Original Article

US Hereditary Angioedema Association Medical Advisory Board 2013 Recommendations for the Management of Hereditary Angioedema Due to C1 Inhibitor Deficiency

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What is already known about this topic? The treatment of hereditary angioedema (HAE) has undergone dramatic changes as newer medicines have become available and management has become more complex.

What does this article add to our knowledge? This article provides recommendations for the treatment and management of HAE due to C1 inhibitor deficiency in the United States, which covers development of an overall management plan, treatment of angioedema attacks, prophylactic treatment, and patient monitoring.

How does this study impact current management guidelines? Based on the criteria developed in this article, physicians can provide optimized management of patients with HAE by using any of the medications and approaches available for the treatment of HAE.

BACKGROUND: The treatment of hereditary angioedema (HAE) has undergone dramatic changes as newer medicines have become available in recent years. Optimal care of these patients requires a comprehensive management plan. Although several consensus papers have been published concerning the diagnosis and treatment of HAE, guidelines for a comprehensive management plan have not been developed.

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Support: The US Hereditary Angioedema Association provided funding for meetings.

Conflicts of interest: B. L. Zuraw has received travel support from the US Hereditary Angioedema Association; is a member of adjudication boards for Sanofi-Aventis, Novartis, and Genentech; has consultant arrangements with Dyax, Isis, BioCryst, and CSL Behring; has received grants from Shire; has received payment for lectures from Dyax; and has received travel support from ViroPharma. A. Banerji has received grants from Shire, ViroPharma, and Dyax; has consultant arrangements with Shire, CSL, and Dyax; has received fees for participation in review activities from Shire; and has received payment for development of educational presentations from Medscape. J. A. Bernstein is a member of the board of directors for the American Academy of Allergy, Asthma, and Immunology; is a board member for Allergists for Israel; is on the medical advisory boards for the Hereditary Angioedema Association and Mastocytosis; has consultant arrangements with Dyax, Shire, CSL Behring, and ViroPharma; is employed by the Bernstein Allergy Group and Bernstein Clinical Research; has received grants from Boehringer Ingelheim, Forest, ViroPharma, CSL Behring, Dyax, Shire, Pharming, and Novartis; has received payment for lectures from Shire, Teva, Dyax, ViroPharma, and CSL Behring; has received payment for the development of educational presentations from ViroPharma, Shire, and Medscape; and is editor-in-chief of the *Journal of Asthma.* P. J. Busse has consultant arrangements with ViroPharma, Dyax, CSL Behring, and Shire; has received grants from CSL Behring; has a pending grant with ViroPharma; and has received payment for development of educational presentations from the Robert Michael Educational Institute. S. C. Christiansen has received travel support from the US Hereditary Angioedema Association. M. Davis-Lorton has received payment for lectures from Dyax and ViroPharma. M. M. Frank is on a committee that is developing a quality-of-life questionnaire and speaks about the disease without medication bias supported by an educational institute. H. H. Li has consultant arrangements with Dyax and CSL Behring; has received speakers fees from Dyax, CSL Behring, and ViroPharma; and has received research support from Dyax and ViroPharma. W. R. Lumry has received travel support from the Hereditary Angioedema Association Medical Advisory Board; has consultant arrangements with ViroPharma, Dyax, CSL Behring, Shire HGT, and BioCryst; has received grants from ViroPharma, CSL Behring, Dyax, Shire HGT, and Pharming; has received payment for lectures from ViroPharma, CSL Behring, Dyax, and Shire HGT; and has received payment for development of educational presentations from ViroPharma and Shire HGT. M. Reidl has consultant arrangements with ViroPharma, CSL Behring, Dyax, Shire, Isis, and BioCryst; has received grants from ViroPharma, CSL Behring, Dyax, Shire, and Pharming; and has received payment for lectures from ViroPharma, CSL Behring, Dyax, and Shire.

Received for publication May 14, 2013; revised July 10, 2013; accepted for publication July 12, 2013.

Cite this article as: Zuraw BL, Banerji A, Bernstein JA, Busse PJ, Christiansen SC, Davis-Lorton M, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. J Allergy Clin Immunol: In Practice 2013;1:458-67. http://dx.doi.org/10.1016/j.jaip.2013.07.002.

