

# Hereditary Angioedema: A Review

Heidi Zafra, MD

## ABSTRACT

Hereditary angioedema (HAE) is a rare and disabling disorder wherein there is excessive bradykinin production, with subsequent increased vascular permeability in the superficial tissues and gastrointestinal and respiratory mucosa. This article serves as a review of the pathogenesis of the disease, as well as an update of the evidence-based new treatment recommendations to help clinicians with the diagnosis and management of HAE.

## CLINICAL CASE

A 13-year-old White female presented to the emergency department with swelling and pain of the right arm. There was cyanosis of her right distal arm and hand. She underwent emergency fasciotomy because of compartment syndrome. On postoperative day 2, her right arm continued to improve; however, she began to develop edema of the left hand. Her past medical history included recurrent leg swelling and abdominal pain. Family history was significant for the father's diagnosis of hereditary angioedema (HAE). Pertinent laboratory tests showed a complement C4 level that was undetectable (<6 mg/dL; reference range, 13-44 mg/dL), quantitative C1 inhibitor (C1-INH) 7 mg/dL (reference range, 21-39 mg/L), functional C1 inhibitor 47% (reference range, >67%). All other labs for infection, allergic, and autoimmune diseases were normal.

The patient was diagnosed with HAE type 1. Early inpatient treatment was started with intravenous (IV) C1 inhibitor 2000 units, and she was discharged with a scheduled 1500 units IV infusion twice weekly and icatibant 30 mg subcutaneous (SQ)

• • •

**Author Affiliations:** Division of Allergy/Clinical Immunology, Medical College of Wisconsin, Milwaukee, Wisconsin.

**Corresponding Author:** Heidi Zafra, MD, 9000 W Wisconsin Ave, Suite 440, Milwaukee, WI 53226; email hzafra@mcw.edu; ORCID ID 0000-0001-5410-1462.

injections as a rescue medication.<sup>1</sup> An IV port was placed for C1 inhibitor infusions at home. Over the next couple of years, she underwent several port revisions and replacements due to poor flow and port clotting issues. Despite access difficulties, she remained on C1 inhibitor IV treatments with good control of her symptoms until she had the opportunity to enroll in a

clinical trial for lanadelumab. She entered a clinical trial of lanadelumab 300 mg SQ every 2 weeks and continued on this medication when the drug was available commercially. She subsequently entered the clinical trial of berotralstat 150 mg orally and is currently on the commercially available product. She is tolerating this drug well, with minimal breakthrough attacks.

## DEFINITION

Hereditary angioedema (HAE) is a rare disorder caused mainly by the lack of, or diminished function of an enzyme, C1 inhibitor (C1-INH). The end result is the overproduction of bradykinin, which increases localized permeability of blood vessels, resulting in tissue swelling. It is characterized by recurrent facial, abdominal, or extremity swelling—typically without urticaria or pruritus.<sup>2,3</sup>

C1-INH is a member of the serpin (serine protease inhibitor) superfamily, with significant homology to  $\alpha$ 1-antitrypsin. The gene, named SERPING1, is located on chromosome 11 (p11.2-q13). It is a suicide inhibitor, forming a complex with the target protease, followed by clearance of the entire complex.<sup>2-5</sup>

C1-INH inhibits steps in the classical and lectin complement pathways, intrinsic coagulation pathway (contact system), fibrinolytic pathway, and kinin-generating pathways (most directly related to the pathogenesis of HAE) (Figures 1 and 2).<sup>2,5,6</sup>

## Clinical Characteristics

Patients with HAE will complain of episodic, nonpruritic swelling

of skin and submucosal tissues (extremities, abdomen, genitourinary tract, face, oropharynx, larynx). It is usually associated with pain, nausea, vomiting, diarrhea, and possibly life-threatening airway obstruction. A prodromal serpiginous erythematous rash is sometimes seen, but HAE should not have a pruritic urticarial rash. Thus, usually urticaria with pruritus makes the diagnosis of HAE unlikely. The age of onset is variable and may present under 1 year of age. Laryngeal attacks are uncommon before age 3 years and tend to occur later than other symptoms. Angioedema events often worsen with hormonal changes like puberty, the use of estrogen-containing birth control pills, or hormone replacement. Other triggers for HAE attacks include stress, fatigue, infection, mechanical trauma (ie, intubation), and angiotensin-converting enzyme (ACE) inhibitor usage.<sup>3</sup>

