

## A roadmap for optimal care of the patient with hereditary angioedema

The United States **Hereditary Angioedema Association (HAEA)** and *Allergy and Asthma Proceedings* have joined forces to publish an *HAE Primer*, which focuses on the diagnosis and management of hereditary angioedema (HAE), a rare, debilitating, life-threatening genetic condition that causes significant morbidity in individuals who are affected and their families. Founded in 1999 and staffed by people with HAE and caregivers, the HAEA is a nonprofit organization that works to help people with HAE live life to the fullest, ultimately unburdened by symptoms. The HAEA achieves its goals by leading a nationwide advocacy movement that focuses on increasing HAE awareness and education, empowering access to suitable treatment, and fostering ground-breaking research. This mission overlaps with that of *Allergy and Asthma Proceedings*, which is to distribute timely information with regard to advancements in the knowledge and practice of allergy, asthma, and immunology to clinicians entrusted with the care of patients. The wide variety of effective on-demand and prophylactic HAE therapies challenge clinicians to make a correct diagnosis and tailor treatment plans that best fit an individual's lifestyle and needs. In this spirit, we are grateful to the HAEA for having provided funding to support the development and publication of this *HAE Primer*.

The *HAE Primer* commences with a review of the definition and classification of HAE by Proper *et al.*,<sup>1</sup> who emphasize the importance of a thorough clinical history and differential diagnostic evaluation to ensure that patients are accurately diagnosed and classified. A presentation by Lumry and Settupane<sup>2</sup> follows, with a review of the extent and degree to which treatment advances have not only lowered disease and treatment burdens but which have also improved the quality of life of patients with HAE. Wedner<sup>3</sup> provides an overview of HAE pathophysiology by focusing on the central role of uncontrolled production of the vasoactive peptide, bradykinin, which is the flashpoint molecule that ignites the majority of cases of HAE. Hsu *et al.*<sup>4</sup> reviewed the variable presentations of HAE that can make the diagnosis of HAE challenging. Manning<sup>5</sup> reviewed the importance of differential diagnosis, diagnostic tests, and family screening in determining the correct diagnosis.

He emphasized that it is critical to develop an appropriate differential diagnosis, work through the various conditions, and obtain the pertinent laboratory results required to confirm or exclude the diagnosis of HAE.<sup>5</sup> In transitioning to treatment, Christiansen and Zuraw<sup>6</sup> reviewed options with regard to on-demand treatment of acute attacks, Craig<sup>7</sup> reviewed choices for short-term prophylactic treatment, and Li<sup>8</sup> reviewed alternatives for long-term prophylactic treatment. Paige *et al.*<sup>9</sup> addressed essential elements of an individualized comprehensive management plan of patients with HAE by focusing on the need for access to an HAE specialist, continuing patient education, availability of effective treatment options, coordination of care and management of treatment logistics with other health care specialists, ongoing monitoring of attacks and treatments, and other resources for patient support. Women and children with HAE are particular populations known to have unique challenges and vulnerabilities that require specialized needs. Yakoboski *et al.*<sup>10</sup> addressed these special considerations in women; and Johnston and Smith<sup>11</sup> addressed these unique requirements in children. In looking toward the future, Kaplan<sup>12</sup> provided a prescient view of the latest research that involves investigational therapies for HAE. In a concluding presentation, Settupane *et al.*<sup>13</sup> highlights the importance of shared decision-making and development of related aids in facilitating the interrelated and interdependent interaction of practitioners and patients required for success of HAE management.

In summary, this *HAE Primer* is dedicated to assisting health care providers with a comprehensive roadmap to deliver optimal care to patients with HAE. The HAEA and the *Allergy and Proceedings* are pleased to be a part of this important educational process.

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### REFERENCES

1. Proper SP, Lavery WJ, Bernstein JA. Definition and classification of hereditary angioedema. *Allergy Asthma Proc.* 2020; 41:S3-S7.
2. Lumry W, Settupane RA. Hereditary angioedema: epidemiology and burden of illness. *Allergy Asthma Proc.* 2020; 41:S8-S13.
3. Wedner HJ. Hereditary angioedema: Pathophysiology (HAE type I, HAE type II, and HAE nC1-INH). *Allergy Asthma Proc.* 2020; 41:S14-S17.

4. Azmy V, Brooks JP, Hsu FI. Clinical presentation of hereditary angioedema. *Allergy Asthma Proc.* 2020; 41:S18–S21.
5. Manning ME. Hereditary angioedema: differential diagnosis, diagnostic tests and family screening. *Allergy Asthma Proc.* 2020; 41:S22–S25.
6. Christiansen S, Zuraw B. Hereditary angioedema: on-demand treatment of acute attacks. *Allergy Asthma Proc.* 2020; 41:S26–S29.
7. Craig T. Hereditary angioedema: triggers and short-term prophylactic treatment. *Allergy Asthma Proc.* 2020; 41:S30–S34.
8. Li HH. Hereditary angioedema: long-term prophylactic treatment. *Allergy Asthma Proc.* 2020; 41:S35–S37.
9. Paige D, Maina N, Anderson J. Comprehensive management plans and patient support with hereditary angioedema. *Allergy Asthma Proc.* 2020; 41:S38–S42.
10. Johnston DT, Smith RC. Hereditary angioedema: special considerations in children. *Allergy Asthma Proc.* 2020; 41:S43–S46.
11. Yakoboski E, Motazedi T, Banerji A. Hereditary angioedema: special considerations in women. *Allergy Asthma Proc.* 2020; 41:S47–S50.
12. Kaplan A. Hereditary angioedema: investigational therapies and future research. *Allergy Asthma Proc.* 2020; 41:S51–S54.
13. Settiane RA, Bukstein D, Riedl M. Shared decision making in HAE management. *Allergy Asthma Proc.* 2020; 41:S55–S60. □

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# Definition and classification of hereditary angioedema

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## ABSTRACT

Hereditary angioedema (HAE) is defined as a rare genetic disease with recurrent episodes of localized bradykinin-mediated swelling of the deep tissues of the skin, respiratory, and gastrointestinal tracts that can be life threatening. Classification of HAE has evolved over time with our further understanding of clinical phenotypes, underlying causes, and available testing. In most cases, HAE is caused by a deficiency of C1-esterase inhibitor (C1-INH) on the Serpin Family G Member 1 (SERPING1) gene, either through decreased amounts of C1-INH protein (C1-INH-HAE, type 1) or decreased function of C1-INH (C1-INH-HAE, type 2). HAE with normal C1-INH levels and function are divided into unknown cause or into non-C1-INH-HAE forms, which include known mutational defects in factor XII (called FXII-HAE in the Hereditary Angioedema International Working Group consensus), angiopoietin-1, plasminogen, and kininogen 1 genes. It is possible that, after an initial workup, a patient without a family history of HAE could be classified with an acquired form of angioedema (nonhereditary) that may later prove to be HAE due to a *de-novo* SERPING1 mutation. Because there are forms of nonhistaminergic (H<sub>1</sub>-antihistamine unresponsive) angioedema that appear clinically very similar to HAE, it is essential that the patient undergoes a thorough clinical history and diagnostic evaluation to ensure that he or she is properly diagnosed and classified.

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## DEFINITION OF HEREDITARY ANGIOEDEMA

Angioedema is defined as “a localized, self-limiting, asymmetric and disfiguring non-inflammatory edema of the deep dermis or subcutaneous or submucosal tissues that occurs as a result of vasodilation and increased vascular permeability. HAE [hereditary angioedema] comprises a group of diseases characterized by recurrent angioedema caused by excess bradykinin production, with an autosomal dominant inheritance pattern.”<sup>1</sup> Angioedema is seen in ~40% of patients with chronic spontaneous urticaria (CSU) but can appear alone in up to 20% of patients. The initial approach in evaluating a patient who presents with isolated angioedema is to determine if the angioedema is responsive or unresponsive to treatments that control CSU; however, appropriate diagnostic testing, *e.g.*, a serum C4 level, to exclude HAE as a potential cause should be obtained simultaneously. An algorithm for evaluating patients who present with wheals and/or angioedema has been adapted as part of an international guideline for the treatment of angioedema and CSU (Fig. 1).<sup>2</sup> In a

patient who presents with isolated angioedema and without a family history, response to treatment with H<sub>1</sub>-antihistamines is helpful both therapeutically and diagnostically. However, if a patient is not responsive to high-dose H<sub>1</sub>-antihistamines, advocated as step 2 therapy in the urticarial guidelines, it is still possible that a patient may respond to step 3 or step 4 treatments recommended for CSU with or without angioedema. In these circumstances, clinicians should broaden their differential diagnosis to include bradykinin-mediated causes of angioedema.<sup>2,3</sup>

Patients with HAE experience recurrent angioedema attacks anywhere in the body but, most notably, areas that involve the extremities, gastrointestinal tract, oropharynx, face, and genitalia. In addition, they have a reliable family history of angioedema in 75% of cases (usually in a first-degree relative) associated with C1-esterase inhibitor (C1-INH) functional deficiency.<sup>4</sup> However, in 25% of patients with HAE, there may be no family history because of a spontaneous *de novo* mutation.<sup>4</sup> Bradykinin, the mediator involved in HAE, is significantly increased as the result of a deficiency and/or functional abnormality of C1-INH, which is important for regulating bradykinin formation at many sites in the contact pathway.<sup>5</sup>

Original work by Donaldson and Evans<sup>6</sup> revealed, when using complement component antibodies, that patients with HAE had deficient C1-INH and that other complement components were decreased during and/or between swelling attacks. The relevance of these findings has subsequently been confirmed in a number of knockout mouse models and *in vitro* experiments that ultimately led to the development of several novel and effective therapies designed to either replace C1-INH, block bradykinin 2

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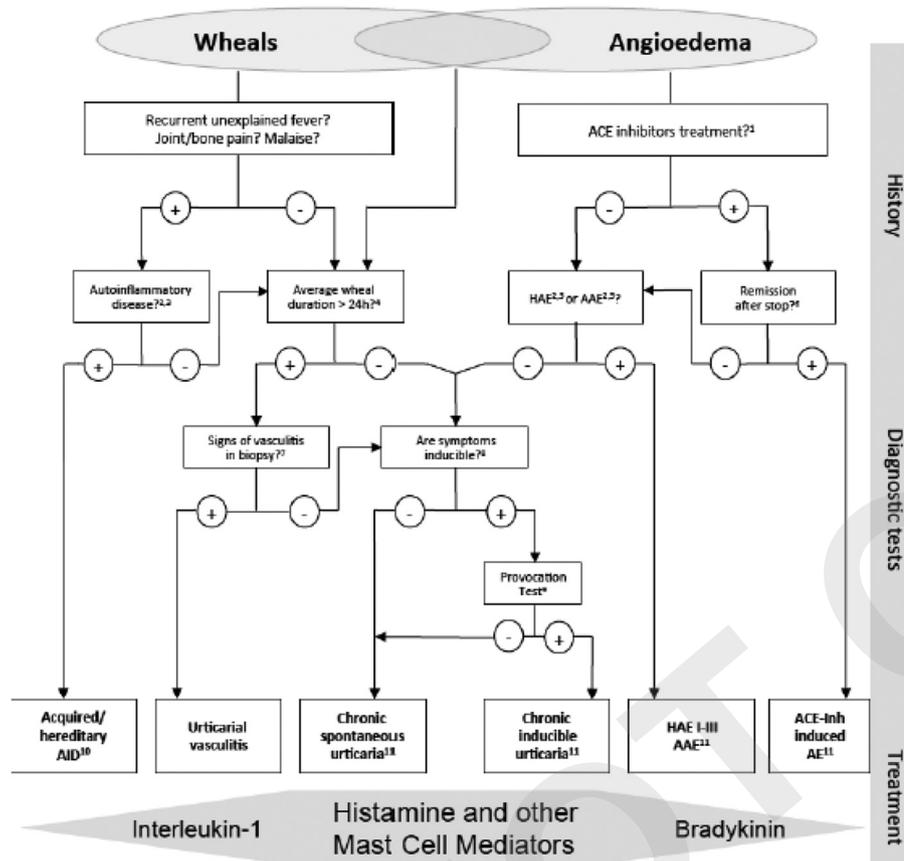


Figure 1. Algorithmic approach for evaluating patients who present with wheals and/or angioedema (from Ref. 2).

receptors, or inhibit the critical protein, kallikrein, important for converting high-molecular-weight kininogen to form bradykinin, thereby vastly improving the quality of life of the patient with HAE.<sup>7-13</sup>

### CLASSIFICATION OF HAE BY COMPLEMENT TESTING

Although complement testing is considered an important method for classifying patients with HAE, complement consumption has very little involvement in the pathogenesis of HAE. The C1-INH and complement components that differentiate various forms of nonhistaminergic angioedema are summarized in Table 1 and is one approach used to classify different types of non-histaminergic angioedema. For HAE type 1, the patient should have a low C4, C1-INH functional and quantitative level, and a normal C1q, whereas patients with HAE type 2 should have a low C4, low C1-INH functional level, and normal or high C1-INH quantitative level, with a normal C1q level.<sup>4,14</sup> The only difference based on complement testing between HAE and acquired C1-INH angioedema is that the latter will typically have a low C1q level. All the other forms of bradykinin-mediated angioedema will have normal complement levels.<sup>4,14</sup>

Because HAE is a relatively rare disease that occurs in 1:50,000 or fewer patients, obtaining a full battery of

complement testing on every patient with isolated angioedema is costly and not warranted unless there is a clear family history. Therefore, screening with a C4 level is the first step in classifying and diagnosing patients with HAE; however, this test can be normal in a small subset of patients with a C1-INH-HAE deficient if measured when they are asymptomatic. If low, then obtaining a C1-INH functional and quantitative level and a C1q level is appropriate to confirm or exclude HAE and to further classify whether the patient has HAE type 1 or type 2.<sup>4,14</sup>

There are certain caveats that require consideration when ordering complement testing to classify patients with HAE. First, C4 is a good screening tool but sometimes can be slightly or significantly low due to laboratory handling and processing or due to an unrecognized C4 heterozygous or homozygous deficiency. In the former scenario, repeating the test is appropriate, and, in the latter instance, if C1-INH functional and quantitative testing is normal, then genotyping to further confirm a genetic C4 deficiency and a workup for underlying disease processes, such as sarcoidosis, celiac disease, lymphoma, or systemic lupus erythematosus, may be warranted, depending on the patient's clinical presentation.<sup>15,16</sup> In addition, C2 is not a useful laboratory test for screening because it is often normal between attacks.<sup>4</sup> Also, the results of tests for C1-INH

**Table 1 Classification of HAE and other nonhistaminergic angioedema types by C1-INH and complement component levels**

Type of Angioedema	C1-INH Antigen*	C1-INH Function*#	C4	C2§	C1q¶	Autoantibody to C1-INH
HAE type 1 (85% of C1-INH-HAE)#	↓	↓	↓	↓	NI	Usually absent
HAE type 2 (15% of C1-INH-HAE)#	NI or ↑	↓	↓	↓	NI	Usually absent
HAE-normal-complement (nC1-INH-HAE or U-HAE)	NI	NI	NI	NI	NI	Absent
C1-INH-AAE	NI or ↓	↓	↓	↓	↓	Present**
ACEI-AAE	NI	NI	NI	NI	NI	Absent
InH-HAE	NI	NI	NI	NI	NI	Absent

HAE = Hereditary angioedema; C1-INH = C1-esterase inhibitor; ↓ = decreased; NI = normal; ↑ = increased; nC1-INH-HAE = non-C1-esterase inhibitor form of HAE; U-HAE = HAE-normal-complement of unknown cause; AAE = acquired angioedema; ACEI = Angioedema Converting Enzyme-inhibitor induced; InH = idiopathic nonhistaminergic.

\*The C1-INH levels and functional activity when low in C1-INH HAE are usually <50% of normal; marginally low or borderline levels do not confirm C1-INH HAE.

#Results may vary, depending on the whether an enzymatic or chromogenic assay is used.

§Not consistently low between angioedema attacks and, therefore, is an unreliable screening test.

¶May be normal in AAE 30% of the time and low in HAE in some cases.

||C1-INH autoantibodies can generally be found at low titers in some in patients with C1-INH-HAE deficiency and in healthy subjects.

\*\*The presence of a lymphoproliferative disorder or monoclonal gammopathy of unknown significance is also frequently seen with or without a C1-INH autoantibody; whereas, high-titer autoantibodies to C1-INH are supportive of AAE-C1-INH deficiency, they are not required for diagnosis.

functional levels may vary, depending on whether a chromogenic or an enzymatic assay is used.<sup>17</sup>

### CLASSIFICATION OF HAE BY GENETIC TESTING

Previously, a consensus classification schema for bradykinin-mediated angioedema was developed by the Hereditary Angioedema International Working Group, which met in 2012 (Fig. 2).<sup>4</sup> This classification differentiates HAE from HAE-normal-complement, acquired angioedema, angioedema converting enzyme (ACE)-induced angioedema, HAE-normal-complement of unknown cause, and idiopathic histaminergic and nonhistaminergic angioedema. HAE types 1 and 2 have genetic mutations in the *SERPING1* gene, which results in a C1-INH functional deficiency. Patients with type 1 HAE have an actual defect in the *SERPING1* gene, with reduced production of functionally normal C1-INH protein, whereas patients with HAE type 2 are believed to have a mutation at or near the active site of the reactive mobile loop of C1-INH, which results in a functionally abnormal C1-INH protein.<sup>7</sup> Very recently, four genetic mutations in patients with HAE and with normal C1-INH levels and/or function have been identified in key non-C1-INH components of the kinin-kallikrein system, including factor

XII (*F12*), angiotensin-1 (*ANGPT1*), plasminogen (*PLG*), and kininogen 1 (*KNG1*). These additional mutations have been included in Fig. 2, our updated version of this classification scheme.<sup>18-21</sup> It is likely that the HAE-normal-complement of unknown cause will narrow as research in this area continues to evolve.<sup>4</sup>

HAE with normal C1-INH function used to be referred to as HAE type 3, but this nomenclature is no longer used and is now replaced by newer precise consensus definitions, in part because of recognition that there are now many examples of HAE-normal-complement associated with non-*SERPING1* gene mutations, as discussed above.<sup>1,18-21</sup> Currently, the HAE-normal-complement group is broadly divided into HAE-normal-complement of unknown cause or due to specific mutations that involve *F12*, *ANGPT1*, *PLG*, or *KNG1*.<sup>18-21</sup> The *F12* gene mutation is believed to result in increased factor XII activity due to a specific mutation in exon 9.<sup>21</sup> This angioedema type seems to affect females more than males, which has been speculated to be due to estrogen playing an important role in precipitating angioedema attacks.<sup>22</sup>

However, the role of estrogen has not been definitively confirmed, partly because males have also been identified with this mutation and, therefore, the lack of a relationship between increased estrogen and attacks should not discourage a workup for this mutation.<sup>23</sup> In

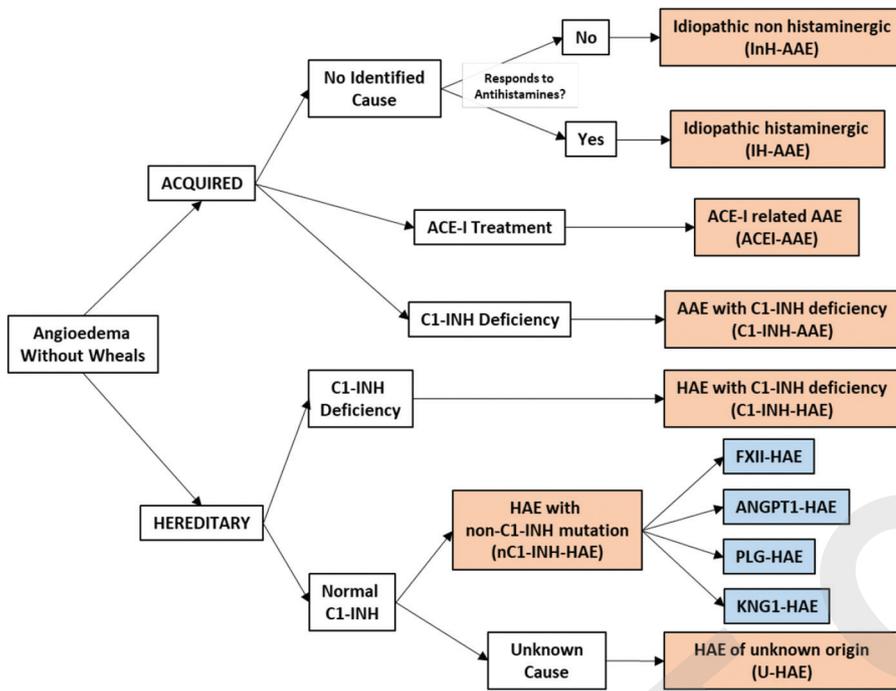


Figure 2. Specific classification of angioedema without wheals, which has been modified to incorporate some of the newer known mutations in non-C1-esterase inhibitor forms of HAE (nC1-INH-HAE) (from Ref. 4).

2018, a family that exhibited a mutation in the gene encoding for *ANGPT1* was identified.<sup>18</sup> *ANGPT1* is important for endothelial function, and it is believed that the mechanism in *ANGPT1*-HAE likely involves disruption of endothelial integrity.<sup>18</sup> Also discovered that same year in families with HAE-normal-complement was a *PLG* gene mutation.<sup>20</sup> The mechanism responsible for *PLG*-HAE is believed to be related to the conversion of *PLG* to plasmin, which results in activation of a contact system as well as factor XII.<sup>20</sup> The latest of these HAE-normal-complement mutations was identified in 2019 in a single family with a pathologic variant of *KNG1*, which suggests that changes in the N-terminal cleavage site of kininogen could result in a more active protein.<sup>19</sup> Research is ongoing to better characterize the mechanisms that underlie these genetic mutations that lead to angioedema.

In summary, HAE can be classified by C1-INH with complement component testing, and genetic testing. Our understanding of HAE types 1 and 2 bradykinin-mediated forms of angioedema is reflected by the rapid development of effective therapies. In contrast, our understanding of HAE-normal-complement forms of angioedema is still slowly evolving, which is evident by current gaps in diagnosis and treatment.

### Clinical Pearls

- HAE is caused by C1-INH deficiency due to a defect or mutation in *SERPING1*. A clear family history of angioedema is present in ~75% of cases of HAE due to C1-INH deficiency.

- Of patients with HAE, ~85% who have C1-INH-HAE have type 1, which is associated with a defect in the *SERPING1* gene, which results in decreased functional levels of normal C1-INH, whereas ~15% of patients with C1-INH-HAE have type 2, believed to be the result of a mutation at or near the active site of the reactive mobile loop of C1-INH, which results in a C1-INH protein lacking functional activity.
- All patients with recurrent angioedema or recurrent unexplained abdominal pain without urticaria and/or wheals should be screened for HAE with a C4 level and, if low, additional screening for C1-INH quantitative level and functional assay should be pursued. If there is a family history of angioedema, then a C1-INH quantitative level and functional assay should be obtained at the initial visit in conjunction with a C1q level.
- Rare forms of HAE-normal-complement that involve non-C1-INH genetic mutations involve *F12*, *ANGPT1*, *PLG*, and *KNG1* genes, although more may be identified.
- When a genetic cause is not identified for a patient with HAE-normal-complement in the presence of a family history, the patient is classified as HAE of unknown origin.

### REFERENCES

1. Giavina-Bianchi P, Arruda LK, Aun MV, et al. Brazilian guidelines for hereditary angioedema management - 2017 update part 1: definition, classification and diagnosis. *Clinics (Sao Paulo)*. 2018; 73:e310.

2. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018; 73:1393–1414.
3. Zuraw BL, Christiansen SC. Hereditary angioedema and bradykinin-mediated angioedema. In: Burks AW, Holgate ST, O’Hehir RE, Bacharier LB, Broide DH, Khurana-Hershey N, et al. editors. *Middleton’s allergy: principles and practice*. 9th ed. Elsevier, 2019; 576–590.
4. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy*. 2014; 69:602–616.
5. 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; 131:1491–1493.
6. Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C’ 1-esterase. *Am J Med*. 1963; 35:37–44.
7. Kaplan AP, Joseph K. Pathogenesis of hereditary angioedema: the role of the bradykinin-forming cascade. *Immunol Allergy Clin North Am*. 2017; 37:513–525.
8. Lumry WR, Craig T, Zuraw B, et al. Health-related quality of life with subcutaneous C1-inhibitor for prevention of attacks of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2018; 6:1733–1741.e3.
9. Baker JW, Bernstein JA, Harper JR, et al. Efficacy of recombinant human C1 esterase inhibitor across anatomic locations in acute hereditary angioedema attacks. *Allergy Asthma Proc*. 2018; 39:359–364.
10. Bernstein JA, Li HH, Craig TJ, et al. Indirect comparison of intravenous vs. subcutaneous C1-inhibitor placebo-controlled trials for routine prevention of hereditary angioedema attacks. *Allergy Asthma Clin Immunol*. 2019; 15:13.
11. Bernstein JA, Qazi M. Ecallantide: its pharmacology, pharmacokinetics, clinical efficacy and tolerability. *Expert Rev Clin Immunol*. 2010; 6:29–39.
12. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med*. 2010; 363:532–541.
13. Craig T, Zuraw B, Longhurst H, et al. Long-term outcomes with subcutaneous C1-inhibitor replacement therapy for prevention of hereditary angioedema attacks. *J Allergy Clin Immunol Pract*. 2019; 7:1793–1802.e2.
14. Bernstein JA. Update on angioedema: evaluation, diagnosis, and treatment. *Allergy Asthma Proc*. 2011; 32:408–412.
15. Liesmaa I, Paakkanen R, Jarvinen A, et al. Clinical features of patients with homozygous complement C4A or C4B deficiency. *PLoS One*. 2018; 13:e0199305.
16. Macedo AC, Isaac L. Systemic lupus erythematosus and deficiencies of early components of the complement classical pathway. *Front Immunol*. 2016; 7:55.
17. Li HH, Busse P, Lumry WR, et al. Comparison of chromogenic and ELISA functional C1 inhibitor tests in diagnosing hereditary angioedema. *J Allergy Clin Immunol Pract*. 2015; 3:200–205.
18. Bafunno V, Firinu D, D’Apolito M, et al. Mutation of the angiotensin-converting enzyme 1 gene (*ANGPT1*) associates with a new type of hereditary angioedema. *J Allergy Clin Immunol*. 2018; 141:1009–1017.
19. Bork K, Wulff K, Rossmann H, et al. Hereditary angioedema cosegregating with a novel kininogen 1 gene mutation changing the N-terminal cleavage site of bradykinin. *Allergy*. 2019; 74:2479–2481.
20. Bork K, Wulff K, Steinmüller-Magin L, et al. Hereditary angioedema with a mutation in the plasminogen gene. *Allergy*. 2018; 73:442–450.
21. Dewald G, Bork K. Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. *Biochem Biophys Res Commun*. 2006; 343:1286–1289.
22. Bork K, Wulff K, Witzke G, et al. Antihistamine-resistant angioedema in women with negative family history: estrogens and F12 gene mutations. *Am J Med*. 2013; 126:1142.e9–e14.
23. Veronez CL, Moreno AS, Constantino-Silva RN, et al. Hereditary angioedema with normal C1 inhibitor and F12 mutations in 42 Brazilian families. *J Allergy Clin Immunol Pract*. 2018; 6:1209–1216.e8. □

# Hereditary angioedema: Epidemiology and burden of disease

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## ABSTRACT

Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder characterized by swelling of subcutaneous, mucosal, and submucosal tissue without associated pruritus or wheals caused by a temporary localized increase in vascular permeability. Swelling attacks primarily affect the cutaneous tissue, abdominal viscera, genitals, or airways.

Reports of the prevalence of HAE C1 inhibitor (C1-INH) deficiency varies widely, from 1:50,000 to 1:100,000. The prevalence of HAE normal C1-INH is unknown but is likely much lower than HAE C1-INH. Approximately one-third of patients with recurrent angioedema without wheals have HAE.

The burden of disease for patients with HAE is substantial. Attacks are unpredictable with respect to frequency, severity, and the site that swells. Laryngeal attacks can be fatal if not treated promptly and appropriately. Feelings of stress, anxiety, and depression can trigger attacks, and begin a cycle of attacks that cause anxiety that, in turn, triggers further attacks. Despite full physical recovery between attacks, patients often experience continual emotional impairment and reduced quality of life (QoL). Absenteeism from work and presenteeism at work or educational activities for patients and caregivers increase stress and reduce productivity during and between attacks. Missed opportunities for career development are common.

Significant advances have been made in the past decade to expand both acute and prophylactic treatment options for patients with HAE, lowering both the disease and treatment burden, and improving the QoL of patients with HAE.

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Hereditary angioedema (HAE) is a rare genetic disorder characterized by swelling of subcutaneous, mucosal, and submucosal tissue without associated pruritus or wheals. Swelling attacks can affect the cutaneous tissue, abdominal viscera, genitals, and airways, resulting from a temporary and localized increase in vascular permeability.<sup>1</sup> This article reflects content derived from a PubMed (U.S. National Library of Medicine, Bethesda, MD) search on “epidemiology” and “burden of disease” attributable to HAE as well as from other sources.

