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REVIEW

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Clinical manifestations of hereditary angioedema and a systematic review of treatment options

Mattie Rosi-Schumacher MD[1] | Sejal J. Shah MD[2] | Timothy Craig DO[3] | Neerav Goyal MD, MPH[4]

[1]Department of Otolaryngology-Head and Neck Surgery, Jacobs School of Medicine and Biomedical Sciences at The State University of New York at Buffalo, Buffalo, New York, USA

[2]Department of Surgery, Penn State College of Medicine, Penn State University, Hershey, Pennsylvania, USA

[3]Department of Medicine and Pediatrics, Penn State College of Medicine, Penn State University, Hershey, Pennsylvania, USA

[4]Department of Otolaryngology-Head and Neck Surgery, Penn State College of Medicine, Penn State University, 500 University Drive, Hershey, Pennsylvania, MC H091, USA

Correspondence
Neerav Goyal, FACS, Department of Otolaryngology—Head and Neck Surgery, Penn State Milton S Hershey Medical Center, Hershey, PA, USA.
Email: ngoyal1@pennstatehealth.psu.edu

Abstract

Objective: This study systematically reviews the existing literature on the management of hereditary angioedema (HAE) and provides an update on the clinical presentation and specific therapies.

Methods: A literature search of PubMed and Embase databases was conducted from start of the database to February 2021. Inclusion criteria included relevant systematic reviews, randomized control clinical trials, prospective and retrospective cohort studies, and outcomes research published in English and available in full-text. Out of 310 candidate articles, a total of 55 articles were included in our study.

Results: The most common genetic form of HAE in up to 85% of cases is caused by low levels of C1 esterase inhibitor (C1-INH) protein, leading to a bradykinin-mediated increase in vascular permeability. During an attack of HAE, abortive treatment with C1-INH replacement is most commonly described, however, icatibant, ecallantide, or fresh frozen plasma are also used. Long-term prophylaxis in the form of C1-INH replacement (subcutaneous or intravenous), monoclonal antibodies targeting plasma kallikrein, attenuated androgens, and transexemic acid should be considered for those who suffer from frequent, severe attacks.

Conclusion: Progressively distal involvement of the upper airway, especially the larynx, has been shown to pose an increased risk of asphyxiation and death in the acute presentation of HAE. Evaluation by an otolaryngologist is often sought during the emergent clinical management of HAE; therefore, it is prudent that the consulting physician is well-versed in the prompt recognition, triage of patients, and appropriate treatment modalities.

Level of Evidence: 1A.

KEYWORDS

clinical manifestations, hereditary angioedema, pathogenesis, pharmacologic treatment, upper airway

1 | INTRODUCTION

Hereditary angioedema (HAE) is a rare, autosomal dominant disorder that is commonly characterized by repeated episodes of cutaneous or submucosal swelling affecting the skin, gastrointestinal tract, face, upper airway and other organs.[1-3] The incidence of HAE is estimated to be 1 in 50 000, but ranges from 1 in 10 000 to 1 in 150 000.[2-5] HAE is often classified into three major types, which are defined by the amount or function of C1 esterase inhibitor (C1-INH) present in an individual. C1-INH is a serine protease inhibitor that plays an important regulatory role in the complement cascade, coagulation cascade, fibrinolytic pathway and contact pathway. Initial presenting symptoms of angioedema are most commonly thought to be related to allergic reactions resulting in mast-cell mediated angioedema. The diagnosis of HAE presents a unique challenge to clinicians due to the rarity of disease, similar presentation to other more common allergic conditions, and lack of pathognomonic tests available in the acute and emergency setting. In the acute setting, a high clinical suspicion may allow for a diagnosis of exclusion made through clinical evaluation and the lack of response to epinephrine, antihistamine, or glucocorticoid treatments in patients with HAE. However, these factors often lead to missed diagnosis and delay of the appropriate treatment. One of the most life-threatening presentations of HAE is with localized swelling in the structures of the head and neck as a manifestation of cutaneous or submucosal angioedema. Due to the risk of airway asphyxiation, angioedema of the upper aerodigestive tract requires prompt recognition and intervention. The expertise of an otolaryngologist may be sought in the diagnosis and management of this condition. The objective of this review is to (a) draw attention to important features of the genetics, pathogenesis, manifestations, and diagnosis of HAE, (b) to provide an updated and comprehensive review of current pharmaceuticals and their utility in the management of HAE, and (c) provide a clinical reference for the managing physician.

