Special Article

US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema

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Scientific and clinical progress together with the development of effective novel therapeutic options has engendered multiple important changes in the diagnosis and management of hereditary angioedema (HAE). We now update and extend the 2013 United States Hereditary Angioedema Association Medical Advisory Board guidelines for the treatment and management of HAE. The guidelines are based on a comprehensive literature review with recommendations indicating both the strength of our recommendation and the quality of the underlying evidence. Guidelines are provided regarding the classification, diagnosis, on-demand treatment, prophylactic treatment, special considerations for women and children, development of a comprehensive management and monitoring plan, and assessment of burden of illness for both HAE due to C1 inhibitor deficiency and HAE with normal C1 inhibitor. Advances in HAE treatment now allow the development of management plans that can help many patients with HAE lead a normal life. Achieving this goal requires that physicians be familiar with the diagnostic and therapeutic transformations that have occurred in recent years.   Published by Elsevier Inc. on behalf of the American

Hereditary angioedema (HAE) is a rare autosomal dominant disease characterized by episodic unpredictable swelling. The United States Hereditary Angioedema Association Medical Advisory Board (US HAEA MAB) published guidelines for HAE management in 2013.[1] In the 6 years since that publication, considerable progress has been made in our classification and understanding of HAE as well as major changes in the therapeutic armamentarium. This document reflects our current understanding of HAE and serves as a foundation for clinicians to optimize its diagnosis and management.

Resources available for the diagnosis and treatment of HAE vary widely between different countries. International differences also exist in the regulatory approvals of medicines to treat HAE. This

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Abbreviations used
BOI- Burden of illness
C1INH- C1 inhibitor
ER- Emergency room
FDA- Food and Drug Administration
FFP- Fresh frozen plasma
HAE- Hereditary angioedema
HAE-C1INH- HAE due to a deficiency of C1INH
HAE-nl-C1INH- HAE with normal C1INH
HAE-U- HAE-unknown
HRQoL- Health-related quality of life
IV- Intravenous
LTP- Long-term prophylaxis
MAB- Medical Advisory Board
OLE- Open-label extension
pdC1INH- Plasma-derived C1INH
QoL- Quality of life
rhC1INH- Recombinant human C1INH
SC- Subcutaneous
US HAEA- United States Hereditary Angioedema Association

paper focuses on the current situation in the United States, reflecting the consensus of a broad panel of expert US HAE physicians.

METHODS

The US HAEA MAB consists of 11 clinicians, each of whom treats large numbers of patients with HAE. In 2013, the US HAEA MAB published recommendations for the management of HAE due to C1 inhibitor (C1INH) deficiency (HAE-C1INH). This document builds upon the 2013 paper, updating and expanding those recommendations to reflect the rapid progress during the intervening years and incorporating recommendations for HAE with normal C1INH (HAE-nl-C1INH).

This report has been divided into 7 sections: (1) classification and pathophysiology; (2) diagnosis; (3) treatment; (4) specific issues for children; (5) specific issues for women; (6) management plans; and (7) disease burden and impact on quality of life (QoL).

Each recommendation reflects both the strength of the authors' recommendation (strong or weak) and the quality of the underlying evidence (high, moderate, or low).[2] The methodology used to develop the recommendations is available in this article's Online Repository at www.jaci-inpractice.org. All recommendations were approved by a unanimous vote. The recommendations are presented in Table I.

CLASSIFICATION AND PATHOPHYSIOLOGY OF HAE

This section will very briefly summarize the current classification of HAE and its pathophysiology. The clinical presentation of HAE is also reviewed, focusing on characteristics that help distinguish HAE from other forms of angioedema.

HAE classification

HAE can be broadly divided into 2 fundamental types: HAE-C1INH or HAE-nl-C1INH (Figure 1). HAE-C1INH is further divided into 2 subtypes: type I HAE, characterized by deficient levels of C1INH protein and function; and type II HAE, characterized by the normal level of C1INH protein that is dysfunctional, resulting in diminished C1INH functional activity.[3,4] Both type I and type II HAE are caused by mutations in the gene that encodes C1INH (SERPING1).[5] The estimated prevalence of type I and type II HAE is 1 per 50,000, suggesting that there are approximately 6000 affected individuals in the United States.

HAE-nl-C1INH was first described in 2000[6,7] and is not as well understood as HAE-C1INH. At the current time, there are 5 subtypes of HAE-nl-C1INH based on the underlying mutation[8]: HAE-FXII is due to mutations in F12, the gene encoding coagulation FXII[9]; HAE-PLG is due to mutations in PLG, the gene encoding plasminogen[10]; HAE-ANGPT1 is due to mutations in ANGPT1, the gene encoding angiopoietin-1[11]; HAE-KNG1 is due to a mutation in the kininogen 1 gene[12]; and HAE-unknown (HAE-U) represents patients with HAE-nl-C1INH for whom the responsible mutation has not yet been defined. The overall prevalence of HAE-nl-C1INH is not known. HAE-XII comprises approximately 20% of HAE-nl-C1INH cases in Europe but for reasons that are not clear is exceedingly rare in the United States.[13] HAE-nl-C1INH was previously referred to as type III HAE, but this term is obsolete and should not be used.

HAE pathophysiology

HAE-C1INH. There is strong evidence that the mediator of swelling in HAE-C1INH is bradykinin (reviewed in the paper by Zuraw and Christiansen[14]). Cleavage of high-molecular-weight kininogen by plasma kallikrein results in generation of bradykinin. This occurs with activation of contact system proteases (factor XIIa and plasma kallikrein), which are normally regulated by C1INH. Bradykinin leads to angioedema by binding to the bradykinin B2 receptor resulting in vascular permeability. A role for the bradykinin B1 receptor in HAE attacks has been postulated but not proven.[15]

HAE-nl-C1INH. Several features suggest that HAE-nl-C1INH, like HAE-C1INH, may be bradykinin mediated, including the lack of response to antihistamines, corticosteroids, and epinephrine; and the favorable response to bradykinin pathway—targeted medications to a similar degree as seen in HAE-C1INH.[13] The best evidence for a key role of bradykinin in HAE-nl-C1INH comes from studies of HAE-FXII. The most common form of HAE-FXII, p.Thr309Lys, was recently shown to enhance susceptibility of contact system activation (presumably leading to generation of bradykinin) ex vivo and in vivo.[16] F12 mutations associated with HAE-FXII were also shown to enhance susceptibility of FXII to activation by plasmin.[17] In contrast, HAE-ANGPT1 appears to involve a loss of an endothelial cell brake on vascular permeability,[11] suggesting that these patients may be susceptible to multiple mediators of increased vascular permeability.

DIAGNOSIS OF HAE
Recognition of clinical symptoms

The timely diagnosis of HAE is dependent on recognition of suggestive clinical symptoms. HAE has a highly variable clinical course with numerous presentations and symptoms, but the hallmarks of all forms of HAE are recurrent angioedema causing cutaneous swelling, abdominal symptoms from gastrointestinal angioedema, and respiratory symptoms due to airway involvement. HAE is not associated with urticaria or pruritus, but can have prodromal symptoms of erythema marginatum, an

evanescent, nonpruritic macular rash that may mimic urticaria.[18,19] Exogenous estrogens or angiotensin-converting enzyme inhibitors often make symptoms worse. HAE symptoms often progress to maximal severity over several hours. HAE swelling is protracted, compared with histamine-induced angioedema; untreated HAE angioedema symptoms commonly last 3 to 5 days from start to resolution with considerable morbidity and mortality if not treated with effective medication.[20] Importantly, HAE symptoms do not respond to antihistamines, corticosteroids, or epinephrine; this lack of clinical response to common mast cell–targeted treatments is an important clue in the history of patients affected by HAE. Persistent swelling for weeks or longer is not consistent with HAE.

HAE is an autosomal dominant disorder, signifying that each child of a patient with HAE has a 50% potential for inheritance. HAE-C1INH typically becomes symptomatic during childhood or young adulthood, sometimes as early as 2 years of age. Approximately 50% of HAE-C1INH manifest symptoms of swelling by the age of 10,[21] with the frequency and severity of attacks often increasing after puberty. Almost all patients with HAE-C1INH manifest symptoms by the age of 20, although rare patients never experience symptoms. The severity and frequency of swelling in HAE is highly variable, even between different affected members of the same family.

The clinical presentation of HAE-nl-C1INH is similar to HAE-C1INH though some differences may exist. Angioedema symptoms may affect the face and tongue more frequently in HAE-nl-C1INH with fewer abdominal symptoms compared with HAE-C1INH. HAE-nl-C1INH is also autosomal dominant, although the penetrance is variable and often lower than for HAE-C1INH. Females with HAE-nl-C1INH are more likely to be symptomatic than males, and the swelling is often estrogen-sensitive such that exposure to endogenous or exogenous estrogens is a strong exacerbating factor, especially in HAE-FXII.[22] Rare cases of HAE-nl-C1INH in males have been described. HAE-nl-C1INH symptoms typically begin in late teenage or early adult years.[22]

Given the clinical variability associated with bradykinin-mediated angioedema, laboratory testing is indicated in any patient with suggestive clinical symptoms.

Laboratory diagnosis of HAE-C1INH

Laboratory testing is necessary to identify or exclude HAE-C1INH. A serum C4 level is a useful screening test for HAE-C1INH. Sensitivity varies from 81% to 96% on screening of C1INH-deficient patients between angioedema episodes[23,24]; however, a normal C4 during an angioedema episode excludes the diagnosis of HAE-C1NH. Measurement of C1INH protein antigenic and functional levels is necessary to definitively confirm or exclude HAE-C1INH and should be ordered when the clinical suspicion for HAE is high. C1INH quantitative and functional levels are low (<50% of normal) in type I HAE, whereas only the functional level is low (<50% of normal) in type II HAE.[5] Once C1INH deficiency has been established by laboratory testing, further repeated testing is neither necessary nor useful; however, repeat testing should be done if the diagnosis is unclear. In patients with onset of isolated angioedema symptoms after the age of 40 or with concomitant lymphoproliferative or autoimmune conditions, a C1q level is useful to help distinguish between HAE-C1INH and acquired C1INH

deficiency. C1q levels are decreased in 80% of acquired C1INH deficiency and rarely low in HAE-C1INH.[25] Lab results must always be interpreted in conjunction with clinical history.

