Vázquez et al. World Allergy Organization Journal (2026) 19:101335
http://doi.org/10.1016/j.waojou.2026.101335

WORLD ALLERGY ORGANIZATION JOURNAL

GUIDELINE

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The 2025 WAO Guidelines for the classification, diagnosis, and treatment of hereditary angioedema, with consideration of worldwide disparities

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http://doi.org/10.1016/j.waojou.2026.101335

Received 14 January 2026; Accepted 15 January 2026
Online publication date 19 March 2026

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ABSTRACT

The 2025 World Allergy Organization (WAO) Guidelines for the Classification, Diagnosis, and Treatment of Hereditary Angioedema (HAE) with Consideration of Worldwide Disparities provide a comprehensive, evidence-informed, and globally applicable framework for the care of this rare and potentially life-threatening disorder. HAE is a genetic disease characterized by recurrent episodes of subcutaneous and submucosal swelling, most commonly mediated by bradykinin, and is associated with substantial morbidity, impaired quality of life, and a lifelong risk of fatal laryngeal edema.

The Guidelines were developed by an international panel of 40 experts from 22 countries, with representation from all world regions, reflecting the commitment of WAO to geographic diversity, inclusiveness, and global relevance. The development process for these guidelines followed a structured and transparent methodology that integrated systematic literature review, appraisal of real-world evidence, and application of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework adapted for rare diseases, complemented by a formal Delphi consensus process. This approach was specifically designed to address the limitations of conventional evidence hierarchies in rare disorders, while ensuring clinical applicability across heterogeneous healthcare systems and resource settings.

A central element of the guidelines is an updated classification of HAE based on underlying pathophysiology and disease endotypes. The traditional distinction between HAE types 1 and 2 is unified under the term HAE with C1 inhibitor deficiency (HAE-C1-INH), reflecting shared biological mechanisms and management principles. The guidelines also recognize an expanding spectrum of HAE with normal C1 inhibitor (HAE-nC1-INH), including forms associated with pathogenic variants in F12, PLG, ANGPT1, KNG1, MYOF, HS3ST6, CPN1, and DAB2IP, as well as cases with currently unidentified genetic causes.

The diagnostic strategy emphasizes early clinical recognition based on characteristic features, including recurrent angioedema without urticaria, abdominal or laryngeal involvement, early symptom onset, and family history. A simplified diagnostic algorithm is proposed, prioritizing the C1 inhibitor functional assay as the preferred initial test when performed in a reliable specialized laboratory. Alternative diagnostic pathways are outlined for settings with limited access to specialized testing, including pragmatic combinations of biochemical assays and selective use of genetic testing, particularly relevant for HAE-nC1-INH and family screening.

Management recommendations address on-demand treatment of acute attacks, short-term prophylaxis, and individualized long-term prophylaxis. Universal access to on-demand therapy is emphasized for all patients with confirmed HAE, including those who are asymptomatic, given the unpredictable nature of attacks and lifelong risk. Long-term prophylaxis is addressed within a treat-to-target framework aimed at achieving complete disease control and sustained

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improvement in health-related quality of life, with regular reassessment and shared decision-making. Empowering patients and caregivers through structured education, access to appropriate medications, and integration with specialized referral centers is associated with earlier treatment, reduced healthcare utilization, and improved equity of care and reduced avoidable morbidity and mortality worldwide.

The 2025 WAO Guidelines for Hereditary Angioedema establish an evidence-informed, patient-centered, and forward-looking framework for the classification, diagnosis, and management of HAE. By integrating advances in pathophysiology, diagnostics, and therapeutics with global expert consensus and real-world considerations, the guidelines aim to support consistent, equitable, and high-quality care for patients with HAE across regions and healthcare systems.

Keywords: Hereditary angioedema, Guideline, Diagnosis, Therapy, C1 inhibitor, Real-world evidence, Quality of life, Prophylaxis, Bradykinin, Kallikrein, Rare disease, Genetic mutation, SERPING1, Factor 12

INTRODUCTION

Hereditary angioedema (HAE) has been recognized as a distinct clinical entity since the 19th century and represents a disabling health problem for affected individuals and families that can be potentially life-threatening.[1] A new era in HAE management began with the discovery of C1 inhibitor deficiency as the main cause, along with establishing its genetic basis and the subsequent development of targeted therapies.[2]

The World Allergy Organization (WAO) issued and published guidelines for the diagnosis and treatment of HAE in 2012, followed by updated versions (in collaboration with the European Academy of Allergy and Clinical Immunology) in 2017 and 2021.[3–5] Evidence-based medicine is currently considered the gold standard for guiding clinical practice, but the very nature of rare disorders (by European definitions, those with a prevalence of <1 in 2000 individuals), including most genetic conditions, inherently challenges the generation and application of data on screening, diagnosis, management, and follow-up.[6,7] In the context of research on these conditions, sources traditionally considered low or very low quality – such as small or non-randomized clinical trials, open-label studies, compassionate use programs, observational or qualitative studies, and case reports – are the rule rather than the exception.

Most guidelines addressing rare disorders are based on expert opinion rather than on data derived from well-designed clinical trials, meta-analyses, or other high-quality information sources, and proper guidance on the application of criteria, such as Grading of Recommendations, Assessment, Development and Evaluation (GRADE), is scarce.[8,9] The current update is needed thanks to recent advances in diagnosis and treatment and expanded real-world evidence (RWE) on HAE, including regional differences in management. A revision of the classification of the disease also is proposed.

METHODS

All relevant published data – including original articles involving patients with HAE who were tested or treated in clinical trials or described in observational studies, as well as selected review articles – were evaluated using a systematic review strategy. Both MEDLINE-indexed publications and the gray literature, such as records registered in OpenDOAR (Nottingham, UK), were included. No publication year limitations were established, and articles published up to June 30, 2025, were included. Publicly available natural language processing (artificial intelligence) services were used to summarize articles beyond their published abstract.[10] A final manual review followed, and evaluation of generated data was conducted through a rigorous multi-step process to ensure accuracy and reliability. Two independent assessors meticulously examined the data,

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each providing individual assessments. In cases of discrepancies, a third assessor, independent of the initial evaluation, conducted a comprehensive review. Discrepancies were resolved through collaborative discussion, ensuring a consensus-based approach.

To enhance the robustness of our evaluation, the HAE guidelines steering committee played a pivotal role. This committee re-evaluated all generated data, adding complementary and pertinent information to enrich the dataset. The committee's expertise in the field ensured a comprehensive and thorough examination of the data, contributing valuable insights to the final evaluation.

This international consensus on the management of HAE was developed by 40 experts from 22 countries, selected through internal discussions within the WAO. Experts were divided into task forces, each of which was responsible for predefined subthemes. A comprehensive review of the literature was conducted, and each task force developed a set of initial statements based on summarized evidence.

All statements were submitted to a Delphi voting process.[11] Participants rated their level of agreement on a 5-point Likert scale (1 = Strongly Disagree; 5 = Strongly Agree), based on clinical experience and the literature reviewed. Voting occurred over 2 asynchronous and anonymous rounds, using an ad hoc online platform designed to ensure equitable participation from experts across diverse geographic regions. Anonymity was used with the aim of minimizing bias and preventing the disproportionate influence of dominant voices, while the asynchronous nature accommodated participant availability.

"Agreement" was defined as at least 75% of participants rating a statement as 4 or 5. "High agreement" corresponded to 90% or more of participants endorsing the statement. After the first round, participants who rated statements as 1–3 could suggest revisions. Respective task forces reviewed this feedback, rephrased the statements as needed, and submitted them for a second round of voting. Standardized phrasing was consistently applied. Statements were developed where supported by the available evidence, and recommendations were provided when the anticipated benefits clearly outweighed the potential risks, even in the context of low-quality evidence.

The quality of evidence supporting therapeutic interventions was assessed using the GRADE methodology developed at McMaster University.[12,13] With this methodology, study design is considered, along with 8 criteria: risk of bias, inconsistency, indirectness, imprecision, publication bias, magnitude of effect, dose-response relationship, and confounding. Population, intervention, comparator, outcome (ie, PICO) questions were formulated to guide the evidence review and statement development.[14] The GRADEpro tool (Evidence Prime) supported evidence grading and recommendation development.[15]

To address the challenges of evidence generation in rare diseases such as HAE, frameworks such as those proposed by the RARE-Bestpractices project were employed.[9,16,17]

Evidence quality was classified as follows:

⊕⊕⊕⊕ High: Further research is very unlikely to change confidence in the estimate of effect.

⊕⊕⊕◯ Moderate: Further research may affect confidence and may change the estimate.

⊕⊕◯◯ Low: Further research is likely to have a significant impact and may change the estimate.

⊕◯◯◯ Very Low: The estimate is highly uncertain.

Recommendations were classified as Strong, Moderate, Weak, or Recommend Against, according to the balance between benefits and risks, evidence quality, expert opinion, resource use, equity, and patient acceptability. In cases where a statement addressed multiple outcomes, the final recommendation and quality rating reflected a weighted analysis of the subcomponents.

Whenever appropriate, therapeutic interventions were categorized hierarchically into first-, second-, and third-line options, based on the strength and consistency of the available scientific evidence. In general terms, this hierarchical classification reflects the preference for each intervention, assuming that if the first-line option is not available or feasible, the second-line option

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should be considered, followed by the third-line option as necessary. This guidance is intended to support clinical decision-making and does not override the need for individualized treatment, which must always consider each patient's characteristics, preferences, and local or regional conditions and resource availability.

A total of 3004 citations were identified (2105 from PubMed and 899 from OpenDOAR). After removal of duplicates and overlapping records, a total of 2841 unique citations were reviewed. Among these, a total of 2454 were new references, in addition to 387 that already had been included in the 2021 version of the guideline.

DEFINITIONS, NOMENCLATURE, AND CLASSIFICATION

Angioedema is a localized, self-limiting, asymmetric, and disfiguring non-inflammatory edema of the subcutaneous and submucosal tissues that arises because of increased vascular permeability.[18,19] HAE comprises a group of genetic disorders characterized by recurrent episodes of angioedema, inherited across generations and typically mediated by bradykinin. It may affect any area of the skin – most commonly the lips, face, neck, genitalia, and extremities – as well as the gastrointestinal (GI) tract (mimicking an acute surgical abdomen), oral cavity, and/or larynx. Laryngeal involvement can be life-threatening due to the risk of asphyxiation.[18,19] The acute, circumscribed edema of the skin (angioedema) was first described by Quincke in 1882, and in 1888, Osler documented its hereditary nature, followed by several case reports during the 20th century.[20] Sixty years ago, the absence of plasma C1 inhibitor, also known as C1 esterase inhibitor (C1-INH), was identified by Donaldson and Evans as the biochemical cause of HAE.[21] The role of C1-INH in regulating activation of the contact system – through inactivation of plasma kallikrein and factor XIIa – was well established during the 1970s and 1980s.[22–24] In 1986, Davis and Bock reported the chromosomal locus and structure of the serine protease inhibitor gene, later named *SERPING1*, which was confirmed the following year as the genetic basis of what is now referred to as HAE type 1 and HAE type 2.[25–27]

In 1983, a pivotal study by Fields et al. implicated bradykinin as the likely primary mediator responsible for angioedema attacks.[28] This hypothesis was further supported in 1999 by Nussberger et al, who analyzed plasma samples from individuals with HAE and reported elevated bradykinin levels in blood drawn from edematous sites compared to unaffected areas.[29] Shortly thereafter, in 2002, a landmark experimental study using a double-knockout murine model deficient in both C1 inhibitor (C1-INH) and bradykinin B2 receptor (Bk2R) further confirmed the critical role of C1-INH deficiency and bradykinin in the pathogenesis of HAE.[30] These groundbreaking studies shed light on the pathophysiology of HAE, marking crucial milestones in understanding how the angioedema associated with C1-INH deficiency arises. Furthermore, in 2000, a new type of HAE was described in patients with normal C1-INH function, a form initially known as HAE type 3 but currently called HAE with normal C1-INH (HAE-nC1-INH).[31,32]

HAE (ORPHA:91378, OMIM: PS106100) is most commonly caused by a deficiency of C1 inhibitor (C1-INH), which can be confirmed through biochemical and genetic testing. It is subclassified into type 1 HAE (quantitative deficiency) and type 2 HAE (dysfunctional protein).[33–35] Since both classic forms– types 1 and 2 – share the same clinical management, this guideline proposes a simplified classification: C1 inhibitor deficiency angioedema (HAE-C1-INH). HAE is primarily mediated by bradykinin. (Fig. 1).[36]

Further research has identified additional genes associated with HAE in patients with normal *SERPING1* genetic testing and normal C1-INH measurements.[37,38] Abnormalities in proteins/genes, such as factor XII (encoded by the *F12* gene), plasminogen (*PLG*), angiopoietin-1 (*ANGPT1*), kininogen 1 (*KNG1*), myoferlin (*MYOF*), and heparan sulfate-3-O-sulfotransferase 6 (*HS3ST6*), have been associated with these forms of HAE (collectively HAE-nC1-INH), and the involvement of bradykinin has not been confirmed in all cases.[39–45] Currently, these forms of HAE are designated respectively as HAE-FXII, HAE-PLG, HAE-ANGPT1, HAE-KNG1, HAE-MYOF, and HAE-HSST. HAE of unknown origin (ie, with negative genetic test results) is