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2213-2198/$36.00

http://dx.doi.org/10.1016/j.jaip.2013.07.002

Abbreviations used
BID- Twice a day
C1INH- C1 inhibitor
FDA- US Food and Drug Administration
HAE- Hereditary angioedema
HAEA- Hereditary Angioedema Association
MAB- Medical Advisory Board
n/a- Not available
TID- 3 times a day

OBJECTIVE: To develop state-of-the-art recommendations for the treatment and management of HAE due to C1 inhibitor (C1INH) deficiency in the United States.
METHODS: Members of the US Hereditary Angioedema Association Medical Advisory Board began by reviewing the literature concerning treatment of HAE. Preliminary recommendations were developed based on the literature review, discussions in a face-to-face meeting, and refinements in a series of drafts. Final recommendations reflect the unanimous consensus of the medical advisory board and the US Hereditary Angioedema Association leadership.
RESULTS: Recommendations are provided regarding a comprehensive care plan for HAE, including the following: development of an overall management plan, treatment of angioedema attacks, prophylactic treatment, and patient monitoring.
CONCLUSION: A comprehensive individualized management plan developed between an expert HAE physician and the patient, in collaboration with local medical providers and emergency departments, can provide patients with the best opportunity to lead a normal life. **(J Allergy Clin Immunol: In Practice 2013;1:458-67)**

Key words: *Hereditary angioedema; C1 inhibitor; Bradykinin; Management; On-demand treatment; Prophylactic treatment*

Hereditary angioedema (HEA) is a rare autosomal dominant disease characterized by episodic unpredictable swelling. Two types of HAE are associated with deficiency of circulating levels of C1 inhibitor (C1INH): type I HAE is characterized by deficient levels of C1INH protein, whereas type II HAE is characterized by a dysfunctional C1INH protein that results in normal C1INH protein levels but diminished C1INH functional activity.[1,2] Both type I and type II HAEs are caused by mutations in the gene that encodes C1INH (*SERPING1*).[3] The estimated prevalence of type I and type II HAE is 1 per 50,000, which suggests that there are approximately 6000 affected individuals in the United States. A third form of HAE with normal C1INH was described in 2000.[4,5] The prevalence of HAE with normal C1INH is not known.

Attacks of angioedema are often severe and may be associated with significant morbidity or mortality.[6,7] Due to this variability, it is critical that physicians and patients work together to design individualized treatment plans that optimize care for each patient. Over the past 5 years, multiple novel medications have been approved in the United States for the treatment of HAE.[8-11] The medications available to treat HAE have very different modes of action, methods of administration, and risk-to-benefit profiles. The complexity of the available treatment options combined with the potential morbidity and mortality of HAE necessitate that the physician develop an evidence-based plan that reflects the appropriate standard of medical care. To address these issues, the medical advisory board (MAB) of the US Hereditary Angioedema Association (HAEA) has developed a set of recommendations for the optimized management of patients with HAE due to C1INH deficiency.

An accurate diagnosis of HAE due to C1INH deficiency must be made before treatment options become relevant. Not surprisingly, HAE deaths have been shown to be far higher in patients without an accurate diagnosis than in those in whom the correct diagnosis was made.[12] Although the diagnosis of HAE is not addressed in this article, it has been reviewed in recent articles.[3,13,14] Several international consensus papers have been published.[13-17] The diagnosis and treatment of HAE with normal C1INH (sometimes called type III HAE) is an area of considerable uncertainty. A separate set of guidelines and recommendations has recently been developed and published for HAE with normal C1INH.[18] The recommendations presented herein pertain exclusively to HAE due to C1INH deficiency and reflect the current state-of-the-art treatment of HAE due to C1INH deficiency in the United States.

METHODS

The US HAEA MAB consists of 10 clinicians, each of whom treats a large number of patients with HAE. In 2011, the MAB began working on defining recommendations for the treatment of HAE. The original draft of these recommendations was posted on the US HAEA Web site. The recommendations are divided into 4 sections: (1) management plan, (2) treatment of angioedema attacks, (3) prophylactic treatment, and (4) patient monitoring. To assure that the recommendations were based on the best available data, a literature search was conducted to identify published articles that involved either treatment of HAE or consensus and/or guidelines and/or recommendations for the treatment of HAE. In 2013, the US HAEA convened a meeting that included the members of the HAE MAB as well as several patient representatives to review the original draft recommendations, comments to the original draft, and the literature. Before the meeting, drafts for each of these sections were reviewed and the relevant literature was reviewed by members of the MAB, who led the discussion of that section at the meeting. Recommendations reflect the unanimous consensus of the MAB and the US HAEA leadership.

HAE management recommendations

Section 1. HAE management plan. The overall goals of HAE treatment are to reduce morbidity and mortality, and to restore a normal quality of life to the patient. To achieve these goals, an individualized comprehensive management plan must be developed and implemented. The US HAEA MAB recommends the following components of a treatment plan for every patient.

