Optimizing Screening and Management of the Patient with Hereditary Angioedema: A Primer for Primary Care Practice

Learning Objectives
After participating in this educational activity, participants should be better able to:

1. Apply available screening and diagnostic tools to promptly differentiate between clinical presentations and symptoms of HAE to accurately identify patients with HAE

2. Customize treatment utilizing consensus algorithms, published clinical evidence, and new therapeutic options for acute attacks of HAE

3. Implement strategies to ensure “attack vigilance” by treating HAE symptoms early and employ prophylactic strategies in patients with recognizable prodromal symptoms
Clinical Case Challenge

Brittney J. is a 22-year-old white female college student who presents to the campus primary care clinic during final exam week in mid-December. Her chief complaints are headache, nausea, vomiting, and severe abdominal pain that have been ongoing for approximately 24 hours. She tells the examining physician that she has "not been able to keep any food down" since the previous day. She comments that several of her classmates, including her 2 roommates, appear to have come down with "the flu" and somewhat similar symptoms.

Medical history reveals that since she was 15 years old, Brittney has experienced intermittent, recurrent episodes of severe abdominal pain along with swelling in her hands and feet. During these attacks, typically her abdomen is distended and her hands and feet swell significantly without pain or itching. These episodes last 2 or 3 days and have on some occasions required urgent medical treatment when the abdominal pain was severe. These attacks have previously been attributed to food allergies, although the patient has never been tested for any specific allergies. Her mother and maternal grandmother experienced similar episodes that were never formally diagnosed; they would just "wait them out," seeking urgent care when needed. Brittney now follows a gluten-free, predominantly vegetarian diet, although she consumed some food and drink (bread, cookies, chocolate, and alcohol) not in her usual diet over the past week at campus holiday parties. She is sexually active and uses a hormonal contraceptive vaginal ring. She uses no other medications aside from a daily multivitamin recommended by her family doctor because of her somewhat restrictive usual diet.

Brittney’s examination in the clinic reveals a moderately distended abdomen that is tender to the touch and exhibits moderate rebound. Her right hand and left foot are swollen as well. Her pelvic exam reveals no distinct abnormalities or discharge, although she complained of discomfort related to her abdominal pain during the exam. Her heart rate is elevated (110 beats per minute), her blood pressure is normal (110/60 mm Hg), and her temperature is 98.4 °F. Complete blood count (CBC)/differential and laboratory metabolic panel are normal, although a kidney, ureters, and bladder (KUB) flat plate radiograph of her abdomen shows somewhat distended loops of small bowel.

Case Challenge Question 1:
What is the potential cause of Brittney's current abdominal distress?
   a. Pelvic inflammatory disease (PID)
   b. Irritable bowel syndrome
   c. Endometriosis
   d. Food allergies
   e. Viral gastroenteritis
   f. Any of the above
**Case Challenge Question 2:**
How would you manage this patient if you were the examining physician at this visit?

a. Treat this as a viral illness and advise her to consume only clear liquids until the nausea, vomiting, and abdominal pain resolve
b. Restrict her to her usual diet and recommend that she avoid unfamiliar foods at holiday celebrations
c. Advise her to see her gynecologist and be tested for potential sexually transmitted disease (STD)/PID
d. Refer her to a gastroenterologist
e. After acute illness symptoms have resolved, obtain further diagnostic laboratory testing

**Case Challenge Question 3:**
After acute illness symptoms have resolved, which of the following tests may be helpful in diagnosing Brittney’s underlying disorder?

a. ImmunoCap® tests for food allergy
b. Test for anti-gluten antibodies
c. C4 and C1 esterase inhibitor quantitative and functional assay
d. Liver function tests
e. Other

**Angioedema**
Angioedema is characterized by asymmetric, circumscribed swelling, which may involve the skin, mucosal membranes, and sometimes the viscera. It may or may not be associated with urticaria. Angioedema can occur as a result of an allergic reaction following ingestion of foods or drugs or after an insect sting. Other causes include ingestion of nonsteroidal anti-inflammatory agents such as aspirin, use of radiocontrast media, and use of angiotensin-converting enzyme inhibitors (ACEIs). Angioedema can be associated with other medical problems, including infection, connective tissue disorders, and malignancy. In some cases, the cause of angioedema cannot be identified and the angioedema is considered idiopathic. Angioedema can also be associated with disorders in which C1 esterase inhibitor (C1 inhibitor; C1-INH) function is deficient, including hereditary angioedema and acquired angioedema (AAE) with C1-INH deficiency. AAE often occurs in the presence of a lymphoproliferative neoplasm.[1,2]