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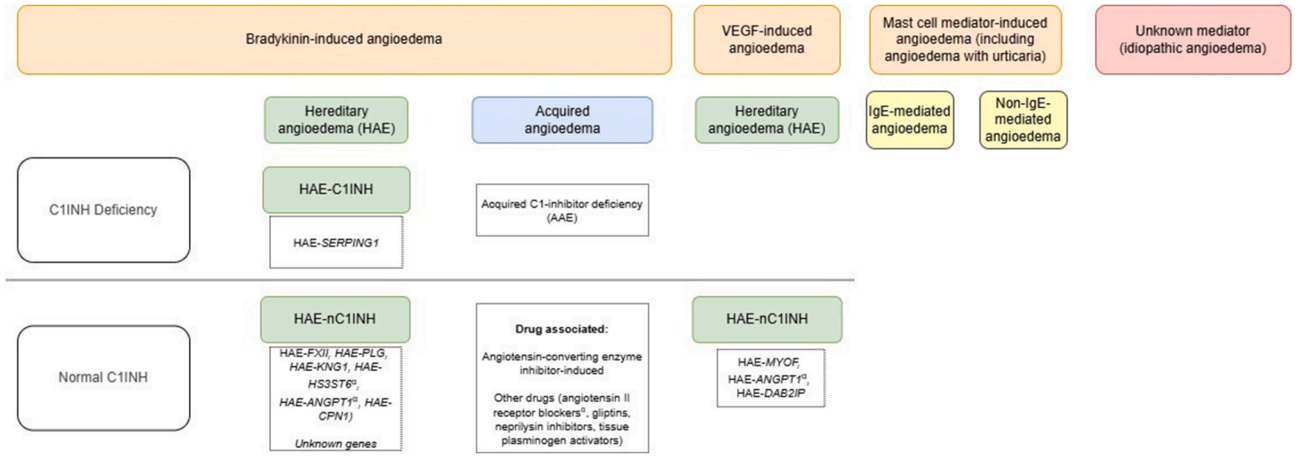

Fig. 1 Proposed classification of recurrent angioedema based on underlying endotypes. Footnote: This classification is based on current knowledge and existing scientific evidence and may evolve as understanding of HAE expands with new data. [a] The mechanism has not been fully elucidated and may not involve the bradykinin pathway. Abbreviations: HAE: hereditary angioedema; AAE-C1-INH: acquired angioedema; C1-INH: C1 inhibitor; VEGF: vascular endothelial growth factor; HAE-C1-INH: HAE with C1-INH deficiency; HAE-nC1-INH: HAE with normal C1-INH; HAE-ANGPT1: HAE with angiopoietin-1 (ANGPT1) mutation; HAE-CPN1: HAE with carboxypeptidase N (CPN1) mutation; HAE-DAB2IP: HAE with DAB2-interacting protein (DAB2IP) mutation; HAE-FXII: HAE with factor 12 (F12) mutation; HAE-HS3ST6: HAE with heparan sulfate-3-O-sulfotransferase 6 (HS3ST6) mutation; HAE-KNG1: HAE with kininogen 1 (KNG1) mutation; HAE-MYOF: HAE with myoferlin (MYOF) mutation; HAE-PLG: HAE with plasminogen (PLG) mutation.

referred to as HAE-UNK.[46–48] Efforts to identify causes in patients with HAE-UNK/HAE-nC1-INH have led to the discovery that the carboxypeptidase N (*CPN1*) and DAB2-interacting protein (*DAB2IP*) genes also can cause this condition, adding 2 forms that we now recommend be designated respectively as HAE-CPN1 and HAE-DAB2IP.[49,50] Recently, a classification of "recurrent angioedema" based on endotypes was proposed and now also includes a group (endotype) primarily linked to defective vascular endothelial growth factor (VEGF) signaling (HAE-ANGPT1, HAE-MYOF, and HAE-DAB2IP), which may be a second mediator of hereditary angioedema.[51,52]

Recognizing these ongoing advances in understanding of hereditary angioedema, the guidelines authors advocate for an improved classification system based on endotypes, as depicted in Fig. 1, with consideration of pathophysiologic mechanisms (Fig. 2). Accurate diagnosis and classification of HAE are crucial to ensuring appropriate management, treatment, and genetic counseling when considering HAE-C1-INH versus HAE-nC1-INH. This classification is based on current knowledge and existing scientific evidence and may evolve as understanding of HAE expands with new data.

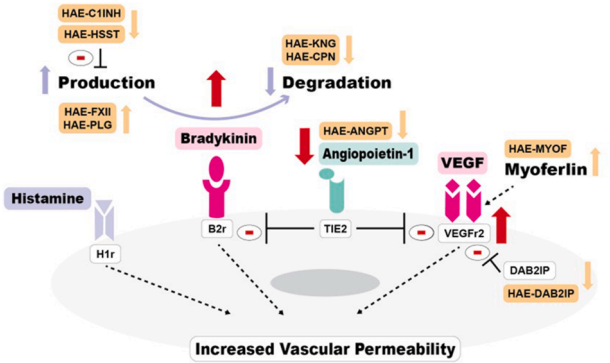

Fig. 2 Pathophysiology of recurrent angioedema. Footnote: Adapted from Giavina-Bianchi P et al [51,52]. Orange boxes: Endotypes of HAE; Pink boxes: mediators directly involved in hereditary angioedema; Green: mediators indirectly involved in hereditary angioedema; Blue: mediator involved in mast cell–induced angioedema.These pathophysiological mechanisms are based on current knowledge and existing scientific evidence and may evolve as understanding of HAE expands with new data. Abbreviations: HAE: hereditary angioedema; AAE: acquired angioedema; C1-INH: C1 inhibitor; VEGF: vascular endothelial growth factor; HAE-C1-INH: HAE with C1-INH deficiency; HAE-ANGPT1: HAE with angiopoietin-1 (ANGPT1) mutation; HAE-CPN1: HAE with carboxypeptidase N (CPN1) mutation; HAE-DAB2IP: HAE with DAB2-interacting protein (DAB2IP) mutation ; HAE-FXII: HAE with factor 12 (F12) mutation; HAE-HS3ST6: HAE with heparan sulfate-3-O-sulfotransferase 6 (HS3ST6) mutation; HAE-KNG1: HAE with kininogen 1 (KNG1) mutation; HAE-MYOF: HAE with myoferlin (MYOF) mutation; HAE-PLG: HAE with plasminogen (PLG) mutation.

EPIDEMIOLOGY

The exact prevalence of HAE remains uncertain and likely varies across countries. Available

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estimates suggest a range from 1:50,000 to 1:100,000 individuals. For HAE-C1-INH, a global prevalence of approximately 1:67,000 has been reported, with more than 85% of cases classified as type 1 HAE-C1-INH.[53] This prevalence rate suggests that >100,000 patients are affected around the world and that underdiagnosis rates are likely high.[54] The worldwide distribution of patients reported in the literature to be affected by HAE is shown in Fig. 3, but epidemiological and clinical data from many more patients are available to researchers through national and international registries. No significant differences in the incidence of C1-INH deficiency across ethnic groups have been confirmed. Allergy societies from several countries, including Argentina, Brazil, Canada, France, Japan, Italy, Slovakia, Spain, and the United States, have published their own guidelines on management of this condition.[55–61]

PATHOPHYSIOLOGY OF HAE

Advances in the understanding of the pathophysiological basis of HAE may enable improved classification strategies based on endotypes, which in turn can help refine diagnostic and therapeutic algorithms.[52] In HAE-C1-INH, bradykinin is the primary mediator of swelling. This molecule arises from cleavage of high-molecular-weight kininogen by plasma kallikrein, which is activated from prekallikrein by factor XII.[103] The resulting bradykinin nonapeptide increases vascular permeability and induces swelling (angioedema) through a specific receptor, B2,[105] and is in turn degraded by endogenous metalloproteases, including angiotensin-converting enzyme (ACE).[103,104] C1-INH is a serine protease inhibitor protein synthesized in hepatocytes that is crucial in regulating the plasma kallikrein–kinin system (KKS) and preventing excessive bradykinin production. More broadly, C1-INH is the main inhibitor of several components of the contact and complement system (Fig. 4).[106–109]

HAE-C1-INH is caused by mutations in *SERPING1*, which encodes C1-INH, leading to reduced levels or impaired activity of C1-INH. This deficiency in turn leads to uncontrolled activation of the KKS and excessive bradykinin production, with bradykinin acting as the key mediator of the condition.[110,111]

In contrast, several causative genes have been implicated in HAE-nC1-INH. Current evidence indicates that excessive bradykinin generation is still involved in most cases (HAE-FXII, HAE-PLG, HAE-KNG, HAE-HSST, and HAE-CPN). However, other mediators such as VEGF and angiopoietin have emerged as candidate contributors, potentially

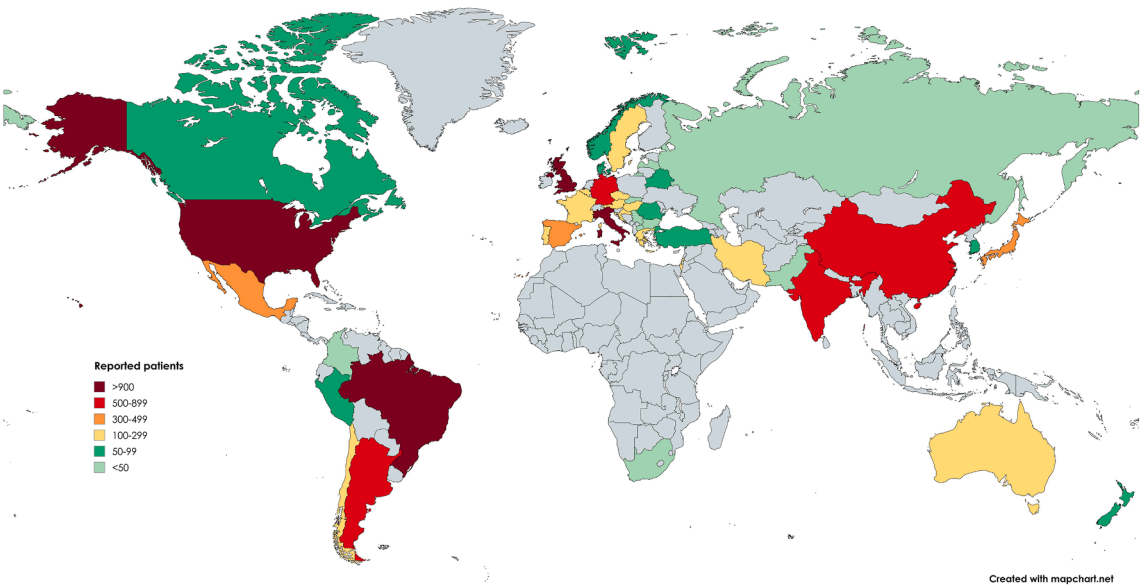

Fig. 3 Geographic distribution of reported hereditary angioedema (HAE) patients, by country. Note: The publicly available number of patients reported to be diagnosed with (and/or treated for) HAE, by country, excluding case reports of single patients. Because of a high estimated risk of underdiagnosis bias, the absolute number of patients was used instead of prevalence.[62–102]

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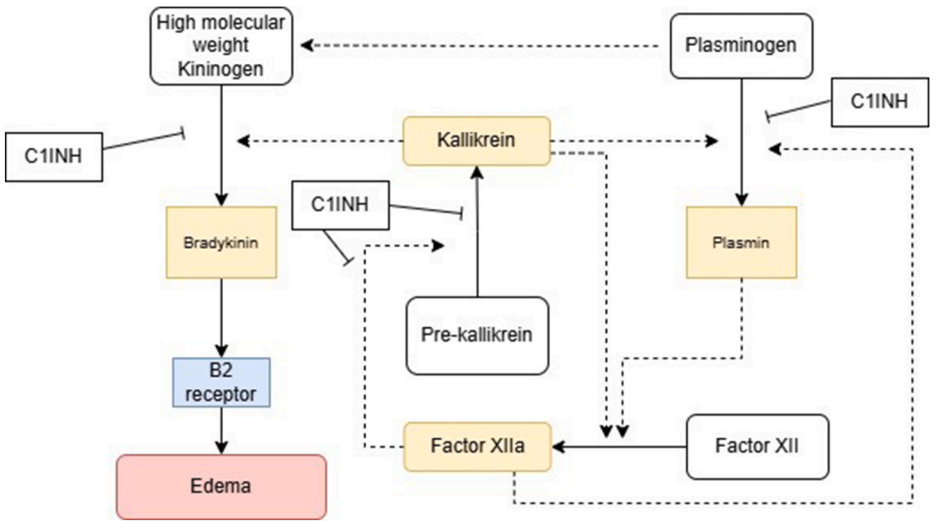

Fig. 4 Main pathways involved in bradykinin-induced angioedema, including HAE-C1-INH. Abbreviations: HAE: hereditary angioedema; C1-INH: C1 inhibitor.