2 | METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The National Library of Medicine through PubMed and Embase via Elsevier databases were searched. Searches were conducted to find papers with a major focus on hereditary angioedema as well as treatment, management, diagnosis, clinical presentation, upper airway manifestations, and otolaryngology. Exact search algorithms with keywords, MeSH terms, and Emtree terms are available in the supplemental documents (Supplement S1). Our search strategy included studies published in any language from the inception of the database to the time of the search in February 2021. The bibliographies of identified articles were searched for additional cross references. Relevant systematic reviews, randomized control clinical trials, prospective and retrospective cohort studies, and outcomes research were included for initial review if they were published in English and available in full-text. Studies presenting information exclusively about angioedema of other etiologies (not hereditary), those with limited scope of the study or limited clinical outcomes, commentaries, and non-expert opinion pieces were excluded. Data including study design, methods, pathogenesis, genetics, diagnosis, clinical manifestations of disease, evidence supporting the development and proper use of pharmaceuticals, and treatment options were extracted by co-authors to compose consensus statements. Articles were reviewed by two authors independently, with discrepancies resolved after joint article review and discussion. The strength of clinical data and subsequent recommendations presented in the papers reviewed were graded according to the Oxford Centre for Evidence-Based Medicine 2011 levels of evidence (Supplement S2). Database search identified 2897 articles for review and 15 additional record were identified through bibliography cross-reference. After removal of duplicates and screening based on title and abstracts, 310 full text articles were assessed for eligibility. After inclusion and exclusion criteria were applied a total of 55 studies were included in the final review. PRISMA flow diagram is available for reference in the supplemental material (Supplement S3).

2.1 | Pathogenesis

Within the contact system, C1-INH blocks bradykinin synthesis through inhibition of the protease kallikrein, inhibition of Factor XII (FXII) activation and inhibition of high-molecular-weight kininogen (Figure 1).[2,5] Thus, if deficient or dysfunctional, it leads to uncontrolled activation of FXII and increased formation of active kallikrein. Kallikrein releases bradykinin from high molecular weight kallikrein (HMWK). C1-INH also plays an important role in the fibrinolytic system, inhibiting the conversion of plasminogen to plasmin by blocking the effects of Factor XIIa and kallikrein on the pathway. Therefore C1-INH deficiency leads to high levels of plasmin, which acts as a facilitator of the split of bradykinin from HMWK induced by kallikrein. Bradykinin binds to the B2 receptor on endothelial cells, generating GMP, prostacyclin and nitrous oxide resulting in smooth muscle cell relaxation, vasodilation, increased vascular permeability, and edema.[1,3,4]

In the complement cascade, C1-INH inhibits the activation and activity of C1 esterase of the classical pathway and MASPs 1 and 2 of the lectin pathway. Without C1-INH, unchecked activation of the complement cascade by C1 esterase causes cleavage of the C4 and C2 proteins, resulting in decreased levels of these proteins. Finally, in the coagulation system, C1-INH inhibits the activation of Factor XI and Factor IX, thus preventing the conversion of prothrombin to thrombin and fibrinogen to fibrin. In patients with deficient or dysfunctional C1-INH activity, the coagulation cascade is unregulated and results in an increase in thrombin levels which increases vascular permeability, contributing to edema during HAE attacks. In addition, due to increased levels of fibrin degradation products, it is important to note that the D-dimer level of patients with angioedema may be elevated.[6] Dysregulation of C1-INH causes disruption to all these systems, and results in an increase in bradykinin, plasmin, complement activation, thrombin and fibrin degradation products.

