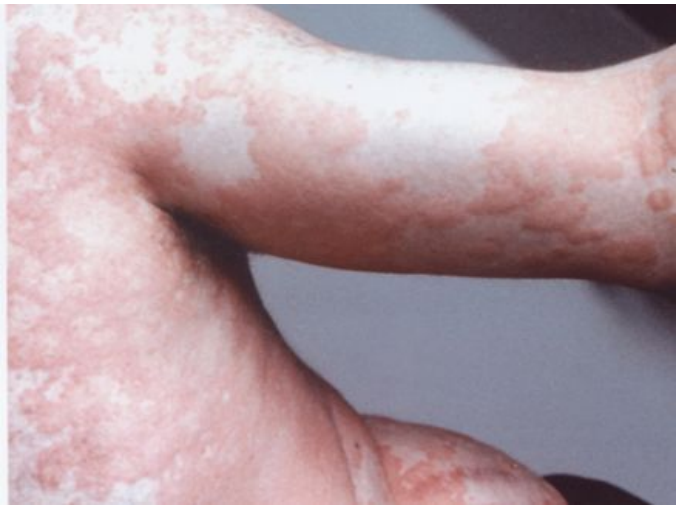
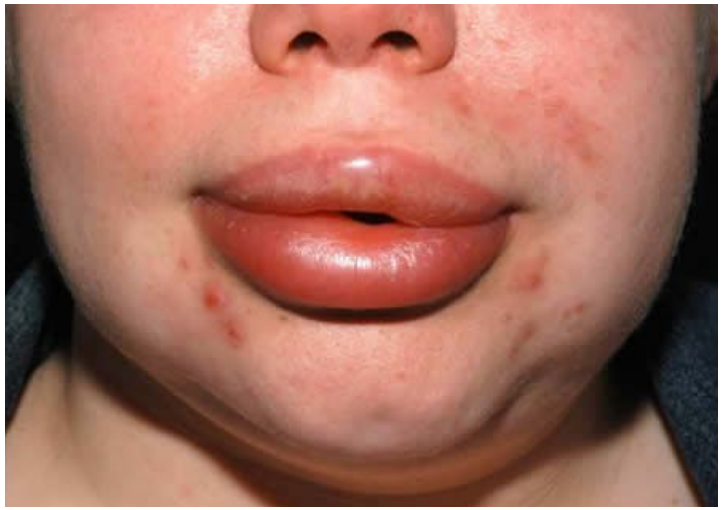
Angioedema: Allergic and Non-Allergic Variants





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Disclosures

- No relevant conflict of interests to disclose

Objectives

- Identify Angioedema in patients with or without urticaria
- Discuss pathophysiology different mechanisms leading to Angioedema (allergic v. non-allergic)
- Provide an approach to diagnose and manage patients
  - Allergic Angioedema
  - Acquired Angioedema
  - ACE inhibitor Angioedema
  - Hereditary Angioedema (Type I, Type II and HAE normal complement)

Angioedema

- Definition: Increased permeability of blood vessels (“angio”) leads to swelling of the deep dermal and subcutaneous or submucosal tissues (“edema”)
- Angioedema is characterized by:
  - A sudden, pronounced erythematous or skin-colored deep swelling in the lower dermis and subcutis or mucous membranes
  - Tingling, burning, tightness, and sometimes pain rather than itch
  - A resolution slower than that of wheals (can take up to 72 hours)
- Chronic spontaneous (“autoallergy”) urticaria presents with:
  - Urticaria-predominant phenotype in 50% of patients
  - Urticaria and angioedema in 40% of patients
  - Mainly angioedema in 10%

The EAACI/GA²LEN/EuroGuiDerm/APAACI guidelines for the definition, classification, diagnosis and management of urticaria. Allergy. 2022;Mar 77(3):734-66

Classification of Angioedema

- Angioedema is typically broadly classified as:
  - **Histamine**-mediated vs. **Bradykinin**-mediated
- **Histamine-mediated angioedema** (“histaminergic,” mast-cell mediated):
  - Responds to antihistamines, corticosteroids, and epinephrine
  - Can be part of an allergic or anaphylactic reaction – e.g., food, venom, drug allergy
    - Chronic spontaneous (“autoallergic”) angioedema (and urticaria)
      - Angioedema occurs with or without urticaria
      - Omalizumab (anti-IgE) treatment for antihistamine resistant cases
- **Bradykinin-mediated angioedema**
  - Angioedema **without urticaria**
    - ACE inhibitors
    - Hereditary angioedema (HAE) - C1 inhibitor deficiency or low C1 inhibitor function
    - Acquired Angioedema (AAE) - Acquired C1 inhibitor deficiency
  - **Does NOT respond to** epinephrine, antihistamines, or corticosteroids

Causes of Angioedema

Histaminergic

- IgE mediated: foods, venom, drugs
- Non-IgE mediated:
  - Radiocontrast Media
  - Opioids
  - Vancomycin
- Chronic spontaneous ("autoallergy") urticaria/angioedema
  - Mast cell mediated
  - Idiopathic
- Physical urticaria/angioedema
- NSAIDs/ASA

Non-Histaminergic (Bradykinin)

- ACE inhibitors
- Hereditary Angioedema (HAE): C1-INH deficiency
  - HAE Type I: low C1-INH
  - HAE Type II: poor C1-INH function
  - "Hereditary with normal C1-INH"
    - Estrogen exacerbated
    - Bradykinin mediated
    - Multiple pathway defects
- Acquired Angioedema (AAE)
  - Lymphoproliferative Disorders
  - Autoimmune Diseases

Clinical Course Distinguishes Pathophysiology of Angioedema

	Histaminergic / Mast Cell mediated	Non-Histaminergic / Kinin Mediated
Urticaria	Yes	No
Pruritus	Yes	No
Pain / Burning / Tingling	No	Often present
Response to Antihistamines	Yes	No
Response to Steroids	Yes	No
Onset ("Trajectory")	1-4 hours	12-36 hours
Duration	Less than 12 hours	2-4 days

Maurer M, et al, *Clin Rev Allergy Immunology.* 2021.

Bernstein JA, et al, *Int J Emerg Med.* 2017

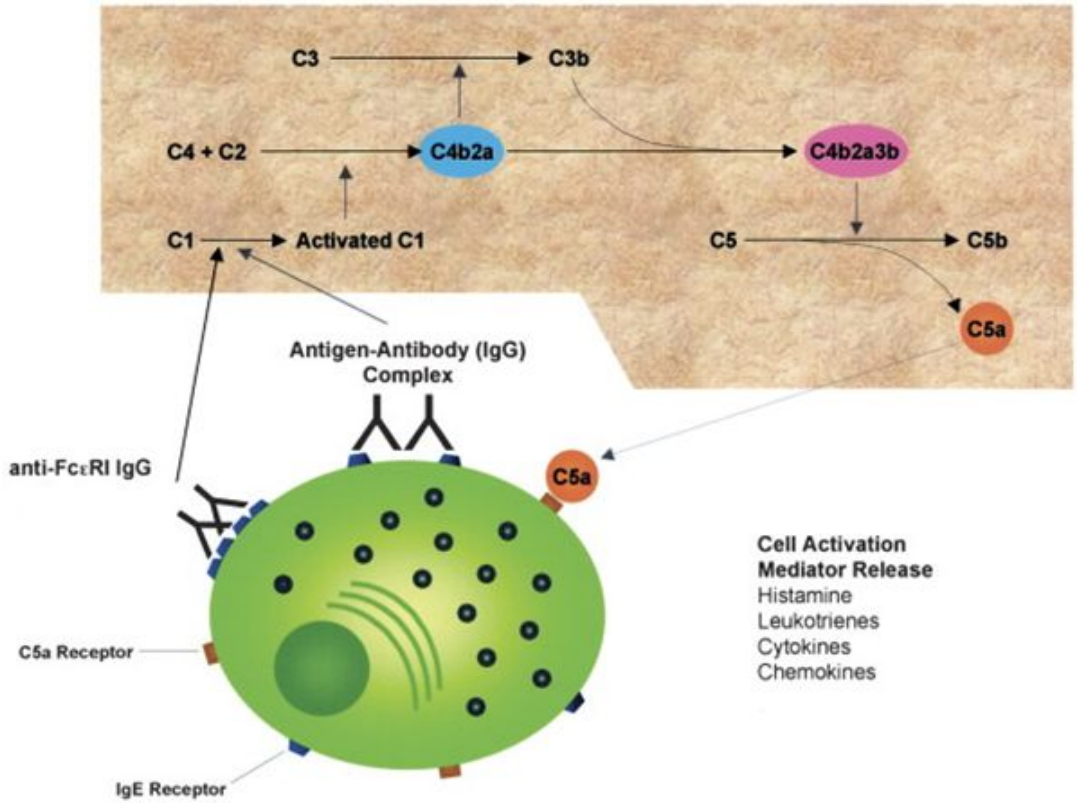
Histamine Mediated Angioedema: Pathophysiology