increasing vascular permeability either directly (HAE-MYOF, HAE-DAB2IP) or indirectly (HAE-ANGPT).[44,52,112-117]

HAE-C1-INH is an autosomal dominant disorder characterized by high penetrance, with only about 5% of mutation carriers remaining asymptomatic over their lifetime. The risk of parent–child transmission is 50%, but up to 25% of cases result from *de novo* genetic mutations.[118-120] HAE-nC1-INH forms also usually follow an autosomal dominant inheritance pattern, although autosomal recessive forms have been reported.[35,49,121]

DIAGNOSIS OF HAE

The diagnosis of HAE relies on clinical and laboratory criteria, and distinguishing between acquired and hereditary angioedema, as well as between HAE-C1-INH and HAE-nC1-INH, is essential for proper management. A comprehensive approach that integrates clinical presentation, laboratory testing, and genetic analysis is therefore warranted.[122-126] Although the signs and symptoms of HAE are well recognized, they can vary in expression. Suggestive features include recurrent swelling of the skin and mucous membranes, typically involving the abdomen and larynx (Table 1). Diagnosis can be particularly challenging for physicians who are not familiar with this rare disorder.[127-131]

Onset of HAE episodes may occur at any age but is most common during childhood or adolescence, with a reported mean age of around 11 years (range 1 to 40 years), and approximately 50% of patients having their first attack before age 10 years.[132] The episodes typically involve nonpruritic, nonpitting swelling that worsens over the first 24 hours and gradually subsides over the next 48 to 72 hours, usually lasting no more than 5–7 days.[19,131,133] Angioedema attacks commonly affect the skin of the face and extremities (known as peripheral attacks) but can involve the trunk. Additionally, swelling can occur in the genital area, the oropharynx (including the tongue and uvula), the larynx, and the intestinal loops. Abdominal involvement occurs in 70%–90% of all individuals and is associated with high morbidity. Laryngeal involvement, although accounting for less than 1% of all attacks, poses a risk of death and occurs at least once in about half of patients. Headaches and episodes involving the urinary bladder, chest, muscles, joints, kidneys, and esophagus (<1% each) also are observed.[131,132,134]

Angioedema attacks are unpredictable, focal, asymmetric, and disfiguring and may occur at different locations simultaneously, but they are not typically systemic.[135] Non-specific prodromal symptoms are common and can include anxiety, nausea, paresthesia, and fatigue.[136] One third of patients with HAE, especially children, experience erythema marginatum (a nonpruritic form of flat, figurate erythema) as an initial

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Recurrent swelling of any skin surface, particularly the extremities, face, or genitals, as well as subcutaneous tissues
Recurrent gastrointestinal symptoms (eg, severe, long-lasting abdominal colic and/or vomiting) accompanied by abnormal abdominal imaging findings (eg, ascites, bowel wall edema)
Episodes of upper airway (mouth, tongue, larynx) edema
Early onset of symptoms (childhood/adolescence) in HAE-C1-INH
Prodromal signs and symptoms preceding angioedema attacks
Attacks not accompanied by urticaria, except in cases of HAE-CPN1
No response to treatment of attacks with epinephrine, H1-antihistamines, or glucocorticoids
Recurrent angioedema unresponsive to fourfold doses of antihistamines and to an anti-IgE monoclonal antibody (for HAE-nC1-INH)
Positive family history, especially if suggestive of autosomal dominant inheritance

Table 1. Clinical criteria for suspecting hereditary angioedema. *Abbreviation: HAE: Hereditary angioedema; C1-INH: C1 esterase inhibitor; HAE-C1-INH: HAE with C1-INH deficiency; HAE-CPN1: HAE with carboxypeptidase N (CPN1) mutation; HAE-nC1-INH: HAE with normal C1-INH*

manifestation, which may mimic the skin lesions of urticaria.[137–139] The severity and location of attacks vary considerably, even within affected families who generally harbor the same genetic mutation.[132] Some associations between phenotypic differences and regional ancestry/ethnicity have been reported, such as less frequent abdominal attacks in HAE patients from China and Taiwan in comparison with patients from Western countries.[140]

Abdominal attacks can cause severe abdominal pain, nausea, and vomiting and may lead to unnecessary abdominal surgery, as the clinical presentation can resemble an acute surgical abdomen. In some cases, intestinal angioedema may be accompanied by ascites and, very rarely, by hypovolemic shock.[141,142] Laryngeal edema presents the greatest risk due to the potential for asphyxiation and death and requires advanced airway management. In the absence of the HAE diagnosis, the risk of death with laryngeal edema is estimated at 20%–25%. Facial edema is considered a potential risk factor for laryngeal involvement.[141,143–147] On average, the first episodes of laryngeal edema occur later in life (average age, ~26 years) compared with initial episodes of skin swelling (age ~11 years) or abdominal pain (age ~16 years). Nevertheless, laryngeal edema has been reported in children as young as age 3 years. As previously noted, approximately 50% of patients are expected to experience laryngeal edema at some point in their lifetime.[148] A recent Brazilian study identified 39 deaths due to asphyxiation from laryngeal angioedema among 170 patients with HAE from 46 families. Of those who died, 87.2% had no prior diagnosis of HAE, 41% of the deaths occurred outside of a hospital, and in half of the cases, more than 8 hours had passed since the onset of the HAE attack.[149] Other authors also have described a rapid progression from onset to peak of laryngeal edema, with a mean duration of 8 hours.[148] Untreated patients with HAE may experience attacks every 7–14 days on average, although some report attacks as frequently as every 3 days, while others may experience them rarely or never.[118,132]

The clinical manifestations of HAE-nC1-INH are similar to those of HAE-C1-INH, and the 2 are largely indistinguishable based on signs and symptoms alone. However, in certain HAE-nC1-INH subtypes, angioedema attacks tend to have a later onset and may be accompanied by local hematomas.[150] For HAE-FXII, the onset is consistently reported after puberty, secondary to increased estrogen production. Women may experience the onset of attacks or worsening symptoms after using estrogen-based contraceptives, during pregnancy, or while undergoing hormone replacement therapy during menopause.[151]

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A few years ago, the use of the abbreviation "HA4E" was proposed to highlight the clinical warning signs of HAE, aiming to improve diagnosis and assist general practitioners in identifying this often-neglected condition based on how most patients typically present. The abbreviation incorporates the initials of hereditary angioedema (ie, HAE), with 4 As strategically placed between the H and the E. "HAAAAE" or "HA_4E" stands for **H**ereditary, recurrent **A**ngioedema, **A**bdominal angioedema/pain, **A**bsence of urticaria, **A**bsence of response to antihistamines, and **E**strogen association.[100]

In most of the world, blood testing for the C4 complement fragment and C1-INH antigen levels has long been considered the first step in diagnosing HAE. This testing can be confirmatory in most patients who present with the most common form, HAE-C1-INH type 1, which is characterized by reduced levels of C1 inhibitor. C4 levels are low in 90%–95% of patients with HAE-C1-INH during asymptomatic periods and are almost always low during acute attacks. A low C4 level in association with a clinical presentation suggestive of HAE supports the diagnosis and should prompt further confirmatory testing.

The C1-INH antigenic assay is widely available, simple to perform, and generally accessible. In HAE type 1, C1-INH antigen levels are reduced, whereas in HAE type 2, they are normal or elevated. Therefore, the C1-INH antigenic assay cannot confirm the diagnosis of type 2 HAE, in which C1-INH levels are normal but functional activity is decreased. The combination of a low C4 level with normal or elevated C1-INH antigen levels increases the positive predictive value for diagnosing HAE type 2.[152] Assessing the functional activity of C1-INH, although more sensitive than C1-INH antigen levels and more sensitive and specific than C4 levels, is a complex process requiring rigorous quality control, proper sample handling, and access to specialized laboratories, which limits its availability in low-income countries. In HAE-C1-INH, functional activity is typically less than 50% of normal levels.[110]

Results for all 3 of these tests are normal in HAE-nC1-INH and in ACE inhibitor–induced angioedema and decreased in acquired C1-INH deficiency (ie, acquired angioedema [AAE-C1-INH]). C1q levels are often reduced (in ∼75% of cases) in AAE-C1-INH and should be measured when it is suspected.[153] Additionally, testing for antibodies against C1-INH is recommended whenever possible, as they are detected in 50%–60% of AAE-C1-INH cases.

Building on recent studies of HAE-C1-INH diagnosis that indicate good reproducibility, 100% sensitivity, streamlined techniques, and enhanced standardization of the C1-INH functional assay, we propose a revised and simplified diagnostic algorithm for HAE. This approach involves performing only the C1-INH functional assay whenever this test is available and reliable, rather than following the traditional recommendation of conducting all 3 tests (C1-INH levels, C1-INH functional assay, and C4 level), potentially reducing diagnostic costs (Fig. 5).[154–158] If the test result is inconsistent with the clinical history, the test should be repeated.

Statement 1	*Agreement level:*
We recommend that all patients for whom HAE is suspected undergo an initial assessment with a C1-INH functional assay, as long as it is performed by a specialized laboratory using an accurate, validated method.	**85%**

If the C1-INH functional assay is unavailable or unreliable, the diagnosis can still be confirmed through quantitative C1-INH measurement and/or genetic testing for *SERPING1*. Functional activity testing of C1-INH and genetic testing are both rarely available in low- and middle-income countries, and genetic testing is often expensive in high-income countries.[159] In such situations, dried blood spots can be used to detect genetic abnormalities and measure C1-INH levels by liquid chromatography–tandem mass spectrometry. This method offers several advantages over fresh blood testing, including minimal sample processing, simplified transport, and easier storage, thereby improving patient access to diagnostic testing.[160–162] Routine testing for CH50 or C3 is not

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recommended, as neither adds to the diagnosis of HAE.[163,164]

C4 and C1-INH antigenic levels can be considered for diagnosis if the functional assay is not available. Due to the serious implications of the HAE diagnosis, the functional or antigenic assay should be repeated for confirmation if the test result and clinical assessment do not agree, ideally 1–3 months later.[129,157,165-167] Once a diagnosis of HAE-C1-INH has been established, testing does not need to be repeated given that the condition is lifelong.

Statement 2	*Agreement level:*
If the C1-INH functional assay cannot be conducted in a specialized laboratory and/or is unreliable or inconsistent with the clinical history, we recommend repeating the test to confirm the diagnosis of HAE-C1-INH.	**100%**

Statement 3	*Agreement level:*
If the C1-INH functional assay is not available, a C1-INH antigenic level should be requested to possibly confirm the diagnosis of HAE-C1-INH, although a normal result does not exclude the diagnosis.	**100%**

Statement 4	*Agreement level:*
If C1-INH testing is not available, measuring C4 levels may help support and strengthen the diagnostic suspicion of HAE-C1-INH.	**97%**

Statement 5	*Agreement level:*
In settings where access to and accuracy of C1-INH testing are limited, ordering simultaneous measurements of C4, C1-INH antigenic level, and C1-INH function may be considered an acceptable approach to expedite diagnosis and reduce the risk of losing the patient to follow-up during the diagnostic process.	**97%**

In HAE-C1-INH, the diagnosis is typically confirmed through biochemical testing, and genetic testing is rarely required. However, in cases of diagnostic uncertainty, identifying a pathogenic variant in *SERPING1* may confirm the diagnosis (Table 2).[121,168-170] C4, C1-INH antigenic levels, and functional activity are within normal ranges in HAE-nC1-INH and typically reduced in AAE-C1-INH. In both scenarios, HAE-nC1-INH and AAE-C1-INH – in the latter, particularly if C1q levels are normal – genetic testing is essential to advance the diagnostic workup and support appropriate clinical decision-making.[5]

Patients with more than 1 form of HAE have been reported, such as a family with mutations in both *SERPING1* and *PLG*, which highlights the relevance of molecular testing for proper genetic counseling and management.[171] Differences in the most prevalent pathogenic or likely pathogenic (P/LP) variants in *SERPING1* have been noted among several countries, which are common for genetic conditions associated with dominant-negative physiopathology. Therefore, genetic testing should include all 7 protein-coding exons, as all of them are known to potentially harbor causal variants.[172-184] Increasingly available whole genome sequencing will likely improve the diagnostic yield of HAE, especially for patients with less clear phenotypes and without a family history (Table 2). The capture of additional genes or gene variants using these tests will probably be increasingly useful if analysis of modifying genes or polygenic scores are brought to the clinic.[185,186]

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Statement 6	*Agreement level:*
We recommend genetic testing for HAE-nC1-INH in patients for whom there is high clinical suspicion of HAE and who have normal C1-INH functional assay results.	**100%**

Statement 7	*Agreement level:*
We recommend *SERPING1* genetic testing after a diagnosis of HAE-C1-INH is confirmed in cases where prenatal, neonatal, or preimplantation genetic testing is being considered for the family.	**85%**

