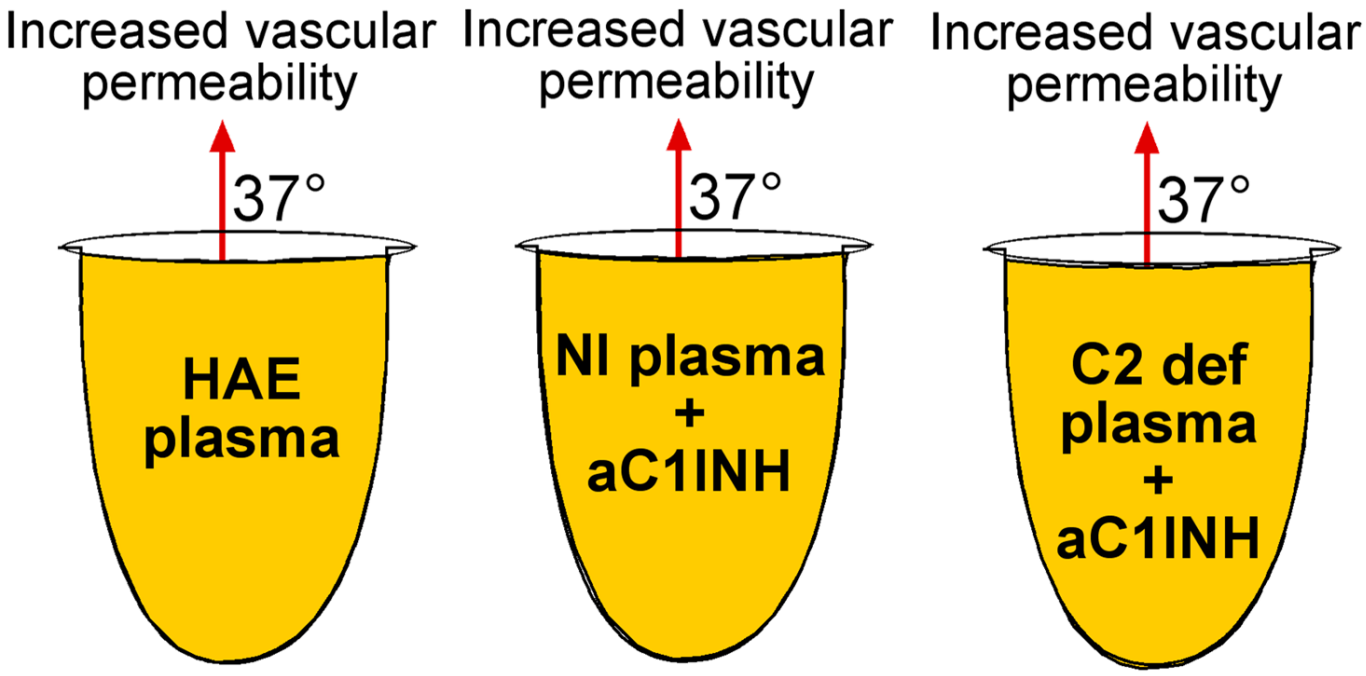
Generation of Vascular Permeability–Enhancing Activity



Depletion of C1INH from normal plasma led to a similar increase in vascular permeability

Shoemaker LR, et al. *Clin Exp Immunol*. 1994;95:22-28.

