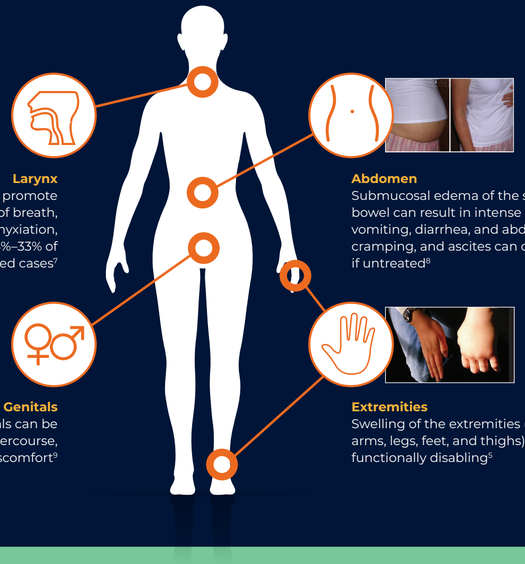
PHYSICAL IMPACT AND MANIFESTATION

HAE commonly presents as nonpitting, nonpruritic swelling of the skin, mucous membranes, or both; it typically presents without urticaria and can vary in frequency, severity, and location.[1]



Larynx
Swelling of the airway can promote voice changes, shortness of breath, and, in severe cases, asphyxiation, with mortality in 15%–33% of untreated cases[7]

Abdomen
Submucosal edema of the small bowel can result in intense pain, vomiting, diarrhea, and abdominal cramping, and ascites can occur if untreated[8]

Genitals
Swelling of the genitals can be triggered by bike riding, intercourse, etc, and can cause discomfort[9]

Extremities
Swelling of the extremities (hands, arms, legs, feet, and thighs) can be functionally disabling[5]

Episodes can cause significant pain and discomfort, and untreated laryngeal attacks can result in life-threatening respiratory obstruction and asphyxiation[7]

Treatment of HAE should be individualized for each patient[16]

There are 2 functional treatment categories: on-demand attack resolution and prophylactic attack avoidance[16]

On-demand treatment

Goal: Resolve HAE attack symptoms as quickly as possible, limiting the severity and duration of an ongoing attack.[16,17]

World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI) 2021 Treatment Guideline recommendations: Every patient has ready access to on-demand medication for the treatment of at least 2 attacks.[10]

All attacks should be considered for on-demand treatment; treatment of attacks affecting the upper airway is time-sensitive, and attacks should be treated as early as possible.[10]

Prophylactic measures

Short-term prophylaxis (STP)

Goals: Minimize attack potential in situations where there is a known risk.[16]

WAO/EAACI 2021 Treatment Guideline recommendations: Consider STP before medical, surgical, or dental procedures, as well as exposure to other angioedema attack–inducing events.[1]

Long-term prophylaxis (LTP)

Goal: Reduce the number and severity of attacks, limit the burden of disease, and improve the patient's quality of life.[10,16]

WAO/EAACI 2021 Treatment Guideline recommendations: Achieve complete control of the disease and normalize patients' lives. Currently, the ability to achieve these goals can only be achieved with LTP.[10]

Evaluate patients for LTP at every visit, considering disease activity, burden, control, and patient preference.[16]

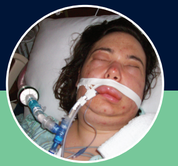
Consensus guidelines underscore that optimal HAE treatment outcomes require[16]:

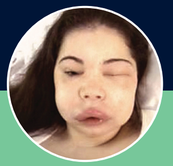
1. Regular shared decision-making discussions about current patient needs
2. Understanding patient circumstances and treatment goals
3. Corresponding adjustments to their management plan to optimize outcomes