Of note, negative genetic test results should not be considered definitive for excluding HAE-C1-INH or HAE-nC1-INH. Unknown genes or atypical mutational mechanisms could underlie the disease in certain families, and despite a good sensitivity of current high-throughput genetic testing technologies, such as next-generation sequencing, the sensitivity is not 100%.[187] Additionally, challenges in interpreting genetic sequences persist, particularly when analyzing the pathogenicity of variants found in individuals from ethnic or ancestral backgrounds that are underrepresented in most databases. Furthermore, many detected variants are classified as being of uncertain significance and do not alone confirm a diagnosis of HAE.[188,189] Of particular relevance, a Hereditary Angioedema Variant Curation Expert Panel is being established to create gene- and disease-specific variant classification guidelines for HAE, including HAE-nC1-INH.[190] A genotype–phenotype correlation has been observed for certain variants, with deletions and other non-functional mutations being associated with a higher risk of disease. However, in most cases – particularly for novel variants – these correlations cannot be accurately predicted.[98,191–193]

Cascade screening refers to the process of sequentially testing close blood relatives, beginning with first-degree relatives and extending to siblings, parents, and children when a family member is found to be affected. This approach helps reduce costs, improves management of currently asymptomatic but affected individuals, and alleviates anxiety for unaffected family members. It is recommended for dominant conditions such as HAE.[194] Prenatal diagnosis of HAE is rare, but if the causative genetic variant in the parents has been identified, it can be performed via invasive prenatal testing. Variability in

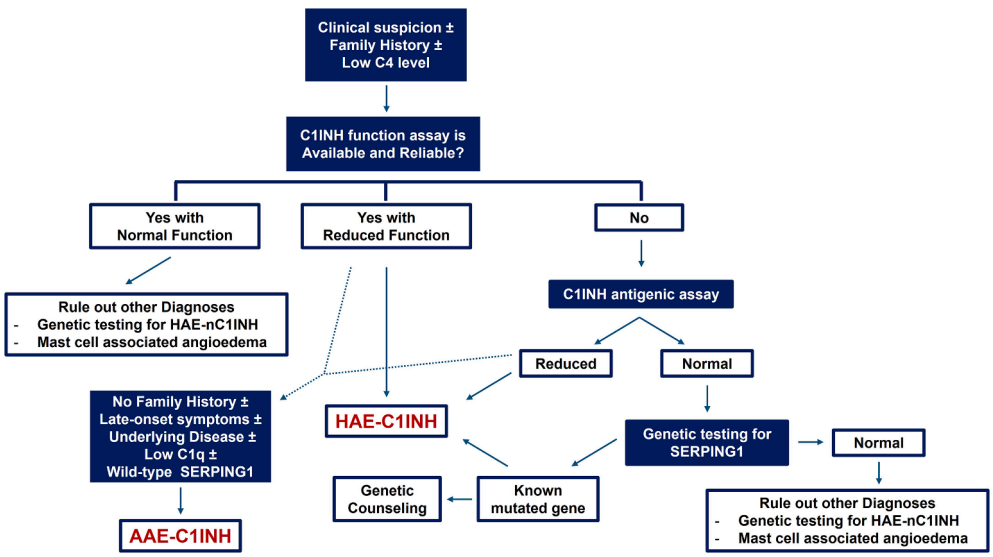

Fig. 5 Diagnostic workup for patients with suspected HAE. Abbreviations: HAE: hereditary angioedema; C1INH: C1 inhibitor; HAE-C1-INH: HAE with C1-INH deficiency; AAE-C1-INH: acquired angioedema; HAE-nC1-INH: HAE with normal C1-INH.

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Variant segregation testing in asymptomatic family members
Variant segregation testing in symptomatic and asymptomatic family members when a variant of uncertain significance is found in an affected proband
Prenatal diagnosis
Preimplantation genetic testing
Newborn diagnosis
Suspicion of gonadal mosaicism (>1 affected child of an unaffected couple)
De novo cases with borderline results on C1-INH functional assays
Genetic epidemiology research
Research on genotype–phenotype correlations
Research on pharmacogenetic aspects of HAE (response to treatment, risk of adverse effects)

Table 2. Situations where *SERPING1* genetic testing can be valuable in HAE-C1-INH patients and their families. *Abbreviation: HAE: Hereditary angioedema; C1-INH: C1 esterase inhibitor; HAE-C1-INH: HAE with C1-INH deficiency*

penetrance and expressivity, as well as current and potential future advances in therapy, should be discussed with the couple in the context of genetic counseling.[168,195,196]

Statement 8	*Agreement level:*
We recommend cascade family testing for HAE when an index case is diagnosed, either through C1-INH testing or genetic testing, as appropriate based on age and diagnosis (HAE-C1-INH vs. HAE-nC1-INH).	**100%**

Fortunately, diagnostic delay in HAE has declined considerably in the last decades, from an average of 21 years in the 1970s to around 7–10 years currently, but >50-year-old previously undiagnosed patients with lifelong symptoms are still being reported.[64,96,197-199] Time to diagnosis varies considerably, from less than 6 months (in <6% of patients) to more than 10 years. Under 40% of patients receive a diagnosis within 1 to 3 years after symptom onset. This gap highlights the need for enhanced education of health care providers regarding warning signs and the interpretation of diagnostic tests, along with improved access to biochemical and genetic testing.[100,199] Delays in HAE diagnosis can lead to serious consequences, including reduced quality of life (QoL), loss of productivity and income, depression, unnecessary medical interventions, increased healthcare costs, and an imminent risk of death. Patients with HAE often require more than 4 visits to emergency departments annually, with 1 in 5 receiving treatment for anaphylaxis. Unnecessary abdominal surgeries, such as appendectomies, along with exploratory diagnostic procedures such as colonoscopy, also are frequent.[197,200,201]

Diagnostic confirmation requires targeted biochemical assessment, including measurement of C4 and C1INH levels and function. Repeat testing should be performed whenever there is discordance between the clinical presentation and laboratory findings. Accurate classification—distinguishing HAE with C1INH deficiency, HAE with normal C1INH, and acquired forms—may be further supported by genetic evaluation, which can be of substantial value in selected and more complex diagnostic scenarios. Organizing the diagnostic process into these 3 interconnected components enhances clinical decision-making, improves diagnostic reliability, and facilitates timely intervention, thereby reducing morbidity, preventing unnecessary procedures, and lowering the risk of potentially fatal laryngeal edema.

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Statement 9	*Agreement level:*
We recommend further efforts to raise awareness in medical schools and among physicians regarding the criteria for suspecting HAE and the appropriate management of angioedema.	**100%**

THE DIFFERENTIAL DIAGNOSIS OF HAE

The differential diagnosis of HAE includes other angioedema endotypes, which may generally be associated with either the kinin system or mast cells.

Regarding the bradykinin-mediated angioedema (BK-AE) endotype, other potential causes should likewise be evaluated. These conditions include AAE-C1-INH from acquired C1 inhibitor deficiency, which is typically linked to autoimmune or lymphoproliferative disorders, and BK-AE with normal C1-INH, often caused by adverse drug reactions, such as to ACE inhibitors.[72,122,141]

Other conditions that may mimic hereditary angioedema should be considered in the differential diagnosis. These conditions include abdominal disorders such as intestinal obstruction, porphyria, and familial Mediterranean fever; localized edema syndromes such as Melkersson-Rosenthal syndrome, Gleich's syndrome, and contact dermatitis; and iatrogenic causes such as reactions to facial fillers, among others.[122,141,202]

Patients with acquired angioedema due to C1-INH deficiency typically lack a family history of recurrent angioedema, and the condition usually presents later in life compared with HAE. The acquired form often is associated with underlying disorders such as lymphoproliferative diseases, including monoclonal gammopathy and lymphoma, or autoimmune conditions, possibilities that should be investigated. As C1q levels are reduced in approximately 75% of cases and C1-INH autoantibodies are detected in 50%–60% of cases, testing is recommended when there is no family history of angioedema (Table 3).[203,204] ACE inhibitors can cause angioedema with a recurrent pattern and, due to their widespread

Angioedema endotype	C1-INH antigenic level	C1-INH functional activity	C4	C1q	Anti-C1-INH	Genetic testing
HAE-C1-INH type 1	<50%	<50%	Decreased (80-95% of time)	Normal	Absent	*SERPING1*
HAE-C1-INH type 2	Normal or elevated	<50%	Decreased (80-95% of time)	Normal	Absent	*SERPING1*
HAE-nC1-INH	Normal	Normal	Normal	Normal	Absent	*FXII*, *PLG*, *ANGPT1*, *KNG1*, *MYOF*, *HS3ST6*, *CPN1*, *DAB2IP*
AAE-C1-INH	Decreased	Decreased	Decreased	Decreased (75% of time)	Present (50% of time)	None
AAE-ACEi	Normal	Normal	Normal	Normal	Absent	None

Table 3. Laboratory and genetic characteristics of bradykinin-mediated angioedema. *Abbreviation: C1-INH: C1 esterase inhibitor; HAE-C1-INH: HAE with C1-INH deficiency; HAE-nC1-INH: HAE with normal C1-INH; AAE-C1-INH; AAE-ACEi*

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use, represent the most common cause of emergency room admissions for BK-AE and a frequent differential diagnosis of HAE. However, HAE can manifest in individuals who were previously asymptomatic and only become symptomatic after initiating these drugs, and C1-INH testing should be performed in such cases. Other medications, including DPP-4 inhibitors (gliptins) and neprilysin inhibitors, also can induce angioedema. Although angiotensin II receptor blockers have been implicated in some reports, their role in causing bradykinin induced angioedema remains controversial.[205-207]

Mast cell–mediated angioedema represents an important differential diagnosis due to its high frequency in the general population. It falls within the clinical spectrum of disorders such as chronic spontaneous urticaria (CSU), encompassing both phenotypes—those exacerbated and those not exacerbated by the use of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs may also induce isolated angioedema in the absence of urticaria among predisposed individuals. Furthermore, IgE-mediated allergic reactions resulting from intermittent allergen exposure should be considered, as they may manifest as recurrent angioedema.[208]

NSAIDs always should be investigated as a potential trigger in patients with or without chronic spontaneous urticaria.[208] However, up to 22% of HAE patients are reported to have been misdiagnosed with drug hypersensitivities, leading to delays in the diagnosis of HAE and adverse clinical outcomes.[209] Similarly, as noted, CSU is a common condition associated with recurrent angioedema, with or without pruritic wheals (hives). Cases of patients affected by both CSU and HAE have been reported, and the presence of wheals should not automatically exclude a diagnosis of HAE. An observational, real-world study that included over 600 HAE patients showed that almost half had been previously misdiagnosed, leading to a median additional delay of 1.7 years to the correct diagnosis, and patients without a family history of HAE had an almost 60% higher likelihood of misdiagnosis.[210]

HAE-CPN patients present a phenotype characterized by both angioedema and urticaria episodes. Carboxypeptidase N plays a crucial role in cleaving and degrading bradykinin, lys-bradykinin, and the anaphylatoxins C3a and C5a. Mutations in *CPN* impair its function, leading to reduced degradation of bradykinin and anaphylatoxins, which may trigger both angioedema and urticaria attacks. This scenario challenges the conventional belief that urticaria is not a characteristic feature of HAE, adding potential complexity to the presentation of the syndrome. The discovery of the HAE-CPN endotype has enhanced understanding of HAE while highlighting the need for a comprehensive approach to diagnosis and treatment.[49,211] However, these findings still require confirmation, and the global prevalence of HAE-CPN is unknown.

Statement 10	*Agreement level:*
We recommend measuring C1q levels and testing C1-INH antibodies when acquired C1-INH angioedema is suspected due to late-onset angioedema, absence of family history, and evidence of an underlying hematologic or autoimmune disease or low C3-C4 levels.	**97%**

Statement 11	*Agreement level:*
We recommend that HAE be considered as a potential diagnosis in patients with recurrent angioedema, even in the presence of medications known to induce angioedema or concomitant urticaria, particularly when there is a positive family history.	**94%**

GENERAL PREEMPTIVE STRATEGIES

Although several triggers for HAE attacks have been identified, including physical trauma and injury, dental work, surgery and manipulation of

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the upper airway, endoscopy or other medical procedures, stress, infections, and intake of estrogens or ACE inhibitors, most episodes are spontaneous.[131,212-216] An individualized risk assessment is warranted, as some patients could be affected by specific triggering factors, especially those related to emotional disturbance.[217] Measures to prevent exposure to frequent triggers include using hormonal contraception with progesterone-only pills (instead of estrogen-based products), avoiding ACE inhibitors if antihypertensive medication is required, following good dental care, receiving vaccines for influenza and COVID-19, and other routine infection-prevention measures. Additionally, hepatitis A/B vaccination should be considered in patients who regularly receive plasma-derived products and fresh frozen plasma (FFP).[218-223] Of note, even though COVID-19 infection has been confirmed as a trigger for HAE attacks, infection severity and the mortality rate associated with this virus do not appear to be higher in HAE patients, and vaccination is considered safe.[223-227]

Statement 12	*Agreement level:*
We recommend educating patients about avoiding common and individual triggers of HAE attacks.	**97%**

TREATMENT

Acute attack and on-demand treatment

For patients experiencing HAE attacks, regardless of the location or severity of symptoms, on-demand treatment (ODT) is essential. Antihistamines, corticosteroids, and epinephrine are ineffective for BK-AE and should not be used, as their use may delay the administration of specific treatments for BK-AE.[137,228,229] All patients with confirmed HAE, even if asymptomatic, must have access to ODT, as the risk of a severe attack is unpredictable and persists throughout life. ODT, regardless of HAE endotype, reduces the risks of asphyxiation, abdominal symptoms, and functional impairment of the limbs.[230,231] When laryngeal or upper airway involvement is evident or suspected, urgent administration of ODT is essential, and immediate emergency care should be sought, with airway patency being the foremost priority in management.[232-234] Compared to delayed treatment, early treatment is associated with better outcomes, including faster symptom resolution, shorter episode duration, and greater efficacy, regardless of the severity of the attack.[235-237]

Prodromal symptoms, traditionally reported in up to 65%–70% of attacks, present an opportunity for early intervention but may lead to overuse of ODT. Recent studies indicate that although the specificity of prodromal symptoms for an attack exceeds 95%, their sensitivity for accurately predicting an attack varies from 18% to 64%, depending on the attack site.[238-241]

Statement 13A	*Quality of evidence:* ⊕⊕◯◯ *Low*
We recommend that every patient, even if asymptomatic, must have ODT available at home because the risk of a serious attack is unpredictable and persists throughout their lifetime.	*Recommendation:* Strong *Agreement levels:* **91% (statement 13A)** **97% (statement 13B)** **100% (statement 13C)**
Statement 13B	
We recommend that ODT be considered for all HAE attacks, which is mandatory when upper airway involvement is detected, and should be instituted as early as possible.	
Statement 13C	
We recommend that in the case of upper airway swelling, ODT should be given as early as possible, and patients should seek emergency care.	