## EPIDEMIOLOGY

Several types of HAE have been identified. HAE with C1 inhibitor (C1-INH) deficiency is caused by mutations of the Serine Protease Inhibitor Gene 1 (*SERPING1*) gene, which results in a deficiency (type I) or dysfunction (type II) of C1-INH in the plasma, kinin

and/or contact system dysregulation, excess bradykinin production, localized vasodilation, vascular leakage, and swelling.<sup>2</sup> HAE with normal C1-INH (nl-C1-INH), formally known as HAE type III, has been associated with mutations of the *F12* gene, which codes for factor XII (HAE-FXII),<sup>3</sup> the angiotensin 1 gene (HAE-ANGPT1),<sup>4</sup> and the plasminogen gene (HAE-PLG).<sup>5</sup> HAE nl-C1-INH without an identified mutation is referred to as HAE-unknown (Table 1).<sup>6</sup>

The true prevalence of HAE is unknown. HAE C1-INH is the most commonly occurring type, with reports of the prevalence varying widely by region, from 1:50,000 to 1:100,000. A systematic review of epidemiologic studies reported that HAE C1-INH types I and II had been diagnosed in an estimated 1 in 67,000 individuals, with ~90% of cases attributable to type I.<sup>7</sup> This prevalence rate predicts ~5000 patients in the United States and 116,100 worldwide, given 2020 population estimates. HAE has been diagnosed throughout the world and does not seem to be more common in any ethnic group. Even less is known about the epidemiology of HAE nl-C1-INH. What has been observed in the United States is that HAE-FXII has infrequently been diagnosed, and HAE-ANGPT1 and HAE-PLG have not been diagnosed to date. Further insight to the relative occurrence of different types of HAE was provided by a review of 1058 patients with recurrent angioedema without wheals who were evaluated at a single angioedema reference center.<sup>8</sup> They reported finding 353 subjects (33%) who manifested

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Table 1 Current understanding of types of HAE and their mechanism of swelling\*

HAE Due to C1-INH Deficiency	Mechanism	Mediator
Type I	Impaired secretion of C1-INH	Bradykinin
Type II	Secretion of dysfunctional C1-INH	Bradykinin
HAE with normal C1-INH		
HAE-FXII	Enhanced activation of contact system	Bradykinin
HAE-ANGPT1	Impaired ability to limit vascular permeability	Unknown
HAE-PLG	Unknown	Unknown
HAE-unknown	Unknown	Unknown

HAE = Hereditary angioedema; C1-INH = C1 inhibitor; FXII = factor XII; ANGPT1 = angiotensin 1; PLG = plasminogen.

\*Adapted from Ref. 6.

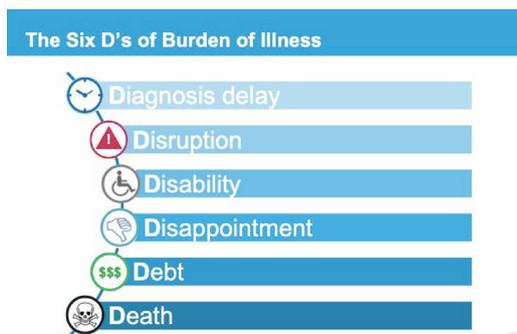


Figure 1. The six “Ds” of burden of illness. From Ref. 10. Reproduced with permission.

HAE C1-INH, 6 with HAE-FXII, 18 with HAE-unknown, and 70 with acquired nonhistaminergic angioedema, which suggest that, in this population, HAE was a more common cause of angioedema than previously appreciated.

### BURDEN OF DISEASE

The substantial burden of disease that exists for patients with HAE has been well documented for time periods both before and after the availability of HAE-specific treatments.<sup>9–13</sup> The following six “Ds” highlight the challenges and burden this disease presents (Fig. 1): (1) Delay in diagnosis; (2) Disruption in the daily life of patients, family members, and caregivers; (3) Disability imposed by frequent and unpredictable swelling attacks; (4) Disappointment in the medical system that fails to make a correct diagnosis or provide effective treatment, which contributes to depression and anxiety; (5) Debt as the result of unattained educational or career goals, missed work, and the cost of medication and medical care; and (6) The ever present fear of death from asphyxiation as the result of an airway attack. The evidence that supports these areas of burden is outlined below.

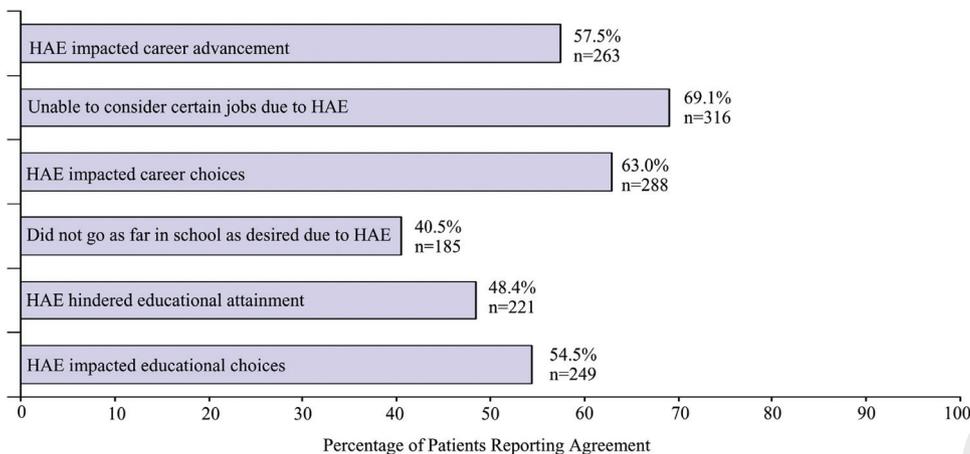
#### Diagnostic Delay

HAE is a chronic and currently incurable disease. Delay in diagnosis remains a problem. Factors,

including the lack of awareness of this rare condition and the intermittent nature of the disorder, contribute to underdiagnosis and undertreatment of the condition. An International Patient Experience of HAE Study,<sup>14</sup> published in 2010, found that 43% of the 313 respondents waited >1 year after their first attack before seeking medical attention, the average time to diagnosis was 8.3 years, and patients visited an average of 4.4 physicians before receiving the correct diagnosis. Sixty-five percent were misdiagnosed, and, as a result, 24% underwent an unnecessary surgical procedure (most commonly abdominal exploratory surgery).<sup>14</sup> On a brighter note, the time to an accurate diagnosis is improving as a result of dispersion of knowledge *via* the Internet, educational programs, physician education, and patient advocacy organizations but remains a substantial barrier to care.<sup>15</sup>

#### Disruption, Disability, Death

Attacks are disabling and potentially life threatening and unpredictable with respect to frequency, severity, and the site that swells. Laryngeal attacks can be fatal if not treated promptly and appropriately.<sup>16</sup> The true burden of this disease is best documented by studies conducted before 2008 when disease-specific therapies for HAE first became available in the United States. An Internet survey completed by patient members of the U.S. Hereditary Angioedema Association (HAEA) in 2007 found that patients experienced an average of 26.9 swelling attacks per year that lasted 61.3 hours, each resulting in 68 days of symptoms each year.<sup>10</sup> More than 80% of attacks were considered to be of moderate-to-severe intensity. These attacks were often disfiguring and debilitating, and resulted in lost time from school, work, and family and social activities. Also contributing to patient frustration and anxiety, it has been reported that <50% of attacks present with prodromal symptoms that could reliably predict the onset of an attack.<sup>17</sup> In addition, patients have reported not feeling completely well between attacks as well as feeling anxious and fearful, anticipating the next attack.<sup>18</sup>



*Figure 2. Missed opportunities due to hereditary angioedema (HAE). Percentage of patients who reported that HAE hindered their education and work opportunities. From Ref. 10. Reproduced with permission.*

## Disappointment

Although giant strides have been made in the past 12 years in the treatment of HAE, many patients remain disappointed by the lack of effective treatment options. Both on-demand treatment of attacks and attack prevention require intravenous or subcutaneous administration.<sup>19,20</sup> Some therapies must be administered in a medical setting due to adverse effects or the inability of the patient to safely administer them. Treatment options for children, adolescents, and pregnant women are limited.<sup>21,22</sup> Regulatory authority for registration of the newer HAE-specific treatments outside of the United States and western Europe limits their widespread use.<sup>23</sup> Even when a new treatment has been registered and is available, governmental regulatory authorities and insurance payers may limit or delay access. Use of older drugs not specific for HAE, particularly androgenic steroids, are associated with significant and detrimental adverse effects.<sup>24</sup>

## Debt

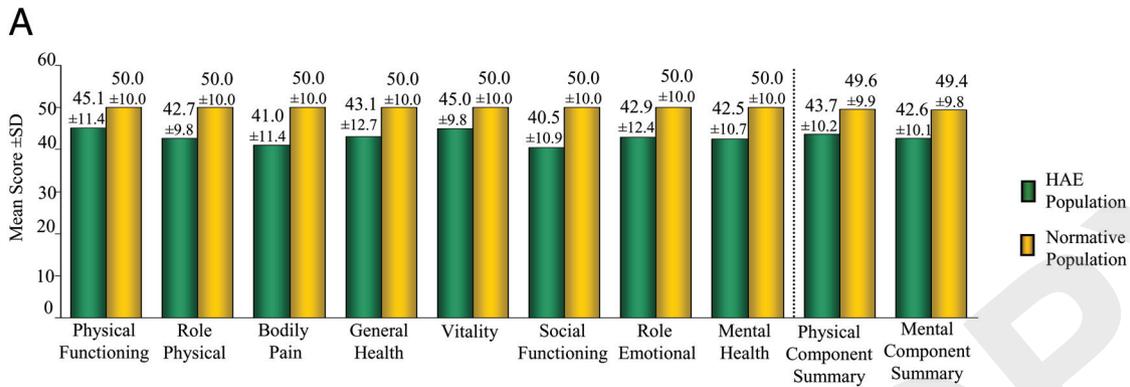
The costs attributable to HAE can be divided into direct and indirect costs, including the impact on productivity, career opportunities, and, in some cases, mortality. With regard to direct costs, the total annual cost of having and treating HAE was assessed in a 2007 HAEA survey.<sup>25</sup> The average annual cost per patient was \$41,993. Cost varied, depending on the severity of the disease, ranging from \$14,379 for mildly affected patients to \$26,915 and \$96,460 for those moderately and severely affected, respectively. The total mean annual expenditure per patient with HAE of \$41,993 included direct medical costs of \$25,885 composed of \$17,335 for hospital admissions, \$2603 for emergency department visits, \$3699 for outpatient care, and \$2248 for medications; and indirect costs of \$16,108, including \$5750 for reduced productivity, \$6512 for reduced income, \$3402 for missed work, and \$444 for travel and childcare.<sup>25</sup> When accounting for

inflation, the average annual cost per patient in 2020 would be \$67,000.

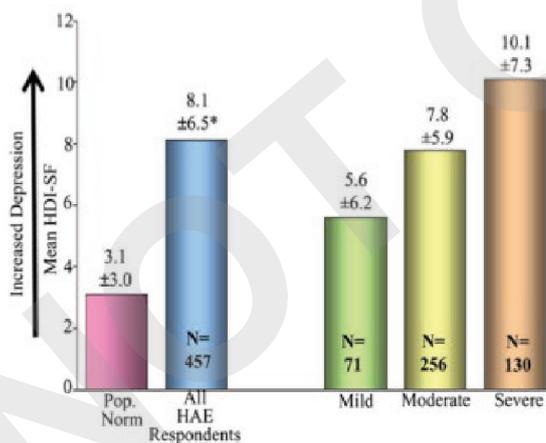
In addition to the direct cost of care, indirect costs must be considered. Missed time from work or school, decreased productivity at work, and loss of opportunity are significant costs to the patient and society. Patients report a decrease of workplace productivity due to HAE.<sup>25</sup> An E.U. study of the socioeconomic burden of HAE revealed that both patients and caregivers were affected, with each losing an average of 20 days from work or school per year.<sup>11,12,18</sup> Loss of productivity due to absenteeism from work and presenteeism at work or educational activities for patients and caregivers has a significant negative economic impact, increases stress, and reduces productivity during and between attacks.

Loss of educational and career opportunity is also commonly reported. In the 2007 HAEA survey, 57% of patients with HAE reported having career advancement hindered, 69% felt that they could not consider certain types of jobs because of their disease, 63% felt HAE impacted their career choices, 40% did not go as far in school as desired due to HAE, 48% felt that educational advancement had been hindered, and 55% had to limit their educational choices (Fig. 2).<sup>10</sup> Even after HAE-specific therapies became available, decreased opportunity remains a problem. In the European Union, a socioeconomic burden of disease report published in 2014 after current therapies became available, which indicated that 42% patients reported that their educational advancement was hindered, 40% were prevented from applying for certain jobs, 36% felt that their career advancement was diminished, 9% switched positions within their company, and 10% left their position permanently because of this disabling disease.<sup>12</sup>

A fatal HAE attack with the loss of the individual both from the workforce and from society is the ultimate burden of this disease and results in significant social and economic hardship to the patient's family and to society. Although attacks that affect the airway



**B**  
**Mean Depression (HDI-SF) Scores in the Normative Population and Patients with HAE by Average Attack Severity<sup>1</sup>**



**Figure 3.** (a) Health-related quality of life (HRQoL); 12-item Short Form scores. Patients with hereditary angioedema (HAE) reported decreased physical and mental health versus the normative population ( $p < 0.001$ ) for all subscales and overall summary components, based on t-tests. From Ref. 10. Reproduced with permission. (b) Depression (Hamilton Depression Inventory – Short Form scores) Numbers are mean  $\pm$  standard deviation. Patients with HAE are more likely to experience symptoms of depression than population norms ( $p < 0.0001$ , based on the t-test). Depression increases with attack severity. From Ref. 10. Reproduced with permission.

account for only  $\sim 0.5\%$  of all attacks,  $>50\%$  of patients will have an airway attack at some point in their lifetime. Unfortunately, patients with HAE continue to succumb to this treatable disease. In a 2012 German study, which included 728 patients from 182 families with HAE type I and type II, 214 deaths were recorded.<sup>16</sup> The mean age of death from an HAE attack was 40.6 years. Mortality by asphyxiation was substantially higher in patients with undiagnosed HAE C1-INH than in patients with diagnosed HAE C1-INH.

Fortunately, over the past 12 years, the introduction of HAE-specific medications for both on-demand treatment of attacks and prevention of attacks has significantly decreased the frequency of emergency department visits and hospitalizations where these are available. Economic savings due to this lower utilization are, in part, offset by the high cost of these treatments. In 2020, in the United

States, the annual cost of nanofiltered C1-INH, subcutaneous C1-INH, and lanadelumab, all of which are indicated for routine prophylaxis of HAE attacks, when used at the approved dosage and interval was  $>\$500,000$  per patient. Current average wholesale prices for treatments of acute attacks range from  $\$5000$  to  $>\$10,000$  per attack treated. Unfortunately, worldwide, cost considerations frequently present insurmountable barriers to treatment for many patients, depending on the health care system in the individual country.<sup>12</sup>

### Quality of Life

Patient health-related quality of life (HRQoL) is significantly affected by the episodic, unpredictable, and chronic nature of HAE. HRQoL has been assessed before and after HAE-specific therapies became

available. A variety of patient-reported outcome tools have been used to assess HRQoL and problems related to it, including Short Form Health Surveys (12- and 36-item Short Forms), European Quality of Life (EuroQoL) Five Dimensions (EQ-5D), the Hamilton Depression Inventory–Short Form, and the Work Productivity and Activity Impairment-General Health Questionnaire.

In the 2007 HAEA survey, patients consistently reported poorer HRQoL measurements compared with a healthy control population.<sup>10</sup> The 12-item Short Form Physical Component Summary score was lower in patients with HAE versus a control population (mean 43.7 versus 49.6;  $p < 0.001$ ), as was the Mental Component Summary score (mean 42.6 versus 49.4;  $p < 0.001$ ). The Hamilton Depression Inventory–Short Form questionnaire revealed that depression was more prevalent in the HAE population versus the control group (mean 8.1 versus 3.1;  $p < 0.001$ ) (Fig. 3 a). Depression scores increased, based on attack severity, with mean scores of 5.6 for mild, 7.8 for moderate, and 10.1 for severe attacks. Overall, 42.5% of patients with HAE in the survey exhibited at least mild symptoms of depression (Fig. 3 b). The impact of HAE on QoL parameters is comparable with that of other chronic diseases associated with morbidity and mortality, such as severe asthma and Crohn disease.<sup>10</sup>

Depression was assessed in 26 patients with HAE in 2012 after HAE-specific medications became available.<sup>26</sup> Thirty-nine percent reported mild (19.23%), moderate (15.38%), or severe (3.85%) depressive symptoms. Anxiety was reported at much higher rates than the normal population, with 15% of the group reporting mild (7.5%), moderate (3.75%), or severe (3.75%) anxiety. Feelings of stress, anxiety, and depression cannot only trigger individual attacks but also lead to a cycle of repeated attacks, with each attack exacerbating the anxiety, which, in turn, triggers further attacks.

A Swedish survey used the EQ-5D-5L to describe the baseline health state “now” (in between attacks) and during the most recent HAE attack.<sup>18</sup> A significant difference between the EQ-5D now and EQ-5D attack was observed for mild (0.07;  $p < 0.005$ ), moderate (0.39;  $p < 0.0001$ ), and severe (0.486;  $p < 0.0001$ ) attacks. With increasing attack severity, the EQ-5D attack value was lower and the difference between the EQ-5D now to be consistent and EQ-5D attack was higher. The mean EQ-5D now was 0.825 (full health, 1.00), with a trend for female patients to be lower. For the sake of comparison, the EQ-5D values for controlled asthma and migraine in between attacks are 0.86 and 0.87, respectively. Despite full physical recovery between angioedema attacks, patients with HAE continue to experience emotional impairment and reduced HRQoL. Increased attack frequency was seen to have a negative impact on the “in between attack” HRQoL.

## IMPACT OF NEW THERAPIES FOR HAE

Many patients with HAE have benefited from regulatory approval of novel, disease-specific drugs that treat and prevent swelling attacks. The benefits include improvement in health and QoL, increased ability to work and pursue educational and career goals, reduced disability, and reduction of costly urgent care visits and hospitalizations as longer survival.<sup>27–33</sup> The hope for the future is reduction of barriers that lead to the current health care disparities. These include earlier diagnosis, reduced costs, the alternative of oral medications, and worldwide access to advanced therapeutics.

## PEARLS

- HAE imposes a significant burden on a patient’s QoL and educational and work opportunities.
- Anxiety, depression, and overall QoL significantly worsens during attacks and does not return to normal in between.
- HAE-specific treatments have significantly decreased the burden of disease and improved QoL.
- Health care disparities worldwide limit the availability of treatments, which can cost as much as \$500,000 annually for prevention and \$10,000 per treatment of acute attack.

## REFERENCES

1. Azmy V, Brooks JP, Hsu FI. Clinical presentation of hereditary angioedema. *Allergy Asthma Proc.* 2020; 41:S18–S21.
2. Wedner HJ. Hereditary angioedema: Pathophysiology (HAE type I, HAE type II, and HAE nC1-INH). *Allergy Asthma Proc.* 2020; 41:S14–S17.
3. Dewald G, Bork K. Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. *Biochem Biophys Res Commun.* 2006; 343:1286–1289.
4. Bafunno V, Firinu D, D’Apolito M, et al. Mutation of the angiotensin-converting enzyme 1 gene (ANGPT1) associates with a new type of hereditary angioedema. *J Allergy Clin Immunol.* 2018; 141:1009–1017.
5. Bork K, Wulff K, Steinmüller-Magin L, et al. Hereditary angioedema with a mutation in the plasminogen gene. *Allergy.* 2018; 73:442–450.
6. Zuraw BL. Hereditary angioedema with normal C1 inhibitor: four types and counting. *J Allergy Clin Immunol.* 2018; 141:884–885.
7. Aygören-Pürsün E, Magerl M, Maetzel A, et al. Epidemiology of Bradykinin-mediated angioedema: a systematic investigation of epidemiological studies. *Orphanet J Rare Dis.* 2018; 13:73.
8. Mansi M, Zanichelli A, Coerezza A, et al. Presentation, diagnosis and treatment of angioedema without wheals: a retrospective analysis of a cohort of 1058 patients. *J Intern Med.* 2015; 277:585–593.
9. Banerji A, Davis KH, Brown TM, et al. Patient-reported burden of hereditary angioedema: findings from a patient survey in the United States. *Ann Allergy Asthma Immunol.* 2020; 124:600–607.
10. Lumry WR, Castaldo AJ, Vernon MK, et al. The humanistic burden of hereditary angioedema: impact on health-related quality

- of life, productivity, and depression. *Allergy Asthma Proc.* 2010; 31:407–414.
11. Longhurst H, Bygum A. The humanistic, societal, and pharmacoeconomic burden of angioedema. *Clin Rev Allergy Immunol.* 2016; 51:230–239.
  12. Aygören-Pürsün E, Bygum A, Beusterien K, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. *Orphanet J Rare Dis.* 2014; 9:99.
  13. Caballero T, Aygören-Pürsün E, Bygum A, et al. The humanistic burden of hereditary angioedema: results from the Burden of Illness Study in Europe. *Allergy Asthma Proc.* 2014; 35:47–53.
  14. Lunn ML, Santos CB, Craig TJ. Is there a need for clinical guidelines in the United States for the diagnosis of hereditary angioedema and the screening of family members of affected patients? *Ann Allergy Asthma Immunol.* 2010; 104:211–214.
  15. Banerji A, Li Y, Busse P, et al. Hereditary angioedema from the patient's perspective: a follow-up patient survey. *Allergy Asthma Proc.* 2018; 39:212–223.
  16. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol.* 2012; 130:692–697.
  17. Reshef A, Prematta MJ, Craig TJ. Signs and symptoms preceding acute attacks of hereditary angioedema: results of three recent surveys. *Allergy Asthma Proc.* 2013; 34:261–266.
  18. Nordenfelt P, Dawson S, Wahlgren C-F, et al. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. *Allergy Asthma Proc.* 2014; 35:185–190.
  19. Christiansen S, Zuraw B. Hereditary angioedema: on-demand treatment of acute attacks. *Allergy Asthma Proc.* 2020; 41:S26–S29.
  20. Li HH. Hereditary angioedema: long-term prophylactic treatment. *Allergy Asthma Proc.* 2020; 41:S35–S37.
  21. Johnston DT, Smith RC. Hereditary angioedema: special considerations in children. *Allergy Asthma Proc.* 2020; 41:S43–S46.
  22. Yakaboski E, Motazed T, Banerji A. Hereditary angioedema: special considerations in women. *Allergy Asthma Proc.* 2020; 41:S47–S50.
  23. Lumry WR. Hereditary angioedema: the economics of treatment of an orphan disease. *Front Med (Lausanne).* 2018; 5:22.
  24. Bork K, Bygum A, Hardt J. Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. *Ann Allergy Asthma Immunol.* 2008; 100:153–161.
  25. Wilson DA, Bork K, Shea EP, et al. Economic costs associated with acute attacks and long-term management of hereditary angioedema. *Ann Allergy Asthma Immunol.* 2010; 104:314–320.
  26. Fouche AS, Saunders EF, Craig T. Depression and anxiety in patients with hereditary angioedema. *Ann Allergy Asthma Immunol.* 2014; 112:371–375.
  27. Christiansen SC, Bygum A, Banerji A, et al. Before and after, the impact of available on-demand treatment for HAE. *Allergy Asthma Proc.* 2015; 36:145–150.
  28. Longhurst H, Cicardi M, Craig T, et al. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. *N Engl J Med.* 2017; 376:1131–1140.
  29. Aygören-Pürsün E, Bygum A, Grivcheva-Panovska V, et al. Oral plasma kallikrein inhibitor for prophylaxis in hereditary angioedema. *N Engl J Med.* 2018; 379:352–362.
  30. 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; 320:2108–2121.
  31. Lumry WR, Miller DP, Newcomer S, et al. Quality of life in patients with hereditary angioedema receiving therapy for routine prevention of attacks. *Allergy Asthma Proc.* 2014; 35:371–376.
  32. Lumry WR, Craig T, Zuraw B, et al. Health-related quality of life with subcutaneous C1-inhibitor for prevention of attacks of hereditary angioedema. *J Allergy Clin Immunol Pract.* 2018; 6:1733–174.e3.
  33. Lumry W, Maurer M, Magerl M, et al. Long-term lanadelumab treatment improves health-related quality of life: HELP Open label Extension Study interim findings [ACAAI abstract P156]. *Ann Allergy Asthma Immunol.* 2019; 123:S29. □

# Hereditary angioedema: Pathophysiology (HAE type I, HAE type II, and HAE nC1-INH)

H. James Wedner, M.D.

## ABSTRACT

The pathophysiology of hereditary angioedema (HAE) in virtually all cases is the result of the uncontrolled production of the vasoactive peptide bradykinin. C1 inhibitor (C1-INH) is a serine protease inhibitor, which, under normal circumstances, is the regulator of critical enzymes that are active in the cascades that result in bradykinin generation. In the classic forms of HAE, C1-INH is not produced in sufficient quantities (<40% of normal) or the function is <40% of normal activity. The major pathway for the production of bradykinin is the "contact system," also known as the kallikrein-kinin system. This system begins with the activation of factor XII (FXII) to FXIIa, by a variety of physiologic and pathologic stimuli. FXIIa is a serine protease that binds to surfaces and cleaves prekallikrein to the active serine protease kallikrein. Kallikrein then cleaves high-molecular-weight kininogen to release the nonapeptide bradykinin. Bradykinin binds to the bradykinin  $\beta$ 2 receptor, which increases vascular permeability and allows the flow of fluids into the extracellular space and results in angioedema. The two major enzymes generated in this cascade FXIIa and kallikrein are inhibited by C1-INH, which is the major regulator of this cascade. Failure to adequately control the production of bradykinin is thus the major mechanism for HAE. Several other types of HAE in which C1-INH is not decreased (HAE nC1-INH) have been described. The alterations in FXII and plasminogen (also a serine protease inhibited by C1-INH) like with classic HAE are the result of dysregulation of bradykinin generation. Only genetic alterations in angiopoietin-1 may not be related to bradykinin generation, rather related to the control of the effect of bradykinin on the vascular endothelium.

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Angioedema is defined as "swelling of the lower layer of skin and tissue just under the skin or mucous membranes." (American Academy of Allergy Asthma and Immunology) Two broad pathways for the generation of angioedema have been described; the first is the result of the generation of mediators from mast cells and basophils generally referred to as "histaminergic,"<sup>1</sup> and the second is the result of the generation of bradykinin by several pathways.<sup>2</sup> The pathways for the histaminergic type of angioedema are well described elsewhere and only the bradykinin type will be described in the current chapter. In the majority of patients, HAE is the result of an abnormality in the gene coding for the inhibitor of complement factor 1 (C1-INH). C1-INH is a serine protease inhibitor that belongs to a large superfamily of serine protease inhibitors (serpins). In humans, ~32 serpin genes have been identified, which are divided into groups called clades, based on gene similarity. There are 16 clades, labeled A through P, and each clade may

contain one or more serpin genes. C1-INH is the sole member of clade G.

Several forms of HAE have been described. Types I and II are the result of aberrant C1-INH. Type I is the lack of sufficient C1-INH, whereas type II is a nonfunctional protein. HAE nC1-INH (formerly type III) has multiple genetic abnormalities (currently four are described), of which most are not well understood at the genetic level.<sup>3</sup> The genetic defects that result in each form of HAE are described elsewhere in this Primer. It is important to note that HAE types I and II are heterozygous abnormalities and that the disease is the result of significantly decreased C1-INH function. However, the levels of C1-INH vary widely among patients with HAE. In general, in patients with HAE, levels <40% of the lower limit of normal result in symptoms.<sup>4</sup>

C1-INH is responsible, in part, for the control of three interlocking cascades, which include the kallikrein-kinin pathway, also called the contact system, which is responsible for bradykinin generation and is the major pathophysiologic mechanism that leads to the signs and symptoms of HAE; the complement system, both the "classic" and lectin pathways (from which HAE C1-INH get its name); and, to a lesser degree, the fibrinolytic system (Fig. 1).

The kallikrein-kinin pathway, *i.e.*, the contact system is pathophysiologic, the most important in the symptoms associated with HAE. To understand the

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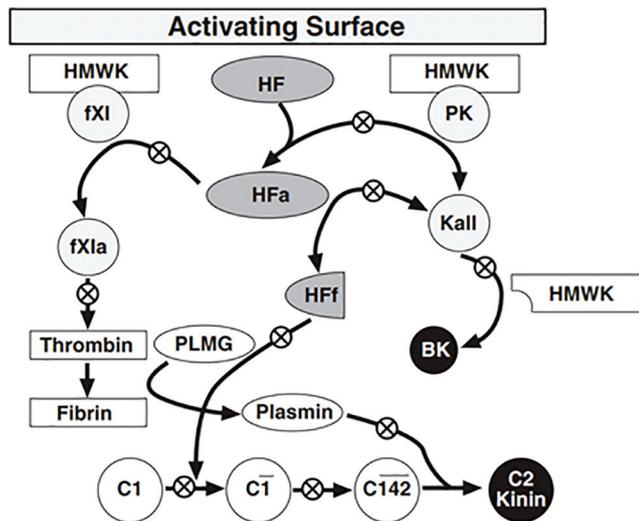


Figure 1. Pathways for hereditary angioedema (HAE) pathophysiology (from ref. 22).

pathophysiology of this system, one must be familiar with normal contact system physiology. This system has been described as “an interface between inflammation, coagulation, and innate immunity.”<sup>5</sup> The key factors in this system are factor XII (FXII), factor XI (FXI), plasma prekallikrein, high-molecular-weight kininogen (HK), and C1-INH. The initiation of the cascade is the activation of FXII by a variety of physiologic and pathologic activators.<sup>6</sup> These stimulate the autoactivation of FXII to generate FXIIa.<sup>5</sup> These include, but are not limited to physiologic activators, many of which are associated with tissue damage and pathologic activators, including bacteria and virus. This system can also be activated in the laboratory by using artificial substrates, such as kaolin or dextran-sulfate. The common factor among these activators is a negatively charged surface.