1.1. Expert physician. Because of the complexity and variability of HAE and treatment, it is strongly recommended that every patient with HAE be followed up by a physician who is (1) knowledgeable about the condition, (2) experienced in managing patients with HAE, and (3) familiar with all HAE treatment options. These expert physicians should work with their patients to assure that a defined and individualized HAE

management plan is established and should also actively coordinate the patient's care with other health care providers.[16] The coordinating physician will need to work with the patient and his or her family, his or her primary health care providers and the local community emergency department or hospital to ensure that components of the treatment plan are clearly communicated. The US HAEA MAB also recommends that the coordinating expert physician see the patient for follow-up visits on a periodic basis to monitor for treatment efficacy and adverse effects. Follow-up with the expert physician should occur at least annually or more frequently, depending on the clinical course (see Section 4. Patient monitoring).

1.2. Patient education. Patients and families affected by HAE benefit from education about the condition at the time that the diagnosis is made. All immediate family members should be tested for HAE once an individual is diagnosed, given the demonstrated mortality risk associated with undiagnosed HAE[12] and the fact that, in some patients, manifestations of HAE may appear relatively late in life. Testing of young infants is often postponed until they reach at least 1 year of age when their complement levels reach normal adult levels. Patients should understand the cause of HAE, the genetics and inheritance pattern of the disease, potential benefits of family testing, common attack manifestations, potential risks and complications from attacks, possible attack triggers, and existing treatment options.[13] Because patients may find it difficult to rapidly assimilate the information, education should be geared to the patient's level of understanding, and enduring educational materials are recommended. Use of printed handouts, video media, or online educational modules that the patient can review at home are strongly encouraged (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).[19] The information should be discussed and reviewed during follow-up visits. In addition to education about HAE, it is important that patients are provided guidance about navigating the health care system. Given the rarity of their condition, patients should be prepared to tactfully inform providers who are not familiar with HAE about the unique features and treatment requirements of HAE.

1.3. Treatment options. Therapeutic approaches for HAE include both "on-demand" treatments given at the onset of symptoms to abrogate angioedema attacks as well as prophylactic treatment administered at regular intervals to prevent or minimize attack numbers and severity. All patients require a readily available on-demand treatment to terminate unpredictable angioedema episodes.[16,20] For some patients, on-demand treatment alone is sufficient; for other patients, prophylactic treatment is indicated as first-line treatment together with on-demand treatment for breakthrough attacks; and, in other patients, prophylactic treatment may be added to existing on-demand treatment when necessary to maintain acceptable quality of life.[3,20] Because of the dramatic intra- and interindividual clinical variability of HAE, optimal treatment strategies for a patient with HAE must be individualized based on patient-specific factors and preferences. Factors such as age, comorbidities, access to emergency medical facilities, and the patient's past experience must be considered when making treatment choices. It should also be recognized that HAE severity may wax and wane over time, and that the physician needs to periodically review and potentially refine the treatment plan based on the clinical course and dynamic patient factors (ie, pregnancy, rural vs urban residence, etc).

1.4. Coordination of care. Patients with HAE often experience angioedema attacks that require intervention by physicians other than the expert HAE physician. Because these needs are likely to be emergent, it is mandatory that the expert HAE physician discuss this issue with the patient in advance and help the patient anticipate this need as much as possible. The expert physician should communicate management plan details to the health care providers who will care for the patient should he or she have an attack that requires assistance. This requires that the local primary care clinician be educated about HAE. When feasible, the local emergency department also should be informed about the patient as well as the potential treatment. The local providers should also know how to reach the expert physician should they require additional recommendations. All patients with HAE should carry identification that alerts health care providers about their HAE and that includes contact information for their expert physician. This may be done by using medical identification bracelets, letters, and/or USB drives. In addition, flagging of electronic medical records to denote the patient's rare and potentially fatal condition is advisable. It is strongly recommended that all patients with HAE be given a card that provides patient-specific treatment guidelines should they experience an attack.

1.5. Treatment logistics. The expert physician should ensure that each patient with HAE has specific detailed plans in place to treat any attack that may occur. This should include preplacement of US Food and Drug Administration approved HAE-specific medication for each affected patient. Patients should understand the medication that they will use to treat an attack, where and how the medication is stored, when they will use the medication, who will administer the medication (self-administered vs health care provider administered), where the medication will be administered (home vs health care facility), and how they will monitor whether they need to seek additional assistance or require additional dosing of medication. Treatment plans should include contingencies in the event that the initial treatment fails or the patient experiences an acute adverse event from the therapy. Given the unpredictable onset of HAE attacks, patients should also understand the process by which their medication is refilled so that they are appropriately prepared for the next attack. Patients must have plans that will allow treatment to be efficiently and reliably administered whether they are at home, at school or work, or are traveling.

