

Accreditation Information

Target Audience

This educational activity is designed for physicians and other healthcare practitioners that diagnose and provide care to patients with Hereditary Angioedema (HAE).

Learning Objectives

Upon completion of this Continuing Education activity, the participant will be able to:

- Identify the symptoms of HAE and what characteristics differentiate it from other diseases with similar presentations
- Describe the differential diagnosis for HAE and the appropriate tests to confirm the diagnosis
- Identify the traditional treatments for HAE and discuss how new and emerging therapies may improve clinical outcomes

Content Delivery and Learning Methodology

This Educational Activity is delivered as an enduring material. In order to obtain the maximum of 2 continuing education credit hours for this self-directed learning activity, the participant must read the educational content and then complete the CME Quiz (post-learning assessment score of 70% required) and the Evaluation and Request for Credit Form. The completed documents must be printed and sent to:

CMEsolutions
P.O. Box 68680
Tucson, AZ 85737
Fax: 866-540-0038

Once the completed forms are received by CMEsolutions, a certificate of completion will be sent to the address on the Credit Request form. It is important to ensure the information is legible in order for CMEsolutions to send the CE documentation to you.

Educational Activity Dates

This educational activity is valid for credit beginning March 23, 2009.

This program will terminate on March 22, 2010.

Faculty Disclosures

Dr. Mark A. Davis-Lorton reports that within the last 12 months, he has had a relationship with the following companies who manufacture products used in the treatment of the subject under discussion. *Research Support:* Dyax Corp, ViroPharma Incorporated; *Consultant:* ViroPharma Incorporated.

Dr. Mark A. Davis-Lorton reports that within the last 12 months, he has had the following relationship with commercial supporters of this activity. *Research Support:* ViroPharma Incorporated.

Dr. Douglas T. Johnston reports that within the last 12 months, has had the following relationship with companies who manufacture products used in the treatment of the subject under discussion. *Research Support:* ViroPharma Incorporated

Dr. Douglas T. Johnston reports that within the last 12 months, he has had the following relationship with commercial supporters of this activity. *Research Support:* ViroPharma Incorporated.

Discussion of Products Not Approved for Use in the United States

The content includes discussion of therapies for the management of HAE that are not currently approved by the FDA for some or all uses described. The content clearly notes when a therapy discussed is not currently approved by the FDA.

NOTE: There is no cost to the participant for this educational activity.

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Understanding the True Scope of Hereditary Angioedema

Hereditary angioedema (HAE) is a rare and potentially fatal genetic disorder involving a deficiency or dysfunction of C1 inhibitor (C1-INH).¹ HAE typically manifests as cutaneous, laryngeal, genital, or intra-abdominal swelling. Despite its often dramatic presentation, HAE tends to mimic other disease states which may delay the diagnosis. The condition was described in 1876 as "giant urticaria" by John Laws Milton² and fully described by William Osler in 1888 as *angio-neurotic edema*.³ In the early 1960s, Donaldson and Evans demonstrated that patients with HAE were lacking the serum inhibitor directed against the first component of the complement system, C1 esterase inhibitor, now referred to as C1 inhibitor.⁴ At the end of that same decade, Donaldson et al found that the permeability-increasing factor in the plasma of patients during acute HAE also displayed kinin-like activity.⁵ Since that time research has focused on the detailed exploration of the genetic basis of HAE. By the end of the twentieth century, more than 100 different C1-INH gene mutations had been described in HAE patients.⁶ Currently 150 mutations of the gene located in the q12-q13.1 sub-region of chromosome 11 have been identified in patients with HAE.^{7,8} However, specific gene mutations do not seem to correlate with disease variability or severity.

HAE is an autosomal dominant disease (Mendelian Inheritance in Man #106100) that occurs in approximately 1/10,000 to 1/50,000 individuals with no racial or gender predilection having been recognized.⁹⁻¹¹ The symptoms of HAE usually present in early childhood, worsen at puberty, persist throughout life, and are unpredictable.¹¹ The frequency of attacks ranges from frequent—every 3 days—to very rare.¹¹ Trauma (commonly dental procedures), stress, fever, and infection can be triggering factors, but many attacks occur without an identifiable trigger.¹ The diagnosis of HAE is most frequently made in the second or third decade of life, although symptoms often begin earlier. Because the disease is rare and the symptoms resemble many other disorders, HAE patients often remain undiagnosed for many years.⁹

Role of C1 Inhibitor and Mediators of Angioedema in HAE

C1-INH is a heavily glycosylated plasma protein which was discovered by Ratnoff and Lepow in 1957.^{12,13} This protein is a serine protease inhibitor which binds to and forms covalent bonds with a variety of plasma proteases, thus inhibiting their activity.^{8,9} C1-INH is the primary regulator of contact and classical complement system activation and also plays a role in the regulation of coagulation and fibrinolysis.¹⁴ In addition to protease inhibition, C1-INH interacts with endogenous proteins, cells, and infectious agents.¹² In the classical complement pathway, C1-INH inhibits activated C1r and C1s, causing their disassociation from C1. **(Figure 1)** Under normal physiologic conditions, C1-INH prevents inappropriate or excessive activation of the classical pathway. It also inhibits mannan-binding lectin-associated serine protease 2 involved in the early steps of the mannan-binding pathway of complement activation.¹² C1-INH inhibits the following plasma components of these pathways: factors XI and XIIa, plasma kallikrein, plasmin, thrombin, and tissue plasminogen activator.