**Hereditary Angioedema**
Hereditary angioedema (HAE) is an autosomal-dominant disorder characterized by recurrent attacks of facial, abdominal, genital, or peripheral skin edema without accompanying urticaria. These episodes can be life-threatening if they involve the larynx or the upper airway.[2] This form of angioedema was first described as having a hereditary component in 1888 by Sir William Osler, and the biochemical defect was discovered 75 years later by Donaldson and Evans, who demonstrated that patients with HAE were lacking the serum inhibitor directed against the first component of the complement system, C1-INH.[1,3,4] Most cases of HAE are attributed to a C1-INH deficiency due to a mutation in SERPING1, the gene on chromosome 11 encoding C1-INH. Two distinct forms of HAE have been identified: HAE type 1, characterized by substantially reduced levels of C1-INH, and HAE type 2, characterized by normal C1-INH levels but impaired protein function caused by the genetic mutation. The swelling seen in HAE is independent of histamine release, and is instead related to increased production of vasoactive peptide kinin hormones in the tissues affected, particularly bradykinin. More recently, a form of HAE with normal C1-INH function has been described. This condition has been reported primarily in women and is usually associated with high estrogen levels associated with menstruation.
pregnancy, or use of estrogen-containing medications. Individuals with this condition exhibit normal C1-INH concentration and function but have a family history of angioedema and experience swelling attacks similar to those seen in HAE with C1INH deficiency. This form of HAE has been termed “HAE with normal C1-INH”.[2,5]

Clinical Features of HAE
Clinical features of HAE include angioedema without urticaria. Attacks may be precipitated by trauma, infection, or psychological stress, and may be preceded by prodromal symptoms including rash (erythema marginatum) and fatigue. The angioedema itself is often very severe, involving the face, oropharynx, gastrointestinal system, genitourinary tract, and extremities. In contrast with allergic angioedema, the swelling attacks are slow to develop and may persist for 2 to 4 days without treatment. Unlike allergic angioedema, HAE attacks do not respond to therapy with antihistamines, corticosteroids, or epinephrine; they can be unpredictable; and they vary in type, severity, and frequency even among patients with the same genetic mutation. Attacks frequently worsen when a patient begins puberty, when a patient uses ACEIs, or in women during menstruation or when estrogen-containing drugs are taken.[1,6,7]

Epidemiology and Prevalence of HAE
The exact prevalence of HAE is difficult to determine. Current estimates of the number of individuals with HAE vary from as high as 1 case per 10,000 persons in the general population to as low as 1 case per 50,000 persons. It is believed that there are between 6,000 and 30,000 individuals with HAE in the United States alone. No differences between ethnicities or sexes have been found in the incidence of HAE. It is important to recognize that there does not appear to be a simple correlation between serum C1-INH level, genetic mutation, and disease severity. It is also important to note that 50% of HAE patients will have an attack involving the airway at some point in their lifetimes. Mortality from asphyxiation due to edema of the airway has been reported in up to 40% of these attacks, whether or not a diagnosis of HAE has been made.[1,6,8,9]

Signs and Symptoms during Attacks of HAE
A study by Bork et al found that in 131,110 edema episodes among 221 patients, skin swellings, including facial, trunk, genital, and extremity swellings, and abdominal attacks occurred in more than 97% of all HAE episodes. More than half of the patients studied experienced laryngeal edema. The observed time pattern of HAE showed onset of clinical symptoms in the first or second decade of life, and the subsequent years were characterized by recurrent episodes, with only a small minority of patients having symptom-free years between episodes. A number of organs may be affected by HAE, including the skin, muscles, gastrointestinal tract, respiratory tract, and genitourinary tract.[10]

Extremity attacks affect 96% of patients; however, these attacks can be overlooked by managing physicians as insignificant in comparison with other major organs affected. Extremity attacks must be addressed, as they can be functionally disabling. Edema within the hands may hinder the patient’s ability to type, drive, or use a phone, and swelling in the feet may be severe enough to impede standing and walking. While HAE attacks of the extremities do not often result in hospitalization, they can substantially interfere with a patient’s ability to work or attend school and can negatively affect quality of life.[6,11] Abdominal attacks can cause significant morbidity. Characteristic radiographic findings include spiculation and thickening of intestinal folds (Figure 1), and endoscopy may demonstrate mucosal edema (Figure 2). Abdominal attacks can cause severe abdominal pain, nausea, and vomiting. Bowel sounds are often diminished or silent, and guarding and rebound tenderness are frequently present on physical
examination. Ascites may also be present, and third spacing of fluid can lead to significant hypotension and hemoconcentration. In some cases, patients with HAE have undergone unnecessary surgery because the symptom severity suggested an acute surgical abdomen requiring emergency intervention.[6]

Polling question #1
The severity of HAE attacks can vary significantly both between patients and within families.

a. True
b. False

Figure 1. Characteristic radiographic pattern of HAE attack, small bowel.