Section 2. Treatment of angioedema attacks. The goal of acute treatment in HAE is to minimize morbidity and prevent mortality from an angioedema attack. Treatment of attacks "on demand" (ie, whenever they occur) is essential for accomplishing this goal.[21] Multiple specific and effective medications are available for the on-demand treatment of angioedema attacks (Table I).[8-11] The US HAEA MAB makes the following general recommendations for on-demand treatment of angioedema attacks.

2.1. Availability of on-demand treatment. All patients with HAE due to C1INH deficiency should have access to at least 2 standard doses of US Food and Drug Administration

TABLE I. Medications for on-demand treatment of HAE

Generic name (trade name, company)	FDA approval status	Dosage	Mechanism	Efficacy	Storage	Anticipated potential adverse effects
Newer						
Plasma-derived C1INH (Berinert, CSL Behring, King of Prussia, Pa)	Approved for acute attacks in adults and adolescents	20 U/kg intravenous	Inhibit plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	+++	Store between 2°C and 25°C; stable for up to 30 mo	Rare: risk of anaphylaxis; theoretical: transmission of infectious agent
Plasma-derived C1INH (Cinryze; ViroPharma, Exton, Pa)	Not FDA approved for on-demand treatment	1000 U intravenous	(Same as above)	+++	Store between 2°C and 25°C	Rare: risk of anaphylaxis or thrombosis; theoretical: transmission of infectious agent
Recombinant human C1INH (Rhucin, Ruconest, Santarus, San Diego, Calif)	Not FDA approved for on-demand treatment	50 U/kg intravenous	(Same as above)	+++	Store between 2°C and 25°C; stable for up to 4 y	Rare: risk of anaphylaxis
Ecallantide (Kalbitor, Dyax, Burlington, Mass)	Approved for acute attacks in patients ≥16 y old	30 mg subcutaneous	Inhibits plasma kallikrein	+++	Store between 2°C and 8°C; stable for up to 36 mo	Common: prolonged PTT; uncommon: risk of anaphylaxis (must be administered by health care professional)
Icatibant (Firazyr, Shire, Lexington, Mass)	Approved for acute attacks in patients ≥18 y old	30 mg subcutaneous	Bradykinin B2 receptor antagonist	+++	Store between 2°C and 25°C; stable for up to 2 y	Common: discomfort at injection site; theoretical: worsening of an ongoing ischemic event
Older						
Fresh frozen plasma	Not FDA approved for on-demand treatment	2 units	Inhibit plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	++	n/a	Rare: risk of anaphylaxis; possible: transmission of infectious agent; sudden worsening of an attack

++, moderate efficacy; +++, excellent efficacy; *MASP,* mannose-associated serine protease; *n/a,* not available; *PTT,* partial thromboplastin time.

medicine for on-demand treatment of acute HAE attacks. Because not all patients respond the same to each medication, it is the responsibility of the coordinating expert physician to work with each patient to define the optimal medication(s) for that particular patient. In cases in which more than one on-demand medication is prescribed, the justification for use of more than a single medication should also be both explicit and understood by the patient. There should be ongoing monitoring of frequency and efficacy of on-demand treatments by the physician with regular follow-up visits, the frequency of which will depend on the patient's course of treatment.

2.2. Existing management plan. As mentioned above (Section 1. HAE management plan), patients should have a management plan in place with ready access to their health care provider during an acute attack. The management plan should include the name(s) of the medication(s) and the methods of administration. Most HAE attacks can be treated outside a medical facility. Treatment can be rendered by self-administration, a trained family member, or a home health professional. Not all patients can be treated outside a medical facility. Arrangement for streamlined access to a medical facility or health care provider is strongly encouraged for all patients, even for those who can be treated outside a medical facility.

2.3. Early treatment. On-demand treatment of attacks is most effective when administered early in the attack.[21] Patients should be counseled to treat as soon as the attack is clearly recognized. In cases in which the patient can reliably predict an attack (ie, erythema marginatum), logistical arrangements for treatment may be initiated during the prodrome[22]; 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 unusual, their response to self-treatment is inadequate, or they experience an attack that involves the airway.

2.4. Attack location. Decisions about which attacks to treat with on-demand medications should be based on the goals of minimizing morbidity, preventing mortality, and increasing quality of life 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. There is overwhelming consensus that all abdominal, facial, oral, and upper respiratory attacks should be treated as early as possible. Extremity attacks are often disabling, and early treatment can prevent dysfunction.[16,23] The decision about whether it is necessary to treat an extremity attack can be left to the patient's sense of whether the swelling location is likely to result in disability.