### Classification

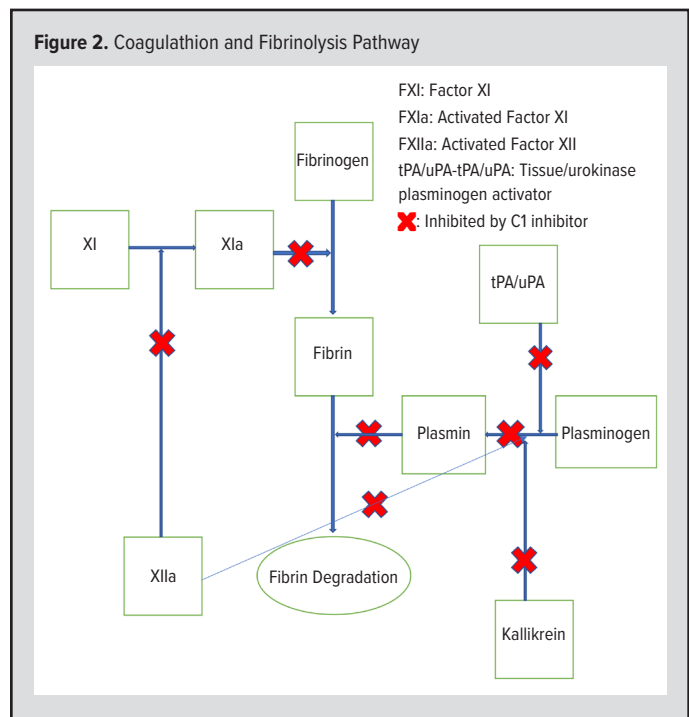
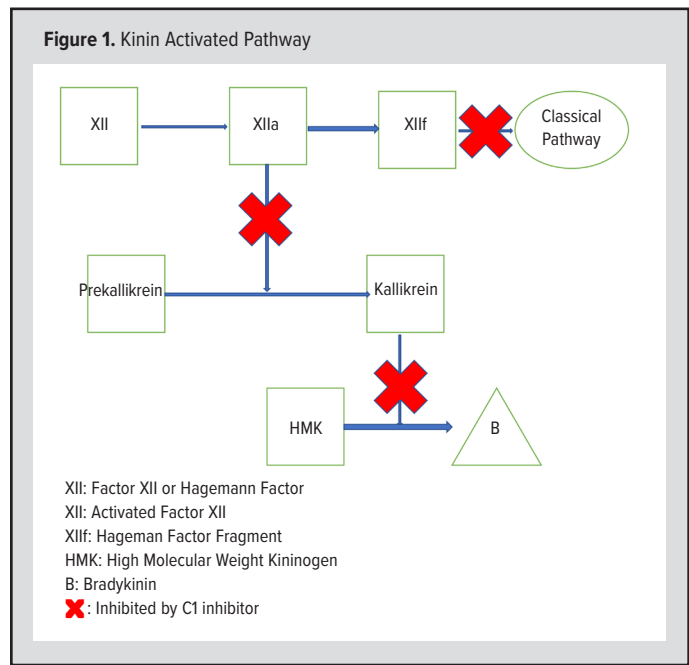
The prevalence of HAE in North America and Europe is about 1.1 and 1.6 per 50,000, respectively.<sup>3</sup> There are different forms of HAE currently recognized: HAE type 1, HAE type 2, and HAE with normal C-INH.

HAE type 1, due to low quantitative and functional C1-INH levels, is an autosomal-dominant disease and occurs in 85% of cases. However, patients do not always have a positive family history. Approximately 25% of the patients with HAE have a de novo mutation in the C1-INH gene (SERPING1). During episodes of angioedema in patients with HAE, plasma bradykinin levels have been shown to be 7-fold higher than normal.<sup>2-4</sup>

HAE type 2 is also autosomal dominant and occurs in 15% of cases. It is characterized by normal quantitative and low functional C1-INH levels. These patients have the same clinical features as HAE type 1.<sup>3</sup>

The primary mediator of swelling in HAE type 1 and 2 is bradykinin, which is generated when plasma kallikrein cleaves high-molecular-weight kininogen. It is metabolized by endogenous metalloproteases like ACE. Plasma kallikrein is activated from its inactive zymogen prekallikrein by the protease factor XII. Both plasma kallikrein and factor XII are inhibited by C1-INH. Increased vascular permeability induced by the liberation of bradykinin in angioedema is primarily mediated through the bradykinin B2 receptor.<sup>2,3,5</sup>