The 2 commercially available functional C1INH assays (ELISA and chromogenic) demonstrate differences in sensitivity and specificity. The chromogenic assay is the more sensitive test for C1INH deficiency.[26,27] Chromogenic functional testing should be considered, therefore, in any patient when the diagnosis of HAE-C1INH is uncertain. Proper handling and prompt processing of blood samples is important for accurate C1INH functional testing.[26] C1INH concentrates and anabolic androgen treatment may affect complement test results; therefore, these medications could be discontinued for at least 2 weeks (with ready access to on-demand medications) if diagnostic testing is necessary.[28]

The biochemical tests for HAE-C1INH are sufficiently sensitive and specific such that genetic sequencing for SERPING1 mutations is usually unnecessary for establishing the diagnosis.[13] Specific clinical scenarios where genetic testing may be necessary include differentiating HAE-C1INH from acquired C1INH deficiency in patients without a clear family history, prenatal testing due to family request, or situations where biochemical C1INH test results are repeatedly equivocal.

Once a diagnosis of HAE has been confirmed by laboratory testing, testing of parents, siblings, and children should be strongly encouraged. The testing of infants within the first year of life is an area of some uncertainty. Previously, C1INH testing was not recommended before 12 months of age due to highly variable C4 and C1INH antigenic levels in the first year of life.[29] More recent data suggest that C1INH functional assays are sensitive and specific in diagnosing C1INH deficiency in young infants such that functional testing could be considered earlier than 1 year of age if necessary.[30] If the underlying mutation is known, screening can be done at any age.

Laboratory diagnosis of HAE-nl-C1INH

HAE-nl-C1INH presents a diagnostic challenge given the current lack of a validated biochemical test to confirm the diagnosis.[31] Genetic testing may be helpful in confirming HAE-nl-C1INH. The most common mutations linked to HAE-nl-C1INH involving the F12 gene can be detected by a commercially available PCR assay, whereas a comprehensive assessment of all of the genes implicated in HAE-nl-C1INH is commercially available through licensed laboratories using custom-targeted whole-exome sequencing approaches. It is anticipated that next-generation sequencing panels including the genes linked to HAE-nl-C1INH will become available as this technology is adopted by more clinical laboratories. In addition, the identified mutations only account for a subset of HAE-nl-C1INH, such that individuals affected by HAE of unknown etiology (HAE-U) remain, without an available confirmatory biomarker or diagnostic test. The diagnosis of HAE-nl-C1INH frequently must be made based on clinical criteria as previously published and refined[31,32] (Table II).

The recommended clinical criteria for HAE-nl-C1INH are based on currently available evidence and expert consensus[32]; the sensitivity and specificity of this approach has not been established. Criteria for HAE-nl-C1INH should be used in conjunction with expert clinical assessment and judgment. Evaluation by an experienced angioedema specialist may be of critical importance in confirming the diagnosis. Documentation

TABLE I. Summary of recommendations

Section	Recommendation	Strength of recommendation	Quality of evidence
1. Classification and pathophysiology of HAE			
	HAE should be broadly divided into HAE due to C1INH deficiency (HAE-C1INH) and HAE-nl-C1INH. HAE-C1INH is further subdivided into type I and type II, which appear to be clinically similar. HAE-nl-C1INH is further subdivided based on the underlying mutation or unknown in cases where the mutation has not been found.	Strong	High
2. Diagnosis of HAE			
	Recognition of clinical symptoms associated with HAE is a critical step in guiding appropriate diagnostic tests. Common HAE symptoms include recurrent cutaneous angioedema (in the absence of urticaria), abdominal symptoms from gastrointestinal angioedema, and airway symptoms due oropharyngeal/laryngeal swelling.	Strong	High
	When HAE is suspected based on the clinical presentation, appropriate testing includes measurement of the serum C4 level, C1INH antigenic level, and C1INH functional level. Low C4 plus low C1INH antigenic or functional levels are consistent with a diagnosis of HAE-C1INH.	Strong	High
	Because of the autosomal dominant inheritance pattern and significant clinical risk associated with HAE, screening should be performed in all first-degree relatives of an affected individual.	Strong	High
	When a diagnosis of HAE-nl-C1INH is suspected based on symptoms and normal C1INH tests, additional genetic tests for factor XII, plasminogen, angiopoetin-1, and kininogen mutations should be performed when available. Diagnosis of HAE-U should involve the input of an HAE specialist.	Strong	Low
3A. On-demand treatment of HAE attacks			
	Patients must have ready access to effective on-demand medication to administer at the onset of an HAE attack. An FDA-approved on-demand HAE medication (ecallantide, icatibant, pdC1INH, or rhC1INH) should be used as first-line treatment for attacks whenever possible.	Strong	High for HAE C1INH; low for HAE-nl-C1INH
	On-demand treatment of HAE attacks should be self-administered (or administered by a caregiver) whenever feasible except when treating with ecallantide that needs to be administered by a health care provider.	Strong	High for HAE C1INH; low for HAE-nl-C1INH
	All HAE attacks are eligible for treatment irrespective of the location of the swelling or the severity of the attack.	Strong	High for HAE C1INH; low for HAE-nl-C1INH
3B. Prophylactic treatment			
	Short-term prophylaxis is indicated when patients are at increased risk of having an attack associated with known triggers such as invasive dental or medical procedures or stressful life events.	Strong for HAE-C1INH; weak for HAE-nl-C1INH	Moderate for HAE C1INH; low for HAE-nl-C1INH
	The decision on when to use long-term prophylactic treatment cannot be made on rigid criteria but should reflect the needs of the individual patient.	Strong	High for HAE C1INH; low for HAE-nl-C1INH
	Long-term prophylactic treatment of HAE-C1INH should include first-line medications (IV C1INH, SC C1INH, or lanadelumab).	Strong	High
	Progestin-only medication or an antifibrinolytic drug should be considered for initial long-term prophylactic treatment of HAE-nl-C1INH.	Weak	Low
4. Additional considerations for children			
	HAE-C1INH often presents in childhood and an early diagnosis is essential for minimizing the risks of morbidity and mortality.	Strong	High
	Indications for the use of first-line HAE medications are the same in children as in adults, although regulatory differences affect the use of some medications depending on the child's age.	Strong	Moderate

(continued)

TABLE I. (Continued)

Section	Recommendation	Strength of recommendation	Quality of evidence
5. Specific issues in the management of HAE in women			
	Exogenous estrogens such as birth control pills or hormonal replacement therapy can precipitate HAE attacks and should therefore be used only with caution in individuals with HAE.	Strong	Moderate
	During pregnancy and breast-feeding, C1INH is the recommended HAE medication for use as either on-demand or prophylactic therapy.	Strong	Moderate
6. Management plans			
	HAE management plans must be individualized to each patient's needs due to wide variability in HAE symptoms, response to and tolerance of various HAE medications, and numerous factors impacting clinical course and quality of life. Treatment plans should be monitored regularly and adjusted based on the needs of the patient.	Strong	Moderate
	HAE management plans should include: (A) effective on-demand medication for every patient, (B) consideration of long-term prophylactic medications to prevent HAE attacks, and (C) use of short-term prophylactic medications before medical procedures or other events known to trigger HAE symptoms.	Strong	Moderate
	Consultation with an HAE expert physician is recommended to optimize individualized treatment plans, assist with coordination of care, and provide important patient and family education.	Strong	Low
	Patients should maintain a symptom/treatment diary to monitor angioedema symptoms, medication requirements, and any adverse effects of treatment. These data should be reviewed regularly at follow-up visits.	Weak	Low
7. Burden of illness			
	Clinicians should explicitly consider the impact of HAE on their patients' lives.	Strong	Low
	Management plans should be individualized to lessen the burden of illness and provide patients with HAE with a normal quality of life.	Strong	Low
	Economic considerations should not be the determining factor in deciding the physician's recommendations for optimal management of HAE.	Strong	Low

C1INH, C1 inhibitor; *FDA*, Food and Drug Administration; *HAE*, hereditary angioedema; *HAE-nl-C1INH*, HAE with normal C1INH; *IV*, intravenous; *pdC1INH*, plasma-derived C1INH; *rhC1INH*, recombinant human; *SC*, subcutaneous.

of resistance to histamine-targeted therapy requires close clinical follow-up and expert assessment as partial responses to high-dose antihistamines may in some circumstances warrant a trial of additional mast cell—targeted therapies such as montelukast or omalizumab.

A critical need remains for validated biomarkers to identify individuals with HAE-nl-C1INH or other idiopathic bradykinin-mediated angioedema conditions. Recent research has identified novel assays including alternate methods for assessing C1INH function and measurement of stimulated kallikrein activity.[31,33] The stimulated kallikrein activity assay has been studied in a cohort of clinically diagnosed patients with HAE-U and demonstrated high sensitivity and specificity for differentiating these patients from mast cell—mediated angioedema and normal controls. Currently, these assays are not commercially available, but may provide future diagnostics to identify HAE-normal C1INH with greater precision.

