Angioedema without Urticaria

Diagnosis and Management

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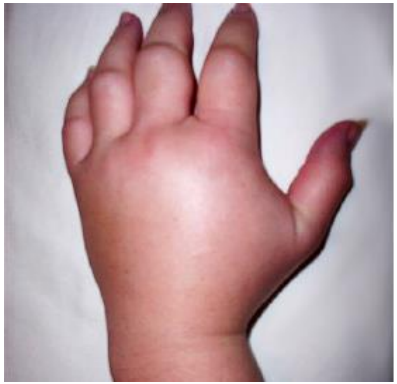
Professor, Harvard Medical School
Co-Director, MGH ELEVATE Leadership Program

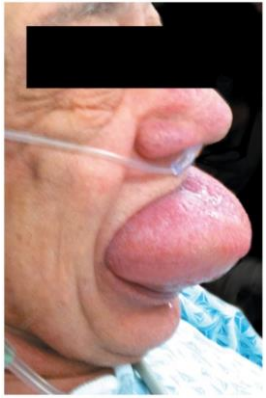
Learning Objectives

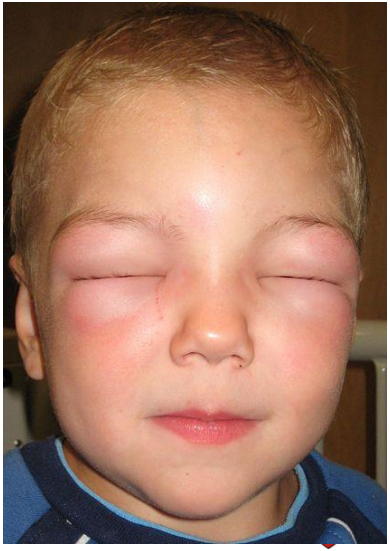
- Upon completion of this learning activity, participants should be able to differentiate bradykinin and histamine mediated angioedema
- Upon completion of this learning activity, participants should be able to describe the kallikrein-kininogen cascade and role of C1-inhibitor
- Upon completion of this learning activity, participants should be able to manage patients with hereditary angioedema following guidelines

Angioedema: Definition

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



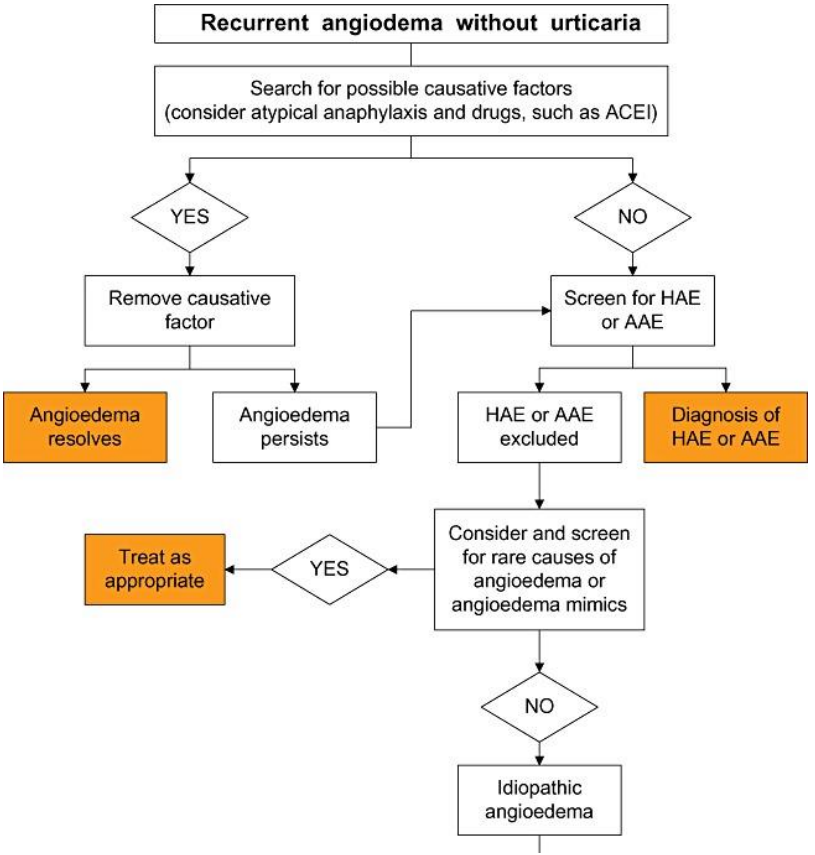




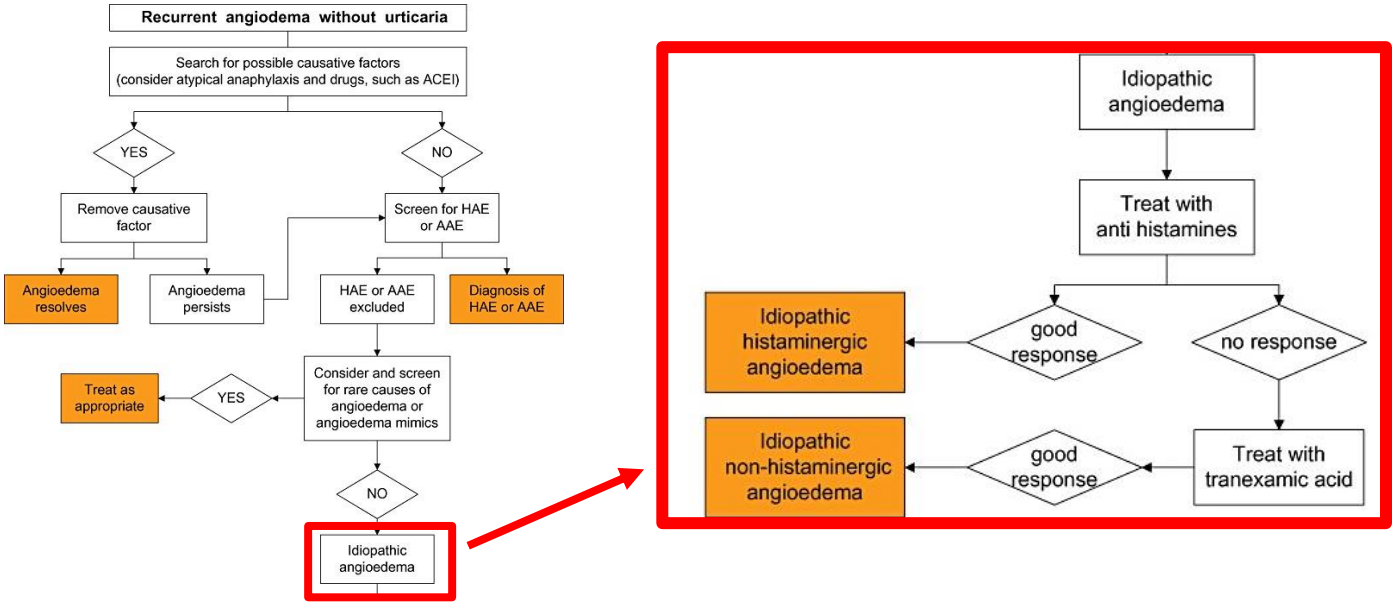
Bradykinin vs. Histamine Mediated Angioedema