HAE with normal C1-INH shares the same clinical features of HAE types 1 and 2, but with normal quantitative and functional C1-INH levels. It has been associated with different genetic mutations. One mutation is in the factor XII gene. There have been reports of 2 new mutations in angiotensin-1 and plasminogen. However, in most patients with HAE with normal C1-INH, no gene mutation can be found and the exact pathogenesis is unknown. There is some evidence that bradykinin may play a role in some types of HAE with normal C1-INH, primarily in patients with a FXII mutation.<sup>2,5</sup>



### Differential Diagnosis

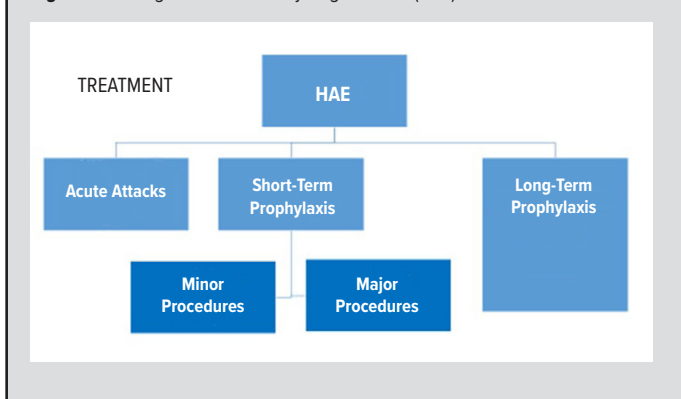
**ACE Inhibitor Angioedema:** ACE inhibitor angioedema is associated primarily with ACE inhibitor use. It is a bradykinin-induced angioedema that results from medications that increase production or decrease degradation of bradykinin. Other medications implicated in this category include blockers of the renin-angiotensin-aldosterone system like angiotensin receptor blockers (ARB), dipeptidyl peptidase 4 inhibitors, and neprilysin inhibitors. Incidence is about 0.1% to 0.7% of patients on an ACE inhibitor.<sup>7,8</sup> Symptoms prominently involve the face and tongue. Higher

**Table.** Laboratory Value of the Different Types of Angioedema

	C1-INH Level	C1-INH Function	C4	C3	C1Q
HAE type 1	Low	Low	Low	Normal	Normal
HAE type 2	Normal-High	Low	Low	Normal	Normal
HAE-nC1-INH	Normal	Normal	Normal	Normal	Normal
Acq-AE	Low	Low	Low	Low-Normal	Low
ACEi-AE	Normal	Normal	Normal	Normal	Normal
IAE	Normal	Normal	Normal	Normal	Normal

Abbreviations: C1-INH, C1 inhibitor; HAE, hereditary angioedema; HAE-nC1-INH, HAE with normal C1-INH; Acq-AE, acquired angioedema; ACEi-AE, ACE inhibitor angioedema; IAE, idiopathic angioedema.

**Figure 3.** Management of Hereditary Angioedema (HAE)



risk is shown in African Americans. Other risk factors for ACE inhibitor angioedema include smoking, increasing age, and female sex. Laboratory findings for patients with ACE inhibitor angioedema include a normal C4, normal C1-INH, and normal C1Q. Treatment includes discontinuation of ACE inhibitor angioedema/ARB. Efficacy of icatibant/fresh frozen plasma has been described but has not been reproduced in phase 3 trials and, therefore, is not approved by the US Food and Drug Administration (FDA) for this indication.<sup>9,10</sup>

**Acquired Angioedema:** Acquired angioedema is angioedema usually associated with lymphoproliferative diseases (lymphoma and autoimmune disorders like systemic lupus erythematosus). Laboratory workup will show a low C4, low C-INH (quantitative and functional), and low C1Q. Acquired angioedema may be associated with C1-INH autoantibodies. Androgens and antifibrinolytics have been used for long-term prophylaxis. Ecallantide and icatibant treatment has been reported to be effective as on-demand therapy for attacks.<sup>11</sup>

**Idiopathic Angioedema:** Idiopathic angioedema is a diagnosis of recurrent angioedema after having ruled out all other angioedema diagnoses. Idiopathic histaminergic angioedema is the most common form of angioedema observed in clinical practice. Laboratory

workup will show a normal C4, normal C1-INH, normal C1Q, and normal trypsin. Since it is mostly histaminergic in nature, initial treatment would include continuous administration of a 4-fold antihistamine dose. After failure of antihistamines, omalizumab, an anti-IgE monoclonal antibody, is suggested for 6 months. Failure of omalizumab suggests an idiopathic, nonhistaminergic angioedema<sup>12</sup> (Table).

