
Hereditary angioedema: a current state-of-the-art review, IV: short- and long-term treatment of hereditary angioedema: out with the old and in with the new?

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Objective: To provide a context to understand the opportunity for novel therapeutic modalities to transform the treatment of hereditary angioedema (HAE).

Data Sources: MEDLINE and PubMed were searched to identify studies involving current treatment of HAE in the United States.

Study Selection: Studies were selected based on their relevance to the treatment of HAE.

Results: The current HAE treatment strategy is far from satisfactory, and its limitations create an unmet clinical need. Current prophylactic treatment exposes patients with HAE to significant risk of adverse effects, and the efficacy of prophylactic treatment, although generally good, is far from perfect.

Conclusions: No specific treatment is currently available in the United States for acute HAE attacks that will reliably work, resulting in a significant unmet clinical need. The emergence of several promising drugs for the treatment of HAE attacks is, thus, an extraordinarily important development in the management of these patients.

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INTRODUCTION

Hereditary angioedema (HAE) is an autosomal dominant disease characterized by recurrent episodes of angioedema. The prevalence of HAE is not known, but it has been estimated to range from 1:10,000 to 1:150,000 in the general population,¹ suggesting that there are 2,000 to 30,000 affected patients in the United States. The pathophysiologic basis of HAE as a deficiency of complement 1 (C1) inhibitor was discovered independently by Landerman et al² and Donaldson and Evans.³ The fundamental abnormality in HAE was subsequently shown to be a mutation of the C1 inhibitor gene, resulting in decreased synthesis of functional protein.^{4–6}

In the more than 40 years since the seminal observation that patients with HAE are deficient in the plasma protein C1 inhibitor, impressive progress has been achieved in understanding the biochemical and molecular biological features of HAE. However, these advances in elucidating the pathogenesis of HAE have not been accompanied by equivalent progress toward improving the clinical management of HAE, particularly in the United States. Recent developments in the pharmaceutical industry, however, provide encouraging signs that new therapeutic options will shortly become available for the treatment of HAE. To provide a context for understanding

the opportunity for novel therapeutic modalities to transform the treatment of HAE, this article reviews the current diagnosis and treatment of HAE and highlights areas where improvements are urgently needed.

CLINICAL HISTORY OF HAE

Attacks of angioedema in HAE are distinct from other forms of angioedema and can often be suspected based on history. A positive family history of angioedema is present in most patients, although a few have negative family histories with de novo C1 inhibitor mutations.⁷ Patients with HAE typically begin to swell in childhood and often experience increased symptoms beginning about the time of puberty.⁸ Patients with HAE then typically continue to experience recurrent attacks of angioedema throughout their lives, although some may report decreased symptoms with older age. Most attacks are sporadic, without clear initiating events. Several stimuli, however, have been repeatedly associated with precipitating attacks of HAE, particularly trauma (even minor trauma) and stress.

Attacks of HAE are often heralded by prodromal symptoms involving the area that subsequently swells, and many patients sense when they are about to have an attack. A few patients with HAE also experience erythema marginatum, a characteristic serpentine macular nonpruritic rash, at the beginning of the attack. This erythema marginatum is clearly different from urticaria and should not be confused as such.

The swelling is nonpitting and nonpruritic, most frequently involving the extremities or bowel and sometimes affecting the genitalia, face, tongue, and larynx. Angioedema of the

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larynx can occlude the airway and result in asphyxiation. Many patients with HAE are reported to have died of laryngeal angioedema, and this continues to be a significant problem. In a large retrospective study of 131,110 attacks in 221 patients with HAE, Bork et al⁹ found that just fewer than 1% of attacks involved laryngeal angioedema but that more than 50% of patients had experienced a laryngeal attack at some point. Patients with HAE continue to die of laryngeal attacks.^{10,11}

The angioedema attacks in HAE are relatively prolonged, with the typical episode worsening for the first 24 to 36 hours, then slowly resolving during the subsequent 36 to 48 hours. Severe attacks often last 3 to 5 days. Attacks frequently result in hospitalization, may lead to inappropriate intra-abdominal surgery, and can be life-threatening when involving the airway.^{1,9} Abdominal attacks were reported in more than 93% of patients and composed almost 50% of all angioedema attacks.⁷ The disease, thus, imposes an enormous burden on patients and their families, often preventing them from leading a productive life. After resolution of an attack, most (but not all) patients with HAE are relatively resistant to another episode of angioedema for approximately a week, a phenomenon that has been called the *refractory period*. Thus, many patients with untreated HAE have a natural attack frequency of every 10 to 14 days.

