Hereditary Angioedema

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KEYWORDS

• Hereditary angioedema • C1-inhibitor • Bradykinin • Complement
• Quincke disease • Difficult airway

KEY POINTS

- HAE-C1-INH type I is due to a quantitative deficiency of C1-INH. HAE-C1-INH type II is due to C1-INH that has reduced function. In HAE where there is normal C1-INH, HAE-nl-C1-INH, mutations have been found in the genes that code for factor XII, plasminogen, HMWK, LMWK, and angiopoietin-1.
- In almost all cases of HAE, bradykinin is the final common product that leads to the development of angioedema.
- Clinical findings associated with need for definitive airway management include voice change, hoarseness, stridor, and dyspnea.
- Targeted treatment for acute HAE attacks focuses on decreasing the production of bradykinin through inhibition of kallikrein, and replacement of C1-INH, or by inhibiting the action of bradykinin on the bradykinin B2 receptor.
- In patients who have angioedema involving the tongue, soft palate, or floor of the mouth, the use of fiberoptic nasopharyngoscopy to help identify the presence of swelling of the deeper upper airway structures is recommended.

INTRODUCTION

Hereditary angioedema (HAE) is a rare, potentially life-threatening genetic disorder that presents with episodic swelling of the skin or mucosal tissue of the upper respiratory and gastrointestinal tracts. Heinrich Quincke[1] provided the first description of the disease in 1882, and its heritable nature was documented by William Osler[2] in 1888. Since those first descriptions made more than 100 years ago, there has been remarkable progress made in the classification, diagnosis, and treatment of HAE through a better understanding of the different pathophysiological processes that lead to its multiple types.

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Because of the risk of airway obstruction and the substantial morbidity that can be associated with attacks of HAE, it is important for the emergency physician to be aware of this disease and the mechanisms that underlie the treatment options that have become available. Since the first disease-specific medication was approved by the United States Food and Drug Administration (FDA) in 2008, there have been major advances in the range of treatment options that are focused on the kallikrein-kinin system, a pathway that leads to the formation of bradykinin. The action of bradykinin on its specific receptors located on the endothelial layer of blood vessels leads to increased vascular permeability and the extravasation of fluid into the surrounding structures.

It is important to distinguish HAE from other forms of angioedema that may be encountered in the emergency department (ED). Although the skills required for airway management are the same, the potential therapeutic agents used for treatment differ based on the underlying mechanism that leads to the development of angioedema. This article provides a comprehensive review of HAE and the therapeutic options that are now available.

EPIDEMIOLOGY AND TIMING OF DISEASE

The prevalence of HAE has been estimated to be approximately 1:50,000 to 1:100,000 individuals.[3] A recent systematic review of epidemiologic studies found 6 studies that were each focused on an individual country in Europe. The overall prevalence of HAE found in these studies was approximately 1:67,000 individuals.[4] Because of the homogeneity of the study populations included, it is unknown if this prevalence would hold true for the general worldwide population. If true in the United States, there would be approximately 5000 individuals who have HAE. HAE is classified as an orphan disease because of the fact that it affects fewer than 200,000 people in the United States.[5] HAE type 1 accounts for approximately 85% of cases, whereas type 2 accounts for ~15%. The prevalence of HAE with normal C1-esterase inhibitor (C1-INH) is not known but is likely a small fraction of the prevalence of type 1 and 2. No differences in prevalence have been found based on race and ethnicity.[6]

Patients with HAE are born with the genetic defect that accounts for the disease. In approximately 25% of cases of HAE, the mutation is de novo, and therefore, there will be no family history of the disease.[7] The phenotypic expression varies considerably among those affected. In a recent survey of patients identified through the US Hereditary Angioedema Association, the mean age of onset of symptoms was 12.5 years, but the mean age of diagnosis was 20.1 years. This suggests that the current delay in diagnosis is 8.6 years.[8] An earlier study found that 7% of patients had symptoms of HAE before age 1 and that those with earlier onset tended to have a more severe course of disease.[9]

CLASSIFICATION AND PATHOPHYSIOLOGY

The genetic defects that cause HAE are inherited in an autosomal dominant fashion. In most forms of HAE, the common mediator for the development of angioedema is bradykinin, a nonapeptide that functions as a potent vasodilator leading to increased vascular permeability and subsequent tissue swelling.[10] In the broadest sense, HAE can be classified based on the presence or absence of normal levels of functioning C1-INH. Most cases of HAE are due to reduced levels of normally functioning C1-INH (HAE-C1-INH). There are very rare cases of HAE where there are normal quantitative and functional levels of C1-INH (HAE-nl-C1-INH). In the predominant forms of HAE, there is either a quantitative deficiency (HAE-C1-INH type I) or reduced function