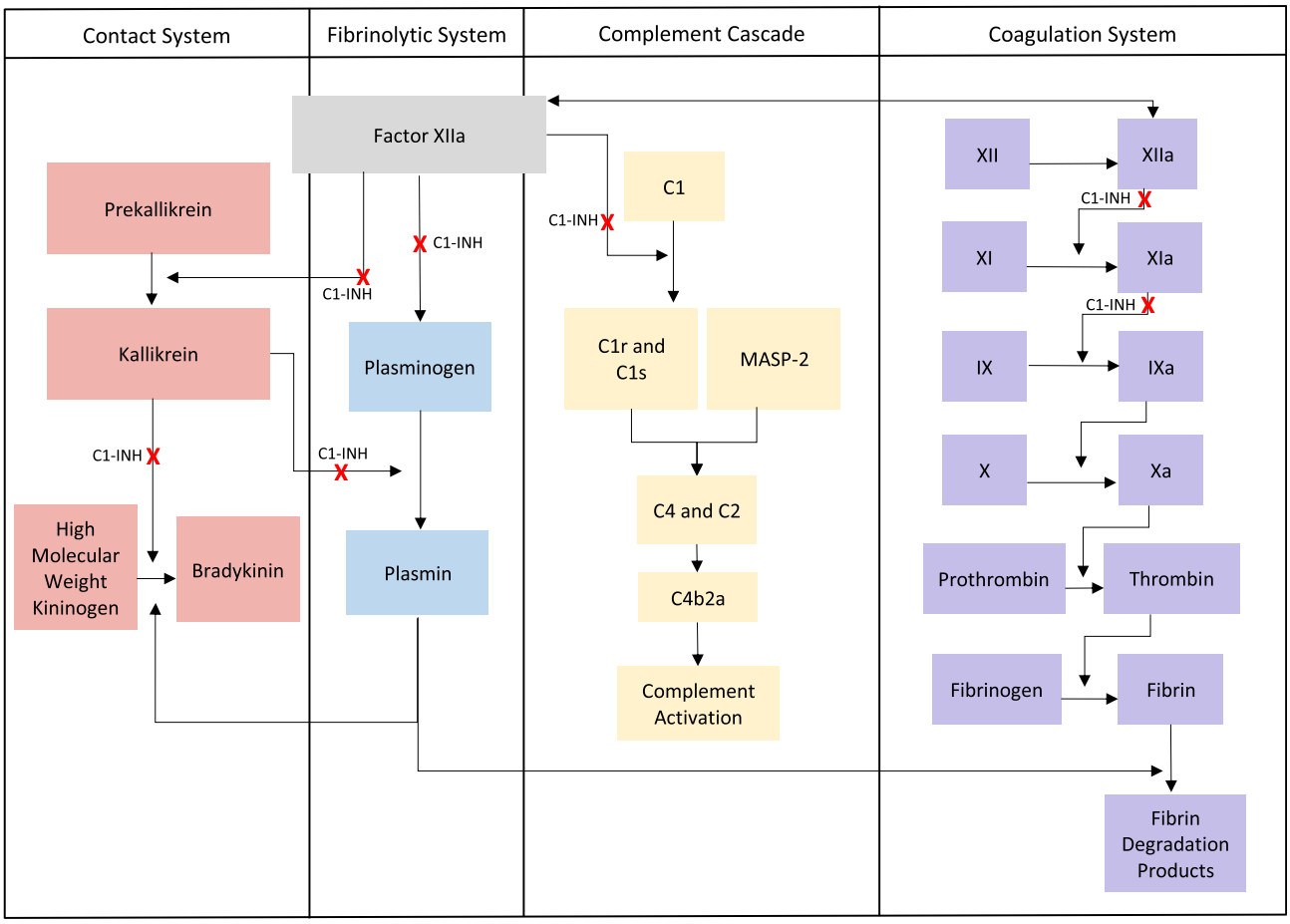

FIGURE 1 Pathogenesis of hereditary angioedema. C1-INH affects several pathways, including the contact system, fibrinolytic system, complement cascade and coagulation cascade. With deficient or dysfunctional C1-INH, there will be an increase in vascular permeability, tissue edema, inflammation and clotting

TABLE 1 Classification of hereditary angioedema based on C1-inhibitor and complement levels. An abnormal C1q level would indicate an acquired etiology instead of hereditary. ACE-inhibitor induced angioedema and acquired angioedema with low C1-inhbitor are both bradykinin dependent and not hereditary

Classification	Prevalence	C1-INH	C4	C1q
HAE with deficient C1-INH previously called Type I	Up to 85%	Low levels of protein and function	Low	Normal
HAE with dysfunctional C1-INH previously referred to as Type II	Up to 15%	Normal or high levels of protein, but dysfunctional protein and thus low function	Low	Normal
HAE with normal C1-INH previously referred to as Type III	Very rare	Normal protein and function	Normal	Normal
Acquired angioedema with deficient C1-Inhibitor	Very rare	Low protein and function	Low	Low
ACE-inhibitor angioedema	Common	Normal	Normal	Normal