The diagnosis of HAE is often suggested by the history. Differential diagnosis includes other forms of angioedema, such as idiopathic angioedema, acquired C1 inhibitor deficiency (ACID), angiotensin-converting enzyme inhibitor-associated angioedema, acute allergic angioedema, nonsteroidal anti-inflammatory drug-associated angioedema, and episodic angioedema associated with eosinophilia.¹² Table 1 lists the distinguishing features of the most difficult-to-differentiate angioedema syndromes: HAE, ACID, and idiopathic angioedema. In general, all patients with recurrent angioedema without urticaria should be tested to exclude the diagnosis of HAE.

LABORATORY DIAGNOSIS OF HAE

A definitive diagnosis of HAE requires a laboratory diagnosis establishing C1 inhibitor deficiency. Two distinct HAE sub-

types are distinguished based on plasma levels of C1 inhibitor. Type 1 HAE (approximately 80%–85% of patients with HAE) is characterized by low antigenic and functional C1 inhibitor levels¹³; type 2 HAE (the other 15% of patients with HAE) is characterized by normal or elevated C1 inhibitor concentrations with low C1 inhibitor functional activity due to the secretion of a dysfunctional C1 inhibitor protein.¹⁴ Type 1 and type 2 HAE cannot be clinically distinguished but must be differentiated by the laboratory profile.

Decreased functional levels of C1 inhibitor allow continuous activation of the classic complement and contact systems.^{15–17} Activation and consumption of the early complement components, C4 and C2, are used to help establish the diagnosis of HAE. In contrast, the C1q level is normal in HAE but reduced in ACID. Thus, a diagnosis of HAE is confirmed by low C1 inhibitor functional levels and decreased C4 levels together with a normal C1q level. Because measurement of the C1 inhibitor antigenic level is often more accurate than that of the C1 inhibitor functional level, it is frequently used in place of the functional assay to make the diagnosis; however, only approximately 85% of patients with HAE (type 1) will have reduced C1 inhibitor antigenic levels. Therefore, the functional test must be used to confirm the diagnosis in patients with normal levels of C1 inhibitor. If this level is low, then patients have type 2 HAE.

Measuring serum C4 levels is effective for screening patients suspected of having HAE, and C1 inhibitor antigenic or functional tests can be avoided in most patients with normal C4 screening results. C4 levels are almost always low in untreated HAE, are usually low even in the face of prophylactic treatment, and are invariably low during attacks of angioedema.^{9,18,19} The C4 activation neoantigen C4d was demonstrated to be invariably elevated in patients with HAE¹⁸; however, this test is not always available. Table 2 provides the laboratory profiles of HAE, ACID, and idiopathic angioedema.

Several caveats need to be considered in the laboratory evaluation of HAE. First, the complement proteins being measured are labile, and results can be inaccurate if the samples are not processed and handled correctly. Thus, abnormal results should be confirmed. Second, complement

Table 1. Clinical Characterization of HAE

	HAE	ACID	Idiopathic
Angioedema	Yes	Yes	Yes
Urticaria	No	No	Usually
Most frequent age at onset	6–20 y	>50 y	Anytime
Family history	Usually	No	No
Underlying disease	No	Yes	No
Location of swelling	All	All	Especially face/lip
Precipitated by trauma	Yes	Yes	No
Duration of swelling, h	48–72	48–72	2–48
Responds to treatment with epinephrine, antihistamines, or corticosteroids	No	No	Yes

Abbreviations: ACID, acquired C1 inhibitor deficiency; HAE, hereditary angioedema.

Table 2. Laboratory Characterization of HAE

	HAE	ACID	Idiopathic angioedema
C1 inhibitor functional level	Low	Low	Normal
C1 inhibitor antigenic level	Low (85%)/normal (15%)	Low	Normal
C4 level	Low	Low	Normal
C1q level	Normal	Low	Normal

Abbreviations: ACID, acquired C1 inhibitor deficiency; HAE, hereditary angioedema.

testing is not dependable in newborns and infants (<1 year old) owing to changing normal levels during development. Third, C4 levels are occasionally normal between attacks, and if the diagnosis of HAE is strongly suspected, the patient should be retested during an episode of angioedema. Occasionally, genetic testing is needed to establish the diagnosis.