	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

Algorithmic Approach to Recurrent Angioedema

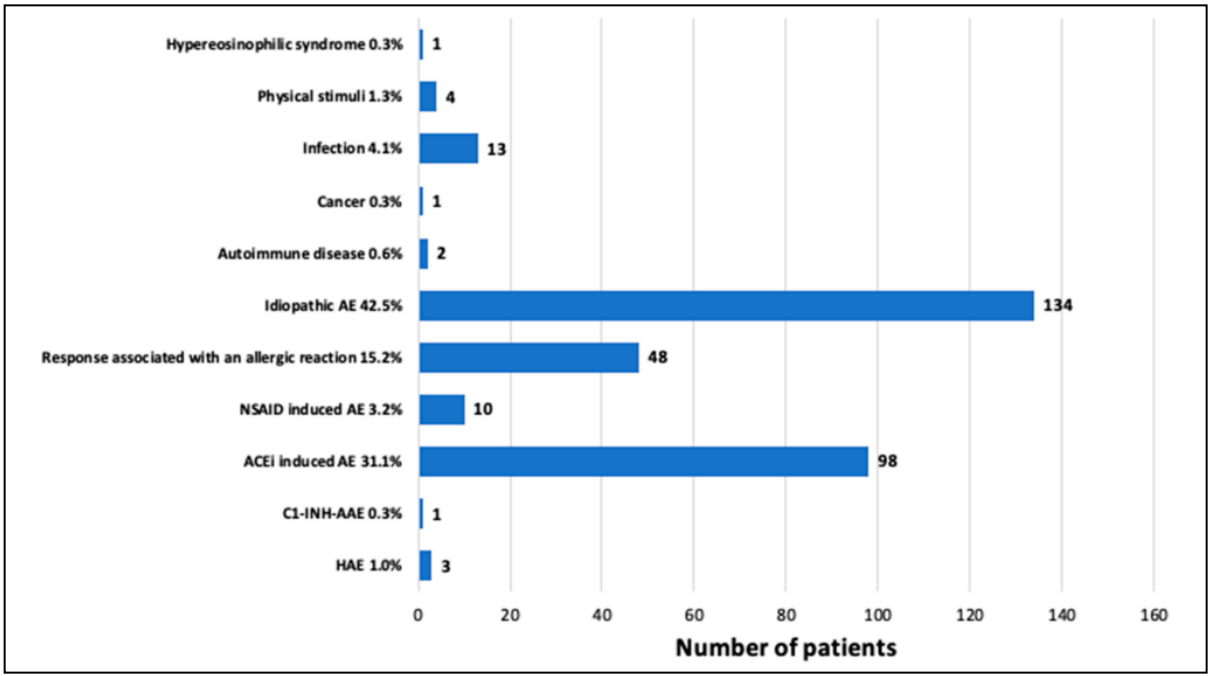


Algorithmic Approach to Recurrent Angioedema



Clinical Features and Disease Course of Primary Angioedema Patients in a Tertiary Care Hospital

Retrospective cohort study of patients referred to an outpatient dermatology due to angioedema from 1996 to 2014



MASSACHUSETTS GENERAL HOSPITAL

Pall et al., J Asthma Allergy. 2020

RESEARCH

Angioedema without urticaria: a large clinical survey

Lorenza C. Zingale, Laura Beltrami, Andrea Zanichelli, Lorena Maggioni, Emanuela Pappalardo, Benedetta Cicardi, Marco Cicardi

- 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

Angioedema without Urticaria: 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

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	—	

Recurrent Angioedema without Urticaria: *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)

Recurrent Angioedema without Urticaria: ACEI

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

	Patients		M:F ratio	Age at onset, yr	
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Peripheral/generalized edema	21	3	0.17	—	

Recurrent Angioedema without Urticaria: C1 inhibitor deficiency

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

	Patients		M:F ratio	Age at onset, yr	
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Histaminergic	254		0.56	40	7-86
Nonhistaminergic	40		1.35	36	8-75
Peripheral/generalized edema	21	3	0.17	—	

Recurrent Angioedema without Urticaria: Edema

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

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Histaminergic	254		0.56	40	7-86
Nonhistaminergic	40		1.35	36	8-75
Peripheral/generalized edema	21	3	0.17	—	