Binding of FXII to surfaces (*i.e.*, contact) results in a conformational change, which results in the autoactivation to FXIIa, which is a serine protease.<sup>6</sup> Plasma prekallikrein circulates in a complex with HK and is inactive.<sup>7</sup> When the plasma prekallikrein–HK complex is cleaved by FXIIa, the resulting plasma kallikrein becomes an active serine protease, which acts on the bound HK to generate a low-molecular-weight vasoactive peptide, bradykinin. Bradykinin interacts with the bradykinin  $\beta$ 2 receptor on the vascular endothelium. The bradykinin  $\beta$ 2 receptor is constitutively expressed on the vascular endothelium and other tissues.<sup>7</sup>

The  $\beta$ 2 receptor is a classic G-protein–coupled receptor. This interaction results among other biochemical alterations in the generation of nitrous oxide as well as other factors and results in the opening of the vascular endothelium and the extrusion of fluid into the extracellular space, *i.e.*, angioedema.<sup>8</sup> From a physiologic standpoint this allows plasma proteins such as

antibodies to exit the vascular space and get to sites of tissue injury or infection. The change in the vascular endothelium results in other changes, such as the binding of platelets and other inflammatory cells to areas of injury. The activation of the vascular endothelium represents a mechanism to initiate innate immune responses, another component of contact system activation.<sup>9,10</sup> Of interest is the bradykinin  $\beta$ 1 receptor that interacts with bradykinin des-Arg. The  $\beta$ 1 receptor is not constitutively expressed but is expressed in association with tissue injury.<sup>10</sup> Its role in HAE pathophysiology is briefly discussed below.

In addition to the cleavage of HK to form bradykinin, plasma kallikrein also acts on FXII to form additional FXIIa in a positive feedback loop. This serves to increase the amount of bradykinin generated and, in an unregulated system such as HAE, may serve to perpetuate the episodes. An additional event in the contact system cascade is the cleavage of FXI to its active form (XIa). This initiates another cascade, which can result in thrombin generation and fibrin deposition, often referred to as the intrinsic clotting cascade. Plasma kallikrein can also cleave plasminogen (*via* a prourokinase to urokinase intermediate) to plasmin activating the fibrinolytic mechanism and coupling the three systems activated by FXII activation. Both FXIIa and PK are regulated by C1-INH, which makes this inhibitor an important component of the kinin system.

In patients with type I or type II HAE, there is failure of regulation of the kallikrein-kinin system by C1-INH. This results in the relatively unchecked activation of kinin generation and appearance of angioedema at times when it is not warranted. In addition, there is failure to “turn off the system” and so the angioedema is prolonged compared with the physiologic situation. The reason that patients with type I or II HAE have episodic and not continuous swelling as well as why some individuals have multiple episodes per month, whereas, in other patients, their swelling is infrequent, is not well known. It should be noted that there are other inhibitors of FXIIa (albeit significantly less active than C1-INH), including  $\alpha$ 1-antitrypsin and plasminogen activator inhibitor, which are still active in HAE and may, in part, play a role in HAE, particularly in the resolution of the episodes. In addition, why some patients will have predominately abdominal swelling whereas others will have swelling of their extremities is not clear. What is clear is that stimulation, such as a minor injury or dental work, that might not result in significant swelling in normal individuals can result in disastrous swelling in patients with HAE.

In the complement system, the first step in classic complement activation is the assembly of the C1q, C1r, and C1s complex, which is initiated by the binding of C1q to several classes of antibodies (in humans, immunoglobulin M [IgM], IgG1, IgG3) complexed to

antigen. The binding of immune complexes to C1q results in the binding of C1r and then C1s to form the C1 complex. The binding of these components of C1 result in the activation of C1r/C1s (the C1 convertase) to a serine protease, which cleaves both C4 and C2 to their active forms, and activates the future steps in the classic complement pathway. The C1r/C1s convertase is regulated by C1-INH. As a result, in HAE, there is increased consumption of C4, and the decrease in plasma C4 is a useful tool in the diagnosis of HAE. It is of interest that C2 is not normally decreased in HAE and that overall complement activity functions normally in HAE.<sup>11</sup> However, C2 may be consumed and levels may be depressed during an angioedema episode.<sup>12</sup> It is for this reason that patients with HAE do not demonstrate increased infections, which might be seen in patients with a genetic complement deficiency. Interestingly, there is some evidence to demonstrate that patients with HAE have an increase in autoimmune phenomena, and this has been suggested to be similar to that seen with abnormalities in the early complement components. A full discussion of autoimmunity in HAE is beyond the scope of this communication.

Another of the mechanisms for the activation of the complement system, the lectin pathway, has recently been suggested as a potential mechanism for HAE types I and II. Mannan binding lectin can be activated by a variety of factors, including trauma, stress, or infection<sup>13</sup> and interact and activate one of two mannan-associated serine proteases.<sup>14</sup> These proteases can feed back and activate the C1r,s complex and initiate the cascade, and may also cleave HK to form bradykinin.<sup>12</sup> There is also some evidence to suggest that these proteases may also result in the upregulation of the bradykinin  $\beta 1$  and  $\beta 2$  receptors.<sup>12</sup> As with the other serine proteases discussed, mannan-associated serine proteases 1 and 2 are inhibited by C1-INH. This provides another mechanism for the unregulated production of angioedema in patients with HAE.

The final pathway that is controlled by C1-INH is the plasminogen-plasmin system. As noted above, the activation of FXII can result in the concomitant activation of the fibrinolytic system. Plasmin, the major component of the fibrinolytic pathway, is also a serine protease that is inhibited by C1-INH, although this inhibition is not as significant as the inhibition of other serine proteases noted above.<sup>15,16</sup> The plasminogen-plasmin system provided an additional feedback loop that is unregulated.

The discussion of the pathophysiology that results from the lack of regulation of the contact system and other cascades is clearly relevant to patients with HAE. However, as noted above and in other sections in the primer, there is an alternative type of HAE, that with nC1-INH. Although the vast majority of individuals with this condition do not have a

described biochemical or genetic abnormality, several groups have described alterations in FXII,<sup>13</sup> plasminogen,<sup>17</sup> angiotensin-1,<sup>18</sup> and HK.<sup>19</sup> The pathophysiology of these three conditions has not been fully established. However, there is speculation as to how each of these genetic abnormalities may result in the signs and symptoms of HAE. For FXII abnormalities, the defect seems to be in the activation of the abnormal FXII by plasmin to its active form in the absence of physiologic or pathologic stimulation.<sup>19</sup> This type of HAE is much more common in female patients and seems to be under the control of estrogen because the episodes can be related to patients' menstrual cycle as well as the use of estrogen-containing contraceptives. Bradykinin is clearly the final common pathway because inhibitors of PK or the  $\beta 2$  receptor are beneficial in this type of HAE.

A potential mechanism for those individuals who have HAE nC1-INH with plasminogen relates to the feedback of the fibrinolytic system on the contact system cascade. As noted above, plasmin is a serine protease that can act on FXII to generate additional FXIIa. This will perpetuate and perhaps initiate bradykinin generation in patients with HAE-Plasminogen (HAE-PLG).

The pathophysiology of the alteration in angiotensin-1 is clearly not well worked out. However, this may be the only form of HAE that does not involve overproduction of bradykinin. Angiotensin-1 works in contrast to bradykinin and serves as a stabilizer of the vascular endothelium decreasing vascular permeability. A non-functional angiotensin-1 will then increase the sensitivity of the vascular endothelium and will increase or perpetuate the angioedema seem with normal activation of the contact system.<sup>20</sup>

## CONCLUSION

With the possible exception of HAE-angiotensin, HAE is the result of overproduction of bradykinin due to the lack of regulation of the contact system by C1-INH. However, many questions with regard to the pathophysiology of this condition remain. Why this disease is episodic rather than continuous is not clear, and, although some of the stimulate that can induce the symptom of this disease are well known, why there is often spontaneous onset of angioedema is not clear. Certainly, hormones, particularly estrogens, play a significant role in the pathophysiology of HAE. Recent evidence demonstrates that high levels of estrogen, such as those seen in pregnancy and the use of estrogen-containing contraceptives results in elevated FXII, providing additional substrate for the contact system.<sup>21</sup> The exact mechanism by which androgens increase C1-INH is still not clear. What is clear is that an understanding of the pathophysiology of HAE has been instrumental in the design of therapies for HAE.

## CLINICAL PEARLS

1. HAE is a bradykinin-mediated disease; it does not involve histamine.
2. The pathophysiology of HAE type I and type II is the uncontrolled overproduction of bradykinin.
3. Based on the known pathophysiology, the therapy for HAE has evolved.
4. Although levels of C4 are low in HAE (in some cases, only during an HAE episode), the complement system functions normally, and there is no increase in infections associated with HAE.
5. HAE nC1-INH has at least four genetic abnormalities; however, the full pathophysiology for this condition is not, as yet, well established.

## REFERENCES

1. Busse PJ, Smith T. Histaminergic angioedema. *Immunol Allergy Clin North Am*. 2017; 37:467–481.
2. Cicardi M, Zuraw BL. Angioedema due to bradykinin dysregulation. *J Allergy Clin Immunol Pract*. 2018; 6:1132–1141.
3. Banday AZ, Kaur A, Jindal AK, et al. An update on the genetics and pathogenesis of hereditary angioedema. *Genes Dis*. 2020; 7:75–83.
4. Longhurst H, Cicardi M, Craig T, et al. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. *N Engl J Med*. 2017; 376:1131–1140.
5. Joseph K, Kaplan AP. Formation of bradykinin: a major contributor to the innate inflammatory response. *Adv Immunol*. 2005; 86:159–208.
6. Schmaier AH, Stavrou EX. Factor XII – what’s important but not commonly thought. *Res Pract Thromb Haemost*. 2019; 3:599–606.
7. Prado GN, Taylor L, Zhou X, et al. Mechanisms regulating the expression, self-maintenance, and signaling-function of the bradykinin B2 and B1 receptors. *J Cell Physiol*. 2002; 193:275–286.
8. Demirturk M, Gelincik A, Cinar S, et al. Increased eNOS levels in hereditary angioedema. *Int Immunopharm*. 2014; 20:264–268.
9. Mai J, Virtue A, Shen J, et al. An evolving new paradigm: endothelial cells-conditional innate immune cells. *J Hematol Oncol*. 2013; 6:61.
10. Joseph K, Tholanikunnel BG, Ghebrehiwet B, et al. Interaction of high-molecular-weight binding proteins on endothelial cells. *Thromb Haemostasis*. 2004; 91:61–70.
11. Qadri F, Bader M. Kinin B1 receptors as a therapeutic target for inflammation. *Expert Opin Ther Targets*. 2018; 22:31–44.
12. Csuka D, Veszeli N, Varga L, et al. The role of the complement system in hereditary angioedema. *Mol Immunol*. 2017; 89:59–68.
13. Davis AE III. The pathophysiology of hereditary angioedema. *Clin Immunol*. 2005; 114:3–9.
14. Dobo J, Major B, Kekesi KA, et al. Cleavage of kininogen and subsequent bradykinin release by the complement component: mannose-binding lectin-associated serine protease (MASP)-1. *PLoS One*. 2011; 6:e20036.
15. deMaat S, Bjorkqvist J, Suffritti C, et al. Plasmin is natural trigger for bradykinin production in patients with hereditary angioedema with factor XII mutations. *J Allergy Clin Immunol*. 2016; 138:1414–1423.e9.
16. d’Apolito M, Santacrose R, Colia AL, et al. Angiotensin-converting enzyme 1 haploinsufficiency affects the endothelial barrier and causes hereditary angioedema. *Clin Exp Allergy*. 2019; 49:626–635.
17. Bork K, Gul D, Hardt J, et al. Hereditary angioedema with normal C1 inhibitor: clinical symptoms and course. *Am J Med*. 2007; 120:987–992.
18. Bork K, Wulff K, Steinmuller-Magin L, et al. Hereditary angioedema with a mutation in the plasminogen gene. *Allergy*. 2018; 73:442–450.
19. Bafunno V, Firinu D, D’Apolito M, et al. Mutation of the angiotensin-converting enzyme 1 gene (ANGPT1) associates with a new type of angioedema. *J Allergy Clin Immunol*. 2018; 141:367:1009–1017.
20. Bork K, Wulff K, Rossmann H, et al. Hereditary angioedema cosegregating with a novel kinogen 1 gene mutation changing the N-terminal cleavage site of bradykinin. *Allergy*. 2019; 74:2479–2481.
21. Binkley KE. Factor XII mutations, estrogen-dependent inherited angioedema, and related conditions. *Allergy Asthma Clin Immunol*. 2010; 6:16.
22. Zuraw B, Christiansen S. Pathogenesis and laboratory diagnosis of hereditary angioedema. *Allergy Asthma Proc*. 2009; 30:487–492. □

# Clinical presentation of hereditary angioedema

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## ABSTRACT

Hereditary angioedema (HAE) is a rare, autosomal dominant disease caused by a deficiency in the C1-inhibitor protein. It is characterized by recurrent episodes of nonpruritic, nonpitting, subcutaneous or submucosal edema that typically involves the extremities or the gastrointestinal tract. However, the genitourinary tract, face, oropharynx, and/or larynx may be affected as well. Symptoms often begin in childhood, worsen at puberty, and persist throughout life, with unpredictable severity. Patients who are untreated may have frequent attacks, with intervals that can range from every few days to rare episodes. Minor trauma and stress are frequent precipitants of swelling episodes, but many attacks occur without clear triggers. HAE attacks may be preceded by a prodrome and/or be accompanied by erythema marginatum. The swelling typically worsens over the first 24 hours, before gradually subsiding over the subsequent 48 to 72 hours. Although oropharyngeal swelling is less frequent, more than half of patients have had at least one episode of laryngeal angioedema during their lifetime. Attacks may start in one location and spread to another before resolving. HAE attacks that involve the abdomen or oropharynx have been associated with significant morbidity and mortality. Abdominal attacks can cause severe abdominal pain, nausea, and vomiting. Bowel sounds are often diminished or silent, and guarding and rebound tenderness may be present on physical examination. These findings may lead to unnecessary abdominal imaging and procedures. Fluid shifts into the interstitial space or peritoneal cavity can cause clinically significant hypotension. Laryngeal edema poses the greatest risk for patients with HAE. Although prompt diagnosis and treatment improves outcomes, the variable presentation of HAE can make it difficult to diagnose.

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Angioedema (AE) is defined as submucosal or subcutaneous nonpruritic, localized swelling that commonly affects the face, mouth, larynx, extremities, gastrointestinal tract, and genitourinary tract caused by the release of mediators of vascular permeability.<sup>1–3</sup> This mediator release leads to extravasation of fluid into the interstitial compartment of the deep dermis and subcutaneous tissue, and has no concomitant urticaria.<sup>1</sup> The clinical presentation of AE is explained by the accumulation of several vasoactive peptides, including bradykinin, histamine, prostaglandins, and interleukins in body tissues.<sup>1,4,5</sup> Acute attacks may result in edema that involves the upper airway, which leads to difficulty breathing and hypoxemia, or that involves the gastrointestinal tract, which leads to severe abdominal pain.<sup>1,4,5</sup> Etiologies of AE include allergen-mediated, medication-induced, underlying genetic conditions, and idiopathic.<sup>6</sup>

In this article, we will focus on the clinical presentations of hereditary AE (HAE) due to C1 esterase inhibitor (C1-INH) deficiency or with normal C1-INH.

## HAE WITH C1-INH DEFICIENCY

HAE with C1-INH deficiency is a rare, autosomal dominant condition characterized by quantitative (type I) or qualitative (type II) deficiencies in C1-INH protein.<sup>5,7</sup> This leads to repeated attacks of localized, nonpruritic, submucosal or subcutaneous swelling. Type I HAE is responsible for ~85% of patients with the disorder, whereas type II accounts for the remaining 15%. The clinical characteristics were first described in 1888 by William Osler in his case of a 24-year-old woman who had lifelong episodes of recurrent nonpruritic swelling of the “fleshy parts” of her body, and whose mother had the same symptoms.<sup>8</sup> Clinical manifestations of HAE often begin in the first and second decades of life.<sup>9</sup> The age at presentation often differentiates HAE from acquired AE, which usually presents after the fourth decade and should prompt a workup for underlying autoimmune or lymphoproliferative disorders.<sup>2</sup> Although autosomal dominant inheritance, ~25% of patients with HAE have a *de novo* genetic mutation.<sup>6</sup>

Common clinical manifestations include episodic pronounced swelling of subcutaneous or submucosal tissues. The swelling usually has an asymmetric distribution and is not dependent or pitting. There is no associated urticaria or pruritis, but transient tingling may be

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observed. Patients may also report pain syndromes, including recurrent abdominal, extremity, or urogenital pain caused by vascular congestion.<sup>10</sup> Symptoms are often self-limited and progress over hours, with the frequency of attacks varying from weekly to a few attacks per year.<sup>5</sup> Many patients will describe prodromal symptoms, including nausea, rash, fatigue, muscle aches, and neurologic symptoms.<sup>5,11</sup> Prodromal cutaneous symptoms include a serpentine, erythematous discoloration on the extremities and trunk, known as erythema marginatum (Fig. 1A).<sup>12</sup>

A cutaneous attack that involves swelling of the skin is the most common symptom and occurs in > 95% of patients.<sup>5,8</sup> The face, genitals, and extremities are the most common locations affected. Laryngeal edema is less common but is the most serious complication, which can become life-threatening if not acted on promptly. It has been reported to occur in up to 50% of patients.<sup>5</sup> Patients without a known history of laryngeal edema may report a sensation of throat tightness, dysphagia, hoarseness, and/or dysphonia in their lifetime. In addition to laryngeal edema, there can also be

swelling of the lips, tongue, soft palate, and uvula. Abdominal pain may be acute or gradual in onset, cramp-like, and accompanied by vomiting and diarrhea. There can be changes in vital signs, *e.g.*, hypotension and tachycardia. Physical examination findings may demonstrate tenderness to palpation of the abdomen, and imaging of the abdomen may identify bowel edema. In a rare case, intussusception has been described.<sup>5</sup> A summary of the symptoms and physical findings that can be seen in HAE can be found in Table 1 and visual examples are seen in Fig. 1.

If left untreated, AE can be expected to resolve over the course of 2 to 4 days but may recur or migrate to affect other parts of the body in sequential fashion over a longer period of time. AE often leads to significant morbidity due to discomfort or pain, dysfunction of the affected area, temporary disfigurement, and mortality through asphyxiation if the airway is involved. Episodes of AE, commonly referred to as “attacks,” may be triggered by factors such as physical trauma; infection; stress; hormonal fluctuations; or medications, including estrogens and angiotensin-



**Figure 1.** Examples of physical findings during hereditary angioedema attacks. (A) Erythema marginatum rash located on patient's torso. (B) Images of abdomen at baseline and when affected by gastrointestinal swelling. (C) Unilateral right hand swelling. (D) Images of a patient at baseline and with facial swelling. \*Patient consent was obtained from all subjects to share their images for educational purposes. Photographs courtesy of the US Hereditary Angioedema Association (A, B) and F. Ida Hsu, M.D. (C, D).

Table 1 Common symptoms and physical findings in hereditary angioedema by organ system

Organ System	Symptoms	Findings
Constitutional	Fatigue, malaise, flu-like symptoms	None
Upper respiratory	Throat tightness, hoarseness, difficulty breathing or swallowing	Laryngeal edema, uvular or pharyngeal edema, tongue swelling, hypoxemia
Cardiovascular	Lightheadedness, palpitations	Hypotension, tachycardia
Cutaneous	Facial swelling, lip swelling, or localized asymmetric nondependent extremity swelling without pruritis	Nonpitting asymmetric edema, erythema marginatum (variable prodrome)
Gastrointestinal	Abdominal pain, nausea, vomiting, cramping sensation, diarrhea	Bowel edema, intestinal obstruction, ascites
Genitourinary	Pain in genitals, cramping sensation	Genital area swelling
Neurologic	Numbness, tingling at sites of impending attacks	Decreased sensation

converting enzyme inhibitors. Nonsteroidal anti-inflammatory drugs, which may trigger histamine-mediated AE, are typically well tolerated in HAE. Laboratory result abnormalities include low complement C4 and, in cases of type I HAE, a low protein level of C1-INH. In type II HAE, there is normal or even a slightly elevated C1-INH level but impaired functional assay. Complement C4 is often a good screening tool for HAE. Further discussion of diagnostic studies can be found in the accompanying article by Manning in this supplement.<sup>13</sup>

#### HAE WITH NORMAL C1-INH

In the year 2000, 10 families with symptoms consistent with HAE were described and a total of 36 women, all with a normal C1-INH level and function were identified.<sup>7,14</sup> Later, men were also found to have the disease. Initially referred to as “estrogen-dependent” or “HAE type III,” this has since been named HAE with normal C1-INH (HAE-nl-C1INH) and has increasingly been recognized as a related clinical entity, with several possible underlying mutations, including those of coagulation factor XII, angiotensin-1, and plasminogen.<sup>7,15</sup> These also are observed to have a dominant inheritance pattern, with a variable degree of symptoms.<sup>9</sup>

The clinical symptoms of HAE-nl-C1INH also include recurrent skin swelling, tongue swelling, abdominal pain, and laryngeal edema without urticaria. Skin swelling and abdominal attacks last 2 to 5 days.<sup>7</sup> In a recent study that looked at a total of 138 patients from 43 unrelated families, the majority of patients had skin swelling (92.8%), tongue swelling (53.6%), and abdominal pain (50%), with laryngeal and uvular edema occurring in approximately a fourth of patients.<sup>16</sup> According to one account, facial swelling and tongue

involvement may occur more frequently in HAE-nl-C1INH compared with C1-INH deficiency. In addition, there seems to be a greater number of patients with recurrent edema of only one organ.<sup>7</sup> Erythema marginatum was not observed in this cohort. In HAE-nl-C1INH, the number of patients with disease onset in adulthood is also significantly higher, with the mean age of onset at ~27 years.<sup>7</sup>

Several additional studies have noted that many women experience symptom onset or exacerbation after the initiation of oral contraceptives or hormone replacement therapy, or during pregnancy.<sup>16,18</sup> Other studies demonstrated that this finding is not specific to HAE-nl-C1INH<sup>17</sup> and that more than one-third of women tolerated estrogens without any influence on their disease.<sup>18</sup> Exacerbations of symptoms have also been linked to angiotensin-converting enzyme inhibitors in HAE-nl-C1INH.<sup>7,19</sup>

#### CLINICAL PEARLS

- HAE is characterized by episodes of nonpruritic, nonpitting edema, which commonly affects the skin and mucosal surfaces.
- The majority of patients have a family history with autosomal dominant inheritance, but patients may present with *de novo* mutations.
- The initial presentation of HAE can be variable and may include gastrointestinal pain as the sole presenting symptom.
- Although urticarial lesions are not associated with HAE, erythema marginatum occurs in approximately a third of patients.

- Prompt treatment of symptoms can lead to the avoidance of significant morbidity and mortality.

## REFERENCES

- Collins-Yoder AS. Angioedema: clinical presentations and pharmacological management. *Dimens Crit Care Nurs.* 2016; 35:181–189.
- Guo C, Settupane RA. Clinical presentation, pathophysiology, diagnosis, and treatment of acquired and hereditary angioedema: exploring state-of-the-art therapies in RI. *RI Med J.* 2013; 99:41.
- Kaplan AP, Pawaskar D, Chiao J. C1 Inhibitor activity and angioedema attacks in patients with hereditary angioedema. *J Allergy Clin Immunol Pract.* 2020; 8:892–900.
- Nzeako UC, Longhurst HJ. Many faces of angioedema: focus on the diagnosis and management of abdominal manifestations of hereditary angioedema. *Eur J Gastroenterol Hepatol.* 2012; 24:353–361.
- Patel N, Suarez LD, Kapur S, et al. Hereditary angioedema and gastrointestinal complications: an extensive review of the literature. *Case Reports Immunol.* 2015; 2015:925861.
- Wedner HJ. Hereditary angioedema: Pathophysiology (HAE type I, HAE type II, and HAE nC1-INH). *Allergy Asthma Proc.* 2020; 41:S14–S17.
- Bork K. Hereditary angioedema with normal C1 inhibitor. *Immunol Allergy Clin North Am.* 2013; 33:457–470.
- Bellanti JA, Settupane RA. Hereditary angioedema: an instructive model of clinical description, molecular discovery, and development of new effective treatments. *Allergy Asthma Proc.* 2011; 32(suppl 1):S1.
- Bork K, Meng G, Staubach P, et al. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med.* 2006; 119:267–274.
- Bowen T, Cicardi M, Farkas H, et al. International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol.* 2010; 6:24.
- Prematta MJ, Bewtra AK, Levy RJ, et al. Per-attack reporting of prodromal symptoms concurrent with C1-inhibitor treatment of hereditary angioedema attacks. *Adv Ther.* 2012; 29:913–922.
- Yucelten D, Kus S. Chicken-wire erythema, but not urticaria, as the presenting sign of hereditary angioedema. *Eur J Dermatol.* 2006; 16:197–198.
- Manning ME. Hereditary angioedema: differential diagnosis, diagnostic tests and family screening. *Allergy Asthma Proc.* 2020; 41:S22–S25.
- Bork K, Barnstedt SE, Koch P, et al. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet.* 2000; 356:213–217.
- Zuraw B. Hereditary angioedema with normal C1 inhibitor: four types and counting. *J Allergy Clin Immunol.* 2018; 141:884–885.
- Bork K, Gül D, Hardt J, et al. Hereditary angioedema with normal C1 inhibitor: clinical symptoms and course. *Am J Med.* 2007; 120:987–992.
- Bork K, Wulff K, Hardt J, et al. Hereditary angioedema caused by missense mutations in the factor XII gene: clinical features, trigger factors, and therapy. *J Allergy Clin Immunol.* 2009; 124:129–134.
- Bork K, Fischer B, Dewald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy. *Am J Med.* 2003; 114:294–298.
- Agostoni A, Cicardi M. Contraindications to the use of ace inhibitors in patients with C1 esterase inhibitor deficiency. *Am J Med.* 1991; 90:278. □

# Hereditary angioedema: Differential diagnosis, diagnostic tests, and family screening

Michael E. Manning, M.D.<sup>1</sup>

## ABSTRACT

*Hereditary angioedema is a rare, autosomal dominant genetic disorder that leads to sporadic episodes of swelling, which can affect any part of the body. With a prevalence of 1 in 10,000 to 1 in 50,000, there are other, more common causes of angioedema. Differentiating between bradykinin-mediated and histamine-mediated causes of swelling remains a major challenge. It is critical to develop an appropriate differential diagnosis, work through the various conditions, and obtain the pertinent laboratory evaluation to rule in or out the proposed diagnosis. As an autosomal dominant genetic disorder, there is a 50% chance with each pregnancy of passing on the genetic mutation in the SERPING1 gene. This review addressed the differential diagnosis to consider, the appropriate laboratory evaluation, and the importance of family screening.*

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Angioedema, defined as swelling of the deep dermal, subcutaneous, and submucosal tissues, occurs due to increased vascular permeability and fluid extravasation into the surrounding tissues. Marcello Donati first reported angioedema in 1586 when an Italian Count developed lip swelling secondary to an egg allergy.<sup>1</sup> John Laws Milton described the clinical features in 1876, and Heinrich Quinke coined the term angioneurotic edema in 1882 as he observed the effect of stress on the development of attacks of swelling.<sup>2</sup> Sir William Osler first described the hereditary nature of angioedema in 1888.<sup>1,2</sup> There are a variety of conditions that will result in episodes of angioedema, and being able to distinguish the different causes is vital to the proper management of the patient. Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder that leads to unpredictable attacks of swelling that can affect any part of the body but most commonly the extremities, gastrointestinal tract, face, urogenital area, and larynx, which can be life threatening. With a prevalence of 1 in 10,000 to 1 in 50,000, HAE is not the most common cause of swelling but must be considered when evaluating any patient with angioedema.<sup>3</sup>

## DIFFERENTIAL DIAGNOSIS

It is important to differentiate HAE from other forms of angioedema because the approach to treatment is quite different. The foundation to developing a

diagnosis is with an in-depth history and physical examination. Angioedema can occur with or without urticaria, be triggered by a variety of mediators, and be classified as acquired or hereditary. An in-depth review of all the forms of angioedema is beyond the scope of this article. Simply, the different forms of angioedema can be classified as histamine mediated (histaminergic), bradykinin mediated, leukotriene mediated, and idiopathic angioedema.

Histaminergic forms include food allergy, drug allergy, insect sting reactions, and spontaneous and/or idiopathic urticaria and/or angioedema. Histaminergic angioedema is the most common form of angioedema. Allergic or immunoglobulin E mediated forms typically occur quickly after exposure and are associated with urticaria. Nonallergic mast cell-mediated angioedema is seen with a variety of medications, *e.g.*, opioids, along with radiocontrast media and infections. However, frequently, the cause remains a mystery. Chronic idiopathic urticaria and/or angioedema is the focus of national and international guidelines.<sup>4</sup>

Bradykinin-mediated angioedema includes HAE types I and II, HAE with normal C1 esterase inhibitor (C1-INH) level, acquired C1-INH deficiency, and angiotensin-converting enzyme inhibitor (ACE-I) induced angioedema. The leukotriene-mediated category includes nonsteroidal anti-inflammatory drug- and/or aspirin-induced urticaria and angioedema.<sup>2,3</sup> As clinicians we must also consider disorders that mimic angioedema. This category of “pseudoangioedema” includes conditions such as acute contact DRESS (dermatitis, drug rash with eosinophils, and systemic symptoms), dermatomyositis, hypothyroidism, superior vena cava syndrome, persistent edema of rosacea (*morbus Morbihan*), Gleich syndrome, cluster headaches, Clarkson disease, hypocomplementemic urticarial vasculitis, orofacial granulomatosis, subcutaneous emphysema, and idiopathic edema.<sup>6</sup> The differential diagnoses of angioedema are summarized in Table 1.