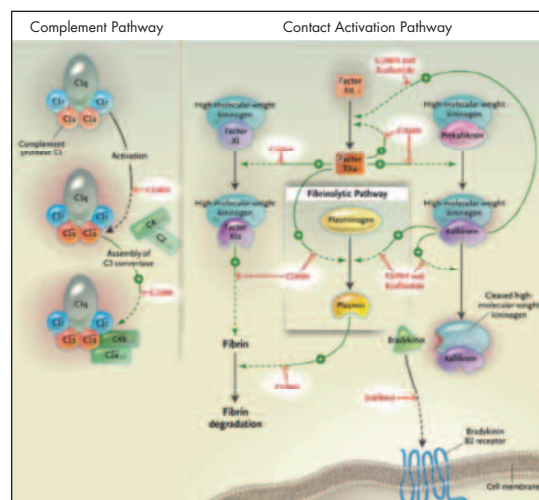


Figure 1. Pathways inhibited by C1-INH and new drugs
From Zuraw BL. *N Engl J Med.* 2008;359:1027-1036.

C1-INH is a major regulator of contact system mediator, bradykinin, a potent vasodilatory peptide regulated by factor XII and plasma kallikrein.¹⁰ Bradykinin binds to B2 receptors on endothelial cells which lead to vasodilation and increased microvessel permeability. The edema is caused by plasma leakage from postcapillary venules due to bradykinin-induced changes.^{1,8} In addition, bradykinin causes tissue smooth muscle contraction which leads to pain and cramping.¹⁵

Unlike allergic angioedema, swelling in HAE is not mediated by histamine and does not respond to antihistamine or corticosteroids.⁹ Most published work agrees that bradykinin is the major mediator of swelling in HAE.¹⁶⁻¹⁸ Supporting studies have shown elevated bradykinin levels and low pre-kallikrein and high-molecular-weight kininogen levels during attacks of swelling in HAE.^{19,20} The data suggests that bradykinin is involved but may not be the sole mediator of angioedema.⁸ The exact biochemical events responsible for an attack have not been fully elucidated.

Clinical Characteristics of Hereditary Angioedema (HAE)

Hereditary angioedema is characterized by edema and swelling of one or several organ systems, predominantly involving the skin, intestinal tract, and respiratory tract. The symptoms of HAE can begin at any age, however the attacks are usually mild or rare during early childhood typically becoming more severe during the second decade of life.^{1,22} Attacks can occur in any part of the body and the frequency is highly variable, ranging from no attacks to those that occur frequently.^{9,21} Without treatment, patients experience angioedema episodes on an average of every 1-2 weeks.¹¹ Typical attacks last 2 to 5 days before resolving spontaneously.²² In some cases, HAE attacks may resolve within 24 hours or last as long as 9 days.¹

A prodromal tingling sensation precedes most attacks and about one third are accompanied by erythema marginatum, a nonpruritic, serpiginous rash. While most acute episodes do not have an identifiable trigger, some are associated with local trauma, medical procedures, emotional stress, inflammation, infections, menstruation, oral contraceptive use, and the use of medications such as angiotensin-converting enzyme (ACE) inhibitors.^{1,8,22}

Table 1 summarizes the clinical and laboratory findings associated with HAE. Attacks most often affect three anatomical locations: the skin (cutaneous attacks), the larynx (laryngeal attacks), and the gastrointestinal tract (abdominal attacks).

Table 1. Clinical and laboratory findings associated with angioedema of various causes

Type of Angioedema	Clinical Findings	Laboratory Findings				
		C4 Level	Antigenic C1-INH level	Functional C1-INH level	C1q level	C3 level
Hereditary angioedema (HAE)	Recurrent angioedema and abdominal attacks without urticaria; attacks are episodic, with intervals between periods of swelling; onset in childhood or young adulthood, with worsening around puberty; prolonged attacks (typically 72-96 hr in duration); family history in 75% of patients; attacks do not respond to antihistamines or corticosteroids	Decreased	Decreased (in type 1) or normal (in type 2)	Decreased	Normal	Normal
Acquired C1-INH deficiency	Attacks similar to those in HAE; onset in middle age or later; absence of family history; attacks do not respond to antihistamines or corticosteroids	Decreased	Decreased or normal	Decreased	Decreased	Normal or decreased
Inherited angioedema with normal C1-INH levels	Family history of angioedema; possible preponderance among women; may be estrogen-dependent; typically manifests after childhood; face, tongue, and extremities affected more than abdomen; attacks do not respond to antihistamines or corticosteroids	Normal	Normal	Normal	Normal	Normal
ACEI-associated angioedema*	History of ACEI use; angioedema tends to affect face and tongue; more common in blacks and smokers than other subgroups; patients can usually tolerate ARBs†	Normal	Normal	Normal	Normal	Normal
Idiopathic angioedema	Angioedema sometimes accompanied by urticaria; swelling typically lasts up to 48 hr; attacks may occur daily and are relieved with antihistamines or corticosteroids	Normal	Normal	Normal	Normal	Normal
Allergic angioedema	Angioedema usually accompanied by urticaria and sometimes anaphylaxis; may be pruritic; associated with exposure to food, venom, latex, drug or environmental allergens; attacks typically last 24-48 hr; attacks relieved with antihistamines or corticosteroids	Normal	Normal	Normal	Normal	Normal
NSAID-associated angioedema‡	Angioedema after ingestion of an NSAID; typically accompanied by urticaria; usually class-specific reaction due to pharmacologic effect of cyclooxygenase inhibition, but allergic in rare instances	Normal	Normal	Normal	Normal	Normal