Acute oropharyngeal/laryngeal attacks are potentially life-threatening events that require careful monitoring and airway management, with intubation or tracheotomy needed in some cases (Figure 3). In a retrospective survey of 58 HAE patients by Bork et al, the incidence of asphyxiation in untreated laryngeal attacks was as high as 40% (23 deaths by asphyxiation in the population studied), underscoring the severity of this potential adverse event.[12] Most of the patients studied died between the 20th and 50th year of life, although it is important to note that asphyxiation can occur at any age, including during childhood. It is important to note that fatal airway attacks occur not only in patients with frequent edema attacks, but also in those who experience only rare swelling episodes. Clinicians must maintain a high degree of awareness that severe laryngeal edema can occur and must emphasize the possibility of laryngeal attacks to patients as well as their relatives and caregivers.[9,12]
Figure 3. Patient with HAE, A, before facial/laryngeal attack, and B, after facial/laryngeal attack, requiring airway management with intubation. (Images courtesy of Dr. William Lumry.)
Function and Dysfunction of C1-INH

C1-INH inhibits all active enzymes of the bradykinin-forming cascade (Figure 4). It inhibits all functions of factor XIIa (factor XII autoactivation and conversion of prekallikrein to kallikrein), and it is a major inhibitor of kallikrein. C1-INH blocks the feedback activation of factor XII (Figure 4, bold arrow) and the cleavage of high molecular weight (HMW) kininogen that generates bradykinin. A second cleavage by kallikrein converts factor XIIa (80 Kd) to factor XIIIf (fragment of 30 Kd), and factor XIIIf activates the C1r subcomponent of complement C1. The C1 then digests and activates its substrates C4 and C2. Both factor XIIIf and activated C1 are inhibited by C1-INH. Although C4 levels are low in asymptomatic patients, the formation of factor XIIIf and its activation of C1r during an attack of swelling is the likely reason that C4 levels then approach zero and C2 is depleted (Figure 5).[13]

Figure 4. Function of C1-INH.

Figure 5. Lack of function of C1-INH.

Lack of Function of C1-INH

Trace FXIIa or Trace activity in native FXII

FXII → FXIIa

Prekallikrein

Surface HMW Kininogen

HMW Kininogen

Kallikrein

HMW Kininogen

Bradykinin

FXII → FXIIa → FXIIIf

Autodigestion Kallikrein

C1

C1bar = Not Inhibited by C1-INH

C4 & C2 Digestion

Diagnosis of HAE

Assessing a patient’s complement profile can assist in determining the type of HAE that is present. These laboratory characteristics can help to differentiate among types of HAE and to distinguish between HAE and other forms of angioedema, such as idiopathic angioedema or ACEI-associated angioedema (Table 1).[6,7]

Table 1. Laboratory Characteristics of the Various Forms of HAE.

<table>
<thead>
<tr>
<th>Type</th>
<th>C1-INH Level</th>
<th>C1-INH Function</th>
<th>C4 Level</th>
<th>C3 Level</th>
<th>C1q Level</th>
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<tr>
<td>HAE type 1</td>
<td>&lt;30%</td>
<td>&lt;30%</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>HAE type 2</td>
<td>Normal</td>
<td>&lt;30%</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>HAE with normal C1-INH</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>AAE</td>
<td>Low</td>
<td>Low</td>
<td>&lt;30%</td>
<td>Normal/Low</td>
<td>Low</td>
</tr>
<tr>
<td>ACEI-associated angioedema</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Idiopathic angioedema</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

AAE = acquired angioedema; ACEI = angiotensin-converting enzyme inhibitor; C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema. (Adapted from the New England Journal of Medicine, Zuraw BL. Hereditary angioedema, Vol 359, pages 1027-1036. Copyright © 2008 Reprinted with permission from Massachusetts Medical Society.)

Measuring the level of complement C4 is the best initial screening test to exclude HAE in the differential diagnosis of angioedema. However, C4 levels can be normal if the patient has idiopathic or HAE with normal C1-INH or is receiving 17a-alkylated androgen therapy or ACEIs. When measurements are repeated during an attack, however, the C4 should always be low in HAE. Once a low C4 level is confirmed, the next step should be to measure the C1-INH level. If this level is normal, C1-INH function should be measured. If there is no family history of angioedema or if attacks begin after age 30 years, AAE should be considered (C1-INH level will be low in 70% of these individuals). Acquired C1-INH deficiency should be excluded by measuring the complement C1q antigenic level, as this level would be low in AAE. It should be noted that there is no reliable method to accurately test for HAE with normal C1-INH at this time.[7] Figure 6 provides a basic algorithm for the diagnosis of HAE.