(HAE-C1-INH type II) of C1-INH because of a heterogeneous group of mutations of the SERPING1 gene located on chromosome 11 (11q12-q13.1).[11] More than 450 different mutations of the SERPING1 gene that lead to the development of HAE have been reported.[12] C1-INH, which belongs to the superfamily of serine protease inhibitors (serpins), exerts its activity at multiple points in the complement, fibrinolytic, and the contact activating systems (**Fig. 1**). When functional C1-INH decreases to less than a critical threshold of approximately 40%, the risk of an attack of HAE increases.[13] Restoration of C1-INH to levels higher than the 40% threshold has been associated with clinical protection against attacks.[14]

Two independent groups first described HAE with normal C1-INH levels and function in 2000.[15,16] In the past, HAE-nl-C1-INH was referred to as HAE type III; however, it is now known that there are multiple distinct causes of this form of HAE, so the classification HAE type III should not be used. Currently, there are 5 subtypes of HAE-nl-C1-INH based on the underlying genetic mutation that leads to the development of angioedema. These mutations lead to defects in the F12 gene that encodes for coagulation factor XII (FXII), the PLG gene that encodes for plasminogen,[17,18] the KNG1 gene that encodes for high- and low-molecular-weight kininogen,[19] and the ANGPT1 gene that encodes for angiopoietin-1.[20] The fifth subtype of HAE-nl-C1-INH is for patients with a genetic mutation that has not yet been determined. One possible cause of HAE-Unknown is due to a mutation in the MYOF gene that was described recently. This leads to a gain-of-function mutation in the myoferlin protein, an integral

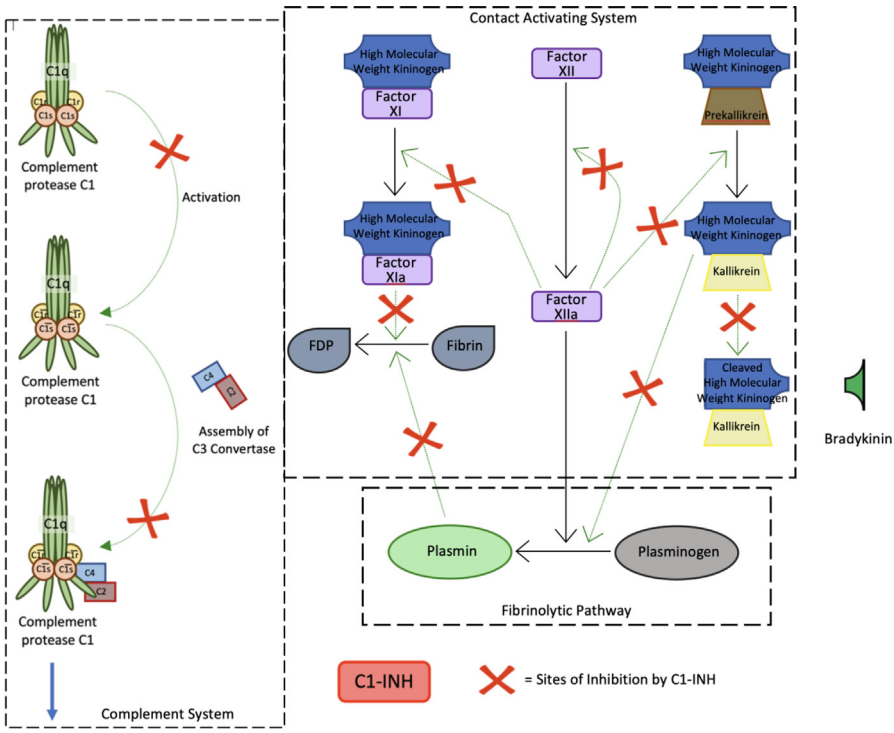

Fig. 1. The interplay between the complement, fibrinolytic, and the contact activating systems with sites of inhibition by C1-INH.

membrane protein of endothelial cells that modulates permeability through VEGF signal transduction.[21]

HAE owing to defective production of angiopoietin-1 (HAE-ANGPT1) is unique among the different types of HAE in that the underlying mechanism for the development of angioedema is not associated with overproduction of bradykinin. Instead, defective angiopoietin-1 loses its ability to effectively stabilize vascular endothelium leading to increased vascular permeability. Phenotypic expression is thought to be due to the mechanism of haploinsufficiency in which there is a loss of function in one of the genes coding for a protein that requires both genes to function to have complete function.[22]

In all forms of HAE, except HAE-ANGPT1, bradykinin is the mediator leading to the development of angioedema. Bradykinin binds to and activates the bradykinin B2 receptor on vascular endothelial cells, leading to dissolution of the adherens junctions formed by vascular endothelial-cadherin and loss of integrity of the cell membrane.[23] Under normal conditions, multiple enzymes, collectively known as kininases, quickly metabolize bradykinin. The most important of these enzymes is ACE, which is also known as kininase II. Other kininases include aminopeptidase P, carboxypeptidase M and N, neutral endopeptidase, and dipeptidyl peptidase IV.[24]