A third type of HAE has been described and is called type 3 HAE, HAE with normal C1 inhibitor function, or estrogen exacerbated angioedema. Initially reported to affect women and to often be exacerbated by estrogens,^{20,21} subsequent studies^{22,23} have described affected males and attacks in the absence of hyperestrogen states. It does seem clear, however, that C1 inhibitor is not involved in type 3 HAE. Several affected kindreds have been shown to have coding mutations in codon 309 of Hageman factor (coagulation factor XII),²⁴ although other kindreds with type 3 HAE do not have this mutation. The Thr to Lys mutation at this codon was recently demonstrated to result in a gain-of-function mutation that is regulated by estrogen and might, therefore, explain the pathogenesis of this disease in that particular kindred.²⁵ Currently, there is no reliable way to confirm a diagnosis of type 3 HAE in a kindred with recurrent angioedema and normal C1 inhibitor function. It is likely that the so-called type 3 HAE kindreds will turn out to be a heterogeneous group with diverse underlying pathophysiologic features.

CURRENT TREATMENT OF HAE

Because of the significant morbidity and mortality associated with HAE, a strategy involving careful treatment of acute attacks and prevention of HAE attacks is essential for proper management of these patients. This article briefly reviews the current treatment protocols available in the United States. The treatment of HAE is typically divided into 3 areas: long-term prophylaxis, short-term prophylaxis, and treatment of acute episodes of angioedema.

In addition to the pharmacologic treatment of HAE, several additional areas merit attention due to their ability to affect HAE disease severity. Stress and trauma are clearly defined provocateurs of swelling in HAE, and patients should be informed of these associations and make efforts to limit them. Because of their ability to increase bradykinin-mediated effects, angiotensin-converting enzyme inhibitors need to be avoided in patients with HAE.²⁶ Birth control pills and hormone therapy also frequently exacerbate disease severity in women.²⁷

Long-term Prophylaxis of HAE

The goal of long-term prophylaxis in HAE is to decrease the frequency and severity of swelling attacks. The frequency and severity of angioedema attacks are highly variable in patients with HAE, ranging from attacks occurring as often as twice per week to immunochemical evidence of HAE without symptoms. Thus, the first question concerning long-term prophylaxis that should be addressed is whether the patient requires prophylactic treatment. Patients with frequent attacks or a history of serious attacks involving the upper airway should, in general, be treated prophylactically. Patients with significant swelling occurring more frequently than once every 3 months may be good candidates for long-term prophylactic therapy, although it is the impact of the episodes on the patient's ability to lead a normal life that is the deciding factor. The decision of whether to initiate long-term prophylactic therapy is also affected by the location of attacks (airway attacks causing increased concern) and the accessibility of the patient to appropriate medical care in case of a serious swelling episode.

Two modalities of treatment are available for long-term prophylaxis of HAE: anabolic androgens and antifibrinolytics.²⁸ In 1960, Spaulding²⁹ published the first study of the beneficial impact of methyltestosterone. This observation was confirmed and extended in a pivotal 1976 study³⁰ using danazol to treat patients with HAE. The efficacy of antifibrinolytics for HAE was first reported in an uncontrolled study³¹ and was later confirmed in a double-masked placebo-controlled study.³²

The best tolerated and most effective long-term prophylactic drugs for HAE are 17- α -alkylated anabolic androgens, which increase C1 inhibitor and C4 plasma levels and decrease HAE attacks.³⁰ The role and safety of these agents in the treatment of HAE are discussed in a separate article in this supplement.³³ Danazol, stanozolol, and oxandralone are synthetic 17- α -alkylated androgens that are widely used for this purpose, and they are less virilizing than methyltestosterone.³⁴ When initiating treatment with an anabolic androgen (10 mg/kg per day), the physician can start with a high dose (danazol, 600 mg/d) and taper down or with a low dose (danazol, 50–200 mg/d) and increase as required. The best strategy typically is determined by the physician's sense of whether it is more important to control the angioedema attacks as rapidly as possible or to minimize the potential adverse effects. In either case, the final dose of anabolic