Recurrent Angioedema without Urticaria: Idiopathic

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C1-inhibitor deficiency	197	25			
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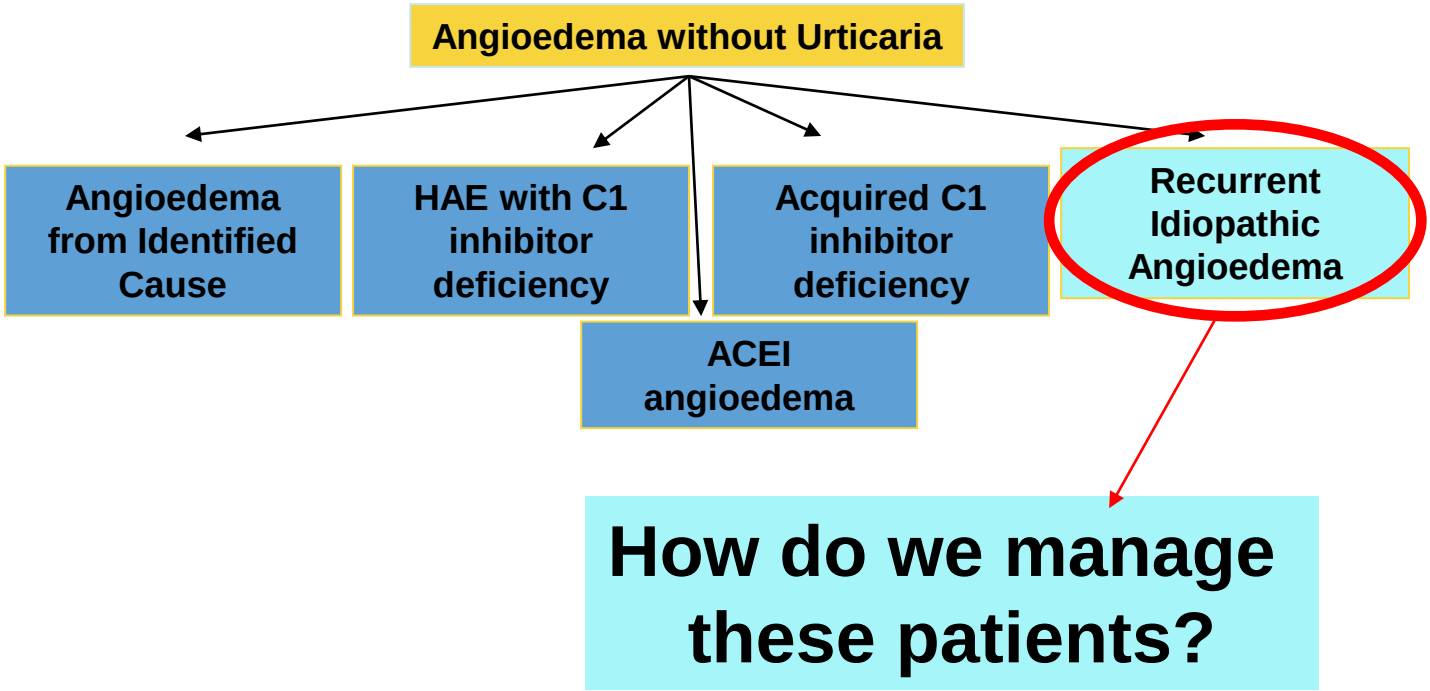
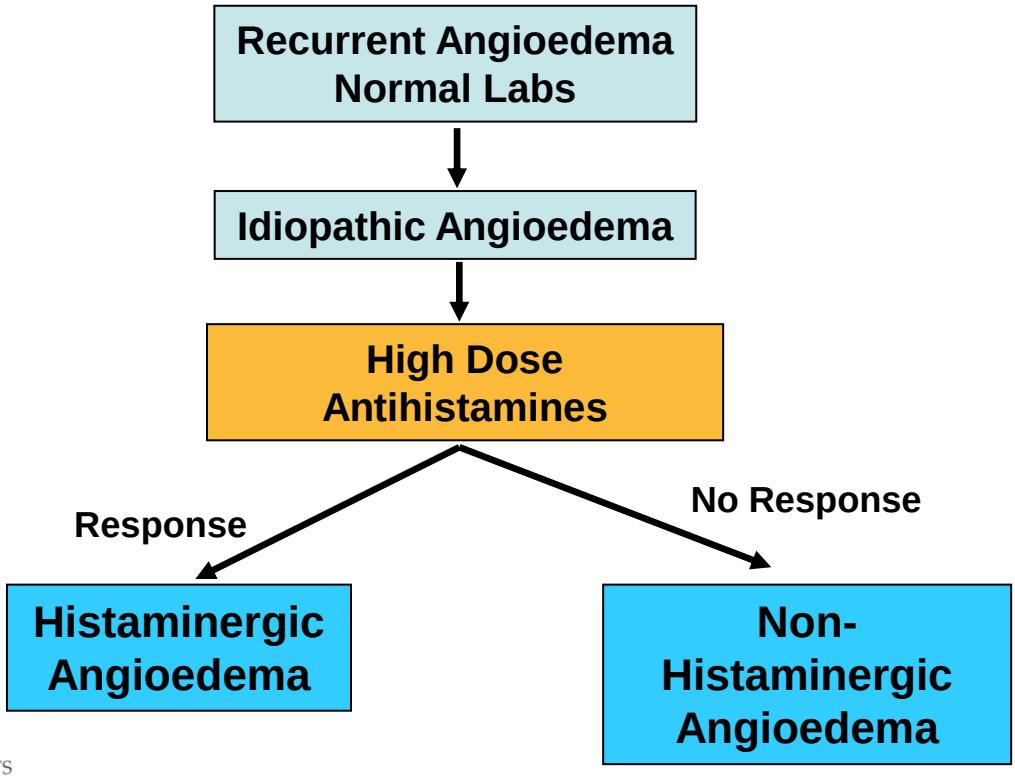
Histaminergic	254		0.56	40	7-86
Nonhistaminergic	40		1.35	36	8-75
Peripheral/generalized edema	21	3	0.17	—	

Recurrent Idiopathic Angioedema



Idiopathic Angioedema



Idiopathic Histaminergic 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
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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	—	

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

Zingale CMAJ 2006

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 Recurrent Angioedema: Histaminergic

Similar to refractory cases of idiopathic urticaria and angioedema

- High dose antihistamines (4x standard doses)
- Leukotriene receptor antagonists
- Omalizumab
- Immunosuppressants
- Corticosteroids

Idiopathic Non-Histaminergic 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
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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	—	

- Initial evaluation completely normal
- 40 patients did not respond to antihistamine therapy

Zingale CMAJ 2006

Nonhistaminergic Angioedema Treatment

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

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

HAE Pathophysiology

HEREDITARY ANGIONEUROTIC EDEMA

II. Deficiency of Inhibitor for Serum Globulin Permeability Factor and/or Plasma Kallikrein

Nathaniel S. Landerman, Major, MC, USA, Marion E. Webster, Ph.D.,** Elmer L. Becker, Ph.D., M.D.,*** and Harold E. Ratcliffe, Colonel, MC, USA,**** Washington, D. C., and Bethesda, Md.*