CLINICAL PRESENTATION

Clinically, HAE presents with transient asymmetric swelling of subcutaneous and submucosal tissues of the skin as well as the respiratory and gastrointestinal tracts. The subcutaneous swelling is neither pitting nor dependent. HAE is typically not associated with the development of urticaria or pruritus, a feature helpful in distinguishing from angioedema secondary to histamine release. Transient numbness or a tingling sensation in the affected areas has been reported during the prodromal period.[25] Up to one-half of patients with HAE develop a characteristic rash, erythema marginatum, during the prodromal period that is not pruritic but may be confused for an urticarial lesion.[26] Minor trauma and medical procedures, such as dental procedures, may precipitate acute attacks of HAE.[27] Other precipitants include infection and emotional stress. In many instances, an identifiable cause is not found.

The “attacks” of angioedema typically occur earlier in HAE than in acquired C1-INH deficiency (AAE-C1-INH). The symptoms of HAE develop at a median age of 12.5 years,[8] whereas AAE-C1-INH typically develops after the fourth decade of life.[28] In AAE-C1-INH, the lack of appropriate levels of functioning C1-INH develops secondary to the development of some other process, usually an autoimmune or malignant (often B-cell lymphoproliferative disorders or monoclonal gammopathy of undetermined significance) process.

The characteristic presentation of a patient presenting with an attack of HAE is pronounced swelling of the extremities, face, and oropharyngeal structures. Involvement of the upper airway may lead to obstruction and is a significant cause of morbidity and mortality in patients with HAE. Patients may present with complaints of tongue swelling, difficulty speaking and hoarseness, difficulty swallowing, and shortness of breath. Vital sign abnormalities may include tachycardia and hypotension secondary to third spacing. On physical examination, the patient may be noted to have voice change, difficulty tolerating secretions, and difficulty breathing. The extremities and face may be visually swollen. Clinical findings associated with need for definitive airway management include voice change, hoarseness, stridor, and dyspnea.[29,30] Isolated swelling of the genitals may be the only manifestation of an HAE attack.[31,32] Any structure in the oropharynx and deeper upper respiratory tract may show signs of

edema, and up to 50% of patients with HAE will experience laryngeal edema at some point.[33] The risk of asphyxiation is higher in patients with undiagnosed HAE than in those that have correctly been diagnosed.[34]

Although HAE is most recognizable for the disfiguring swelling of the face and extremities, abdominal pain is the most commonly encountered symptom.[30,35] Nausea, vomiting, and sometimes diarrhea will often accompany the development of abdominal pain, which may be described as crampy and colicky. Patients may develop abdominal distention and large-volume ascites. Hypotension and tachycardia may develop because of fluid shifts. Small bowel obstruction and intussusception are reported complications of angioedema of the bowel wall.[36,37] Patients with HAE have a higher likelihood than the general population to undergo abdominal surgery. A survey of German patients found that patients with HAE had a rate of appendectomy that was double that of those who did not have HAE (37.7% vs 18.9%).[38] Exploratory laparotomy may be performed when the diagnosis of HAE attack is not considered.[39,40] Recurrent bouts of unexplained abdominal pain may be the presenting feature in some cases of patients who were previously not diagnosed with HAE. The emergency provider should consider HAE in the differential diagnosis of patients presenting with recurrent abdominal pain.

DIAGNOSTIC EVALUATION

Laboratory Testing

In the ED, there is a limited role for laboratory testing. Most laboratory tests that are useful in the setting of HAE have long turnaround times such that the results of these tests are not available during the time that the patient is in the ED. There may be some value in sending certain tests during the ED visit, as the discriminatory value of these tests is best during an acute attack of angioedema. Such tests will be extremely helpful during follow-up appointments with an allergist.

The complement component 4 (C4) level is the most cost-effective screening test for HAE.[41] Decreases in the levels of C4 are not directly responsible for the increases in bradykinin levels that cause angioedema, but it serves as an indicator that there is a problem in the complement pathway. As described in the Classification and Pathophysiology section above, C1-INH is involved in multiple steps of the complement, fibrinolytic, and the contact activating systems. The first step in the classical complement pathway after activation of the C1 complex is the cleavage of C4 and then C2 to generate C4b and C2b, which together form C3 convertase.[42] This step is normally inhibited in the presence of C1-INH. Most cases of HAE are due to mutations in the SERPING1 gene that encodes the C1-INH protein. Therefore, in most cases, the level of C4 will be low during an acute attack; however, during normal periods, the sensitivity of C4 is decreased to between 81% and 96%.[43–45]