2.5. Laryngeal attacks. There is a substantial risk of mortality associated with laryngeal attacks, and appropriate caution needs to be exercised in the management of these attacks.[12] Patients who experience symptoms of laryngeal,

TABLE II. Medications for prophylactic treatment of HAE

Generic name (trade name, company)	FDA indications	Usual adult dosage*	Mechanism	Anticipated potential adverse effects
Newer				
Plasma-derived C1INH (Cinryze; ViroPharma)	Approved for prophylaxis in adults and adolescents	1000 U intravenous twice/wk	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis or thrombosis; theoretical: transmission of infectious agent
Older				
Danazol (Danacrine, Sanofi-Synthelabo, New York, NY)	Approved for prophylaxis in adults	200 mg/d or less	17-α-alkylated androgen, mechanism of action 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)	Approved for prophylaxis	2 mg/d or less	(Same as above)	
Oxandralone (Oxandrin, Savient, Bridgewater, NJ)	Not FDA approved	10 mg/d or less	(Same as above)	
Methyl-testosterone (Android, Valeant, Bridgewater, NJ)	Not FDA approved	10 mg/d or less	(Same as above)	
Epsilon aminocaproic acid (Amicar, Xanodyne, Newport, Ky)	Not FDA approved	1-2 g TID	Antifibrinolytic, mechanism of action in HAE is unknown	Common: nausea, vertigo, diarrhea, postural hypotension, fatigue, muscle cramps, muscle injury; uncommon: thrombosis, seizures
Tranexamic acid (Lysteda, Ferring, Parsippany, NJ)	Not FDA approved	1 g BID	(Same as above)	

BID, Twice a day; *MASP,* mannose-associated serine protease; *TID,* 3 times a day.
*These are average doses that must be individualized.

tongue, or throat swelling should seek emergency medical care as soon as possible, even after initial self-treatment.

2.6. Assessment of on-demand treatment efficacy.

Realistic expectation of treatment efficacy should be discussed with patients. On-demand treatments work well to prevent swelling attack from progressing further; however, the swelling present at the time of treatment may take time to resolve even after treatment. Therefore, treating earlier in the attack results in better control of symptoms. Once treatment has been initiated, onset of treatment effect may take 30 to 60 minutes. In general, a second dose of the on-demand treatment is not warranted unless the attack begins worsening again.

Section 3. Prophylactic treatment. In addition to treating acute 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 number and severity of angioedema attacks (long-term prophylaxis). The medications used for HAE prophylaxis are shown in Table II.[10,24-28] Because there are significant differences in route of administration, adverse effect profiles, and cost among the prophylactic medications, patient preference needs to be considered in the selection of the most appropriate therapy. The HAEA MAB makes the following recommendations regarding prophylactic treatment.

3.1. Need for short-term prophylaxis.

Trauma and stress are well-known provocateurs of angioedema attacks.[7] 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 medical, surgical, or dental procedures; however, relatively little is known about the risk of swelling after these procedures. A large retrospective study found a 19.9% risk of swelling after a tooth extraction. The risk of swelling was 21.5% in patients who did not receive any prophylaxis and fell to 16% and 7.5% in patients who received 500 or 1000 units of C1INH 1 hour before the dental extraction.[29] The extent of the local trauma may influence the decision about whether to treat the patient prophylactically. C1INH given for short-term prophylaxis should be administered 1-12 hours before the stressor. Anabolic androgens used for short-term prophylaxis should be started 7-10 days before the stressor. It is critically important that effective on-demand treatment be available whether the patient is given short-term prophylaxis or not.

3.2. Need for long-term prophylaxis. The decision about when to use long-term prophylactic treatment cannot be made on rigid criteria but should reflect the needs of the individual patient. Decisions regarding which patients should be considered for long-term prophylaxis should take into account attack frequency, attack severity, comorbid conditions, access to emergent treatment, and patient experience and preference. Because disease severity may change over time, the need to start or continue long-term prophylaxis should be periodically reviewed and discussed with the patient.

3.3. Dosing. It is impossible to predict the optimal dose of a long-term prophylaxis medication *a priori*. Furthermore, the optimal dose is not predicted by the C4 or C1INH levels but must be determined clinically. Prophylactic medications should be titrated to the lowest effective dose that controls disease activity and maintains normal quality of life.