androgens used to treat HAE should be titrated to find the lowest dose that confers adequate prophylaxis, typically 50 to 200 mg of danazol daily or every other day. Detailed recommendations for dose titration have recently been published.³⁵ Although all the anabolic androgens increase C1 inhibitor and C4 levels, symptomatic benefit is generally achieved at doses less than those required to significantly change the complement levels. Therefore, it is important to base the dosage on the clinical effect and not on the laboratory values. Most patients with HAE tolerate anabolic androgens at the doses described previously herein³⁶; however, sustained use at higher doses often results in significant adverse effects. The adverse effects of anabolic androgens are dose related, with the most important being hepatotoxicity and virilization.³⁷ Anabolic androgens have also been reported to cause a variety of other adverse effects, including weight gain, menstrual abnormalities, acne, altered libido, mood alteration/anxiety, hypertension, and proatherogenic abnormalities in the lipid profile.³⁸ Patients taking anabolic androgens should have their liver enzyme levels checked every 6 months. Evidence of hepatic injury should precipitate tapering or discontinuation of the drug, with documentation of normalization of the hepatic test results. Because hepatic adenomas have been reported as a consequence of anabolic androgen use³⁹ and hepatocellular carcinoma has been suggested to be associated with danazol treatment,⁴⁰ ultrasonography of the liver is warranted in the presence of persistently elevated liver enzyme levels. Although many patients complain of androgen-induced adverse effects, most patients with HAE can obtain at least moderate benefit from anabolic androgens, with an acceptable risk profile.

The antifibrinolytic drugs ϵ -aminocaproic acid (Amicar; Amgen, Thousand Oaks, California) and tranexamic acid are frequently, but not always, effective in preventing angioedema attacks in HAE.^{32,41,42} The mechanism of their efficacy in HAE is unknown, and they do not increase plasma C1 inhibitor levels. Because anabolic androgens are more reliably effective for the control of HAE, they are generally the treatment of choice. Antifibrinolytic drugs are often reserved for patients who do not tolerate anabolic androgens. The typical therapeutic dose of ϵ -aminocaproic acid is 1 g orally 3 to 4 times daily. Adverse effects of antifibrinolytic drugs include nausea, diarrhea, vertigo, postural hypotension, fatigue, muscle cramps/weakness with an increase in muscle enzyme concentrations, possibility of enhanced thrombosis, enhanced tumor growth, and concerns regarding teratogenicity. Tranexamic acid is more potent than ϵ -aminocaproic acid, with fewer adverse effects⁴³; however, it is not currently available in the United States.

Short-term Prophylaxis of HAE

Short-term prophylaxis should be used to prevent attacks of angioedema when a patient with HAE is at high risk for swelling, particularly before expected trauma, such as surgery, other invasive medical procedures, or significant dental procedures. To avoid potentially catastrophic swelling, it is

critically important that all patients with HAE be made aware of the need for short-term prophylaxis in these situations. High-dose anabolic androgen therapy (danazol, 200 mg 3 times daily) begun at least 1 week before the procedure affords moderate protection.³⁵ Alternatively, the patient can be infused with 2 U of fresh frozen plasma several hours before the procedure,⁴⁴ an approach that provides better protection.

Treatment of Acute HAE Attacks

Attacks of angioedema in patients with HAE involve subcutaneous tissues (primarily involving the extremities, genitalia, or face), the intestine, and the airway. Attacks typically, but not invariably, follow a trajectory in which the angioedema increases for 24 to 36 hours then slowly decreases during the following 48 to 72 hours. A key concept in approaching the treatment of acute HAE attacks is that the angioedema does not respond reliably to the drugs used in treating other forms of urticaria/angioedema, such as antihistamines, epinephrine, and corticosteroids. Although epinephrine, in particular, may have a transient effect on swelling, it does not alter the course of the attack.

Currently, there is no drug approved in the United States that is predictably effective for the treatment of acute HAE attacks. Anecdotal and published experiences suggest that administration of fresh frozen plasma can abort ongoing HAE attacks by replacing plasma C1 inhibitor levels.⁴⁵ There is, however, a theoretical and demonstrated risk that fresh frozen plasma can worsen acute swelling, possibly due to replenishment of plasma proteases and substrates involved in the generation of peptides that mediate angioedema.^{46,47} Regardless, the use of fresh frozen plasma seems to be safe but not always effective. ϵ -Aminocaproic acid has also been used intravenously for acute episodes of angioedema, and anecdotal reports suggest that it may be modestly helpful; however, there is no published evidence, to our knowledge, that it provides significant benefit. Anabolic androgens, which are effective prophylactic agents, require at least 1 to 2 days before they begin to be effective and, therefore, are not useful in the short-term treatment of attacks.