Quantitative and functional measurements of C1-INH antigen are used to confirm or exclude the diagnosis of HAE and to differentiate HAE-C1-INH type 1 from type 2. C1-INH antigenic levels are quantified by radial immunodiffusion (RID), turbidimetry, or nephelometry methods.[46] The method of testing is determined by local laboratory test demands and cost considerations. The choice can have substantial impact on the time to result, as the RID method is more time consuming.[47] In HAE-C1-INH type 1, both the quantitative and the functional levels are less than 50% of normal. Results of C1-INH testing in infants and pregnant women should be interpreted with caution, as C1-INH production does not reach normal rates until after the age of 1 year and because of the transient decrease in C1-INH quantity resulting from the increase in plasma volume normally seen during later stages of pregnancy.[48,49]

In HAE-C1-INH type II, quantitative levels of C1-INH are normal or elevated; however, C1-INH function is decreased. In laboratory measurements, C1-INH function is expressed as a percentage of the value found in normal subjects. In the United States, the only test approved by the FDA to measure C1-INH function is an enzyme-linked immunosorbent assay (ELISA) that measures the ability of C1-INH to bind C1s. For the ELISA test, C1-INH function is classified as abnormal if the percentage of mean normal is 40% or less. It is considered equivocal at 41% to 67% and normal at greater than 67% of mean normal.[50] Alternatively, a chromogenic assay directly measures the ability of C1-INH to inhibit the C1 complex. Measurements less than 70% are considered abnormally low.[51] Recent guidelines from the US Hereditary Angioedema Association Medical Board recommend chromogenic testing if initial testing is equivocal.[52] The chromogenic assays are approved for use in Europe, but in the United States, these tests can only be performed for research purposes and in specialist laboratories.[53]

Patients with HAE-nl-C1-INH have normal levels of C4, C1-INH antigen, and C1-INH function. Most cases are due to a genetic defect in the gene encoding for FXII. A commercially available polymerase chain reaction test is available to identify these mutations.[54] Specialized genetic testing is required for cases of HAE-nl-C1-INH due to mutations in the genes for plasminogen, high- and low-molecular-weight kininogen, or angiopoietin-1. Informed consent from the patient is required for all types of genetic testing.

In contrast to HAE, patients who are not born with deficiencies in C1-INH owing to genetics but develop a deficiency later in life are diagnosed with AAE-C1-INH. The underlying cause of this deficiency is due to the development of autoantibodies to C1-INH, increased consumption of C1-INH owing to increased activation of the pathways where C1-INH is involved, or some combination of these 2 mechanisms. At one point, AAE-C1-INH was classified as type I (overconsumption) and type II (destruction by autoantibodies). The subsequent understanding that there was significant contribution by both mechanisms in many cases of AAE-C1-INH has led to this classification falling out of favor.[55] Cases of AAE-C1-INH usually have low levels of C4, C1-INH antigen, and C1-INH function. It can often be distinguished from HAE-C1-INH through testing for concentration of C1q. The level of C1q will be normal in cases of HAE-C1-INH, whereas in AAE-C1-INH the levels are low when there is activation of the classical pathway of the complement system. Detection of autoantibodies to C1-INH is helpful to make the diagnosis of AAE-C1-INH, but they are found in only about 70% of cases.[54]

Radiographic Testing

There is a limited role for radiologic imaging in cases of HAE. Imaging studies may identify the presence of angioedema in locations not visible on physical examination, such as in the case of bowel wall angioedema.[43] This can help establish angioedema as the cause of a patient's presenting complaint. The specific type of angioedema cannot be determined by imaging. In cases of angioedema involving the airway, the use of imaging studies should be done with caution, as the patient may suddenly decompensate while in an area distant from the clinical team and the equipment needed to secure the airway. Use of point-of-care ultrasound imaging has been described for both intestinal[56,57] and upper airway[58] angioedema.

Fiberoptic Nasopharyngoscopy

In patients who have angioedema involving the tongue, soft palate, or floor of the mouth, the use of fiberoptic nasopharyngoscopy to help identify the presence of

swelling of the deeper upper airway structures is recommended in consensus guidelines endorsed by the American College of Allergy, Asthma, and Immunology and the Society for Academic Emergency Medicine.[59] Before performing any evaluation of the deeper upper airway structures, preparation for intubation should be performed because of the potential for worsening angioedema from minor trauma. The findings from a nasopharyngoscopic examination help to categorize a patient according to the Ishoo Staging System or Chiu Classification (see section entitled Airway Management).[29,60]

MEDICAL MANAGEMENT

The 3 therapeutic strategies for HAE are focused on long-term prophylaxis, short-term prophylaxis, and on-demand treatment of acute attacks. Before 2009 in the United States, there were no approved treatments for acute attacks of HAE. In the past, long-term prophylaxis was limited to treatment with an attenuated androgen, such as danazol, or an antifibrinolytic, such as ε-aminocaproic acid (EACA). Attenuated androgens and antifibrinolytics are now considered second-line therapies for long-term prophylaxis with the approval of new medications over the last decade.[57] With the approval of a plasma-derived C1-INH concentrate (pd-C1-INH) for HAE prophylaxis in 2008, there have been numerous advances in the treatment of this disease.[61] HAE treatments generally target 3 areas in the pathway of bradykinin formation: replacement of C1-INH, inhibition of bradykinin formation through the inhibition of kallikrein, and antagonism of the bradykinin B2 receptor. Steroids, antihistamines, and epinephrine are considered ineffective in the treatment of bradykinin-mediated angioedema, such as HAE.[62] A major advance in the treatment of HAE is approval of self-administered on-demand treatment. Currently, it is recommended that patients with HAE should have access to 2 doses of on-demand medication that can be self-administered in the event of an acute attacks of HAE.[57]