Degranulation of mast cells and basophils

- Release of histamine, prostaglandin metabolites, leukotrienes, platelet activating factor, and other proinflammatory mediators
- Chemokines from mast cells recruit other cell types

Autoimmunity or Autoreactive IgE

- IgG may react with the IgE receptor (30-45%)
  - Chronic Urticaria Histamine Release Assay



Kaplan. J Allergy Clin Immunol 2004;114:465-74

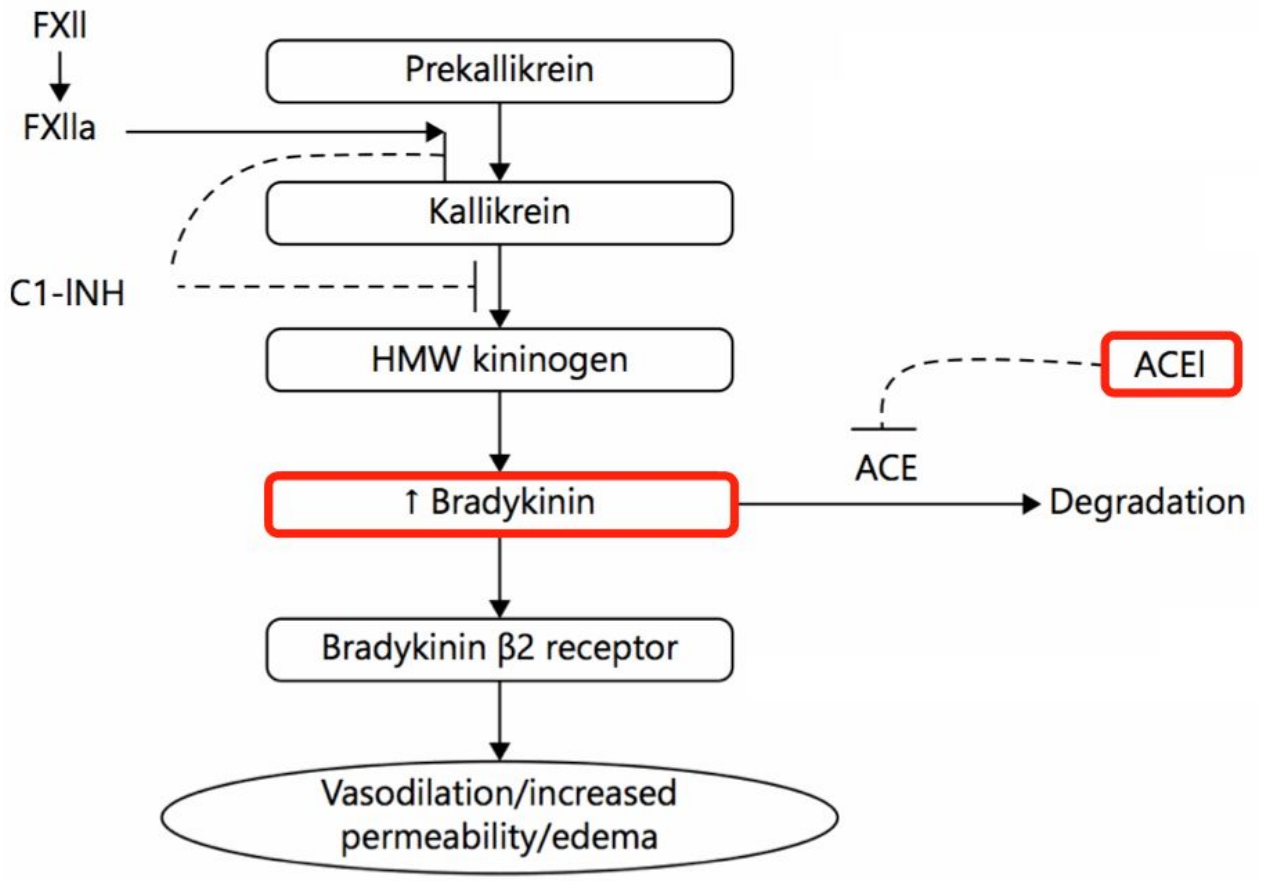
Giménez-Arnau et al. J Allergy Clin Immunol 2000;105:664-72.

Saini et al. J Allergy Clin Immunol Pract 2020;8:1866-74

Bradykinin Mediated Angioedema: Overview

- Hereditary Angioedema
- Acquired Angioedema

- ACE-I induced angioedema



Craig 2014 Int Arch Allergy Immunol

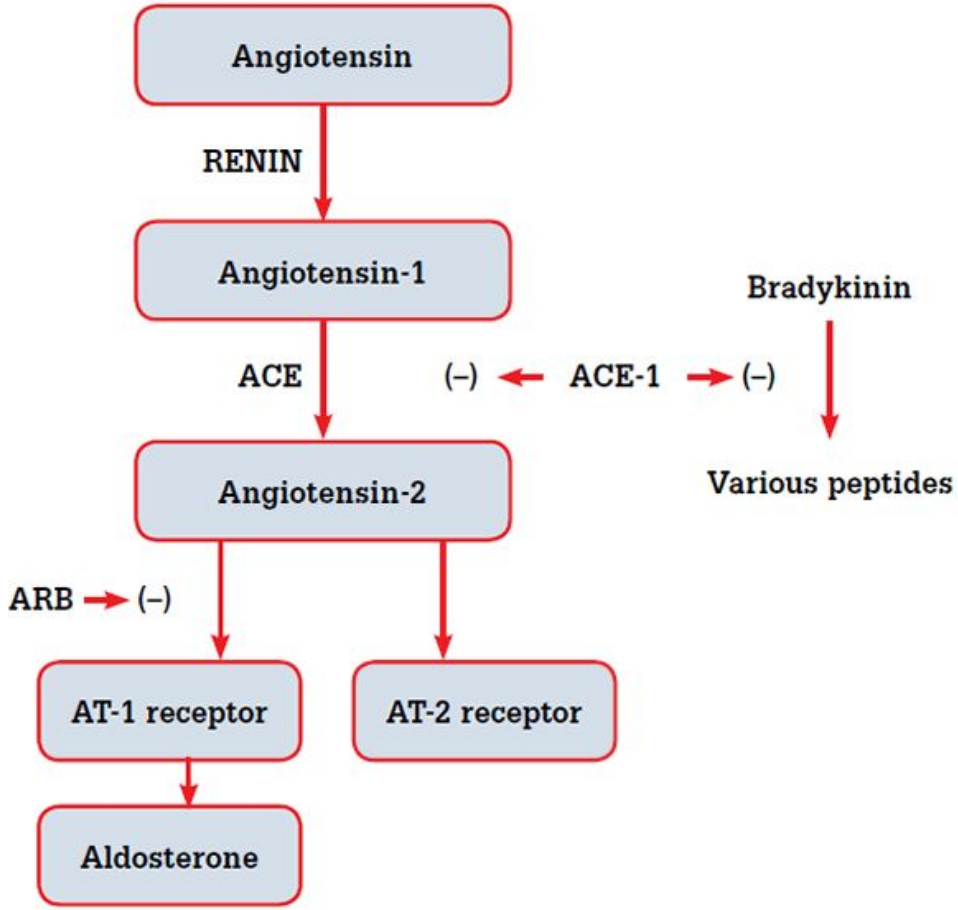
Kim SJ, etc al. *Ann Allergy Asthma Immunol. 2014.* Medscape.