## TREATMENT

Treatment of HAE type 1 and type 2 consists of on-demand therapy, short-term prophylaxis, and long-term prophylaxis. (See Figures 3 and 4.)

**On-demand Therapy:** On-demand therapy is given during acute attacks, especially attacks involving the upper airway. Attacks of the airway can be life-threatening and need attention and on-demand treatment immediately. Abdominal attacks could cause extreme pain. Extremity attacks of the hands and feet could be debilitating. Therefore, acute attacks—especially those affecting the airway—should be treated immediately. It is recommended that all patients have sufficient medication for on-demand treatment of 2 attacks and carry on-demand medication at all times.<sup>2,3</sup>

**Bradykinin-Receptor Antagonist:** Icatibant (Firazyr; Shire) is an antagonist of the bradykinin B2 receptor and prevents binding of bradykinin. When bradykinin binds to the bradykinin B2 receptor, there is subsequent vasodilation and increased capillary permeability. Icatibant is a self-administered on-demand treatment for HAE attacks in adults and children (> 2 years) with a plasma half-life of 1 to 2 hours. Allergic reactions have not been reported, but there are reports of transient local injection site reactions (erythema, wheal, pruritus, and burning sensation).<sup>10</sup> Adult dosing for icatibant is 30 mg SQ, which may be repeated every 6 hours for a maximum dose of 90 mg/day. Pediatric dosing for children older than 2 years is 0.4 mg/kg once SQ, with a maximum dose of 30 mg/dose.

**C1-Inhibitor Concentrate:** Plasma derived C1-INH concentrate or recombinant C1-INH concentrate replaces the deficient/dysfunctional protein in HAE type 1 and type 2 patients. Exogenous C1-INH concentrate acts on the same targets as endogenous C1-INH. Treatment results in an increase of the plasma levels of C1-INH and helps to regulate all cascade systems involved in the production of bradykinin during attacks. One unit of C1-INH concentrate corresponds to the mean quantity of C1-INH present in 1 mL fresh normal plasma. Plasma-derived C1-INH concentrate is obtained by separating C1-INH from cryodepleted human plasma by adsorption and precipitation, purification, pasteurization, and virus filtration. Currently 2 plasma-derived C1-INH concentrates are available for on-demand treatment of HAE type 1 and type 2: Berinert (CSL Behring) and Cinryze (Shire).<sup>13,14</sup> Berinert dosing for on-demand therapy in children older than 5

years and adults is 20 units/kg IV; Cinryze dosing for children older than 6 years and adults is 1000 units IV, which may be repeated in 1 hour if needed.

**Recombinant C1-INH:** The only currently available recombinant human C1-INH is Ruconest (Pharming). There is a similar mode of action to plasma-derived C1-INH. It is indicated for on-demand treatment for HAE attacks in adults and adolescents older than 13 years. It is derived from the milk of transgenic rabbits, thus contraindicated in patients with a suspected or known rabbit allergy. The plasma half-life is approximately 3 hours. Transmission of human viruses is not a concern.<sup>13,14</sup> Dosing for on-demand therapy is 50 units/kg (max dose of 4200 units as a single dose) for <84 kg and 4200 units as a single dose for ≥84 kg.

**Kallikrein Inhibitor:** Ecallantide is a kallikrein inhibitor (Kalbitor; Shire) currently indicated for the on-demand treatment of HAE attacks in patients aged 12 years and older. Inhibition of kallikrein activity inhibits the cleavage of high-molecular-weight kininogen to bradykinin, as well as the further activation of activated factor XII. Ecallantide is a protein produced in the yeast *Pichia pastoris*. It has a plasma half-life of 2 hours. The main safety concern is potentially serious hypersensitivity reactions, including anaphylaxis, which was reported in 3% to 4% of treated patients. Thus, ecallantide has a black box warning for anaphylaxis and should be administered in a health care setting with appropriate medical support to manage anaphylaxis.<sup>15</sup> Dosing for HAE attacks in children older than 12 years and adults is 30 mg SQ (in three 10 mg injections); if attacks persist, another 30 mg may be repeated within 24 hours.