Generation of Vascular Permeability–Enhancing Activity



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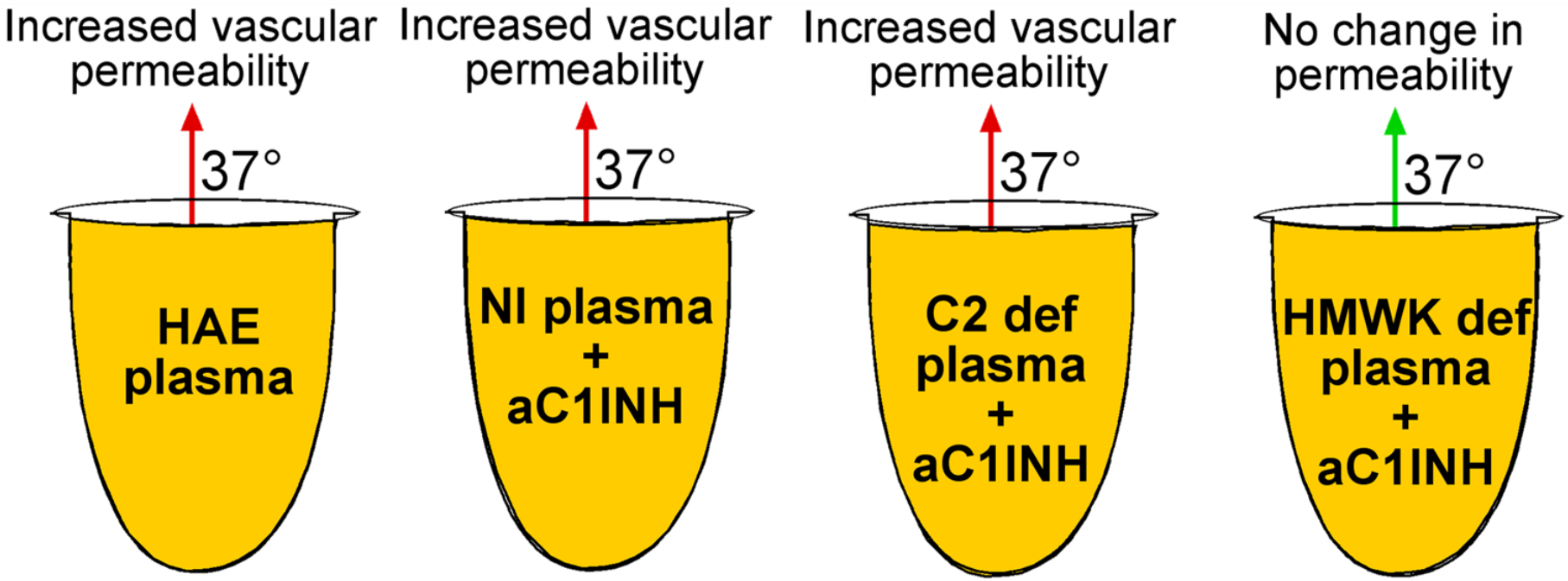
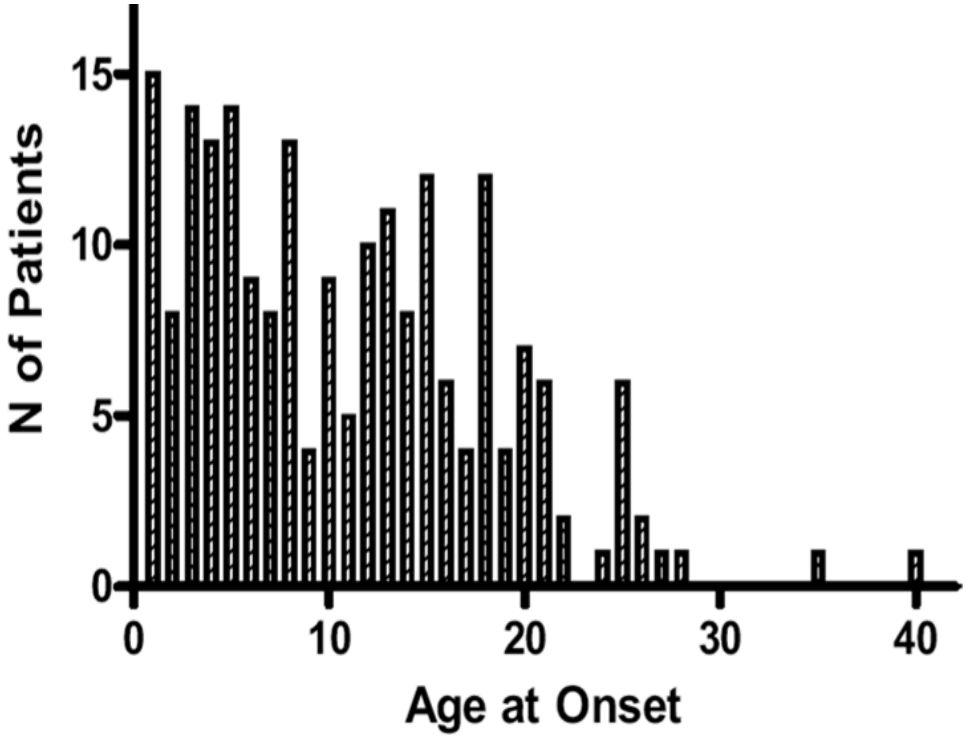


Shoemaker LR, et al. *Clin Exp Immunol*. 1994;95:22-28.

Laboratory Evaluation in C1Inhibitor Deficiency

	C1-INH Level	C1-INH Function	C4 Level	C3 Level	C1q Level
HAE type I	<30%	<30%	Low	Normal	Normal
HAE type II	Normal	<30%	Low	Normal	Normal
HAE type III	Normal	Normal	Normal	Normal	Normal
Acquired C1-INH I/II	Low	Low	<30%	Normal/Low	Low
ACE inhibitor	Normal	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal	Normal

Age at Onset of HAE Attacks



- Clinical symptoms start at a mean age of 11 (SD 7.7) years
- On average, women more severe course of HAE than men
- Patients with early onset of clinical symptoms were affected more severely than those with late onset