Banerji A, etc all, *J Allergy Clin Immunology Pract.* 2017

ACE-I Induced Angioedema

- Approximately 35% of hypertension prescriptions are for ACE inhibitors with over 40 million patients on an ACE-I
- ACE-I induced angioedema:

- Incidence: 0.1-0.7%
- Accounts for 20%-40% of ER visits for angioedema
- 2/3rd occur within the first three months of therapy
- Occurs more frequently in African Americans, those over 65, and smokers



Banerji A, etc all, *J Allergy Clin Immunology Pract.* 2017. Royal Australian College of General Practitioners (RACGP). Zuraw BL, etc all, *J Allergy Clin Immunology.* 2013

Acquired Angioedema (AAE): Overview

- Acquired angioedema due to C1 inhibitor deficiency presents with similar symptoms
- Patients are often middle-aged or older
- Underlying mechanism is not due to impaired synthesis or function of C1 esterase inhibitor, but rather due to **increased catabolism of C1 esterase inhibitor**
- **C1q is often low**
- Acquired Angioedema just as HAE is similarly classified as type I or type II
- Type 1 is often associated with lymphoproliferative disorders
  - Most common: **Non-Hodgkin's Lymphoma**
- Type II is often associated with monoclonal gammopathy and auto-antibodies directed towards the C1 esterase inhibitor

Zuraw BL, etc all, *J Allergy Clin Immunology.* 2013.

Riedl M, etc all. *Ann Allergy Asthma Immunol.* 2011.

Breitbart SI, Bielory L. *Allergy Asthma Proc.* 2010

Hereditary Angioedema (HAE)

- HAE is a rare, potentially life-threatening condition
- HAE with C1 inhibitor deficiency is autosomal dominant
- Prevalence is 1:10,000 to 1:50,000
- Women have more severe course of HAE than men
- HAE is often under recognized, delay to diagnosis 8-10 years – leads to inappropriate treatment for histamine-mediated angioedema (e.g., antihistamines and glucocorticoids)
- HAE I & II mean age of onset 8-12 years, usually worsens during puberty
  - Patients with early symptom onset affected more severely than those with late onset
- Disease severity is highly variable
  - Between patients and within families
  - No correlation between disease severity and C1 INH concentration
  - 1/3 few symptoms, 1/3 intermittent, 1/3 severe
- Family history is key, but 25% of mutations are de novo

Adapted from Farkas H, et.al. JACI 2013; 131(3):909-11.

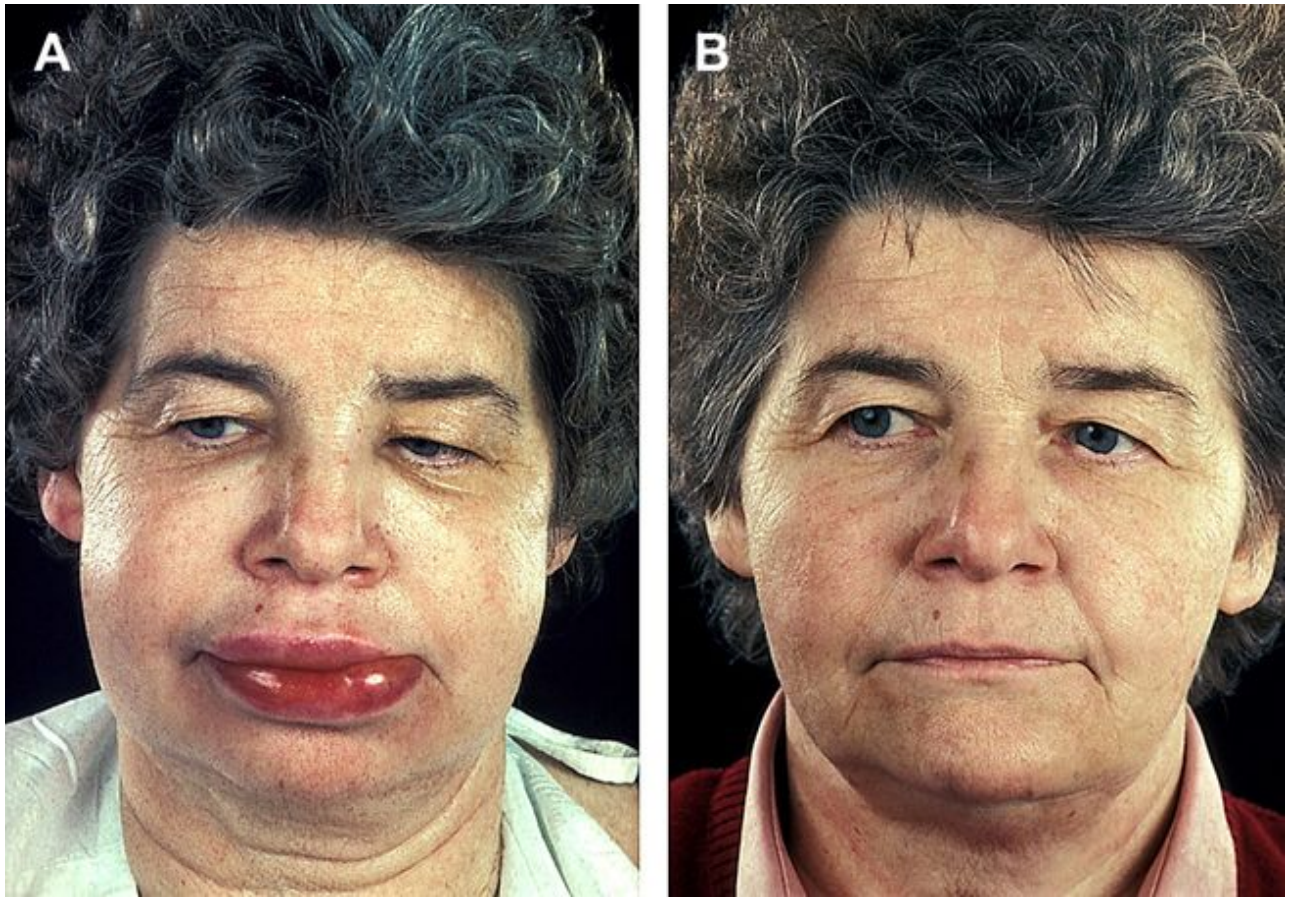
HAE Clinical Manifestations

- Recurrent, episodic symptoms of angioedema last 2-5 days
- Asymmetric, nonpruritic, disfiguring, without urticaria
- Involves face, lips, tongue, throat, ears, hands and feet, bowel wall, and genitalia
- Laryngeal episodes – account for only <1% of attacks, but >50% of patients have laryngeal attack during lifetime, can be initial presentation
- Abdominal attack manifestation
  - Severe abdominal pain and/or swelling; can mimic acute abdomen
  - Abdominal ultrasound or CT – bowel wall edema – circumferential thickening of bowel wall, +/- ascites, no associated lymphadenopathy

HAE Clinical Manifestations, cont.

- Other rare areas: bladder, muscle, joint swelling
- Swelling attack can be preceded by prodromal symptoms
  - Erythema marginatum – serpiginous, non-pruritic rash (not to be confused with urticaria) in one-third of patients
  - Fatigue, tingling at site of emergent swelling
- Triggers: Exogenous estrogen, infections, trauma, stress
  - Invasive dental or surgical procedures