**Short-Term Preprocedural Prophylaxis:** Patients with HAE may have episodes of swelling near the site of intervention during procedures such as surgical trauma, dental surgery, endotracheal intubation, bronchoscopy, or esophagogastroduodenoscopy. Swellings associated with these procedures usually occur within 48 hours. Therefore, preprocedural prophylaxis with C1-INH concentrate is recommended as close as possible to the start of the procedure, 1000 units or a dose of 20 units/kg of plasma-derived C1-INH. Fresh frozen plasma may be used for short-term prophylaxis and on-demand therapy but is not as safe as C1-INH concentrate and is a second-line agent because of the greater risk of bloodborne disease transmission and allosensitization.<sup>2,16</sup>

**Anabolic Androgens (17 $\alpha$ -alkylated Androgens):** Attenuated androgens danazol (2.5-10 mg/kg/d, max 600 mg) and stanozolol

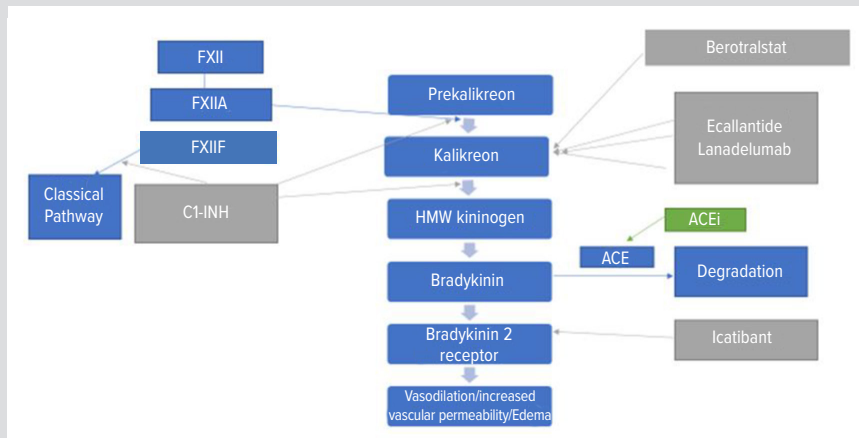
(4-6 mg/d) can be used for preprocedural prophylaxis as an alternative to C1-INH concentrates. For scheduled preprocedural prophylaxis, androgens are started for 5 days before and 2 to 3 days after procedure. Short courses of androgen are even considered safe for children.<sup>2,16</sup>

With all preprocedural prophylactic treatments, breakthrough attacks can occur, so patients should remain under observation, and on-demand treatment needs to be available.<sup>2,16</sup>

**Long-Term Prophylaxis (LTP):** In patients with confirmed HAE type 1 and type 2 with frequent attacks, scheduled or regular use of medication is considered to reduce the burden of the disease. Individualized treatment plans should be considered, taking into account the activity of the disease, frequency of attacks, patient's quality of life, availability of health care resources, and failure to achieve adequate control by appropriate on-demand therapy. The patient's preferences should be taken into consideration because successful long-term prophylaxis requires a high degree of compliance. All patients with HAE should be evaluated for long-term prophylaxis at every visit, at least once a year. Patients with ongoing long-term prophylaxis should be assessed regularly for efficacy and safety of the therapy, and dosage and/or treatment interval should be adapted according to the clinical response. Breakthrough symptoms like upper airway edema and other attacks may occur, despite the use of long-term prophylaxis. Therefore, all patients using long-term prophylaxis should also have on-demand medication (eg, icatibant, C1-INH concentrate, or ecallantide) readily available.<sup>2</sup>

**Plasma-Derived C1-INH:** Plasma-derived C1-INH is a safe and effective long-term prophylaxis for the prevention of HAE attacks. Dosing should be at least twice a week based upon its half-life. Dose and/or frequency may need adjustment for optimum efficacy, typically at 40 U/kg or 60 U/kg body weight to pro-

**Figure 4. Targeted New Treatments for Hereditary Angioedema**



Abbreviations: FXII, factor XII; C1-INH, C1 inhibitor; HMW, high molecular weight kininogen; ACE, angiotensin converter enzyme; ACEi, ACE inhibitor.

vide satisfactory dose-dependent preventive effects. The SQ route (Haegarda, CSL Behring) may provide more convenient administration and maintain improved steady-state plasma concentrations of C1-INH.<sup>6,14</sup>