HAE plasma failed to inhibit plasma kallikrein and released a permeability enhancing factor

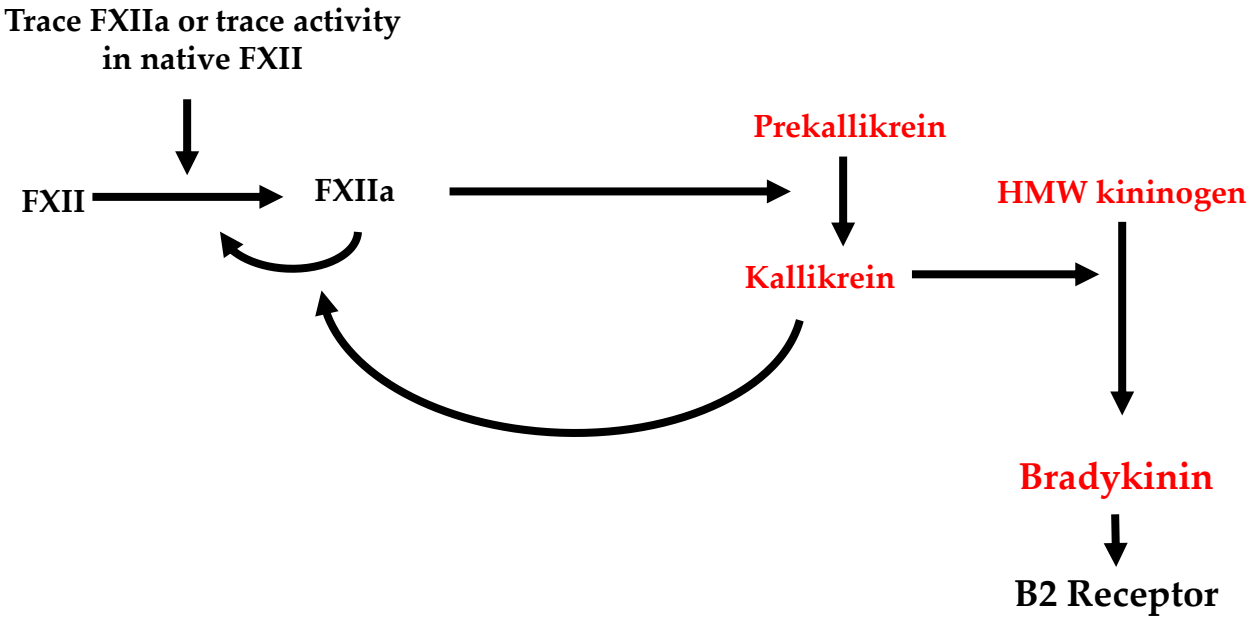
VOL. 35, JULY 1963 37 AMERICAN JOURNAL OF MEDICINE

A Biochemical Abnormality in Hereditary Angioneurotic Edema*

Absence of Serum Inhibitor of C′1-Esterase

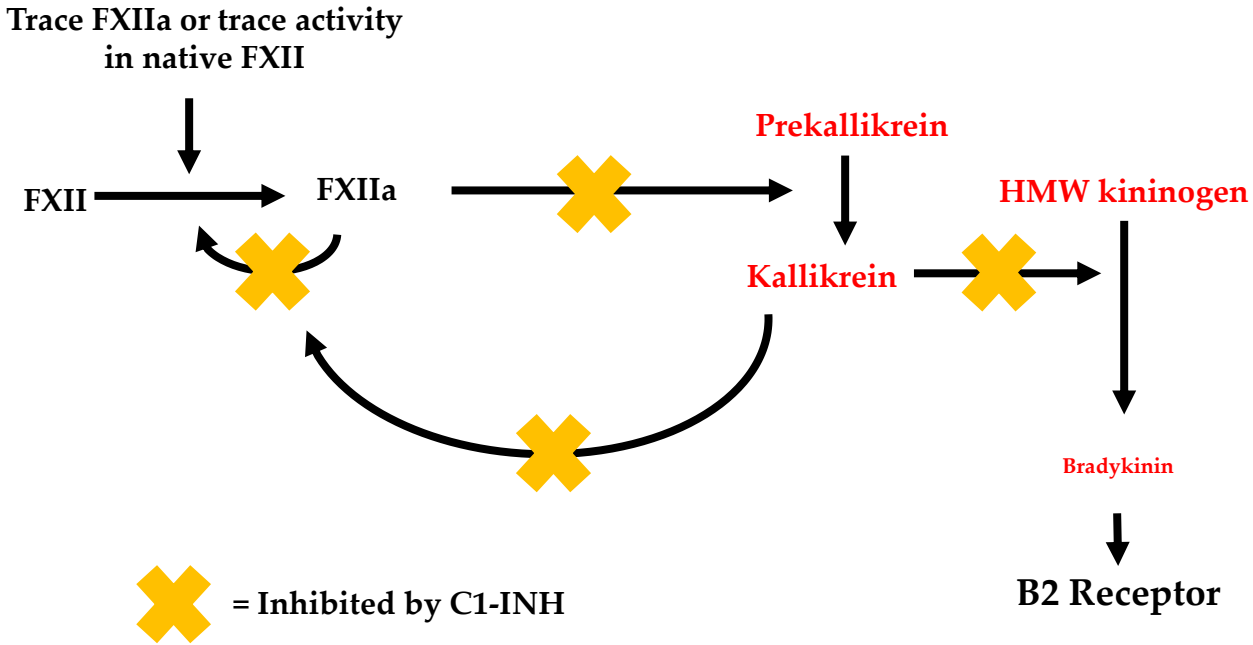
VIRGINIA H. DONALDSON, M.D.† *and* RICHARD R. EVANS, M.D.