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**Table 1 Angioedema differential diagnoses**

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Histamine mediated
Allergy: food, drug
Hymenoptera hypersensitivity
Spontaneous and/or idiopathic urticaria and angioedema
Bradykinin mediated
Hereditary angioedema types I/II
Hereditary angioedema with a normal C1 esterase inhibitory level
Acquired C1 esterase inhibitor deficiency
Angiotensin-converting enzyme inhibitor
Leukotriene mediated
Nonsteroidal anti-inflammatory drug
Aspirin
Idiopathic angioedema
Autoimmune diseases
Thyroid disease
Hydrostatic edema
Gleich syndrome
Clarkson syndrome
Protein deficiency
Acute contact dermatitis
DRESS (dermatitis, drug rash with eosinophils, and systemic symptoms)
Dermatomyositis
Superior vena cava syndrome
Morbus Morbihan
Hypocomplementemic urticarial vasculitis
Orofacial granulomatosis
Subcutaneous emphysema
Cluster headaches
Idiopathic edema

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As a clinician, being able to distinguish between histamine-mediated angioedema and bradykinin-mediated angioedema remains our biggest challenge.<sup>7</sup> The response to previous treatment will help identify the type of angioedema that a patient has. Histaminergic forms of angioedema will typically respond to standard or high-dose H<sub>1</sub> antihistamines, glucocorticoids, and epinephrine, whereas bradykinin-mediated angioedema will not. Although the presence of urticaria, in association with angioedema, typically eliminates the diagnosis of HAE from consideration, this does not preclude a patient with HAE from having episodes of urticaria independent of his or her HAE.<sup>8,9</sup> In contrast to histaminergic angioedema, HAE swelling develops slower, over 12–24 hours, then plateaus, and resolves, on average, over 2–5 days.

Three types of HAE have been identified based on the antigenic levels and function of C1-INH. The clinical presentation of HAE types I and II are indistinguishable,

with type I accounting for ~85% of all cases of HAE. The differentiation is seen on laboratory analysis. HAE with normal C1-INH is the least common form and is clinically similar to HAE types I/II. Again, the differentiation is made based on laboratory evaluation, along with the response or lack of a response to specific therapeutic interventions. The underlying cause of HAE types I/II is one of >400 mutations of the *SERPINC1* gene encoding for C1-INH located on chromosome 11.<sup>2,7,10</sup> The specific mutation leads to either decreased production of C1-INH (type I) or the production of a dysfunctional C1-INH (type II).<sup>11,12</sup> The cause of HAE with normal C1-INH is much less clear. There currently are four different types of HAE with normal C1-INH, including mutation of the *F12* gene, which encodes Factor XII; mutation in the angiotensin 1 gene; mutation in the plasminogen gene; and unknown cause.<sup>13</sup>

Acquired angioedema due to C1-INH deficiency (acquired C1-INH deficiency) is much less common than HAE types I/II. However, the symptoms of acquired C1-INH deficiency are similar to the symptoms of HAE types I/II, and the basic laboratory evaluation seems similar to HAE type I.<sup>11</sup> The distinguishing features of acquired C1-INH deficiency are the age of onset, typically after the fourth decade of life, and the association with lymphoproliferative diseases, autoimmune disease, and other malignancies. Measurement of the C1q level can differentiate between acquired C1-INH deficiency and HAE types I/II.

ACE-I associated angioedema is thought to be mediated by bradykinin. HAE types I/II results from an overproduction of bradykinin, whereas ACE-I angioedema is due to decreased degradation of bradykinin and other ACE-I substrates, *e.g.*, substance P. Other pathways are sure to be involved beyond bradykinin because specific bradykinin  $\beta$ 2 receptor blockers have failed to speed the resolution of ACE-I-induced angioedema in limited clinical trials.<sup>14</sup> Unlike the cough associated with ACE-I use that typically occurs within the first 9–12 months of starting the medication, attacks of angioedema are greatest in the first weeks to months of starting the medication but can occur at any point during the course of taking the ACE-I. ACE-I angioedema is more common in women than in men, is 4–5-fold higher in patients of African descent, is uncommon in Asians, and is more common in smokers and former smokers and in patients with seasonal allergic rhinitis and antihistamine or corticosteroid use. Patients with type 2 diabetes have a decreased risk.<sup>14</sup> Similar to HAE types I/II, the swelling secondary to ACE-I develops slowly, then plateaus before resolving over several days.<sup>7</sup>

#### DIAGNOSTIC TESTING

Clinicians must first suspect HAE before a diagnosis can be made. Once HAE is considered, then the

diagnosis is confirmed with diagnostic testing. The simplest and most cost-effective initial test is a complement component 4 (C4) level. Patients with HAE I/II or acquired C1-INH deficiency typically have a low C4 level during and in between attacks of swelling. If the C4 level is borderline low or low normal during a quiescent period, then repeat the laboratory work during an attack because the levels will uniformly be low or even undetectable in patients with HAE types I/II. The other confirmatory tests to obtain are an antigenic C1-INH level, C1-INH functional level, and C1q level.<sup>15</sup> The antigenic C1-INH level is low in HAE type I, however the antigenic C1-INH level is normal, or even elevated, in HAE type II. The C1q level is normal in both HAE types I/II. As the name implies, the laboratory test values in patients with HAE with normal C1-INH are all normal. ACE-I-associated angioedema also has normal laboratory test values. The sentinel result for both HAE types I/II is the functional C1-INH level.<sup>16</sup>

There are two primary tests for measuring functional C1-INH levels. The prevailing commercial test is an enzyme-linked immunosorbent assay known as the Quidel assay (Quidel Corporation, San Diego, California, USA). This assay measures the ability of C1-INH to bind C1s, which is a prerequisite for inhibition but not a direct measure of C1-INH function.<sup>17</sup> If the patient's clinical history is strongly suggestive of HAE and the Quidel assay has a normal or equivocal value, you may want to repeat the functional C1-INH test *via* the chromogenic assay.<sup>18</sup> The chromogenic assay is a direct measure of functional C1-INH. The Quidel assay results are classified as low (<41%), equivocal (41–67%), and normal (>67%). Chromogenic assay results are classified as low (<74%) and normal (74–174%).<sup>17</sup> The positive predictive value of the Quidel assay was found to be 100%, but the negative predictive value was only 62%. Therefore, a false-negative result is highly possible. The chromogenic assay, however, had a positive predictive value of 98% and a negative predictive value of 100%.<sup>17,18</sup>

Acquired C1-INH will have similar laboratory findings as HAE type I but will typically have a low C1q level, whereas HAE type I has a normal level. If the

clinical suspicion is still high for HAE and the laboratory analysis is not diagnostic, then a genetic analysis can be undertaken, with sequencing of the *SERPING1* gene. Genetic analysis is mainly reserved for the research setting at this time because complement evaluation is much less costly. A summary of the profiles that differentiate the various forms of HAE and other causes of angioedema is presented in Table 2.

## FAMILY SCREENING

A family history of swelling is an important part of the diagnostic evaluation of HAE, but it is not an absolute requirement. Seventy-five percent of patients will have a positive family history of HAE or swelling, but it is estimated that ~25% of patients with HAE have had a spontaneous or *de novo* mutation of the *SERPING1* gene.<sup>19</sup> As mentioned earlier, HAE is an autosomal dominant genetic disorder. Therefore, an parent who is affected has a 50% chance of passing on the specific genetic mutation to each child conceived. An autosomal dominant disorder only requires one mutated gene to be present to express the condition. In comparison, an autosomal recessive condition needs two copies of the mutated gene for the specific disease to be expressed.

There is no carrier state with autosomal dominant disorders. An individual either has or does not have the disease. However, how the individual expresses the mutated gene, known as phenotypic expression, is variable. This means that a parent who is affected and a child who is affected can have completely different clinical presentations of the same mutation, including frequency, severity, location, triggers, and response to treatment. Because of this genetic pattern, experts stress the importance of screening all family members of patients with HAE, including offspring, siblings, parents, grandparents, aunts, and uncles. Amazingly, many immediate family members of a patient with HAE have never been screened. Also, do not assume that a relative who reports episodes of swelling has HAE until confirmatory testing is performed.<sup>20</sup>

Screening laboratory work should not be obtained until after a child is  $\geq 1$  year of age. Although antigenic C1 and functional C1-INH levels could be measured

Table 2 Laboratory complement findings

	C4	C1-INH Antigenic Level	C1-INH Functional	C1q
HAE type I	Low	Low	Low	Normal
HAE type II	Low	Normal or elevated	Low	Normal
HAE with normal C1-INH	Normal	Normal	Normal	Normal
Acquired C1-INH deficiency	Low	Normal or Low	Low	Low
ACE-I angioedema	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; ACE-I = angiotensin-converting enzyme inhibitor.

early, C4 levels for HAE screening should not be measured during the first year of life.<sup>20</sup> Genetic screening may be done before 1 year of age, but this is not standard.<sup>10,12</sup> Although parents may hesitate at testing children for a variety of reasons, it is important that a family be prepared. The first attack that a child experiences could be a life-threatening laryngeal attack. HAE is a disease of childhood, with at least 50% of patients developing their first symptoms by the age of 10 years and another 35% by the age of 20 years. HAE tends to worsen at puberty. Having the diagnosis already elucidated can prevent unwanted morbidity, unnecessary medical or surgical procedures, and, possibly, mortality. The same complement analysis is used when screening children of a parent with HAE. Proper screening of patients leads to knowledge and the correct management of patients with HAE.

## CLINICAL PEARLS

- An in-depth history and physical examination is the foundation for ruling in or out the diagnosis of HAE.
- A lack of response to H<sub>1</sub> antihistamines, steroids, and epinephrine is key difference between HAE, bradykinin-mediated swelling, and histaminergic swelling.
- The C4 level is almost always low in patients with HAE types I/II and is a simple cost-effective screening test.
- Consider obtaining a chromogenic functional C1-INH level to confirm or eliminate suspected HAE when commercially available C1-INH functional results are nondiagnostic.
- All family members of a patient with HAE should be screened.

## REFERENCES

1. Gill P, Betschel S. The clinical evaluation of angioedema. *Immunol Allergy Clin North Am.* 2017; 37:449–466.
2. Banerji A. Hereditary angioedema: classification, pathogenesis and diagnosis. *Allergy Asthma Proc.* 2011; 32:403–407.
3. Proper SP, Lavery WJ, Bernstein JA. Definition and classification of hereditary angioedema. *Allergy Asthma Proc.* 2020; 41:S3–S7.
4. Busse PJ, Smith T. Histaminergic angioedema. *Immunol Allergy Clin North Am.* 2017; 37:467–481.
5. Bernstein J. Update on angioedema: evaluation, diagnosis, and treatment. *Allergy Asthma Proc.* 2011; 32:408–412.
6. Andersen MF, Longhurst HJ, Rasmussen ER, et al. How not to be misled by disorders mimicking angioedema: a review of pseudoangioedema. *Int Arch Allergy Immunol.* 2016; 169:163–170.
7. Cicardi M, Zuraw BL. Angioedema due to bradykinin dysregulation. *J Allergy Clin Immunol Pract.* 2018; 6:1132–1141.
8. Craig TJ, Bernstein JA, Farkas H, et al. Diagnosis and treatment of bradykinin-mediated angioedema: outcomes from an angioedema expert consensus meeting. *Int Arch Allergy Immunol.* 2014; 165:119–127.
9. Lumry W, Settignano RA. Hereditary angioedema: epidemiology and burden of illness. *Allergy Asthma Proc.* 2020; 41:S8–S13.
10. 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; 73:1575–1596.
11. Azmy V, Brooks JP, Hsu FI. Clinical presentation of hereditary angioedema. *Allergy Asthma Proc.* 2020; 41:S18–S21.
12. 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; 131:1491–1493.
13. Zuraw B. Hereditary angioedema with normal C1 inhibitor: four types and counting. *J Allergy Clin Immunol.* 2018; 141:884–885.
14. Stone C, Brown N. Angiotensin-converting enzyme inhibitor and other drug-associated angioedema. *Immunol Allergy Clin North Am.* 2017; 37:483–495.
15. Banerji A, Busse P, Christiansen SC, et al. Current state of hereditary angioedema management: a patient survey. *Allergy Asthma Proc.* 2015; 36:213–217.
16. Mansi M, Zanichelli A, Coerezza A, et al. Presentation, diagnosis and treatment of angioedema without wheals: a retrospective analysis of a cohort of 1059 patients. *J Intern Med.* 2015; 277:585–593.
17. Li HH, Busse P, Lumry WR, et al. Comparison of chromogenic and ELISA functional C1 inhibitor tests in diagnosing hereditary angioedema. *J Allergy Clin Immunol Pract.* 2015; 3:200–205.
18. Frazer-Abel A, Giclas P. Update on laboratory tests for the diagnosis and differentiation of hereditary angioedema and acquired angioedema. *Allergy Asthma Proc.* 2011(suppl); 32:17–21.
19. Kaplan AP, Pawaskar D, Chiao J, et al. C1 inhibitor activity and angioedema attacks in patients with hereditary angioedema. *J Allergy Clin Immunol Pract.* 2020; 8:892–900.
20. Li H. Pearls and pitfalls in the diagnosis of hereditary angioedema. *Allergy Asthma Proc.* 2019; 40:282–284. □

# Hereditary angioedema: On-demand treatment of angioedema attacks

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## ABSTRACT

The availability of effective acute treatment for angioedema has been fundamental in reducing the burden of illness for patients with hereditary angioedema (HAE). In building on the foundation of scientific advances that elucidate the pathomechanism(s) of attacks related to vascular permeability, novel targeted on-demand treatments have been developed and approved. These therapies have provided the means to arrest episodes of swelling, which, in the past, had the potential to inexorably lead to morbidity, and even mortality, for patients with HAE. Access to these medications, along with an emphasis on early administration and guidance that all attacks are candidates for treatment, has shifted the management paradigm for HAE. Although unmet needs remain, these acute therapies, coupled with advances in prophylactic treatment, have furthered the goal for all patients with HAE to live a normal life.

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**H**ereditary angioedema (HAE) is clinically characterized by recurrent attacks of swelling that affect cutaneous and submucosal tissues. Attacks can be disfiguring, painful, and, in the case of laryngeal angioedema, life threatening.<sup>1</sup> In the past, much of the morbidity and mortality associated with HAE stemmed from the absence of available medications for treating attacks. Drugs (antihistamines, epinephrine, or corticosteroids) that can successfully treat histamine-mediated angioedema are not beneficial for HAE. HAE related to a deficiency of functional C1 inhibitor (HAE C1-INH types I and II) involves activation of the contact system cascade with the generation of bradykinin. Engagement of bradykinin with its receptor on endothelial cells results in an increase in capillary permeability, with ensuing angioedema. The cause of angioedema in the more-recently described HAE with normal levels of functional C1-INH (nl-C1-INH) is also presumed to be mediated by bradykinin, although the evidence for this is much less robust.<sup>2,3</sup>

In the past, options for the treatment of HAE attacks beyond supportive care had been limited to infusion of fresh frozen plasma (FFP), which contains C1-INH. Over the past decade, a number of effective on-demand treatments for HAE have been developed and licensed, transforming the management of HAE. In this review, we focused on the current approach and available acute

treatment for HAE attacks. S.C. Christiansen and B.L. Zuraw contributed equally to the work.

## ON-DEMAND HAE TREATMENT OPTIONS

Four effective on-demand treatment options have become available in the United States since 2009, each of which targets either the generation or effect of bradykinin (Fig. 1). These include plasma-derived C1-INH (pd-C1-INH) (Berinert, CSL Behring, King of Prussia), an inhibitor of plasma kallikrein (ecallantide [Kalbitor]), recombinant C1-INH (rh-C1-INH) (Ruconest, Pharming, Leiden, Netherlands), and an inhibitor of the  $\beta_2$  bradykinin receptor (icatibant [Firazyr, Takeda, Cambridge]). Each of the therapies has been shown in randomized controlled studies to be effective in arresting the progression of HAE C1-INH attacks (Table 1).<sup>3–7</sup> Open-label extension data, along with patient registries, have further highlighted the long-term efficacy and safety of these medications.<sup>8–12</sup> Randomized controlled studies of on-demand treatment for patients with HAE nl-C1-INH are lacking; however, numerous open-label reports have revealed successful responses to each of the on-demand treatments used for HAE C1-INH.<sup>13–16</sup>

C1-INH concentrates (pd-C1-INH [Berinert]) and recombinant human C1-INH (rh-C1-INH [Ruconest]) each require intravenous injection. The plasma kallikrein inhibitor ecallantide and the bradykinin  $\beta_2$  receptor antagonist icatibant are administered subcutaneously. Ecallantide has been associated with allergic and even anaphylactic reactions in a relatively small number of cases (<2%), and, therefore, needs to be administered by a health care provider. Self-administration, including intravenous injection, is otherwise advocated both to reduce the time to administration and minimize disruption in the daily life of patients.<sup>17</sup> These medications typically become effective within 60 minutes.

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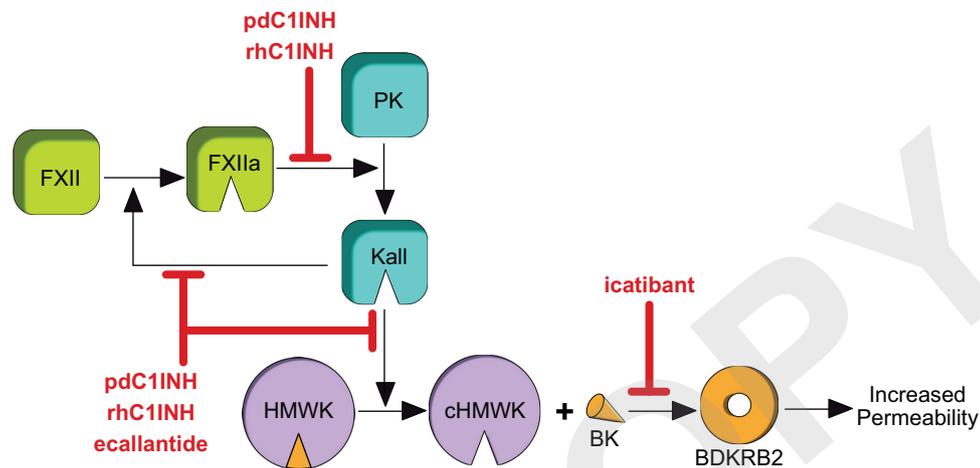
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**Figure 1.** Mechanistic targets for on-demand treatment. Schematic of the plasma contact system activation, leading to the generation of bradykinin, with ensuing angioedema due to increased permeability via the bradykinin  $\beta_2$  receptor. Actions of the on-demand medications are shown in red. FXII = Factor XII; FXIIa = activated factor XII; PK = plasma prekallikrein; kall = plasma kallikrein; HMWK = high-molecular-weight kininogen; cHMWK = cleaved HMWK; BK = bradykinin; BDKRB2 = bradykinin  $\beta_2$  receptor.



### On-Demand Management of Acute Attacks

The cornerstones for management of acute attacks of HAE include the following: availability of effective on-demand acute therapy for all patients, early administration to prevent attack progression, and treatment of attacks, irrespective of the site of swelling. Despite the compelling evidence that patients will experience a substantial reduction in attack frequency and severity after incorporation of the approved long-term prophylactic options discussed in other papers in this primer, immediate access to on-demand treatments will continue to be essential to ensure patient safety.

**Access.** There is a general consensus that all patients with laboratory-confirmed HAE C1-INH should have access to at least two standard doses of an U.S. Food and Drug Administration (FDA) approved on-demand medication for treatment of acute attacks.<sup>18–20</sup> For those patients with a diagnosis of HAE nI-C1-INH in whom laboratory test confirmation is not feasible (*i.e.*, genetic mutations for which commercial testing is not available or HAE-unknown), it is critical for the clinician to determine that the response to the on-demand treatment is in keeping with the expected pharmacokinetic and/or pharmacodynamic profile of the drug. This is of particular importance when the frequency or dose required for perceived improvement seems to be out of the expected range, which thereby raises questions as to the accuracy of the diagnosis (reviewed in other papers of this primer).

Due to the observed therapeutic variability among patients, it is important to optimize the selection of on-demand treatment based on efficacy and/or tolerability for the individual. In those instances in which prescribing more than one on-demand agent is deemed appropriate, the justification should be clearly documented by the physician and communicated to the patient. In critical situations, when none of these effective FDA-approved on-

demand medications are available, the use of FFP can be considered for treatment of an HAE attack.<sup>21</sup>

Given the accepted anecdotal reports of HAE attacks that precipitously worsen after FFP, preparations for its administration should include the ability to protect the patient's airway (particularly if oropharyngeal or laryngeal swelling is present). Solvent detergent-treated plasma may be safer than FFP due to the reduced viral risk. In the unfortunate and, it is hoped, an increasingly rare situation in which no effective on-demand treatment is available, supportive care (*i.e.*, intravenous fluids, anti-emetics, narcotic pain medication, or intubation) should be provided. This is with the caveat that, in contrast to the favorable impact that effective on-demand treatment has imparted for patients with HAE, reliance on supportive care is associated with an enhanced morbidity and mortality risk.

**Early Treatment of Attacks.** It is now widely recognized that, to be most effective, on-demand treatment should be administered as soon as the attack is recognized.<sup>17</sup> Emphasis on self-administration of on-demand medications is advocated to reduce a delay in administration, which thereby arrests the progression of swelling and minimizes morbidity, and the risk of mortality. In cases in which the patient experiences a reliable attack prodrome, preparation for treatment may be initiated.<sup>22</sup> Of interest, the single recognized physical prodrome (erythema marginatum) in patients with HAE C1-INH has recently been associated with evidence of contact system activation.<sup>23</sup> However, treatment should be administered only when the patient can identify that an attack has begun. Patients must be cautioned to seek medical care if the features of their attack are atypical, their response to self-treatment is inadequate, or they experience an attack that involves the airway.<sup>24</sup> In the latter instance, elective intubation should be considered for

Table 1 Regulatory agency approved on-demand treatments for hereditary angioedema

Drug Name or Trade Name (company)	Approved Indications	Dosage	Mechanism of Action	Anticipated Potential Adverse Effects
Plasma-derived C1-INH, Berinert (CSL Behring)	Acute attacks  All age groups*	20 IU/kg given intravenously	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis  Theoretical: transmission of infectious agent
Recombinant-human C1-INH	Acute attacks	50 U/kg given intravenously (maximum dose, 4200 U)	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis (individuals sensitized to rabbit)
Ruconest (Pharming)	Adolescent and adult#			Theoretical: transmission of infectious agent
Ecallantide	Acute attacks#	30 mg given by subcutaneous injection	Inhibits plasma kallikrein	Common: prolonged PTT (not clinically significant)
Kalbitor (Takeda)	Age ≥12 y			Rare: risk of anaphylaxis; uncommon: antidrug antibodies
Icatibant	Acute attacks	Adult: 30 mg given by SC injection	Bradykinin $\beta_2$ receptor antagonist	Common: discomfort at injection site
Firazyr (Takeda)	Age ≥18 y (U.S.); age ≥2 y (E.U.)	Pediatric: 12–25 kg, 10 mg SC; 26–40 kg, 15 mg SC; 41–50 kg, 20 mg SC; 51–65 kg, 25 mg SC; >65 kg, 30 mg SC		

C1 INH= C1 inhibitor; C1s = complement component 1s; C1r = complement component 1r; MASP = mannose-associated serine protease; PTT = partial thromboplastin time; SC = subcutaneous.

\*Preferred for pregnant women and women who are breast-feeding.

#Must be administered by a medical professional prepared to treat anaphylaxis.

any patient with signs of respiratory distress who is not improving after treatment.

It is important to convey to patients what to expect from the administration of on-demand therapy. These treatments are designed to arrest the progression of swelling during an attack. Thus, early administration cannot be overemphasized: the longer the swelling has been allowed to progress, the longer it will take for the attack to resolve. Effective treatment halts the progression of an attack but cannot undo the swelling that has already occurred. Once treatment has been initiated, the time to onset of relief should occur within 30 to 120 minutes.<sup>25</sup> In general, a second dose of the on-demand therapy is not warranted unless the attack begins to worsen. Failure to respond to one of the licensed on-demand therapies could

indicate that the symptoms are due to a condition other than an HAE attack.

All attacks, irrespective of location, may be treated as soon as they are clearly identified. The morbidity devolving from abdominal attacks and potentially fatal risk of laryngeal involvement coupled with facial, oral, and upper respiratory attacks have long been recognized as an impetus for acute early intervention. It is worth emphasizing that extremity attacks are also disabling and clearly worthy of early treatment to prevent dysfunction and to improve quality of life.<sup>26,27</sup>

## CONCLUSION

The lives of patients with HAE have been transformed by the development, approval, and availability

of effective targeted on-demand therapy. Appropriate management of HAE requires that all patients have rapid access to effective on-demand medications to reduce disease morbidity and prevent mortality. Emphasis on early administration to prevent attack progression, coupled with the understanding that all sites are candidates for care, should inform treatment decisions. Given the expanding options for effective and safe long-term prophylaxis, the frequency of on-demand treatments is anticipated to substantially decline; however, it will remain critical for patient safety that even patients with well-controlled HAE have ready access to on-demand treatment.

## CLINICAL PEARLS

- Patients with HAE must have ready access to two doses of an effective FDA-approved on-demand HAE medication (ecallantide, icatibant, pdC1INH, or rhC1INH) for the acute treatment of an HAE attack.
- On-demand treatment should be administered as soon as an attack is recognized to reduce morbidity and prevent mortality.
- On-demand medications should be self-administered (or administered by a caregiver) whenever feasible to minimize a delay in treatment and disruption of daily life.
- All HAE attacks are eligible for treatment, irrespective of the location of the swelling or the severity of the attack.

## REFERENCES

1. Zuraw BL. Clinical practice. Hereditary angioedema. *N Engl J Med.* 2008; 359:1027–1036.
2. Cicardi M, Zuraw BL. Angioedema due to bradykinin dysregulation. *J Allergy Clin Immunol Pract.* 2018; 6:1132–1141.
3. Busse PJ, Christiansen SC. Hereditary angioedema. *N Engl J Med.* 2020; 382:1136–1148.
4. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med.* 2010; 363:532–541.
5. Cicardi M, Levy RJ, McNeil DL, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med.* 2010; 363:523–531.
6. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med.* 2010; 363:513–522.
7. Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol.* 2009; 124:801–808.
8. Malbran A, Riedl M, Ritchie B, et al. Repeat treatment of acute hereditary angioedema attacks with open-label icatibant in the FAST-1 trial. *Clin Exp Immunol.* 2014; 177:544–553.
9. Riedl MA, Levy RJ, Suez D, et al. Efficacy and safety of recombinant C1 inhibitor for the treatment of hereditary angioedema attacks: a North American open-label study. *Ann Allergy Asthma Immunol.* 2013; 110:295–299.
10. Lumry WR, Bernstein JA, Li HH, et al. Efficacy and safety of ecallantide in treatment of recurrent attacks of hereditary angioedema: open-label continuation study. *Allergy Asthma Proc.* 2013; 34:155–161.
11. Riedl MA, Bygum A, Lumry W, et al. Safety and usage of C1-inhibitor in hereditary angioedema: Berinert registry data. *J Allergy Clin Immunol Pract.* 2016; 4:963–971.
12. Busse P, Bygum A, Edelman J, et al. Safety of C1-esterase inhibitor in acute and prophylactic therapy of hereditary angioedema: findings from the ongoing international Berinert patient registry. *J Allergy Clin Immunol Pract.* 2015; 3:213–219.
13. Bouillet L, Ponard D, Rousset H, et al. A case of hereditary angio-oedema type III presenting with C1-inhibitor cleavage and a missense mutation in the F12 gene. *Br J Dermatol.* 2007; 156:1063–1065.
14. Vitrat-Hincky V, Gompel A, Dumestre-Perard C, et al. Type III hereditary angio-oedema: clinical and biological features in a French cohort. *Allergy.* 2010; 65:1331–1336.
15. Bouillet L, Boccon-Gibod I, Ponard D, et al. Bradykinin receptor 2 antagonist (icatibant) for hereditary angioedema type III attacks. *Ann Allergy Asthma Immunol.* 2009; 103:448.
16. Bouillet L, Boccon-Gibod I, Launay D, et al. Hereditary angioedema with normal C1 inhibitor in a French cohort: clinical characteristics and response to treatment with icatibant. *Immun Inflamm Dis.* 2017; 5:29–36.
17. Tourangeau LM, Castaldo AJ, Davis DK, et al. Safety and efficacy of physician-supervised self-managed C1 inhibitor replacement therapy. *Int Arch Allergy Immunol.* 2012; 157:417–424.
18. Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol Pract.* 2013; 1:458–467.
19. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—the revision and update. *Allergy.* 2018; 73:1575–1596.
20. Betschel S, Badiou J, Binkley K, et al. The International/Canadian Hereditary Angioedema Guideline. *Allergy Asthma Clin Immunol.* 2019; 15:72.
21. Wentzel N, Panieri A, Ayazi M, et al. Fresh frozen plasma for on-demand hereditary angioedema treatment in South Africa and Iran. *World Allergy Organ J.* 2019; 12:100049.
22. Prematta MJ, Bewtra AK, Levy RJ, et al. Per-attack reporting of prodromal symptoms concurrent with C1-inhibitor treatment of hereditary angioedema attacks. *Adv Ther.* 2012; 29:913–922.
23. Nguyen A, Zuraw BL, Christiansen SC. Contact system activation during erythema marginatum in hereditary angioedema. *Ann Allergy Asthma Immunol.* 2020; 124:394–395.e1.
24. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol.* 2012; 130:692–697.
25. Tourangeau LM, Zuraw BL. The new era of C1-esterase inhibitor deficiency therapy. *Curr Allergy Asthma Rep.* 2011; 11:345–351.
26. Kusuma A, Relan A, Knulst AC, et al. Clinical impact of peripheral attacks in hereditary angioedema patients. *Am J Med.* 2012; 125:937.e17–24.
27. Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy.* 2012; 67:147–157. □

# Triggers and short-term prophylaxis in patients with hereditary angioedema

Timothy Craig, D.O.