Polling Question #2

The first laboratory test that should be performed when considering HAE in the differential diagnosis of angioedema is:

a. C1q
b. C3
c. C4
d. C1-INH level
Available Treatments for HAE

Conventional treatment of HAE has not greatly changed in the past 40 years. The general approach to treatment can be classified according to 3 goals:[14]

- Long-term prophylaxis
- Short-term prophylaxis
- Treatment of acute attacks

Long-term prophylaxis is intended to minimize attack frequency and severity and prevent hospitalizations and emergency department visits, as well as to prevent consequent morbidity and mortality.[14,15] Short-term prophylaxis is designed to prevent attacks that may occur following trauma, and this form of prophylaxis may be administered prior to elective surgery and other invasive procedures that might trigger an attack. Treatment of acute attacks is intended to terminate ongoing attacks and prevent the potential morbidity and mortality associated with these episodes.[14,15]

Historically, attacks were managed with supportive care: keeping the airway open, administering analgesics for pain, maintaining fluids, and simply allowing the episode to pass over time. However, with the availability of safe and effective treatment for attacks, including human plasma-derived C1-INH, ecallantide, and icatibant, attacks can now be promptly treated and terminated. Short-term or pre-procedural prophylaxis may be accomplished using human–plasma-derived C1-INH, high-dose androgens such as danazol or stanazol, or administration of fresh frozen plasma. Long-term prophylaxis may involve the use of androgens, antifibrinolytics (e-aminocaproic acid, tranexamic acid), and human–plasma-derived C1-INH.[14,16]
Treatment of Swelling Attacks in HAE

C1-INH replacement therapy

Treatment using C1-INH concentrates was introduced into clinical practice in Germany in 1978. Use of C1-INH concentrates was initially regarded solely as emergency therapy for very severe attacks, owing to concerns over its derivation from human plasma and the risk for potential viral transmission with administration. Once virus inactivation was incorporated into the manufacturing process, indications for use of C1-INH were expanded to include less severe attacks. The preparations now comprise purified and virus-inactivated concentrates from human plasma. C1-INH preparations are highly effective in preventing and treating acute attacks due to C1-INH deficiency.[16] Multiple studies have demonstrated the effectiveness of C1-INH concentrates. In a study of more than 4000 abdominal attacks in 75 patients, patients treated with C1-INH concentrate experienced a mean attack duration that was significantly less than those left untreated (approximately 40 hours vs. 92 hours, respectively). Mean time to relief was approximately 53 minutes in the treatment cohort versus 114 minutes in those not treated, and no significant drug-related adverse events were reported.[16] Similarly, in a study of 42 patients with HAE and 517 episodes of laryngeal edema, the mean time to relief and resolution of symptoms was 42 minutes when C-1INH concentrate was administered, and, importantly, the duration of airway obstruction was substantially reduced. The effective response rate was virtually 100%, as C1-INH concentrate was effective in all laryngeal edema episodes.[15] C1-INH concentrates appear to have equivalent efficacy for all types of HAE attacks, and this therapy can be life-saving for those with laryngeal attacks (Figure 7).[15,16]

Figure 7. Combined data, abdominal and laryngeal attacks (629/630 attacks, 193/193 laryngeal).[15,16] (Image courtesy of Dr. Bruce Zuraw.)

In the United States, 1 human-derived C1-INH (Berinert®) is approved for acute laryngeal, facial, and abdominal attacks of HAE in adult and adolescent patients by the Food and Drug Administration (FDA). The drug is administered at a dose of 20 IU per kilogram of body weight by intravenous administration.[17] Data from the IMPACT series of trials demonstrated that this C1-INH concentrate provided rapid symptom relief in patients with acute abdominal or facial
Attacks associated with type 1 or 2 HAE, with a median time to the onset of symptom relief that was significantly shorter in those receiving the C1-INH concentrate compared with those who received placebo (0.5 vs 1.5 hours, respectively). A subsequent noncomparative extension trial demonstrated ongoing effectiveness of on-demand treatment; median time to onset of symptom relief was 30 minutes with this C1-INH concentrate.[18]