2.2 | Genetics

HAE has a strong hereditary component and is inherited in an autosomal dominant pattern, although 20% of cases do not have a familial history and are caused by sporadic mutations (Table 1).[4] In contrast, the most well-known and common form of angioedema is not hereditary, but associated with a reaction to angiotension-converting enzyme inhibitors (ACEIs) and characterized by normal levels of C1-INH and complement. Angioedema may also result from an acquired deficiency in C1-inhibitor, which is characterized by low protein levels and function as well as low complement levels. Case reports have demonstrated an association of late-onset angioedema without urticaria with an increased risk of autoimmune disease, blood conditions, or underlying malignancy, specifically non-Hodgkin lymphoma.[7-9] In the case of normal C1 esterase inhibitor protein levels with low function, the presence of antibodies against C1 esterase inhibitor secondary to an underlying lymphoproliferative disorder should be considered.

The gene that has been implicated in C1-INH deficiency is the SERPING1 gene on chromosome 11 (11q12-q13.1).[2-5] HAE with

deficient C1-INH, previously called Type I HAE, is the most common form, occurring in up to 85% of cases and is caused by a reduced concentration of circulating C1-INH due to mutations that alter effective gene transcription and result in abnormal folding of the protein. HAE with dysfunctional C1-INH, previously referred to as Type II HAE, occurs in up to 15% of cases and while C1-INH levels are relatively normal or even high, the protein is dysfunctional. Similar to Type I, this type of HAE is characterized by low C4 levels and decreased functional C1-INH.

HAE with normal C1-INH, previously referred to as Type III HAE, has normal C1-INH levels and function as well as normal C4 levels. This type of HAE has been associated with coagulation factor XII (FXII), plasminogen, and angiopoietin-1 gene mutations.[2,4,10] In HAE associated with FXII gene mutations, the onset of clinical symptoms typically begins in adulthood and predominantly affects females. The symptoms for Type III HAE manifest as facial and tongue swelling and can be exacerbated with oral contraceptives, hormonal replacement therapy or pregnancy.[2] HAE with plasminogen gene mutations have a particularly high incidence of tongue swelling that increases the risk of airway obstruction. Plasminogen gene mutations lead to an overproduction of bradykinin, while angiopoietin-1 gene mutations directly affect vascular permeability.[2] This manuscript will focus on HAE type I and II unless specified.

2.3 | Diagnosis

While most patients are symptomatic before the age of 20 and have a positive family history of HAE, the clinical diagnosis is often delayed for up to 20 years and may involve multiple physicians before the diagnosis is made.[1,3,4] This can be due to the misattribution of symptoms to other diseases, such as appendicitis or gastroenterocolitis and at times has led to unnecessary surgical procedures.[2] The clinical presentation of HAE can include general symptoms common to other diseases and this unspecific profile may play a role in delaying appropriate diagnostic testing of the disorder.

Diagnosis of HAE can be accomplished through laboratory testing of C1-INH protein and function and C4 levels obtained from blood samples. Some guidelines recommend genetic testing for the diagnosis of very young children and fetuses, however, biologic testing may be delayed until 2 years of age or older as C1-INH levels are typically lower in patients younger than 1 year and symptoms seldom manifest so early in life.[11] The World Allergy Organization and European Academy of Allergy and Clinical Immunology (WAO/EAACI) recommend testing children from HAE-affected families as soon as possible and also testing siblings of an affected parent.[12] Early diagnosis of HAE can reduce the possible risks of morbidity and mortality.