References: 1. Bernstein JA. Severity of hereditary angioedema, prevalence, and diagnostic considerations. *Am J Manag Care*. 2018;24(14 suppl):S292-S298. **2.** Busse PJ, Christiansen SC. Hereditary angioedema. *N Engl J Med*. 2020;382(12):1136-1148. **3.** Kaplan AP, Joseph K. The bradykinin-forming cascade and its role in hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;104(3):193-204. **4.** Henao MP, Kraschnewski JL, Kelbel T, Craig TJ. Diagnosis and screening of patients with hereditary angioedema in primary care. *Ther Clin Risk Manag*. 2016;12(0):701-711. **5.** Johnston DT. Diagnosis and management of hereditary angioedema. *J Am Osteopath Assoc*. 2011;111(1):28-36. **6.** Zuraw BL. The pathophysiology of hereditary angioedema. *World Allergy Organ J*. 2010;3(suppl 3):S25-S28. **7.** Christiansen SC, Zuraw BL. Hereditary angioedema: management of laryngeal attacks. *Am J Rhinol Allergy*. 2011;25(6):379-382. **8.** Rubinstein E, Stolz LE, Sheffer AL, Stevens C, Bousvaros A. Abdominal attacks and treatment in hereditary angioedema with C1-inhibitor deficiency. *BMC Gastroenterol*. 2014;14(1):71. **9.** Caballero T, Farkas H, Bouillet L, et al. International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. *J Allergy Clin Immunol*. 2012;129(2):308-320. **10.** Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.e3. **11.** Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema–the 2021 revision and update. *Allergy*. 2022;77(7):1961-1990. **12.** Riedl MA, Noble L, Ray T, Johnston DT, Murphy C, Li HH. Characterization of prodromes in hereditary angioedema: findings from an online patient forum. Poster presented at: 2024 HAEi Regional Conference Americas; March 15-17, 2024; Panama City, Panama. **13.** Banerji A. The burden of illness in patients with hereditary angioedema. *Ann Allergy Asthma Immunol*. 2013;111(5):329-336. **14.** Pagnier A, Dermesropian A, Kevorkian Yerguet C, et al. Hereditary angioedema in children: review and practical perspective for clinical management. *Pediatr Allergy Immunol*. 2024;35(12):e14268. **15.** Bernstein JA. HAE update: epidemiology and burden of disease. *Allergy Asthma Proc*. 2013;34(1):3-6. **16.** Craig T, Busse P, Gower RG, et al. Long-term prophylaxis therapy in patients with hereditary angioedema with C1 inhibitor deficiency. *Ann Allergy Asthma Immunol*. 2018;121(6):673-679. **17.** Cicardi M, Agostoni A. Hereditary angioedema [editorial]. *N Engl J Med*. 1996;334(25):1666-1667.

IDENTIFYING AND ADDRESSING HAE

Hereditary angioedema (HAE) is a rare genetic disease characterized by **unpredictable**, **recurrent**, and **potentially fatal** swelling attacks[1]





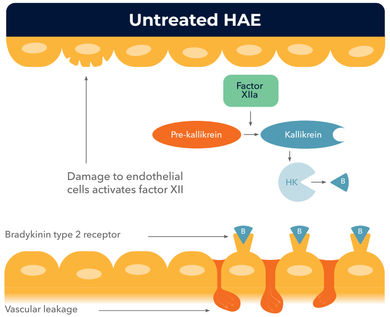
The consequences of HAE can be devastating for some patients.[1]

Images obtained from www.haeimages.com

The effects of bradykinin overproduction

In HAE, uncontrolled plasma kallikrein activity triggers an overproduction of bradykinin, which leads to vasodilation, vascular leakage, and subsequent swelling.[2,3]

These events may happen in cases of C1-inhibitor deficiency or dysfunction or unknown drivers of bradykinin overproduction.[3]



Patient clinical history can help identify the shared and unique presentations of each HAE type

Shared across all types

- **Family history:** Approximately 75% inherited mutation and 25% spontaneous mutations with no known genetic link[4]
- **Well-known attack triggers*:** Stress, physical trauma, infection (common attack trigger in childhood), menses, and estrogen use[4]
- **Tried and failed:** Antihistamines, corticosteroids, and epinephrine[4]
- **Prodromes*:** Unusual fatigue, numbness, headaches, muscle aches, joint pain, and tightness or prickling/tingling sensation in the skin[4]