HAE TREATMENT

The core approach to the pharmacologic care for HAE rests on 4 guiding principles: availability of effective on-demand acute therapy for all patients; early treatment to prevent attack progression; treatment of attacks irrespective of the site of swelling;

and incorporation of long-term prophylaxis (LTP) based on highly individualized decision-making reflecting a physician-patient partnership.[34] Although these fundamental values have not changed since the 2013 US HAEA MAB treatment recommendations, the landscape of LTP has been transformed by the emergence of novel therapies, offering improved efficacy, ease of use, and safety. These treatments, with their potential to normalize the lives of patients with HAE, are anticipated to shift the management paradigm toward an expanded adoption of LTP. Even though it is anticipated that patients will experience a substantial reduction in the ever-present fear of attacks with newer LTP options, immediate access to on-demand treatments will still be required.

On-demand treatment of HAE attacks

The goal of acute therapy for HAE is to minimize morbidity and prevent mortality from an ongoing angioedema attack. The ability to treat episodes of swelling "on-demand" has been a critical advance in accomplishing this objective.[35] Improved understanding of the pathophysiologic mechanism of swelling in HAE-C1INH has catalyzed the development and approval of 4 specific products for on-demand treatment (Table III), each of which has been shown in randomized controlled studies to be effective and safe.[36-39] Subsequent open-label extension data
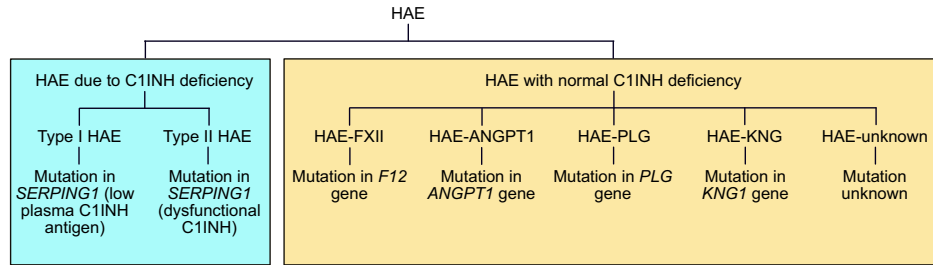
FIGURE 1. Current HAE classification. Schema showing the major grouping of HAE into HAE-C1INH and HAE-nl-C1INH. Within each major group, subgroups are recognized based on the criteria shown. *C1INH*, C1 inhibitor; *HAE*, hereditary angioedema; *HAE-C1INH*, HAE due to a deficiency of C1INH; *HAE-nl-C1INH*, HAE with normal C1INH.

along with registry data have underscored the enduring efficacy and continued safety of these drugs.[40-44]

Although there have been no randomized controlled studies of on-demand treatment during attacks in patients with confirmed HAE-nl-C1INH, numerous open-label reports have revealed successful responses to each of the on-demand treatments used for HAE-C1INH.[45-48]

On-demand medications. Four different medications have been approved for use to treat HAE attacks (Table III). Plasma-derived C1INH concentrates (pdC1INH, Berinert) and recombinant human C1INH (rhC1INH, Ruconest) are given by intravenous (IV) injection. The plasma kallikrein inhibitor ecallantide and the bradykinin B2 receptor antagonist icatibant are administered subcutaneously. All 4 on-demand medications are very effective and generally safe. Ecallantide has been associated with allergic and even anaphylactic reactions in a relatively small number of cases (<2%) and therefore needs to be administered by a health care provider. These medications typically become effective within 60 minutes but have a relatively short half-life and cannot be used for prophylaxis (with the exception of pdC1INH that has a longer half-life). Anabolic androgens and anti-fibrinolytic agents have no role in on-demand treatment.

Availability of on-demand treatment. All patients with laboratory confirmed HAE should have access to at least 2 standard doses of a Food and Drug Administration (FDA)-approved on-demand medication for treatment of acute attacks. For patients without clear laboratory confirmation of HAE (ie, HAE-U), it is incumbent on the clinician to carefully document that onset and duration of response to the on-demand treatment is consistent with the expected pharmacokinetic/pharmacody-namic profile of the drug. Caution should be exercised in cases where the frequency or dose required for perceived improvement appears to be out of the expected range; validation that the diagnosis is correct should be revisited in these instances.

The efficacy or tolerability of a given on-demand medication can vary between patients. The coordinating expert physician should work with each patient to define the optimal drug(s) for treating acute attacks. In cases where more than 1 on-demand drug is prescribed, the justification for use of more than a sin-gle drug should be explicitly documented by the physician and understood by the patient. Regular follow-up visits with the physician are necessary to monitor the frequency and outcome of on-demand treatments; the frequency of these visits will depend on the patient's course.

Fresh frozen plasma (FFP) contains C1INH and can be used to treat HAE attacks if none of the FDA-approved on-demand medications are available.[49] The efficacy of FFP has not been studied in randomized trials, and there are anecdotal reports of HAE symptoms precipitously worsening after FFP administration possibly due to the fact that FFP contains factors that could lead to the generation of more bradykinin (HMWK, plasma prekallikrein, and FXII) in addition to C1INH. If another acute therapy is not available, FFP remains an option as long as precautions are taken to protect the patient's airway (particularly if oropharyngeal or laryngeal swelling is present). Solvent detergent–treated plasma may be safer than FFP due to reduced viral risk. In the absence of effective on-demand treatment, patients may require supportive care (ie, IV fluids, antiemetics, narcotic pain medication, or intu-bation). When effective on-demand treatment is not given, significantly higher morbidity is seen.[50]

HAE attacks should be treated early. On-demand treatment of attacks is most effective when administered early after attack onset.[35] The key to reducing HAE morbidity is to arrest the progression of swelling to prevent disruption to a pa-tient's life. Self-administration of on-demand medications allows patients to treat promptly as soon as they clearly recognize the attack. In cases where the patient can reliably predict an attack (ie, erythema marginatum), logistical arrangements for treatment may be initiated during the prodrome[51]; however, treatment should be administered only when the patient can identify that an attack has begun. Patients who self-administer treatment should seek medical care if the features of their attack are un-usual, their response to self-treatment is inadequate, or they experience an attack involving the airway.

Attack location. Decisions about which attacks to treat with on-demand medications should be based on the goals of mini-mizing morbidity, preventing mortality and increasing QoL rather than an arbitrary distinction based on location. All attacks, irrespective of location, should be considered for treatment as soon as they are clearly recognized. Although there is over-whelming consensus that all abdominal, facial, oral, and upper respiratory attacks should be treated as early as possible, ex-tremity attacks are also disabling and clearly worthy of early treatment to prevent dysfunction.[52,53]

There is a substantial risk of mortality associated with laryn-geal attacks, and appropriate caution must be exercised in the management of these attacks.[54] Patients who experience symp-toms of laryngeal, tongue, or throat swelling should seek

TABLE II. Criteria for the diagnosis of HAE

Weight	Criteria
HAE-C1INH	
Required	A history of recurrent angioedema in the absence of concomitant urticaria and no concomitant use of medication known to cause angioedema
Required	Low (<50% of normal) C1INH antigenic or functional level
Required	Low C4 level (either at baseline or during an attack)
Supportive	Demonstration of a pathologic SERPING1 mutation (not required for diagnosis)
	Family history of recurrent angioedema
	Age of symptom onset <40
HAE-nl-C1INH	
Required	A history of recurrent angioedema in the absence of concomitant urticaria and no concomitant use of medication known to cause angioedema
Required	Documented normal or near normal C4, C1-INH antigen, and C1-INH function
Either (at least 1 required)	(1) Demonstration of a mutation associated with the disease; OR (2) A positive family history of recurrent angioedema and documented lack of efficacy of high-dose antihistamine therapy (ie, cetirizine at 40 mg/d or the equivalent) for at least 1 mo or an interval expected to be associated with 3 or more attacks of angioedema, whichever is longer
Supportive	(1) A history of rapid and durable response to a bradykinin-targeted medication; AND (2) Predominant documented visible angioedema; or in patients with predominant abdominal symptoms, evidence of bowel wall edema documented by CT or MRI

C1INH, C1 inhibitor; *CT*, computed tomography; *HAE*, hereditary angioedema; *HAE-C1INH*, HAE due to a deficiency of C1INH; *HAE-nl-C1INH*, HAE with normal C1INH; *MRI*, magnetic resonance imaging.

emergency medical care as soon as possible, even after initial self-treatment. Elective intubation should be considered for any patient with signs of respiratory distress who is not improving after treatment. Repeat treatment during a single attack has been approved for icatibant (maximum of 3 doses within a 24-hour period at intervals of at least 6 hours) as well as ecallantide and rhC1INH (both with maximum of 2 doses within a 24-hour period). In general, a second dose of the on-demand therapy is not warranted unless the attack begins to worsen.

Assessment of on-demand treatment efficacy. Realistic expectations of treatment efficacy should be discussed with patients. On-demand treatments work well to prevent attacks from progressing further; however, the swelling present at the time of treatment takes time to resolve. It is imperative to convey to patients that early treatment translates into better symptom control. Once treatment has been initiated, time to onset of relief should occur within 30 to 120 minutes.[55] In general, a second dose of the on-demand therapy is not warranted unless the attack begins to worsen.

Prophylactic Treatment

In addition to treating attacks of angioedema, patients with HAE may require prophylactic treatment. The goal of prophylactic treatment is either to reduce the likelihood of swelling in a patient undergoing a stressor or procedure likely to precipitate an attack (short-term prophylaxis) or to decrease the overall number, severity, and burden of angioedema attacks (LTP). Table IV shows HAE prophylactic therapies.[38,56-60] As there are significant differences in route of administration, side effect profiles, and efficacy between these drugs, patient preference and experience need to be considered in the selection of the most appropriate therapy. Because there are substantial differences in the approach to prophylactic treatment between HAE-C1INH and HAE-nl-C1INH, these will be discussed individually. It is important to communicate to patients that even if they are well controlled on a prophylactic treatment regimen, they must continue to have access to effective on-demand treatment for attacks.