ATTACK RESOLUTION



Bork K, et al. JACI 2009;124(1):129-34

HAE Attacks Can Be Frequent, Prolonged, and Debilitating

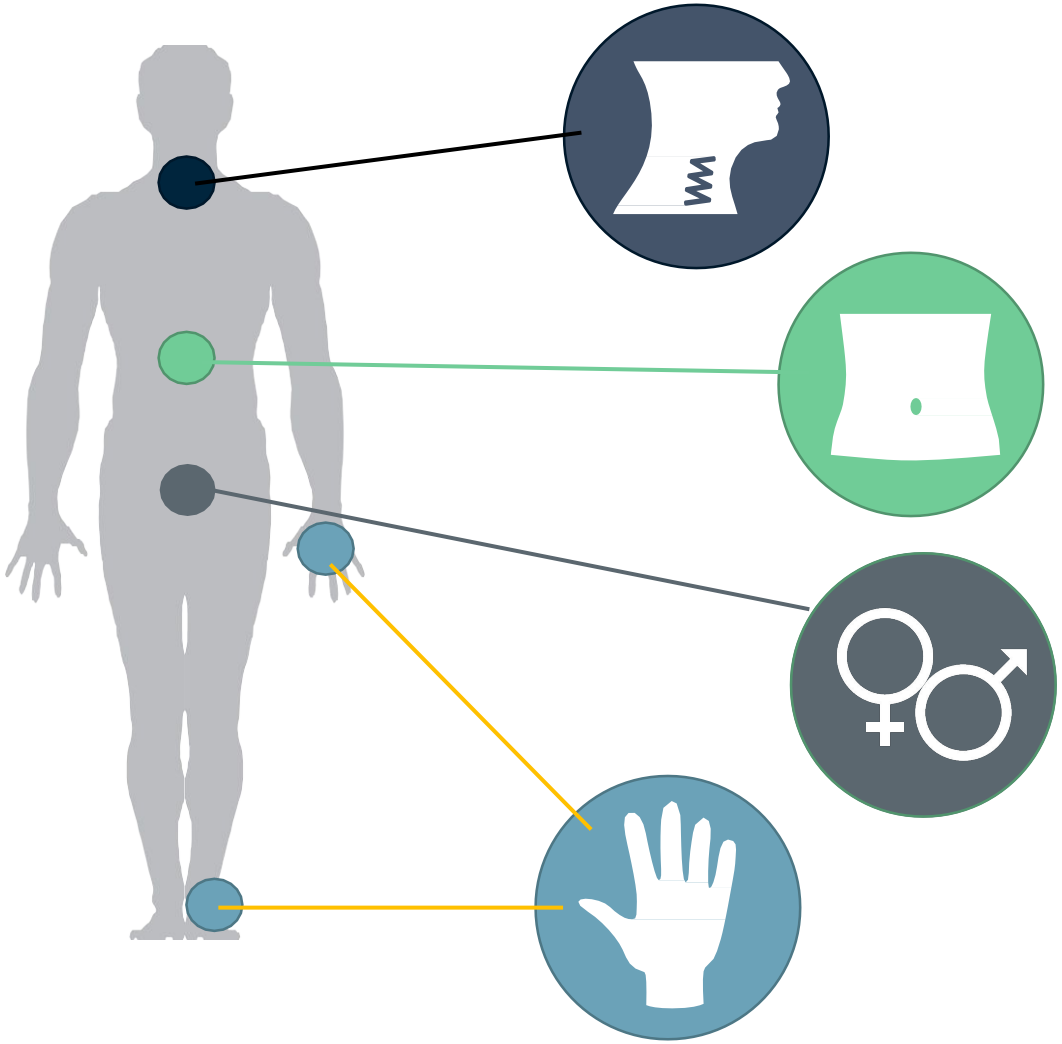
Swelling gradually worsens over **24 to 36 hours**, intensifies, and then resolves over 48 hours[1]

On average, patients not taking prophylaxis experience 1 to 3 attacks per month, potentially resulting in **20 to 100 days of incapacitation** every year[2]

75% of patients with HAE experience an attack at least once a year[2]

1. Johnston D, et al. *J Am Osteopath Assoc*. 2011;111:28-36.
2. Bernstein JA. *Allergy Asthma Proc*. 2013;34:3-6

HAE Attack Locations



Larynx
Swelling of the airway can promote voice changes, shortness of breath, and, in severe cases, asphyxiation[1]

Abdomen
Submucosal edema of the small bowel can result in intense pain, vomiting, diarrhea, and abdominal cramping,[2] and ascites can occur if untreated

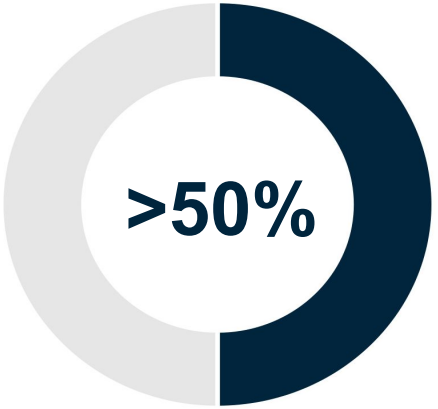
Genitals
Swelling of the genitals can be triggered by bike riding, intercourse, etc. and cause swelling and discomfort [3]

Extremities
Swelling of the extremities (hands, arms, legs, feet, and thighs) can be functionally disabling

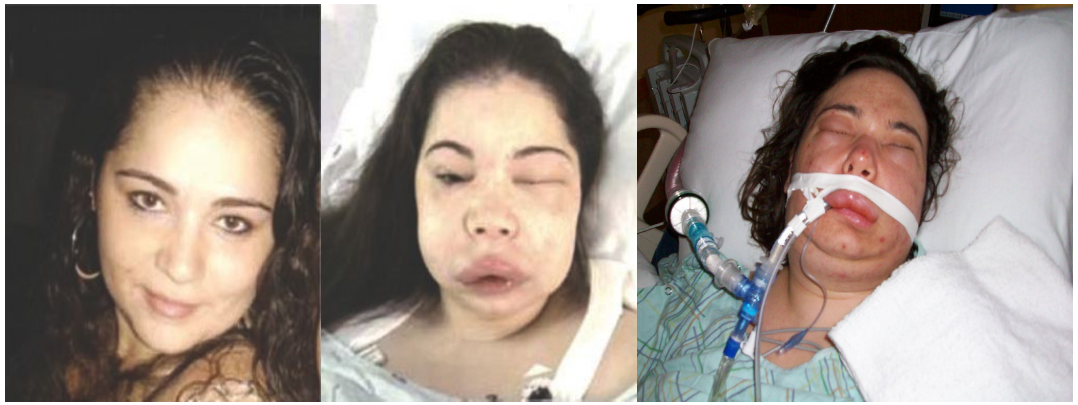
1. Bork, et al. *Am J Med*. 2006;119:267-274. 2. Rubinstein, et al. *BMC Gastroenterology*. 2014;14:71. 3. Caballero, et al. *J Clin Immunol*. 2012;129(2):308-20.

Laryngeal Attacks Present High Risk for Asphyxiation

- Can occur in association with facial or tongue swelling
- Patients can experience dysphonia (voice changes), dysphagia, dyspnea, and, in severe cases, asphyxiation
- Untreated laryngeal attacks have a high rate of mortality estimated to be between 15% and 33%



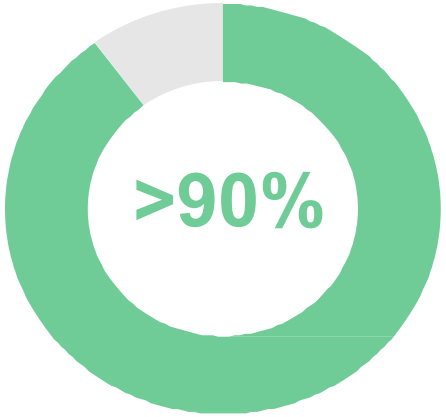
>50% of patients experience laryngeal attacks at least once in their lifetime[1]



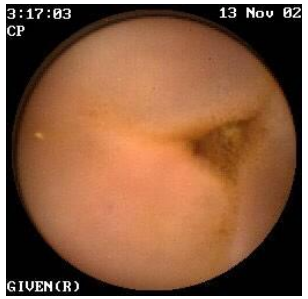
1 Christiansen S, et al. *Am J Rhinol Allergy*. 2011;25:379-382. Banerji E, et al. *Allergy Asthma Proc.* 2018;39(3):212-23.