Unique to each type

- **Age of onset:** Typically presents in childhood for HAE Types 1 and 2, but typically presents later for HAE-C1-INH[4]
- **HAE Type 1- and 2-specific prodrome†:** Erythema marginatum (nonpruritic rash)[6]
- **HAE-nl-C1-INH prodrome†:** Bruising or hemorrhaging on skin[6]

*Majority of attacks not preceded by an identifiable trigger.[4]

†Set of signs or symptoms that sometimes occur before attacks. While the presence of prodromes is strongly predictive of an oncoming attack, they can be unreliable indicators, as not all patients experience prodromal symptoms prior to any/all attacks.[4,12]

Even after a diagnosis is confirmed, the burden of HAE extends beyond attacks

Attacks

- If left untreated, protracted swelling can last 2–5 days[13]
- Earlier disease manifestation often results in more frequent attacks and hospitalizations[14]
- Uncertainty about attack evolution[13]

Disease management

- ER visits and hospitalizations[13]
- Loss of income/productivity[13]
- Challenges with medication access, storage, administration, side effects, and costs[13]

Quality of life

- More time away from school/work[13]
- Missing social activities[13]
- Limiting ability to travel[13]
- Stress[2]
- Depression[13]
- Fear[13]
- Shame[10]
- Anxiety[13]

HAE identification and classification are multifaceted with varying prevalence

Each type of HAE is based on C1-INH levels.

	C1-INH antigenic levels	C1-INH protein function	Frequency	Commonly observed attacks
HAE Type 1	Decreased[4]	Decreased[4]	~85% of HAE-C1-INH cases[4]	>90% abdominal attacks[4] 96% extremity attacks[5]
HAE Type 2	Normal or elevated[4]	Decreased[4]	~15% of HAE-C1-INH cases[4]	
HAE-nl-C1-INH	Normal[4]	Normal[4]	Unknown[4]	Early data suggest associations with more face, tongue, and throat swelling[6]

When HAE is suspected, a diagnosis should be confirmed

Laboratory testing, in concert with clinical history, reinforces the differential diagnosis of HAE.[1,‡]

Screening	Both lab parameters should be measured to confirm diagnosis		Additional testing
C4 antigenic levels	**C1-INH function**	**C1-INH antigenic levels**	**C1q antigenic levels**
Low C4 levels, either at baseline or during an attack, are consistent with a diagnosis of HAE–C1-INH[10]	Low functional levels of C1-INH are indicative of HAE–C1-INH type 1 or type 2[10]	Low antigenic levels of C1-INH are observed only in HAE–C1-INH type 1[10]	C1q level is almost always normal in HAE. Consider acquired angioedema if test yields low C1q level[11]

‡Cold storage of samples is necessary to avoid the decay of functional C1-INH, which may produce equivocal results.[4]

HAE-nl-C1-INH confirmation[6]

- Positive family history, noting potential for incomplete penetrance and de novo mutations
- Recurrent angioedema, typically without urticaria
- Positive medication history showing lack of treatment response to antihistamines, corticosteroids, and epinephrine
- Treatment response to HAE-targeted treatments

Optional genetic testing[6]

The absence of a genetic finding cannot definitively rule out HAE. Mutations in the *SERPING1* gene account for most cases of **HAE-C1-INH**. While the genetic cause remains unknown in most cases for **HAE-nl-C1-INH**, mutations currently identified include: coagulation factor XII (FXII), angiopoietin-1 (ANGPT1), plasminogen (PLG), kininogen-1 (KNG1), myoferlin (MYOF), and heparan sulfate-glucosamine 3-O-sulfotransferase-6 (HS3ST6).

Many patients with HAE experience daily hurdles§

NOT CONSIDERING JOB OPPORTUNITIES

Report not considering certain job opportunities because of HAE[15]

LOSS OF LEISURE ACTIVITIES

Report significant loss of leisure activities in the prior year[15]

MISSING WORK OR SCHOOL

Report missing work or school in the prior year as a result of an HAE attack[15]

UP TO 100 DAYS OF INCAPACITATION/YEAR

On average, patients who are long-term prophylaxis (LTP)-naive experience 1–3 attacks/month, resulting in **20 to 100 days of incapacitation each year**.[15]

§According to work productivity and impairment general health survey scores based on a 2008 survey of 457 people with HAE.