## ABSTRACT

**Background:** Hereditary angioedema (HAE) is a rare disease that affects 1 in 60,000; however, despite being extremely rare, the severity of the disease can cause significant limitations to quality of life. In addition, attacks can be fatal and require urgent care.

**Methods:** We searched PubMed and Google for Hereditary Angioedema and prophylaxis, short term prophylaxis, surgery, medical procedures, dental work, triggers.

**Results:** The main triggers are estrogens, Angiotensin Converting Enzyme Inhibitors (ACE) inhibitors, trauma, dental work, stress, surgery, manipulation of the upper airway, and medical procedures. Prophylaxis is often used long term to prevent attacks; before known triggers, prophylaxis is referred to as short-term prophylaxis (STP). When to initiate STP, what to use, and what dose to use have not been adequately researched, but there is consensus that, whenever the upper airway is manipulated, STP is essential. In addition, consensus has been reached that an IV C1 inhibitor is the preferred STP agent, and it is my opinion that dosing at 20 units/kg allows dosing for all ages and also allows average-size adults to receive >1000 units because failures at 1000 units have been documented in the literature.

**Conclusions:** This article focused on triggers and preprocedural STP and not on pre-event STP, which is often used before important life events; however, medications and dosing are the same for pre-event prophylaxis.

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Hereditary angioedema (HAE) is a rare disease, with recurrent swelling of the bowel wall, skin, and upper airway. Triggers for attacks are variable and include estrogen, mental stress, infections, physical exertion, mechanical trauma, medical procedures, angiotensin-converting enzyme inhibitors, dental work, and surgical procedures. Most HAE attacks do not have an exacerbating factor; however, identification, recognition, and prevention of triggers may prevent future attacks. Avoidance is important but not always possible, and, for this reason, short-term prophylaxis (STP) is often essential.<sup>1–4</sup>

## MANAGEMENT OF TRIGGERS

Understanding the triggers is important for the prevention of attacks by avoidance or by use of either STP or long-term prophylaxis. It is important to remember that triggers may not consistently exacerbate attacks in HAE, and, for this reason, if a procedure was well tolerated in the past, it cannot be assumed that future procedures will also be tolerated without attacks. Avoidance of exacerbating factors is appropriate if

practical and if it does not impose unnecessary restrictions on a person's life. For this reason, all patients should be made aware of potential HAE triggers. Patients also should be requested to reach out to their health care provider if potential exposure to a trigger is likely. Preventive therapy, such as colonoscopy, Papanicolaou test, breast examinations, mammograms, vaccines, and, especially, dental care, should be encouraged to decrease the need for future procedures or more elaborate and traumatic procedures. Many of the current guidelines were developed based on limited and rarely controlled data; therefore, most of the discussion that follows is based on expert opinion.<sup>1–5</sup>

With regard to an anticipated procedure, preparation to avoid triggers and thus an HAE attack should usually be preferred to therapeutic interventions. An example of minimizing risk is when a patient needs to undergo a surgical procedure and the anesthesiologist works to avoid general anesthesia and intubation, and instead uses local anesthetics and twilight sedation, possibly to prevent a catastrophic event from intubation.<sup>6</sup> When intubation and general anesthesia are essential, or if the surgery will have significant trauma to the skin or other organs, then STP should be used. A low clinical threshold for STP treatment is advised in the setting of any procedure, including dental extractions and oral and nasal surgery, which approximates the upper airway. Because STP is not always effective, trauma should be minimized if possible and two doses of "on-demand" therapy should be available to administer if an attack occurs (Table 1).<sup>6</sup>

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**Table 1 Preparation for surgery, dental, and medical procedures, and perioperative care**

Medications	Avoid angiotensin-converting-enzyme inhibitors and estrogens	
Preparation for surgery	Avoid general anesthesia if possible  Avoid intubation if possible Minimize trauma Determine if short-term prophylaxis is needed	Use local anesthesia if possible  Minimize trauma to the upper airway Use minimal invasive surgery if possible If upper airway will be involved or the procedure is major, then order C1-INH for infusion 1 hr before the procedure; the alternatives are androgens or FFP if C1-INH is not available Intravenous C1-INH can be given in addition to other prophylaxis agents
Day of surgery	If on long-term prophylaxis, then do not discontinue it Infuse C1-INH 1 hr before the procedure or ensure that the patient was compliant with androgen use Consider triggers for angioedema	Reduce trauma, stress, and other important variables Ensure that two doses of on-demand therapy are available to treat angioedema
Postoperative	Observe or educate the patient because angioedema may occur up to 3 days after the procedure	Ensure that the patient has two doses of on-demand therapy if discharged before 3 days

*C1-INH = C1 inhibitor; FFP = fresh frozen plasma.*

### COMPARING DIFFERENT STP AGENTS

Studies based on dosage and the comparison of therapies for STP have been accomplished, but comparative data are few. Farkas *et al.*<sup>7</sup> compared oral therapies, tranexamic acid (TA) 200 mg three times a day for 5 days before and 2 days after a procedure, and danazol 200 mg three times a day for 5 days before and 2 days after a procedure, to C1 esterase inhibitor (C1-INH) 500 IU and no STP. With prophylaxis, the rate of angioedema occurred in 15% of patients, whereas the rate without prophylaxis was 35% after a surgical or medical procedure and 17.5% after dental work. C1-INH was superior to the oral therapies because, with danazol, swelling occurred in 36% of patients, TA in 50% of patients, whereas, with 500 units of intravenous (IV) C1-INH, swelling occurred in only 9% of patients.<sup>7</sup> In 1999 Farkas *et al.*<sup>8</sup> performed a prospective study by using danazol 600 mg a day in 12 patients, without controls. During the procedure, all 12 patients were protected from post-dental work attacks.<sup>8</sup> The adverse effects when using androgens for STP are minimum, and, most populations, including children, seem to tolerate them well.<sup>7,8</sup> Androgens should be avoided during pregnancy and lactation.

Early studies with TA demonstrated a positive benefit when compared with procedures not preceded with TA.<sup>9</sup> The study by Sheffer *et al.*<sup>9</sup> was not randomized; however, the patients were compared with and without

TA during surgical and dental procedures. Use of the regimen of 1 g of TA by mouth every 6 hours starting 48 hours before and continuing for 48 hours after the procedure demonstrated no episodes of angioedema in the 14 participants.<sup>9</sup> Bork *et al.*<sup>10</sup> demonstrated the effectiveness of C1-INH in a dose-ranging study. They compared the use of no therapy with the use of IV C1-INH at 500 and 1000 units given before dental extractions.<sup>10</sup> The attack rate with no therapy was 21.5%, and the attack rate with 500 and 1000 units was ~15% and 7%, respectively.<sup>10</sup> Analysis of these data suggests that a dose > 1000 units of IV C1-INH is needed to completely eliminate post-dental extraction swelling.<sup>10</sup> Grant *et al.*<sup>11</sup> used a retrospective study approach to assess data that suggested that 1000 units before a procedure was 98% effective. Another retrospective study of C1-INH for STP administered 1000 units before the IMPACT trial; however, after the IMPACT trial, the dose was increased to 20 units/kg.<sup>12</sup> The investigators reported no postoperative HAE attacks with either dose.<sup>13</sup> Also, Magerl *et al.*,<sup>14</sup> by extrapolating data from the Berinert (CSL Behring, King of Prussia, PA, USA) Patient Registry determined that patients who received ≥ 15 units/kg or ≥ 1500 units of C1-INH had fewer postoperative attacks than those with fewer doses (Table 2).

The above-mentioned studies used human plasma-derived C1-INH (pdC1-INH). However, recent data

**Table 2 A review of available hereditary angioedema drugs and if they are effective for STP**

Drug	Indicated?	Important Considerations	Dose
Icatibant	No	The half-life is too short	
Ecallantide	No	The half-life is too short	
Cinryze (Taketa, Deerfield, MA, USA)	Yes (off label)	The long half-life is optimum	IV at 1000 units
Berinert	Yes (off label)	The long half-life is optimum	IV at 20 units/kg
Subcutaneous C1-INH	No	Delayed absorption leads to delayed protection	No data are available if STP can be deferred if controlled on subcutaneous C1-INH and C1-INH function level is normal
Recombinant C1-INH	Yes (off label)	There are data that this is effective, but the half-life is short	50 units/kg
Lanadelumab	No	Delayed onset of activity leads to delayed protection	No data are available whether STP can be deferred if attack-free while on lanadelumab
Danazol	Yes, but needs to be started at least 5 days before surgery (off label)	Inexpensive	200 mg 3 times a day; reduce dose in children
Tranexamic acid	No	Lack of recent data to support its use	More comparative data are needed

STP = Short-term prophylaxis; IV = intravenous; C1-INH = C1 inhibitor.

that support the benefit of recombinant C1-INH, given as a weight-based dose (50 units/kg for those < 84 kg and 4200 units for those > 84 kg) showed that 97% of the 70 procedures performed resulted in no attacks during and up to 2 days after surgery.<sup>15</sup> When other therapies are not available, fresh frozen plasma (FFP) can be used for STP.<sup>16</sup> Angioedema only occurred in 10% of surgical patients pretreated with FFP. An earlier work, by Atkinson and Frank,<sup>17</sup> demonstrated the effectiveness of FFP in preventing angioedema, and only 3 of 45 patients (6.7%) had a minor angioedema attack. Although effective, some risks to consider with FFP are bloodborne diseases and possible allosensitization. The drugs used for HAE and whether they are effective for STP are listed in Table 2.

## CONSENSUS DOCUMENTS RECOMMENDATIONS FOR STP

### International Guidelines on the Gynecologic and Obstetric Management 2012

The treatment of choice for STP is pdC1-INH and, if not available, then FFP can be used. If a caesarean section is needed, then epidural anesthesia is preferred to general anesthesia and intubation. STP is not considered to be indicated for vaginal delivery unless there are additional risk factors.<sup>5</sup>

### International Consensus on the Diagnosis and Management of Pediatric Patients 2017

For minor interventions, on-demand therapy is recommended instead of STP. For any procedures that involve manipulation of the airway, pdC1-INH specified at a dose of 15–30 units/kg either during or as close as possible to the procedure is recommended. If pdC1-INH is not available, then an alternative is an androgen, *e.g.*, danazol 5 mg/kg to a maximum of 200 mg dosed orally three times daily for 5 days before and 2 days after the procedure. The authors of the guideline<sup>3</sup> state that it is safe to use androgens, even in young children for a short period, such as for STP. TA at a dose of 20 to 50 mg/kg per day to a maximum of 1 to 2 g three times a day, also 5 days before and 2 days after the procedure was also recommended as an alternative. For emergency surgery when C1-INH is not available, an option is solvent detergent plasma at 10 mL/kg.<sup>3</sup>

### The International World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) Guideline, 2018

STP is recommended for all medical, surgical, and dental procedures associated with mechanical effects on the upper aerodigestive tract. The preferred treatment was with C1-INH at a dose of either 1000 units IV or 20 units/kg IV just before the procedure. FFP

may be used instead but is not as safe. An alternative is an oral androgen 200 mg three times a day 5 days before and 2–3 days after the procedure. TA was not recommended. Because STP is not always effective, two doses of on-demand therapy should be available for an attack.<sup>1</sup>

### The International/Canadian Guideline 2019

A specific recommendation is that STP should be considered for a known trigger and any medical, surgical, and dental procedure. Factors such as the degree of trauma, proximity to the airway, a known trigger for the patient should all be included on whether to use STP. If the decision is to avoid STP, two doses of on-demand therapy should be available. The preferred STP was pdC1-INH at a dose of 20 units/kg 1 hour before the procedure, despite the European Union (EU) approval of alternate dosing of 500 units and 1000 units. If pdC1-INH is not available, then androgens or FFP can be considered as an alternative. The dose for danazol suggested was 2.5–10 mg/kg per day for 5 days before and 2–3 days after the procedure to a maximum total daily milligram amount of 200 mg three times daily but never to lactating or pregnant females. For FFP, the dose was 2 units for adults and 10 mL/kg in children 1 to 2 hours before the procedure. The use of anti-fibrinolytics was discouraged unless no other therapies are available.<sup>2</sup>

### CONCLUSION

There is a lack of a firm indication for when STP is necessary. Trauma severity and proximity to the upper airway are the most important variables when considering STP. All procedures that cross or that are near the airway should be preceded with STP. Minor medical or dental procedures, such as teeth cleaning or the repair of a small dental cavity as well as procedures distant from the airway (*e.g.*, colonoscopy and vaginal delivery), probably do not need STP. If STP is needed, then C1-INH 1 hour before the procedure is the preferred therapy. The dose of C1-INH can be debated, but the study by Bork *et al.*<sup>10</sup> demonstrated that a one-time dose of 1000 units has a 7% chance of the patient having swelling. From analysis of their data, it seems that 20 units/kg, which would equal 1500 units in an average-size male, seems a reasonable dose. Dosing per kg also prevents very young children from being administered the same dose that an extremely large adult would receive.

With IV C1-INH, the need for dosing the day of the procedure seems to be obvious by the pharmacokinetics. The benefit of IV C1-INH lasts for ~3 days. Because angioedema may follow a procedure as far out as 3 days, it is sensible to pretreat with IV C1-INH 1 hour before the procedure so that the effect is available for 3 days. Whether STP is necessary while patients are on subcutaneous C1-INH or lanadelumab is not known.<sup>18,19</sup> The

same question will arise if the new oral therapies, such as the oral kallikrein inhibitors, are approved.<sup>20</sup>

### CLINICAL PEARLS

- STP should be considered before specific triggers, such as surgery, medical procedures, or dental care.
- The most appropriate STP for moderate or major procedures is C1-INH; the preferred dose of C1-INH is 20 units/kg IV 1 hour before the procedure.
- Androgens or FFP may be used as an alternative.
- With or without the use of STP, two doses of rescue therapy is essential to have available.

### REFERENCES

1. 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; 73:1575–1596.
2. Betschel S, Badiou J, Binkley K, et al. The International/Canadian Hereditary Angioedema Guideline. *Allergy Asthma Clin Immunol*. 2019; 15:72.
3. Farkas H, Martinez-Saguer I, Bork K, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. *Allergy*. 2017; 72:300–313.
4. Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol Pract*. 2013; 1:458–467.
5. Caballero T, Farkas H, Bouillet L, et al. International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. *J Allergy Clin Immunol*. 2012; 129:308–320.
6. Williams AH, Craig TJ. Perioperative management for patients with hereditary angioedema. *Allergy Rhinol (Providence)*. 2015; 6:50–55.
7. Farkas H, Zotter Z, Csuka D, et al. Short-term prophylaxis in hereditary angioedema due to deficiency of the C1-inhibitor—a long-term survey. *Allergy*. 2012; 67:1586–1593.
8. Farkas H, Gyenyey L, Gidofalvy E, et al. The efficacy of short-term danazol prophylaxis in hereditary angioedema patients undergoing maxillofacial and dental procedures. *J Oral Maxillofac Surg*. 1999; 57:404–408.
9. Sheffer AL, Fearon DT, Austen KF, et al. Tranexamic acid: preoperative prophylactic therapy for patients with hereditary angioneurotic edema. *J Allergy Clin Immunol*. 1977; 60:38–40.
10. Bork K, Hardt J, Staubach-Renz P, et al. Risk of laryngeal edema and facial swellings after tooth extraction in patients with hereditary angioedema with and without prophylaxis with C1 inhibitor concentrate: a retrospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2011; 112:58–64.
11. Grant JA, White MV, Li HH, et al. Preprocedural administration of nanofiltered C1 esterase inhibitor to prevent hereditary angioedema attacks. *Allergy Asthma Proc*. 2012; 33:348–353.
12. Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol*. 2009; 124:801–808.
13. Gavigan G, Yang WH, Santucci S, et al. The prophylactic use of C1 inhibitor in hereditary angioedema patients undergoing

- invasive surgical procedures: a retrospective study. *Allergy Asthma Clin Immunol.* 2014; 10:17.
14. Magerl M, Frank M, Lumry W, et al. Short-term prophylactic use of C1-inhibitor concentrate in hereditary angioedema: findings from an international patient registry. *Ann Allergy Asthma Immunol.* 2017; 118:110–112.
  15. Valeriewa A, Staevska M, Jesenak M, et al. Recombinant human C1 esterase inhibitor as short-term prophylaxis in patients with hereditary angioedema. *J Allergy Clin Immunol Pract.* 2020; 8:799–802.
  16. Prematta M, Gibbs JG, Pratt EL, et al. Fresh frozen plasma for the treatment of hereditary angioedema. *Ann Allergy Asthma Immunol.* 2007; 98:383–388.
  17. Atkinson JC, Frank MM. Oral manifestations and dental management of patients with hereditary angioedema. *J Oral Pathol Med.* 1991; 20:139–142.
  18. Craig T, Zuraw B, Longhurst H, et al. Long-term outcomes with subcutaneous C1-inhibitor replacement therapy for prevention of hereditary angioedema attacks. *J Allergy Clin Immunol Pract.* 2019; 7:1793–1802.e2.
  19. Hwang G, Johri A, Ng S, et al. A review of kallikrein inhibitor lanadelumab in hereditary angioedema. *Immunotherapy.* 2019; 11:937–944.
  20. Hwang JR, Hwang G, Johri A, et al. Oral plasma kallikrein inhibitor BCX7353 for treatment of hereditary angioedema. *Immunotherapy.* 2019; 11:1439–1444. □

# Hereditary angioedema: Long-term prophylactic treatment

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## ABSTRACT

*Hereditary Angioedema (HAE) is a potentially life-threatening condition. With episodic, unpredictable swelling, HAE negatively affect the quality of life for those affected individuals. To reduce the morbidity and mortality of HAE are the primary goal for the disease management. In addition to have access to therapeutic drugs for their acute HAE attacks, many patients require long term prophylaxis (LTP) to reduce their attack frequency and severity. Preventing HAE attack by regular administration of medicine has become an important part of HAE disease management. Over the past few years, growing number of therapeutic options for the HAE LTP have made it possible for physicians to choose the most appropriate and effective treatment for individual patients. C1 INH concentrate and plasma kallikrein inhibitors (IV or SC) have largely replaced the older modality of treatment consisting different androgen derivatives or antifibrinolytics. Additional options, such as oral kallikrein inhibitor, antisense RNA/plasma kallikrein, anti-Factor 12a, bradykinin receptor blocker or future gene therapy are under clinical investigation. The significant cost and the uncertainty of its long term safety may be the primary limiting factors for its clinical application. The limited data for young children and pregnant women pose additional challenge for physicians to assess the risk and benefit when considering LTP treatment.*

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**H**ereditary angioedema (HAE) attacks are often associated with significant pain, disfiguration, and disability. Many patients are living with constant fear and anxiety about their attacks.<sup>1</sup> The quality of life is compromised, even between the attacks. HAE swelling attacks interrupt daily activities and family and social life, and may impede education and work.<sup>2</sup> The disease burden varies tremendously among individuals who are affected and even among different stages of an individual's life. Close to 50% of patients report at least one attack a month, a fourth of the patients have one or more attacks a week.<sup>3</sup>

Treating acute episodes alone may not be adequate for patients who have frequent or severe attacks, particularly those who do not respond adequately to acute attack treatment. The regular use of a medicine to reduce the frequency and severity of HAE attacks is often referred to as HAE long-term prophylaxis (LTP). Most HAE management guidelines recommend individualized treatment recommendations.<sup>4–6</sup> Who should be considered for LTP, what treatment should be used, when to start the treatment, and how to measure the treatment response may vary among individuals. The decision for starting LTP should consider individual patient's HAE history, disease burden, response to

and tolerability of other treatment modalities, comorbidities, and psychosocial impact, as well as patient preference.

This article was limited to a discussion of an overview of LTP options in patients with type I and type II HAE. Because the evidence for LTP in patients with HAE with normal C1 esterase inhibitor (C1-INH) is less robust, the reader is referred to recently published guidelines for an in-depth discussion of LTP in patients with this type of HAE.<sup>7</sup>

## ANDROGEN DERIVATIVES

Androgen derivatives (AD), represented by danazol, had been widely used for HAE LTP for a few decades. Although effective in certain individuals with HAE, clinical use of ADs has been limited by their adverse effects. Weight gain, dyslipidemia, hypertension, headache, liver toxicity, depression, anxiety, emotional irritability, and aggressive behavior are also linked to the use of ADs.<sup>8</sup> In women, the androgenic capacities of ADs may cause menstrual irregularity, masculinization, voice changes, and hirsutism. For men, ADs may negatively affect libido, sperm count, and fertility. Many of these adverse effects are not readily reversible. Due to concerns of their adverse effects, in most recent guidelines, ADs are not recommended as the first-line LTP.<sup>4–6</sup> To minimize adverse effects, the lowest effective dose should be used. Most guidelines recommend avoiding dosages of >200 mg/day for danazol. ADs should be avoided in children, especially before puberty, and in patients with androgen-dependent malignancy, in patients with liver diseases, and in during pregnancy and lactation.

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## ANTIFIBRINOLYTIC AGENTS

Tranexamic acid (TA) and  $\epsilon$ -aminocaproic acid are not approved by the U.S. Food and Drug Administration (FDA) for HAE LTP. The efficacy of TA in HAE LTP was supported by a few single-center, randomized, placebo controlled studies.<sup>9</sup> A significant proportion of patients do not see any clear benefit with the treatment. The overall efficacy is moderate. Although  $\epsilon$ -aminocaproic acid is rarely used nowadays, the role of TA in current HAE LTP is limited to those who do not have access to the newer treatment (C1 INH concentrate intravenous [IV] or subcutaneous [SC] or lanadelumab [Takhzyro, Shire-Takeda]), and/or are not able to tolerate ADs. The recommended dosage for TA is 30–50 mg/kg daily divided in two or three doses to a maximum of 6 g per day. Although less effective, due to its lack of virilizing adverse effects, TA has been more favorably considered in women (when C1 INH IV or SC and lanadelumab are not available). However, TA is not recommended for women during pregnancy or lactation.

## PROGESTERONE

Progesterone has not been approved for HAE LTP. Its clinical benefit for HAE was only supported by some retrospective studies.<sup>10</sup> These agents could be considered for contraception in child-bearing women, with the added value of adjuvant treatment against angioedema attacks. It is of note that they should not be combined with estrogens, which are known to exacerbate HAE.

## C1-INH CONCENTRATE

C1-INH replacement therapy (IV or SC) had been approved for LTP of HAE. In a controlled crossover study of six patients over 17 days per treatment period, plasma-derived C1-INH (pdC1-INH) given *via* IV at 25 U/kg every 3 days versus placebo reduced HAE attacks by 60%.<sup>11</sup> In a subsequent multicenter placebo controlled, randomized, crossover trial that used a pdC1-INH concentrate in a dose of 1000 U every 3 to 4 days for 12 weeks reduced the HAE attack rate by 50% (a normalized attack rate of 12.7 and 6.3 per 12 weeks for placebo and active dose, respectively). In addition, attack severity, duration of attacks, and rescue medicine requirement were reduced.<sup>12</sup> A pdC1 INH IV (marketed as Cinryze, Shire-Takeda, Boston, MA) was approved by the FDA in June 2008 for HAE LTP.

SC delivery of a pdC1-INH (marketed as Haegarda, CSL Behring, King of Prussia, PA) was evaluated in a randomized, placebo controlled, crossover study.<sup>13</sup> Patients with HAE and with frequent attacks received pdC1-INH SC at 40 or 60 U/kg every 3 to 4 days.<sup>13</sup> The higher dose treatment group demonstrated a median HAE attack rate reduction by 95%, with a normalized attack rate per month that decreased from 4.03 in the placebo group to 0.52.<sup>13</sup> In addition, the treatment

reduced rescue medicine use by 99% as well as HAE attack severity and duration.<sup>13</sup> More than 50% of the patients in the treatment group had no moderate-to-severe attacks over the study duration of 16 weeks, and ~90% of the subjects who received treatment showed an HAE attack reduction by at least 50%.<sup>13</sup> The 60-U/kg dose was approved by the FDA (June 2017) for HAE LTP in adolescents and adults, including the approval for self-administration.

Theoretical adverse effects of pdC1-INH may include infection and thromboembolic events. Fortunately, with the modern plasma screening and purification technology, infection related to pdC1-INH concentrates has not been reported.<sup>14</sup> No thromboembolic events have been linked to pdC1-INH use, either IV or SC. Recombinant human C1-INH (marketed as Ruconest, Pharming, Leiden, The Netherlands) has been studied for HAE LTP, with a favorable clinical outcome.<sup>15</sup> This study supports its efficacy in LTP for HAE; however, the IV administration may still be a major obstacle for patient acceptance. It is not yet approved by the FDA for HAE LTP at this time.

## LANADELUMAB

Lanadelumab, a fully human monoclonal antibody that specifically targets plasma kallikrein was approved by the FDA for HAE C1-INH LTP in August 2018 for adolescents and adults. This drug is also approved to be self-administered. The starting dose is 300 mg SC, every 2 weeks, with an option of changing to 300 mg every 4 weeks for patients who are doing well with the initial dosing regimen.

In a phase III, randomized, double-blind, parallel-group, placebo controlled trial, lanadelumab (compared with placebo) reduced HAE attack frequency, severity, and rescue medicine requirement in all dose arms: 150 mg every 2 weeks, 300 mg every 2 weeks, and 300 mg every 4 weeks.<sup>16</sup> The 300 mg every 2 weeks arm had reduced HAE attacks by 87% (1.97 attacks/month in placebo versus 0.26 attacks/month in the 300 mg every 2 weeks arm).<sup>16</sup> The reduction in the 300 mg every 4 weeks and the 150 mg every 2 weeks arms compared with placebo were 73% and 76%, respectively ( $p < 0.01$  in all comparison arms).<sup>16</sup> In addition, during the 26-week study period, all the lanadelumab treatment arms showed higher percentages of the subjects being attack free, *e.g.*, 44.4% in the 300 mg every 2 weeks arm, 2.6% in the placebo arm ( $p < 0.01$  in all comparisons). The proportion of severe attacks and duration of attacks were reduced in all the lanadelumab treatment groups.

Other than injection-site pain, no significant adverse events were observed in the pivotal clinical study.<sup>16</sup> Activated partial prothrombin time prolongation was observed; however, there was no clinical evidence for coagulopathy; the increase in activated partial

prothrombin time returned to normal once the treatment was discontinued. Anti-lanadelumab antibodies were observed in 11.9% of patients in the treated group, whereas the placebo had 4.9% as positive (low titer). Neutralizing antibodies were observed in 3 of 113 patients (<3%). It is still not clear whether the autoantibodies are transient or permanent, whether longer treatment duration may induce more autoantibody production, and whether these antibodies are going to affect the clinical response. There is no clear correlation between a clinical response to lanadelumab and the development of anti-lanadelumab antibodies.

## LIMITATIONS OF LTP

Multiple agents are available for the LTP in patients with HAE C1-INH. Despite great efficacy, none of the agents can completely prevent HAE attacks. Therefore, despite the use of LTP, patients still require on-demand treatment for any breakthrough attacks. There are no head-to-head comparisons among different agents. Differences in trial design, study population, and end point assessment make the comparisons difficult. The risk and benefit of LTP should be assessed based on individual patient's clinical and historical condition. Settupane *et al.*<sup>17</sup> emphasize the important role of shared decision-making as an integral component of the physician-patient partnership and how this process can facilitate an optimal discussion of LTP.

Recommendations with regard to LTP in specific populations such as in women during pregnancy and/or lactation are addressed by Yakaboski *et al.*<sup>18</sup> and such as in children are addressed by Johnston and Smith<sup>19</sup> Because most LTP studies do not provide adequate information with regard to these populations, more research is needed to rectify this unmet need. Newer treatment modalities are likely to provide easier and more cost-effective treatment options in LTP. Further in the future, gene therapy may even offer a potential cure or sustained disease control.

## PRACTICE PEARLS

- LTP is one of the most important treatment strategy for HAE disease management.
- The decision for choosing LTP should consider the individual's disease burden; response of acute treatment; and accessibility, efficacy, safety, tolerability, and ease of use of the medicine.
- The choice of LTP should be individualized; C1 INH (SC or IV) and lanadelumab are the preferred LTPs for HAE.