Bork et al., Am J Med 2006

Clinical Presentation

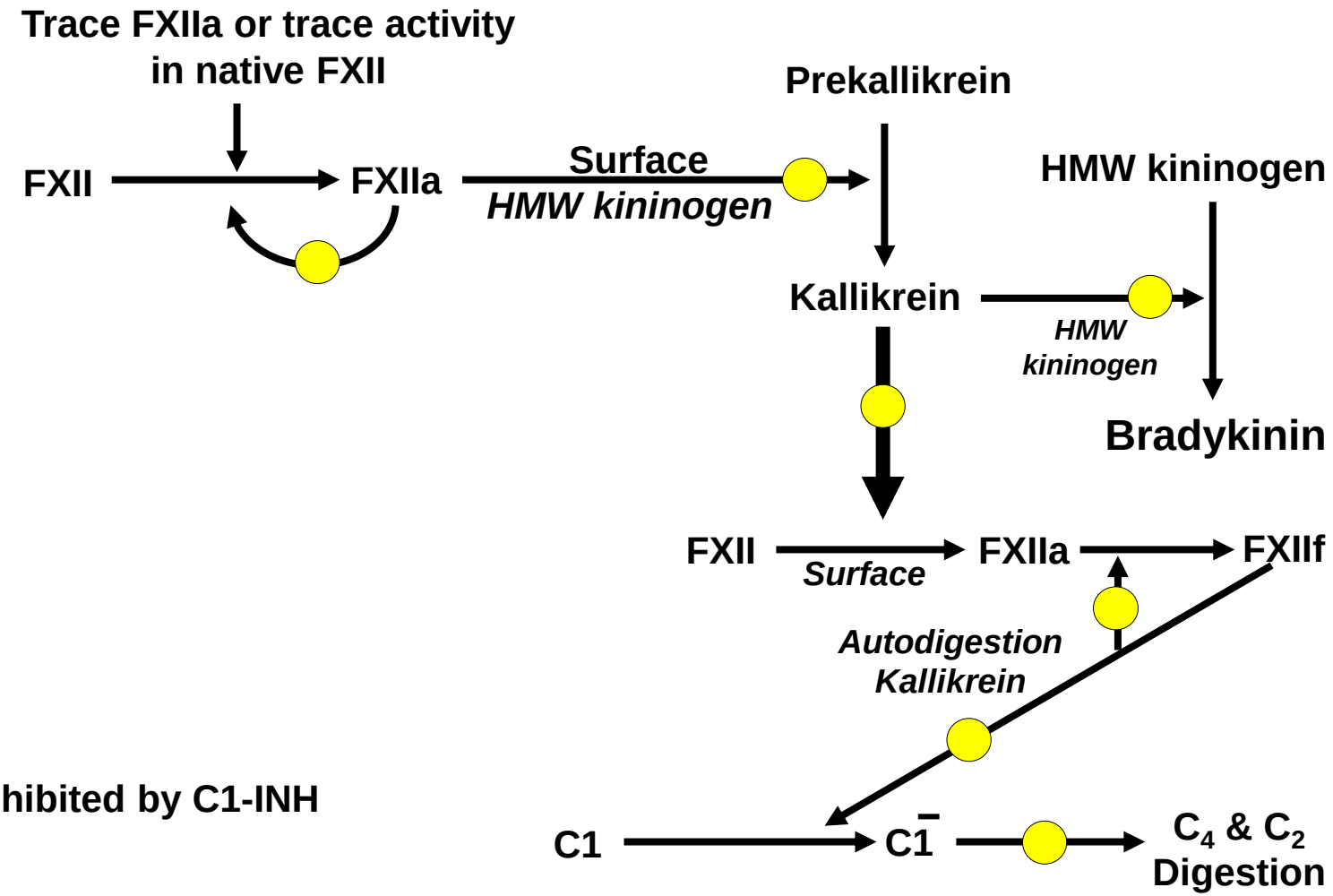
Angioedema

- Repeated bouts of swelling of the face, extremities, genitals, intestines and larynx
- Edema is *not* warm, usually nonpruritic and nonpitting

No Urticaria

- Erythema marginatum present but **no urticaria**

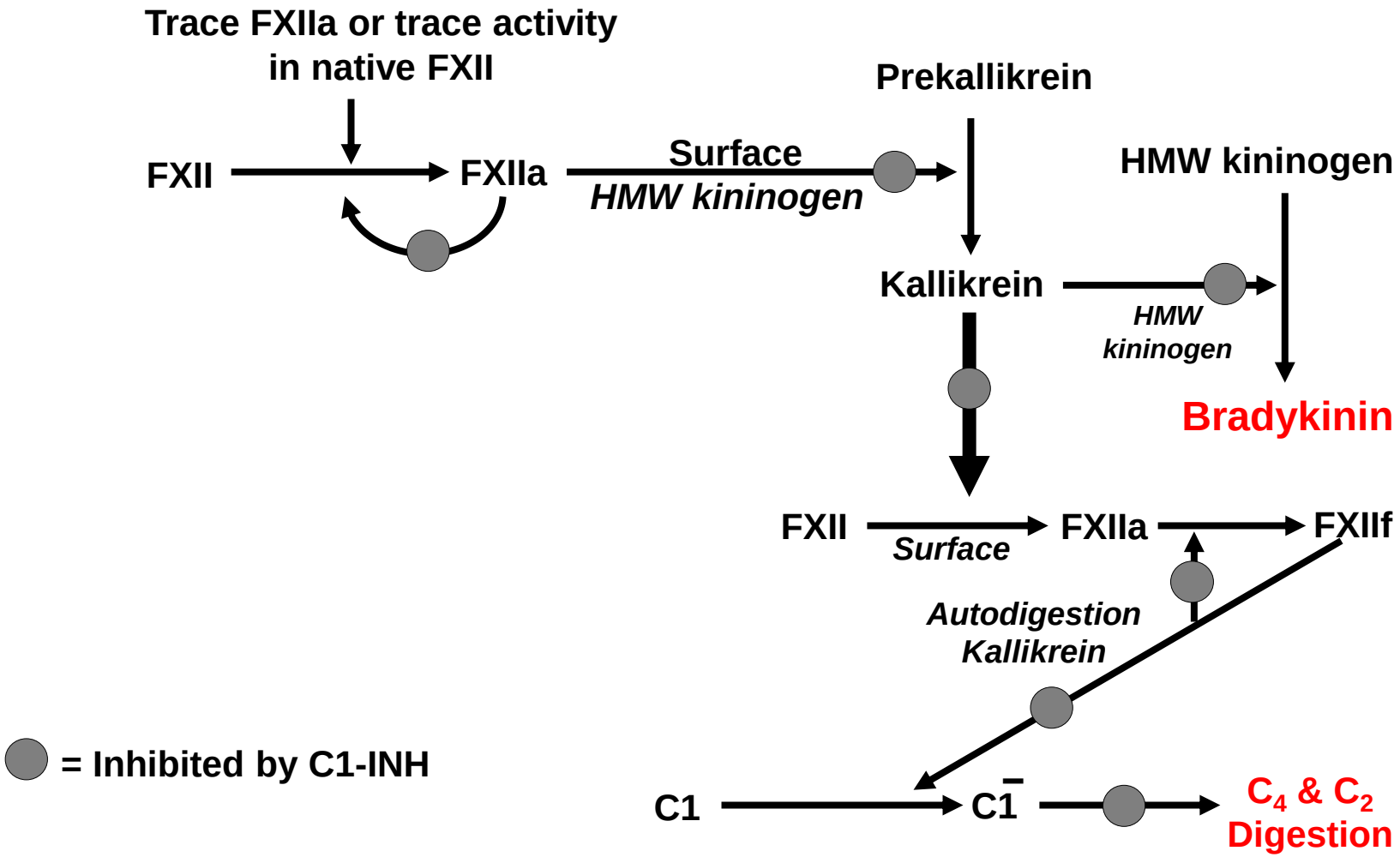
Function of C1-INH



FXII, factor XII; HMW, high molecular weight.