* ACEI, angiotensin converting enzyme inhibitor

† ARB, angiotensin receptor blocker

‡ NSAID, non-steroidal anti-inflammatory drug

Adapted from Zuraw BL. *N Engl J Med.* 2008;359:1027-1036.

Cutaneous angioedema

Cutaneous attacks are common and temporarily disfiguring although not generally dangerous. While angioedema *without* urticaria is the hallmark of HAE, approximately one third of patients do develop a non-pruritic erythematous rash, erythematous mottling, or erythema marginatum at the start of an attack,¹ sometimes accompanied by pain. The extremities face, and genitals are the most common sites affected. The usual facial areas involved are the lips, eyelids, and tongue. **(Figure 2)** Trauma during intercourse or parturition can result in genital edema. In all cases, swelling is highly variable and often not symmetrical. The cutaneous edema in HAE occurs in non-dependent areas and is non-pitting and minimally painful. Angioedema typically builds within the first 36 hours and then gradually subsides within 5 days, though the initial swelling may occur very rapidly.¹



Figure 2. Cutaneous edema

Photos reproduced with permission from the HAEA (www.haea.org)

Laryngeal edema

The most serious symptoms of HAE occur when edema obstructs the airway and larynx which, in severe occurrences, may lead to a compromised airway and death from suffocation.²² Laryngeal swelling can occur in isolation or in association with cutaneous or abdominal symptoms. In a survey of 221 patients with HAE, Bork and colleagues evaluated the long-term course of the disease in order to establish a specific pattern of swelling.²¹ In 50 out of 158 patients (32%) an episode of facial swelling extended to laryngeal edema at least once. Over the course of their lifetime, up to 50% of patients will experience laryngeal edema; however, only a small percentage experience recurrent episodes. Laryngeal attacks account for less than 1% of all angioedema episodes, occurring much less frequently in patients older than 45 years.²³ Laryngeal swelling usually develops over a period of hours, with a reported mean of 7 hours.²⁴ Although each laryngeal attack has the potential to become life-threatening, the majority resolve before complete airway obstruction occurs.²⁴

If undiagnosed, mortality from HAE can be as high as 30% to 40%, mostly due to respiratory tract obstruction,²⁴ with patients at risk of asphyxia even if they have no previous history of upper airway involvement.^{22,24} A study by Frank et al. noted a history of asphyxiation from airway swelling in a third of untreated patients²⁵ and asphyxiation rates as high as 50% have been reported.^{23,24} This death from suffocation can result in as little as 20 minutes from onset of laryngeal edema.²⁴ The photos in **Figure 3** show a HAE patient suffering from an attack; the series shows that such attacks are progressive, incapacitating, and life-threatening. Thus the greatest mortal threat to patients from HAE is the spontaneous and unpredictable nature of laryngeal attacks.²³

Abdominal Pain

Angioedema of the gastrointestinal tract can lead to a variety of symptoms including pain (frequently excruciating), nausea, anorexia, vomiting, and diarrhea resulting from edema of the bowel wall.^{1,22} Gastrointestinal attacks are experienced by a majority of patients with HAE, and can be the principal presentation in 25% of patients.^{21,26} Abdominal pain, caused by swelling of the intestinal wall, is reported by 70% to 80% of patients with HAE.⁹ The



Figure 3. Sequential Photos of a Laryngeal Attack
From AMCP Dossier, p 21.

pain can be severe and is often spasmodic rather than steady in nature.¹ Pseudo-obstruction secondary to gastrointestinal wall edema has been described.²⁷ The abdomen is typically sensitive to palpation, usually without guarding, while ascites may occur as a result of fluid extravasation from the vasculature into the peritoneal cavity.²² Gastrointestinal attacks of HAE typically subside within 5 days.¹

The diagnosis of abdominal HAE can be difficult because many patients with HAE present with isolated abdominal pain that may be severe enough to mimic an acute surgical abdomen. In fact, before a diagnosis of HAE has been made, patients frequently undergo unnecessary appendectomy or exploratory laparotomy.²⁶ HAE episodes involving the gastrointestinal tract may remain undiagnosed for decades despite repeat visits to the emergency department. At times, patients have been inappropriately referred for psychiatric assessment when the symptoms were considered psychosomatic.²²