Need for short-term prophylaxis. Trauma and stress are well-known provocateurs of angioedema attacks.[61] Dental surgery, in particular, is associated with swelling of the oral cavity that can progress and cause airway obstruction. Short-term prophylaxis may be indicated before invasive medical, surgical, or dental procedures; however, relatively little is known about the risk of swelling after these procedures. A large retrospective study found a 21.5% risk of swelling in patients who did not receive any prophylaxis. The risk fell to 16% and 7.5% in patients who received 500 or 1000 units of C1INH 1 hour before the dental extraction.[62] The extent of the local trauma may influence the decision on whether to treat the patient prophylactically. Short-term prophylaxis may also be considered in advance of stressful life events.

Medications for short-term prophylaxis. It is important that effective on-demand treatment be available whether the patient is given short-term prophylaxis or not. As part of the overall management plan, the patient and provider should be educated to be alert for delayed swelling in the wake of the procedure.

HAE-C1INH. Short-term prophylaxis can be either a single dose of pdC1INH or a course of anabolic androgen.[62-65] A single dose of 20 IU/kg pdC1INH can be given 1 to 12 hours before the stressor. Alternatively, anabolic androgens (ie, 400-600 mg/day of danazol) can be started 5 to 7 days before the stressor and continued for 2 to 5 days after the procedure. rhC1INH (50 IU/kg) has also been used successfully for short-term prophylaxis,[66,67] although there is less data and experience compared with pdC1INH products. FFP can be used in the event that the treating physician cannot obtain pdC1INH and there is insufficient time for a course of anabolic androgens.

HAE-nl-C1INH. There are no data on short-term prophylaxis for HAE-nl-C1INH. For patients with a confirmed diagnosis, the same approach as HAE-C1INH may be used with the important caveat that on-demand therapy be available if needed.

Need for long-term prophylaxis. The decision on when to use long-term prophylactic treatment cannot be made on rigid criteria but should reflect the needs of the individual patient.[1] Decisions regarding which patients should be considered for LTP should take into account the patient's QoL and treatment

TABLE III. FDA-approved on-demand medications for HAE attacks

Drug (trade name, manufacturer)	Regulatory status	Self-administration	Dosage	Mechanism	Anticipated potential side effects
Ecallantide (Kalbitor, Dyax)	Approved in the United States for patients ≥12 y of age	No	30 mg SC	Inhibits plasma kallikrein	Uncommon: antidrug antibodies, risk of anaphylaxis
Icatibant (Firazyr, Takeda)	Approved in the United States for patients ≥18 y of age; approved in Europe for patients ≥2 y of age	Yes	Pediatric (EU): 12-25 kg, 10 mg SC; 26-40 kg, 15 mg SC; 41-50 kg, 20 mg SC; 51-65 kg, 25 mg SC; >65 kg, 30 mg SC Adults: 30 mg SC	Bradykinin B2 receptor antagonist	Common: discomfort at injection site
Plasma-derived nanofiltered C1INH (Berinert, CSL Behring)	Approved in the United States and Europe for children and adults	Yes	20 U/kg IV	Inhibits plasma kallikrein, coagulation factors XIIa, XIIf and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis Theoretical: transmission of infectious agent
Recombinant human C1INH (Ruconest, Pharming)	Approved in the United States and Europe for adolescents and adults	Yes	50 U/kg up to 4200 U IV	Inhibits plasma kallikrein, coagulation factors XIIa, XIIf and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Uncommon: risk of anaphylaxis in rabbit-sensitized individuals Theoretical: transmission of infectious agent

C1INH, C1 inhibitor; *FDA,* Food and Drug Administration; *HAE,* hereditary angioedema; *IV,* intravenous; *MASP-1, -2,* mannose-binding lectin–associated serine proteases 1, 2; *SC,* subcutaneous.

preferences in the context of attack frequency, attack severity, comorbid conditions, and access to emergent treatment. Because disease severity may change over time, the need to start or continue LTP should be periodically reviewed and discussed with the patient.

Long-term prophylaxis for HAE-C1INH. Medications for LTP in HAE-C1INH can be divided into 2 broad categories: first-line or second-line. The first-line therapies include IV pdC1INH replacement (Cinryze), subcutaneous (SC) pdC1INH replacement (Haegarda), and a monoclonal inhibitor of plasma kallikrein (lanadelumab, Takhzyro). Second-line therapies include the anabolic androgens (ie, Danazol) and antifibrinolytics (tranexamic acid or epsilon aminocaproic acid). The US HAEA MAB recommends the use of any of the first-line medications when LTP is indicated for patients with HAE-C1INH. Second-line prophylactic medications should be reserved for when first-line medications are not available or when the patient will only accept oral therapy, with acknowledgment of potential side effects. The potential availability of new first-line oral prophylactic medications in the future (see below) may also influence this choice. The LTP medicines are presented by first-line versus second-line and then in the order they were approved for HAE.

Intravenous C1INH replacement (first-line). IV replacement therapy with pdC1INH concentrate (Cinryze) has been shown to be both safe and effective for the prophylactic treatment of HAE.[38] IV pdC1INH prophylaxis was initially approved in 2008 for adolescents and adults based on an approximately 50% reduction in attack rate. After favorable outcomes of a second phase III study, indications were expanded in 2018 to include treatment of children as young as age 6.[68]

Open-label extension (OLE) data for IV pdC1INH revealed improved outcomes with continued use. Efficacy of IV pdC1INH prophylaxis directly correlated with the interval

between dosing. Five subjects, all with risk factors for thromboembolic events, experienced serious adverse events of a thromboembolic nature but none were considered study drug related. Additional safety concerns such as infectious transmission, hypersensitivity reactions, and formation of anti-C1INH antibodies were not apparent during the study.[60] Another 7.5% of subjects in the OLE cohort failed to improve. For patients who continue to have attacks despite receiving the standard dose of 1000 IU twice weekly, dose (up to 2500 IU) and frequency (3 times per week) escalation has been shown to improve efficacy.[60,69]

Repeated IV administration can result in loss of readily available venous access unless great care is taken to preserve the veins. In some cases, indwelling ports have been placed to allow easier IV administration. Indwelling ports pose a significant risk of thrombosis and infection.[70,71] Although a careful technique may reduce these risks, they cannot be eliminated. For these reasons, the US HAEA MAB discourages the use of indwelling ports unless deemed medically necessary, and further recommends that patients who require IV administration of drug exercise great care in protecting their veins by using butterfly needles with careful attention to technique, withdrawing the needle without pressure and then applying light pressure for 5 minutes after infusion without bending the elbow if an antecubital vein is used. Veins that are inflamed should not be used until the phlebitis is resolved. As outlined below, safe and effective alternative SC LTP treatments are now available, thus eliminating many of the problems associated with venous access for the future.

Subcutaneous pdC1INH replacement (first-line). SC C1INH replacement (Haegarda) has recently been shown to be highly effective in preventing attacks of angioedema in patients with HAE-C1INH. The pivotal phase III trial demonstrated a statistically significant median reduction in attack rates of 95% at 60 IU/kg during the 16-week treatment period. There was a corresponding dramatic reduction in rescue medication use and

TABLE IV. FDA-approved prophylactic medications for HAE

Drug (trade name, manufacturer)	HAE regulatory status	Self-administration	Dosage	Mechanism	Anticipated potential side effects
Plasma-derived nanofiltered C1INH (Cinryze, Takeda)	Approved in the United States and Europe for patients ≥6 y of age	Yes	Pediatric (6-11 y): 500 IU every 3-4 d IV Adolescents and adults: 1000 U IV every 3-4 d Doses up to 2500 U IV every 3-4 d may need to be considered based on individual patient response	Inhibits plasma kallikrein, coagulation factors XIIa, XIIf and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis Theoretical: transmission of infectious agent
Plasma-derived nanofiltered C1INH (HAEGARDA, CSL Behring)	Approved in the United States for adolescents (≥12 y) and adults	Yes	60 IU/kg SC twice-weekly	Inhibits plasma kallikrein, coagulation factors XIIa, XIIf and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis Theoretical: transmission of infectious agent
Lanadelumab (Takhzyro, Takeda)	Approved in the United States for adolescents and adults	Yes	300 mg SQ every 2 wk 300 mg every 4 wk may be considered if a patient is well controlled (eg, attack free) for more than 6 mo	Inhibits plasma kallikrein	Rare: risk of anaphylaxis Common: injection site reactions
Danazol (Danocrine, Sanofi-Synthelabo)	Approved in the United States for adults	Yes	Adult: 200 mg/d PO (100 mg every 3 d to 600 mg/d) Pediatric: 50 mg/d PO (50 mg/wk to 200 mg/d)	Unknown	Common: weight gain, virilization, acne, altered libido, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual abnormalities, increase in liver enzymes, hypertension, and alterations in lipid profile Uncommon: decreased growth rate in children, masculinization of the female fetus, cholestatic jaundice, peliosis hepatis, and hepatocellular adenoma
Stanozolol (Winstrol, Winthrop)	Approved in the United States for adults and children	Yes	Adult: 2 mg/d PO (1 mg every 3 d to 6 mg/d) Pediatric: 0.5 mg/d PO (0.5 mg/wk to 2 mg/d		Same as danazol
Oxandrolone	Not approved for HAE indication	Yes	Adult: 10 mg/d PO (2.5 mg every 3 d to 20 mg/d) Pediatric: 0.1 mg/kg/d PO (2.5 mg/wk to 7.5 mg/d	Unknown	Same as danazol
Methyltestosterone (Android)	Not approved for HAE indication	Yes	Adult men: 10 mg/d PO (5 mg every 3 d to 30 mg/d) Women and pediatric: not recommended	Unknown	Same as danazol
Epsilon aminocaproic acid (Amicar, Xanodyne Pharmaceuticals)	Not approved for HAE indication	Yes	Adult: 2 g PO tid (1 g bid to 4 g tid) Pediatric: 0.05 g/kg PO bid (0.025 g/kg bid to 0.1 g/kg bid)	Inhibits activation of plasminogen and activity of plasmin	Common: nausea, vertigo, diarrhea, postural hypotension, fatigue, muscle cramps with increased muscle enzymes Theoretical: thrombosis
Tranexamic acid (Cyklokapron, Pfizer; Lysteda, Ferring)	Not approved for HAE indication	Yes	Adult: 1 g PO bid (0.25 g bid to 1.5 g tid) Pediatric: 20 mg/kg PO bid (10 mg/kg bid to 25 mg/kg tid)	Inhibits activation of plasminogen and activity of plasmin	Same as epsilon aminocaproic acid