Replacement of C1-Esterase Inhibitor

The discovery by Donaldson and Evans[63] in 1963 that HAE was the result of a deficiency in C1-INH provided the rationale for replacement therapy to treat this disease. The use of pd-C1-INH was first described in 1973, where it was given to 2 patients with one showing a decrease in the usual time of resolution of an acute attack.[64] Following that, there were multiple other reports demonstrating the efficacy of C1-INH replacement therapy for acute attacks[65–67] as well as for prophylaxis. An intravenous form of pd-C1-INH was first approved for use in Germany in 1979.[68] Currently, there are 3 formulations of pd-C1-INH available in the United States: Berinert (CSL Behring, Marburg, Germany), Cinryze (Takeda, Lexington, MA, USA), and Haegarda (CSL Behring, King of Prussia, PA, USA).

In October 2008, Cinryze became the first of a series of new treatments for HAE when the FDA approved its use in adults and adolescents for prophylaxis against HAE attacks. Initial approval was based on the data from 2 studies that were published in a single article. In the first study, 65 subjects were included for analysis, which showed there was a shorter time to unequivocal relief for Cinryze at a fixed dose of 1000 U versus placebo (2 hours vs 4 hours; $P = .02$). The second study was a crossover trial that enrolled 22 subjects to receive twice-weekly injections of Cinryze for two 12-week periods whereby the subjects served as their own controls. Patients who were treated with Cinryze had a decrease in the number of attacks per study period (6.26 attacks vs 12.73 attacks; $P<.001$).[69] The FDA expanded the indication for Cinryze to include pediatric patients over the age of 6 in 2018.[70]

The industry-funded IMPACT (International Multi-centre Prospective Angioedema C1-Inhibitor Trials) studies were conducted in the United States to determine the efficacy of Berinert (pd-C1-INH produced by CSL Behring) in the treatment of acute attacks of HAE. The IMPACT-1 trial was a randomized double-blind placebo-controlled study of 125 subjects that compared intravenous Berinert at doses of 10 or 20 U/kg with placebo. The 10-U/kg dose was not found to be effective, but the 20-U/kg dose shortened the time to onset of symptom relief (0.5 hours vs 1.5 hours, $P = .0025$).[71] An open-label, uncontrolled extension study was performed (IMPACT-2) whereby Berinert was used to treat 1085 episodes in 57 patients. The median time to onset of symptom relief was 0.46 hours.[72] Berinert received FDA approval in 2009 for the treatment of acute abdominal, facial, or laryngeal attacks of HAE in adult and adolescent patients. The FDA approved expanded labeling in 2012 to include self-administration of Berinert for the treatment of acute laryngeal attacks.[73]

Conestat alfa, distributed under the brand name Ruconest, is a recombinant human C1-INH (rhC1-INH) made from the milk of transgenic rabbits that undergoes extensive posttranslational glycosylation that decreases the mean plasma half-life from 33 hours to 3 hours as compared with pdC1-INH.[74,75] The decrease in the plasma half-life does not appear to decrease the ability of rhC1-INH to treat acute attacks of HAE, as multiple studies have demonstrated its effectiveness.[76–79] Pooled data from early trials demonstrated that median time to the onset of symptom relief was 67 minutes and that 91.1% of subjects with upper airway symptoms had onset of relief by 4 hours.[80] Ruconest was demonstrated to have a sustained effect despite having a relatively short half-life in a pooled post hoc analysis of 2 trials whereby relapse of symptoms occurred in no patients at 24 hours and 7.1% at 72 hours.[81] The FDA approved Ruconest in 2014 for use in adults and adolescents for acute HAE attacks not involving laryngeal structures. It is contraindicated in patients with an allergy to rabbits or rabbit-derived products.[82] The European requirement that patients are screened with a rabbit-specific immunoglobulin E (IgE) immunoassay before administration of Ruconest was removed in 2016.[83] Additional studies have evaluated the use of rhC1-INH for both short- and long-term prophylaxis of HAE; however, it is not currently approved for this indication in the United States.[84–86]