## REFERENCES

1. Busse PJ, Christiansen SC. Hereditary angioedema. *N Engl J Med.* 2020; 382:1136–1148.
2. Banerji A. The burden of illness in patients with hereditary angioedema. *Ann Allergy Asthma Immunol.* 2013; 111:329–336.
3. Banerji A, Li Y, Busse P, et al. Hereditary angioedema from the patient's perspective: a follow-up patient survey. *Allergy Asthma Proc.* 2018; 39:212–223.
4. Betschel S, Badiou J, Binkley K, et al. The International/Canadian Hereditary Angioedema Guideline. *Allergy Asthma Clin Immunol.* 2019; 15:72.
5. Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy.* 2012; 67:147–157.
6. 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; 73:1575–1596.
7. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol Pract.* 2020; S2213-2198:30878-3.
8. Riedl MA. Critical appraisal of androgen use in hereditary angioedema: a systematic review. *Ann Allergy Asthma Immunol.* 2015; 114:281–288.e7.
9. Sheffer AL, Austen KF, Rosen FS. Tranexamic acid therapy in hereditary angioneurotic edema. *N Engl J Med.* 1972; 287:452–454.
10. Bouillet L, Longhurst H, Boccon-Gibod I, et al. Disease expression in women with hereditary angioedema. *Am J Obstet Gynecol.* 2008; 199:484.e1-4.
11. Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. *N Engl J Med.* 1996; 334:1630–1634.
12. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med.* 2010; 363:513–522.
13. Longhurst H, Zinser E. Prophylactic therapy for hereditary angioedema. *Immunol Allergy Clin North Am.* 2017; 37:557–570.
14. De Serres J, Groner A, Lindner J. Safety and efficacy of pasteurized C1 inhibitor concentrate (Berinert P) in hereditary angioedema: a review. [jean.de.serres@aventis.com](mailto:jean.de.serres@aventis.com). *Transfus Apher Sci.* 2003; 29:247–254.
15. Riedl MA, Grivcheva-Panovska V, Moldovan D, et al. Recombinant human C1 esterase inhibitor for prophylaxis of hereditary angio-oedema: a phase 2, multicentre, randomised, double-blind, placebo-controlled crossover trial. *Lancet.* 2017; 390:1595–1602.
16. 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; 320:2108–2121.
17. Settupane RA, Bukstein D, Riedl M. Shared decision making in HAE management. *Allergy Asthma Proc.* 2020; 41:S55–S60.
18. Yakaboski E, Motazed T, Banerji A. Hereditary angioedema: special considerations in women. *Allergy Asthma Proc.* 2020; 41:S47–S50.
19. Johnston DT, Smith RC. Hereditary angioedema: special considerations in children. *Allergy Asthma Proc.* 2020; 41:S43–S46. □

# Hereditary angioedema: Comprehensive management plans and patient support

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## ABSTRACT

Hereditary angioedema (HAE) is a rare disease. Regardless, patients with HAE have access to multiple state-of-the-art medications available for on-demand use and prevention that reduce the frequency and burden of HAE attacks. These treatments have greatly reduced the burden of disease and helped patients achieve improved quality of life. However, with greater numbers of therapeutic options, HAE care has become more complex. In this review, we addressed essential elements of an individualized comprehensive management plan for a patient with HAE. We focused on access to an expert physician, ongoing patient education, access to effective treatment options, coordination of care and management of treatment logistics, ongoing monitoring of attacks and treatments, and other resources for patient support. This plan will need to be communicated with the patient and other care providers, especially during emergent conditions, and accommodate the patient's lifestyle with consideration for work, school, travel, etc. Periodically, the physician and the patient will need to review information about attacks, triggers, and treatments to identify areas for improvement and update the plan.

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Hereditary angioedema (HAE) is a lifelong genetic condition with significant variability in presentation and disease burden.<sup>1–3</sup> With the advent of newer treatments for HAE, the attack burden has been reduced, but care plans have become more complex.<sup>4</sup> The goal of care is to help patients achieve a normal quality of life. To help patients achieve this goal, an individualized comprehensive management plan should be developed, implemented, reviewed, and revised regularly.<sup>4–6</sup> Previous guidelines offered essential components of a treatment plan.<sup>4,6</sup> These include access to an expert physician, ongoing patient education, access to effective treatment options, coordination of care and management of treatment logistics, and ongoing monitoring of attacks and treatments.<sup>4,6</sup> In addition, patients and physicians can benefit from the resources available through national and international care organizations.

## ACCESS TO AN EXPERT PHYSICIAN

The HAE expert should have comprehensive knowledge of the disease state, treatment options available, and current best practices for the care of patients with HAE.<sup>4–6</sup> This individual will serve as the coordinator of HAE care

by helping the patient develop a treatment plan and regularly reviewing and making adjustments to the plan as needed. In addition to evaluating and managing symptoms of HAE, the HAE expert is often called on to communicate best management practices, which take into account other medical comorbidities. Certain conditions, treatments, or procedures may inherently increase the risk of HAE attacks.<sup>7,8</sup> The HAE expert has a commitment to anticipate these needs and educate patients and colleagues in the medical community about such risks while also helping to actualize an effective treatment plan. Certain conditions that deserve special attention (such as antihypertensive medications, pregnancy, use of estrogen-containing medications) can be found in the other sections of this primer.<sup>7,8</sup> Recommended follow-up with the HAE expert should be at least once or twice a year to ensure implementation of the treatment plan.<sup>5,6</sup> Previous guidance has been provided with regard to suggested topics at initial and follow-up visits.<sup>4,6</sup> Herein, we provided an updated, inclusive list of these important topics (Table 1).

## ONGOING PATIENT EDUCATION

HAE is a complex condition that affects all aspects of a patient's health and well-being.<sup>2</sup> Once diagnosed, patients are encouraged to become educated about their condition.<sup>4,6</sup> The larger aim of ongoing education is to help patients to become better decision makers and better advocates for themselves and their families.<sup>9</sup> Education helps patients place HAE into the context of other life stages, e.g., childhood, adolescence, pregnancy.<sup>7,10</sup>

Education is often initiated by the HAE expert and/or HAE trained nurses. Given that assimilation of knowledge and experience with HAE varies from person to person, ongoing patient education should be tailored to each individual.<sup>6</sup> Some of the specific goals of

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**Table 1 Comprehensive management plan checklist\***

Assess current features of angioedema	Frequency, severity, location, treatment, impact on activities and quality of life
Educate patient and family on HAE	Symptoms, triggers, prodromes, risks of laryngeal attack, treat attacks early, screening family; provide and/or review HAE educational materials; direct patients to care organizations, <i>e.g.</i> , U.S. Hereditary Angioedema Association and its sister group, HAE International
Establish the best method to contact the physician	
Discuss goals for treatment	
Discuss treatment options for on-demand therapy and prophylaxis	Mechanism of action; anticipated benefit; administration, emphasizing the benefits of self-administration; potential adverse effects and monitoring; arrange for training on dosing of selected medications with the patient and family; provide guidance on prescription management with payer and specialty pharmacy
Create and/or review plans for the following	Emergency plan; travel; school, sports, other; short-term prophylaxis for medical, dental, surgical, other
Develop and/or review HAE swelling attack log	Attack location, severity, triggers, prodromes, treatment(s) used; response to treatment, adverse effects, barriers to treatment
Review other medical conditions and treatments	Discuss the risks of using estrogen-containing medications and angiotensin-converting enzyme inhibitors
Assess impact of HAE on quality of life	Consider use of newly developed patient-reported outcomes
Monitor on-demand therapy	Review swelling attack log; review frequency of treatment; verify two unexpired doses are available; review any drug-specific safety monitoring; ensure ongoing access to treatment
Monitor prophylactic therapy	Assess the need and/or interest for prophylactic therapy; review adherence to treatment; review the effectiveness of treatment, adverse effects, and/or issues with administration; review any drug-specific safety monitoring; ensure ongoing access to treatment

HAE = Hereditary angioedema.

\*Adapted from Refs. 4 and 6.

education include the following: understanding the disease presentation, diagnosis of HAE, inheritance pattern; screening family members; helping patients recognize their attack triggers, and learning the signs and symptoms of an emerging attack.<sup>3,11,12</sup> Patients should become familiar with their specific treatments as well as other therapeutic alternatives.<sup>13,14</sup> This may include management of an intravenous medication, potential adverse effects, train one's self or a caregiver in the administration of medication, and processes required to manage a specialty drug.<sup>4,6</sup> Currently, less is known about the pathophysiology and best treatment strategy for HAE with normal C1-INH.<sup>3,8,13,14</sup> Nevertheless, the HAE expert should strive to provide these individuals with current up-to-date information and guide them to appropriate educational resources.

#### ACCESS TO EFFECTIVE TREATMENT OPTIONS

Currently, patients with HAE have the benefit of an unprecedented development of multiple state-of-the-art medications used as on-demand therapy to reduce the symptoms of an attack and as preventative

medication to reduce the frequency and burden of future attacks.<sup>13,14</sup> In addition, several other therapies are in development.<sup>15</sup> With the help of the HAE expert, patients can give voice to their needs and preferences as treatment is offered.<sup>9</sup> All patients need access to on-demand therapy, ideally two doses available at any given time.<sup>6</sup> Patients are encouraged to learn about and consider prophylactic options as well.<sup>4-6,13</sup> The treatment plan should communicate the specific details of the therapy available for on-demand treatment, options for short-term prophylaxis if needed, and the treatment and schedule for prophylactic therapy if ordered. Ongoing access to treatment is vital for the treatment plan to be effective.<sup>4-6</sup> Ensuring access requires time and effort from the patient, physician, and clinical support staff to effectively navigate the health care system. Renewing authorization forms, updating changes to insurance and contact information, and regularly communicating with the specialty pharmacy become the ongoing shared labor among the patient, HAE expert, and other clinical support staff.<sup>4</sup>

Box 1

Sample Letter

RE: (NAME) (DOB)

To Whom It May Concern,

(NAME) carries the diagnosis of **C1 esterase inhibitor deficiency, also known as hereditary angioedema (HAE)** and is under my medical care to treat this condition.

This genetic condition is characterized by sporadic episodes of cutaneous, intestinal, and/or laryngeal angioedema. These episodes may cause severe pain, nausea, vomiting, and airway compromise, including fatal asphyxia.

(NAME) is currently prescribed (drug/dose/route) as prophylaxis. For treatment of acute attacks, (NAME) uses (drug/dose/route), which is U.S. Food and Drug Administration approved to treat HAE. A second dose of medication may be necessary in the event of a partial response or recurring angioedema symptoms. **In the event of any laryngeal symptoms, administer HAE medication immediately.**

In addition to this medication, management of acute attacks may include supportive care, including airway monitoring, analgesic and antiemetic medications, and intravenous fluids as appropriate.

**Efficacy of epinephrine, steroids, and antihistamines is doubtful** when treating HAE, a bradykinin-mediated form of angioedema.

It is medically necessary that the patient carry the listed HAE medications and related treatment supplies while traveling. In addition (NAME) has been instructed to bring their rescue medication to the emergency facility in the event they are needed.

If there are any questions, please contact (Care team 24-hour contact info)

Sincerely,

Letters for planned procedures should also include plans for preprocedure prophylaxis and extended monitoring, sample below.

Procedure and Date:

Before the procedure, (NAME) should receive prophylactic (drug/dose/route) and have additional doses of prophylactic medication available in the event of a hospital stay longer than 3–4 days.

In the event of postoperative swelling, (NAME) is to have access to U.S. Food and Drug Administration approved on-demand treatment, as above. If (NAME) is to have endotracheal anesthesia, it is recommended to have rescue medication immediately available and that the patient be monitored for a minimum of 24 hours after surgery.

## COORDINATION OF CARE AND MANAGEMENT OF TREATMENT LOGISTICS

Most often, HAE attacks can be treated outside of the hospital.<sup>8,16</sup> With proper education and training, many patients and/or family members should be able to self administer on-demand therapy.<sup>5,6,14</sup> Having the ability to self administer on-demand therapy assures a more timely intervention and allows treatment to be administered as soon as attacks are recognized.<sup>5,16</sup> Notwithstanding, patients who are having laryngeal symptoms or other severe symptoms of HAE attacks may require emergency management.<sup>5</sup> Before such circumstances arise, it is important for the HAE expert to provide the patient with a written communication that can then be shared with the treating physician and team. This plan should communicate information about HAE and specific treatment options available to the patient, considerations for redosing, monitoring, and how to contact the HAE-treating physician.<sup>4–6</sup>

A recent study showed that a prepopulated electronic plan at the emergency department (ED) can help to decrease ED wait times and increase administration of appropriate U.S. Food and Drug Administration approved HAE treatments.<sup>17</sup> In our experience, having a nurse or physician HAE expert available to communicate with the patient and/or the ED staff during these episodes of care also helps to foster adherence to the treatment plan. Similar communication is also helpful in promoting ongoing management of HAE should a patient need hospital care for other medical and/or surgical conditions. Here, we provide a sample letter used for ED visits and other episodes of care, please see Box 1.<sup>5,6</sup>

Patients with HAE report increased anxiety about travel and the risk of an HAE attack.<sup>2,18</sup> Some of the unique travel and logistical considerations for patients with HAE include proper storage and handling of HAE treatment medication and equipment, and

**Table 2 Recommended data collection for an angioedema attack log\***

Description of attack	Date and time of onset; location of swelling; prodrome (yes/no; if yes, then describe); triggering event if known; severity based on impact on activities
Treatment of attack	Was on-demand treatment given (yes/no; if yes, give details); date and time that the treatment was given; any problems or adverse events associated with the treatment; date and time when symptoms began to improve; date and time when symptoms were completely resolved
Response to treatment	Was the physician contacted; were emergency department or hospital services required; was there a need for additional therapy (including a second dose of initial medicine, pain medication, antiemetic, fluids, etc.)

\*Adapted from Refs. 4 and 6.

identification of local venues of health care should assistance be required. Before traveling, it is helpful for patients to plan out the trip and to have a letter that communicates the treatment plan and need to travel with medical equipment.<sup>6</sup> Other considerations for the treatment plan include how to accommodate the common activities of work, school, and hobbies and/or sports. Information should be shared in an effort to provide education and to help facilitate early treatment should it be required in these settings.<sup>4-6</sup>

### ONGOING MONITORING OF ATTACKS AND TREATMENTS

Just as disease burden of HAE is variable, response to treatment is also variable.<sup>5,6</sup> As such, treatment plans need to be reviewed regularly and be adjusted. U.S. guidelines recommend that patients and an HAE expert review information about attack frequency, disease burden, treatment efficacy, and adverse effects.<sup>4,6</sup> Patients are encouraged to record information about each and every attack, including triggers, location, intensity and/or severity, treatment(s) used, and response to treatment (Table 2).<sup>4-6</sup> This information can help the patient and the expert evaluate the efficacy of the treatment plan and highlight areas in which adjustments may be needed.

Potential outcomes of this review include consideration of prophylaxis, a switch in medication, and re-

**Table 3 Drug specific-safety monitoring**

Androgens	Every 6 months: LFTs, UA, lipid profile, blood pressure, weight, signs of virilization; yearly: liver ultrasound if equivalent androgen dose is greater than danazol 200 mg daily
Antifibrinolytics	Every 6 months: LFTs, creatinine level, CPK level, aldolase, UA; yearly: ophthalmologic examination
pdC1-INH	At follow-up visits: address issues with administration
Ecallantide	At follow-up visits: assess for hypersensitivity reactions
Icatibant	At follow-up visits: assess injection-site reactions
Monoclonal kallikrein inhibitor	At follow-up visits: assess injection-site reactions

LFT = Liver function test; UA = urinalysis; CPK = serum creatine kinase; pdC1-INH = plasma-derived C1 esterase inhibitor.

\*Adapted from Ref. 6.

education about the effect or adverse effects of treatment. Other outcomes include reclarifying treatment goals and expectations, identifying any new triggers or other aspects of the patient's health that may be affecting HAE disease activity. In addition, certain drugs have specific safety monitoring recommendations that need to be taken into account (Table 3).<sup>6</sup>

In an effort to better assess treatment effect and disease burden of HAE, newer patient-reported outcome measures are being developed, which can quantify the attack frequency and severity, elements of overall health, and quality of life.<sup>19,20</sup> As these tests become more widely accepted, their efficacy as a clinical tool will be revealed.

### PATIENT SUPPORT

Patient organizations can provide critical support to the activities reviewed in this section. The U.S. Hereditary Angioedema Association and its sister group, HAE International, are nonprofit patient advocacy organizations that serve patients with HAE, caregivers, and the families. These organizations are committed to advancing modern care of patients with HAE by identifying areas of unmet need, including development and access to effective therapies worldwide, communicating best practices for patient care, and developing educational materials for patients and physicians.<sup>5</sup>

## CONCLUSION

Patients with HAE require ongoing, complex care. To assure the best outcomes for patients, the HAE expert must commit to ongoing patient education, routine follow-up to review and adjust the care plan, and facilitating open communication with other primary and specialty care givers. This review offered several essential elements needed for an effective care plan, and an inclusive list of topics to be referenced when following up with patients with HAE. Assuring good quality of life becomes the shared goal of the patient and the physician.

## CLINICAL PEARLS

- Patients with HAE need access to an HAE expert who can help facilitate a comprehensive management plan and direct patients to appropriate educational and support resources.
- The management plan needs to address specific treatments, including on-demand therapy and prophylaxis if chosen, and provide instruction with regard to travel, sports, school, work, etc.
- This plan needs to be communicated with the primary care provider and emergency and other medical and/or surgical specialties as need of care arises.
- Periodically, the physician and the patient will need to review information about attacks, triggers, and treatments to identify areas for improvement and update the plan.

## REFERENCES

1. Proper SP, Lavery WJ, Bernstein JA. Definition and classification of hereditary angioedema. *Allergy Asthma Proc.* 2020; 41:S3–S7.
2. Lumry W, Settipane RA. Hereditary angioedema: epidemiology and burden of illness. *Allergy Asthma Proc.* 2020; 41:S8–S13.
3. Wedner HJ. Hereditary angioedema: Pathophysiology (HAE type I, HAE type II, and HAE nC1-INH). *Allergy Asthma Proc.* 2020; 41:S14–S17.
4. Riedl MA. Creating a comprehensive treatment plan for hereditary angioedema. *Immunol Allergy Clin North Am.* 2013; 33:471–485.
5. 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; 73:1575–1596.
6. Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol Pract.* 2013; 1:458–467.
7. Yakaboski E, Motazed T, Banerji A. Hereditary angioedema: special considerations in women. *Allergy Asthma Proc.* 2020; 41:S47–S50.
8. Craig T. Hereditary angioedema: triggers and short-term prophylactic treatment. *Allergy Asthma Proc.* 2020; 41:S30–S34.
9. Settipane RA, Bukstein D, Riedl M. Shared decision making in HAE management. *Allergy Asthma Proc.* 2020; 41:S55–S60.
10. Johnston DT, Smith RC. Hereditary angioedema: special considerations in children. *Allergy Asthma Proc.* 2020; 41:S43–S46.
11. Azmy V, Brooks JP, Hsu FI. Clinical presentation of hereditary angioedema. *Allergy Asthma Proc.* 2020; 41:S18–S21.
12. Manning ME. Hereditary angioedema: differential diagnosis, diagnostic tests and family screening. *Allergy Asthma Proc.* 2020; 41:S22–S25.
13. Li HH. Hereditary angioedema: long-term prophylactic treatment. *Allergy Asthma Proc.* 2020; 41:S35–S37.
14. Christiansen S, Zuraw B. Hereditary angioedema: on-demand treatment of acute attacks. *Allergy Asthma Proc.* 2020; 41:S26–S29.
15. Kaplan A. Hereditary angioedema: investigational therapies and future research. *Allergy Asthma Proc.* 2020; 41:S51–S54.
16. Longhurst HJ, Farkas H, Craig T, et al. HAE international home therapy consensus document. *Allergy Asthma Clin Immunol.* 2010; 6:22.
17. Hews-Girard J, Poon MC, Goodyear MD. Effect of an electronic treatment plan on acute management of hereditary angioedema. *Ann Allergy Asthma Immunol.* 2019; 123:98–100.
18. Caballero T, Aygören-Pürsün E, Bygum A, et al. The humanistic burden of hereditary angioedema: results from the Burden of Illness Study in Europe. *Allergy Asthma Proc.* 2014; 35:47–53.
19. João Forjaz M, Caballero T, et al. HAE-AS, a specific disease activity scale for hereditary angioedema with C1-inhibitor deficiency. *J Investig Allergol Clin Immunol.* 2020.
20. Weller K, Donoso T, Magerl M, et al. Development of the Angioedema Control Test—a patient-reported outcome measure that assesses disease control in patients with recurrent angioedema. *Allergy.* 2020; 75:1165–1177. □

# Hereditary angioedema: Special considerations in children

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## ABSTRACT

Patients with hereditary angioedema (HAE) can experience attacks at any age; however, the onset of swelling is typically in childhood. Unlike adults, this population is uniquely vulnerable; attacks in young children may be subtle, resemble other diseases, and often lead to a delay in diagnosis. Misdiagnosis contributes to significant delays in treatment, painful attacks, increased emotional stress, unnecessary procedures, and a potential risk of death. Older children may hide their symptoms due to anxiety or fear of social isolation. Attacks typically become more severe and more frequent during and after puberty. The impact of HAE attacks on school attendance and school performance may prevent future career or education opportunities. Living with HAE poses significant psychosocial stress on children and their families. In the United States, medical treatments for acute attacks in children approved for self-administration are limited to intravenous therapies, which complicates early treatment. To provide optimal care, we suggest that physicians screen all children with a family history of HAE, appreciate the dynamic nature of the disease during adolescence, proactively assess the psychosocial impact of disease, and continually reassess the treatment plan.

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Hereditary angioedema (HAE) is a rare disease, which typically presents during childhood, with ~90% of patients experiencing their first swelling attack before age 20 years.<sup>1</sup> The onset of symptoms can occur at any age; however, results of a two large studies suggest a mean age of onset by age 12 years.<sup>1,2</sup> This highlights the importance of HAE symptom awareness among pediatric providers. Despite improved recognition of HAE over the past decade, patients are still frequently misdiagnosed, which results in a delay in diagnosis from the first onset of symptoms.<sup>3</sup> In one study, by Zanichelli *et al.*,<sup>4</sup> ~42% of children with a family history of HAE and >65% without a family history of HAE were misdiagnosed during their first attack.

The most common diagnoses were allergic angioedema and acute appendicitis.<sup>4</sup> An incorrect diagnosis in these instances can lead to administration of ineffective therapies and to unnecessary surgical procedures and imaging. Although any attack can be distressing for a child, attacks that involve the upper airway without appropriate interventions can be fatal. Patients with undiagnosed HAE have a higher risk of mortality from asphyxia, up to 30%, than those with a correct diagnosis.<sup>5,6</sup> This is the most compelling argument to

screen children with a family history of HAE and provide a treatment plan with on-demand therapy on hand before their first attack. Additional consequences of a misdiagnosis to consider include increased anxiety, decreased overall quality of life, delays in seeking care, and unnecessary hospitalization.<sup>7,8</sup> Factors that contribute to delays in an HAE diagnosis in children are summarized in Table 1.

In a child suspected of having HAE, a thorough clinical history of swelling and abdominal pain episodes should be obtained. The clinician should ask about the family history, frequency, duration, onset to peak swelling, associated symptoms, and attack triggers. Swelling due to histamine release typically has a rapid onset to peak swelling, unlike the more gradual onset of HAE. Pruritus is not a feature of bradykinin-induced angioedema of HAE; however, HAE should not be assumed if itching is absent. In our experience, post-viral angioedema, idiopathic angioedema, and nonsteroidal anti-inflammatory drug induced angioedema can present with nonpruritic angioedema; however, the onset to peak swelling is typically more rapid than HAE. A family history should be obtained because 75% of cases of HAE are familial.<sup>9,10</sup>

The World Allergy Organization recommends screening all children when a parent is diagnosed or suspected of having HAE.<sup>11</sup> C4 level, C1 inhibitor (C1-INH) level, and C1 inhibitor function testing are encouraged once the child is 1 year of age. Complement testing before age 12 months of age may not be accurate and is not recommended. Genetic testing can be helpful when the initial complement tests are inconclusive and the specific HAE mutation of the parent is known.<sup>12,13</sup> Obtaining plasma C4, C1-INH functional activity, and C1-INH antigen levels are recommended in all pediatric

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**Table 1 Factors that may contribute to a delay in diagnosis in children**

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Lack of HAE awareness in the medical community
Lack of family history
Lack of symptom recognition and appropriate testing
Inaccurate test results in children < 12 months of age
Delaying HAE testing until symptoms develop
Family refusing HAE testing due to denial or guilt
Less severe symptoms in younger children
Child's inability to verbalize symptoms
Early misdiagnosis of symptoms

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*HAE = Hereditary angioedema.*

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patients with a high suspicion for HAE regardless of family history because 25% of HAE type I and II have a *de novo* mutation.<sup>9,10</sup>

### EARLY RECOGNITION OF ATTACKS

HAE symptoms in early childhood can be subtle, and children may be unable to describe their symptoms. This can make diagnostic accuracy a challenge; however, recognizing the onset of swelling attacks in children with HAE is critical for an early diagnosis and prevention of future attacks. These early attacks are often incorrectly treated, are associated with increased pain, or are in need of hospitalization. Negative experiences can leave a lingering impression, contribute to fear of future attacks, and create mistrust in the medical community. Notably, pediatricians are often the first to examine children with HAE before diagnosis. However, the diagnosis of HAE is made by pediatricians in only 3% of cases. This highlights the challenges of early diagnosis and the need for ongoing health care provider education.<sup>14</sup>

Physicians and caregivers should be on the lookout for the typical 2–5-day duration of angioedema, abdominal involvement, gradual worsening over several hours, and intensifying severity during or after puberty. As in adults, childhood HAE attacks are characterized by localized painful swelling without urticaria. As such, crying, mood changes, or tantrums may be presenting features in younger children. Recurrent unexplained abdominal pain may be the only presenting feature in some children. In older children, physical trauma due to sports activities or dental procedures may trigger local skin or airway swelling. Older children may confuse symptoms of laryngeal swelling with the symptoms of postnasal drip or upper airway infections. Notably, clinicians should be aware that attacks typically worsen in frequency and severity with the hormonal changes of puberty. Females are disproportionately affected because estrogen can contribute to worsening symptoms. Other diagnostic clues may include reports of prodromal symptoms, *e.g.*, skin tingling, in the

affected area. Importantly, the skin finding of erythema marginatum is more frequently seen in children and typically precedes attacks.<sup>15,16</sup>

### BURDEN OF DISEASE IN CHILDREN

Living with HAE can be difficult for both patients and their families, both during and in between swelling episodes. At times, the unpredictability of attacks can be more stressful to children than the attacks themselves. When attacks occur, children often miss school and perform poorly in comparison with peers. In a study of >450 patients with HAE, >50% felt that HAE impacted education choices and career advancement.<sup>17</sup>

Fear of attacks is common in children with HAE. Emotional stress can result in lifestyle modifications to avoid HAE triggers such as physical activity, sports, or travel. This increased level of anxiety can potentially act as a trigger and worsen attacks, which further reduces quality of life.<sup>18</sup> Results of studies have indicated that children with HAE have higher anxiety levels than age-matched controls who self-reported avoidance of activities and social events.<sup>8</sup> Children with HAE have been shown to display an impaired ability to recognize and express emotions.<sup>8</sup> This problematic phenomenon is called alexithymia and correlates with a reduced ability to self-regulate and cope with stress, which contributes to the cycle of attacks. Alexithymia may be particularly problematic in adolescent patients who may be fearful of speaking up about symptoms in class secondary to fear of isolation and/or exclusion from sports or other school activities.

External barriers can prevent children with HAE from receiving appropriate and timely care. In the United States, self-administered oral and subcutaneous therapies for attack treatment are not approved by the U.S. Food and Drug Administration (FDA) for children at this time. The lack of the ability to self-administer treatment during an attack takes away an element of control and security from the family and the patient. Intravenous (IV) C1-INH therapy can be self-administered or administered by the parents. However, obtaining IV access in children can be challenging and may result in the need for emergency management. The need for repeated IVs and emergency department visits may contribute to stress, anxiety, and overall disease burden. Emergency department health care providers may be unfamiliar with HAE symptoms and appropriate treatment. Misdiagnosis or late treatment of attacks by frontline providers can contribute to an increased duration and intensity of episodes. Some community hospitals may not have HAE medications in their formulary or lack pediatric trained personnel to intervene if a child's airway is compromised.

In our opinion, the burden of attacks, barriers to treatment, trigger avoidance, misdiagnosis, and fear of

attacks themselves can exacerbate the overall stress and anxiety in both patients and their families, which contributes to reduced quality of life.<sup>8,17</sup> Stress is a major trigger of HAE attacks, which often propagates a vicious cycle of uncontrolled disease. Creating an open, inclusive environment where children feel comfortable discussing their symptoms is an important aspect of caring for children with HAE. Early diagnosis, education, and successful treatment may impact how children think about HAE, prevent avoidable anxiety, and ultimately improve overall quality of life.

### TREATMENT OF HAE IN CHILDREN

Weight-based plasma-derived C1-INH is the first-line FDA approved treatment for acute attacks in children of all ages.<sup>19</sup> Both ecallantide and recombinant C1-INH are FDA-approved treatment options in adolescents. In the European Union, icatibant, a convenient subcutaneous therapy approved for self-administration, is approved down to age 2 years; however, icatibant is not FDA approved for children in the United States. Treatment of HAE attacks are discussed by Christiansen and Zuraw<sup>20</sup> in on-demand treatment of acute attacks in this issue.

Plasma-derived C1-INH can also be used for both short- and long-term prophylaxis. Short-term prophylaxis is discussed by Craig<sup>21</sup> in Triggers and Short-Term Prophylactic Treatment in this issue. Preprocedural prophylaxis is recommended in children with HAE as in adults.<sup>11</sup> Providers should recognize that a dental procedure, a common procedure in children, may induce oral or laryngeal angioedema, which may be life threatening.<sup>22</sup> Prophylaxis should be individualized and may be considered for stressful life events, such as school examinations, travel, and family crises.

