Biotherapies for Life™ CSL Behring

HEALTHCARE PROFESSIONAL RESOURCE AND TRAINING GUIDE

ALL ABOUT HAEGARDA®

This Resource Guide is intended to be a tool to educate Health Care Professionals on HAEGARDA® Home Infusion, and not for patient training.

For patient training, see the HAEGARDA® Patient Resource Binder, available through CSL Behring Canada.

HAEGARDA®
C1 Esterase Inhibitor
Subcutaneous (Human)

CHAPTER 1

UNDERSTANDING HEREDITARY ANGIOEDEMA

LEARNING OBJECTIVES

After completing this chapter, you will be able to:

- Summarize the clinical characteristics of Hereditary Angioedema (HAE).
- Describe the effects HAE has on the patient's quality of life.
- Explain the genetic features involved in the pathogenesis and inheritance of HAE.
- Explain how a deficiency of C1 esterase inhibitor (C1-INH) results in the clinical manifestations of HAE.
- Identify factors that may trigger an angioedema attack in HAE patients.
- Identify treatment options for HAE.

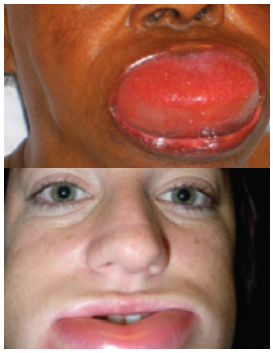
HAE, hereditary angioedema; C1-INH, C1 esterase inhibitor

UNDERSTANDING HEREDITARY ANGIOEDEMA

What is Hereditary Angioedema (HAE)?

- HAE is a rare inherited disease that results in a quantitative and/or qualitative deficiency in C1 esterase inhibitor (C1-INH).
- HAE is characterized by acute, recurrent **episodes of swelling** in different areas of the skin or internal organs.
- Identify treatment options for HAE.
- This condition affects approximately **1:10,000 to 1:50,000** individuals.
- Patients usually experience their first attack during childhood or adolescence.
- 61% of HAE patients in Canada report ≥**7 attacks/year**[†]**.**
- Lack of correct diagnosis can lead to: **morbidity**, complications, burden on quality of life and psychiatric referral.

Facial edema



34% of patients with abdominal attacks undergo **unnecessary surgery** due to misdiagnosis

Death by asphyxiation is reported in 30% of patients with untreated laryngeal (in the throat) attacks

Untreated patients can lose 100 to 150 work days per year

HAE, hereditary angioedema; C1-INH, C1 esterase inhibitor

[†]HAE Canada conducted a nation-wide survey in 2017 to provide data on demographics of HAE patients in Canada: Rowe 2018; https://www.haecanada.net/real-world-data.

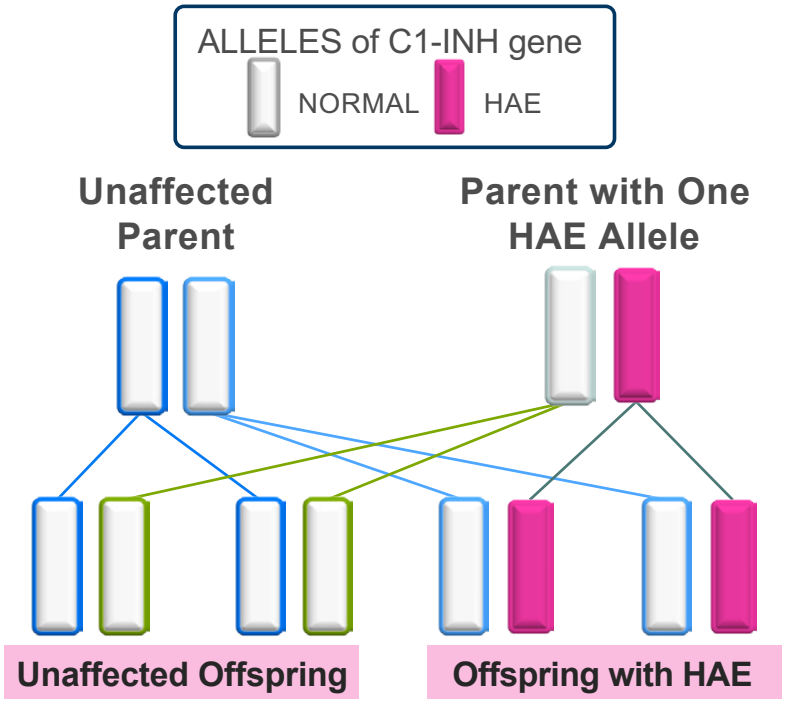
Altman KA and Naimi DR. *Curr Med Res Opin*. 2014;30(5):923–930.