For patients who are on plasma-derived C1-INH, there is a rare occurrence of thromboembolic events that may occur in patients with underlying thromboembolic risk factors (eg, implanted central venous catheters). Vaccination for hepatitis A and B also should be considered in patients requiring repeated administration of human plasma-derived products due to the concern of transmission of blood-borne viruses.<sup>12,17</sup>

**Lanadelumab:** Lanadelumab (Takshyro, Shire Pharmaceuticals) was approved by the FDA in 2018. It is a recombinant, fully human immunoglobulin monoclonal antibody inhibitor of kallikrein produced in Chinese hamster ovary cells. Dosing is 300 mg SQ every 2 weeks; spacing out to every 4 weeks may be considered in some patients. This medication may be self-administered at home. A phase 3, randomized, double-blind, parallel-group, placebo-controlled trial, 26-week treatment with SQ lanadelumab 150 mg every 4 weeks (n=28), 300 mg every 4 weeks (n=29), 300 mg every 2 weeks (n=27), or placebo (n=41), showed that treatment with SQ lanadelumab for 26 weeks significantly reduced the attack rate compared with placebo. The most common adverse drug reactions in patients are injection site reactions, upper respiratory infections, headache, rash, muscle pain, dizziness, and diarrhea.<sup>17</sup>

**Berotralstat:** Berotralstat (Orladeyo, Biocryst) is an oral, once-daily tablet, inhibitor of plasma kallikrein. Dosing is 110-150 mg daily with meals for adults and children older than 12 years. In a double-blind, parallel-group study that randomized 120 patients to receive once-daily berotralstat in a dose of 110 mg, 150 mg, or placebo, berotralstat demonstrated a significant reduction in attack rate at both 110 mg (1.65 attacks per month;  $P=.024$ ) and 150 mg (1.31 attacks per month;  $P<.001$ ) relative to placebo (2.35 attacks per month). The most frequent reported adverse events with berotralstat were abdominal pain, vomiting, diarrhea, and back pain. Doses >150 mg have been associated with QT prolongation.<sup>18</sup>

**Androgens:** Androgen derivatives have long been used for long-term prophylaxis in HAE type 1 and type 2. Oral administration makes these medications easy to use; however, there are major concerns about their androgenic and anabolic adverse effects, especially in women. Androgens can cause virilization, menstrual disorders, and even amenorrhea. They can also cause weight gain, headache, myalgia, depression, and acne. Androgens are contraindicated during pregnancy, as they can cause virilization of the fetus. In children and adolescents, therapy with androgens may interfere with growth and maturation. Androgens also cause numerous drug interactions (as with statins). Patients on androgens should routinely have liver panel and urine tests and an annual ultrasound of the liver.<sup>2,16</sup>

The dose of androgens needed to control HAE attacks is from 100 mg every other day to 200 mg of danazol 3 times a day. The minimal effective dose should be used. Dosages above 200 mg of danazol daily for extended periods of time are not recommended because of side effects. The dosage should be adjusted according to clinical response and not adjusted based on C4 and C1-INH results.<sup>2,16</sup>

**Antifibrinolytics:** Epsilon aminocaproic acid and tranexamic acid (20-50 mg/kg/d) are oral antifibrinolytics widely used in Europe (not available in the US). These medications are not licensed for long-term prophylaxis although often are used for this indication. The mechanism of action for control of HAE is not completely understood. Common adverse reactions include nausea, diarrhea, vertigo, postural hypertension, fatigue, and muscle cramps/weakness from increased muscle enzyme concentrations. A major concern with use of this drug is enhanced thrombosis.<sup>16</sup>

**Avoidance of Triggers:** Triggers of HAE attacks include accidental trauma, surgical procedures, estrogen-containing oral contraceptive agents, and hormone replacement. Antihypertensive agents containing ACE inhibitors also may precipitate HAE swelling. Other triggers include stress, fatigue, infections, and the menstrual cycle. Mindful awareness and avoidance of triggers as much as possible can minimize precipitation of attacks; however, many attacks are unpredictable. Physicians should recommend judicious avoidance of suspected triggers and encourage a normal quality of life.<sup>2</sup>

## CONCLUSIONS

HAE patients are encouraged to find a health care provider with expertise in the disease and a health care facility that can manage and provide emergency treatment for severe attacks. Family members of HAE type 1 and type 2 patients should be screened for C1-INH function, C1-INH protein, and C4 plasma levels. Delayed diagnosis could lead to increased morbidity with life-threatening consequences. A comprehensive and tailored therapeutic strategy to include avoidance of triggers and pharmacotherapy options can effectively mitigate morbidity and mortality and improve quality of life for patients with HAE.