Plasma Kallikrein-Kininogen Pathway



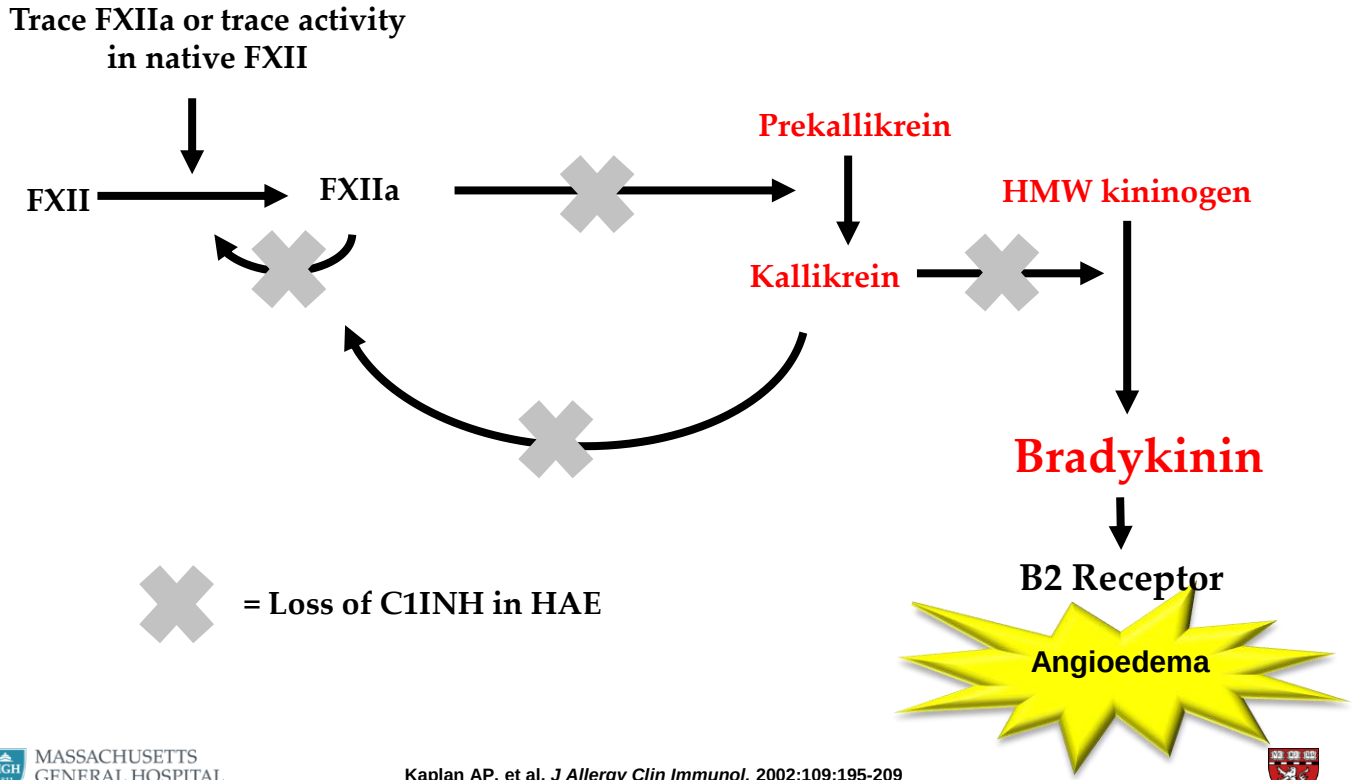
Kaplan AP, et al. *J Allergy Clin Immunol.* 2002;109:195-209

Role of C1 Inhibitor Protein



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

HAE: Generation of Bradykinin



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

Clinical Presentation

Angioedema

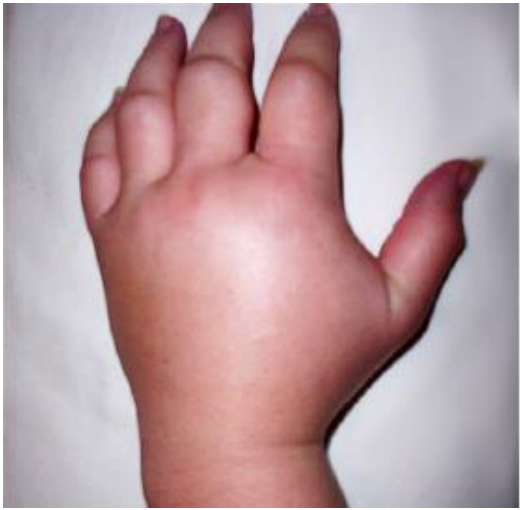
- Repeated bouts of swelling of the face, extremities, genitals, intestines and larynx

No Urticaria

- Edema is *not* warm, usually nonpruritic and nonpitting
- Erythema marginatum present but **no urticaria**

HAE Extremity Attacks

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

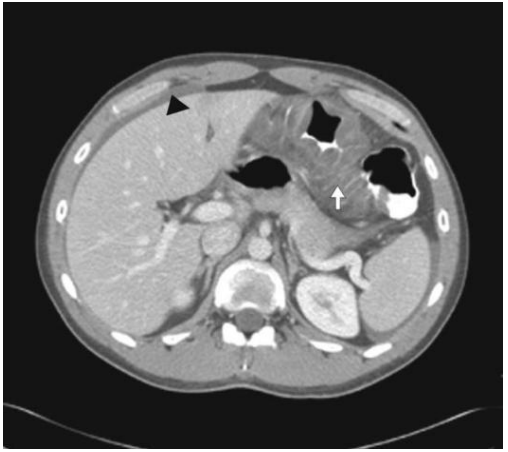


Peripheral Angioedema

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

HAE Abdominal Attacks

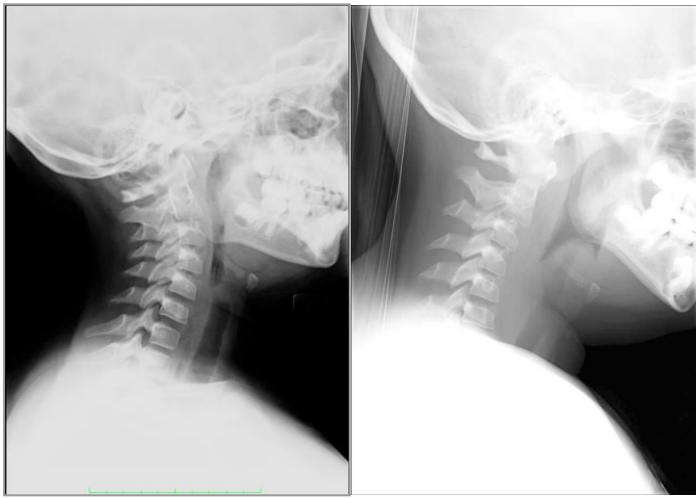
- Occur in >90% of patients with HAE
- Can be mild to severe colicky pain
- Vomiting common
- Functional intestinal obstruction
- Protuberant abdomen, tenderness, and rebound possible
- Fluid loss leads to hemoconcentration and hypovolemic shock
- Symptoms mimic surgical emergencies, resulting in misdiagnosis 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 with HAE during their lifetime
- Requires airway management to prevent asphyxiation
- Even higher concern in children, given the increased risk of asphyxiation 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.