3.4. Special considerations in the use of androgens. Although anabolic androgens (17-α-alkylated androgens) have been successfully used for prophylaxis for many years, they can cause dose-related adverse effects that may be significant. It is important to avoid the use of anabolic androgens for long-term prophylaxis in patients under the age of 16 years or in pregnant or breastfeeding women. The use of anabolic androgens should also be avoided when the patient does not tolerate them or in patients who experience troubling adverse effects. All patients receiving attenuated androgens need to be carefully followed-up for the potential of medication-related adverse effects. It is the position of the HAEA MAB that these medications should not be used in patients who express a preference for an alternative therapy and that patients should not be required to fail androgen therapy as a prerequisite to receiving prophylactic C1INH concentrate.

3.5. Special considerations in the use of C1INH concentrates. Plasma-derived C1INH concentrate has been shown to be both safe and effective for the prophylactic treatment of HAE; however, repeated intravenous administration can result in loss of readily accessible veins unless great care is taken to preserve the veins. In some cases, indwelling ports have been placed to allow easier intravenous access. Indwelling ports pose a significant risk of thrombosis and infection.[30] Although 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 intravenous administration of a medication 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. Increasing grip strength also can result in better and enlarged veins.

3.6. On-demand treatment. Patients on a prophylactic treatment regimen must also have access to effective on-demand treatment of acute attacks.

Section 4. Patient monitoring. HAE disease severity is highly variable, both among patients but, also over time in an individual patient.[3,31] Patients may be symptom free for years, then begin to have attacks. Conversely, availability of effective treatment options or other stress reducers may lessen anxiety and decrease attack frequency. In addition, some of the medications used to treat HAE may have adverse effects on the patient. For these reasons, the HAEA MAB recommends that physicians who are treating patients with HAE must carefully and regularly monitor their patients and make the following recommendations (summarized in Table III).

4.1. Monitor attack frequency and severity. Attack frequency and severity should be evaluated by the physician on an ongoing basis. The US HAEA MAB recommends that patients keep a record of all of their attacks, regardless of severity (mild, moderate, or severe). These logs or attack records should be maintained in a format (eg, electronic, paper) that is decided upon between the patient and physician and is easy for the patient to complete. Regardless of format, these records should specifically identify the following 3 domains: description of attack, treatment of attack, and response to treatment. Specific key points to address for each of these 3 domains are illustrated in Table IV. Physician knowledge of the patient's HAE attack frequency and severity is critical to determine the ongoing management of HAE for several reasons. One, it will allow the physician to monitor the use of on-demand therapies and to potentially suggest the use of a prophylactic regimen to patients (see Section 4.2. Monitor use of on-demand medications). Two, it will capture potential difficulties in administration of rescue medications. Three, it may identify attacks (potentially less severe) that may not be otherwise appreciated by the patient and may be considered by the patient as a "normal" part of their disease. Awareness of these less-severe attacks may lead the physician to consider alternative therapies, including prophylaxis, or to encourage the patient to treat more of his or her attacks. Data captured from the attack logs are considered vital information to be documented in the patient's medical records. This attack diary should be provided to the treating physicians and reviewed on a regular basis by a means (ie, in person or electronically) predetermined between the patient and the physician. At present, there are no validated questionnaires specific for HAE to quantify attack severity or disease control. HAE attack severity is a subjective measure, which can frequently be determined by patients, often by past experience, or once the current attack has progressed. The attack severity, however, may be characterized by the impact on a patient's ability to perform his or her normal daily activities[16]: no limitations (mild), able to perform activities with some limitations (moderate), or unable to perform activities (severe). The location of the attack may have an impact on the severity, eg, an airway attack is likely to be considered severe. However, many patients experience severe limitations with extremity attacks, and, therefore, peripheral attacks may also be classified as severe.[23] Several different scales were used to assess disease severity and response to medications in the HAE clinical trials, including visual analog scales,[8,32] Likert-type scales,[10,11] and composite scales.[9] At present, there is no blood test that can accurately determine a patient's HAE severity or control of the disease. There is no relationship between disease severity and C4-, C1INH antigen level, and function,[7] and the members of the MAB do not recommend that these tests be repeated for monitoring purposes after the diagnosis of HAE has been established.