Identification of HAE Patients: Screening and Diagnosis

Identifying patients with HAE

The diagnosis of HAE is often delayed, even by years, because of low awareness among clinicians and similarities to other disorders.⁹ The average time between symptom onset and diagnosis in 1977 was 22 years and the average delay still exceeded 10 years as recently as 2005.^{25,28}

Recurring angioedema in the absence of urticaria; unexplained abdominal pain; and/or the presence of erythema marginatum prior to swelling; and a poor response to antihistamines, corticosteroids, or epinephrine may each suggest HAE. If signs and symptoms are suggestive of HAE, screening should be done even in the absence of a positive family history. Approximately 25% of patients diagnosed with HAE have *no* family history, suggesting a new genetic mutation.^{11,29}

There are two predominant types of HAE: type 1 (85% of cases) and type 2 (15% of cases).¹¹ The two types are clinically indistinguishable, but are caused by different genetic mutations. The mutations that cause type 1 HAE are mostly heterozygous⁸ and occur throughout the gene, resulting in proteins that are not efficiently secreted, with decreases in both antigenic and functional levels of C1-INH. These levels are usually in the range of 5% to 30% of normal¹⁰ and, interestingly, the level of C1-INH is not associated with disease severity.¹

Patients with type 2 HAE usually have single point mutations resulting in a protein that is secreted but non-functional.^{1,8} Levels of C1-INH are normal or elevated, but functional C1-INH levels are low.^{8,11} In both type 1 and type 2 HAE, C4 levels are low, while C1q and C3 levels are normal.¹ Virtually all HAE patients (type 1 and 2) have persistently low C4 levels both during and between attacks, with normal C1 and C3 levels.^{1,11} This makes the measurement of serum C4 a good screening test for HAE.^{9,26} If the C4 level is low, the C1-INH level and function should be assessed next²⁶ as measurement of antigenic and functional C1-INH levels will confirm the diagnosis of HAE and distinguish between type 1 and type 2.¹¹ HAE is unlikely if both C4 and C1-INH levels are normal.⁹

A third, very unusual type of HAE was first reported in 2000 and did not show a deficiency of C1-INH.³⁰ Initially it was thought that this third type only affected women, but in 2006 Bork and colleagues identified a family where five female and three male family members spanning four generations were affected. The authors postulate that this may represent a new disease entity, with a different underlying defect that involves an abnormal factor XII.³¹

Differential Diagnosis

Other disorders may present with symptoms similar to HAE, as summarized in **Table 1**.

Allergic angioedema is frequently associated with pruritis and urticaria and can be distinguished from HAE by its clinical response to antihistamines and corticosteroids.

Acquired C1 inhibitor deficiency may be associated with lymphoproliferative disorders; autoimmunity with antibodies directed against C1-INH; or occasionally with other neoplastic, infectious, or autoimmune diseases.⁹ About 14% of patients with acquired angioedema have no other underlying disease.⁹ Unlike those with HAE, acquired angioedema patients often present after the fourth decade of life, and do not have a family history of swelling.⁹ Patients have almost undetectable serum levels and/or activity of C1-INH, C4, and C1q.⁹ The low C1q is unique to acquired C1-INH deficiency.

Inherited angioedema with normal C1-INH/Estrogen-dependent/HAE Type III closely resembles those with C1-INH deficiency. In initial reported cases angioedema occurred exclusively in women during pregnancy or exogenous estrogen therapy.^{9,30} These patients have normal C1-INH levels (antigenic and functional) with normal C4 levels. Mutations in factor XII have been described in this abnormality, which has been seen in both women and men. Since no commercial test is available for factor XII mutations, distinguishing between inherited angioedema with normal C1-INH and idiopathic angioedema is difficult.

Idiopathic angioedema is a diagnosis of exclusion (not attributable to HAE, acquired angioedema, allergic disorders, or any known drug-induced or physical cause). The clinical presentation is similar to HAE, and while typically accompanied by pruritis, laryngeal edema is rare.²² Patients with idiopathic angioedema have normal complement values and may be unresponsive to antihistamines.⁹

ACE inhibitor (ACEI)-induced angioedema may be the result of an adverse drug reaction that is not induced by an allergic mechanism. The incidence of ACEI-induced angioedema is 0.1% to 1% of patients taking the drug.³² ACE degrades bradykinin into inactive metabolites.³³ Therefore ACE inhibition causes increased levels of not only bradykinin but of its active metabolite, causing angioedema in susceptible patients. ACEI-induced angioedema normally occurs within the first 6 weeks of starting the medication. However, this side effect may be underestimated as it may appear after years of ACEI use, thus obscuring its relationship with the drug. Use of ACEIs should be avoided in patients with HAE or acquired angioedema.⁹ Angiotensin receptor blockers (ARBs) do not affect the breakdown of bradykinin. However, though ARBs may be used safely in most patients with ACEI-induced angioedema, swelling from ARBs has been described in patients with and without ACEI-induced angioedema. The etiology of ARB-induced angioedema has not yet been elucidated.