C1INH, C1 inhibitor; *FDA*, Food and Drug Administration; *HAE*, hereditary angioedema; *IV*, intravenous; *SC*, subcutaneous.

a meaningful improvement in measures of health-related quality of life (HRQoL). SC C1INH appears safe and well tolerated with adverse events predominantly being transient local site reactions.[72] In OLE studies, up to 83% of patients were free of attacks, and continuing improvements in HRQoL were seen.[73,74]

Lanadelumab (first-line). Lanadelumab (Takhzyro), a fully human monoclonal antibody inhibitor of plasma kallikrein, was shown to be safe and effective for LTP in HAE-C1INH. The phase III study showed that lanadelumab at 150 mg q4 weeks, 300 mg q4 weeks, and 300 mg q2 weeks significantly reduced attacks with the highest dose being most effective (86.9% reduction in attacks).[75] Use of on-demand treatment and incidence of high morbidity attacks were substantially reduced on lanadelumab. There were no significant safety concerns with the most common adverse events site reactions or dizziness. The FDA-recommended starting dose is 300 mg every 2 weeks. A dosing interval of 300 mg every 4 weeks may be considered after 6 months for well-controlled patients (attack free).

Anabolic androgens (second-line). Although anabolic androgens (also known as 17α-alkylated androgens) have been successfully used for prophylaxis for many years,[58,76-78] they can cause significant dose-related side effects.[79-82] When used, anabolic androgens should be given at the lowest effective dose to minimize side effects. It is important to avoid the use of anabolic androgens for LTP in patients under the age of 16 and in pregnant or breastfeeding women.[83] All patients receiving anabolic androgens need to be carefully followed for the potential of drug-related side effects. It is the position of the US HAEA MAB that these drugs should not be used in patients who express a preference for an alternative therapy and that patients should not be required to fail anabolic androgen therapy as a prerequisite to receiving first-line LTP. Given the current therapeutic options for LTP in the United States, the US HAEA MAB does not recommend the routine use of anabolic androgens for the treatment of HAE.

Antifibrinolytics (second-line). Antifibrinolytic medications (tranexamic acid or epsilon aminocaproic acid) have been successfully used for LTP in HAE-C1INH,[56] but are less effective than the other drugs described and are therefore seldom used for LTP of HAE-C1INH in the United States.

Additional potential considerations. Although not yet FDA approved for LTP, rhC1INH (Ruconest) demonstrated significant LTP efficacy in a phase II study.[84] Given the periodic shortages that have impacted pdC1INH product availability in the past, the use of rhC1INH for prophylactic as well as on-demand treatment is an important consideration. In addition, the orally available once daily small molecule plasma kallikrein inhibitor berotralstat (BioCryst, Durham, NC) recently completed a pivotal phase III study in which it met its endpoints for LTP of HAE-C1INH.

LTP in patients with HAE-nl-C1INH. LTP for patients with HAE-nl-C1INH has not been studied in randomized placebo-controlled trials. Nevertheless, smaller open-label trials have suggested potential LTP strategies that can be used for HAE-nl-C1INH. The 2 major LTP modalities frequently used for HAE-nl-C1INH are hormonal therapy and antifibrinolytics.

LTP with C1INH concentrates has been occasionally used but should be approached with significant cautions as described below.

Hormonal therapy for LTP of HAE-nl-C1INH. Given the prominent role of estrogens in escalating HAE-nl-C1INH disease severity, stopping exogenous estrogens in women with HAE-nl-C1INH is a first step for treatment.[85] Treatment with a progestin only pill, in contrast, has been shown to be beneficial in women with HAE-nl-C1INH with 45 of 55 (82%) of women experiencing benefit.[86-88] In the United States, norethindrone 0.35 per day has been used although optimal dosing has yet to be established, and progestin therapy should be instituted in collaboration with a gynecologist or endocrinologist. Anabolic androgens have also been documented for multiple cases of HAE-nl-C1INH with the same concerns regarding the adverse side effect profile as HAE-C1INH.[6,89]

Antifibrinolytics for LTP of HAE-nl-C1INH. Tranexamic acid has been used successfully for LTP with speculation that reducing the sensitivity to plasmin cleavage may provide the mechanism.[22,90] In the United States, tranexamic acid (Lysteda) is available with the usual dose starting at 650 mg bid and increasing to 1300 mg bid if required. Creatinine should be monitored for any impairment requiring dose adjustment. There is a slight risk of thrombosis with additional side effects of gastrointestinal upset, myalgia, and dysmenorrhea.[91]

C1INH replacement for LTP of HAE-nl-C1INH. Use of C1INH replacement in HAE-nl-C1INH is complex and controversial. C1INH cleavage has been demonstrated during pregnancy and with attacks in HAE-XII,[45] providing a rationale for on-demand use. Successful LTP with pdC1INH during pregnancy was reported for 3 patients with HAE nlC1INH, 2 with HAE-XII and 1 with HAE-U.[92] There are anecdotal reports that LTP with C1INH helps some nonpregnant patients with HAE-nl-C1INH, but there is insufficient evidence and experience to recommend C1INH LTP more broadly for this subgroup of patients. In exceptional circumstances with frequent attacks not manageable with other therapies, patients with HAE-nl-C1INH could be tried on a short course of C1INH LTP. A clear indication of high efficacy should be documented to warrant its continued use, but this indication should be restricted to clinicians who are highly experienced in treating HAE.

Lanadelumab for HAE-nl-C1INH. As reviewed in the previous sections, the attacks of swelling for patients with HAE-nl-C1INH appear to involve the generation of bradykinin by plasma kallikrein. Given the mechanism of action for lanadelumab, it would be anticipated to be an effective therapy in this cohort—with theoretical advantages over C1INH for LTP. For patients who are candidates but have failed tranexamic acid and progestins, the US HAEA MAB would favor a trial of lanadelumab with the same caveats as above to support its continued use.

ADDITIONAL CONSIDERATIONS FOR CHILDREN
Disease presentation in children
HAE-C1INH. Bowel wall edema with resultant abdominal pain is the most frequently reported initial symptom in

TABLE V. Recommended monitoring plan

Activity/assessment	At initial visit	At follow-up	Every 6 mo	Every 12 mo
Initial evaluation and education				
Provide HAE educational materials	x			
Discuss HAE triggers	x	x		
Develop/review treatment action plan	x	x		
Develop HAE swelling attack log	x			
Establish best method to contact physician	x			
Review HAE medication options	x	x		
Prescribe on-demand treatment	x	x		
Review treatment options during travel	x	x		
Review need for preprocedural prophylaxis	x	x		
Review other current medications	x	x		
Assess impact of HAE on QoL	x	x		
Discuss screening of family members for HAE	x			
Review long-term prophylaxis options	x	x		
Discuss anticipated pregnancy	x	x		
Review medication self-administration techniques	x	x		
Monitor on-demand therapy				
Review swelling attack log		x		
Review frequency of treatment		x		
Review effectiveness of treatment		x		
Verify 2 unexpired doses available		x		
Monitor long-term prophylactic therapy (if applicable)				
Review preventative efficacy		x		
Monitor for adverse effects		x		
Adjust dosing or preventative agent as needed		x		
Monitor for medication adverse effects				
Androgens				
LFTs, UAA, lipid profile			x	
Liver ultrasound*			x*	x
BP, weight, signs of virilization			x	
Antifibrinolytics				
LFTs, creatine, CPK, aldolase, UA			x	
Ophthalmologic exam				x
C1INH concentrates				
Address issues with administration		x		
Lanadelumab				
Assess for injection site reactions		x		
Ecallantide				
Assess for hypersensitivity reactions		x		
Icatibant				
Assess injection site reactions		x		
Visit with HAE specialist	x			x

HAE, Hereditary angioedema; *QoL*, quality of life.
*If androgen dosage equivalent greater than danazol 200 mg/d or equivalent.

children.[93] Although rare, airway swelling may be the initial symptom of HAE in children and can be fatal.[54,94] Children may be at increased risk for asphyxia due to their smaller upper airway diameter.[95-97] Rarely, newborns may have erythema marginatum as their initial indication of HAE-C1INH.[98]

HAE-nl-C1INH. HAE-nl-C1INH is uncommon in children. Approximately 10% to 14% of patients with HAE-FXII, however, have symptoms before the age of 12 years.[99,100] Although the prevalence of HAE-nl-C1INH is greater in females, males developing symptoms as young as 4 years of age have been reported.[101]

Diagnosis of HAE in children
Early symptom onset has been found to correlate with more severe HAE in later life.[21] Early symptom onset also tended to have a greater delay in diagnosis.[21] Screening first-degree relatives of affected patients is therefore critical.[102]

HAE-C1INH. Complement testing in children has been described above. In families with HAE-C1INH, in whom there is a known mutation in the SERPING1 gene, DNA analysis can be performed at any age.