In 2017, the FDA approved Haegarda for subcutaneous administration as long-term prophylaxis. Evidence supporting this came from the COMPACT (Clinical Study for Optimal Management of Preventing Angioedema with Low-Volume Subcutaneous C1-Inhibitor Replacement Therapy) trial, a randomized, placebo-controlled study with crossover design that enrolled 90 patients to receive pdC1-INH at 40 or 60 IU/kg every 3 to 4 days versus placebo. For the group treated with 60 IU/kg, the normalized attack rate was 0.52 per month, whereas the rate was 4.03 per month in the placebo group.[87] A post hoc analysis of the data from the COMPACT study demonstrated that there were improvements in measures of quality of life for patients receiving either dose of the study drug compared with placebo.[88] An open-label, extension study enrolled patients who completed the COMPACT trial and had high attack frequency before enrollment in the original study. This demonstrated continued efficacy and safety of subcutaneous pdC1-INH.[89] Haegarda is FDA approved for routine prophylaxis to prevent HAE attacks in patients 6 years of age and older.[90]

Kallikrein Inhibition

Ecallantide is a 60-amino-acid recombinant protein produced by the yeast *Pichia pastoris*[91] that functions as a potent and reversible inhibitor of the enzyme kallikrein, preventing it from cleaving bradykinin from HMWK.[92] A series of clinical trials collectively

known as the Evaluation of DX-88's Effects in Mitigating Angioedema (EDEMA) studies established the effectiveness of this treatment. The EDEMA0 trial, only published as an abstract, was a phase 2 open-label, dose escalation trial of intravenous ecallantide in 7 patients.[93] The EDEMA1 trial was also a dose escalation trial of intravenous ecallantide but designed as double blind and placebo controlled. Of the different doses of ecallantide studied (5, 10, 20, and 40 mg/m^2), only the 40-mg/m^2 dose was shown to be statistically superior to placebo (P = .0128).[94] The next study, EDEMA2, compared escalating intravenous doses (5, 10, and 20 mg) of ecallantide and a single subcutaneous 30-mg dose. The results of this study were not published but can be obtained in the application to the FDA. The percentage of patients with a response that was considered successful was the highest with the 30-mg subcutaneous dose (82%). The best result for the different intravenous doses was with the 10-mg dose, which had a 68% rate of successful outcomes. Statistical comparisons were not performed.[95] Next, EDEMA3 was a phase 3 randomized, double-blind, placebo-controlled trial whereby patients 10 years of age and older who presented with an acute HAE attack within 8 hours were randomized to receive either ecallantide 30 mg subcutaneously or placebo. Treatment with ecallantide was associated with a significantly higher treatment outcome score at 4 hours compared with placebo.[96] Last, EDEMA4 was also a phase 3 randomized, double-blind, placebo-controlled trial evaluating the use of subcutaneous ecallantide 30 mg versus placebo. The patients who received ecallantide had a greater decrease in the mean symptom complex severity score.[97] A post hoc analysis of multiple ecallantide trials demonstrated that with repeated administration, ecallantide was associated with a 3.5% rate of anaphylaxis.[95] Ecallantide is approved for subcutaneous administration in the United States for the treatment of acute attacks of HAE in patients 12 years of age and older. Because of the risk of anaphylaxis, ecallantide is not approved for self-administration.[98] The application for approval in Europe was withdrawn in 2011.[99]

Lanadelumab, a recombinant human IgG1 monoclonal antibody, is a potent and specific inhibitor of kallikrein that is produced using Chinese hamster ovary cells. Based on the results of a phase 3 trial that showed a reduced frequency of attacks with subcutaneous administration of lanadelumab, it was recently approved in the United States for the prevention of HAE attacks in patients aged $\geq$12 years. The objective of the Hereditary Angioedema Long-term Prophylaxis (HELP) clinical trial was to determine the efficacy of lanadelumab compared with placebo for preventing attacks of HAE. Three dose regimens were assessed versus placebo: 150 mg every 4 weeks, 300 mg every 4 weeks, and 300 mg every 3 weeks. There was a significant decrease in the number of HAE attacks for each of the 3 lanadelumab doses that were assessed.[100] The benefits were sustained in an open-label extension study. The investigators reported that HAE attack rate was reduced by 87.4% and that 68.9% of subjects treated with 300 mg every 2 weeks had an attack-free period of more than 12 months.[101] The recommended starting dose is 300 mg given subcutaneously every 2 weeks with a reduction in frequency to every 4 weeks if the patient is well controlled without attacks for 6 or more months.[102]