Non-steroidal anti-inflammatory drug (NSAID)-induced angioedema follows ingestion of NSAIDs, and is typically accompanied by urticaria.¹¹ Inhibition of the cyclooxygenase-1 (COX-1) enzyme is the likely mechanism.¹¹ Thus, all COX-1 inhibiting NSAIDs need to be avoided in patients with NSAID-induced angioedema. Multiple reports have noted that NSAID-induced swelling have a predilection for the face, primarily causing peri-orbital angioedema.^{34,35}

Gleich's syndrome is episodic angioedema associated with eosinophilia and elevated IgM antibodies.³⁶ If the screening C4 level is normal, the work-up of a patient with episodic, recurrent angioedema should include a quantitative immunoglobulin level and a complete blood count with differential cell count.

Therapeutic Options

In HAE, there are three main therapeutic goals:⁹

1. Treating acute angioedema attacks (exacerbations)
2. Avoiding new attacks through prophylaxis (chronic prophylaxis)
3. Avoiding attacks at times of increased risk (acute prophylaxis).

I. Managing Exacerbations

Treatment options for acute episodes of HAE should take into account the severity of the symptoms. Laryngeal, pharyngeal, and tongue edema may be life-threatening. Prophylactic intubation in cases of laryngeal edema may be prudent as an early measure to maintain the airway and avoid tracheotomy.⁹ Abdominal attacks are often extremely painful and may be accompanied by vomiting and/or diarrhea. Spasmolytics and narcotics may be necessary for treatment of severe pain during acute abdominal attacks.^{1,9}

C1 inhibitor (C1-INH) concentrate

International studies have shown that human C1-INH concentrate is safe and effective for treatment of acute swelling in HAE patients. Initial double-blind, placebo-controlled studies showed C1-INH replacement was effective in treating acute abdominal or laryngeal attacks and increased serum C1-INH levels.^{37,38} The I.M.P.A.C.T.² trial (International Multi-center Prospective Angioedema C1 Inhibitor Trial) studied 640 HAE attacks in 57 patients. Interim results demonstrated that the median time to the onset of symptom relief was 16 minutes for laryngeal attacks, 28 minutes for facial attacks, and 31 minutes for peripheral attacks (hands and feet).³⁹ In a randomized, double-blind, placebo-controlled trial, 69% of attacks involving laryngeal, abdominal, and facial edema responded after 30 minutes and 95% responded within 4 hours of administering C1-INH concentrate.⁴⁰ A study evaluating the treatment of laryngeal edema in patients with HAE demonstrated that C1-INH concentrate was effective in 192 of 193 swelling attacks with symptoms starting to resolve within 30 to 60 minutes of injection. The first symptoms resolved in all patients were difficulty breathing and fear of asphyxiation.⁴¹

Limitations of human C1-INH include its dependency on human blood supply, potential for transmission of infectious agents, and the need for intravenous administration. As of February 2009, C1-INH had not been approved by the FDA for treatment of acute angioedema in patients with HAE. A pending FDA review of C1-INH for use in acute attacks (June 2009) may lead to this drug's availability to HAE patients outside the setting of clinical trials.

Three companies are currently producing C1-INH for HAE. Two products, Cinryze and Berinert P, use human plasma collected in the US.⁴² Cinryze (ViroPharma) is a nano-filtered human C1-INH and is the first C1-INH approved for use as prophylactic therapy for HAE in the US. Berinert P (CSL Behring) is a pasteurized human C1-INH. The third is Rhucin (Pharming), a novel recombinant human C1-INH secreted from transgenic rabbits following the introduction of a cloned human gene for C1-INH.⁴² As a result, it is not dependent on the human plasma supply and has less theoretic risk of infection compared with human C1-INH concentrate. Rhucin has a plasma half-life of 3 hours and is being studied for treatment of acute swelling attacks in HAE.¹⁰

Fresh frozen plasma (FFP)

The lack of availability of C1-INH in the US over the past several decades has made the treatment of acute swelling attacks unsatisfactory. Fresh frozen plasma (FFP) has been used for both short-term prophylaxis and acute attacks of angioedema. FFP, which contains C1-INH, has been used to rapidly decrease swelling particularly in cases of laryngeal involvement or severe abdominal pain. FFP is efficacious in most patients, and can be used in the absence of C1-INH.⁹ However, some have seen symptoms worsen when FFP is administered for swelling attacks in

HAE.⁴² FFP is not virally inactivated, thus increasing the risk of transmitting infectious agents with its infusion. Urticaria, anaphylactic shock, and hemolysis have been reported with the use of FFP.⁹

Other Potential Agents for Acute HAE Management

The most current evidence suggests bradykinin is the primary mediator of swelling in HAE. Two novel therapies based on that premise are under development. (**Figure 1**)