The primary goal of long-term prophylaxis in children is to reduce the frequency and severity of attacks. Long-term prophylaxis is further discussed by Li in this issue.<sup>23</sup> Children may not be as adept at recognizing the early symptoms of their attacks. This may lead to late treatment, recurrent school absences, and an increase in overall disease burden. Patients should be evaluated for symptoms of anxiety and alexithymia at each visit. Therefore, the threshold for initiation of long-term prophylaxis may be different in children. We would argue that early long-term prophylaxis potentially reduces anxiety, prevents alexithymia, and improves disease burden.

Much like adults with HAE, all children with the disease should have specific, individualized treatment action plans.<sup>11</sup> Patients should be evaluated at least annually for treatment with long-term prophylaxis or more frequently if HAE is poorly controlled. More frequent monitoring may be needed during puberty when attack severity and frequency may worsen. Children who are recurrently sick may require prophylaxis because infections are a

known trigger in HAE.<sup>24</sup> Clinicians managing patients with HAE and uncontrolled anxiety may need to consider counseling or supplemental anxiety medications to assist in disease control.<sup>22</sup> The use of shared decision-making when creating a treatment plan should incorporate both parents and child.

### ACHIEVING DISEASE CONTROL

Currently, formal criteria that define HAE control do not exist. The goal of therapy may vary among patients but ultimately converge on the desire to live a normal life. For some patients, this may mean no attacks, for other patients, the ability to rapidly treat attacks provides adequate disease control. One of the most important aspects of disease control is education. It is important to provide appropriate education relative to the development of the child and to review the treatment plan at each visit. Parents should be frequently re-educated and should be encouraged to advocate for their child. It is important for parents to take an active teaching role and be cognizant that some health care professionals may not be familiar with HAE. Teachers, daycare staff, coaches, extended family members, and close friends should all be taught the symptoms and treatment of an acute attack. Once the child is old enough, he or she should be encouraged to educate and advocate, ultimately to improve the lives of future generations.

Recommendations for treating children with HAE:

- Obtain C4 value, C1-INH level, and C1-INH function at age 1 year in children of an affected parent.
- Once a diagnosis is made, consider referral to an HAE specialist.
- Create a treatment action plan and review it at least annually.
- Review attack triggers at every visit.
- Avoid estrogen-containing hormonal contraceptives in adolescent girls.
- Evaluate the need for both short- and long-term prophylaxis at each visit.
- Provide on-demand treatment to children at the time of the HAE diagnosis before onset of the first attack.
- Closely monitor patients going through puberty or stressful life events.
- Consider counseling for comorbid anxiety, alexithymia, or depression.
- Provide educational information for parents
- Encourage accessing resources from the Hereditary Angioedema Association.

### CLINICAL PEARLS

- Slow onset to peak swelling and duration of 2–5 days raise suspicion of HAE in children.

- Screen children of affected parents at age 1 year and have a treatment plan with on-demand medications available at the time of HAE diagnosis before the first attack.
- Incorporate children into the decision-making process as much as possible.
- Routinely screen for anxiety and depression at each visit.
- Encourage school involvement and early medical treatment, as soon as HAE attacks are recognized.

## REFERENCES

1. Bork K, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med.* 2006; 119:267–274.
2. Roche O, Blanch A, Caballero Sastre N, et al. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. *Ann Allergy Asthma Immunol.* 2005; 94:498–503.
3. Nanda MK, Elenburg S, Bernstein JA, et al. Clinical features of pediatric hereditary angioedema. *J Allergy Clin Immunol Pract.* 2015; 3:392–395.
4. Zanichelli A, Longhurst HJ, Maurer M, et al. Misdiagnosis trends in patients with hereditary angioedema from the real-world clinical setting. *Ann Allergy Asthma Immunol.* 2016; 117:394–398.
5. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol.* 2012; 130:692–697.
6. Agostoni A, Aygören-Pürsün E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol.* 2004; 114(Suppl):S51–S131.
7. Bork K, Hardt J, Schicketanz K-H, et al. Clinical studies of sudden upper airway obstruction in patients with hereditary angioedema due to C1 esterase inhibitor deficiency. *Arch Intern Med.* 2003; 163:1229–1235.
8. Savarese L, Bova M, Guarino MD, et al. Emotional processes and stress in children affected by hereditary angioedema with C1-inhibitor deficiency: a multicenter, prospective study. *Orphanet J Rare Dis.* 2018; 13:115.
9. López-Lera A, Garrido S, Roche O, et al. SERPING1 mutations in 59 families with hereditary angioedema. *Mol Immunol.* 2011; 49:18–27.
10. Pappalardo E, Cicardi M, Duponchel C, et al. Frequent de novo mutations and exon deletions in the C1inhibitor gene of patients with angioedema. *J Allergy Clin Immunol.* 2000; 106:1147–1154.
11. 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; 73:1575–1596.
12. Aabom A, Andersen KE, Fagerberg C, et al. Clinical characteristics and real-life diagnostic approaches in all Danish children with hereditary angioedema. *Orphanet J Rare Dis.* 2017; 12:55.
13. Pedrosa M, Phillips-Angles E, López-Lera A, et al. Complement study versus CINH gene testing for the diagnosis of type I hereditary angioedema in children. *J Clin Immunol.* 2016; 36:16–18.
14. Grumach AS, Longhurst HJ, Aberer W, et al. Pediatricians diagnosed few patients with childhood-presented hereditary angioedema: Icatibant Outcome Survey findings. *J Allergy Clin Immunol Pract.* 2019; 7:1078–1080.
15. Farkas H, Visy B. Erythema marginatum preceding an acute oedematous attack of hereditary angioneurotic oedema. *Acta Derm Venereol.* 2001; 81:376–377.
16. Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. *Br J Dermatol.* 2009; 161:1153–1158.
17. Lumry WR, Castaldo AJ, Vernon MK, et al. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc.* 2010; 31:407–414.
18. Kessel A, Kohalmi KV, Engel-Yeger B. The relationship between anxiety and quality of life in children with hereditary angioedema. *Pediatr Allergy Immunol.* 2017; 28:692–698.
19. Schneider L, Hurewitz D, Wasserman R, et al. C1-INH concentrate for treatment of acute hereditary angioedema: a pediatric cohort from the I.M.P.A.C.T. studies. *Pediatr Allergy Immunol.* 2013; 24:54–60.
20. Christiansen S, Zuraw B. Hereditary angioedema: on-demand treatment of acute attacks. *Allergy Asthma Proc.* 2020; 41:S26–S29.
21. Craig T. Hereditary angioedema: triggers and short term prophylactic treatment. *Allergy Asthma Proc.* 2020; 41:S30–S34.
22. Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol Pract.* 2013; 1:458–467.
23. Li HH. Hereditary angioedema: long term prophylactic treatment. *Allergy Asthma Proc.* 2020; 41:S35–S37.
24. Zotter Z, Csuka D, Szabó E, et al. The influence of trigger factors on hereditary angioedema due to C1-inhibitor deficiency. *Orphanet J Rare Dis.* 2014; 9:44. □

# Hereditary angioedema: Special considerations in women

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## ABSTRACT

There are several challenges that arise in caring for women with hereditary angioedema (HAE). Most notably, the disease course during pregnancy is unpredictable, but studies show that plasma-derived C1-inhibitor is effective and safe for treatment of attacks as well as long-term prophylaxis (LTP) in select patients. Vaginal deliveries are preferred to caesarean sections, and epidural anesthesia is preferred to general anesthesia in lowering the risk of an acute attack. Lactation postpartum may increase HAE attacks. With regard to contraception, combined oral contraceptive pills that contain estrogen exacerbate symptoms. Similarly, estrogen-replacement therapy in menopause may increase attacks and is contraindicated. Fertility is not impacted by HAE itself or by HAE medications. The risk of breast cancer and female reproductive cancer in women with HAE is comparable with that of the general population, but, in patients with HAE and breast cancer, LTP with androgens is contraindicated. Estrogen modulators, e.g., tamoxifen, should be used with caution. Here, we reviewed these special considerations and others that are vital to providers in caring for women with HAE.

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In caring for women with hereditary angioedema (HAE), there are several unique and significant challenges that arise.<sup>1,2</sup> This article aimed to highlight the special considerations of which clinicians who care for women with HAE should be knowledgeable. Of note, the majority of data presented here are from studies on HAE due to C1-inhibitor (C1-INH) deficiency.

## MENSTRUATION

In 35% of patients, an increased frequency of attacks with menstruation has been reported.<sup>3</sup> Ovulation, however, is a less often reported trigger of HAE attacks (14%). Although a diagnosis of an abdominal HAE attack is difficult during menstruation, severe abdominal pain and a response to HAE treatment would be suggestive of this diagnosis. Ultrasound can be used to assess for the presence of bowel wall edema.<sup>1</sup>

## CONTRACEPTION

Progestin-only oral contraceptive pills (OCPs) are recommended in patients with HAE and may lessen attacks,<sup>2,4</sup> whereas estrogen-containing OCPs may actually exacerbate symptoms.<sup>2,5,6</sup> In fact, >70% of women reported that estrogen-containing OCPs were associated with either an initial onset of HAE attacks or an exacerbation of HAE attacks in those in whom the disease already manifested.<sup>6</sup>

As expected, discontinuation of the estrogen-containing OCP reduces these effects.<sup>2,5</sup>

Intrauterine devices (IUDs) are well tolerated in this population. Although short-term prophylaxis (STP) before IUD insertion is unnecessary, rescue treatment should be readily available for use in the event of an HAE attack. For emergency postcoital contraception, use of a progestin-only OCP has been shown to be well tolerated, whereas the estrogen and combined OCPs can worsen HAE attacks.<sup>2</sup>

## FERTILITY

Although there have not been any studies to date with regard to the effect that HAE medications have on fertility,<sup>1</sup> HAE C1-INH in itself has not been shown to affect fertility.<sup>3</sup> If *in vitro* fertilization is attempted in this population, then it is recommended that gonadotropin injections be given at a time when estradiol levels are low because these injections can induce estrogen surges and, subsequently, precipitate HAE attacks.<sup>1,2</sup> In addition, STP with C1-INH should be considered before these procedures and should also be available for use in the event of an HAE attack.

## PREGNANCY

In HAE C1-INH, the frequency of attacks during pregnancy generally increases in one-third of patients, decreases in one-third of patients, and remains unchanged in the remaining one-third of patients, although there are mixed data.<sup>2</sup> In addition, the clinical course of one pregnancy does not necessarily predict that of subsequent pregnancies.<sup>1</sup> Together, these observations highlight the uncertainty that these patients face with each pregnancy and the difficulty providers may have in providing satisfactory counseling with regard to expectations for the disease course during pregnancy. LTP for HAE is not

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universally recommended in pregnancy and is often driven by patient preference. With regard to specific HAE agents in pregnancy, either plasma-derived C1-INH (pdC1-INH) or recombinant C1-INH (rhC1-INH) is an appropriate treatment choice.<sup>2</sup> There are numerous case reports of successful pregnancies managed with C1-INH,<sup>1</sup> and retrospective analyses have supported the safety and efficacy of C1-INH in pregnancy when used for both prophylaxis and acute treatment.<sup>7-10</sup>

One retrospective analysis included 16 pregnant women who received pdC1-INH for LTP, STP, and/or treatment of HAE attacks as part of open-label extensions of two randomized, double-blind, placebo controlled trials or a compassionate-use program.<sup>7</sup> Of these 16 women, 13 delivered 14 healthy neonates (including one set of twins). There were two adverse fetal outcomes that were not considered to be related to the pdC1-INH, and one pregnancy outcome that was unknown.<sup>7</sup> In the 11 subjects who received pdC1-INH as LTP only, there was a reduction in monthly HAE attack rates for most of the subjects.<sup>7</sup> In another retrospective analysis, of 118 pregnancies in 41 subjects from the National HAE Registry, the patients received 91 vials of pdC1-INH for LTP, STP, or treatment of HAE attacks.<sup>8</sup> This therapy was effective in all patients without any associated adverse effects.<sup>8</sup>

In an observational study of 22 subjects and 35 pregnancies, data from patient diaries, interviews, and case reports showed that pdC1-INH was effective in treating attacks when used in 11 of these pregnancies.<sup>9</sup> Use of pdC1-INH for treatment in these 11 pregnancies and for LTP in 18 pregnancies was not associated with any adverse effects for the subjects or infants.<sup>9</sup> In a recent literature review, the use of pdC1-INH was identified in 136 pregnancies in 91 patients with HAE, with the majority (90.1%) having HAE C1-INH. Outcomes were reported for 128 fetuses, with 93% having healthy outcomes, similar to that of the general population. Overall use of pdC1-INH was well tolerated, with a favorable safety profile.<sup>10</sup> As with this review, much of the data on HAE in pregnancy is from subjects with C1-INH deficiency. However, studies have also described the efficacy of pdC1-INH for LTP in patients with HAE with normal C1-INH.<sup>11,12</sup>

Similarly, although pdC1-INH is the first-line agent for LTP based on U.S. Food and Drug Administration approvals, the literature to date supports that rhC1-INH is both effective and safe for STP and treatment in pregnancy.<sup>13,14</sup> In one case series of 14 women with HAE treated with rhC1-INH, two of the women received rhC1-INH for STP, and all the women received rhC1-INH for treatment of attacks, with the number of doses between 1 and 41.<sup>13</sup> There were no adverse events that were considered to be related to the rhC1-INH treatments, and all 14 women delivered healthy full-term babies.<sup>13</sup> Similarly, in another case series, of 10 women with HAE,

in which one received rhC1-INH for STP and nine received 1 to 41 doses of rhC1-INH for HAE attacks, there were no adverse events associated with rhC1-INH, and all 10 pregnancies resulted in healthy full-term babies.<sup>14</sup>

Per the international consensus and practice guidelines on the gynecologic and obstetric management of female patients with HAE C1-INH, if C1-INH is unavailable, then fresh frozen plasma may be considered for STP and treatment of HAE attacks during pregnancy, and either fresh frozen plasma or tranexamic acid can be used for LTP during pregnancy.<sup>2</sup> Of note, tranexamic acid crosses the placenta, and studies of its use in humans are lacking. However, tranexamic acid still may be considered if necessary for LTP in pregnancy because no harmful effects on fetal development have been reported in animal studies.<sup>15</sup> The United States Hereditary Angioedema Association's guidelines<sup>16</sup> do not specify the use of tranexamic during pregnancy but do comment that, although it is [neither] standard practice in the United States, nor U.S. Food and Drug Administration approved for this indication, physicians should still be knowledgeable with regard to its use and guidelines for monitoring for adverse effects. Attenuated androgens (*e.g.*, danazol, stanozolol, and oxandrolone) are contraindicated during pregnancy because they may alter fetal development.<sup>1,2,16</sup>

## GENETIC COUNSELING

Because HAE is an autosomal dominant disorder, there is a 50% chance of inheritance with each pregnancy. However, there is highly variable expression among individuals with the disease.<sup>1</sup> Regardless, given that the first HAE attack can be fatal, United States Hereditary Angioedema Association's guidelines<sup>16</sup> recommend that all family members of an individual with HAE be tested. Typically, this testing is performed postnatally. While it is possible, a prenatal diagnosis requires that the parental mutation is known and that cells either from a chorionic villus sample after the 10th week of gestation or an amniotic fluid sample after the 15th week of gestation are tested.<sup>1,2</sup> In the case of *in vitro* fertilization, successful application of preimplantation genetic testing has been described.<sup>17</sup>

## LABOR AND DELIVERY

Despite the trauma induced by labor and delivery, the incidence of HAE attacks during vaginal delivery is relatively low.<sup>2,3</sup> The use of C1-INH for HAE STP is not routinely recommended during vaginal delivery but is a shared decision between the provider and the patient. For example, in a patient who is well controlled on a LTP agent without any attacks and who does not have a history of attacks after surgical procedures or attacks that involve laryngeal edema, it may be appropriate

to have on-demand therapy available for treatment only should an attack occur. However, in patients who are not on LTP, STP may be used more liberally, especially in patients with a history of attacks triggered by trauma, a history of laryngeal attacks, or in women in whom forceps or vacuum-assisted delivery is likely to be required.<sup>1,2</sup> Cesarean section is more likely to trigger an HAE attack due to the stresses induced by the procedure, including intubation and surgical incision. Therefore, vaginal delivery is preferred to cesarean section in patients with HAE. For those who undergo cesarean delivery, STP is indicated and, ideally, with C1-INH. Epidural anesthesia is preferred to intubation and general anesthesia, given the risk of laryngeal HAE attacks associated with the localized trauma of intubation.

## POSTPARTUM

Lactation increases the frequency of HAE attacks.<sup>13</sup> This is thought to be due to increased prolactin levels, and subsequent cessation of breast-feeding has been shown to decrease attacks in these women. For women who opt to continue breast-feeding and merit the use of prophylaxis, subcutaneous or intravenous pdC1-INH is recommended for LTP, but either pdC1-INH or rhC1-INH can be used for acute treatment.<sup>2</sup> Tranexamic acid, however, is excreted into the breast milk, and, therefore, is contraindicated in patients who are lactating.<sup>1</sup> Although it is unknown whether anabolic androgens are secreted into the breast milk, these agents should also be avoided due to the potential for adverse effects on the infant.<sup>16</sup>

## MENOPAUSE

In a survey of postmenopausal patients with HAE, the majority (55%) reported no change in their symptoms, whereas 32% reported worsening and 13% reported improvement.<sup>3</sup> Estrogen replacement therapy may exacerbate symptoms<sup>5</sup> and is contraindicated in this population, with progesterone and progestin alternatives preferred.<sup>1,2</sup> Phytoestrogens, which have been used for hot flashes are also not recommended due to their estrogenic properties.<sup>2</sup> Of note, the nonhormonal treatments of menopause have not been shown to affect the frequency of HAE attacks.

## BREAST CANCER AND FEMALE REPRODUCTIVE CANCERS

The incidence of breast cancer in patients with HAE is comparable with that of the general population. Given the adverse effects of androgens on breast cancer, the use of these medications as prophylactic agents for HAE should be avoided in patients with breast cancer.<sup>18,19</sup> However, there is no contraindication to androgen use in patients with endometrial or cervical cancers.<sup>2</sup> Estrogen modulators, *e.g.*, tamoxifen, should

be used with caution because these agents can have agonistic effects on estrogen receptors in certain tissues and thereby exacerbate HAE symptoms.<sup>20</sup>

## CLINICAL PEARLS

- Female gender in HAE poses several unique and significant challenges in the clinical management of this disease.
- C1-INH is the therapy of choice for both treatment and for LTP in select patients during pregnancy and lactation.
- Attenuated androgens are contraindicated in pregnancy and lactation, and tranexamic acid is contraindicated in lactation.
- Vaginal delivery is preferred to cesarean delivery, and routine STP during vaginal delivery is not required for all patients.
- Estrogen-containing OCPs can precipitate symptoms onset or exacerbate attacks in this population, whereas progestin-only OCPs may lessen attacks and IUDs are well tolerated.

## REFERENCES

1. Banerji A, Riedl M. Managing the female patient with hereditary angioedema. *Womens Health (Lond)*. 2016; 12:351–361.
2. Caballero T, Farkas H, Bouillet L, et al. International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. *J Allergy Clin Immunol*. 2012; 129:308–320.
3. Bouillet L, Longhurst H, Boccon-Gibod I, et al. Disease expression in women with hereditary angioedema. *Am J Obstet Gynecol*. 2008; 199:484.e1–e4.
4. Saule C, Boccon-Gibod I, Fain O, et al. Benefits of progestin contraception in non-allergic angioedema. *Clin Exp Allergy*. 2013; 43:475–482.
5. Bork K, Fischer B, Dewald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy. *Am J Med*. 2003; 114:294–298.
6. Bork K, Wulff K, Hardt J, et al. Hereditary angioedema caused by missense mutations in the factor XII gene: clinical features, trigger factors, and therapy. *J Allergy Clin Immunol*. 2009; 124:129–134.
7. Baker JW, Craig TJ, Riedl MA, et al. Nanofiltered C1 esterase inhibitor (human) for hereditary angioedema attacks in pregnant women. *Allergy Asthma Proc*. 2013; 34:162–169.
8. Czaller I, Visy B, Csuka D, et al. The natural history of hereditary angioedema and the impact of treatment with human C1-inhibitor concentrate during pregnancy: a long-term survey. *Eur J Obstet Gynecol*. 2010; 152:44–49.
9. Martinez-Saguer I, Rusick E, Aygören-Pürsün E, et al. Characterization of acute hereditary angioedema attacks during pregnancy and breast-feeding and their treatment with C1 inhibitor concentrate. *Am J Obstet Gynecol*. 2010; 203:131.e1–e7.
10. Brooks JP, Radojicic C, Riedl MA, et al. Experience with intravenous plasma-derived C1-inhibitor in pregnant women with hereditary angioedema: a systematic literature review. *J Allergy Clin Immunol Pract*. 2020; 8:1875–1880.e3.

11. Garcia JFB, Takejima P, Veronez CL, et al. Use of pdC1-INH concentrate for long term prophylaxis during pregnancy in hereditary angioedema with normal C1-INH. *J Allergy Clin Immunology Pract.* 2018; 6:1406–1408.
12. Gibbons KR, Abraham T, Sandhu M, et al. Successful perinatal management of hereditary angioedema with normal C1 esterase inhibitor and factor XII mutation using C1 esterase inhibitor therapy. *Ann Allergy Asthma Immunol.* 2017; 119:558–559.
13. Moldovan D, Bernstein JA, Hakl R, et al. Safety of recombinant human C1 esterase inhibitor for hereditary angioedema attacks during pregnancy. *J Allergy Clin Immunol Pract.* 2019; 7:2938–2940.
14. Bernstein J, Moldovan D, Hakl R, et al. Experience with recombinant human C1 esterase inhibitor for hereditary angioedema attacks during pregnancy. *Ann Allergy Asthma Immunol.* 2018; 121:S33.
15. Geng B, Riedl MA. HAE update: special considerations in the female patient with hereditary angioedema. *Allergy Asthma Proc.* 2013; 34:13–18.
16. Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol Pract.* 2013; 1:458–467.
17. Bautista-Llácer R, Alberola TM, Vendrell X, et al. Case report: first successful application of preimplantation genetic diagnosis for hereditary angioedema. *Reprod Biomed Online.* 2010; 21:658–662.
18. Zeleniuch-Jacquotte A, Afanasyeva Y, Kaaks R, et al. Premenopausal serum androgens and breast cancer risk: a nested case-control study. *Breast Cancer Res.* 2012; 14:R32.
19. Endogenous Hormones and Breast Cancer Collaborative Group; Key TJ, Appleby PN, et al. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. *Lancet Oncol.* 2013; 14:1009–1019.
20. Rousset-Jablonski C, Thalabard J-C, Gompel A. Tamoxifen contraindicated in women with hereditary angioedema? *Ann Oncol.* 2009; 20:1281–1282. □

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# Hereditary angioedema: Investigational therapies and future research

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## ABSTRACT

*The future therapies for hereditary angioedema will likely involve the development of oral agents as alternatives to parenteral administration of drugs, specific targeting of proteins and/or enzymes that are not yet possible (e.g., factor XIIa), new agents that target the  $\beta_2$  receptor with sustained action properties, testing of products to determine whether the  $\beta_1$  receptor contributes significantly to attacks of angioedema, disrupting protein synthesis by using RNA technology as an alternative to enzyme inhibition, and, finally, gene therapy to attempt to cure the disease. Complete inhibition of attacks may well require sustained blood levels of C1 inhibitor that exceed 85% of normal, and it may be possible to delete the prekallikrein gene (analogous to familial prekallikrein deficiency), which is the one factor that might alleviate bradykinin formation, even by factor XII-independent initiating mechanisms, with the possible exception of Mannose Associated Serine Protease 1 (MASP-1) cleavage of high molecular weight kininogen (HK). Deletion of the light chain of high-molecular-weight kininogen would eliminate all possibilities for bradykinin formation, except tissue kallikrein cleavage of low-molecular-weight kininogen to support normal physiologic function to at least 50%.*

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Therapy of hereditary angioedema (HAE) types I and II due to C1 inhibitor (C1-INH) deficiency requires targeting the plasma bradykinin-forming cascade to inhibit the functioning of bradykinin acutely or to prevent its formation for prophylactic therapy. At the present time, we can inhibit bradykinin function with icatibant, which binds the  $\beta_2$  receptor and blocks bradykinin-dependent receptor stimulation. Elevated bradykinin levels can then be abrogated by endothelial-dependent kininases in the lung as well as the plasma; however, excessive bradykinin formation continues. Yet a temporary (which lasts hours) inhibition is sufficient to stop acute attacks of angioedema. It is also possible to treat acute attacks of swelling with subcutaneous ecallantide, which inhibits the enzyme kallikrein, prevents further bradykinin formation, and allows effective bradykinin destruction by the various kininases. Prophylactic therapy involves inhibition of the enzymes that are required for sustained bradykinin formation.<sup>1</sup> The current choices are C1-INH replacement therapy, which inhibits activated factor XII and plasma kallikrein, and administration of a monoclonal antibody to kallikrein. C1-INH given intravenously is also effective for acute therapy of accelerating angioedema.

Although tremendous progress has been made, there is no perfect approach to acute therapy or prophylaxis, and many potential new therapies are being studied, some of which will undoubtedly be approved and increase the choices available. There is no specific inhibitor of activated factor XII (C1-INH is nonspecific), so development of such is one consideration. We have two specific approved agents that target plasma kallikrein; however, both are administered subcutaneously and the possibility of developing low-molecular-weight oral antagonists is of considerable interest. Also, genetic approaches are possible, including replacement of the C1-INH gene in an attempt to cure the diseases or RNA approaches to inhibit synthesis of any of the proteins requisite for bradykinin formation (Table 1).

## TARGETING PROTEINS OF THE BRADYKININ-FORMING CASCADE

### Factor XII

Factor XII, once activated, yields two major molecular forms. Cleavage within a key disulfide bridge at Arg 353 yields a 2-chain active enzyme (designated factor XIIa or  $\alpha$  factor XIIa) with a heavy chain of 50 Kd disulfide linked to a light chain of 28 Kd. The active site serine is within the light chain. Further cleavage at Arg 334 and Arg 343 yields the second form of activated factor XII (factor XIIIf or  $\beta$  factor XIIa), which is, in reality, a mixture of two species at 30 Kd and 28.5 Kd. The 28 Kd light chain becomes the heavy chain of factor XIIIf and is disulfide linked to a small remnant of the original heavy chain at 1.5 Kd or 0.5 Kd. These

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**Table 1 Curing HAE types I and II**

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Replace the *C1-INH* mutated gene with normal *C1-INH*

Insert a normal (second) *C1-INH* gene into the genome to augment *C1-INH* production

Eliminate the ability to produce bradykinin *via* the pathway that requires factor XII and plasma kallikrein

Knockout factor XII gene

Eliminate prekallikrein

Prevent HK cleavage or knockout HK light chain

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*HAE* = Hereditary angioedema; *C1-INH* = *C1* inhibitor; *HK* = High Molecular Weight Kininogen.

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molecular species result from either autoactivation of factor XII or cleavage by kallikrein (the “kallikrein feedback”) or by plasmin. The active site does not vary so that active-site inhibition of one form inhibits them all.

A fully humanized monoclonal antibody (IgG 4 subtype) to activated factor XII (CSL 312) has been produced, which is potent and specific, and attenuates vascular permeability in animal models of *C1-INH* deficiency. A phase II trial in adults (intravenous or subcutaneous) is in progress.<sup>2,3</sup> Low-molecular-weight inhibitors that target activated factor XII have been developed but initial studies demonstrated activity toward other proteases, *e.g.*, coagulation factor VII, and are not being pursued. Factor XII is a key initiator of bradykinin formation; however, activation of endothelial cells to release heat shock protein 90<sup>4</sup> or prolylcarboxypeptidase<sup>5</sup> may activate the prekallikrein-HK complex directly, *i.e.*, bypass factor XII. Nevertheless, the feedback activation of factor XII by kallikrein thus formed will, at minimum, result in a major acceleration of bradykinin formation. Whether its inhibition would be as effective as kallikrein inhibition in HAE remains to be seen.

### Plasma Kallikrein Inhibition

Phase III trials of Biocryst BCX7353 (Biocryst Pharmaceuticals Inc., Durham, NC) have been completed<sup>6</sup>; an application has been submitted to the U.S. Food and Drug Administration to be considered for approval for the treatment of HAE types I or II. This is a low-molecular-weight oral inhibitor of plasma kallikrein, taken as a single daily dose. This approach has considerable potential as an oral prophylactic therapy and would be an alternative to the two major choices currently available; namely subcutaneous *C1-INH* (administered twice weekly) or a subcutaneous injection of a monoclonal antibody to plasma kallikrein (administered every 2 weeks). Oral administration of a liquid formulation of BCX7353 has been shown to have rapid and sustained plasma concentrations.<sup>7</sup> In a phase II, randomized, placebo controlled trial for acute treatment of HAE attacks, BCX7353 was found to be superior to placebo and was well tolerated.<sup>8</sup> This would be an interesting alternative to acute treatment with

subcutaneous icatibant (Firazyr, Takeda Pharmaceutical Company, Tokyo, Japan) or ecallantide (Kalbitor, Takeda Pharmaceutical Company, Tokyo, Japan). There are additional oral low-molecular-weight plasma kallikrein inhibitors being studied by Kalvista and Attune Pharmaceuticals for prophylactic therapy (phase I studies) and an additional compound for acute therapy (Kalvista, phase II study).