2.4 | Manifestations

While idiopathic angioedema is self-limited and usually lasts 24-48 hours, attacks of hereditary angioedema can last up to 5 days, often with slow onset and slow resolution and are unresponsive to antihistamines and corticosteroids.[2] Triggers of acute attacks include trauma to the face, mouth or upper airway, as well as surgical, dental and medical procedures.[1,4,5] HAE episodes are often accompanied by prodromal symptoms of fatigue, malaise, mood changes, and joint or muscle pain.[13] HAE can affect the subcutaneous or submucosal tissues of any organ with intestinal swelling being one of the most common manifestations. When the gastrointestinal system is affected, patients often complain of abdominal pain, diarrhea, nausea, and vomiting.[5] Other commonly affected areas can include the extremities, genitalia, face, and buttocks. Hereditary angioedema is a pertinent disease to exclude in a differential diagnosis of skin or submucosal swelling.[14] One way to differentiate HAE from other types of angioedema is the absence of urticaria and pruritis, although prodromal erythema marginatum is a manifestation that can be mistaken for urticaria in these patients.[2,4,5] Patients presentating with late-onset angioedema without urticaria should be worked up for consideration of underlying lymphoproliferative disorder or autoimmune disease. In one case report of acquired angioedema with low C1-INH, the patient presented with pancytopenia, recurrent episodes of soft tissue swelling, and unexplained colicky abdominal pain and was found to have underlying splenic marginal zone lymphoma.[7] He was started on maintenance therapy of danazol (attenuated androgen therapy) to prevent further episodes of angioedema, and after successful treatment of lymphoma with splenectomy, he had resolution of any further angioedema episodes postoperatively.[7]

2.5 | Role for the otolaryngologist

Consultation of the otolaryngologist may be sought due to the involvement of the upper airway as well as presenting signs of dyspnea, stridor, dysphonia, or hoarseness in these patients. Life-threatening asphyxiation due to acute upper airway involvement, specifically laryngeal angioedema, is the leading cause of death in HAE.[2] Fortunately, airway involvement is not common; however, 50% of patients with HAE experience airway involvement during their lifetime. Most deaths associated with airway swelling occur in patients who have not had a formal diagnosis. The otolaryngologist plays a unique role in the evaluation and management of the airway including utilization of specialized laryngoscopes, fiberoptic nasal intubation, and surgical expertise in tracheostomy.[11] As trauma to the airway structures is a known risk factor and trigger for worsening angioedema of the airway, attempts at direct visualization and intubation should be reserved for operators with expertise. Proper and skillful examination of the upper airway may allow for stabilization of the airway and avoid the progression to emergency surgical airway intervention.[15] The emergent clinical management of this disease can be improved through the standardized evaluation by an otolaryngologist to facilitate prompt recognition and triage of patients to the appropriate level of care. The literature supports that with progressively distal involvement of the upper airway, patients should be monitored more closely, with a lower threshold for securing the airway through intubation or surgical means, and consideration for admission to an intensive

TABLE 2 Pharmaceutical products available for hereditary angioedema

Type	Brand drug	Manufacturer	Indication	Route	Approved ages
Plasma-derived C1-INH	Berinert	CSL Behring	IV for attacks; off label for short and long-term ppx	IV only; can be self-administered	Adults, Adolescents, and Pediatric patients
	Haegarda	CSL Behring	Long-term ppx	Subcutaneous; can be self-administered	Adults and Adolescents 12 years and older
	Cinryze	Takeda	Long-term ppx; off label for attacks and short-term	IV only	Adults, Adolescents, and Pediatric patients 6 years and older
Recombinant human C1-INH	Ruconest	Pharming Healthcare, Inc	IV for acute attacks; off label for short and long-term ppx	IV only	Adults and Adolescents 12 years and older
Bradykinin receptor antagonist	Icatibant (Firazyr)	Takeda	Acute attacks	Subcutaneous; can be self-administered	Adults 18 years and older
Plasma kallikrein inhibitor	Ecallantide (Kalbitor)	Takeda	Acute attacks	Subcutaneous; cannot be self-administered	Adults and Adolescents 12 years and older
	ORLADEYO (berotralstat)	BioCryst Pharmaceuticals	Long-term ppx	Oral	Adults and Adolescents 12 years and older
Monoclonal Antibody	TAKHZYRO (lanadelumab-flyo)	Takeda	Long-term ppx	Subcutaneous; can be self-administered	Adults and Adolescents 12 years and older
Attenuated Androgens	Danocrine (Danazol)	Lanett Company	Long-term ppx	Oral	Adults
	Oxandrin (Oxandrolone)	Savient Pharmaceuticals, Inc	Long-term ppx	Oral	All ages with dosing per kg
Tranexamic Acid	Lysteda	Ferring Pharmaceuticals	Long-term ppx	Oral	Adults 18 years and older
	Cyklokapron	Pfizer	Long-term ppx	IV	Adults and limited use in pediatric patients