**Funding/Support:** None declared.

**Financial Disclosures:** None declared.

## REFERENCES

1. Chen WL, Gallagher J, Zafra H, Gedeit R. Hereditary angioedema presenting as compartment syndrome in a white girl. *Ann Allergy Asthma Immunol.* 2016;117(3):321-322. doi:10.1016/j.anai.2016.06.021
2. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—the 2017 revision and update. *Allergy.* 2018;73(8):1575-1596. doi:10.1111/all.13384
3. Zuraw BL, Bernstein JA, Lang DM, et al. A focused parameter update: hereditary

- angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol*. 2013;131(6):1491-1493. doi:10.1016/j.jaci.2013.03.034
4. Zuraw BL. Hereditary angioedema with normal C1 inhibitor: four types and counting. *J Allergy Clin Immunol*. 2018;141(3):884-885. doi:10.1016/j.jaci.2018.01.015
  5. Busse PJ, Christiansen SC. Hereditary angioedema. *N Engl J Med*. 2020;382(12):1136-1148. doi:10.1056/NEJMra1808012
  6. Bork K. Pasteurized and nanofiltered, plasma-derived C1 esterase inhibitor concentrate for the treatment of hereditary angioedema. *Immunotherapy*. 2014;6(5):533-551. doi:10.2217/imt.14.33
  7. Baş M, Greve J, Stelter K, et al. A randomized trial of icatibant in ACE-inhibitor-induced angioedema. *N Engl J Med*. 2015;372(5):418-425. doi:10.1056/NEJMoa1312524
  8. Hudey SN, Westermann-Clark E, Lockey RF. Cardiovascular and diabetic medications that cause bradykinin-mediated angioedema. *J Allergy Clin Immunol Pract*. 2017;5(3):610-615.
  9. Kostis WJ, Shetty M, Chowdhury YS, Kostis JB. ACE inhibitor-induced angioedema: a review. *Curr Hypertens Rep*. 2018;20(7):55. doi:10.1007/s11906-018-0859-x
  10. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med*. 2010;363(6):532-541. doi:10.1056/NEJMoa0906393
  11. Patel G, Pongracic JA. Hereditary and acquired angioedema. *Allergy Asthma Proc*. 2019;40(6):441-445. doi:10.2500/aap.2019.40.4267
  12. Belbézier A, Bocquet A, Bouillet L. Idiopathic angioedema: current challenges. *J Asthma Allergy*. 2020;13:137-144. doi:10.2147/JAA.S205709
  13. Li HH. Self-administered C1 esterase inhibitor concentrates for the management of hereditary angioedema: usability and patient acceptance. *Patient Prefer Adherence*. 2016;10:1727-1737. doi:10.2147/PPA.S86379
  14. Henry Li H, Riedl M, Kashkin J. Update on the use of C1-esterase inhibitor replacement therapy in the acute and prophylactic treatment of hereditary angioedema. *Clin Rev Allergy Immunol*. 2019;56(2):207-218. doi:10.1007/s12016-018-8684-1
  15. Duffey H, Firszt R. Management of acute attacks of hereditary angioedema: role of ecallantide. *J Blood Med*. 2015;6:115-123. doi:10.2147/JBM.S66825
  16. Longhurst H, Zinser E. Prophylactic therapy for hereditary angioedema. *Immunol Allergy Clin North Am*. 2017;37(3):557-570. doi:10.1016/j.iac.2017.04.003
  17. Banerji A, Riedl MA, Bernstein JA, et al. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. *JAMA*. 2018;320(20):2108-2121. doi:10.1001/jama.2018.16773
  18. Zuraw B, Lumry WR, Johnston DT, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial. *J Allergy Clin Immunol*. 2021;148(1):164-172.e9. doi:10.1016/j.jaci.2020.10.015

advancing the art & science of medicine in the midwest

**WMJ**

*WMJ* (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

© 2022 Board of Regents of the University of Wisconsin System and The Medical College of Wisconsin, Inc.

**Visit [www.wmjonline.org](http://www.wmjonline.org) to learn more.**