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Four types of ODT for HAE attacks are recognized as effective: exogenous intravenous (IV) C1-INH (plasma-derived [pdC1-INH] or recombinant [rC1-INH]), icatibant, sebetralstat, and ecallantide (Table 4).[19,242-247] Direct comparisons among these options are limited. Both icatibant and C1-INH effectively reduce attack duration, with icatibant offering faster and more convenient self-administration but more frequently requiring a second dose.[242,243] Reported differences in treatment outcomes may partly reflect variations in dosing practices and suboptimal administration.[231,248] When pdC-1INH is used, it should be administered at a dose of 20 IU/kg, rounded to the nearest 500 IU (as vials contain 500 IU) to minimize product waste. The only oral ODT available is sebetralstat and the dose is 2 300 mg tablets. If IV C1-INH, icatibant, sebetralstat or ecallantide is unavailable, solvent detergent-treated plasma (SDP) or FFP may be considered, provided that a safe and reliable supply of these blood products can be ensured.[249-251] Using antifibrinolytics (such as tranexamic acid) or attenuated androgens (such as danazol) for ODT is discouraged because of a lack of benefit. [252]

For over 20 years, exogenous C1-INH has been proven to effectively increase plasma levels of the protein, aiding in regulation of all bradykinin-related cascade systems involved in HAE attacks. It is commercially available in 2 plasma-derived concentrates and 1 recombinant human product for intravenous administration.[253,254] rC1-INH is produced through genetic engineering, and because it is secreted in the milk of transgenic rabbits, it is contraindicated in patients with a known allergy to rabbits. No risk of transmission of hepatitis B/C or HIV exists for these products, and their tolerability is good.[218,255-258] They have been shown to improve QoL in affected patients and are considered safe, with thromboembolic events rarely reported, and when reported are likely attributable to other underlying risk factors or the use of permanent venous devices.[259-262]

Icatibant is a selective competitive antagonist of bradykinin B2 receptors, administered subcutaneously. It reduces vasodilation and capillary permeability, alleviating symptoms and shortening HAE attacks. It generally has an adequate safety and tolerability profile, although mild injection site reactions may occur in up to 97% of cases.[263-266] Ecallantide, which also is administered subcutaneously, directly inhibits plasma kallikrein activity and is effective in the treatment of HAE attacks. However, concerns about a 3%-4% risk of potentially serious hypersensitivity reactions, including anaphylaxis, led the manufacturer to withdraw its application in Europe. Despite this, it remains approved by the US Food and Drug Administration (FDA) for administration exclusively by healthcare providers in the United States.[244,267-269]

Sebetralstat, an oral plasma kallikrein inhibitor, was recently approved by the United States Food and Drug Administration (FDA) as an ODT for HAE, based on the findings of the KONFIDENT study.[270] Adverse events are limited to headache, nevertheless, long-term data from extension studies and RWE are still lacking, precluding appropriate comparisons between this novel agent and existing first-line ODT options.

Statement 14A	*Quality of evidence:* ⊕⊕◯◯ Low
We recommend that first-line ODT for HAE attacks include either IV C1-INH, icatibant or sebetralstat.	*Recommendation:* Strong *Agreement levels:* **97% (statement 14A)** **94% (statement 14B)**
Statement 14B	
We recommend that patients or their caregivers are advised to always carry enough medication to treat at least 2 HAE attacks.	

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Product/drug	Mechanism of action	Formulation	Uses/posology	Regular dose	Approved age group
Plasma-derived C1-INH concentrate (Berinert®)	Replacement	Intravenous	On-demand	20 IU/kg	All
			Short-terrm prophylaxis	20 IU/kg	
		Subcutaneous**	Long-term prophylaxis (twice weekly)	60 IU/kg	≥6 years
Plasma-derived C1-INH concentrate (Cinryze®)	Replacement	Intravenous	On-demand	500 IU	6-11 years
			Short-term prophylaxis	1000 IU	> 12 years
			Long-term prophylaxis (twice weekly)	500-1000 IU twice a week	6-11 years
				1000-2000 IU twice a week	> 12 years
Recombinant C1-INH	Replacement	Intravenous	On-demand Short-term prophylaxis	50 IU/kg, to a max dose of 4200 IU	>2 years
Icatibant	Bradykinin-2 receptorantagonist	Subcutaneous	On-demand	30 mg adults, pediatrics (0.4 mg/kg up to 30 mg)	>2 years***
Sebetralstat	Kallikrein inhibitor	oral	On-demand	600 mg	≥12 years
Ecallantide	Kallikrein inhibitor	Subcutaneous	On-demand	30 mg	≥12 years
Lanadelumab	Plasma kallikrein monoclonal antibody	Subcutaneous	Long-term prophylaxis (every 2–4 weeks)	150/300 mg ≥12 years: 300 mg every 2 weeks 6 to <12 years: 150 mg every 2 weeks 2 to <6 years: 150 mg every 4 weeks	≥2 years

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Berotralstat	Plasma kallikrein inhibitor	Oral	Long-term prophylaxis (daily)	150 mg (110 mg if hepatic impairment, drug interactions or gastrointestinal symptoms)	≥12 years
Garadacimab	Factor 12A inhibitor	Subcutaneous	Long-term prophylaxis	200 mg once a month	≥12 years
Donidalorsen	Prekallikrein inhibitor	Subcutaneous	Long-term prophylaxis	80 mg once a month, but may extend out to every 8 weeks	≥12 years
Solvent detergent-treated plasma	Replacement	Intravenous	On-demand Short-term prophylaxis	200 ml**	All
Fresh frozen plasma	Replacement	Intravenous	On-demand Short-term prophylaxis	400 ml**	All
Attenuated androgens (danazol)*	Induces C1-INH production	Oral	Short-term prophylaxis	200 mg bid-tid for 5 days before and 2 days after the procedure	Adults
			Long-term prophylaxis	≤200 mg/d	
Antifibrinolytics (tranexamic acid)	Decreases activation of factor XII	Oral	Long-term prophylaxis (2-3 doses per day)	30–50 mg/kg** Adults up to 3 g/d	All

Table 4. Drugs used for on-demand treatment and prophylaxis of HAE attacks. IU: International Units (1 IU is equivalent to the amount of C1-INH present in 1 mL of plasma); C1-INH: C1 inhibitor. Adapted from Zuraw et al. [246], Lunn et al. [247], and the products' prescribing information [277–285] *. *Oxandrolone is still used in some countries* **. *Not an FDA-approved formulation or indication in the US* ***. *Not approved for < 18 years in the US*

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Statement 15	*Quality of evidence:*
We suggest considering ecallantide as a second-line option for ODT for HAE attacks only when first-line therapies are not available or feasible. Due to the risk of hypersensitivity reactions, ecallantide must be administered only under the supervision of healthcare personnel.	⊕ ○ ○ ○ Very low
	Recommendation:
	Moderate
	Agreement level:
	82%

Statement 16	*Quality of evidence:*
We recommend SDP/FFP as third-line treatment, with SDP preferred over FFP if available due to a lower risk of viral transmission.	⊕ ○ ○ ○ Very low
	Recommendation:
	Moderate
	Agreement level:
	100%

HAE attacks can follow an unpredictable clinical course, rebound is possible, and multiple attacks can appear in quick succession. Therefore, patients should always have enough medication available to treat at least 2 acute attacks at home. Furthermore, even when these medications are administered in the emergency room, airway management procedures must be readily available. If intubation is indicated but proves difficult or impossible, an emergency cricothyrotomy or tracheotomy should be performed without delay.[271–273]

Statement 17	*Agreement level:*
We recommend that airway interventions (intubation, cricothyroidotomy, or tracheotomy) be promptly considered during the initial evaluation of patients presenting with signs of upper airway involvement.	**91%**

Educational programs focused on the self-administration of on-demand medications, along with national call centers that provide support to patients during acute attacks, have a significant impact on outcomes. Evidence shows that these initiatives can reduce the need for emergency department visits and hospitalizations.[274,275] Emergency services providers at the local or regional level should receive specialized training on awareness (for fast recognition) and management of HAE attacks.[276]

Statement 18	*Agreement level:*
We recommend that patients and their caregivers be educated in how to administer ODT, including self-administration with all available formulations.	**100%**

Short-term Prophylactic Treatment

Pre-procedural or short-term prophylaxis (STP) refers to preventive treatment for HAE prior to exposure to common triggers or situations that may predispose individuals to angioedema attacks, such as dental procedures, surgeries, or procedures involving manipulation of the aero-digestive tract (eg, endoscopies or endotracheal

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intubation). Angioedema typically occurs within 48 hours of exposure[286,287] and affects greater than 1 in 5 patients, with an overall incidence of up to 30% following invasive procedures.[215,288] Prophylaxis administered before a scheduled invasive procedure is associated with a lower risk of HAE attacks in both children and adults, and it should be given with a lead time that ensures that it remains effective throughout the procedure.[289,290]

Statement 19	*Quality of evidence:*
We recommend considering STP before scheduled exposure to potentially attack-triggering invasive procedures, such as dental interventions, upper airway management, or surgery requiring intubation.	⊕⊕⊕◯ Moderate
	Recommendation:
	Strong
	Agreement level:
	100%

The first-line strategy for STP is administration of IV pdC1-INH less than 6 hours before the procedure. Additionally, some evidence suggests that rC1-INH reduces the rate of procedure-related HAE attacks compared to control procedures without prophylaxis. Nevertheless, an HAE attack may occur despite STP use, and ODT should always be readily available.[94,288,291,292] If these medications are unavailable, FFP or attenuated androgens (such as danazol) may be considered as second-line options for patients at high risk. Note that tranexamic acid is not recommended for this indication. For patients with a complete response to long-term prophylaxis (LTP), additional short-term management is generally unnecessary, although situational prophylaxis may be considered during high-risk events, with therapeutic strategies tailored to individual patients and procedures.[290,293–295]

Statement 20	*Quality of evidence:*
We recommend as first-line STP the use of intravenous C1-INH, preferably plasma-derived products.	⊕⊕⊕◯ Moderate
	Recommendation:
	Strong
	Agreement level:
	97%

Statement 21	*Quality of evidence:*
We recommend as second-line STP the use of attenuated androgens or FFP in patients at high risk of developing periprocedural angioedema, but only if IV C1-INH is not available.	⊕⊕◯◯ Low
	Recommendation:
	Strong
	Agreement level:
	91%

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Statement 22	*Agreement level:*
We suggest that ODT be readily available before scheduled exposure to potential triggers, even if the patient has received STP.	**97%**

Statement 23	*Agreement level:*
We suggest that STP may be considered for patients on successful LTP during high-risk events, with therapeutic strategies tailored to individual patients and procedures.	**97%**

Long-term prophylactic treatment

HAE is associated not only with an increased risk of mortality from asphyxiation and the physical burden of acute attacks but also with a significant reduction in health-related QoL, even in patients with low attack frequencies. This impairment is importantly driven by the fear of unpredictable attacks, missed professional or academic opportunities, and the need to avoid potential triggers.[296–299] School and work absenteeism related to HAE is usually high.[300–302] HAE attacks have a negative impact on patients' mental health, with anxiety and depressive disorders being more common in those with frequent attacks.[303] HAE significantly impacts the daily and emotional lives of patients, and while the availability of ODT offers relief, LTP may lead to greater improvements in QoL compared to treatment limited to acute attacks.[297,304,305]

Guidelines for the management of HAE have evolved to reflect advances in therapeutic options and a more patient-centered approach, with a focus on achieving complete disease control and enabling patients to lead normal lives.[306–308] LTP involves the regular use of medication aimed at achieving complete disease control by preventing attacks and improving, or even normalizing, the lives of HAE patients. This benefit has been documented for several currently available therapies.[309–312] Patients whose disease is well controlled using LTP therapy may be symptom-free for years, even for more than a decade.[132]