Kaplan AP, et al. *J Allergy Clin Immunol.* 2002;109:195-209.

Loss of Function of C1-INH



Kaplan AP, et al. *J Allergy Clin Immunol.* 2002;109:195-209.

HAE Attacks

- Caused by the extravasation of plasma into the deeper cutaneous or mucosal layers as a result of bradykinin release
- Recurrent and unpredictable with painful, localized edema or visceral swelling
- Attacks may be frequent and/or severe, but are highly variable between patients and within families

Nzeako UC, et al. *Arch Intern Med*. 2001;161:2417-2429.
Agostoni A, et al. *J Allergy Clin Immunol*. 2004;114:S51-S131.
Bork K, et al. *Mayo Clin Proc*. 2000;75:349-354.

HAE Extremity Attack

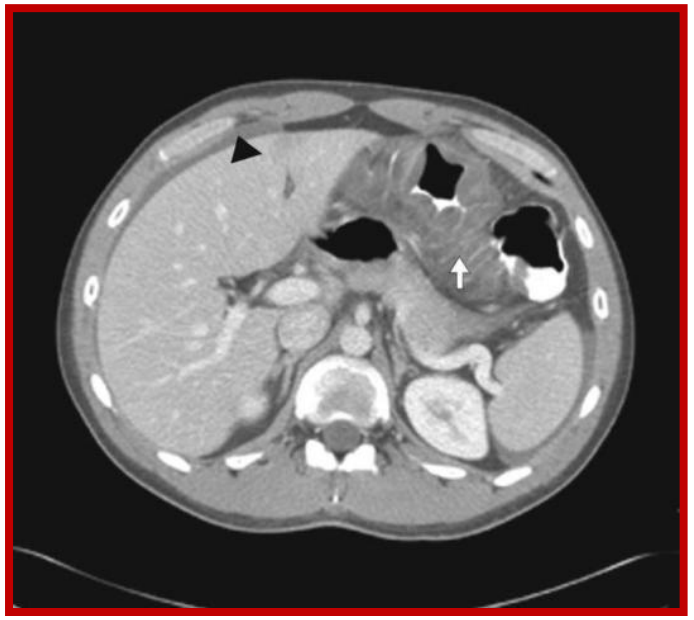
Peripheral Angioedema

- Affects 96% of patients
- Functionally disabling
  - Hands: difficulty holding, typing, use of phone
  - Feet: impedes walking, standing
- Interferes with school
- Rarely results in hospitalization

Frank MM, et al. *Ann Intern Med*. 1976;82:580-593.
Frank MM. *Immunol Allergy Clin North Am*. 2006;26:653-668.

Abdominal Attacks

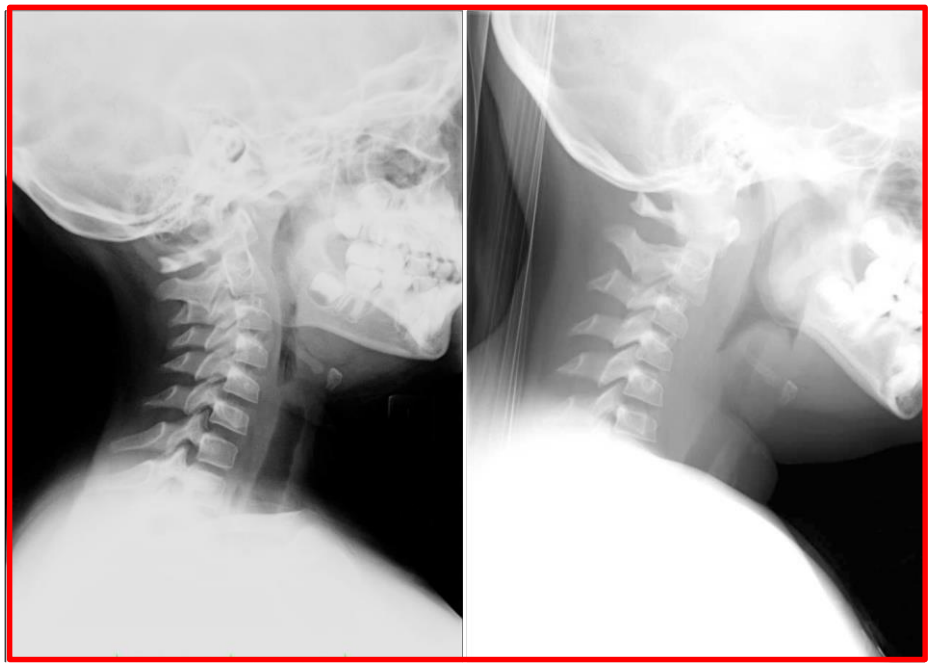
- Occur in 93% of patients with HAE
- Mild to severe colicky pain
- Vomiting common
- Functional intestinal obstruction
- Fluid loss leads to hemoconcentration and hypovolemic shock
- Protuberant abdomen, tenderness, and rebound possible
- Symptoms mimic surgical emergencies, resulting in misdiagnosis 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 North Am*. 2006;26:653-668.
Agostoni A, Cicardi M. *Medicine*.1992;71:206-215.

HAE Laryngeal Attacks

- Occur in ~50% of patients during their lifetime
- Require airway management to prevent asphyxiation
- Are of particular concern in children, given the heightened risk for asphyxiation associated with a smaller airway



Bork K, et al. *Arch Intern Med*. 2003;163:1229-1235.
Bork K, et al. *Mayo Clin Proc*. 2000;75:349-354.
Bork K, et al. *Arch Intern Med*. 2001;161:714-718.
Radiographs courtesy of William Lumry, MD.