Abbreviations: PPX, prophylaxis.

care unit.[16-18] Therefore, the fiberoptic nasolaryngoscopy exam is crucial to precisely delineate involvement of the oral cavity, palate, tongue base, oropharynx, and laryngeal structures. Knowledge of the clinical manifestations of HAE allows the otolaryngologist to help establish a diagnosis, initiate timely referrals, and assist in management of symptoms and complications. An otolaryngologist can also help to assess the stability of the airway and prepare for and manage cases of airway compromise during which surgical management may be indicated. If symptoms are not severe and serial examinations reveal improvement and resolution of symptoms, patients can be observed, admitted to the floor, or discharged home. The implementation of clinical care algorithms and multidisciplinary response teams of expert consultants, including otolaryngologists, can help to improve patient outcomes and decrease rates of airway emergencies and surgical airways secondary to attacks of hereditary angioedema.

2.6 | Pharmaceuticals and treatment options for HAE

Treatment of HAE is focused on alleviating symptoms of acute attacks or on short- and long-term prevention of acute attacks (Table 2). In this way, medical management can improve quality of life and reduce the morbidity and mortality associated with HAE.

2.6.1 | Medications for acute attacks

Plasma-derived or recombinant C1-INH can be administered in the acute setting. This treatment works by replacing the deficient or dysfunctional protein and inhibiting the contact system, thus regulating bradykinin production.[19] Randomized clinical control trials have shown that subjects who received C1 inhibitor concentrate had significant reductions in both the severity and duration of attacks, reduction in the number of days of symptomatic swelling, and decreased need for rescue therapy.[20] Clinical trials demonstrated significantly shorter median time to onset of relief (0.5 hours) with C1 esterase inhibitor concentrate at a dose of 20 U/kg when compared with placebo (1.5 hours).[21]

Several other classes of medication can be used in acute HAE attacks including B2 receptor antagonists and kallikrein inhibitors. Icatibant is a bradykinin B2 receptor antagonist that is approved for treatment of acute HAE attacks in adults greater than 18 years of age.[22] This medication can be self-administered by patients suffering from an acute attack via subcutaneous injection. Self-administration of therapy allows for rapid intervention in the case of an acute HAE attack and can be life-saving. The clinical trial (FAST-3) of Icatibant for acute attacks of HAE randomized patients with moderate to severe abdominal or cutaneous attacks and another group of patients with mild to moderate laryngeal HAE attacks to receive a subcutaneous injection of icatibant (30 mg) or placebo. Icatibant was shown to significantly reduce median times (vs placebo) to 50% or more reduction in symptom severity, onset of primary symptom relief, and almost complete symptom relief.[23] For patients experiencing laryngeal attacks, the median time to onset of symptom relief was 1-2 hours, with complete symptom relief in 1.5-8.1 hours.[24] Recent studies have also shown a potential role for icatibant in ACEI-induced AE, but the benefit of icatibant therapy over placebo or conventional treatment strategies (combination therapy with glucocorticoid and antihistamine) has not been definitively shown.[25,26] Several studies do provide evidence to support that treatment with icatibant shortened the time to achieve complete resolution of edema in these patients with ACEI-induced AE.[27,28]

Ecallantide is a plasma kallikrein inhibitor which is approved for the treatment of acute HAE attacks in patients 12 years of age and older via subcutaneous administration.[29] However, anaphylaxis has been reported as an adverse reaction in 3-4% of patients treated with ecallantide.[30,31] Therefore, ecallantide must be administered by a professional in a health care setting to monitor for hypersensitivity reactions and anaphylaxis. In clinical trials, ecallantide (30 mg subcutaneous) was tested specifically in patients with hereditary angioedema suffering laryngeal attacks and found to be effective in reducing symptom severity.[32] The median time to significant improvement in symptoms was 185 minutes (95% CI, 167-226).[32]

Fresh frozen plasma (FFP) contains C1 esterase inhibitor and may be administered when other therapies are not available. It has been shown to be safe and effective in acute attacks as well as preventing exacerbations before surgery.[33,34] One study demonstrated the median time to resolution of symptoms when administering FFP was 4 hours, with a range of 2-12 hours.[34] In some cases, FFP has been shown to paradoxically worsen angioedema exacerbations and poses the risk of viral transmission unless specifically prepared and inactivated.[33] FFP administration also carries the risk of transfusion reaction and anaphylaxis.[34]