Bracho FA. *Curr Opin Hematol*. 2005;12(6):493–498.

Lumry WR. *Am J Manag Care*. 2013; 19(7 Suppl):s103–110.

HAE is a Genetic Disorder

- HAE is a rare genetic disorder with autosomal dominant inheritance. One defective C1-INH allele leads to the clinical expression of HAE.
- About 75% of cases are inherited and children of one parent with the gene mutation have a **50% chance** of inheriting the disease.
- About 25% of cases arise from de novo mutations.
- Over 250 different C1-INH mutations that can lead to HAE have been identified.



Children with one heterozygous parent have 50% chance of having HAE

HAE, hereditary angioedema; C1-INH, C1 esterase inhibitor

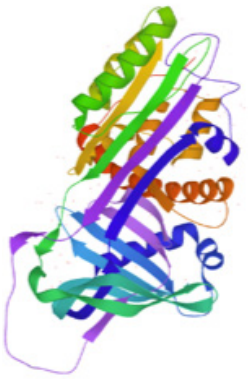
Bork K. *Immunotherapy*. 2014;6:533–551.

UNDERSTANDING HEREDITARY ANGIOEDEMA

HAE is Caused by Deficient or Dysfunctional C1-INH

- C1-INH is a **key regulatory protein** in several pathways
  - Complement cascade
  - Coagulation cascade
  - Contact cascade
  - Fibrinolytic cascade
- Endogenous **C1-INH dampens physiologic response to injury and infection** by negatively regulating the coagulation, complement, and contact cascades.
- HAE patients with deficient or defective C1-INH display an **overactivation of the 4 pathways**, leading to **swelling, inflammation and pain** typical of angioedema attacks.

3D structure of the active form of human C1-INH



HAE, hereditary angioedema; C1-INH, C1 esterase inhibitor

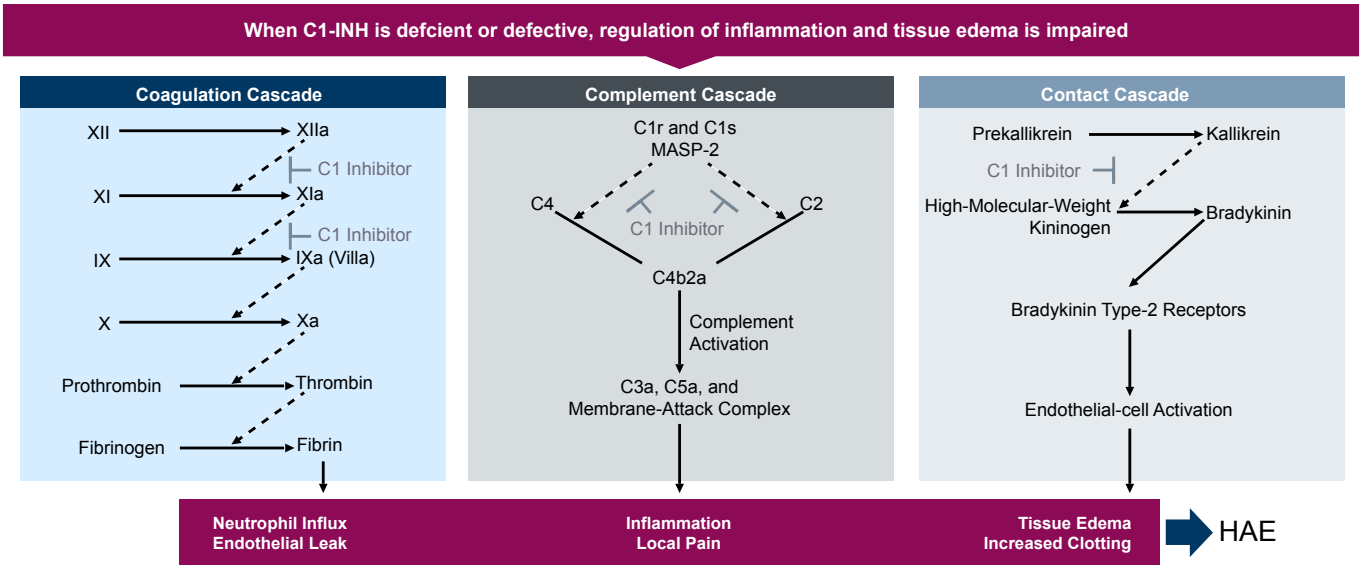
Zuraw BL. *N Engl J Med*. 2008;359:1027–1036.