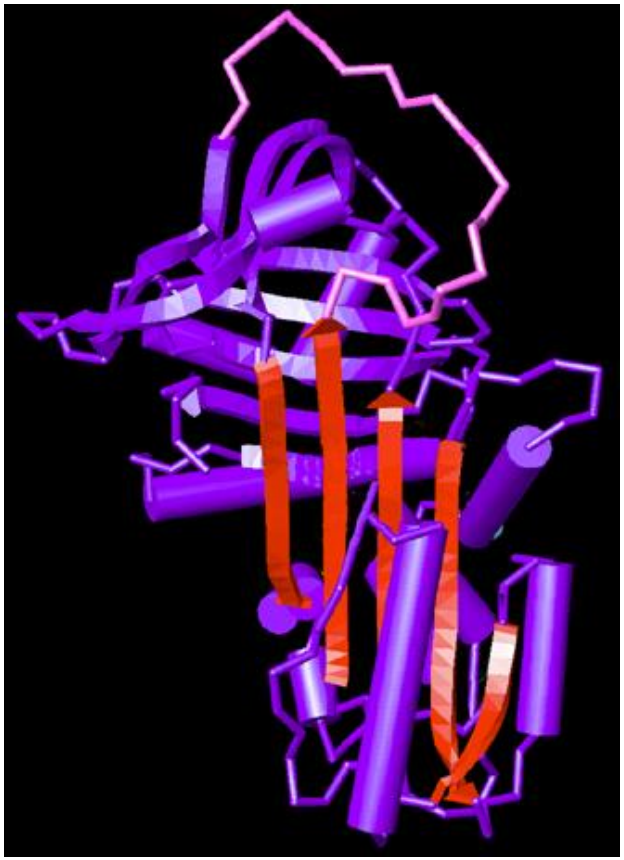
Risk of Asphyxiation

- Patients with Type I/II HAE are at constant risk of asphyxiation
- 3- to 9-fold higher risk in undiagnosed patients emphasizes the need for accurate diagnosis
- In a retrospective review of 70 deaths due to HAE:
  - 63 patients had no diagnosis at time of death despite a family history of HAE
  - Lifespan of asphyxiated patients with undiagnosed HAE was on average ~31 years shorter than undiagnosed patients who died of other causes
  - Mean age at time of asphyxiation was 40.6 ± 14.3 years

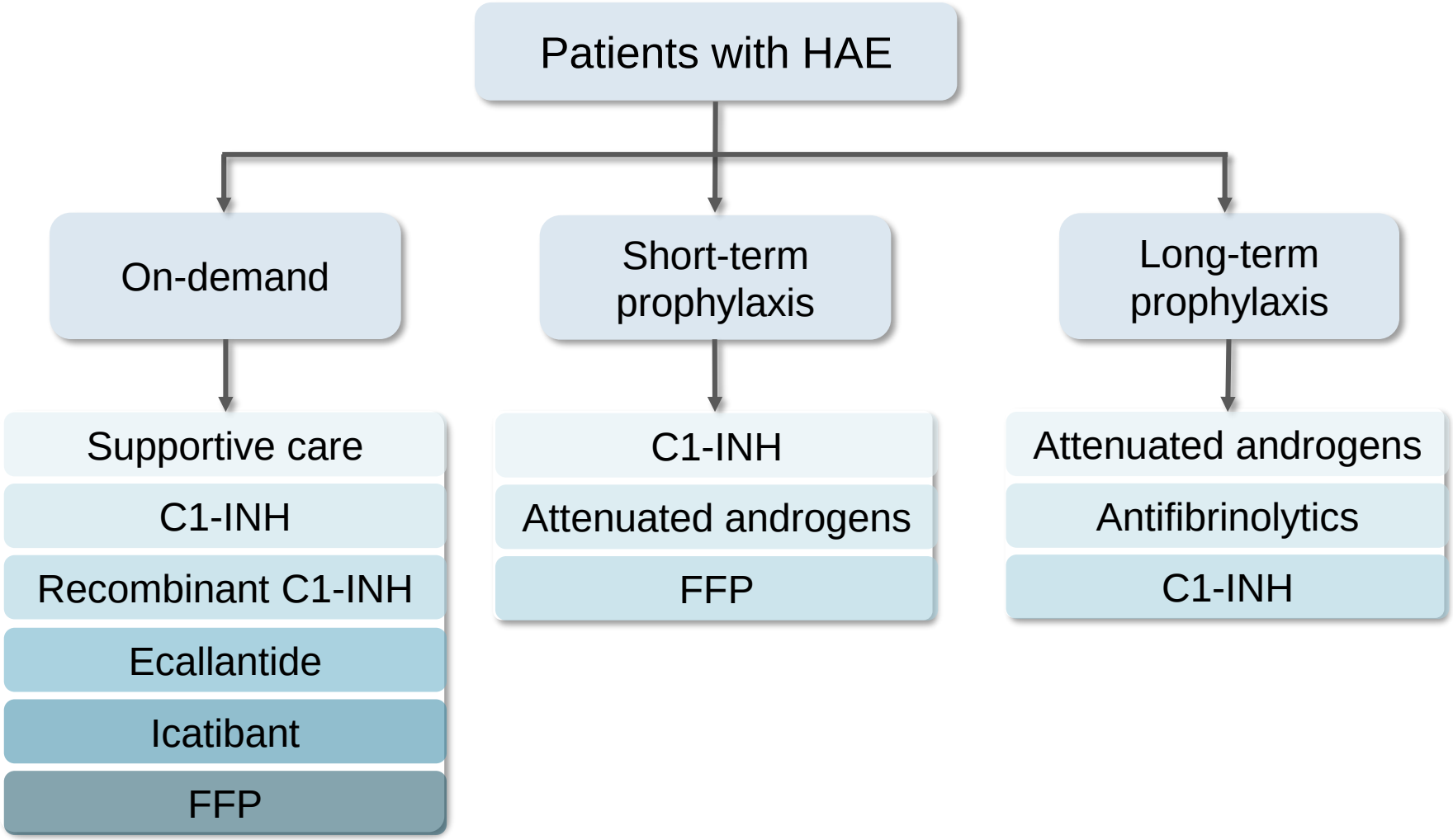
Bork K, et al. *J Allergy Clin Immunol*. 2012;130(3):692-697.