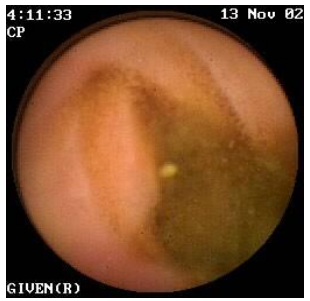
Abdominal Attacks Can Cause Severe Pain for Patients With HAE

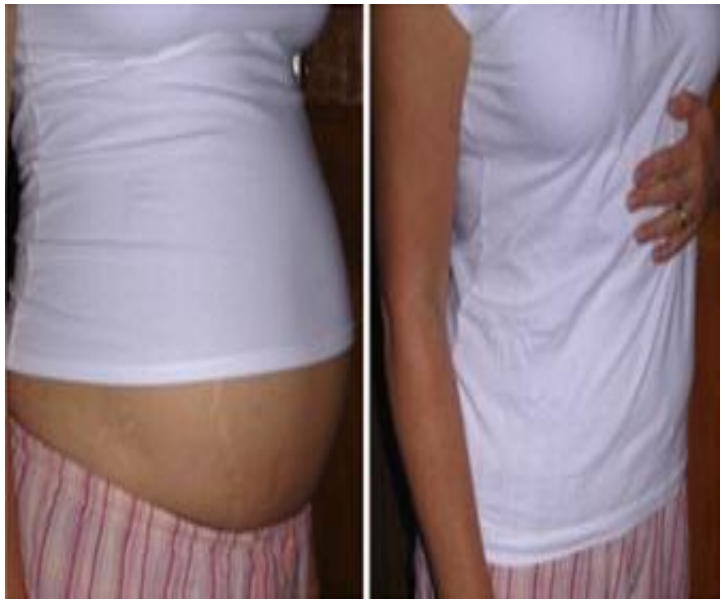
- Can produce severe abdominal pain as well as vomiting, diarrhea, and abdominal cramping and tenderness[1]
- Symptoms can resemble other diseases and, as a result, can often lead to misdiagnosis[1]



Abdominal attacks occur in >90% of patients[2]



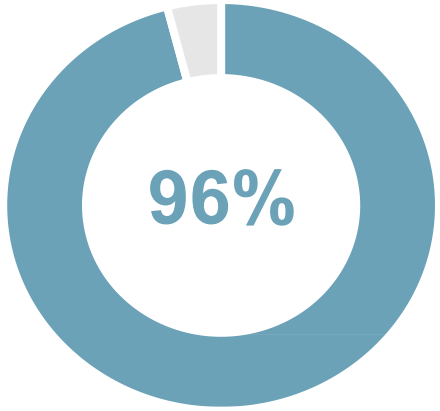




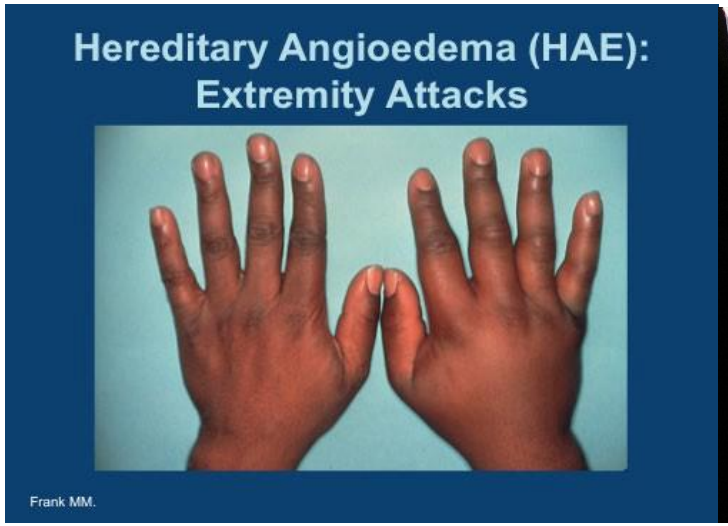
1. Rubinstein, et al. *BMC Gastroenterol*. 2014;14:71. 2. Bork, et al. *Am J Med.* 2006;119:267-274.

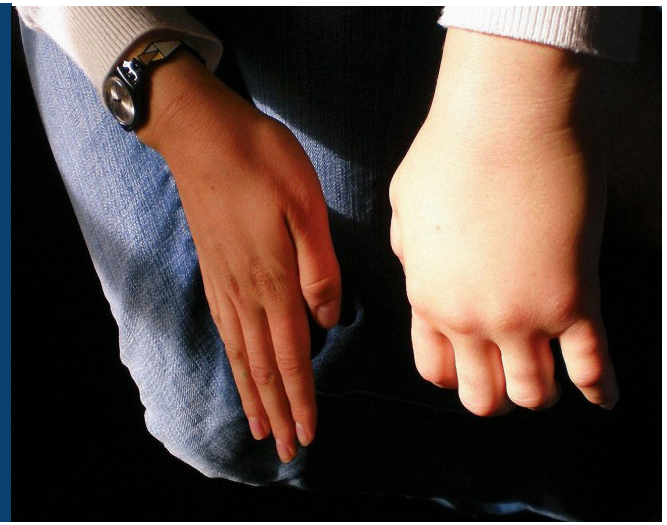
Extremity Attacks Are Most Common Among Patients With HAE

- They often disrupt a patient's ability to perform activities of daily living (eg, typing, writing, walking)
- Although these episodes rarely lead to hospital stays, they can disrupt a patient's normal life (eg, school, work, social life)



Extremity attacks occur in 96% of patients with HAE[2]

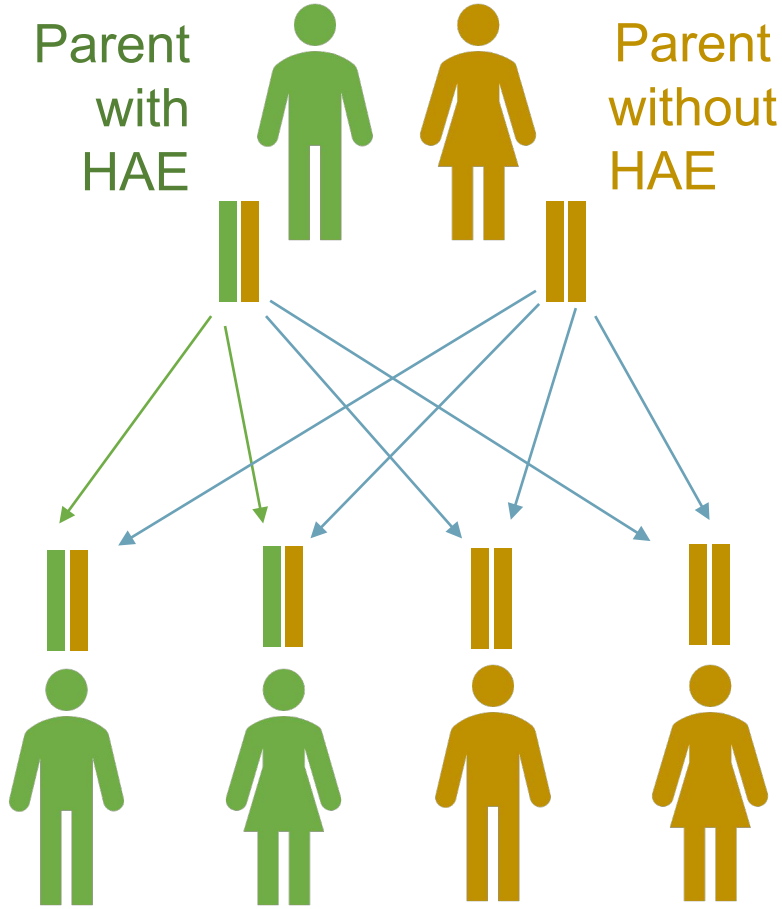




Johnston D, et al. *J Am Osteopath Assoc*. 2011;111:28-36

HAE with C1-Esterase Inhibitor Deficiency Is an Autosomal-Dominant Genetic Disease

- Although most cases are a result of autosomal-dominant inheritance, 25% of cases result from a spontaneous mutation of the C1 esterase inhibitor gene in patients with no family history[2]
- HAE is genetic, primarily caused by loss-of-function mutations in SERPING1 (Chromosome 11q), which encodes the C1 esterase inhibitor[1]
- Offspring have a 50% likelihood of inheritance when 1 parent has HAE[2]
- Phenotypic expression varies
- Females can have a more severe disease pattern due to estrogens[2]



1. Bernstein JA. *Am J Manag Care*. 2018;24:s292-s298.
2. Johnston D, et al. *J Am Osteopath Assoc.* 2011;111:28-36.

HAE Is Classified Based on C1-INH Levels and Activity

Mutations in the C1 esterase inhibitor gene cause a decrease in the levels or function of C1-INH, leading to the classification of different types of HAE