2.6.2 | Short term prophylaxis

Short-term prophylactic (STP) treatment is indicated before an invasive medical, dental or surgical procedure in a patient with a known history of HAE to prevent an attack. STP can also be given before patients are exposed to known triggers such as increased stress, anxiety, infection, sports, or anticipated trauma. Plasma-derived C1-INH and recombinant C1-INH may be used off-label for STP.[35-38] Treatment with C1-INH or FFP is recommended 1 to 2 hours prior to surgical procedures.[11] Other medications for STP include androgens and tranexamic acid.[39] Both tranexamic acid and androgens are started 5 days before the trigger and continued for 3 days after. Both are oral medications, making administration easy. Treatment with these agents is not as effective as replacement of C1-INH and are therefore considered second line treatment options.[12]

2.6.3 | Long-term prophylaxis

The need for long-term prophylaxis (LTP) is determined on a patient-by-patient basis and may be advisable in those who suffer from frequent, severe attacks or are affected in anatomical locations that

increase morbidity and mortality. The use of LTP treatment to reduce the number and frequency of HAE attacks has been shown to improve quality of life for these patients. Replacement therapy with human C1-inhibitor treatment is approved and available as intravenous C1-INH (Cinryze) and subcutaneous C1-INH (Haegarda) preparations. It is indicated for long-term prophylaxis to prevent HAE attacks in adolescent (>12 years) and adult patients.[40] Intravenous CI-INH is approved for twice weekly infusions of 1000 U and subcutaneous C1-INH is intended for twice weekly self-administered injections of 60 IU/kg.[40,41] The clinical trial of subcutaneous C1-INH demonstrated 2.42 fewer attacks per month at a dose of 40 IU/kg and 3.51 fewer attacks per month at a dose of 60 IU/kg.[42] The use of subcutaneous C1 inhibitor preparation was also shown to decrease the need for rescue medications from 5.55 uses per month in the placebo group to 1.13 uses per month in the 40-IU group and from 3.89 uses per month in the placebo group to 0.32 uses per month in the 60-IU group.[42] The adverse effects are minimal and mainly associated with injection site reactions. Current research suggests a greater attack reduction with subcutaneous C1-INH when compared with the intravenous administration.[41] There have also been studies that demonstrate routine prevention with intravenous administration of C1-INH is efficacious, safe, and well tolerated in even younger children (greater than or equal to 6 years of age). Treatment in this age group led to decreased number of attacks and decreased severity.[43]

Lanadelumab is a subcutaneous monoclonal antibody against plasma kallikrein that is indicated for LTP of HAE attacks in patients 12 and older.[2] It is administered subcutaneously every 2 to 4 weeks and may be self-administered by patients. Clinical trials have shown its efficacy in reducing the cleavage of high-molecular-weight kininogen and reducing the number of attacks of angioedema.[44] At a dose of 300-mg 100% of patients were attack-free compared with the placebo group.[44] In another clinical trial, it was shown that patients experienced a mean of 87% reduction in number of attacks per month when compared with the placebo group.[31]

Beroltrastat (Orladeyo, formerly BCX7353) is an oral plasma kallikrein inhibitor that is approved for prophylaxis to prevent attacks of HAE in adults and pediatric patients 12 years and older. It is the first orally administered option for preventing HAE and has demonstrated a 74% lower rate of angioedema attacks at a daily dose of 125 mg when compared with placebo.[45,46] Clinical trials showed that patients receiving placebo experienced 2.35 attacks per month, while a daily dose of 110 mg berotralstat reduced this number to 1.65 attacks per month and the 150 mg dose reduced it to 1.31 attacks per month.[47]

Attenuated androgens have been shown to increase the level of C1-INH either by increased production or decreased breakdown of the protein.[19] Androgens can be used in HAE for LTP, however they have limited use in certain populations such as patients with breast cancer or prostate cancer, pregnant women, breastfeeding women, and prepubescent children.[48] Overall, the use of androgens for LTP is limited by their side effect profile and for this reason have fallen out of favor in the USA.