C1INH Concentrate

- Berinert: C1INH Concentrate
- Cinryze: C1INH Concentrate
- Ruconest: Recombinant C1INH
- HAEGARDA: C1INH Concentrate



HAE: Current Strategies and Treatments



Tourangeau LM, et al. *Curr Allergy Asthma Rep.* 2011

Guidelines for the Treatment of HAE

- All patients should have access to an effective on-demand agent
- Evidence demonstrates efficacy and safety of treatment of HAE attacks with C1-INH concentrates, plasma kallikrein inhibitor, bradykinin B2 receptor antagonist
- FFP is often effective, but may exacerbate some attacks; caution is required
- Androgens and antifibrinolytics do not provide reliably effective treatment of attacks
- Epinephrine, corticosteroids, and antihistamines are not effective
- Management can involve symptomatic treatment based on region of the body

Zuraw BL, et al. *J Allergy Clin Immunol*. 2013

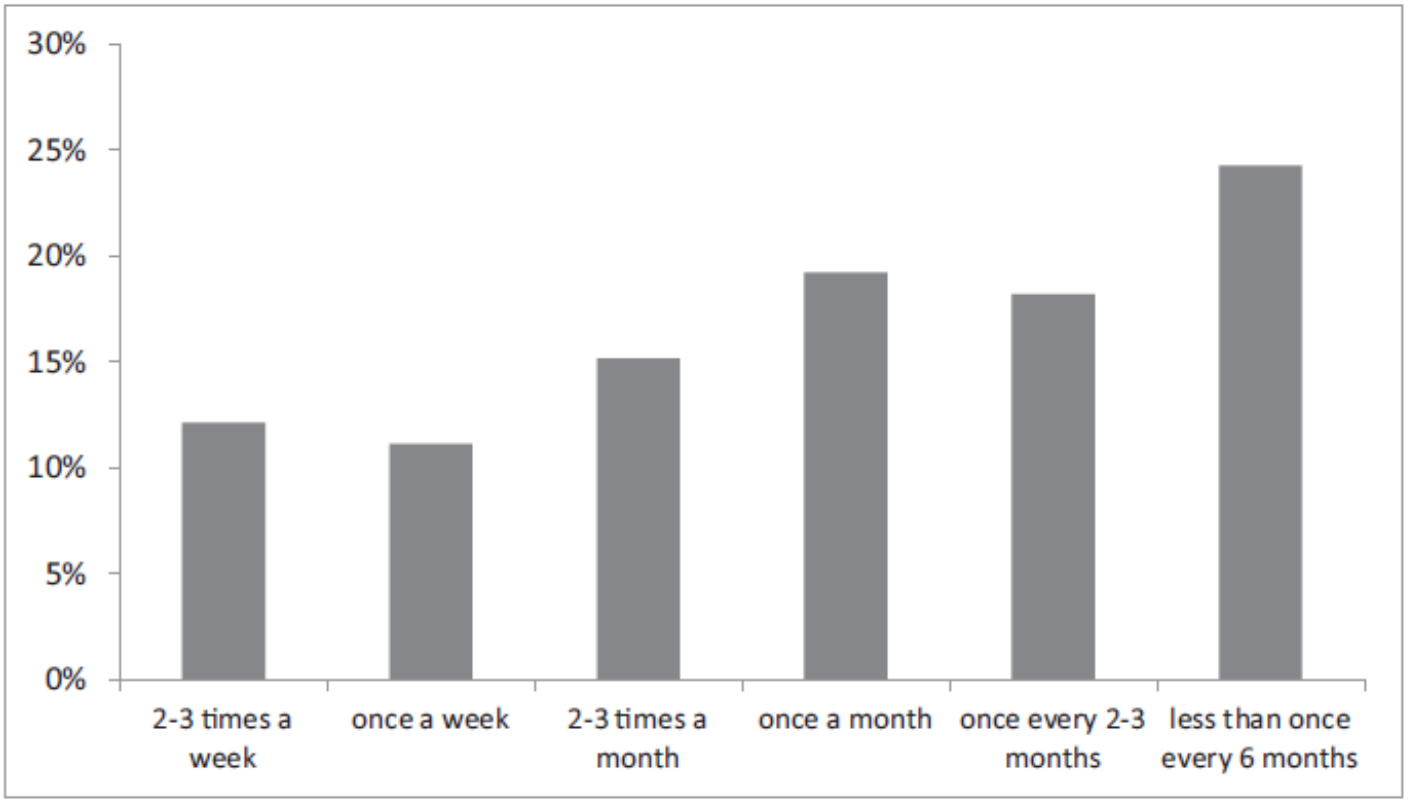
HAEA Patient Summit

Current state of hereditary angioedema management: A patient survey

- We surveyed 149 HAE patients to better understand the current state of HAE care, from a patient perspective, after the introduction of several novel therapies
- 72% of HAE patients reported that HAE had a significant impact on QOL
- A third of HAE patients were diagnosed within one year of their first HAE attack, but another third reported a delay of more than 10 years

Banerji, *Allergy Asthm Proc* 2015

Frequency of Attacks Despite Prophylaxis



- 70% of HAE patients reported being unsatisfied with the care they received during the ED visit