HAE-nl-C1INH. The diagnosis is made using the same criteria in children as in adults.

Specific issues in the management of HAE in children

Patient/family education. As with any chronic disease in childhood, the child and his or her family need to be educated about HAE. The underlying goal of HAE treatment is for patients to live a normal life, which for many children includes participation in sports, although the coach or responsible adult should be informed about HAE. On-demand treatment should be made available for children at all points of care (ie, home, school, camp). It is important to stress that effective therapy needs to be on hand in advance of symptom onset—the first attack can sadly be fatal.

Coordination of care. Coordinating treatment plans for children must include provision of key information including an emergency plan to the network of responsible adults (ie, teachers, school health care providers, caregivers, etc.).

Pharmacologic treatment of HAE in children. Indications for on-demand as well as short-term prophylaxis and LTP in children follow the same guidelines as in adults.[83] An unmet need in the management of children is that HAE clinical trials have largely focused on adults, and therefore several effective medications are not FDA-approved for children. Tables III and IV list the FDA-approved age indications for HAE medications.

The record of safety and efficacy data for pdC1INH in pediatric studies[103-107] has made this the treatment of choice for on-demand use in the United States. The efficacy in children, as measured by median time to onset of symptom relief and complete resolution of symptoms, is similar to that in adults.[104,107] Data on recombinant C1INH treatment in children are limited but encouraging.[108] Self-administration (by the child or his/her caregiver) of C1INH is recommended for children as it is safe, decreases the time to medication administration, and reduces the need for hospitalization.[109]

Ecallantide is approved in the United States for children >12 years of age.[37,110-112] Although icatibant is not currently approved for children <18 years of age in the United States, an open-label study in children (aged 2-17 years) demonstrated that it provided rapid relief and was well tolerated.[113] Icatibant has been approved down to the age of 2 in Europe, New Zealand, and Australia.

The preferred LTP treatment in children is pdC1INH. This is based on substantial safety data on the use of pdC1INH for prophylaxis of HAE-C1INH in children, which has also demonstrated equal efficacy to adults.[103,105] SC C1INH offers a benefit to children in whom repeated venous access for prophylactic medication administration may not be well tolerated and has been approved in the United States for children >12 years of age.[72] Lanadelumab has been approved for children >12 years of age. The US HAEA MAB does not recommend the use of anabolic androgens for children due to the multiple concerns surrounding side effects and potential impact on growth, bone and, sexual development.[114]

SPECIFIC ISSUES IN THE MANAGEMENT OF HAE IN WOMEN

HAE-C1INH is equally prevalent in women and men. Symptoms, however, may be more severe in women presumably due to increased estrogen exposure (endogenous and exogenous). Many women identify menstruation, ovulation, pregnancy, and use of estrogen-containing medications as attack triggers.[115] Despite this, nearly one-third of women have increased numbers of attacks during or after menopause.[115] HAE-nl-C1INH predominantly, but not exclusively, affects women.[116] Similar to patients with HAE-C1INH, attacks frequency is increased with estrogen (endogenous and exogenous) exposure in particular for HAE-XII versus HAE-U.[32,117,118]

Contraception and fertility treatment

Estrogen-containing contraceptives (oral, transdermal) can precipitate attacks for patients with any HAE subtype.[116,119,120] Oral progestin-only contraceptives have been shown to reduce attacks in HAE-nl-C1INH.[115]

Although exogenous estrogens are generally not recommended for patients with HAE due to the risk of worsening disease outcomes, there may be certain circumstances however where the risk/benefit ratio would warrant their use to optimize a patient's QOL and lessen the burden of illness (BOI). Examples include fertility treatments, symptomatic surgical or natural menopause, and feminizing hormone therapy to change secondary sexual characteristics. In each instance, the patient should be carefully monitored and HAE-directed therapy adjusted for optimum control of disease. In these cases, the HAE provider should be part of the management team as hormonal therapies may exacerbate HAE.[121,122] In these instances, prophylaxis with C1INH can be beneficial.

Pregnancy

HAE-C1INH. Pregnancy has variable effects on the frequency and severity of attacks, even for the same patient during different pregnancies.[123-125] The abdomen is the most frequently reported site for attacks during pregnancy, potentially secondary to stretching of the uterus and fetal movement.[123,125] Women should be counseled that with abdominal attacks during pregnancy, there should be a low threshold to contact their obstetrician if there is no response to HAE treatment to not miss pain secondary to potential pregnancy complications.[126] HAE does not increase the rates of premature births, spontaneous abortion, or cesarean delivery.[115,125,127]

C1INH is the preferred treatment in pregnancy due to its safety during pregnancy documented by several case reports and observational studies.[124,125,128] Data for rhC1INH are limited but reassuring, with no adverse on embryofetal development at high doses in rats and rabbits. Short-term prophylaxis with pdC1INH should be given before any procedures performed during pregnancy, including amniocentesis or chorionic villus sampling.

Anabolic androgens are specifically contraindicated during pregnancy as they cross the placenta and may result in virilization of the fetus. Tranexamic acid also crosses the placenta, but limited data from animal studies and humans suggest that it does not produce harmful effects on the fetus.[126] No safety data from clinical trials are available on ecallantide or lanadelumab during pregnancy. Although case reports have demonstrated safe use of

icatibant during pregnancy, the US HAEA MAB cannot endorse its use in pregnancy until further studies are completed.[129-131]

HAE-nl-C1INH. Compared with patients with HAE-C1INH, it appears that patients with HAE-nl-C1INH are more likely to have increased attacks during pregnancy, in particular those with HAE-FXII.[22,92,99,132] Small case reports have shown that some patients given pdC1INH prophylaxis during pregnancy had decreased attack rates.[92,133]

Delivery

Before delivery, the primary HAE provider must discuss treatment of attacks with the obstetrician and anesthesiologist. Attacks are uncommon during vaginal delivery in patients with HAE-C1INH,[115,116] and short-term prophylaxis is not indicated. After delivery, some women may experience increased angioedema of the vulva.[126] Effective on-demand medication should be available in the delivery room for emergency use. If the delivery requires vacuum or forceps, we recommend a dose of pdC1INH. If a planned cesarean delivery is required for patients with HAE-C1INH or HAE-nlC1INH,[118] a preprocedural dose of pdC1INH should be given, and general anesthesia with endotracheal intubation should be avoided if possible as it may produce laryngeal edema.[134] After delivery, patients do not require intensive care unit care; however, the medical team must be prepared for the increased risk of an attack in the post-puerperal period.

Lactation and breast feeding

Lactation may be associated with an increased frequency of HAE attacks, potentially due to increased serum prolactin levels.[123] We recommend pdC1INH or rhC1INH for on-demand or prophylaxis treatment during lactation. Anabolic androgens and tranexamic acid are secreted into the breast milk and should not be used during breast feeding. There are no safety data on the use of ecallantide, icatibant, or lanadelumab during lactation.

Cancer

If patients with HAE are diagnosed with breast cancer, the choice of hormonal therapy requires careful consideration as tamoxifen has been reported to exacerbate symptoms in some patients.[135]

MANAGEMENT PLANS

HAE is a chronic condition with tremendous variability in symptom quality, frequency, and severity. Symptom variability is observed between patients but also within the same individual over time. HAE management plans must be individualized with treatment tailored to each patient's medical needs, life circumstances, and preferences as well as tolerance of and response to specific medications. Furthermore, management plans must be adjusted over time due to changes in HAE symptoms or other concomitant factors. Because of the complexity of HAE treatment, patients should be managed by a physician knowledgeable about HAE, experienced in managing the condition, and familiar with all available treatment options. A collaborative physician-patient relationship with frequent communication is important to facilitate shared decision-making and maintain optimal treatment over time. The goals of the HAE management plan are to "normalize" life as much as possible, ensuring that patients are able to engage in all work, school, family, and leisure activities as desired without limitation from angioedema symptoms.

Treatment logistics

Every individual with HAE should have a detailed individualized treatment plan developed in collaboration with an HAE physician specialist. A detailed HAE treatment plan includes the following components:

(1) *Access to effective on-demand medication.* Every patient diagnosed with HAE must have constant reliable access to effective acute treatment without exception due to the unpredictable and life-threatening nature of HAE attacks.[54]
(2) *Consideration of LTP* for patients who will benefit from this treatment strategy in addition to on-demand treatment. Prophylactic options should be discussed with each patient, and consideration given to numerous individualized factors important in making this treatment decision.[136]
(3) *Plans for as-needed use of short-term prophylaxis* before medical procedures or other events at high risk of triggering HAE attacks.[137]

The following points should be emphasized for effective management:

- Because of the rarity of the condition, HAE-specific medications are not readily available in most hospitals and medical facilities, so must be prescribed for individual patients.
- Patients and caregivers should frequently review details of their specific HAE action plan including: (1) where HAE medication is stored, (2) when it should be administered, (3) how it is administered, and (4) who will administer the medication at their planned treatment location (home, physician office, hospital, etc.).[138]
- Patients and caregivers should be encouraged and taught to self-administer HAE medication whenever possible as numerous studies support the clinical benefits of self-treatment.[139]
- Patients should have a "back-up" plan for administering HAE medication in the event self-administration proves difficult during an attack. This may include assistance from a family member, friend, or medical facility.
- Physicians should provide guidance on when to redose medication and when to seek medical attention for symptoms, including any airway involvement or for abdominal pain that does not respond to standard doses of effective HAE medication.
- Patients should be familiar with refill processes to efficiently replace HAE medications after doses are used.
- Reliable treatment plans should be developed for work, school, home, caregivers, and travel due to the unpredictability of HAE attacks.