4.2. Monitor use of on-demand medications. Physician knowledge of when patients may require and when they have administered on-demand treatment is a key aspect of optimal

TABLE III. 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	×			
Discuss HAE triggers	×	×		
Develop or review treatment action plan	×	×		
Develop HAE swelling attack log	×			
Establish best method to contact physician	×			
Review HAE medication options	×	×		
Prescribe on-demand treatment	×	×		
Review treatment options during travel	×	×		
Review need for preprocedural prophylaxis	×	×		
Review other current medications	×	×		
Assess impact of HAE on quality of life	×	×		
Discuss screening of family members for HAE	×			
Monitor on-demand therapy				
Review swelling attack log		×		
Review frequency of treatment		×		
Review effectiveness of treatment		×		
Verify 2 unexpired doses available		×		
Monitor for medication adverse effects				
Androgens				
LFTs, UA, lipid profile			×	
Liver ultrasound*			×*	×
Blood pressure, weight, signs of virilization			×	
Antifibrinolytics				
LFTs. creatine level, CPK level, aldolase, UA			×	
Ophthalmologic examination				×
pd-C1INH				
Address issues with administration		×		
Ecallantide				
Assess for hypersensitivity reactions		×		
Icatibant				
Assess injection site reactions		×		
Visit with HAE specialist	×			×

CPK, Serum creatine phosphokinase; *LFT,* liver function tests*; UA,* urinalysis.
*If the androgen dosage equivalent is more than danazol 200 mg/d or equivalent.

management of HAE and highlights the importance of a strong patient-physician partnership and communication. When patients self-administer or receive on-demand medications, there must be a plan to have the patient report this use in a timely manner, as discussed above. It may also be beneficial for health care professionals who administer on-demand therapy either in a medical care setting or by a home nursing service to report these treatments to the expert HAE physician. Frequent use of an on-demand medication, deterioration of disease control, or a decreased quality of life should signal the need for reevaluation and a remediation plan.[13,16] The physician should first search for a potential trigger that exacerbates HAE, including the addition of an angiotensin-converting-enzyme inhibitor or estrogen-containing medications, emotional stress, infections, or potential physical traumas (which may include relatively mild trauma or pressure that is repetitive). The HAE provider should also discuss with the patient the timing of administration of rescue medication in relationship to attack onset. Administration of rescue medication is likely more beneficial if given earlier during the course of an attack rather than later.[33] There is variability in the response to any given on-demand medication, and some patients may not respond as well to a particular medication. A lack of response should prompt a reassessment of the patient to evaluate for other potential causes of swelling or abdominal pain. At present, there are no laboratory tests to indicate which medications are more appropriate for certain patients. In some patients, failure to achieve adequate control of HAE will suggest the need to institute a prophylactic medication.[13,16] If patients already treated prophylactically are using frequent on-demand medication for "break-through" swelling attacks, then they should be asked if they have extended the days between administration or lowered the dose of the medication itself. If there are no changes, then it may be beneficial to shorten the frequency of medication administration or increase the dose of therapy. The US HAEA MAB strongly recommends that the treating physician and the patient establish a partnership that will ensure appropriate medical management and clinical follow-up, and will allow for appropriate refills of rescue medications, documented by attack history.

TABLE IV. Recommended data collection for angioedema attacks

Domain	Question
Description of attack	Date and time of onset
	Location of swelling
	Prodrome (yes/no; if yes, then describe)
	Triggering event if known
	Severity based on impact on activities
Treatment of attack	Was on-demand treatment given (yes/no; if yes, give details)
	Date and time treatment given
	Any problems or adverse events associated with treatment
	Date and time when symptoms began to improve
	Date and time when symptoms were completely resolved
Response to treatment	Was physician contacted
	Were emergency department or hospital services required
	Was there a need for additional therapy (including a second dose of initial medicine, pain medication, antiemetic, fluids, etc)

4.3. Monitor adverse medication effects. All patients taking HAE medications, whether on-demand or prophylactically need to be periodically monitored for potential adverse effects of the medications. Patients using anabolic androgens should be evaluated every 6 months by a history and physical examination (in particular, weight, blood pressure, signs of virilization) and blood work, including liver enzymes, lipid profile, urinalysis, and a hepatic ultrasound (ultrasound can be once every 12 months if the androgen dose is $\leq$200 mg/d danazol equivalent).[13,14,16,17] Although not a standard treatment for HAE in the United States, physicians should be knowledgeable about monitoring antifibrinolytic therapy. Patients prescribed antifibrinolytics should have renal and liver function, urinalysis, serum creatine phosphokinase level, and aldolase testing every 6 months, and an annual ophthalmologic examination to check eye pressure.[13] There are no specific guidelines for monitoring other HAE therapies. The potential adverse effects of plasma-derived C1INH concentrate are minimal; however, long-term data are needed to confirm results from clinical trials. Patients using ecallantide should be asked about a hypersensitivity reaction to its administration.[34] Many patients experience pain and erythema at the injection of icatibant and should be questioned if this has occurred.[8]