Inhibition of Bradykinin B2 Receptors

Icatibant is a synthetic peptidomimetic drug 10 amino acids in length that is similar in structure to bradykinin, a nonapeptide that functions as a selective inhibitor of the bradykinin B2 receptor, which is responsible for the major effects of bradykinin involved in attacks of HAE. Icatibant has affinity similar to that of bradykinin to the bradykinin B2 receptor but is resistant to enzymatic cleavage because of the substitution of 5 non-proteinogenic amino acids.[103] The efficacy and safety of icatibant were evaluated in 3

randomized, double-blind, controlled clinical trials collectively known as the For Angioedema Subcutaneous Treatment (FAST) studies. The results of the FAST-1 study, which was placebo controlled, and the FAST-2 study, which used the active comparator tranexamic acid (TXA), were published in the same article. The dose of icatibant used for both studies was 30 mg given subcutaneously. In the FAST-2 study, the comparator dose was oral TXA, at a dose of 3 g daily for 2 days. The primary end point for both studies was the median time to clinically significant relief of symptoms. The FAST-1 trial failed to show a statistically significant difference in the primary endpoint for icatibant versus placebo (2.5 hours vs 4.6 hours, $P = .014$). In the FAST-2 study, the median time to clinically significant relief of symptoms was 2.0 hours for the icatibant group and 12.0 hours for the TXA group ($P<.001$).[104] The dose chosen for TXA was lower than the dose recommended at that time for use as short-term prophylaxis in HAE.[105] The placebo-controlled FAST-3 study assessed median time to 50% reduction in symptom severity. For the group of patients with cutaneous and abdominal attacks but not involving laryngeal structures, the primary outcome was significantly shorter in the icatibant group compared with placebo (2.0 hours vs 19.8 hours, $P<.001$). Only 5 patients enrolled in the double-blind study had laryngeal involvement, limiting the comparison to placebo. The 3 patients who received icatibant during this phase of the study had a median time of 2.5 hours to 50% reduction in symptom severity.[106] Icatibant is approved for the treatment of HAE attacks in adult patients 18 years of age and older, including self-administration by the patient.[107] Generic forms of icatibant have now been approved in the United States.[108]

Attenuated Androgens

Attenuated androgens, such as the 17-α-alkylated anabolic steroids danazol and stanozolol, which are dihydrotestosterone derivatives, have been used for decades to reduce the frequency of attacks of HAE. These medications improve the clinical expression of HAE by increasing the amount of C1-INH produced by the liver[109,110] and by increasing expression of C1-INH messenger RNA in circulating monocytes.[111] Because these medications take 1 to 2 days to have any meaningful effect, they are not useful for the treatment of acute attacks.[112] In 1960, Spaulding[113] demonstrated the effectiveness of methyltestosterone therapy. Danazol, which has fewer adverse effects than methyltestosterone, was demonstrated to be effective by Gelfand and colleagues in 1974.[109] Side effects of therapy with attenuated androgens include hirsutism, weight gain, acne, decreased libido, menstrual irregularities, and liver neoplasms.[114] Attenuated androgens should be avoided in prepubescent children because of the risk of premature closure of epiphyseal plates leading to growth retardation.[115] This class should also be avoided in patients with liver disease, patients with androgen-dependent malignancies, and women who are pregnant or lactating.[116] The incidence and severity of side effects are dose dependent, so the lowest clinically effective dose should be used. Protocols have been published to determine the appropriate long-term dosing for danazol.[117,118] A survey of US physicians showed a decrease in the use of attenuated androgens for long-term HAE prophylaxis from 70% in 2010 to 7% in 2019.[119] Attenuated androgens are not recommended for on-demand treatment of an acute attack of HAE.[30]

Antifibrinolytics

The antifibrinolytic medications EACA and its cyclic analogue, TXA, have been used for long-term prophylaxis of HAE, although current data suggest that antifibrinolytics are now rarely used.[8,78] The proposed mechanism of action is inhibition of plasminogen conversion to plasmin leading to decreased activation of FXII.[120] Antifibrinolytics

have been used for long-term prophylaxis of HAE since 1972.[121,122] TXA is generally better tolerated than EACA.[73] Because of the possible prothrombotic effect of antifibrinolytics, these should be avoided in patients at increased risk of venous thromboembolism. A report in 2003 of a single center's treatment of HAE patients demonstrated a significant benefit with TXA in only 25% of treated patients.[76] An even more recent study failed to demonstrate any benefit from long-term prophylaxis with TXA.[123] Antifibrinolytics are not recommended for on-demand treatment of an acute attack of HAE.[79]

AIRWAY MANAGEMENT

The major focus of an emergency provider's care of a patient presenting with an HAE attack is ensuring airway patency. In 1999, Ishoo and colleagues[29] proposed a 4-tiered system for use in patients with angioedema owing to any cause to help determine the disposition as well as the need for airway intervention based on the site of swelling (**Table 1**). The stages are based on the anatomic location of the swelling and are not considered sequential. In their study, stridor, change in voice, hoarseness, and dyspnea were found to correlate with a need for airway intervention and admission to an intensive care unit (ICU). Patients with stage I (face, lip) and stage II (soft palate) angioedema were managed as outpatients or hospitalized in non-ICU units. Patients with stage III (tongue) angioedema were managed in the ICU two-thirds of the time. All patients with stage IV (laryngeal) angioedema were treated in an ICU setting. An airway intervention was required in 7% of patients with stage III and 24% of patients with stage IV angioedema. This staging system has not been prospectively validated.[34]

A second classification system was published by Chiu and colleagues[60] in 2001 based on a retrospective analysis of 108 patients with angioedema of any type who presented to 2 tertiary care hospitals (**Table 2**). Most patients included in this analysis had angioedema secondary to ACE inhibitor therapy. There were no patients identified with HAE. Patients were classified as having type 1 if the swelling involved the face and oral cavity but not the floor of the mouth. Type 2 cases had swelling that involved the floor of the mouth and other oropharyngeal structures. In type 3, the oropharyngeal swelling extended to the supraglottic and glottic structures. Rates of intubation were 21.4% and 33.3% for types 2 and 3, respectively.