Ecallantide, formerly DX-88

Ecallantide (Dyax Corp.) is a potent recombinant protease inhibitor which can bind and inhibit human kallikrein, thus decreasing bradykinin generation.⁴² Due to its short plasma half-life when administered subcutaneously, ecallantide is only being studied for acute HAE attacks.¹⁰ In randomized, double-blind, placebo-controlled, multicenter Phase 3 clinical trials, ecallantide demonstrated clinical and statistically significant reductions in the severity of acute attacks in HAE compared with placebo.^{10,43} Side effects were rare and included shortness of breath, throat edema, and prolonged prothrombin and thrombin time.¹⁰ In addition, there have been isolated reports of anaphylactic reactions following ecallantide administration.⁴⁴

Firazyr, formerly Icatibant

Firazyr (Jerini AG/Shire Deutschland) is a synthetic bradykinin receptor-2 antagonist with a structure similar to bradykinin.^{8,10} The plasma half-life is approximately 2 to 4 hours and it is intended for subcutaneous use during acute swelling episodes.¹⁸ Firazyr, has been studied in two Phase 3 trials: FAST 1 (For Angioedema Subcutaneous Treatment) and FAST 2. FAST 2 did not achieve its primary endpoint and Firazyr has not received FDA approval for acute attacks of HAE. A third clinical trial is about to begin.

2. Chronic Long-Term Prophylaxis

In the US, no definitive guidelines have been published to recommend specific long-term prophylaxis in this potentially life-threatening illness. Therapeutic options in HAE include attenuated androgens, antifibrinolytic agents, and C1-INH concentrate. All of these have potential adverse effects and the risks and benefits should be discussed prior to long term prophylaxis.

Attenuated androgens (17- α alkylated androgens)

Over the past 30 years, attenuated androgens (17- α alkylated androgens) have been widely used for long-term prophylaxis in HAE.⁹ Studies done almost 3 decades ago demonstrated daily therapy with attenuated androgens decreased the number of swelling episodes in patients with HAE.¹ Attenuated androgens most frequently used for HAE include danazol, stanazol, and oxandrolone.¹ The majority of studies have been done with danazol. Treatment with danazol led to a marked increase in blood levels of C1-INH and normalization of C4 levels. However, danazol takes at least 48 hours for a clinical effect; making it a poor choice for treating acute attacks.¹ Most assume danazol increases hepatic C1-INH production.¹

The dose of danazol needed for clinical response is variable with approximately 95% of patients responding to 600 mg a day, and over 50% of patients responding to 300 mg a day or less.⁸ A common regimen is to start with danazol 400 to 600 mg a day for a month and taper down to the lowest effective dose.⁹ The side effects of attenuated androgens limit its use in some patients, particularly children. Long-term side effects of impeded androgens including masculinization, weight gain, deepening of the voice, fatigue, menstrual irregularities, hemorrhagic cystitis, arterial hypertension, headache, alteration in libido, hair growth or loss, liver function abnormalities, increased risk of thrombosis, hepatic malignancy (hepatic adenoma and carcinoma), and unfavorable abnormalities in serum lipids.^{1,9,10} Long-term use of danazol also has been associated with an increased risk of early atherosclerosis.⁴⁵ Periodic monitoring of serum HDL and LDL may assist in identifying atherosclerosis risk associated with androgens. Contraindications for attenuated androgens include childhood, pregnancy, lactation, and prostate cancer.

Antifibrinolytic agents

Epsilon aminocaproic acid (EACA) is the only antifibrinolytic agent currently available in the US and is primarily used to treat hyperfibrinolysis bleeding during cardiovascular and genitourinary surgery, dental bleeding in

hemophilia A, traumatic hyphema, hereditary hemorrhagic telangiectasia and missed abortion. A double-blind, placebo-controlled study demonstrated the effectiveness of EACA in reducing the frequency of attacks, however this agent was less efficacious than androgens. Unlike attenuated androgens, antifibrinolytic agents have no impact on C4 or C1 inhibitor levels.⁴⁶ EACA has been shown to reduce attack frequency at a daily dose of 8 to 12 g in 4 divided doses.⁹ A number of side effects have been associated with EACA including thrombosis, severe muscle toxicity, and muscular pain and weakness associated with myositis.^{1,9} Contraindications include previous thrombosis, or a procoagulant state.¹ Despite these adverse effects, EACA may be preferred over androgens for use in children.⁹

C1-INH concentrate

C1-INH has been used in both acute attack therapy and long-term prophylaxis of HAE. It represents the most physiologic treatment.²⁵ There have been reports of patients being treated with 500 to 1,000 U once or twice weekly for over a year with marked reduction in acute attacks.^{47,48} A recent study using 1,000 U of nanofiltered human C1 inhibitor biweekly showed a statistically significant decrease in the frequency of attacks compared with placebo.⁴⁹ The risk of blood-borne pathogen exposure is a concern of long-term use of human C1-INH concentrate. Limitations of C1-INH products include dependency on the human blood supply and the need for intravenous access, although the efficacy of subcutaneous administration is presently being investigated. In October 2008, Cinryze was FDA-approved for use in angioedema prophylaxis in HAE patients.