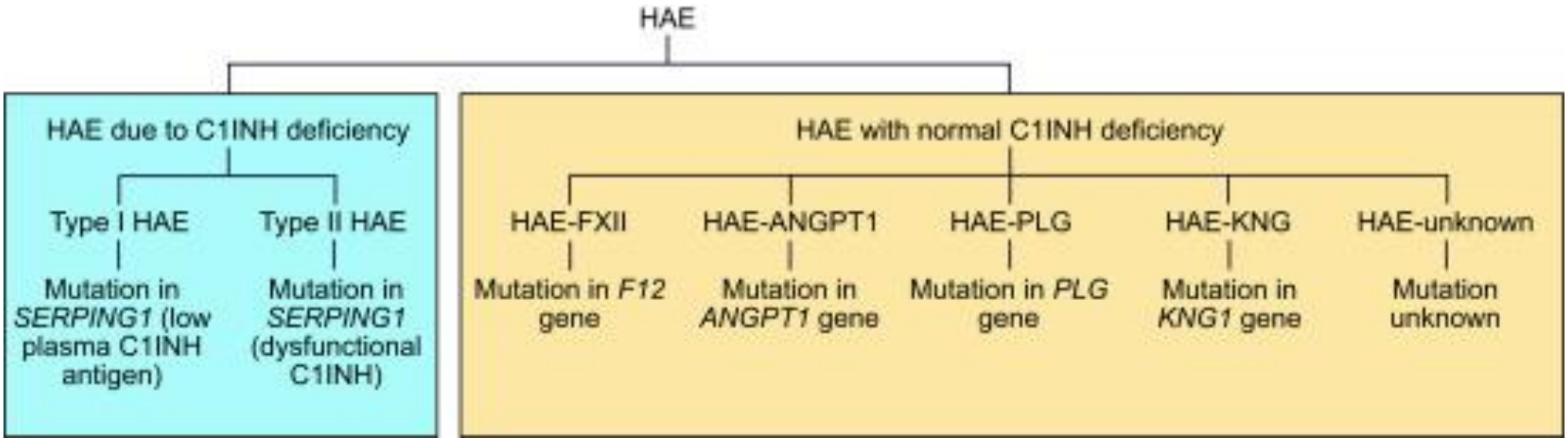
Levels and function of C1-INH are normal

Previously called "Type 3 HAE"

	Type 1 HAE	Type 2 HAE	HAE w/ Normal C1-INH
	Occurs in ~**85%** of all C1- INH deficiency HAE cases	Occurs in ~**15%** of all C1- INH deficiency HAE cases	**Unknown**[2]
C1-INH levels:	**Low**	**Normal**	**Normal**
C1-INH function:	**Low**	**Low**	**Normal**

1. Zuraw. *N Engl J Med*. 2008;359:1027-1036.
2. Longhurst and Bork. *Br J Hosp Med*. 2019;80:391-398

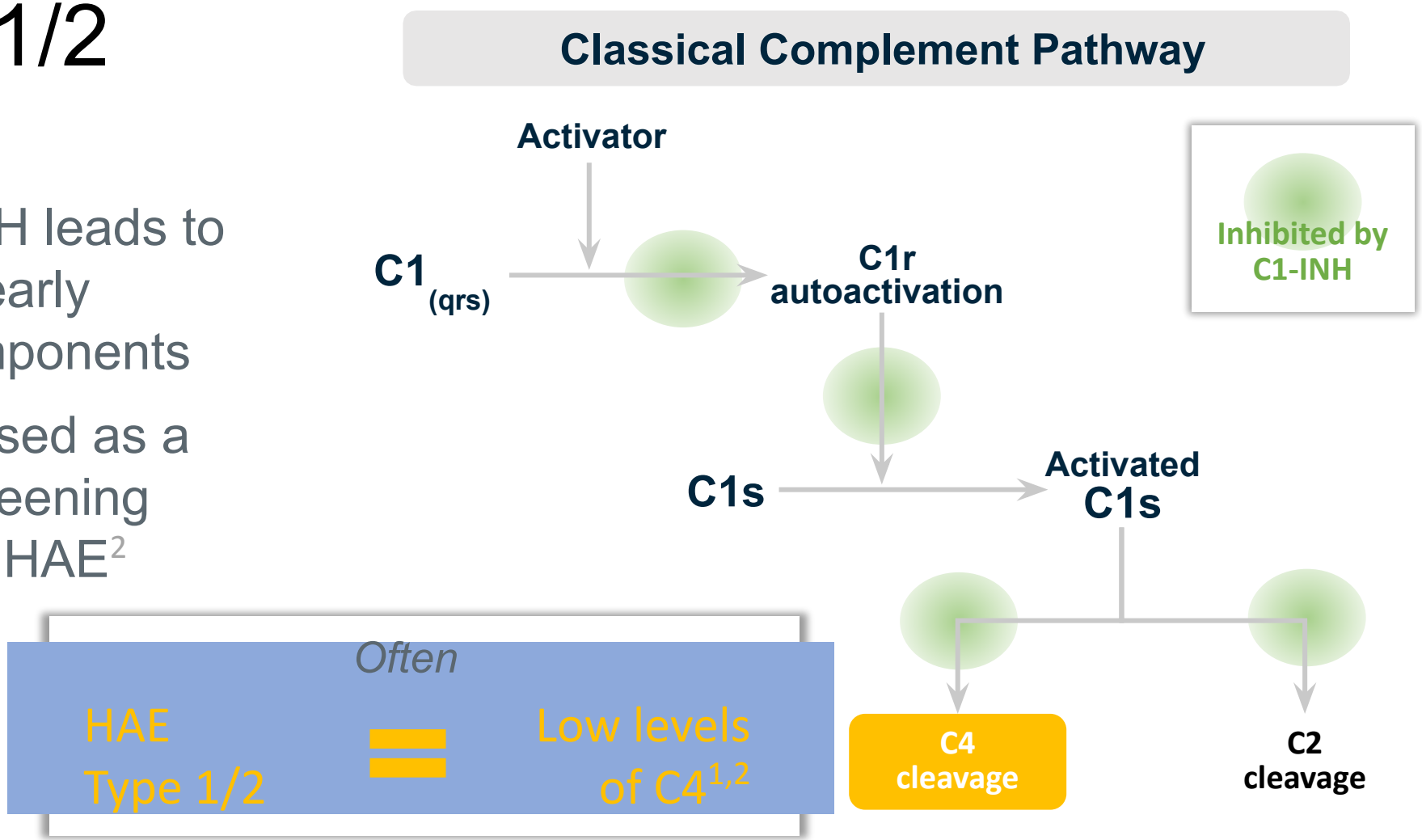
Hereditary Angioedema Classification



Busse et al. (2021) US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. JACI: In Practice, Volume 9, Issue 1, P132-150. https://doi.org/10.1016/j.jaip.2020.08.046

C4 levels Often Low in Patients with HAE Type 1/2

- Defects in C1-INH leads to consumption of early complement components
- Low C4 can be used as a biomarker for screening C1-INH-deficient HAE[2]



1. Kaplan A, et al. *J Allergy Clin Immunol*. 2010;125:918-925.
2. . Kaplan A, et al. *Front Med.* 2017;4:1-8.

Diagnosis

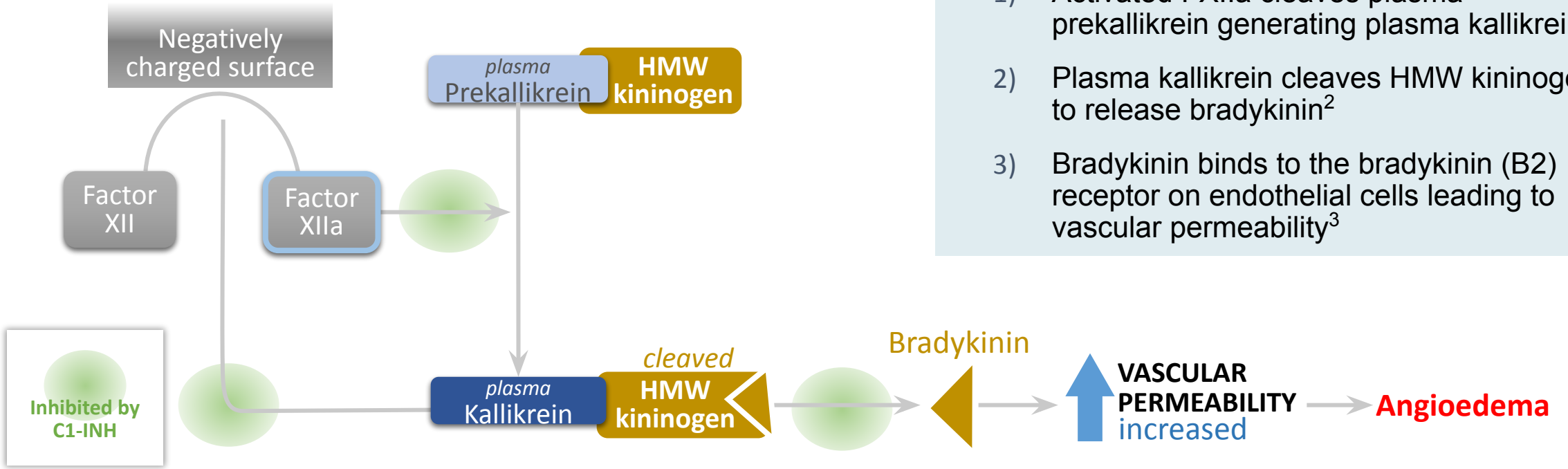
- Serum C4 – good screen test for HAE-C1INH
  - Sensitivity 81-96% in between episodes
  - Normal C4 during episode excludes HAE-C1INH
- Low C1q level helps distinguish C1INH-AAE from HAE-C1INH
- HAE-nl-C1INH – diagnostic challenge; genetic testing can detect mutations in some patients