Laboratory Evaluation in Recurrent Angioedema

	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 with normal labs	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

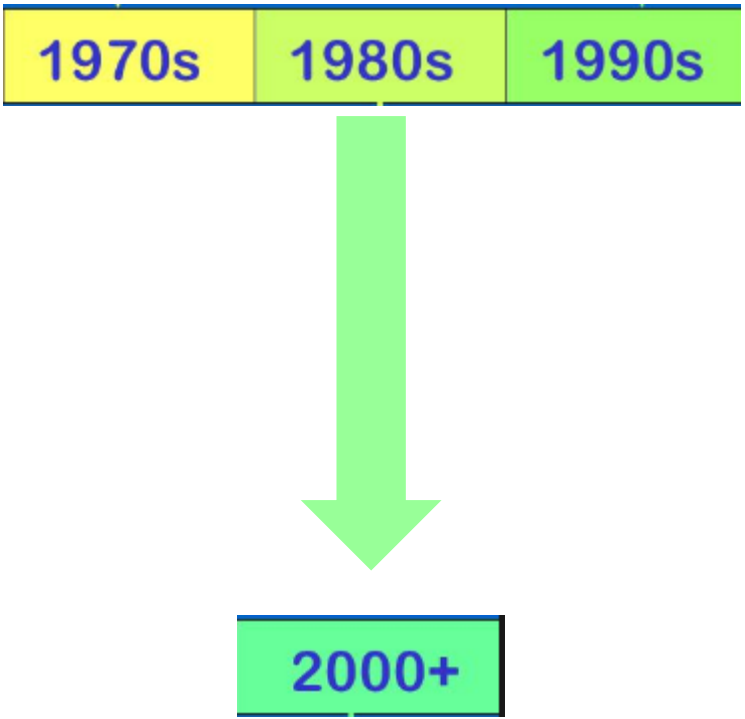
HAE Treatment: Three Goals

- Acute attacks
  - Resolve angioedema symptoms as quickly as possible during an attack
- Long-term prophylaxis
  - Decrease the overall number and severity of angioedema attacks
- Short-term prophylaxis
  - Reduce the likelihood of swelling in response to anticipated events that are likely to precipitate an attack (e.g., medical or dental procedures)