The management of acute attacks is, thus, primarily concerned with symptomatic control of the swelling. Acute angioedema of the extremities does not typically require treatment, although angioedema of the feet or dominant hand can be temporarily disabling and, thus, cause significant morbidity. Abdominal attacks often present with severe pain and nausea and significant dehydration, sometimes accompanied by significant hypotension. Management of these attacks involves aggressive intravenous replacement of fluid and control of pain and nausea with parenteral narcotic and antiemetic drugs. Oropharyngeal attacks may lead to death secondary to asphyxiation and, therefore, require hospitalization for careful monitoring of airway patency. If the airway is threatened, the patient should be intubated by an experienced physician, with the capability for emergency tracheostomy immediately available.

CURRENT UNMET NEEDS AND FUTURE TREATMENT OF HAE

The current HAE treatment strategy summarized herein is far from satisfactory, and its limitations create an unmet clinical need. Current prophylactic treatment exposes patients with HAE to significant risk of adverse effects, and the efficacy of prophylactic treatment, although generally good, is far from perfect. Treatment of pregnant women and children presents particular difficulties. Androgens may interfere with normal sexual maturation, and their effects on the fetus are unknown. Angioedema frequency may not change or may decrease during pregnancy; however, some women experience an increase in attacks during pregnancy (almost all women are protected from swelling during labor and delivery). The virilization effects of anabolic androgens, although relatively modest, are a significant issue for most women.

The most glaring deficiency in the armamentarium against HAE is in the treatment of acute attacks. No treatments are currently available in the United States that predictably work for acute angioedema attacks. All patients with HAE are at risk for severe episodes of angioedema (potentially including life-threatening attacks involving the airway). Without effective therapy for acute attacks, patients with HAE continue to experience significant morbidity and mortality. Many patients with HAE in the United States are, thus, either not adequately controlled using currently available therapy or require doses of medications that expose them to serious adverse effects. There is reason to believe that the clinical paradigm for treating HAE is about to change.⁴⁸

The advances in understanding the fundamental biological features of HAE have led to the development of a variety of novel therapies that are currently undergoing or have recently undergone clinical trials in the United States. These novel therapeutics fall into 2 classes: C1 inhibitor replacement therapy and therapy directed against the kallikrein-kinin system, discussed in a separate article in this supplement.⁴⁹

SUMMARY

The diagnosis of HAE should be considered in any patient with recurrent angioedema without urticaria. Confirmation of the diagnosis requires laboratory testing, with demonstration of low C1 inhibitor levels or functionality and low C4 levels. Treatment of patients with HAE should be individualized based on attack frequency and severity and on access to medical care. Most patients can be managed without long-term prophylaxis or by using low-dose anabolic androgens for long-term prophylaxis. Many patients, however, cannot adequately control their conditions without use of higher doses of anabolic androgens. Adverse effects from the use of anabolic androgens or antifibrinolytics are commonly experienced by patients with HAE and limit their acceptability. All patients with HAE, furthermore, are at risk for a severe episode of angioedema, potentially involving the airway. No specific treatment is currently available in the United States for acute HAE attacks that will reliably work, except possibly

fresh frozen plasma, resulting in a significant unmet clinical need.

The emergence of several promising drugs to treat HAE attacks is, thus, an extraordinarily important development in the treatment of these patients. It is likely that specific and effective treatment for HAE attacks will become available in the United States in the next few years. The emergence of newer, more effective therapy is expected to revolutionize the treatment of HAE and allow patients to begin to live normal lives, free from the fear of incapacitating or potentially fatal attacks of angioedema. Based on the expectation that these novel therapies will show significantly improved efficacy compared with the existing therapies, guidelines for improved management of HAE have been proposed to maximize patient well-being, promote individualized therapy, and minimize disruption of normal life by HAE.⁴⁸ When it comes to the treatment of HAE, it is indeed time to say “out with the old and in with the new.”

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