Banerji, *Allergy Asthm Proc* 2015

Angioedema without Urticaria: Clinical Survey

- Tertiary level center where patients are referred mostly by specialists
- Reviewed all patients with angioedema without urticaria between January 1993 and December 2003
- Identified 929 patients and 776 patients completed the full work up

Zingale CMAJ 2006

Evaluation

- Clinical history and physical examination
- CBC, SPEP, CRP, ESR, LFTs, TSH, ANA
- C4, C1 inhibitor level and function, C1Q
- Stool studies
- Urinalysis
- Sinus and dental x-rays

If evaluation was negative, antihistamine treatment for one month was initiated

Zingale CMAJ 2006

Angioedema without Urticaria: Differential Diagnosis

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 CMAJ 2006

Angioedema: Causative Agent Identified

Not Bradykinin Mediated

Related to a specific factor*

- Recurrence of symptoms was clearly related to an exogenous stimulus with a consistent cause-effect relationship
  - Medications (N=56)
  - Food (N=45)
  - Medication and food (N=10)
  - Insect bite (N=5)
  - Environmental allergen (N=4)
  - Physical irritation/stimulus (N=4)

Zingale CMAJ 2006

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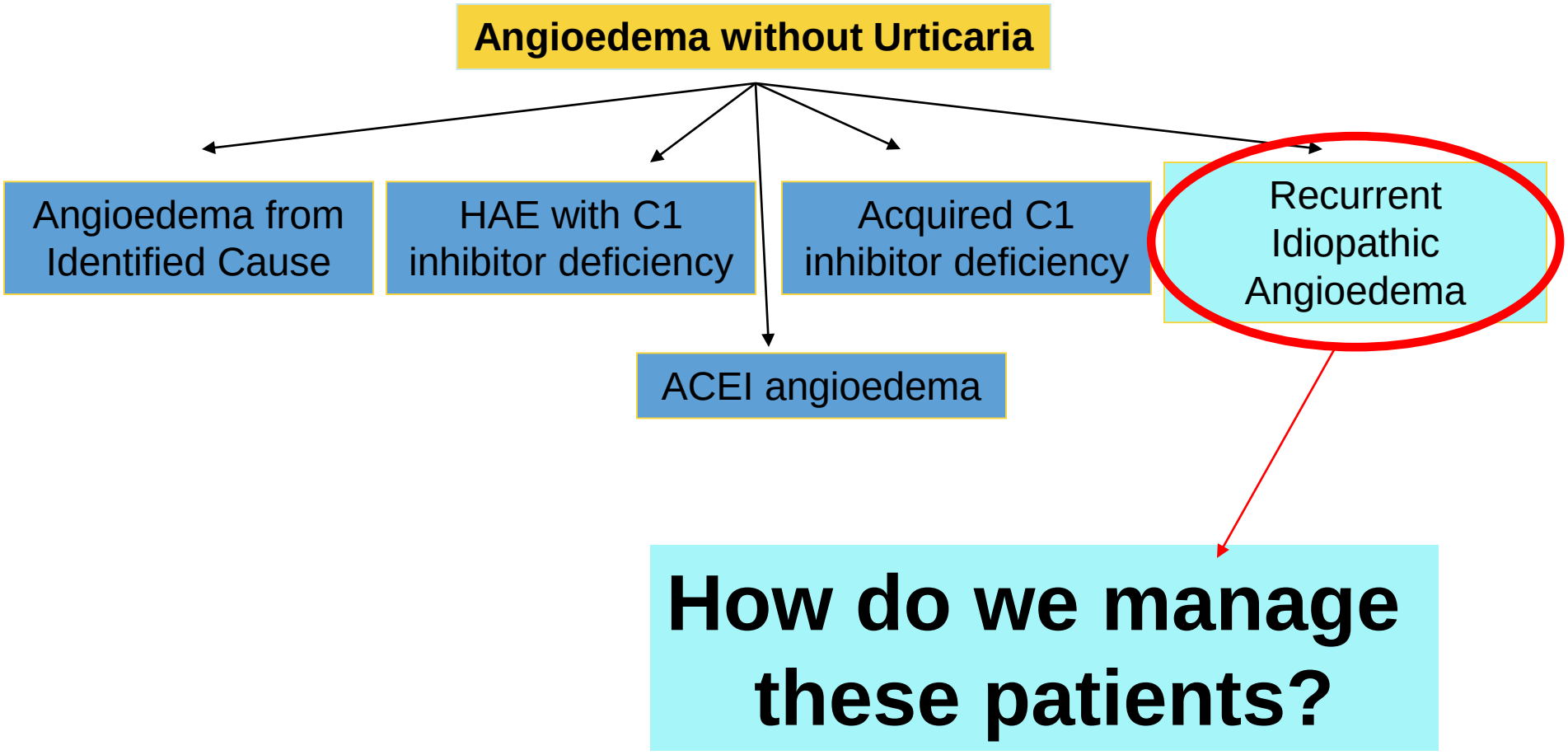
Zingale CMAJ 2006

Recurrent Idiopathic Angioedema



How do we manage these patients?