**Ecallantide**

Ecallantide (Kalbitor®) is a recombinant protein synthesized by the yeast Pichia pastoris. Ecallantide functions as a specific and strong inhibitor of plasma kallikrein. Early trials demonstrated that symptoms of angioedema resolved within 4 hours after ecallantide administration. In the EDEMA 3 trial, 72 patients with angioedema were randomized to receive either ecallantide or placebo ([Figure 8]).[19] The primary endpoint was a treatment outcome score at 4 hours after therapy administration; this score was a composite patient-reported outcome measure based on site or sites of symptoms, symptom severity at baseline, and patient response to treatment. Patients also utilized reports of a mean symptom complex severity score incorporating the symptom site or sites and symptom severity before and after treatment. At 4 hours after administration for acute attacks of angioedema, patient-reported treatment outcomes scores and mean symptom complex severity scores were significantly better with ecallantide compared with placebo. The estimated time to significant improvement was 165 minutes in those who received ecallantide compared with 240 minutes for those who received placebo.[19] In the subsequent EDEMA 4 study ([Figure 8]), 96 patients with a moderate to severe HAE attack were randomized to receive either ecallantide or placebo, again with a primary endpoint of change from baseline in symptom complex severity 4 hours after administration. Mean change in the symptom severity complex score was significantly greater in patients treated with ecallantide, and ecallantide therapy was associated with a significantly higher mean treatment outcome score compared with placebo. Benefits of ecallantide were noticeable within 2 hours of administration and persisted for 24 hours after dosing. The safety profile was similar between both patient treatment cohorts.[20] The drug is indicated for treatment of acute HAE attacks in patients aged 16 years and older and is administered at a dose of 30 mg (3 mL) subcutaneously in 3 doses; another 30 mg may be administered within a 24-hour period if the HAE attack persists. It must be noted that in the EDEMA trials hypersensitivity reactions including anaphylaxis were seen in 2.7% of patients treated with subcutaneous ecallantide. For this reason, the drug must be administered by a healthcare professional trained in the recognition and treatment of anaphylaxis.[21]
Figure 8. Combined data, EDEMA 3 and EDEMA 4 studies.[19,20]

**Ecallantide**

**Improvement of Acute Attack Symptoms at 4 Hours**

![Bar chart showing improvement of symptoms at 4 hours for Ecallantide and Placebo.](chart.png)

Treatment Outcome Score (TOS) is a measure of symptom response to treatment. A TOS value >0 reflected an improvement in symptoms from baseline.


**Icatibant**

Icatibant (Firazyr®) is a specific B2-bradykinin receptor antagonist. This molecule is a small peptide containing several unnatural amino acids that is unlikely to elicit an immunologic reaction. Administered subcutaneously, icatibant has a serum half-life of approximately 1.2 hours. Three randomized, double-blind, controlled studies of icatibant for HAE attacks have been performed. FAST-1, which was conducted mostly in the United States, compared icatibant with placebo and involved 56 patients. FAST-2, which was conducted mostly in Europe, compared icatibant with tranexamic acid and involved 72 patients. FAST-3, also conducted in the United States, compared icatibant to placebo in 88 patients. Time to beginning of relief (defined as 50% reduction of primary symptom score) in icatibant-treated patients was 2.5 hours in the FAST-1 study and 2.0 hours in the FAST-2 study. However, time to beginning of relief in the comparator group was 12 hours in FAST-2 but was unexpectedly only 4.6 hours in the FAST-1 study. This resulted in FAST-2 showing a statistically significant benefit for icatibant, whereas FAST-1 outcomes did not reach statistical significance. In the subsequent FAST-3 study, time to onset of symptom relief, time to onset of primary symptom relief, time to almost complete symptom relief, and time to initial symptom improvement were all significantly shorter for the icatibant group compared with the placebo group (Figure 9). The percentage of patients who experienced adverse events was also lower for the icatibant group compared with the placebo group (41% vs. 51%, respectively). Drug-related adverse events in the icatibant group included diarrhea, nausea, dyspepsia, headache, and injection-site erythema. Drug-related adverse events in the placebo group included headache and pruritus.[22,23] Icatibant is approved for treatment of acute HAE attacks in adults aged 18 years or older. It may be self-administered by the patient subcutaneously in the abdomen at a dose of 30 mg. Additional injections of 30 mg may be administered at 6-hour intervals if response is inadequate, although no more than 3 injections should be given in a 24-hour period.[24]
A comparison of the approved and emerging agents for the treatment of HAE is provided in Table 2 [14,17,24-26], and a summary of their mechanisms of action and effects on the kinin/contact system in HAE is noted in Figures 10 and 11.

Figure 9. Icatibant data from the FAST-3 study.