When a patient with angioedema requires airway management, the treating provider must balance the rapidity with which the airway needs to be secured with the need to prepare for a successful procedure. Before intubation, administration of glycopyrrolate may be useful to decrease secretions, allowing for better visualization of the glottic structures. Rapid sequence intubation, as commonly used by emergency physicians, should not be used initially because paralysis without visualizing the vocal cords could

Table 1
Ishoo staging of angioedema

Stage	Site	Episodes (%)	Outpatient (%)	Floor (%)	ICU (%)	Intervention (%)
I	Facial, lip	31	48	52	0	0
II	Soft palate	5	60	40	0	0
III	Tongue	32	26	7	67	7
IV	Laryngeal	31	0	0	100	24

Table 2
Chiu classification of angioedema based on anatomic location[112]

Type	Site	Episodes (%)	Discharged from ED (%)	Floor (%)	ICU (%)	Intubated (%)	Surgical Airway (%)
I	Facial, oral cavity excluding floor of mouth	57.4	69.4	22.6	8.0	0.0	0.0
II	Floor of mouth, oropharyngeal structures (uvula, base of the tongue, and soft palate)	25.9	10.7	28.6	32.1	21.4	7.1
III	Oropharyngeal structures with extension to supraglottic and glottic structures	16.7	5.6	11.1	50.0	33.3	0.0

prove disastrous. Instead, awake intubation allowing the physician to visualize glottic structures may be safer. Noninvasive positive pressure ventilation does not correct a developing anatomic obstruction and should not be considered a temporizing procedure because barotrauma may worsen the angioedema and does not alleviate the underlying problem of airway obstruction. Driver and McGill[124] reviewed the method of intubation for 45 patients with angioedema at a single center. They found that a variety of methods were used, including nasotracheal intubation, video-assisted and direct laryngoscopy, and fiberoptic-assisted nasal and oral methods. A tracheal tube introducer (Bougie) was used in all cases whereby direct and video-assisted laryngoscopy methods were used. The frequency of utilization and success rates of the different methods are likely a reflection of institutional preferences and patient selection bias. The data demonstrate that successful intubation can be performed using a variety of techniques. Physical manipulation of the airway can cause sudden and severe worsening of the swelling. Before any attempt to evaluate or manage the airway, the provider should be prepared to perform a surgical airway, a preparation known as a double setup.[66]

SUMMARY

The ED management of a patient presenting with an acute attack of HAE requires recognition of the disease and careful evaluation for airway involvement. Angioedema itself is a clinical diagnosis of swelling of the subcutaneous and submucosal tissues. Broadly speaking, angioedema is usually caused by either the release of histamine or the presence of bradykinin. Understanding the underlying pathophysiology will help guide medical management with appropriate and effective medications while avoiding treatments that are ineffective and even potentially harmful. There have been major advances in the treatment of HAE since 2008. The cost of these treatments has been very high, so many hospitals may not have HAE-specific medications on formulary. Being aware of what treatment options are available before the critical HAE patient presents to the ED will help with the timely treatment of an acute attack.

CLINICS CARE POINTS

- Patients presenting with recurrent episodes of swelling or unexplained abdominal pain should be considered for evaluation for hereditary angioedema, as there is frequently a multiyear delay in diagnosis from onset of symptoms.
- Patients with hereditary angioedema have a higher likelihood of undergoing abdominal surgeries, which may be avoided if the diagnosis of an acute attack of hereditary angioedema is considered.
- Hereditary angioedema is typically not associated with the development of urticaria or pruritus, a feature helpful in distinguishing from angioedema secondary to histamine release.
- Up to one-half of patients with hereditary angioedema develop a characteristic rash, erythema marginatum, during the prodromal period, which is not pruritic but may be confused for an urticarial lesion.
- Patients with voice change, hoarseness, stridor, and dyspnea are at high risk for needing an airway.
- Patients with acute attacks of hereditary angioedema can be treated with several medications, all of which result in reduced activation of the bradykinin B2 receptor. No study has compared these medications with one another.
- It is recommended to perform fiberoptic nasopharyngoscopy on patients who may be at risk for airway obstruction. The patient should be prepared for intubation, as performing nasopharyngoscopy may result in worsening of the swelling encountered.

DISCLOSURE

The authors have nothing to disclose.

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