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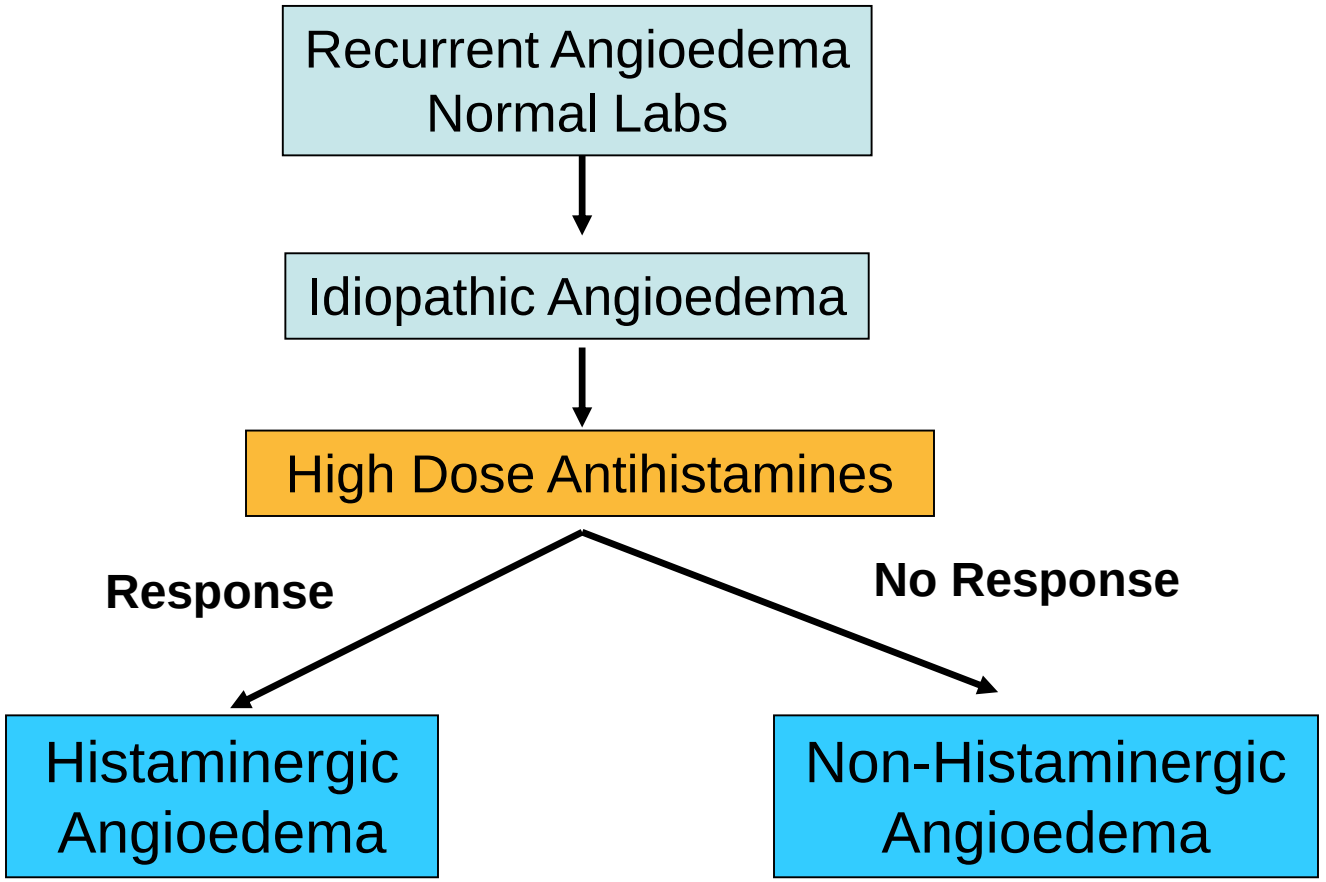
Idiopathic Angioedema



Idiopathic Histaminergic Angioedema

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

- Initial evaluation completely normal
- 254 (86%) patients responded to antihistamine therapy

Zingale CMAJ 2006

What is a high dose of antihistamines?

- The mechanism by which histamine release is initiated in this disorder in not full understood

- Expert opinion suggests that 4 times the typical dose is accepted as high dose

Idiopathic Histaminergic Angioedema

- Most common form of idiopathic angioedema
- Clinical history
  - Age for onset variable
  - No family history of angioedema
  - Develops rapidly reaching maximum in 4-6 hours
  - Gastrointestinal and laryngeal mucosa are spared
  - Death has not been reported
- No precipitating factors identified
- Respond to corticosteroids and epinephrine as acute treatment

Treatment for Idiopathic Angioedema: Histaminergic

- High dose antihistamines (4x standard doses)
- Le
- Co
- Immunosuppressants
- Xolair

Epinephrine should be considered for treatment of severe symptoms in the acute setting

Similar to refractory cases of idiopathic urticaria and angioedema

Nonhistaminergic Idiopathic Angioedema

Idiopathic Nonhistaminergic Angioedema

Marco Cicardi, MD, Luigi Bergamaschini, MD, Lorenza C. Zingale, MD, Daniela Gioffré, MD, Angelo Agostoni, MD

- Sought to describe management of these patients with tranexamic acid
- 25 patients
- Not responsive to antihistamines
- Excluded all known causes of angioedema

Cicardi et al., Am J Med 1999

Table 2. Effects of Treatment with Tranexamic Acid in Patients with Idiopathic Nonhistaminergic Angioedema

Patient	Attacks/ Year without Treatment	Attacks/Year with Tranexamic Acid	Minimal Effective Dose of Tranexamic Acid (g/day)	Length of Treatment with Tranexamic Acid (months)
1	>12	<1	2.5	29
2	6–11	<1	0.5	22
3	6–11	none	1.5	24
4	>12	3	2.0	12
5	>12	2–3	1.0	43
6	>12	3	3.0	12
7	>12	none	2.0	10
8	>12	none	2.0	53
9	>12	<1	1.0	72
10	>12	none	0.5	46
11	12	3	1.0	15
12	>12	none	1.0	21
13	>12	none	1.5	282
14	>12	none	1.5	256
15	>12	none	1.0	56

Cicardi et al., Am J Med 1999

Summary

- Novel therapies are available for HAE treatment
- Attacks still occur and side effects are a concern
- Patients have differential response to treatment
- QOL and BOD remains a significant issue

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