Reprinted from the Annals of Allergy, Asthma & Immunology, Vol. 107/edition 6, Randomized placebo-controlled trial of the bradykinin B₂ receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial, pages 529-537, Copyright 2011, with permission from Elsevier.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Potential Safety Concerns</th>
<th>Disadvantages</th>
<th>Advantages</th>
<th>Status</th>
</tr>
</thead>
</table>
| Plasma-derived C1-INH         | • Infectious risk  
• Potential infusion reactions                   | • Needs IV access  
• Limited supply                                         | • Extensive clinical experience  
• Corrects the fundamental defect  
• Relatively long half-life  
• Both plasma-derived C1-INH products FDA-approved for self-administration | • Berinert®: FDA-approved in 2009 for acute attacks  
• Cinryze®: FDA-approved in 2009 for prophylaxis; additional study requested for acute attacks |
| Recombinant C1-INH            | • Potential allergic reactions  
• Antibody formation to protein                                   | • Needs IV access  
• Short half-life                                              | • Corrects the fundamental defect  
• No human virus risk  
• Scalable supply                                               | • Rhucin®/Ruconest®: approved in Europe; pending approval in the United States |
| Ecallantide                   | • Allergic reactions  
• Antibody formation to protein  
• Local injection reactions                                  | • Short half-life  
• Requires healthcare provider administration due to anaphylaxis risk     | • No infectious risk  
• More potent than C1-INH at site of action  
• Subcutaneous administration                                  | • Kalbitor®: FDA-approved in December 2009 for acute therapy |
| Icatibant                     | • Local injection reactions                                        | • Short half-life                                      | • No infectious risk  
• Stable at room temperature  
• Subcutaneous administration  
• FDA-approved for self-administration                            | • Firazyr®: FDA-approved for acute therapy in August 2011 |

C1-INH = C1 esterase inhibitor; FDA = Food and Drug Administration; HAE = hereditary angioedema; IV = intravenous.
Figure 10. Summary of mechanisms of action for on-demand treatments for HAE.

**Kinin/Contact System in HAE**

- Trace FXIIa or Trace activity in native FXII
- FXII → FXIIa
- Surface HMW Kininogen
- Prekallikrein
- HMW Kininogen
- Kallikrein
- Bradykinin
- Surface B2 Receptor
- ANGIOEDEMA

- C1-INHibitor


Figure 11. Summary of On-Demand Treatments for HAE.

**On-Demand Treatments for HAE**

- Trace FXIIa or Trace activity in native FXII
- FXII → FXIIa
- Surface HMW Kininogen
- Prekallikrein
- HMW Kininogen
- Kallikrein
- Bradykinin
- Surface B2 Receptor
- ANGIOEDEMA

- Ecallantide
- Icatibant
- X - Icatibant

Polling Question #3
On-demand treatments of HAE have which of the following effects on bradykinin?

a. Decrease bradykinin production or action
b. Eliminate bradykinin production or action
c. Increase bradykinin production or action
d. Minimally affect bradykinin production or action

Individualizing Therapy for HAE
Both patient and medication factors must be taken into consideration when one is creating an individual management plan for a patient with HAE. Patient factors such as type and pattern of attacks, patient preference, quality of life, age, and gender must be considered. Hormonal influence also comes into the equation; specifically, it is important to note that estrogens present in oral contraceptives or hormone replacement therapy may tend to increase attack severity and/or frequency. Patient access to care and coexisting medical problems are also important. Medication factors include drug efficacy, safety, route of administration, and potential treatment complications, all of which should weigh into individual treatment decisions. Clinical trial evidence demonstrates that all of the FDA-approved drugs for HAE are efficacious; however, they may not be available in all areas. There may be issues regarding medications in-stock at medical facilities, “brown-bag” medication reviews (in which a patient is required to carry all medications with them during medical consultations) and/or lack of experienced providers and treatment facilities. Cost should also be taken into consideration, as well as the site of delivery of care. Home treatment may be an option for patients who are willing and able to have these functions performed in the home setting. Patients may either self-administer or be treated via home infusion service. In-office administration is also an option.[27-29]