LTP should be individualized using a treat-to-target approach and regularly reassessed – at least annually – based on disease activity, current and anticipated improvements in QoL, resource availability, age-specific drug approvals (Table 4), treatment burden, and patient preferences, all of which may evolve over time.[313–317] Successful LTP implies full disease control with minimal treatment burden and requires patient adherence, so that a shared decision-making approach is essential.[318–321] Attacks can still occur even in patients under LTP, and on-demand medication must remain available to them.[322,323]

Statement 24	*Quality of evidence:*
We recommend that all patients with HAE are evaluated for LTP at every visit, with a shared decision-making approach.	⊕⊕◯◯ Low
	Recommendation:
	Strong
	Agreement level:
	97%

Statement 25	*Agreement level:*
We recommend that patients have access to ODT, even while receiving LTP.	**97%**

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First-line LTP options include plasma-derived subcutaneous (SC)-C1-INH, lanadelumab, garadacimab, donidalorsen and berotralstat due to their proven efficacy and safety in reducing the frequency, severity, and duration of HAE attacks, as well as improving QoL for patients (Table 4).[324–329] SC administration of pdC1-INH results in more consistent plasma C1-INH concentrations than the IV route and mitigates venous access–related complications, such as thrombosis risk.[330–332] The reported median annualized HAE attack rate in patients receiving LTP with SC-pdC1-INH for over 1 year is approximately 1 event, with mean rescue medication use ranging from 0 to 0.2 times per year.[333,334] Additionally, health-related QoL is significantly improved with SC-pdC1-INH, with benefits persisting for up to 88 weeks.[335]

Lanadelumab, a fully human monoclonal antibody directed against plasma kallikrein, reduces the risk of attacks in the context of LTP, with a low risk of adverse events and a positive impact on QoL.[311,313,336,337] Patients receiving LTP with lanadelumab for >2.5 years have been reported to remain attack-free almost 98% of the time. Moreover, more than 82% and 68% of patients remain attack-free for ≥6 and ≥12 months, respectively.[338] Reported attack rates with this drug are less than 0.3 per month with biweekly dosing, and over 95% of treatment-emergent adverse events are non-serious.[339]

Berotralstat, an oral plasma kallikrein inhibitor, demonstrated efficacy in a pivotal trial, achieving a ~50% reduction in attack rate. Gastrointestinal side effects, such as abdominal pain, have been reported but are generally transient and self-limiting. Some patients may favor the oral formulation of berotralstat because of its convenience and ease of use. Patients should be aware of delayed onset of action. [340–342]

Although no direct comparisons between therapies have been published, indirect comparisons and a Cochrane analysis favor lanadelumab and C1-INH as LTP over berotralstat in terms of efficacy.[343,344] Indirect comparisons of lanadelumab versus C1I-NH have favored the former, but the results require cautious interpretation because the IV C1-INH used in those comparisons is being replaced by the SC product for LTP.[345,346] Although the short-term reduction in attack rate was lower with berotralstat than with SC pdC1-INH and lanadelumab in clinical trials, open-label extension studies have demonstrated a further decrease with berotralstat over time, with attack rates reduced by up to 90.8% after 96 weeks of continuous treatment in good responders. The oral formulation of berotralstat may improve patient uptake or support a seamless transition from previous therapies and is considered safe while preserving the therapeutic effects of prior attenuated androgen use.[347,348] Switching to monotherapy with this drug from injectable products appears to be safe and associated with greater patient satisfaction and enables patients to maintain good disease control.[341,349]

Garadacimab is a human monoclonal antibody, given subcutaneously once a month at 200 mg. The first dose is given as a loading dose (total 400 mg as 2 200 mg injections) and secondary to this onset is rapid. It inhibits activated factor XIIa at the top of the kallikrein-kinin pathway. It is tolerated well with minimal injection site reactions. Prolonged PT, INR, PTT and ULN may occur, but no bleeding or thrombosis were evident during prolonged preclinical trials. In the phase 3 Vanguard trial the attack rate was reduced by 87% compared to placebo.[350,351]

Donidalorsen is an antisense oligonucleotide that blocks the production of prekallikrein in the liver, which is primarily synthesized in the liver. The dose is 80 mg subcutaneous once a month but may be extended out to every 8 weeks. Adverse events include decreased platelets, increased liver enzyme levels, and anaphylaxis, but these events were extremely limited, and there is no need to monitor CBC or liver enzymes. Efficacy of every 4- and 8-weeks injections was 81% and 55%, respectively, compared to placebo. Because of a delay in onset of the donidalorsen, when data were compared to placebo starting at week 5, the 4- and 8-weeks dose reduced attacks by 87% and 60%, respectively.[352]

Some patients with HAE-nC1-INH have been successfully treated with lanadelumab, IV C1-INH, garadacimab or berotralstat; however genetic

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testing is essential to determine which medication would be most appropriate. [353–356] In those with negative genetic testing lanadelumab failed to demonstrate any significant benefit.[357]

Statement 26	*Quality of evidence:*
We recommend SC pdC1-INH, lanadelumab, berotralstat, garadacimab, or donidalorsen as first-line options for LTP.	⊕⊕◯◯ Low
	Recommendation:
	Strong
	Agreement level:
	94%

When first-line treatments are unavailable, IV pdC1-INH (approved for LTP in some countries) is a second-line option, supported by scientific evidence of its efficacy. However, it has disadvantages, such as the need for venous access, high cost, and frequent administrations due to its short half-life. Other second-line options include attenuated androgens, which have been used for this indication for many years, and tranexamic acid, which is less effective and supported by limited evidence.[294,358–362]

Attenuated androgens have been used for many years with good efficacy at doses of up to 600 mg per day. However, due to their adverse effects, current recommendations limit the dose to 200 mg per day, which reduces side effects but diminishes efficacy. Attenuated androgens are strongly associated with virilization in women, dyslipidemia, and hepatotoxicity, with an increased risk of hepatic neoplasms. They cannot be used during pregnancy or in the pediatric and adolescent populations because they interfere with growth. We suggest monitoring blood pressure and periodically screening patients with liver ultrasound and blood tests to assess the metabolic profile and liver function.[363–368]

Tranexamic acid shows mediocre efficacy in HAE-C1-INH but performs better in HAE-nC1-INH, particularly in cases involving PLG or FXII variants. It has also been used in special situations, such as pregnancy and childhood, when other specific drugs are unavailable. It has a better safety profile than attenuated androgens but has been associated with a low incidence of gastrointestinal effects and ocular disorders and an increased risk of thrombosis.[369]

Statement 27	*Quality of evidence:*
We suggest IV C1-INH, attenuated androgens (at the lowest effective dose, preferably not exceeding 200 mg per day), or antifibrinolytics as second-line options for LTP in patients for whom first-line therapies are not available, not feasible, or not tolerated.	⊕⊕◯◯ Low
	Recommendation:
	Moderate
	Agreement level:
	94%

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Statement 28	*Quality of evidence:*
We recommend semi-annual monitoring when using androgens, including a complete blood count, chemistry panel, lipid panel, and routine urinalysis, along with annual liver ultrasound.	⊕ ○ ○ ○ Very low
	Recommendation:
	Moderate
	Agreement level:
	97%

Ongoing monitoring of patients on LTP should include regular assessment of disease activity, treatment burden, and QoL, ideally through patient-reported outcomes collected using validated tools.[301,370,371] These tools, which are not all specific to HAE, include the Angioedema Activity Score, the Hereditary Angioedema Activity Score, the Angioedema Quality of Life Questionnaire, the Hereditary Angioedema Quality of Life Questionnaire, and the Angioedema Control Test.[371,372] Some of them have been translated into multiple languages and validated in various populations.[373-375] The Angioedema Activity Score is especially valuable for documenting attack frequency, a practice that should be encouraged among all patients,

Statement 29	*Agreement level:*
We recommend that all patients with HAE use validated instruments to assess disease activity, severity, disease control, treatment efficacy, and QoL, and that they undergo regular reassessments to ensure optimal therapeutic management.	**97%**

and has shown strong reliability and consistency.[376,377]

Management in children

In pediatric patients, diagnosis is especially challenging because of the high prevalence of abdominal pain in this age group and the frequent misdiagnosis of upper airway edema as allergic asthma, pharyngitis or epiglottitis. Asphyxiation in children may develop more quickly because of the smaller diameter of the airway.[137] Symptoms of HAE are rare in neonates, but more than 50% of patients develop symptoms before age 10 years, making it essential to consider appropriate management strategies for children.[273,378] A case of an attack in utero has been described.[379]

Attack severity tends to increase during puberty and adolescence, and early onset of symptoms predicts a more severe disease course.[380,381] In diagnosing of HAE in this population, clinicians should consider that in children under age 1 year, C1-INH levels and functional activity are typically low, which may lead to false-positive tests. Genetic testing is recommended to ensure an accurate and timely diagnosis.[137,382-385]

Statement 30	*Agreement level:*
We recommend genetic testing for children age <1 year if HAE is considered a likely diagnosis. In older children, C1-INH measurements should be considered the first step.	**88%**

Treatment of HAE in pediatric patients includes ODT, STP, and LTP, similar to treatment strategies used in adults. Additionally, an individualized action plan, avoidance of potential triggers, and consideration of QoL aspects related to both the disease and its therapy are essential.[386-388] C1-INH is approved for all indications in children of all ages, as it is considered safe and effective. Icatibant is also approved for ODT in children over age 2 years, sebetralstat (approved for 12 years and older) whereas SDP and FFP are considered second-line options for ODT or

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STP.[270,295,325,388-395] Lanadelumab (approved for children aged 2 years or older), berotralstat (approved for children aged 12 years or older), garadacimab (approved for 12 years and older), donidalorsen (approved for 12 years and older) and antifibrinolytics (if other options are unavailable) may be used for LTP.[350,352,396-400] Caregivers, including educators, should be provided with comprehensive information and instructions about the condition and its management. ODT must be readily accessible at all times, including at school and during activities such as holidays, sleepovers, and field trips.[382,401]

Statement 31	*Quality of evidence:*
For children with HAE, we recommend first-line ODT with IV pdC1-INH, icatibant or sebetralstat.	⊕ ○ ○ ○ Very low
	Recommendation:
	Strong
	Agreement level:
	97%

Statement 32	*Quality of evidence:*
For children with HAE, we suggest using SDP or FFP as a second-line option for ODT if first-line drugs are unavailable.	⊕ ○ ○ ○ Very low
	Recommendation:
	Moderate
	Agreement level:
	97%

Statement 33	*Quality of evidence:*
For children with HAE, we recommend first-line STP with IV pdC1-INH.	⊕ ○ ○ ○ Very low
	Recommendation:
	Strong
	Agreement level:
	97%

Statement 34	*Quality of evidence:*
For children with HAE, we suggest second-line STP with SDP or FFP if first-line drugs are unavailable.	⊕ ○ ○ ○ Very low
	Recommendation:
	Moderate
	Agreement level:
	94%

Management in pregnant and breastfeeding patients

Pregnancy has variable effects on the prevalence and frequency of HAE attacks. It has been reported to both mitigate the risk in some affected patients and aggravate activity in others. In multiparous patients, the course of symptoms during previous pregnancies does not always correlate with current risk.[402-405] In rare cases, HAE may first be suspected during pregnancy. It is important to note that C1-INH levels are normally decreased during pregnancy, which can lead to false-positive results. If clinical suspicion remains high, genetic testing should be considered.[406] Although labor and vaginal

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Statement 35	*Quality of evidence:*
For children with HAE, we recommend first-line LTP with SC pdC1-INH, lanadelumab, berotralstat, garadacimab, or donidalorsen.	⊕⊕◯◯ Low
	Recommendation:
	Strong
	Agreement level:
	91%

Statement 36	*Quality of evidence:*
For children with HAE, we suggest second-line LTP with antifibrinolytics if first-line drugs are unavailable.	⊕◯◯◯ Very low
	Recommendation:
	Moderate
	Agreement level:
	91%

delivery uncommonly trigger HAE attacks, angioedema crises may still occur up to 48 hours postpartum. Therefore, close monitoring for at least 72 hours is recommended, with ODT readily available.[196] STP for delivery is not usually indicated, but it can be considered in special cases, using IV pdC1-INH.[407]

Plasma-derived C1-INH is considered safe and effective for on-demand treatment of HAE attacks during pregnancy, whereas all other drugs are off-label alternatives. Icatibant has emerging evidence of safety, but it has been used only during a limited number of pregnancies.[408-414] SDP or FFP can be deemed third-line options for this indication.[415]

STP with IV pdC1-INH is recommended for patients undergoing invasive procedures such as chorionic villus sampling, amniocentesis, induced surgical abortion, or cesarean section (the latter should include epidural anesthesia).[196]

Statement 37	*Quality of evidence:*
For pregnant patients with HAE, we recommend first-line ODT with IV pdC1-INH.	⊕◯◯◯ Very low
	Recommendation:
	Strong
	Agreement level:
	100%

Statement 38	*Quality of evidence:*
For pregnant patients with HAE, on-demand emergency treatment with icatibant for potentially severe attacks may be considered if pd-C1-INH is unavailable or has failed.	⊕◯◯◯ Very low
	Recommendation:
	Weak
	Agreement level:
	97%