3. Short term prophylaxis/prevention

Therapeutic intervention can be used prior to events that may precipitate attacks, such as dental procedures, endoscopy, endotracheal intubation, or other types of surgery.⁹ Most agree FFP is useful for short-term prophylaxis prior to procedures.⁵⁰ FFP given in two unit doses intravenously the night before or the day of surgery has been successful in preventing angioedematous attacks in patients with HAE. EACA is effective in reducing the frequency of attacks when administered several days prior to triggering events. The daily dose is usually 8 to 12 g in 4 equally divided doses.⁹ Attenuated androgens are used from 5 days before to 3 days after the event; danazol has been administered at a dose of 10 mg/kg/day with a maximum of 600 mg a day.⁹ C1-INH is safe and effective for prophylaxis of acute attacks in adults, children, and pregnant women. The dose for short term prophylaxis is 500 to 1,000 U given the night before or on the day of surgery.^{9,51}

Social and Economic Burden of HAE

HAE has a significant personal and economic impact on patients due to its chronicity and the recurrent and unpredictable nature of acute attacks. The disease has a significant mortality and morbidity burden, with the mortality rate reportedly as high as 33%, primarily due to upper airway obstruction.⁵² HAE can have a devastating impact on a patient's quality of life as the frequency and severity of attacks increase or worsen. Extremity and facial attacks can also be disabling. In the case of extremity attacks, the loss of manual dexterity or ambulation can be problematic. The disfigurement of facial attacks may cause significant social stigma.

Abdominal attacks can be extremely painful, causing substantial incapacity. A prospective evaluation of 153 patients suffering from abdominal attacks demonstrated a mean pain score of 8.4 on a 10-point scale with 4 women reporting that their pain was worse than giving child birth.²¹ Vomiting occurred in 73% of patients and 16 of 169 attacks required medical attention over a period of 24 months.

Patients with HAE require substantially more healthcare resources than patients without the disease, including drug therapy, physician visits and ER visits, and hospitalizations. Analyses of a European registry of 1,168 patients found a total of 1,333 hospitalizations per year attributable to HAE (approximately 1.2 hospitalizations/patient/year). Of these patients, 10% had 4 or more hospitalizations in the past year.⁵³ A separate, US based, patient survey reported that patients averaged 4.7 ER visits per year;⁵⁴ this rate far exceeds the national average of 39.6 ER visits per 100 persons (0.396 visits per person per year) in 2005.⁵⁵ Therefore, HAE may account for 15,000 to 30,000 ER visits annually in the US.⁵² HAE patients also have a greater likelihood of costly invasive procedures, such as emergency tracheotomy or intubation for laryngeal attacks.²⁸

The risk of unnecessary surgery or treatment is an additional concern, especially in undiagnosed HAE. Approximately a third of patients with abdominal attacks undergo unnecessary surgery.⁹ In a chart review of 22 patients diagnosed with HAE, at least three had numerous surgical procedures including appendectomies, laparotomies, and endoscopies/colonoscopies for diagnosis or attempted treatment.⁵⁶ Approximately 25% of patients with laryngeal attacks have been inappropriately treated for anaphylaxis in the ER, delaying appropriate treatment and potentially worsening outcomes.⁵⁴

The Burden of Illness Study was a web-based survey of 457 HAE patients (345 women, 112 men). The survey reviewed attack characterization; acute attack treatment; chronic disease management; and financial, physical, and emotional burden of disease management. Disease-specific questions included: treatment patterns and providers; side-effects and burden of androgen therapy; and the impact of the disease on quality of life.⁵⁷ This study found that HAE has a pervasive and detrimental impact on its sufferers, with 94% of participants experiencing attacks in the past year (mean 26.9 attacks/year). The typical acute attack lasted more than 2.5 days (60 hours).⁵⁸ Monetized cost averaged \$45,000/year/patient, including physician visits, missed work days, reduced productivity, hospital stays, tests, and procedures, chronic therapy, and patient co-pays. Direct medical costs for a patient suffering from severe attacks is an estimated \$71,000 annually.⁵⁸ The total cost of managing acute HAE attacks exceeded \$24,460/patient/year with 81% borne by payers. Disease severity (ie, acute attacks) was associated with increasing costs of both acute and chronic treatment.⁵⁸

The random nature of HAE attacks has a significant impact on quality of life.⁵⁹ The Burden of Illness Study demonstrated a substantial psychological and financial burden of HAE, with non-monetized costs including long-term side effects from anabolic steroids (current standard of care),⁶⁰ missed school, missed educational and career opportunities, and decreased overall mental and physical health. Most respondents (69%) reported they had not been able to consider certain jobs as a result of their condition, and 100% reported that HAE limited them from advancing in school.