Short-Term Prophylaxis in HAE
Short-term prophylaxis is designed to protect the patient from having an HAE attack, to be given at a time before he or she is exposed to a potential triggering event. It is useful for patients who are planning exposure to surgery or other invasive procedures that might trigger an acute HAE attack. Important indications for short-term prophylaxis include extensive dental work, surgery, and other invasive medical procedures. The major modalities used for short-term prophylaxis include infusion of C1-INH (500-1500 units) 1 to 6 hours before, infusion of 2 units of fresh frozen plasma 1 to 12 hours before, or administration of high-dose anabolic androgens for approximately 1 week before the potential triggering procedure.[7] A study by Grant et al evaluated 41 patients (8 children and 33 adults) who received C1-INH prophylaxes for 91 procedures, mainly dental work or other medical/surgical procedures (40 in children, 91 in adults).[30] An HAE attack did not occur in a 72-hour period for almost all of the instances assessed (89/91 procedures, 98%). No adverse events reported were related to the administration of C1-INH or were associated with an HAE attack. The analysis demonstrated both the efficacy and safety of HAE prophylaxis with C1-INH. Consensus guidelines recommend that at-risk patients with HAE be protected from severe swelling by prophylactic administration of C1-INH.[30]
Routine/Long-Term Prophylaxis in HAE

The goals of long-term prophylaxis are to decrease the frequency and severity of HAE attacks. It is important to note that not every patient requires long-term prophylaxis. The decision to use long-term prophylaxis should be based on both the severity of the disease and the patient’s access to healthcare. Two main modalities of long-term prophylaxis have historically been used. One strategy is to use anabolic androgens, which increase C1-INH levels by an unknown mechanism, and another is to use antifibrinolytics, although the mechanisms of action of these agents are also uncertain. C1-INH replacement is FDA-approved for prophylaxis of HAE attacks. It must be kept in mind that for some patients no prophylaxis therapy is necessary; they may simply need episodic treatment for acute attacks. For patients who do require prophylaxis, there are several options. The first option is to provide short-term prophylaxis when indicated (eg, before dental procedure, during pregnancy) or long-term prophylaxis for patients with frequent or severe attacks.[8,29]

In a study evaluating prophylaxis with C1-INH concentrate, 22 subjects received either placebo or nanofiltered C1-INH during a 12-week period (Figure 12).[31] Both treatment groups were given C1-INH 1000 units for treatment of breakthrough swelling attacks. The mean angioedema attack rates were 6.3 and 12.7 attacks per 12-week period for the C1-INH and placebo groups, respectively. The patients who received the C1-INH concentrate as prophylaxis also had significant reductions in both attack severity and duration, along with reduction in the need for rescue therapy and in the total number of days in which they experienced swelling.[31]

Figure 12. HAE Attack Rates, C1-INH versus Placebo.


One human-derived C1-INH (Cinryze®) is FDA-approved for routine prophylaxis against angioedema attacks in adult and adolescent patients with HAE, with additional data requested for use of this drug in acute HAE attacks. It is administered at a dose of 1000 units intravenously every 3 or 4 days at an infusion rate of 1 mL/min.[25] Clinical trials demonstrated that this concentrate effectively relieved angioedema attacks in patients with HAE with a median time to onset of unequivocal relief that was significantly shorter in treated patients compared with those who received placebo. When administered pre-procedurally, this C1-INH concentrate reduced the incidence of angioedema attacks during and after a variety of dental, surgical,
and interventional diagnostic procedures. Routine preventive treatment also reduced the number of angioedema attacks; in a trial including adult and pediatric patients, the mean normalized number of attacks per 12-week period was significantly lower during routine prevention with this form of C1-INH than with placebo. The drug was well tolerated in these studies.[32] One C1-INH product in use in Europe is produced in recombinant form, with the advantage that it does not carry the risk of virus transmission, as it is not human-derived. This agent is currently undergoing study in the United States for treatment and prophylaxis of HAE.[33]

Several studies have demonstrated the efficacy of attenuated androgens in preventing HAE attacks. In addition to studies conducted in the 1970s by Frank and colleagues that initially demonstrated the effect of these agents, recent studies have demonstrated retrospective efficacy data in 118 patients receiving long-term prophylactic therapy with danazol. These patients were treated for a mean of 11 years (SD, 7.9 years; range, 2 months to 30 years). Danazol dose ranged from 40 mg/day to 1000 mg/day, with a mean dose of 170 mg/day. Of 181 patients, 21 were receiving an average dose of greater than 200 mg/day. Over the approximate 30-year period that the retrospective survey examined, almost half of the patients studied discontinued the use of androgen therapy for various reasons, with side effects being the most common reason for discontinuation.[34] Adverse events associated with anabolic androgens include virilization, hepatotoxicity, headache, hypertension, weight gain, menstrual abnormalities, acne, altered mood, and altered libido. It is important to note that liver adenomas and carcinomas have been linked to androgen therapy, and patients with HAE taking androgens have been found to have serum low-density/high-density lipoprotein (LDL/HDL) ratios that are higher than those of patients not receiving this type of therapy.[35,36] The use of androgens is contraindicated in certain individuals with HAE. Contraindications include pregnancy, lactation, hepatic disease, cancer of the breast or prostate, and nephrotic syndrome, and androgens are also contraindicated in prepubertal children.[34] A summary of 17α-alkylated androgens is shown in Table 3.
### Table 3. Summary Data on 17α-alkylated Androgens in HAE.