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Statement 39	*Quality of evidence:*
For pregnant patients with HAE, third-line ODT with SDP or FFP might be reasonable.	⊕ ○ ○ ○ Very low
	Recommendation:
	Weak
	Agreement level:
	94%

Statement 40	*Quality of evidence:*
We recommend that patients with HAE undergoing uncomplicated vaginal delivery should not receive STP, except in cases of high attack frequency.	⊕ ⊕ ○ ○ Low
	Recommendation:
	Strong
	Agreement level:
	85%

Several case reports of successful use of pdC1-INH for HAE LTP during pregnancy have been published, even for patients affected with HAE-nC1-INH.[353,403,416-422] Antifibrinolytics are considered safe and could be effective in this context if first-line therapy is not available, whereas attenuated androgens are strongly contraindicated.[423-426]

Breastfeeding is not discouraged in patients with HAE, and treatment options generally follow the same guidelines as during pregnancy. Treatment with plasma-derived products and tranexamic acid is considered safe during breastfeeding, while androgens should be avoided.[408,427,428]

Statement 41	*Quality of evidence:*
For pregnant patients with HAE undergoing invasive procedures, or C-section we recommend STP with IV pdC1-INH.	⊕ ○ ○ ○ Very low
	Recommendation:
	Moderate
	Agreement level:
	97%

Patient support, home-based therapy, self-administration, and additional management approaches

Similar to other rare genetic disorders, patient organizations and support/advocacy groups play

Statement 42	*Quality of evidence:*
Due to the potential need for an emergency cesarean section, we suggest that LTP should be considered in pregnant patients with HAE who are at higher risk of severe attacks or complications during childbirth.	⊕ ○ ○ ○ Very low
	Recommendation:
	Strong
	Agreement level:
	91%

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Statement 43	*Quality of evidence:*
For pregnant patients with HAE, we suggest first-line LTP with subcutaneous or IV pdC1-INH.	⊕ ○ ○ ○ Very low
	Recommendation:
	Moderate
	Agreement level:
	91%

Statement 44	*Quality of evidence:*
For pregnant patients with HAE, we suggest second-line LTP with IV rC1-INH.	⊕ ○ ○ ○ Very low
	Recommendation:
	Moderate
	Agreement level:
	88%

Statement 45	*Quality of evidence:*
In pregnant patients with HAE, antifibrinolytics may be considered for third-line LTP only when first- and second-line therapies are not available or feasible, and under close medical supervision.	⊕ ○ ○ ○ Very low
	Recommendation:
	Weak
	Agreement level:
	91%

Statement 46	*Quality of evidence:*
We recommend that childbirth be managed in a hospital setting with ODT available when a pregnant patient has HAE.	⊕ ○ ○ ○ Very low
	Recommendation:
	Strong
	Agreement level:
	100%

a crucial role for individuals with HAE and their families and caregivers. These organizations engage in a wide range of activities that can vary based on regional needs, particularly regarding access to care (Table 5).[429-431] Hereditary Angioedema International (HAEi) serves as the umbrella organization for HAE associations worldwide, offering patient information and advocating for enhanced research, diagnosis, and access to treatments. HAEi is a global nonprofit organization dedicated to supporting individuals with HAE and promoting awareness of the condition.[432]

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Statement 47	*Agreement level:*
We recommend that patients be advised to contact or establish local/regional patient associations focused on advocating for their condition, in collaboration with HAEi.	**94%**

Self-administration and home therapy are available for all C1-INH products, icatibant, berotralstat, sebetralstat, donidalorsen, garadacimab, and lanadelumab. These strategies enhance QoL and outcomes by enabling early treatment and preventing attacks through their use as STP and LTP. Their use should be encouraged, with an individualized approach, for all patients with HAE, through direct decision-making with the patient or, if relevant, a caregiver.[433–436] Self-administration is feasible even for 8-year-olds and for older adults, provided that a home therapy partner or caregiver can be properly trained, if needed.[437–439] Data suggest that self-administration of icatibant reduces and delays the need for Emergency Department visits, which are typically required when attacks affect critical anatomical sites.[440]

Patients should be encouraged to always carry their ODT, even if they are on LTP.[441–444] Moreover, identification cards detailing the condition and therapy are essential for proper management of the disease. An example of an emergency identification card can be accessed at HAEi Emergency Cards (https://haei.org/resources/emergency-cards/). Comprehensive and integrated care, led by a healthcare professional with expertise in HAE, improves outcomes and helps patients address challenges common to many rare disorders, including HAE. These challenges include delays in diagnosis, limited access to medication, and insufficient referrals to specialists by general practitioners to address questions and concerns related to the disease.[445,446] Although there are few experts in HAE worldwide, advances in telemedicine, which was proven effective during the COVID-19 pandemic, could help bridge the gap between patients and specialized care.[447–450] Additionally, efforts should be made to educate healthcare professionals and decision-makers about the importance of HAE, as well as to develop local guidelines that consider differences in access to diagnosis and treatment.[56,59,451]

Statement 48	*Quality of evidence:*
We recommend that HAE patients be managed by physicians with expertise in the condition, with the support of a referral center.	⊕ ○ ○ ○ Very low
	Recommendation:
	Strong
	Agreement level:
	97%

Molecules in development and future perspectives

The treatment of HAE has advanced rapidly in recent years, with the continuous development of new drugs for acute attacks and particularly for LTP. These drugs primarily target the KKS through various molecular strategies.[452] Sebetralstat, an oral plasma kallikrein inhibitor, was recently approved by the FDA as an ODT for HAE, based on findings from the phase 3 KONFIDENT trial (NCT05259917). That study demonstrated that sebetralstat provided a faster onset of symptom relief, a greater reduction in attack severity, and more rapid complete resolution of HAE attacks compared to placebo. As an orally administered therapy, sebetralstat offers the added benefit of convenience and ease of use, which may improve treatment adherence and allow for earlier intervention during attacks.[270,453–455] Garadacimab, also newly approved, has demonstrated efficacy and is associated with high treatment satisfaction and improved QoL. It

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Providing information to newly diagnosed patients on self-care, available therapies and access to treatment
Offering updates on disease management and clinical trial opportunities for patients
Increasing awareness of the condition among health authorities and the general community
Achieving recognition of the disease as a serious, potentially disabling, and life-threatening condition
Advocating for research into better diagnostic methods and increasing the availability of testing
Advocating for research into improved treatments, including the development of new, safer, and more effective drugs or strategies (such as appropriate dosing and de-escalation)
Advocating for global access to diagnosis and treatment, especially in low-income countries

Table 5. Activities within the scope of patients' organizations

offers LTP for patients over age 12 years with HAE-C1-INH, with sustained effects lasting beyond 2 years.[350,351,456] Donidalorsen is an antisense oligonucleotide administered subcutaneously every 4 to 8 weeks that specifically reduces prekallikrein production and was newly approved. In recently published findings from a phase 2 study and a phase 3, double-blind, randomized trial, donidalorsen was shown to significantly and safely reduce HAE attack rates and improve QoL compared to placebo.[352,457]

Deucrictibant is a small molecule bradykinin B2 receptor antagonist in clinical development, exhibiting high affinity, potent antagonistic activity (20 times greater than icatibant), and strong selectivity.[458] Two distinct formulations are being investigated: immediate-release capsule (previously referred to as PHVS416) and extended-release tablet (previously referred to as PHVS719). Preliminary study results on the use of deucrictibant for the treatment of HAE attacks have demonstrated its efficacy.[459] ADX-324, a small-interfering RNA, is currently being investigated for HAE and looks promising to be an every 6 month subcutaneously injected medication.[460] Navenibart, a human monoclonal antibody targeting plasma kallikrein and engineered with Fc region modifications that extend its half-life to approximately 100 days, has advanced into phase 3 clinical trials. The therapy is being administered subcutaneously every 3 to 6 months in the ongoing phase 3 Alpha-Orbit study.[461] Additionally, NTLA-2002, an in vivo gene-editing therapy using CRISPR-Cas9 technology, targets the gene encoding kallikrein B1 and is presently in phase 3 trials. The goal of this therapy is to provide lifelong control of HAE attacks with just a single dose. The results of a recent phase 1 and 2 studies suggest that NTLA-2002 is safe and may lead to durable reductions in plasma kallikrein levels.[462,463] A summary of clinical trials investigating new treatments for HAE can be found at ClinicalTrials.gov - Hereditary Angioedema (https://clinicaltrials.gov/search?cond=Hereditary%20angioedema).

HAE IN THE REAL WORLD: REGIONAL REALITIES AND HOW TO BRIDGE THE GAP

By definition, clinical trials are conducted in controlled settings with carefully selected patients and meticulous monitoring of treatment efficacy and safety. Conversely, RWE obtained post-commercialization is valuable for translating clinical trial findings to the broader population and for identifying gaps in patient needs, treatment adherence, and access.[464]

Regarding diagnosis, the availability and quality of functional tests for C1-INH vary globally. Therefore, physicians are encouraged to tailor these guidelines to their specific settings and advocate to health authorities and local laboratories to implement the necessary tests, improving diagnosis and reducing the morbidity and mortality associated with HAE.[465]

The impact of HAE on health-related QoL has been confirmed in studies conducted in several

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low- and middle-income countries.[81,305,466,467] RWE on HAE treatment has shown that several drugs, including pdC1-INH concentrate, recombinant C1-INH, icatibant, berotralstat, sebetralstat, garadacimab, donidalorsen, and lanadelumab, perform in line with their label indications and improve QoL. The recent approval of several generics for icatibant have decreased cost and hopefully will allow broader access. Trends suggest that newer treatments are increasingly being used in countries where they are available, often with concomitantly reduced use of older drugs such as attenuated androgens and tranexamic acid. Adverse effect profiles reported in RWE also are consistent with those observed in clinical trials.[89,468–472]

Nevertheless, even with recent advances, LTP is still not the standard of care, even in high-income countries, with only about 50% of patients currently receiving it. Among those on LTP, the use of emergency services remains common, and older treatments continue to be widely used, particularly in lower-income countries.[69,294,473–482] Despite their greater effectiveness, newer drugs are associated with higher costs that clearly limit their availability, particularly in low- and middle-income countries.[483] Several solutions have been proposed to address the lack of access to first-line, high-cost treatments for HAE. These strategies include the use of lower-efficacy but safe alternatives, such as plasma-derived products, tranexamic acid, or low-dose attenuated androgens. Additional strategies involve local or regional fractionation and production of off-patent medications, as well as participation in international global access programs.[465] Pharmacoeconomic analyses of HAE treatment with targeted therapies have been limited and require additional RWE data, although efforts are under way to address some of these gaps.[483–486]

Additionally, physicians continue to demand more efficient and better-tolerated medications, easier treatment administration, and less-expensive therapies, even in high-income countries.[487] In countries where access to ODT for HAE is guaranteed by law (which is not the case everywhere), long delays in diagnosis still have prevented many patients from receiving adequate care.[79] Of note, the local availability of patient support groups and regional or local guidelines, which are more common in countries where newer drugs are approved, has been associated with improved access to care.[487] An additional recommended strategy to improve understanding of disease epidemiology and to optimize allocation of diagnostic and therapeutic resources is the implementation of HAE registries. Some country-specific and international efforts are already under way in this regard.[62,64,70,75,101,102,261,447,488,489,490-495]

In addition to these regional and structural challenges, emerging digital technologies warrant consideration for their potential impact on HAE diagnosis and management. Artificial intelligence (AI)–assisted tools are increasingly being developed for rare diseases and may offer meaningful benefits in selected settings. Clinical Decision Support Systems (CDSS) have the potential to support earlier recognition of symptom patterns, improve risk stratification, and assist clinicians in therapeutic decision-making. Likewise, digital symptom diaries, mobile-based monitoring tools, and patient-facing platforms may enhance the characterization of attack frequency, triggers, and treatment responses, thereby contributing to more individualized care. Although these technologies are not yet incorporated into the current recommendations, future versions of this guideline should monitor their development and evaluate their potential value for clinical decision support, patient education, and long-term disease management. Incorporating these innovations may strengthen the forward-looking nature of the guideline and align it with global trends in digital healthcare.