	C4	C1 inhibitor protein	C1 inhibitor function	C1Q
HAE-C1INH type I	Low	Low, <50%	Low, <50%	Normal
HAE-C1INH type II	Low	Normal	Low, <50%	Normal
HAE-nl-C1INH	Normal	Normal	Normal	Normal
C1INH-AAE	Low	Low	Low	Low
ACEI	Normal	Normal	Normal	Normal

Bradykinin-Forming Pathway Is Uncontrolled in HAE

- C1-INH normally regulates this system by blocking plasma kallikrein and factor XIIa[3]
- In types 1 and 2 HAE, C1-INH levels/activity are insufficient, resulting in uncontrolled kallikrein activation and angioedema[4]

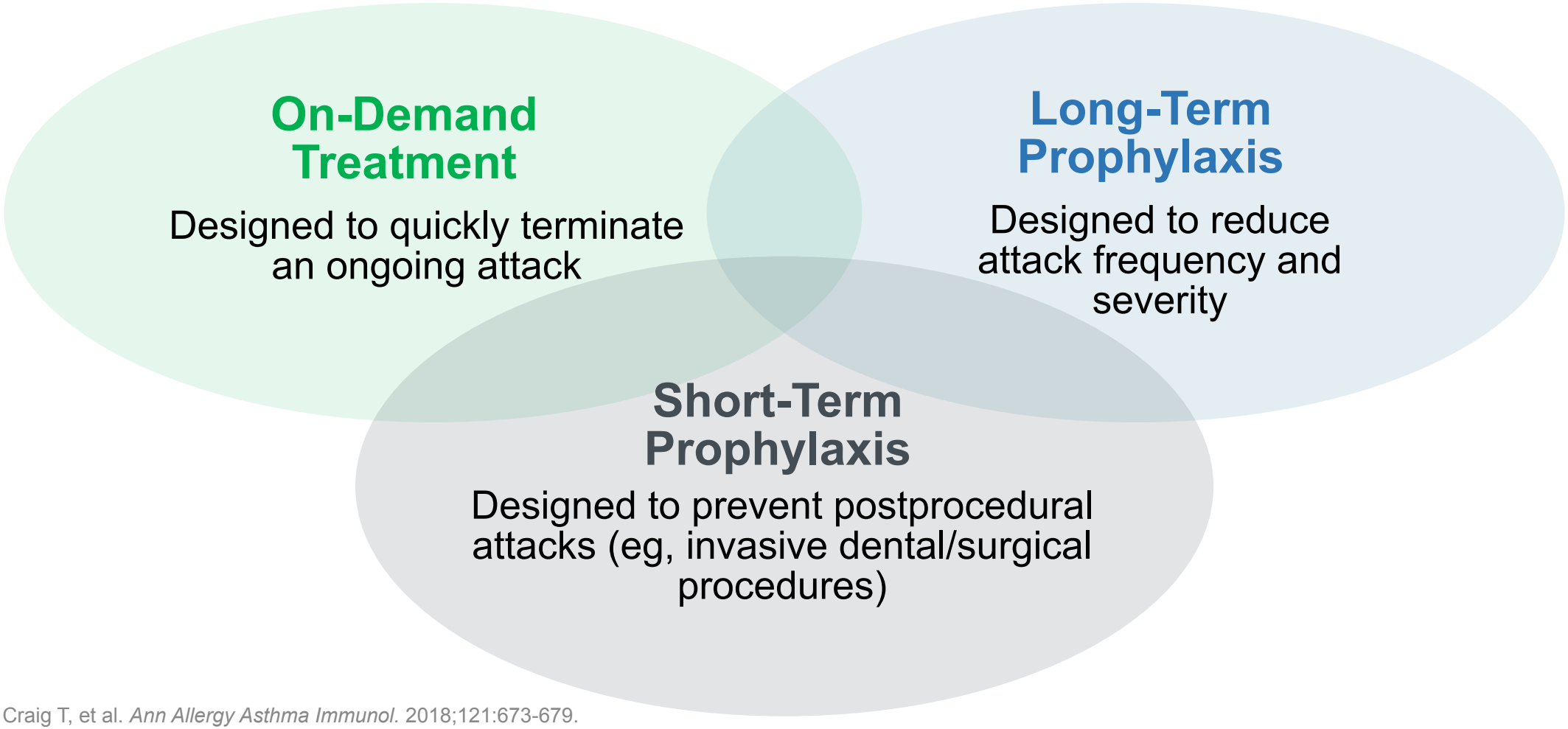
1) Activated FXIIa cleaves plasma prekallikrein generating plasma kallikrein[2]
2) Plasma kallikrein cleaves HMW kininogen to release bradykinin[2]
3) Bradykinin binds to the bradykinin (B2) receptor on endothelial cells leading to vascular permeability[3]



C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; HMW, high molecular weight. FXIIa; factor XIIa

1. Bryant, et al. *Cardiovasc Hematol Agents Med Chem.* 2009;7:234-250. 2. Tse, et al. *Cleve Clin J Med.* 2013;80:297-308. 3. Kaplan A. *J Allergy Clin Immunol.* 2010;126:918-925. 4. Riedl M. *World Allergy Organ J.* 2010;3(suppl):S34-S38.

Treatment Strategies for HAE Can Be Conceptually Divided Into 3 Categories



Craig T, et al. *Ann Allergy Asthma Immunol.* 2018;121:673-679.

On-Demand Therapies: Early Treatment Recommended

Goal: Resolve HAE attack symptoms as quickly as possible

- Treatment focuses on reducing severity and duration of attacks
- Every patient should have an on-demand care plan
- Earlier treatment is associated with reduced duration of swelling and pain
- The most appropriate on-demand treatment should be decided on an individual basis
- The most appropriate on-demand treatment may vary between attacks for a given patient

Longhurst H. *Front Med*. 2018;4:245.

HAE 1st Line (FDA-approved) Therapies for Acute Attacks

	Mechanism	Regulatory status	Notes and adverse reactions
Icatibant (Firzayr)	Bradykinin B2 receptor antagonist	U.S. approved age ≥ 18y, Europe ≥ 2y	- Subcutaneous (SC) - Injection site discomfort
Plasma-derived C1INH (Berinert)	Inhibits kallikrein, factor XII, other factors	U.S. and Europe approved for children & adults	- Intravenous (IV) - Theoretical risk of infection transmission
Recombinant human C1INH (Ruconest)	Inhibits kallikrein, factor XII, other factors	U.S. and Europe approved ≥ 12 y	- IV - Rare anaphylaxis in rabbit-sensitized people
Ecallantide (Kalbitor)	Inhibits kallikrein	U.S. approved ≥ 12 y	- SC - Risk of anaphylaxis (2%) - Administered by health-care provider

Long-Term Prophylaxis

Goals: Reduce the overall number and severity of HAE attacks, reduce the burden of disease, and restore normal quality of life

- Patients should be evaluated for long-term prophylaxis at every visit
- Long-term prophylactic treatments should be individualized and assessed regularly for efficacy, safety, and adherence
  - Consider treatment burden and patient preference
- Prophylactic therapies can improve disease outcomes and quality of life
- All patients using long-term prophylactic medications should also have an on-demand treatment option

Craig T, et al. *Ann Allergy Asthma Immunol.* 2018;121:673-679.