<table>
<thead>
<tr>
<th>Drug (Trade Name)</th>
<th>Usual Adult Dose (Range)*</th>
<th>Usual Pediatric Dose (Range)*</th>
<th>FDA-Approved for HAE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adult</td>
<td>Children</td>
</tr>
<tr>
<td>Danazol (Danocrine®)</td>
<td>200 mg QD</td>
<td>50 mg QD (50 mg/wk to 200 mg QD)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(100 mg every 3 days to 600 mg QD)</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Stanozolol (Winstrol®)</td>
<td>2 mg QD</td>
<td>0.5-1 mg QD for children aged &lt;6 y; 0.5-2 mg QD for children aged 6-12 y</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(1 mg every 3 days to 6 mg QD)</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Oxandrolone (Oxandrin®)</td>
<td>10 mg QD</td>
<td>0.1 mg/kg QD</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>(2.5 mg every 3 days to 20 mg QD)</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Methyltestosterone (Android®)</td>
<td>In men only, 10 mg QD (5 mg every 3 days to 30 mg QD)</td>
<td>Not recommended for use in children</td>
<td>No</td>
</tr>
</tbody>
</table>

*Therapeutic goal is to use lowest possible dose.
FDA = Food and Drug Administration; HAE = hereditary angioedema; QD = every day.
(Adapted from the New England Journal of Medicine, Zuraw BL. Hereditary angioedema, Vol 359, pages 1027-1036. Copyright © 2008 Reprinted with permission from Massachusetts Medical Society.)

### Polling Question #4
Prophylactic therapy should be considered in patients with HAE when:
- a. Swelling attacks vary in severity from one to another
- b. Swelling attacks occur weekly
- c. **Swelling attacks are severe and frequent**
- d. Swelling attacks occur without warning

### Managing the Patient with HAE: International HAE Consensus Recommendations
During the International HAE Conference held in Gargnano, Italy, in 2010, several recommendations for long-term prophylaxis and on-demand therapy for HAE emerged:[28]

- All HAE patients should have on-demand therapy
  - Patients should be trained for self-administration
  - Attacks at all locations are eligible for treatment
  - Attacks should be treated as soon as they are recognized
  - Patients should be hospitalized for progressing laryngeal involvement
• Long-term prophylaxis recommendations
  o Consider long-term prophylaxis when optimized on-demand treatment fails
  o Androgens are contraindicated in patients who are:
    ▪ Aged 16 years or younger
    ▪ Pregnant or breastfeeding
    ▪ Intolerant to or unwilling to use androgens

The Problem of Delayed Diagnosis and Management in HAE
An international Internet survey published in 2010 (with responses from 313 patients and 80 physicians in 5 countries) found that on average more than 1 year elapsed between the first angioedema attack and receipt of medical attention. An average of 8.3 years elapsed between the time of the first attack and an accurate diagnosis of HAE. An average of 4.4 physicians were consulted before the diagnosis was made, and 63% of patients surveyed received a wrong (e.g., allergic angioedema, appendicitis) or missed diagnosis, with 21% undergoing unnecessary surgery.[37] Another Internet-based survey from the United States Hereditary Angioedema Association of 457 patients focused on attack characterization, treatment, side effects, pain, and the functional and emotional burden of HAE. Patients reported significantly worsened health, including 42.5% with depression and 34% with work impairment. The study showed considerable burden across physical and mental domains affecting education, career, and work productivity. There was also a substantial economic burden annually, depending on severity of disease. Costs estimated were $12,000 annually for mild disease, $28,000 for moderate disease, and $105,000 for severe disease.[38,39]

Conclusion
HAE is a rare but serious and potentially life-threatening disease. The key to diagnosing HAE is to have a high index of suspicion when a patient presents with corresponding symptoms. Once a patient is diagnosed, family members should also be tested for the possible presence of HAE. While traditional management techniques and therapies have been used to treat HAE for decades, newer safe and effective therapies have recently been introduced, and research is ongoing. An individualized program and focus are key to successful management of the patient with HAE. All affected patients should have an angioedema treatment plan outlined, including on-demand therapy for all patients and prophylaxis for those who respond ineffectively to on-demand therapy. Patients with unexplained angioedema or idiopathic abdominal pain, particularly those with a personal or family history of angioedema, should be tested for HAE.
References