Tranexamic acid, while not officially FDA-approved for use in HAE, has been shown to be effective in the prevention of HAE attacks and is recommended as an alternative by several guidelines including the World Allergy Organization. Tranexamic acid ultimately lowers the levels of bradykinin through inhibition of the action of plasminogen. In one study of 37 patients with either HAE or idiopathic angioedema, long-term treatment with daily tranexamic acid over 6 months was shown to reduce the number of attacks in 73% of patients.[49] Tranexamic acid is available in generic forms, in both oral and IV formulations, and has a more favorable side effect profile when compared with androgen prophylactic treatment. However, it is less effective than C1-INH products or androgens and is therefore only rarely used in the USA.

2.6.4 | Novel treatment agents

Pharvaris biopharmaceutical company has undertaken phase 1 clinical trials for another oral bradykinin-B2-receptor antagonist for the treatment of hereditary angioedema, which has initially shown effectiveness for both acute and prophylactic treatment. The mechanism of action is similar to that of icatibant, with initial study results suggesting the new agent, PHA121, may be more long-lasting and potent. Clinical trials with the medication have shown it to block the activity of bradykinin within 15 minutes and maintain therapeutic activity for at least 12 hours (clinical trial NCT0461821).[50,51] The company is also working on development of PHVS416, a soft oral capsule formulation, and PHVS719, an oral tablet formulation.[52]

Garadacimab (formerly CSL312) is a human monoclonal antibody directed against FXIIa, which is currently in phase 3 clinical trials for subcutaneous administration for prophylactic treatment of HAE. Initial data demonstrates its effectiveness in reducing the mean number of angioedema attacks (Clinical trials NCT03712228 and NCT04656418).[53,54] Other treatments targeted to inhibit Factor XII are in development using small interfering RNA (siRNA) technology, including ALN-F12 and ARC-F12.[55] Several other new long-term prophylactic treatments target plasma prekallikrein: IONIS-PKK-L_{Rx} works by downregulation of prekallikrein mRNA synthesis by a selective antisense oligonucleotide[56] and NTLA-2002 uses CRISPR/Cas9 technology to knockout the gene encoding prekallikrein.[57] KalVista Pharmaceuticals is developing several kallikrein inhibitor treatments: KVD900 for on-demand treatment and KVD824 for long-term prophylaxis.[58,59] Novel gene therapy strategies are also in preclinical development (BioMarin and Regenxbio), which will work through virus-mediated antibody delivery technology to insert an extrachromosomal copy of the SERPING1 gene to induce in vivo production of C1-INH.[60-62]

3 | CONCLUSION

HAE is a rare disease that can be complicated by acute airway attacks characterized by involvement of the oral cavity, pharynx, or larynx that pose a threat to respiratory stability and subsequent morbidity and mortality. Triggers of angioedema attacks include trauma, stress

and infection. The disease can present with swelling and edema of the face, extremities, gastrointestinal tract, and upper airway. Multiple treatment options are available including medications for acute treatment, short-term prophylaxis and long-term prophylaxis. Most importantly, HAE presenting in the acute setting requires rapid evaluation and action due to the possibility for laryngeal involvement, which poses a risk of death. A physical examination performed by an otolaryngologist can rapidly delineate the anatomic involvement of the upper airway and allow for the appropriate triage and urgent management of patients presenting with an acute attack of HAE. The limitations of this study include the paucity of studies in the literature devoted specifically to hereditary angioedema. The significant variation in methods and approaches of studies included permitted only a narrative systematic review. While the current understanding of HAE has greatly improved, increased awareness and continued review is necessary to facilitate increased clinical suspicion of this rare disease. Consensus guidelines and the implementation of clinical management algorithms will likely help to improve management and patient outcomes. Family screening should be implemented in cases of known hereditary angioedema and patients should be educated about what to do during an acute attack, inform their health care providers, and have abortive medications made readily available. Future studies should continue to investigate the role of biologics in prophylaxis and novel oral agents in the treatment of HAE.

CONFLICT OF INTEREST

Dr. Craig does research, consults and speaks for Biocryst, CSL Behring, Grifols, Pharming, Ionis and Takeda.

ORCID

Mattie Rosi-Schumacher https://orcid.org/0000-0003-4690-151X
Neerav Goyal https://orcid.org/0000-0001-7783-1097

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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