HAE 1st Line (FDA-approved) Treatments for Long-term Prophylaxis

	Mechanism	Regulatory status	Notes and adverse reactions
Plasma-derived C1INH (Cinryze)	Inhibits kallikrein, factor XII, other factors	Approved in U.S. & Europe ≥ 6y	- IV - Theoretical risk of infection transmission
Plasma derived C1INH (Haegarda)	Inhibits kallikrein, factor XII, other factors	Approved in U.S. ≥ 12 y and adults	- SC - Theoretical risk of infection transmission
Landelumab (Takhzyro)	Inhibits kallikrein	Approved in U.S. ≥ 12 y and adults	-SC -Injection site reactions
Oral plasma kallikrein inhibitor (Orladeyo)	Inhibits kallikrein	Approved in U.S. ≥ 12 y and adults	- Oral once daily

Short-Term Prophylaxis Therapies: Preprocedural

Goal: Reduce the likelihood of swelling in response to an anticipated traumatic event

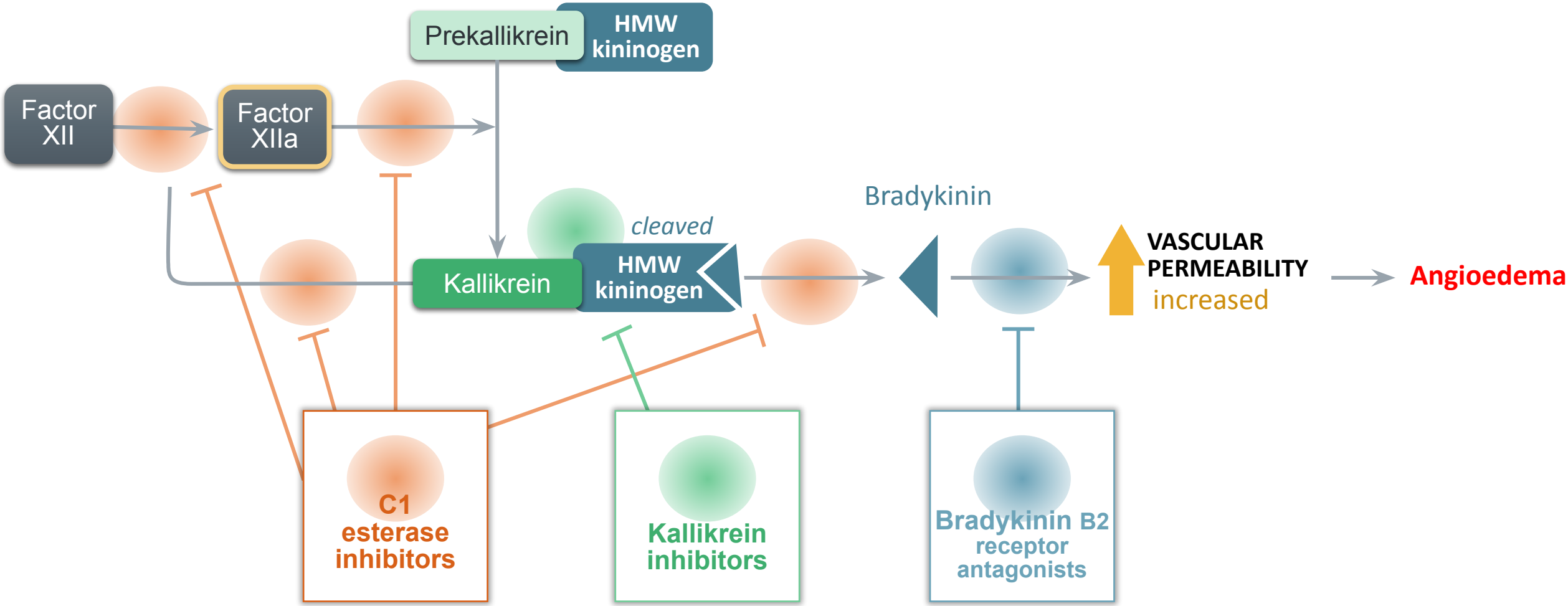
- Short-term prophylactic treatments are used prior to extensive dental work, surgical procedures, or other invasive medical procedures[1]
- Dental procedures are high risk because of proximity of the surgical site to the upper airways[2]

Current therapy option[1,a]	Treatment line[2,3]	Administration[1,2]
C1-INH concentrate	First	1-6 h before procedure
High-dose androgen	Second	5-10 d before the procedure and 2 d after the procedure
Fresh frozen plasma	Second	1-12 h before procedure

[a]No perioperative therapies are currently approved by the US Food and Drug Administration.

1. Zuraw B. *N Engl J Med*. 2008;359:1027-1036.
2. Bhardwaj, et al. *Transfusion*. 2014;54:2989-2996.
3. Maurer M, et al. *Allergy*. 2018;73:1575-1596.

Treatment Strategies Interfere With Different Components of the Bradykinin-Forming Pathway



HMW, high molecular weight.

Kaplan A, et al. *Ann Allergy Asthma Immunol*. 2010;104:193-204.

HAE Management Principles

- All patients should have access to **at least two doses** of on-demand medication that can be self-administered for acute attacks
  - Laryngeal attacks can be fatal: Educate about emergent nature, prioritize airway protection, intubate if needed
  - Most effective when treated early, typically effective within 60 min
- Short-term prophylaxis is indicated prior to known triggers such as invasive dental or surgical procedures
- Long-term prophylaxis is considered based on the individual patient– for example – attacks that are frequent, severe or disfiguring or affect quality of life
- Consideration for women: exogenous estrogens used with caution or avoidance
- Consultation with HAE expert physician to optimize management
- Monitor treatment plans and symptoms regularly
- First-degree relatives should undergo screening

Oral Therapies for HAE in Development

Drug	Target	Dose frequency	Indication	Stage
Sebetralstat (KVD 900)	Kallikrein	NA	Acute treatment	Phase 3
PHA 022121 (PHSV416)	Bradykinin B2 receptor	NA	Acute treatment	Phase 2
PHA 022121 (PHSV416)	Bradykinin B2 receptor	b.i.d.	Prophylaxis	Phase 2
PHA 022121 (PHSV719)	Bradykinin B2 receptor	o.d.	Prophylaxis	Phase 1
ATN-249	Kallikrein	o.d.	Prophylaxis	Phase 1
KV998086	Factor XIIa	?	Prophylaxis	Preclinical

Betschel SD, Banerji A, Busse PJ et al. JACI In Practice, 2023 Aug 11 Vol 11, Issue 8, P 2315-2325.

Intravenous Therapies for HAE in Development

Drug	Target	Class	Dose frequency	Route	Stage
Donidalorsen	Prekallikrein	Oligonucleotide antisense	q. 4 weeks or q. 8 weeks	Subcutaneous	Phase 3
Garadacimab	Factor XIIa	Monoclonal antibody	q. 4 weeks	Subcutaneous	Phase 3
STAR-0215	Kallikrein	Monoclonal antibody	q. 3 months or longer	Subcutaneous	Phase 1
ALN-F12	Factor XII	Small interfering RNA	?	Subcutaneous	Preclinical
NTLA-2002	Prekallikrein	CRISPR/Cas9 gene editing	Single administration	Intravenous	Phase 1/2
BMN 331	C1-esterase inhibitor	AAV5 gene therapy	Single administration	Intravenous	Phase 1/2
OTL-105	C1-esterase inhibitor	Autologous HSC gene therapy	Single administration	Intravenous	Preclinical

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Angioedema Take Home Points

- Angioedema without urticaria should raise suspicion for bradykinin-mediated angioedema, but histaminergic mediated angioedema can present without urticaria
- Bradykinin-mediated angioedema: ACEI, HAE-C1INH, HAE-nl-C1INH, C1INH-AAE
- Diagnosis requires clinical assessment (symptoms, onset, duration), and if appropriate: C4, C1 inhibitor level and function, and C1q (if C1INH-AAE is suspected)
- Antihistamines, epinephrine and corticosteroids are not effective for bradykinin-mediated angioedema
- HAE management consists of: accessible on-demand treatment for acute attacks for all patients, and when indicated – prophylactic therapies

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