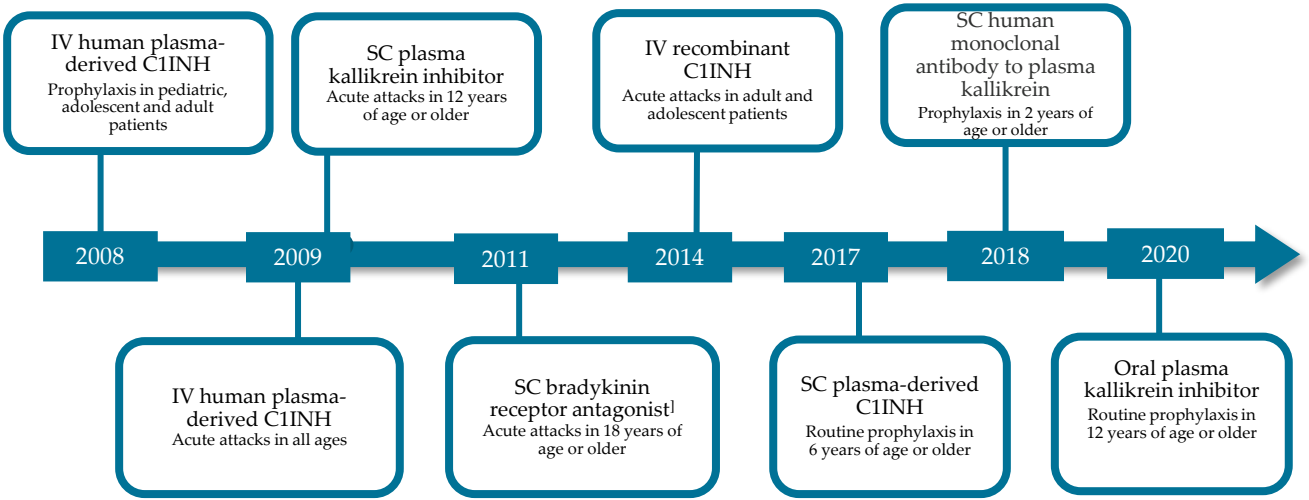
Circardi M, et al. *Allergy*. 2012

“Older” Options for Treatment of HAE

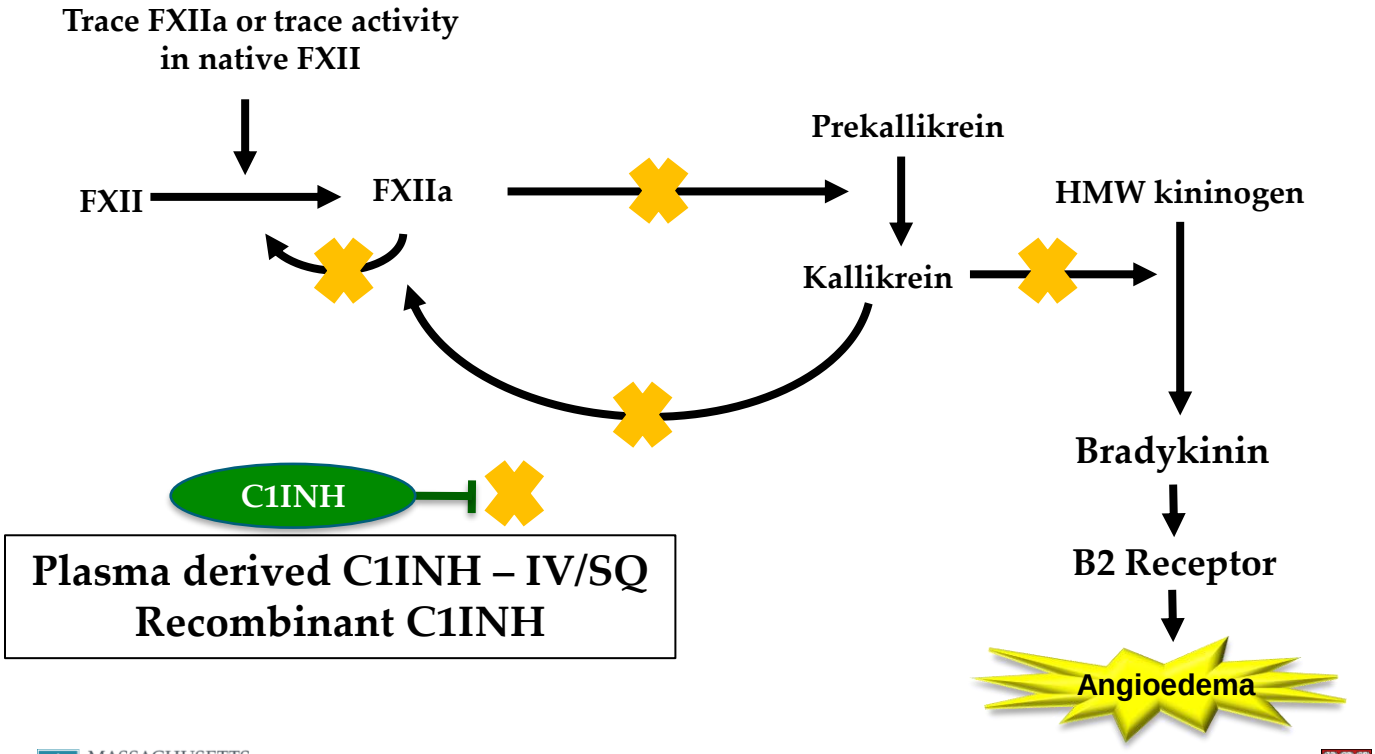
- Acute treatment
  - Supportive care
  - FFP
- Long-term prophylaxis
  - Antifibrinolytics
  - Anabolic androgens
- Short-term prophylaxis
  - FFP
  - Anabolic androgens