As a result of an acute attack, more than half of patients with HAE missed at least 1 day of work (51% of full- or part-time workers), 1 day of school (44% of students), and 1 day of leisure activities (59% of survey respondents).⁶⁰ In addition, 69% of patients reported that their disease affected the ability to consider certain jobs and 58% reported that it affected career advancement.⁶⁰ Nearly half (42.5%) of patients studied had scores indicative of clinical depression, when evaluated with a standardized screening instrument. In comparison to normal populations, HAE patients scored significantly ($P<0.0001$) higher on the HDI-SF depression assessment tool and demonstrated significant ($P<0.0001$) decreases in all the physical and mental components of the SF-12 Health Survey.⁶⁰

HAE also has significant implications on daily functioning and work-life. During an acute attack, patients may miss work due to incapacitating pain or discomfort, or to the inability to perform work activities (eg, inability to type due to edema in the hands). More than 90% of patients with abdominal attacks require bed rest for 24 to 50 hours per attack, preventing them from work as well as activities of daily living.²¹ The productivity impairment suffered by HAE patients is similar to that of patients with other severe chronic diseases. The Work Productivity and Activity Impairment (WPAI) assessment showed overall work impairment at 33.6%, which is between the range of WPAI measurements reported for Crohn's disease patients (45.9%) and severe asthma patients (28%). HAE patients had marked impairment in productivity in all WPAI categories including 45% impairment in overall activity.⁶⁰

HAE provides a series of challenges to the clinician. One of the greatest of these is the unpredictable frequency and severity of acute attacks combined with a lack of FDA-approved therapeutic options. Patients must live with frequent disruptions in social activity and work/education. The risk of life-threatening laryngeal edema may cause ongoing anxiety and reluctance to travel.⁹ With the arrival of new therapeutic options for acute management and prophylaxis combined with a deeper understanding of the pathophysiology of this potentially life threatening disorder, the quality of life for patients suffering from HAE is likely to improve.

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CME Accreditation Documents

HAE: Creating Awareness, Recognition and Improving Therapeutic Management for Patients

Authors

Mark A. Davis-Lorton, MD; Doug T. Johnston, DO

CME Quiz

Please indicate your response by circling the letter of the most appropriate answer for each question.

- Which of the following is a common symptom of HAE?
 - Intermittent angioedema and urticaria
 - Abdominal cramping lasting over 24 hours
 - Generalized pruritis
 - Wheezing and nasal congestion
- Intermittent angioedema, abdominal pain, and urticaria are features of which of the following disorders?
 - Hereditary angioedema
 - Acquired angioedema
 - Idiopathic angioedema
 - All of the above
- Which of the following laboratory results confirms a diagnosis of HAE?
 - Low C4 I and normal C1-INH levels
 - Low C4 levels and low C1-INH levels
 - High functional C1-INH levels
 - Low C1q levels
- Which of the following is thought to be the major mediator of swelling in HAE?
 - Fibrin
 - C1-INH
 - Histamine
 - Bradykinin
- Which of the following symptoms of HAE is associated with the highest mortality risk?
 - Swelling of the lips and, eyelids
 - Laryngeal edema
 - Severe, unexplained abdominal pain
 - Vomiting and diarrhea
- Swelling episodes in HAE typically
 - resolve within 24 hours
 - occur daily if untreated
 - last 2-5 days
 - will not resolve until therapy is administered
- Which of the following therapeutic options is indicated in the US for chronic long-term prophylaxis of HAE?
 - C1 inhibitor concentrate
 - Ecallantide
 - Fresh frozen plasma
 - Icatibant
- C1 inhibitor plays a key role in the complement and contact pathways, including which of the following actions?
 - Activating plasma protease activity
 - Stimulating activation of the classical pathway
 - Regulating bradykinin
 - Activating C1r and C1s
- HAE and ACE-I induced angioedema share which of the following features?
 - Bradykinin is a likely mediator
 - Antihistamines are not effective
 - Laryngeal edema may be fatal
 - All the of the above
- According to the Burden of Illness study, what percentage of HAE patients experienced an acute attack over the course of 1 year?
 - Less than 25%
 - 50%
 - 75%
 - over 90%

(Please Print Legibly)

First Name _____ Last Name _____ Degree _____

Signature _____

Evaluation and Request for Credit Form

HAE: Creating Awareness, Recognition and Improving Therapeutic Management for Patients

Authors

Mark A. Davis-Lorton, MD; Doug T. Johnston, DO

By circling your choice, please evaluate the effectiveness of this CE Activity

	<i>Excellent</i>			<i>Poor</i>
Overall quality of the activity	4	3	2	1
Overall quality of learning materials including handouts	4	3	2	1
Effectiveness of the learning activities	4	3	2	1
Activity provided fair balance of information	4	3	2	1
Content free of commercial bias (Please comment below)	4	3	2	1
Educational objectives achieved:				
• Identify the symptoms of HAE and what characteristics differentiate it from other diseases with similar presentations	4	3	2	1
• Describe the differential diagnosis for HAE and the appropriate tests to confirm the diagnosis	4	3	2	1
• Identify the traditional treatments for HAE and discuss how new and emerging therapies may improve clinical outcomes	4	3	2	1
Level of content appropriate for the target audience	4	3	2	1
Information provided will improve professional effectiveness	4	3	2	1
How will this activity facilitate change in your practice?				

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