4.4. Continuous patient education. Follow-up visits present an important opportunity to reinforce patient education, which includes a discussion that the natural history of HAE is not always predicable and that all patients with HAE are at risk for an airway attack, regardless of the history.[12,35] The "treatment action plan" should be developed at the initial visit and reviewed at each follow-up visit. Specific measures that should be assessed include the treatment options, how patients will have ready access to their rescue medications, what the course of action should be if the rescue medication does not provide relief, and how to access medical personnel familiar with HAE during an attack.[36] Furthermore, patients should be reminded that, even if they are taking prophylactic medication, they may have a "break-through" attack and must be prepared to treat it. The MAB recommends that potential triggers of HAE be reviewed when patients come into the office for visits. This includes an updated list of current medications to ensure that patients are not taking an angiotensin-converting-enzyme inhibitor or estrogen replacement. Re-education during follow-up visits should affirm that patients are aware that surgical procedures and some invasive dental work can trigger attacks, and that short-term prophylaxis is likely indicated. Because infections may trigger HAE in some patients, patients should receive a yearly influenza vaccination.[14] Because invasive dental work may trigger or exacerbate HAE, good dental care may prevent the need for these procedures or prevent oral infections. Before invasive dental work or surgery, the HAE provider should contact the dentist or surgeon to address questions regarding HAE and its management, including potential short-term prophylaxis and the administration of an on-demand therapy in case of an HAE exacerbation. The MAB also recommends that patients have on hand at least 2 doses of on-demand therapy. The expiration date of these medications must be noted. Physicians must also be aware if there is any change of insurance that may affect medication dispensing. Because many patients can self-administer rescue medications, the physician should address whether there have been any difficulties in administration. Follow-up visits offer opportunities for retraining as well as ensuring that other family members or friends can administer medication in case the patient is unable to do so. For patients who receive medication from a visiting nursing service at home or at a local infusion center, discussion of any issues regarding these treatments should take place during follow-up. Management of HAE during travel should be reviewed. Specific measures to discuss include the transport of emergency rescue medications on the airplane and storage in hotels or other travel destinations. In addition, it may be beneficial for the primary HAE provider to coordinate a site of care at the patient's travel destination (if available). This site may be another health care provider familiar with the management of HAE, an emergency department or an infusion center. For patients who are treated prophylactically with C1INH and who are not self-infusing, arrangement for medication administration needs to occur before travel, and/or the timing of prophylactic medication may need to be adjusted. Follow-up visits, in particular, for children with HAE, should ensure that the child's school is informed about HAE and be given written information that clearly explains the disease.[37] It is critical that the school also knows how to initiate the "emergency plan" if the child has an attack. In some cases, it may not be possible for school medical personal to administer intravenous medications, therefore, a plan should be developed *a priori* on how to give these medications.

4.5. Timing of follow-up visits. The need for follow-up visits in the clinic will vary, depending on several patient-specific factors, including disease severity, type of therapy used, response to therapy, and the patient's access to the clinic. For patients who are well controlled, return visits may occur once every 6-12 months.[14,16,17] When treatment (either for acute attacks or long-term prophylaxis) is initiated or the dosing is changed, there should be communication between the patient and physician monthly for the first 4 months or until it is clear that adequate control has been achieved.

4.6. Improving quality of life. The unpredictable nature and severity of angioedema attacks are associated with significant burden of the disease and, subsequently, affect the quality of life of these patients. Providing effective on-demand or prophylactic treatment is an important step toward improving quality of life of patients with HAE and relieving the burden of this disease.

CONCLUSION

The options for treatment of HAE have undergone a dramatic change in the past 5 years. We now have safe, specific, and effective medications for both on-demand and prophylactic treatment of HAE. Although these developments have vastly improved the lives of patients with HAE, optimizing treatment plans have become considerably more complex. Questions about which attacks to treat, when attacks should be treated, what medications should be used, and when to use prophylactic treatment must be addressed. The US HAEA MAB recommends that these and other issues be addressed by using a comprehensive management plan developed between an expert HAE physician and the patient, in collaboration with local medical providers and emergency departments. Patient education and *a priori* planning to remove logistical barriers to treatment should occur during the initial visit after diagnosis as well as regularly during subsequent progress visits. Effective communication between the physician and the patient is essential for recognizing when HAE is not well controlled, which requires the management plan to be changed. Each patient is different and requires his or her own plan. Each patient should expect that his or her HAE can be well controlled, thereby giving him or her the opportunity to lead a normal life.

The US HAEA MAB anticipates that new medications will become available for the treatment of HAE and that our knowledge about the optimal use of all of these medications will continue to improve. Thus, we recognize that these guidelines may change over time. Nevertheless, we suggest that the guidelines outlined in this article represent the best common starting point for treating patients with HAE in 2013.

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