Zuraw et al. *Allergy Asthma Proc*. 2012:33:S145–S156.

Howlett et al. *J Allergy Clin Immunol*. 2019;143(2):SAB172.

Nzeako UC, Frigas E, Tremaine WJ. *Arch Intern Med*. 2001;161(20):2417–2429.

LOSS OF C1-INH-MEDIATED REGULATION LEADS TO SYMPTONS OF HAE



Dashed arrows are enzyme cleavage steps.

HAE, hereditary angioedema; C1-INH, C1 esterase inhibitor; MASP-2, mannose-binding protein-associated serine protease-2

Adapted from Morgan BP. *N Engl J Med*. 2010;363:581–583.

HAE TYPES AND PREVALENCE

	C1-INH level	C1-INH function	C4 level	Global Prevalence
HAE Type I	↓	↓	↓	~ 85%
HAE Type II	↔	↓	↓	~ 15%
HAE with normal C1-INH* (HAE Type III)	↔	↔	↔	~ 1%

↓ low ↔ normal

HAE can be classified into 3 different types:

- **HAE type I** is the most commonly reported type of HAE, characterized by decreased C1-INH protein levels.
- **HAE type II** is caused by a dysfunction in the C1-INH protein function while C1-INH protein levels seem to be normal.
- **HAE with normal C1-INH (HAE type III)** is clinically indistinguishable from types I and II but may be caused by other factors, such as mutations in the gene encoding Coagulation Factor 12.

*HAEGARDA is not indicated for HAE with normal C1-INH (HAE Type III) and Acquired Angioedema

HAE, hereditary angioedema; C1-INH, C1 esterase inhibitor

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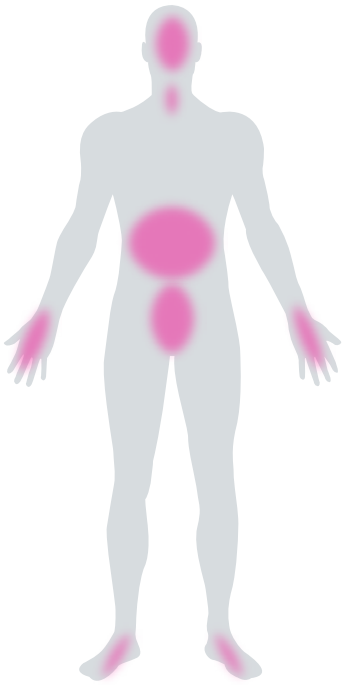
SIGNS AND SYMPTOMS

Signs and Symptoms of HAE Attacks can vary

Potential HAE attack locations



Face
Disfiguring; facial attacks can progress to laryngeal attack

Larynx, Glottis, Tongue
Attacks can lead to asphyxiation and death

Abdomen
Painful, often with nausea, vomiting, diarrhea

Genitourinary System
Painful, less typical

Extremities
- Hands
- Feet

- HAE can produce acute and recurrent episodes of localized nonpitting edema in single or multiple locations including: skin, face, gastrointestinal tract and upper respiratory tract including the larynx.
- Unlike allergic reactions, there is no itching with HAE.
- About 1/3 of patients develop erythema marginatum, a serpentine rash that is not itchy or raised at the start of an attack.
- The swelling associated with an attack often gets worse over a period of 12–24 hours, then typically resolves within 72 hours. However, symptoms can last up to five days.

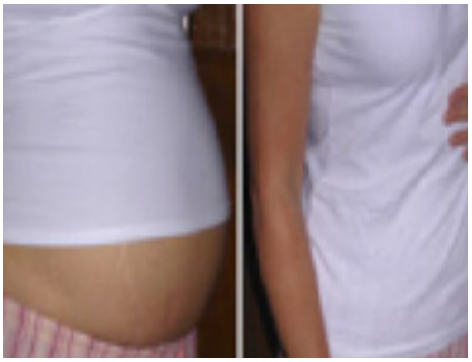
HAE, hereditary angioedema

Zuraw BL. *N Engl J Med*. 2008;359:1027–1036.
Bork K. *Am J Med*. 2006;119:267–274.