Coordination of care

Many health care providers are unfamiliar with the risks associated with HAE as well as the specific medications required for effective treatment.[140,141] The HAE specialist should be made aware of other medical conditions for which the patient receives treatment, so that care can be coordinated, and relevant HAE-specific information can be communicated to the patient and other health care specialists. Examples include the avoidance of ACE inhibitors and exogenous estrogens, care during

pregnancy, and planned surgical or dental procedures requiring short-term prophylactic treatment. The patient's local primary health care team, emergency department, and hospital should be familiar with the HAE treatment plan if local assistance or emergency care is required. It is strongly recommended that individuals with HAE carry a wallet card or letter from their HAE specialist concisely summarizing the condition, the patient's specific HAE treatment plan, and listing contact information for the HAE specialist (an example of the emergency department wallet card and a template of a general letter of medical necessity developed at the UCSD US HAEA Angioedema Center are shown in Figures E1 and E2, respectively, available in this article's Online Repository at www.jaci-inpractice.org). Notifications or flags in electronic medical records are useful for highlighting HAE as a rare condition that requires specific medications for effective treatment.

Patient education

Patients and families should be provided with HAE educational opportunities to equip them for managing their condition and navigating the health care system. The US HAEA, a patient support and advocacy organization serving the patient with HAE community, provides valuable educational resources with updated, accurate information. Education should be appropriate to the individual's level of understanding, and enduring materials such as printed literature, videos, or web-based modules are useful for ongoing reference. The genetic nature of the condition, inheritance patterns, and the importance of family testing should be communicated. Understanding the clinical symptoms, potential risks, and complications of HAE may improve adherence to treatment plans. The benefits and potential adverse effects of HAE medications should be discussed in detail so that patients can make informed choices about their treatment. Routine immunizations and good dental hygiene are recommended measures to prevent infections or invasive dental work from triggering HAE symptoms.

Monitoring

Clinical follow-up with an expert HAE physician on a regular basis is recommended to review and adjust the management plan as needed for optimal care, as symptoms of HAE often change over time. Follow-up visits should include reassessment of the management plan as noted in Table V. The frequency of follow-up visits depends on numerous patient-specific factors. For patients with well-controlled symptoms and minimal disruption of activities, follow-up visits every 6 to 12 months may be sufficient to ensure safety of the treatment plan. Patients with more frequent or disruptive HAE symptoms require more frequent follow-up visits. Changes in medication or dosing also warrant more frequent follow-up to ensure efficacy and tolerability of a new treatment plan.[142]

Patients should record HAE symptoms on a regular basis. Symptom diaries may be paper or electronic and should include attack data on anatomical location, duration, severity, medication used, and response to treatment. Recording medication use provides documentation for prescription renewals and allows tracking should medication recalls occur. Severity assessment of HAE symptoms should include the level of disruption of usual activities. Symptom data should be communicated to the HAE specialist and brought to follow-up appointments for detailed review to inform subsequent medical decision-making. Patients

should be queried regarding difficulties in accessing, administering, or refilling HAE medications. Standardized QoL tools for angioedema conditions may also be useful to monitor treatment efficacy.[143,144] Patients reporting difficulty with frequent, severe, or disruptive HAE symptoms should be assessed for a dosage increase or alternative therapy. Acute treatment logistics should be reviewed, ensuring that acute treatment is administered early in attacks as this has been shown to improve clinical outcomes.

Safety monitoring is recommended for all HAE medications, though certain agents require more rigorous testing due to safety concerns. Anabolic androgen use for prophylaxis requires follow-up at least every 6 months to monitor weight, blood pressure, liver enzymes, lipid profiles, and urinalysis. Patients on anabolic androgens should have a liver ultrasound completed every 12 months and should be cautioned on the potential for virilization and adverse psychiatric effects.[79,82,142] For prophylactic antifibrinolytics, renal and liver function, urinalysis, creatine kinase level, and aldolase should be performed every 6 months and regular eye examinations are recommended.[145] No specific monitoring parameters are recommended for other HAE medications, though patient follow-up visits should include review for any adverse effects associated with each medication. Examples include hypersensitivity symptoms/reactions to ecallantide, injection site reactions with icatibant, lanadelumab, or SC C1INH, and venous complications from the administration of IV C1INH concentrates. Recent study data suggest a potential utility for C1INH functional testing as a predictor of efficacy with SC C1INH prophylaxis, but future research is required to validate the utility of this approach for optimizing the SC C1INH dose.[146]

BURDEN OF ILLNESS

BOI is the broad impact of a particular health disorder or disease on several dimensions of a patient's, his or her family members and caregivers' lives, as well as society as a whole. BOI encompasses both humanistic and economic parameters, which are often intertwined. Table E1 (available in this article's Online Repository at www.jaci-inpractice.org) summarizes some of the features of HAE that affect its BOI beyond the severity of its physical manifestations. Over the past decade, the BOI associated with HAE has become better recognized.[143,147,148] Over this same period, advances in therapeutic modalities have begun to offer the possibility of allowing most patients with HAE to live a normal life. Therefore, a key goal in HAE treatment is to improve patient QoL by recognizing and then ameliorating those factors contributing to HAE BOI. Manifestations of BOI associated with HAE are summarized below.

Anxiety and depression

Anxiety and depression are common in patients with HAE.[149,150] Their etiology may arise from the unpredictability, frequency, and severity of swelling, which can negatively impact work, social, and family life.[151] Before the availability of on-demand therapy and nonanabolic androgen prophylactic options, the rate of symptoms consistent with depression in US patients with HAE was measured at 43% (vs 16% of the population norm).[149] The introduction of modern HAE treatments in the United States coincided with a substantial decrease in the percentage of patients with HAE-C1INH reporting that their HAE had a severe psychological/emotional impact on their lives (53% in 2009 and 17% in 2013).[152] In contrast, patients with

HAE-nl-C1INH did not report any improvement in their psychological burden over this same timeframe.[152] A large European study reported that patients with HAE-C1INH from Germany and Denmark (who were more likely at that time to have better access to HAE medications) had lower rates of depression compared with participants from Spain (more likely to have a decreased access to HAE medications).[151]

Prevention of attacks improves psychological outcomes. Between attacks, patients often fear the onset of the next attack, and that it may be painful or fatal.[148,151,153,154] Prophylactic therapy with SC C1INH or lanadelumab, which significantly decrease attack frequency, led to significant improvements in validated anxiety and depression or QoL scores.[72,73,75]

Despite these improvements, the prevalence of mood disorders in patients with HAE-C1INH still remains relatively high.[150,152] This may be secondary to concerns of having children with HAE.[151,152] Another concern is that there is a general lack of knowledge of HAE among health care providers, particularly in patients with HAE-nl-C1INH[155] for whom diagnosis and understanding of disease pathologies are less well characterized.

Dissatisfaction with care

Satisfaction with care includes the patients' perception of effectiveness, tolerability, and convenience of therapy. Anabolic androgen use is associated with patient dissatisfaction and depression,[79,149] whereas SC C1INH prophylaxis significantly improved patients overall treatment satisfaction.[73] Satisfaction of care also incorporates experiences during emergency room (ER) visits or hospitalizations and comfort with provider care. Patients remain dissatisfied with ER care,[155] preferring to treat at home. As treatment options have improved, patients with HAE-C1INH report increased satisfaction with their primary HAE provider, from 70% in 2013 to 90% in 2015.

Impairment of daily activities

HAE attacks cause significant impairment of work, educational, and social activities,[73,149,151,154,156-158] leading to self-restriction of physical activities and modifications of lifestyle.[148,149,158] Patients with HAE report both missing work due to illness and trying to "work through" attacks, resulting in decreased productivity while at work. Before on-demand treatment in the United States, 40.5% of patients felt that HAE prevented them from going as far in school as they would have liked, and 69.1% that they could not consider certain jobs because of HAE. A total of 59% of patients also reported missing leisure days.[149] Effective prophylactic therapy significantly decreased the overall work impairment in patients,[73] suggesting that effective treatment confers important lifestyle benefits that improve long-term patient outcomes.

Economic costs

Economic costs of acute and long-term management include direct medical costs (eg, medications, hospital and ER care, etc.) and indirect costs (eg, childcare, cost of missed work and loss of productivity, travel to visits/emergent care, etc.). Family members often share the direct and indirect economic burden on patients.[156,159,160] Self-administration of on-demand treatments decreases cost by reducing hospital visits.[153,154] A recent study examining the economics of HAE treatments found that the newest prophylactic agents lead to clinically significant improvements in QoL and avoid the high direct (medical) and indirect (socioeconomic) costs associated with the on-demand

only treatment model[161] (Castaldo et al, manuscript submitted, 2020). The treating physician may need to write letters of medical necessity to support HAE patient access to effective medications. A generic template of a letter of medical necessity for HAE is shown in Figure E2 (available in this article's Online Repository at www.jaci-inpractice.org).

Decreased health-related quality of life

HRQoL is an individual's perception of the impact of a specific disease on several aspects of his or her life including physical, psychological, social and somatic domains of functioning, and well-being.[143] Generic HRQoL instruments (eg, 12-item short-form survey, 36-item short-form survey, EuroQol 5-dimensional questionnaire) and dermatology-specific questionnaires have consistently demonstrated poor QoL in patients with HAE.[119,149,158,162,163] More recently, angioedema or HAE-specific QoL instruments (angioedema [AE]-QoL, HAE-QoL, and HAEA-QoL) have been developed.[164-166]

The introduction of on-demand and LTP therapies with improved efficacy and fewer side effects has consistently demonstrated improvements in patients' QoL and BOI.[152,153] Transition from anabolic androgens to IV C1-INH for prophylactic therapy significantly improved patients' QoL.[167] Home therapy and self-administration improved QoL.[168-171] Prophylactic pdC1-INH treatment significantly improved HRQoL, specifically in the domains of social function and bodily pain, compared with placebo.[172] Newer prophylactic treatments (SC C1INH, lanadelumab, and an oral plasma kallikrein inhibitor) further demonstrated improved QoL using the AE-QoL.[73,173-175]

The BOI from HAE is clearly influenced by the frequency and severity of attacks. Optimizing HAE care should therefore reduce BOI and improve QoL. The sections above explicitly review current best practices to optimize HAE care. Clinicians must be cognizant of these potential burdens associated with HAE, and consequently individualize treatment plans. A number of disease-specific tools are available to evaluate HAE disease activity, QoL, and its impact on daily life.[144] We recommend that these be used as part of the comprehensive management plan. An unmet need is that none of the specific HRQoL tools for HAE have been evaluated in children.