Treatment for Patients with Hereditary Angioedema: *United States*

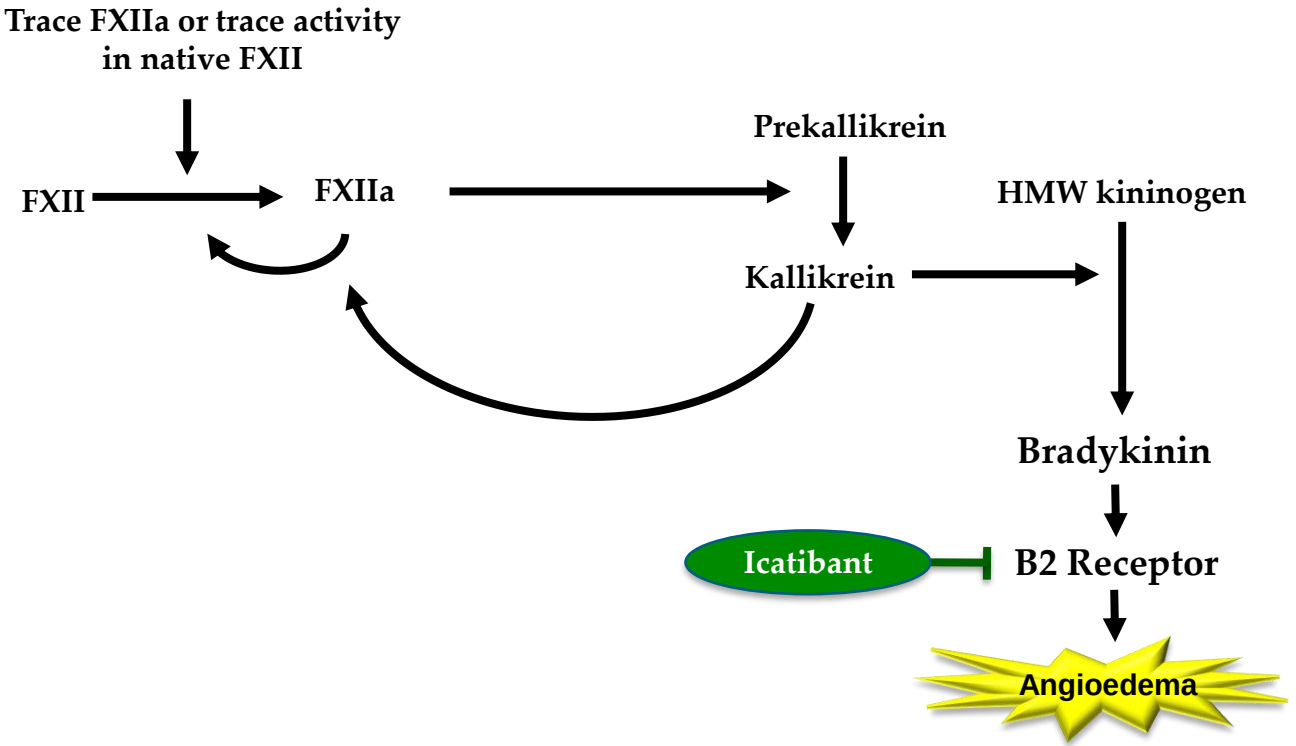


FDA Approved Therapies for HAE



Chen, Riedl. *Immunol Allergy Clin North Am. 2017 Aug*

FDA Approved Therapies for HAE



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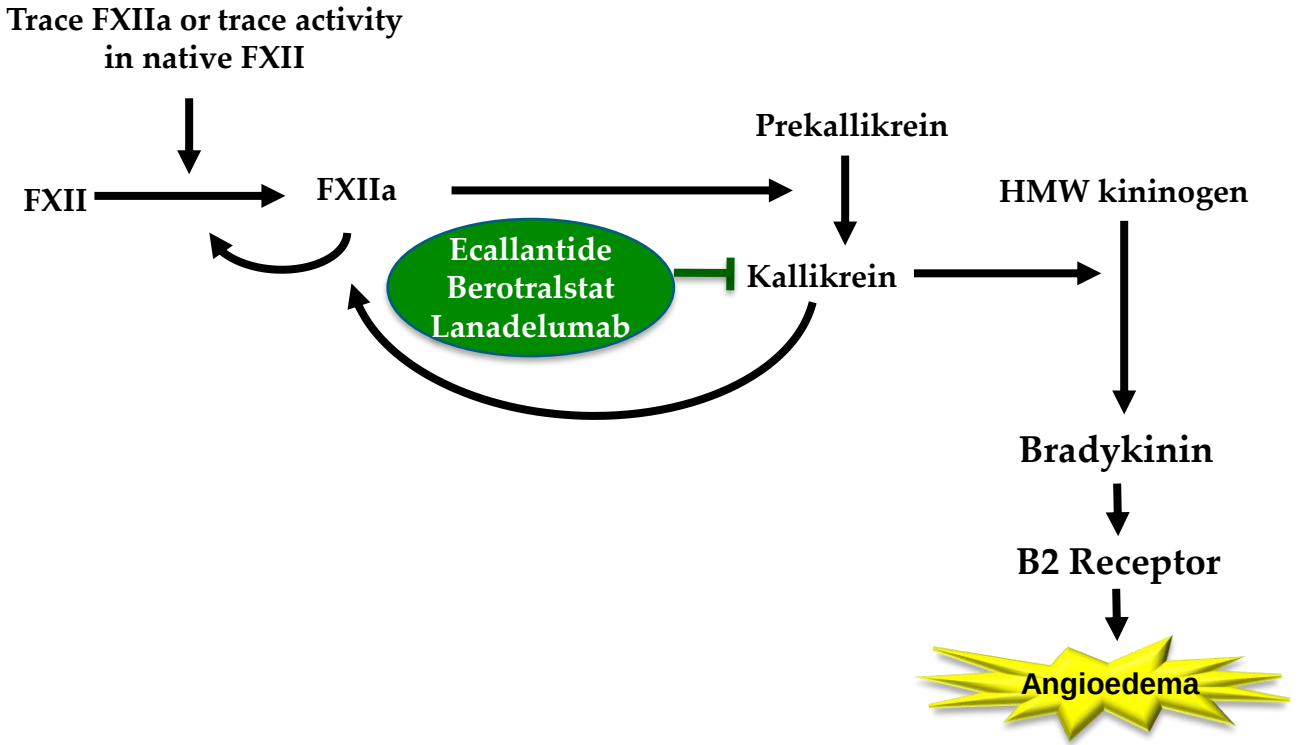

Chen, Riedl. *Immunol Allergy Clin North Am. 2017 Aug*

HAE: Guideline Based Care

POSITION ARTICLE AND GUIDELINES Open Access

The international WAO/EAACI guideline for the management of hereditary angioed – the 2017 revision and update

Marcus Maurer[1*†], Markus Magerl[1†], Ignacio Ansotegui[2], Emel Aygören-Pürsün[3], Stephen Be Tom Bowen[6], Henrik Balle Boysen[7], Henriette Farkas[8], Anete S. Grumach[9], Michihiro Hide[10], Richard Lockey[12], Hilary Longhurst[13], Alexander Nast[17], Ruby Pawankar[18], Mario Sánchez-Borges[23], Yuxiang Zh

CrossMark

Original Article

US Hereditary Angioedema Association Medical Advisory Board 2013 Recommendations for the Management of Hereditary Angioedema Due to C1 Inhibitor Deficiency

ernstein, MD[d], Paula J. Busse, MD[e], ael M. Frank, MD[h], Henry H. Li, MD[i], William R. Lumry, MD[j], alif; Boston, Mass; Cincinnati, Ohio; New York and Mineola, NY;

Management of Children With Hereditary Angioedema Due

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI

imothy Craig, D,[h] William

ORIGINAL ARTICLE

International consensus on the d of pediatric patients with heredit inhibitor deficiency

H. Farkas[1], I. Martinez-Saguer[2], K. Bork[3], T. Bowen[4], T. A. S. Grumach[8], A. Luczay[9], L. Varga[1] & A. Zanichelli[1]

POSITION ARTICLE AND GUIDELINES Open Access

Canadian hereditary angioedema guideline

Stephen Betschel[1*], Jacquie Badiou[2], Karen Binkley[1], Jacques Hébert[3], Amin Kanani[4], Paul Keith[5], Gina Lacuesta[6], Bill Yang[7], Emel Aygören-Pürsün[8], Jonathan Bernstein[9], Konrad Bork[10], Teresa Caballero[11], Marco Cicardi[12], Timothy Craig[13], Henriette Farkas[14], Hilary Longhurst[15], Bruce Zuraw[16], Henrik Boysen[17], Rozita Borici-Mazi[18], Tom Bowen[19], Karen Dallas[20], John Dean[21], Kelly Lang-Robertson[1], Benoît Laramée[22], Eric Leith[23], Sean Mace[1], Christine McCusker[24], Bill Moote[25], Man-Chiu Poon[26], Bruce Ritchie[27], Donald Stark[4], Gordon Sussman[1] and Susan Waserman[5]

Individualized Management Plans

- All patients should have on demand treatment available
- Patients should be counseled to treat as soon as the attack is clearly recognized
- All patients should be trained in self-administration
- Consider unique needs of each patient

Prophylactic Treatment Recommendations

- All patients are candidates for long-term prophylaxis
- Disease burden and patient preference should be taken into strong consideration
- C1-Inhibitor recommended for first-line treatment
  - *Prior to FDA-approval of lanadelumab and berotralstat*
- Suggest modification of long-term prophylaxis in terms of dosage and time interval to minimize burden of disease

On Demand Treatment Recommendations

- All patients should have at least 2 doses of on demand treatment
- All attacks are eligible for treatment with on demand medication
- Attacks should be treated as early as possible - when recognized as an attack
- On demand medications should be self—administered whenever feasible to minimize delay in treatment