### Icatibant

Although icatibant is particularly effective for the acute treatment of angioedema due to HAE types I and II, it can potentially be used for any bradykinin-dependent angioedema. Synthesis of a bradykinin antagonist with comparable (or better) specificity but with a longer half-life has been reported and is being developed by Pharvaris (Pharvaris Pharmaceuticals, Leiden, Netherlands) for prophylaxis of HAE attacks.<sup>9</sup> It would be administered orally.

## DNA AND RNA APPROACHES

### Factor XII, Prekallikrein, HK

Patients are occasionally identified with deficiencies of the various components of the bradykinin-forming cascade, including factor XII deficiency, prekallikrein deficiency (Fletcher trait), and deficiency of HK. Most are healthy individuals but coagulation abnormalities (*i.e.*, thrombosis, not bleeding) are occasionally evident in patients with factor XII deficiency. Prekallikrein deficiency has recently been reviewed<sup>10</sup> and focused on possible effects that are physiologic or predisposing to disease. No clear abnormality was identified.<sup>10</sup> Knockout of the prekallikrein gene is theoretically a better approach than kallikrein inhibition for therapy of HAE types I and II because it not only eliminates factor XII-dependent initiation of the cascade but also any process that might bypass factor XII to activate prekallikrein-HK. Knocking out the *HK* gene is likely more difficult and one would have to target its light chain domain to preserve low-molecular-weight kininogen. This approach eliminates factor XII-dependent and factor XII-independent pathways for HK cleavage, including the possibility that MASP-1 of the lectin

pathway contributes to bradykinin formation. This would preserve tissue kallikrein-dependent bradykinin formation. Otherwise beneficial effects of bradykinin might be abrogated. An antisense prekallikrein is being studied (Ionis Pharmaceuticals, Ionis Pharmaceuticals, Carlsbad, CA) for prophylaxis of HAE and is at the phase II stage. A phase I, blinded, placebo controlled clinical trial demonstrated a 95% reduction in prekallikrein levels in normal volunteers. This has the potential to be the first genetic approach to target bradykinin formation.<sup>11</sup>

### Gene Replacement Therapy

This approach, if successful, would be considered to be a “cure” for HAE types I or II. Adeno-associated virus gene therapy is at the preclinical development stage, and two efforts are underway, by Adverum (ADVM-053) (Adverum Biotechnology Company, Redwood City, CA) and RegenXbio Pharmaceuticals (Regene Rx Biopharmaceuticals, Rockville, MD). The idea is to splice the normal *C1-INH* gene into the patient's genome so that synthesis of at least 50% of normal C1-INH is achieved. If this were to reverse the downregulation of the patient's one normal *C1-INH* gene, then blood levels could approach 100%. Thus far, sustained circulating *C1-INH* levels and reduced vascular permeability was observed in a murine model of HAE.<sup>12</sup>

### ADDITIONAL CONSIDERATIONS

Although the constitutively present  $\beta_2$ -bradykinin receptor is clearly relevant to bradykinin function in HAE types I and II, there is a  $\beta_1$  receptor that is preferentially stimulated by des-Arg<sup>9</sup> bradykinin, the product of carboxypeptidase cleavage at the C-terminus of bradykinin.<sup>9</sup> This receptor is normally not present (or minimally so) but is induced by cytokines such as interleukin 1 or tumor necrosis factor  $\alpha$  or by bradykinin itself.<sup>13</sup> Rodent models of vascular permeability due to C1-INH knockout are partially dependent on the  $\beta_1$  receptor.<sup>14</sup> Further, because the  $\beta_1$  receptor is not rapidly internalized (downregulated) like the  $\beta_2$  receptor, if present, it might contribute to protracted symptoms (typically 3 days) during attacks of angioedema.<sup>15</sup>

Although a  $\beta_1$  receptor antagonist alone is not likely to be helpful in HAE, synthesis of bradykinin analogs that bind to both receptors have been reported and used in animal experiments.<sup>16,17</sup> Perhaps development of an inhibitor of both receptors would be even more effective for therapy of HAE attacks and/or other bradykinin-dependent angioedemas than their blockade of the  $\beta_2$  receptor alone. Most therapeutic approaches that target proteins of the bradykinin-forming cascade have focused on prekallikrein and/or kallikrein or factor XIIa. Removal of high-molecular-weight kininogen would be no less efficacious, theoretically, but more

difficult to accomplish. One suggestion is to use an RNA interference approach to target either domain 5 or 6 of HK, which would limit HK synthesis and leave low molecular weight kininogen (LK) synthesis intact.

### CAN WE TARGET HAE-N?

All of the above approaches could work for one or more types of HAE with normal C1 INH (HAE-N) because we know that mutant factor XII acts through the bradykinin-forming cascade, mutant plasminogen presumably does so, although the mechanism is unclear, whereas mutant HK is likely to affect bradykinin formation. However, mutant angiotensin may require targeting the bradykinin receptor rather than any of the enzymes. The long-acting  $\beta_2$  receptor antagonist might represent therapy with particular efficacy for this form of HAE-N. Because mutant factor XII is particularly susceptible to plasmin activation<sup>18</sup> and is clinically very dependent on estrogen, antifibrinolytics and progesterone seem to be more successful for this disorder than their utility for HAE types I and II.<sup>19,20</sup> Each, nevertheless, is a nonspecific approach. For HAE with factor XII mutation (HAE-XII), therapy with a monoclonal antibody to factor XIIa (which is being considered for HAE types I and II) or development of an antisense RNA or DNA for factor XII might eliminate mutant factor XII as well as the normal allele and thereby ameliorate symptoms in this major subpopulation of HAE-N.

### CLINICAL PEARLS

- Future specific targeting of activated factor XII can provide an additional approach for the treatment of HAE types I and II as well as HAE with factor XII mutations.
- Deletion of the prekallikrein gene(s) or the light chain of high-molecular-weight kininogen is the approach most likely for the efficacy of genetic replacement of C1-INH in prevention of HAE types I and II.
- Cure means replacement of the mutant C1-INH gene, a goal for the future.
- Any current or future therapies for HAE types I and II have the potential to treat forms of HAE with normal C1-INH provided that the angioedema is due to overproduction of bradykinin.

### REFERENCES

1. Wedner HJ. Hereditary angioedema: Pathophysiology (HAE type I, HAE type II, and HAE nC1-INH). *Allergy Asthma Proc.* 2020; 41:S14–S17.

2. Cao H, Biondo M, Lioe H, et al. Antibody-mediated inhibition of FXIIa blocks downstream bradykinin generation. *J Allergy Clin Immunol.* 2018; 142:1355–1358.
3. Cao Z, Biondo M, Rayzman V, et al. Development and characterization of an anti-FXIIa monoclonal antibody for the treatment of hereditary angioedema. *J Allergy Clin Immunol.* 2015; 135(Suppl):AB194.
4. Joseph K, Tholanikunnel BG, Kaplan AP. Heat shock protein 90 catalyzes activation of the prekallikrein-kininogen complex in the absence of factor XII. *Proc Natl Acad Sci USA.* 2002; 99:896–900.
5. Shariat-Madar Z, Mahdi F, Schmaier A. Identification and characterization of prolylcarboxypeptidase as an endothelial cell prekallikrein activator. *J Biol Chem.* 2002; 277:17962–17969.
6. Zuraw B, Lumry W, Banerji A, et al. Oral prophylaxis with BCX7353 reduces HAE attack rates and is well-tolerated: APEX-2 study results. *Ann Allergy Asthma Immunol.* 2019; 123(Suppl):S27.
7. Mathis A, DeSpirito M, Cornpropst M, et al. Liquid formulation of BCX7353 rapidly provides sustained concentrations and kallikrein inhibition. *Ann Allergy Asthma Immunol.* 2018; 121(Suppl):S32.
8. Longhurst H, Moldovan D, Bygum A, et al. Oral plasma kallikrein inhibitor BCX7353 is safe and effective as an on-demand treatment of angioedema attacks in hereditary angioedema (HAE) patients: results of the ZENITH-1 trial. *J Allergy Clin Immunol.* 2019; 143(Suppl):AB36.
9. Lesage ASJ, Knolle J, Marceau F, et al. PHA-022121, the first-in-class orally active bradykinin receptor B2 antagonist for on-demand and prophylactic treatment of HAE. *Allergy Asthma Clin Immunol.* 2019; 15:45.
10. Vardi M, Girolami A, Sexton D, et al. Long-term safety outcomes of prekallikrein deficiency: a systematic literature review. *J Allergy Clin Immunol.* 2018; 141(Suppl):AB58.
11. Bhattacharjee G, Revenko AS, Crosby JR, et al. Inhibition of vascular permeability by antisense-mediated inhibition of plasma kallikrein and coagulation factor 12. *Nucleic Acid Ther.* 2013; 23:175–187.
12. Qiu T, Chiuchiolo M, Whaley A, et al. Gene therapy for C1 esterase inhibitor deficiency in a murine model of hereditary angioedema. *Allergy.* 2019; 74:1081–1089.
13. Leeb-Lundberg LMF, Marceau F, Müller-Esterl W, et al. International Union of Pharmacology. XLV. Classification of the kinin receptor family: from molecular mechanisms to pathophysiological consequences. *Pharmacol Rev.* 2005; 57:27–77.
14. Bossi F, Fischett F, Regoli D, et al. Novel pathogenic mechanism and therapeutic approaches to angioedema associated with C1 inhibitor deficiency. *J Allergy Clin Immunol.* 2009; 124:1303–1310.
15. Hofman ZLM, Relan A, Zeerleder S, et al. Angioedema attacks in patients with hereditary angioedema: local manifestations of a systemic activation process. *J Allergy Clin Immunol.* 2016; 138:359–366.
16. Stewart JM, Gera L, York EJ, et al. Bradykinin antagonists: present progress and future prospects. *Immunopharmacology.* 1999; 43:155–161.
17. Morissette G, Houle S, Gera L, et al. Antagonist, partial agonist and antiproliferative actions of B-9870 (CU201) as a function of the expression and density of the bradykinin B1 and B2 receptors. *Br J Pharmacol.* 2007; 150:369–379.
18. de Maat S, Björkqvist J, Suffritti C, et al. Plasmin is a natural trigger for bradykinin production in hereditary angioedema with factor XII mutation. *J Allergy Clin Immunol.* 2016; 138:1414–1423.e9.
19. Bork K, Wulff K, Witzke G, et al. Treatment of hereditary angioedema with normal C1-INH and specific mutations in the F 12 gene (HAE-XII). *Allergy.* 2017; 72:320–324.
20. Bork K, Wulff K, Witzke G, et al. Treatment of patients with hereditary angioedema with the C.988A > G (p.Lys330GLU) variant in the plasminogen gene. *Orphanet J Rare Dis.* 2020; 15:52. □

# Hereditary angioedema and shared decision making

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## ABSTRACT

*Clinical decision-making in hereditary angioedema (HAE) management involves a high degree of complexity given the number of therapeutic agents that are available and the risk for significant morbidity and potential mortality attributable to the disease. Given this complexity, there is an opportunity to develop shared decision-making (SDM) aids and/or tools that would facilitate the interactive participation of practitioners and patients in the SDM process. This article reviews the general constructs of SDM, the unmet need for SDM in HAE, and the steps necessary to create a SDM tool specific for HAE, and outlines the challenges that must be navigated to guide the establishment and widespread implementation of SDM in the management of HAE.*

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**A**mong the multiple clinical decisions in hereditary angioedema (HAE) management (Table 1), discussion most often centers on the selection of pharmaceutical options for on-demand treatment and whether to start long-term prophylaxis (LTP).<sup>1–6</sup> If the decision is made to proceed with LTP, then a choice arises with regard to the selection of pharmaceutical options. On-demand treatment and LTP are thoroughly discussed in separate sections of this HAE Primer issue.<sup>2,4</sup> However, the goals of on-demand and LTP treatment are different. Whereas the objective of on-demand therapy is to obtain relief of acute angioedema symptoms as quickly and completely as possible, the goals of LTP are to reduce the frequency and severity of attacks. A comprehensive HAE management plan ultimately seeks to significantly reduce or eliminate interference with normal life activities. Clinicians can help patients decide among therapeutic choices through a process called “shared decision making (SDM).” This process, further defined below, involves patients and clinicians working together to develop a shared appreciation of the patient’s situation and deciding how best to respond to it.<sup>7,8</sup> By using the SDM process, clinicians can help their patients choose an on-demand treatment that best meets their needs, determine if LTP is appropriate, and, if so, help them choose a therapeutic agent

as part of a comprehensive care plan.<sup>9</sup> This article addressed the multiple challenges and opportunities for the establishment of SDM in HAE and calls for action to accomplish this goal.

## DEFINITION OF SDM

SDM is a process in which clinicians and patients work together to make decisions and select tests, treatment, and care plans based on clinical evidence that balances risks and expected outcomes with patient preferences and values.<sup>10</sup> To elaborate further, the National Academy for State Health Policy defines SDM as “a process undertaken between providers and a patient with a condition with more than one clinically appropriate management strategy to help the patient decide among multiple acceptable health-care choices in accordance with their preferences and values.”<sup>11</sup> Despite these fairly straightforward definitions, confusion as to what constitutes SDM still exists (Table 2).<sup>7,12</sup> Regardless of how it is defined, the basic tenet of SDM is that clinicians are the experts in the evidence and that patients are the experts in what matters most to them and their families. The ultimate goal for the SDM process is to allow patients and health-care providers to make decisions collaboratively based on available evidence, patient preferences, and factors such as the environment, stress, and health literacy, all of which are extremely important for the underserved population.<sup>13,14</sup>

## UNMET NEED FOR SDM IN HAE

First introduced in 1982 and fueled by the hope of improving value-based care, the 21st century has witnessed the incorporation of SDM by policy makers at both the local and national level. For example, in 2007, Washington State passed legislation that incentivizes SDM as an alternative to traditional informed consent procedures for preference-based treatment decisions that include elective procedures, which range from joint replacement to infusion based

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**Table 1 Topics for which shared decision-making could be useful in hereditary angioedema management**

Topic	Decision	Reference No.
Diagnosis	Genetic testing	1
	Testing family members	1
Treatment	Choice of on-demand treatment options	2
	Choice of short prophylaxis options	3
	Choice of long-term prophylaxis options	4
	Treatment choices in pregnancy	5
	Treatment choices in children	6

**Table 2 SDM defined: What it is and what it is not\***

What SDM is	What SDM is not
A distinctly defined process	An undefined interaction between patients and clinicians in decision making
A collaborative discussion between patients and clinicians	A discussion solely controlled by the patient or clinician
An ongoing discussion throughout the course of the clinician–patient relationship	A single discussion that outlines the risks and benefits of therapeutic options
A process that encompasses the entire visit	A brief conversation during the course of the visit
Sharing and discussing information	Providing educational materials not geared to a specific decision
Literacy and culturally appropriate for population	Providing educational materials that promote adherence or advising patients to choose one option over another

SDM = Shared decision-making.

\*Adapted from Ref. 12.

therapies, including the use of biologic therapies.<sup>15,16</sup> The expansion of SDM is reflected by an accelerating increase in the number of PubMed citations found when using “shared decision making” as the search

term. From 1999 to 2009, the number of citations quadrupled, and, from 2009 to 2019, they increased eightfold. Despite this growing body of literature, there remains an unmet need for education among clinicians, most of whom have limited knowledge of SDM and limited experience with using decision aids in clinical practice.<sup>17</sup>

There is also an unmet need for the development and validation of SDM aids and/or tools, particularly in rare diseases, *e.g.*, HAE, in which no validated decision aids exist. The potential value of decision aids cannot be underestimated. A review of studies that included >30,000 patients showed that, when patients use decision aids as part of SDM, they are more knowledgeable about the options, are clearer about what matters to them, have more accurate expectations about the risks and benefits associated with different options, and are more likely to make decisions that are consistent with their preferences, values, and goals.<sup>18</sup> In addition, in many situations, patients elect for more conservative treatment options.<sup>19</sup>

In line with the benefits of SDM (further elaborated in Table 3),<sup>10</sup> the 2017 World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) HAE guideline states, “An individualized treatment plan should be carefully developed in partnership between the physician and each patient.”<sup>20</sup> The 2020 US HAEA Medical Advisory Board Guidelines for the management of HAE will more specifically advocate for SDM and, by doing so, will help further advance the widespread use of SDM and formal development of SDM aids in HAE.<sup>21</sup> The recognition that informed patients often choose more conservative and, hence, less-expensive medical options has made SDM a focus of value-based care with regard to many biologic- and infusion-based therapies for more common diseases, *e.g.*, asthma,<sup>12</sup> but rare diseases, *e.g.*, HAE, have been overlooked. This is unfortunate because HAE is an ideal disease for the use of SDM and associated SDM aids to help with patient management, especially when selecting among several evidence-based options. Because no head-to-head trial data exist and it, therefore, is not possible to determine “best” evidence-based treatment options, patient preferences play a large role in decisions with regard to therapy, which thus makes HAE management very preference sensitive. The incorporation of SDM into HAE management can ensure that choices in medical care will best align with patients’ preferences and values.

### CHALLENGES TO SDM IMPLEMENTATION IN HAE

To guide the implementation of high-quality and achievable SDM for HAE, the following challenges will need to be addressed:

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**Table 3 Benefits of SDM\***

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When patients engage in SDM they:

- Learn about their health
  - Recognize that a decision needs to be made
  - Understand the pros and cons of different options
  - Gain the information and tools needed to evaluate options
  - Are better prepared to talk with their clinician
  - Collaborate with their health-care team
  - Are more likely to follow through on their decision
- 

*SDM = Shared decision-making.*

*\*Adapted from Ref. 10.*

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**Table 4 Communication skills and suggested language for clinicians to introduce shared decision-making to patients\***

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“Sometimes things in medicine are not as clear as most people think. Let us work together so that we reach a decision that is best for you.”

“People have different goals and concerns. As you think about your options, what is important to you?”

“Do you want to discuss this decision with anyone else?”

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*\*Adapted from Ref. 10.*

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**Table 5 Six steps of shared decision-making\***

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- Invite the patient to participate
  - Present options
  - Provide information on risks and benefits
  - Assist patients in evaluating options based on their goals and concerns
  - Facilitate deliberation and decision making
  - Assist patients to follow through on the decision
- 

*\*Adapted from Ref. 10.*

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1. Clinician education. It is necessary for clinicians to not only grasp the true definition of SDM but also to become competent in facilitating the SDM process. The challenge is that there is a substantial disconnect between what clinicians perceive to be informed decision-making and what actually constitutes informed decision-making.<sup>17</sup> In addition, to promote competency in SDM, active training, in the form of simulations, is optimal for the development of the specific communication skills necessary to successfully facilitate SDM (Table 4).<sup>10</sup>

2. Development, certification, and maintenance of decision aids for HAE. Although the National Quality Forum has issued criteria to certify patient decision aids,<sup>22</sup> there currently are no certified decision aids for HAE and no Center for Medicare and Medicaid Services (CMS)-funded mandates to support the development, certification, and maintenance of decision aids in general (should be updated every 2 years at minimum). The challenge is to create high-quality decision aids that make explicit the decision being considered and provide balanced, evidence-based information about the condition and the risks, benefits, probabilities, and uncertainties that surround the diagnosis and treatment of HAE and associated with different treatment options.
3. Development of SDM measures. Although measures to assess skillfulness exist, measures to assess proficiency in risk communication are not well established.
4. Fostering a SDM culture. Although strategies for how to perform SDM have been well established, most notably the “six steps of shared decision making” (Table 5),<sup>10</sup> this process requires dedicated time and effort. The challenge is how to integrate SDM in clinical practice in a manner that is not a burden to clinicians but rather an enhancement to their practice. Unfortunately, best practices to inform the dissemination and implementation of decision aids and SDM models have not been established, but, if SDM is to achieve its intended goals, the workflow of routine clinical care for HAE must be considered. Decision aids for HAE need to be made readily available to clinicians and easily shareable with patients, such that patients can view them in multiple formats (digital and print) both with the clinician and independently, inside and outside of the clinical encounter. This could be hosted in a patient portal or through an HAE patient support group web site, such as the Hereditary Angioedema Association (Fairfax City, VA), [www.haea.org](http://www.haea.org). Reimbursement incentives and increased protection from litigation akin to Washington State’s SDM legislation may help win the enthusiasm of clinicians to embrace SDM.<sup>16</sup>
5. Overcoming patient issues of low health literacy, low numeracy, and cultural diversity. Although it is important to support patient autonomy and to respect individual competence, the approach, type, and complexity of communication needs to be tailored to each individual. In addition, because the concept of SDM is often novel to patients, it may be appropriate to formally

**Table 6 Benefits and adverse effects of on-demand treatment for HAE attacks**

Drug	Advantages	MOA	Route	Repeated Dosing	Adverse Events	Approved for
PdC1-INH	Decades of treatment and safety data	Replacement; pdC1-INH	IV	A second dose can be admin in 4 hr	Headache, nausea, vomiting, abdominal pain, and muscle spasms	Self-admin for children and adults
Recombinant C1-INH	Scalable production and/or supply, not plasma-derived	Replacement recombinant C1-INH	IV	Maximum of 2 doses in a 24-hr period	Headache, vertigo, diarrhea, anaphylaxis	Self-admin for >12 years old
Ecallantide	SC	Recombinant kallikrein inhibitor	SC	Maximum of 2 doses in a 24-hr period	Headache, nausea, diarrhea, pyrexia, nasal congestion, anaphylaxis	Health-care professional admin to >12 years old
Icatibant	SC, easily self-admin	Bradykinin $\beta_2$ -receptor antagonist	SC	Admin additional doses $\geq 6$ hr apart; no more than 3 doses in a 24-hr period	Injection-site pain and/or reactions, pyrexia, transaminase increase, dizziness, rash	Self-admin for >18 years old

HAE = Hereditary angioedema; MOA = mechanism of action; pd = plasma-derived; C1-INH = C1 esterase inhibitor; IV = intravenous; SC = subcutaneous injection; admin = administer.

**Table 7 Benefits of long-term prophylaxis therapy for hereditary angioedema**

Benefit	Subcutaneous Injection		Intravenous	Oral	
	pdC1-INH	Lanadelumab	pdC1-INH	Berotrastat (investigational at publication)	Danazol
Reduced attack frequency	+	+	+	+	+
Study data on improved quality of life	+	+	+	+	
Oral route				+	+
Dosing frequency	2 times/wk	1–2 times/mo	2 times/wk	Daily	Daily
Non-plasma derived		+		+	+

pdC1-INH = plasma-derived C1 esterase inhibitor; + = yes; wk = week; mo = month.

introduce the process of SDM to the patient before beginning the communication process.

6. Building clinician-patient rapport. Achieving successful SDM depends, in large part, on building a good relationship during the clinical encounter, which thus enables patient education, deliberation, and preference determination. This requires optimizing communication skills and allocating time. A lack of time to interact with the patient is recognized as the biggest impediment to SDM, in part, because there is no system

established for reimbursement of the additional work required to perform SDM.

### MOVING FORWARD

The first step in establishing SDM as a standard component of HAE management is the creation of SDM aids specifically developed for HAE. This project would require prototype development and usability testing with targeted end-users consistent with International Patient Decision Aid Standards.<sup>23</sup> Although validated

**Table 8 Adverse effects and risks of long-term prophylaxis therapy for hereditary angioedema**

Benefit	Subcutaneous Injection		Intravenous	Oral	
	pdC1-INH	Lanadelumab	pdC1-INH	Bertralstat ( <i>investigational at publication</i> )	Danazol
Local injection site pain and/or reaction	+	+	+		
Risk of blood-borne pathogens	Very low	None	Very low	None	None
Hypersensitivity reaction	+	+	+	+	+
Elevated transaminases		+ (rare)			+
Androgenic effects*					+
Gastrointestinal adverse effects				+	
Laboratory monitoring					+#

pdC1-INH = Plasma-derived C1 esterase inhibitor + = yes.

\*Include weight gain, hypertension, hirsutism, hepatic adenoma, psychological effects.

#Complete blood cell count, liver function tests, lipid panel, annual liver ultrasound.

SDM aids do not currently exist for HAE, an informed discussion should at a minimum include a comparison between the benefits and adverse effects of all U.S. Food and Drug Administration approved on-demand treatment and LTP options. The discussion should address the following issues: *What do the treatment options have in common? How do they differ? How does the adverse effect profile of the different options compare?* The information shared with the patient should be unbiased and balanced to the extent that it includes reasons why and why not to seek medical treatment. Examples of preliminary (unvalidated) decision aids that may serve as a catalyst for a more in-depth discussion with regard to on-demand treatment and LTP options are provided in Tables 6–8.

## CONCLUSION

Although on-demand treatment is an absolute necessity for every patient with HAE, the presence of multiple effective therapeutic products presents choices that are ideal for SDM. As opposed to on-demand treatment, LTP, although not necessary for every patient, provides a reduction in attack frequency and severity as well as improved quality of life. Both forms of treatment have associated costs, which need to be balanced by symptom improvement and a diminished need for acute medical care and reduced morbidity. When deciding whether to start a therapeutic course of LTP, it is important to review all benefits and safety issues. To this end, patients are encouraged to engage their clinician in the process of SDM to help them decide if LTP is appropriate for them, and, if so, which medication to use.

## CLINICAL PEARLS

- SDM in HAE is a process in which clinicians and patients work together to make decisions with regard to HAE tests, treatment, and care plans based on clinical evidence that balances risks and expected outcomes with patient preferences and values.
- SDM is not a single step of education to be added into the consultation but should provide the framework for communicating with patients about their health care choices, which will help improve patient-physician conversation quality and outcomes.
- Arguably, the most essential component to SDM and making an informed decision is patient knowledge and understanding of issues related to patient care.
- The same process may not work for all patients; SDM approaches must be individualized to be successful.

## REFERENCES

1. Manning ME. Hereditary angioedema: differential diagnosis, diagnostic tests and family screening. *Allergy Asthma Proc.* 2020; 41:S22–S25.
2. Christiansen S, Zuraw B. Hereditary angioedema: on-demand treatment of acute attacks. *Allergy Asthma Proc.* 2020; 41:S26–S29.
3. Craig T. Hereditary Angioedema: triggers and short-term prophylactic treatment. *Allergy Asthma Proc.* 2020; 41:S30–S34.
4. Li HH. Hereditary angioedema: long-term prophylactic treatment. *Allergy Asthma Proc.* 2020; 41:S35–S37.
5. Yakoboski E, Motazedi T, Banerji A. Hereditary angioedema: special considerations in women. *Allergy Asthma Proc.* 2020; 41:S47–S50.
6. Johnston DT, Smith RC. Hereditary angioedema: special considerations in children. *Allergy Asthma Proc.* 2020; 41:S43–S46.
7. Kon AA, Morrison W. Shared decision-making in pediatric practice: a broad view. *Pediatrics.* 2018; 142(Suppl 3):S129–S132.

8. Elwyn G, Edwards A, Kinnersley P, et al. Shared decision making and the concept of equipoise: the competences of involving patients in healthcare choices. *Br J Gen Pract.* 2000; 50:892–899.
9. Paige D, Maina N, Anderson J. Hereditary angioedema: Comprehensive management plans and patient support. *Allergy Asthma Proc.* 2020; 41:S38–S42.
10. National Learning Consortium. Advancing America’s Health. Shared Decision Making. Fact Sheet [cited 2020 May 13]. Available from: [https://www.healthit.gov/sites/default/files/nlc\\_shared\\_decision\\_making\\_fact\\_sheet.pdf](https://www.healthit.gov/sites/default/files/nlc_shared_decision_making_fact_sheet.pdf).
11. Shafir A, Rosenthal J. Shared decision making: advancing patient-centered care through state and federal implementation [2020 Jun 8]. Available from: [http://www.statecoverage.org/files/NASHP-shared.decision.making.report\\_March\\_2012.pdf](http://www.statecoverage.org/files/NASHP-shared.decision.making.report_March_2012.pdf).
12. Blaiss MS, Steven GC, Bender B, et al. Shared decision making for the allergist. *Ann Allergy Asthma Immunol.* 2019; 122:463–470.
13. Matsui EC, Adamson AS, Peng RD. Time’s up to adopt a biopsychosocial model to address racial and ethnic disparities in asthma outcomes. *J Allergy Clin Immunol.* 2019; 143:2024–2025.
14. Fitzpatrick AM, Gillespie SE, Mauger DT, et al. Racial disparities in asthma-related health care use in the National Heart, Lung, and Blood Institute’s Severe Asthma Research Program. *J Allergy Clin Immunol.* 2019; 143:2052–2061.
15. Spatz ES, Krumholz HM, Moulton BW. The new era of informed consent: getting to a reasonable-patient standard through shared decision making. *JAMA.* 2016; 315:2063–2064.
16. Spatz ES, Krumholz HM, Moulton BW. Prime time for shared decision making. *JAMA.* 2017; 317:1309–1310.
17. Braddock CH III, Edwards KA, Hasenberg NM, et al. Informed decision making in outpatient practice: time to get back to basics. *JAMA.* 1999; 282:2313–2320.
18. Gagné ME, Légaré F, Moisan J, et al. Impact of adding a decision aid to patient education in adults with asthma: a randomized clinical trial. *PLoS One.* 2017; 12:e0170055.
19. Elwyn G, Frosch D, Thomson R, et al. Shared decision making: a model for clinical practice. *J Gen Intern Med.* 2012; 27:1361–1367.
20. 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; 73:1575–1596.
21. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol Pract.* 2020; S2213-2198:30878-3.
22. National Quality Forum. National. Standards for the Certification of Patient Decision Aids [cited 2020 May 14]. Available from: <https://www.qualityforum.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=84189>.
23. IPDAS Collaboration. What are patient decision aids [cited 2020 May 13]? Available from: <http://ipdas.ohri.ca/what.html>. □

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