CONCLUSIONS

Progress in understanding the genetic and biochemical changes in HAE has driven a continuous series of improvements in the classification and treatment HAE. Management begins with diagnosis, which depends on physicians recognizing possible HAE symptoms. The diagnosis of HAE-C1INH deficiency (type I or type II) is readily made with standard testing. In contrast, the diagnosis of HAE-nl-C1INH remains difficult. Targeted next-generation sequencing and novel biomarkers may soon improve the diagnostic approach for HAE-nl-C1INH.

Effective treatment of HAE requires that all patients have rapid access to effective on-demand medications. Crucially, physicians and patients must recognize the value of early treatment to prevent attacks from becoming moderate or severe. The decision on whether to institute LTP treatment of HAE needs to be individualized. Recent advances in the efficacy and tolerability of LTP medications for HAE-C1INH have expanded the number of patients who may elect to pursue and benefit from LTP. HAE treatment for patients with HAE-nl-C1INH remains suboptimal and further studies are required.

The complexity of the diagnostic and therapeutic options requires the active involvement of an expert physician, often working in coordination with the patient's local physician. The expert physician should also help develop comprehensive management plans and help in the management of pregnant or lactating women as well as children, each of whom presents multiple challenges.

Because of treatment advances, many patients with HAE-C1INH can now anticipate the ability to lead a normal life, a development that should meaningfully change our HAE treatment goals and approach. Achieving this goal requires that physicians partner with patients to identify and use optimal treatments for each patient as well as orchestrate the logistics of care. Substantial challenges still exist for patients with HAE-nl-C1INH. Considering how dramatically HAE care has changed over the past decade, there is considerable enthusiasm that many of the extant problems will be solved in the near future.

Acknowledgments

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ONLINE REPOSITORY

METHODOLOGY USED TO DEVELOP GUIDELINE RECOMMENDATIONS

To assure that the guidelines were based on the best available data, each section was assigned to a team of at least 2 Medical Advisory Board (MAB) members who performed a complete review of the current literature up to July 1, 2018. On the basis of their literature search, each team wrote the first draft of their section. The initial drafts were discussed at a face-to-face meeting of the MAB on July 20, 2018. During this meeting, each section was presented by the authors along with the supporting evidence. Each section was then critically reviewed by the MAB members as well as the United States Hereditary Angioedema Association representative. Suggestions for revisions were discussed until a unanimous consensus was reached regarding the information to be included in each section.

The primary authors of each section were then tasked with writing the second draft of their section including writing clear recommendations based on the review of the literature review (updated through January 2019) and the group input. The second draft of the manuscript was combined into a single document then edited by one of the authors (BLZ), who also worked with the principal authors of each section to assign the preliminary assessment of strength and quality of the evidence for each recommendation based on the literature review.

The authors first evaluated the strength of each recommendation. Strength was assessed as either strong or weak. A strong recommendation was given if the authors were confident in the recommendation based on existing evidence or if the risk/benefit ratio was compelling. In the absence of one of these, the recommendation was considered weak. The quality of evidence was assigned into 1 of 3 categories: high quality; moderate quality; or low quality. High quality was assigned to evidence resulting from either well-designed randomized controlled trials or observational studies with very large and clinically important effect sizes. Moderate quality was assigned to evidence from randomized trials with important limitations or observational studies with clear and consistent effect sizes. Low quality was assigned to evidence that failed to achieve either high or moderate quality.

The resulting third draft was circulated to the entire authorship for review. A final face-to-face meeting was held on July 26, 2019, to discuss final changes in the manuscript. During this meeting, the authors discussed and refined each recommendation. After the discussion, the authors voted on each recommendation, including both the strength and quality of the underlying evidence.

US HAEA Angioedema Center at UC San Diego

UC San Diego
HEALTH SYSTEM

US HAEA Angioedema Center at UC San Diego

HAE Emergency Card

Last, First

November 1, 1953

HAE-normal-C1INH

haea

HAE Physicians:

Doctor#1 MD
Doctor#2 MD
Doctor#3 MD

Daytime Telephone:
(xxx) yyy-zzzz

After-Hours Telephone:
(xxx) yyy-zzzz

Emergency Telephone:
(xxx) yyy-zzzz

This patient suffers from Hereditary Angioedema (HAE).
HAE is characterized by unpredictable recurrent attacks of swelling involving the skin (i.e. hands, feet, face and genitals), which are painful and debilitating. Swelling also commonly occurs in the submucosa including the GI tract, mouth, tongue and throat. GI attacks can cause abdominal pain mimicking an acute abdomen. All patients are at risk for laryngeal swelling with possible asphyxiation and death.

The swelling in HAE is caused by bradykinin. It is not allergic and therefore DOES NOT RESPOND to treatments such antihistamines, epinephrine or corticosteroids.

Additional Information

Online: www.haea.org

Zuraw BL et al, US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. JACI In Practice 1:458, 2013.

Moellman JJ, et al. A consensus parameter for the evaluation and management of angioedema in the emergency department. Acad Emerg Med. 21:469, 2014.

Laryngeal Attacks

Because of the risk of asphyxiation during a laryngeal attack and because the effective medicines can take 30-60 minutes to begin to work, physicians should be prepared to emergently intubate the patient or perform a cricothyrotomy.

Signs of impending airway obstruction include stridor, inability to swallow, and change in the voice. The airway may be significantly distorted and these procedures should be performed by an expert.

Treatment of Attacks

Effective emergency treatment should be given as soon as possible to arrest the attack. There are several effective therapies available, including:

1) C1-inhibitor concentrate by IV injection:
  -20 U/kg (Berinert), or
  -1000 U (Cinryze), or
  -50 U/kg (Ruconest)
    [max 4200 U]

2) Icatibant (subcutaneous inj)
  -30 mg in 3 ml (Firazyr)

3) Ecallantide (subcutaneous inj)
  -30 mg, 3x1ml (Kalbitor)

My HAE Medication Care Plan

On-demand medicine(s)

Firazyr (icatibant) 1 injection (30 mg), may repeat in 6 hours if worsening

Prophylactic medicine(s)

Lysteda 650 twice a day

For all attacks remember to treat early to arrest the swelling.
Keep track of how often you are needing the on demand treatment to discuss with your doctor

What to do in the event of an throat/laryngeal attack

Swelling in the upper airways can turn into a life-threatening situation.
Prudent and timely behaviour is vital.

A sleeping person is not going to die by suffocation in his or her sleep.
The onset of breathing difficutles is going to wake you up.

A. At first symptom of throat swelling:

1. Immediately administer on-demand HAE medicine (C1INH, ecallantide, or icatibant)
2. If there is no improvement in 30 minutes, go to step B
3. Stay calm and remain level-headed

B. At onset of breathing difficulty:

1. Call 911 - "I am having a life-threatening attack of hereditary angioedema. My throat is swelling and I feel like I'm suffocating." Provide operator with your name and your location
2. Open the door to provide access and inform friends/neighbors/family
3. Administer on-demand HAE medicine immediately, and repeat as necessary
4. Do not attempt to drive yourself; wait for ambulence and have friend/neighbor/family accompany you if possible.
5. Keep your HAE medicines and emergency card at hand and take them with you.

FIGURE E1. Sample emergency room card. This shows the credit-sized double-sided emergency room card given to patients at the US HAEA Angioedema Center at UCSD. This card provides the diagnosis, contact information, background information about HAE, current prescribed treatments, and information about what to do in an emergency. *C1INH*, C1 inhibitor; *GI*, gastrointestinal; *IV*, intravenous; *UCSD*, University of California San Diego; *US HAEA*, United States Hereditary Angioedema Association.

To Whom It May Concern:

This shall serve as a letter of medical necessity for *[patient name]* who has Hereditary Angioedema (HAE) due to C1INH deficiency and is under my care to treat *[her/his]* condition. This genetic condition leads to unpredictable episodes of cutaneous, intestinal, and/or airway angioedema which are debilitating and life-threatening.

I have recommended and prescribed the following medication for *[acute or preventative]* treatment of HAE attacks:

[medication name, dose, route of administration]

This treatment is necessary to *[terminate/prevent]* the debilitating and life-threatening angioedema episodes caused by HAE. Lack of access or coverage for this effective medication will put the patient at increased risk for serious disease-related complications including disability, emergency care, hospitalization, and death from asphyxiation due to continued unpredictable angioedema symptoms.

[Signature]

FIGURE E2. Sample template of a letter of medical necessity. This shows a typical letter of medical necessity for an HAE medication in a patient who has been diagnosed with HAE. *C1INH*, C1 inhibitor.

TABLE E1. HAE features contributing to burden of illness beyond physical severity

Factor/feature	Impact
Rare disease	Delay in correct diagnosis Inappropriate treatment Lack of available treatment
Symptoms of attack	Unpredictable Disabling pain Inability to perform activities Embarrassment about physical appearance Prolonged duration
Treatment	Often limited access to effective treatments Need for injections or infusions Side effects from older medications
Genetic disease	Guilt of transmitting disease Impact on entire family

HAE, Hereditary angioedema.