SIGNS AND SYMPTOMS

- Abdominal attacks can cause severe abdominal pain, nausea, vomiting, and diarrhea.
- The number of episodes an individual may experience can be unpredictable. Some people experience weekly attacks, while others may go years between attacks.

Abdominal edema



Did you know that time to diagnosis of HAE is often delayed, with the average being 8 years?

HAE, hereditary angioedema

Zuraw BL. *N Engl J Med*. 2008;359:1027–1036.
Bork K. *Am J Med*. 2006;119:267–274.

SOME EARLY SYMPTOMS AND TRIGGERS CAN BE RECOGNIZED

Though many patients may not have an identifiable cause of an attack, the following can trigger one in some patients:

Physical exertion
Trauma
Mechanical pressure
Ex. Exercise, pushing lawnmower, using scissors

Puberty
Pregnancy
Menstruation
Tension or emotional stress

Drugs
Infection
Ex. ARBs and ACE inhibitors, estrogen-containing oral contraceptives, hormone replacement therapy

Many patients develop symptoms that signal the onset of an acute HAE attack, including:

- Tingling
- Parasthesias
- Erythematous rash
- Fatigue
- Malaise
- Nausea
- Vomiting
- Abdominal pain

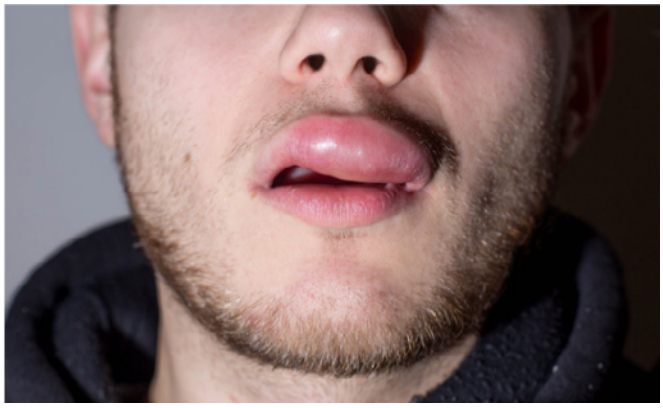
ARBs, Angiotensin II receptor blockers; ACE, angiotensin converting enzyme; HAE, hereditary angioedema

Craig et al. *World Allergy Organ J.* 2012;5:182–199.
Prematta et al. *Allergy Asthma Proc*. 2009;30:506–511.

HAE TREATMENT IS INDIVIDUALIZED TO THE PATIENT

Acute

On-demand treatment of HAE attacks when they occur to minimize morbidity and prevent mortality.



Prophylaxis

Long-term prophylaxis:

- Ongoing treatment to prevent attacks
- When attacks are frequent, severe, or reduce quality of life

Short-term prophylaxis* (sometimes called procedural prophylaxis):

- Treatment given to prevent attacks when a predictable trigger is expected (e.g., dental work)

Despite being on prophylaxis, all patients should be equipped to treat acute attacks.

*No drugs are authorized for this indication in Canada

HAE, hereditary angioedema

Betschel et al. *Allergy Asthma Clin Immunol*. 2014;10(1):50.

Maurer et al. *World Allergy Organization Journal*.2018;11:5.

KEY LEARNINGS

1. HAE is a rare genetic disorder characterized by unpredictable, potentially fatal swelling attacks.
2. Common attack locations include face, abdomen, genitourinary system, and extremities.
3. Most HAE cases are caused by low or dysfunctional C1-INH; an important regulator of the complement, contact, coagulation, and fibrinolytic cascades.
4. Due to low disease awareness and variable presentation, HAE patients are often misdiagnosed. Misdiagnosis can lead to morbidity, complications and burden on quality of life.
5. Currently available HAE treatment options include acute therapy to minimize morbidity and prevent mortality when HAE attacks occur. Prophylaxis is also available to prevent HAE attacks.

HAE, hereditary angioedema; C1-INH, C1 esterase inhibitor

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4. Bork K. *Immunotherapy*. 2014;6:533–55.
5. Bracho FA. *Curr Opin Hematol.* 2005;12(6):493–498.
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13. Morgan BP. *N Engl J Med*. 2010;363:581–583.
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