Abbreviations

AAE-C1-INH, acquired C1-INH deficiency; ACE, angiotensin-converting enzyme; ACEi, angiotensin-converting enzyme inhibitor; Bk2R, bradykinin B2 receptor; BK-AE, Bradykinin-mediated angioedema; C1-INH, C1 esterase inhibitor; CSU, chronic spontaneous urticaria; DPP-4 inhibitors (gliptins), dipeptidyl peptidase-4 inhibitors; FDA, Food and Drug Administration; FFP, fresh frozen plasma; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HAE, Hereditary angioedema; HAE-C1-INH, HAE with C1-INH deficiency; HAE with serine protease inhibitor (SERPING1) mutation; HAE-nC1-INH, HAE with normal C1-INH; HAE-ANGPT1, HAE with angiopoietin-1 (ANGPT1) mutation; HAE-CPN1, HAE with carboxypeptidase N (CPN1) mutation; HAE-DAB2IP, HAE with DAB2-interacting protein

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(DAB2IP) mutation; HAE-FXII, HAE with factor 12 (F12) mutation; HAE-HSST, HAE with heparan sulfate-3-O-sulfotransferase 6 (HS3ST6) mutation; HAE-KNG1, HAE with kininogen 1 (KNG1) mutation; HAE-MYOF, HAE with myoferlin (MYOF) mutation; HAE-PLG, HAE with plasminogen (PLG) mutation; HAE-UNK, HAE of unknown origin; HA4E or HAAAAE, Hereditary, recurrent Angioedema, Abdominal angioedema/pain, Absence of urticaria, Absence of response to antihistamines, and Estrogen association; HAEi, Hereditary Angioedema International; IU, International Units; IV, intravenous; KKS, kallikrein–kinin system; LTP, long-term prophylaxis; NSAIDs, nonsteroidal anti-inflammatory drugs; ODT, on-demand treatment; pdC1-INH, plasma-derived C1-INH; PICO, Population, Intervention, Comparator, and Outcome; QoL, quality of life; rC1-INH, recombinant C1-INH; RWE, Real-World Evidence; SC-C1-INH, subcutaneous (SC)-C1-INH; *SERPING1*, serine protease inhibitor gene; STP, short-term prophylaxis; SDP, solvent detergent-treated plasma; VEGF, vascular endothelial growth factor; WAO, World Allergy Organization

List of Organizations that Reviewed and Endorsed

The 2025 WAO Guidelines for the Classification, Diagnosis, and Treatment of Hereditary Angioedema, with Consideration of Worldwide Disparities; Algerian Academy of Allergology; Allergy Society of Ghana (ASG); Allergy Society of South Africa (ALLSA); Allergy Society of Tanzania (ASOT); Allergy, Asthma and Immunology Association of Thailand (AAIAT); American Academy of Allergy Asthma and Immunology (AAAAI); American College of Allergy, Asthma and Immunology (ACAAI); Argentine Association of Allergy and Clinical Immunology (AAAeIC); Armenian Association of Immunology and Allergy; Asia Pacific Academy of Pediatric Allergy, Respirology and Immunology (APAPARI); Asia Pacific Association of Allergy, Asthma and Clinical Immunology; Austrian Society of Allergology and Immunology (ÖGAI); Bangladesh Society of Allergy and Immunology; Belgian Society of Allergy and Clinical Immunology (BelSACI); Brazilian Society of Allergy and Immunology (ASBAI); British Society for Allergy and Clinical Immunology (BSACI); Bulgarian National Society of Allergology; Chilean Society of Allergy and Immunology (SCAI); Colombian Allergy, Asthma, and Immunology Association (ACAAI); Commonwealth of Independent States Society of Allergology and Immunology (CIS Society); Costa Rican Association of Allergology; Cuban Society of Allergy, Asthma and Clinical Immunology; Czech Society of Allergology and Clinical Immunology (CSAKI); Dominican Society of Allergy, Asthma, and Immunology; Egyptian Society of Pediatric Allergy and Immunology (ESPAI); Federation of Specialists in Immunology and Allergology (FSIA); Finnish Society of Allergology and Clinical Immunology; French Society of Allergology (SFA); Georgian Association of Allergology and Clinical Immunology (GAACI); Guatemalan Allergy, Asthma and Clinical Immunology Association (ASGUAI); Haitian Society of Allergy and Immunology; Hellenic Society of Allergology and Clinical Immunology (EEaKa); Hong Kong Institute of Allergy; Indian College of Allergy, Asthma and Applied Immunology; Iranian Society of Asthma and Allergy; Israel Association of Allergy and Clinical Immunology (IAACI); Italian Association of Territorial and Hospital Allergists (AAIITO); Italian Society of Allergy, Asthma and Clinical Immunology (SIAAIC); Japanese Society of Allergology (JSA); Kazakhstan Association of Allergology and Clinical Immunology; Korean Academy of Allergy, Asthma and Clinical Immunology (KAAACI); Kuwait Society of Allergy and Clinical Immunology; Latin American Society of Allergy and Immunology (SLaai); Lebanese Society of Allergy and Immunology (LSAI); Lithuanian Association of Allergy and Asthma; Mexican College of Allergy and Clinical Immunology (CMICA); Monoglian Society of Allergology; Oman Society of Allergy and Clinical Immunology (OSACI); Pakistan Allergy, Asthma and Immunology Society (PAAIS); Panamanian Association of Allergology and Clinical Immunology; Pan-Arab Society of Allergy, Asthma, and Immunology (PASAAI); Paraguayan Society of Immunology and Allergy (SPAAI); Peruvian Society of Allergy and Immunology; Portuguese Society of Allergology and Clinical Immunology (SPAIC); Qatar Allergy and Immunology Society (QAIS); Saudi Allergy, Asthma & Immunology Society; Turkish National Society of Allergy and Clinical Immunology (TNSACI); Ukrainian Society of Specialists for Immunology; Allergology and Immunorehabilitation (UTIAI); Uruguayan Society of Allergology; Venezuelan Society of Allergy, Asthma, and Immunology

Acknowledgments

The authors wish to acknowledge all individuals living with hereditary angioedema, whose experiences continue to guide and motivate advancements in clinical care. We also extend our sincere appreciation to the healthcare professionals worldwide who are devoted to the diagnosis, treatment, and long-term management of this condition. Furthermore, we are grateful to the supporting medical societies, patient advocacy groups, and institutions whose collaboration and commitment made the development of this guideline possible.

Funding

The World Allergy Organization supported the development of this guideline.

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Consent of authors for publication

All authors have reviewed the final version and approved it for publication in WAO Journal.

Declaration of competing interest

The 2025 WAO HAE Guidelines did not receive any influence from pharmaceutical companies or any organizations involved in the care of patients with the disease. All authors fully disclosed their conflicts of interest, and no author experienced any interference from industry. In addition, the Delphi voting process was conducted anonymously, ensuring independent expert judgment and minimizing any potential bias. No information is provided regarding the licensing of the drugs mentioned for the treatment of the condition. It is the duty of the treating physician to adhere to local regulations.

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REFERENCES

1. Osler W. Hereditary angio-neurotic oedema. 1. *The American Journal of the Medical Sciences (1827-1924)*. 1888;95(4):362.

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2. Gadek JE, Hosea SW, Gelfand JA, Santaella M, Wickerhauser M, Triantaphyllopoulos DC, et al. Replacement therapy in hereditary angioedema: successful treatment of acute episodes of angioedema with partly purified C1 inhibitor. *N Engl J Med*. 1980;302(10):542–546.
3. Craig TP, Aygoren-Pursun E, Bork K, Bowen T, Boysen HB, Farkas H, et al. WAO guideline for the management of hereditary angioedema. *World Allergy Organization Journal*. 2012:182–199.
4. Maurer M, Magerl M, Ansotegui I, Aygoren-Pursun E, Betschel S, Bork K, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2017 revision and update. *Allergy*. 2018:1575–1596.
5. Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. *Allergy*. 2022;77(7):1961–1990.
6. Kruer MC, Steiner RD. The role of evidence-based medicine and clinical trials in rare genetic disorders. *Clin Genet*. 2008;74(3):197–207.
7. Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products [Internet] *OJ L Dec*. 1999;16. Available from: http://data.europa.eu/eli/reg/2000/141/oj/eng.
8. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology*. 2011;64(4):383–394.
9. Pai M, Iorio A, Meerpohl J, Taruscio D, Laricchiuta P, Mincarone P, et al. Developing methodology for the creation of clinical practice guidelines for rare diseases: A report from RARE-Bestpractices. *Rare Diseases*. 2015;3(1), e1058463.
10. AI Chat for scientific PDFs | SciSpace [Internet] [cited 2023 Nov 14]. Available from: https://typeset.io.
11. McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. *Int J Clin Pharm*. 2016;38:655–662.
12. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328(7454):1490.
13. Schünemann H, Brożek J, Guyatt G, Oxman A, eds. *GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group*. 2013. Available from guidelinedevelopment.org/handbook.
14. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.4. Chapter 2: Determining the scope of the review and the questions it will address. Cochrane*; 2023 [Internet]. [cited 2024 Jul 7]. Available from: https://training.cochrane.org/handbook/current/chapter-02.
15. GRADEpro GDT. *GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime*. 2024. Available from gradepro.org.
16. Pai M, Yeung CHT, Akl EA, Darzi A, Hillis C, Legault K, et al. Strategies for eliciting and synthesizing evidence for guidelines in rare diseases. *BMC Medical Research Methodology*. 2019;19(1):67.
17. Taruscio D, Morciano C, Laricchiuta P, Mincarone P, Palazzo F, Leo C, et al. RARE-Bestpractices: a platform for sharing best practices for the management of rare diseases. *Orphanet Journal of Rare Diseases*. 2014;9(1), O14.
18. Depetri F, Tedeschi A, Cugno M. Angioedema and emergency medicine: From pathophysiology to diagnosis and treatment. *Eur J Intern Med*. 2019;59:8–13.
19. Zuraw BL. Clinical practice. Hereditary angioedema. *N Engl J Med*. 2008;359(10):1027–1036.
20. Barnett AF. Hereditary Angioneurotic Edema: A Remarkable Family History. *Calif Med*. 1948;69(5):376–380.
21. 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.
22. Schapira M, Scott CF, Colman RW. Contribution of plasma protease inhibitors to the inactivation of kallikrein in plasma. *J Clin Invest*. 1982;69(2):462–468.
23. Schreiber AD, Kaplan AP, Austen KF. Inhibition by C1INH of Hagemann factor fragment activation of coagulation, fibrinolysis, and kinin generation. *J Clin Invest*. 1973;52(6):1402–1409.
24. Gigli I, Mason JW, Colman RW, Austen KF. Interaction of plasma kallikrein with the C1 inhibitor. *J Immunol*. 1970;104(3):574–581.
25. Davis AE, Whitehead AS, Harrison RA, Dauphinais A, Bruns GA, Cicardi M, et al. Human inhibitor of the first component of complement, C1: characterization of cDNA clones and localization of the gene to chromosome 11. *Proc Natl Acad Sci U S A*. 1986;83(10):3161–3165.
26. Bock SC, Skriver K, Nielsen E, Thøgersen HC, Wiman B, Donaldson VH, et al. Human C1 inhibitor: primary structure, cDNA cloning, and chromosomal localization. *Biochemistry*. 1986;25(15):4292–4301.
27. Stoppa-Lyonnet D, Tosi M, Laurent J, Sobel A, Lagrue G, Meo T. Altered C1 Inhibitor Genes in Type I Hereditary Angioedema. *New England Journal of Medicine*. 1987;317(1):1–6.
28. Fields T, Ghebrehiwet B, Kaplan AP. Kinin formation in hereditary angioedema plasma: evidence against kinin derivation from C2 and in support of "spontaneous" formation of bradykinin. *J Allergy Clin Immunol*. 1983;72(1):54–60.
29. Nussberger J, Cugno M, Cicardi M, Agostoni A. Local bradykinin generation in hereditary angioedema. *Journal of Allergy and Clinical Immunology*. 1999;104(6):1321–1322.
30. Han ED, MacFarlane RC, Mulligan AN, Scafidi J, Davis AE. Increased vascular permeability in C1 inhibitor–deficient mice mediated by the bradykinin type 2 receptor. *J Clin Invest*. 2002;109(8):1057–1063.
31. Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet*. 2000;356(9225):213–217.
32. Binkley KE, Davis A. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol*. 2000;106(3):546–550.
33. Wilkerson RG, Moellman JJ. Hereditary Angioedema. *Immunol Allergy Clin North Am*. 2023;43(3):533–552.

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34. INSERM US14– ALL RIGHTS. Orphanet: Hereditary angioedema [Internet]. [cited 2023 Oct 21]. Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=91378.

35. Phenotypic Series - PS106100 - OMIM [Internet]. [cited 2023 Oct 21]. Available from: https://www.omim.org/phenotypicSeries/PS106100.

36. Donaldson VH, Ratnoff OD, Dias Da Silva W, Rosen FS. Permeability-increasing activity in hereditary angioneurotic edema plasma. II. Mechanism of formation and partial characterization. *J Clin Invest*. 1969;48(4):642–653.

37. Sharma J, Jindal AK, Banday AZ, Kaur A, Rawat A, Singh S, et al. Pathophysiology of Hereditary Angioedema (HAE) Beyond the SERPING1 Gene. *Clin Rev Allergy Immunol*. 2021;60(3):305–315.

38. Marcelino-Rodriguez I, Callero A, Mendoza-Alvarez A, Perez-Rodriguez E, Barrios-Recio J, Garcia-Robaina JC, et al. Bradykinin-Mediated Angioedema: An Update of the Genetic Causes and the Impact of Genomics. *Front Genet*. 2019;10:900.

39. 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(4):1286–1289.

40. Bafunno V, Firinu D, D'Apolito M, Cordisco G, Loffredo S, Leccese A, et al. Mutation of the angiopoietin-1 gene (ANGPT1) associates with a new type of hereditary angioedema. *Journal of Allergy and Clinical Immunology*. 2018;141(3):1009–1017.

41. Bork K, Wulff K, Steinmüller-Magin L, Braenne I, Staubach-Renz P, Witzke G, et al. Hereditary angioedema with a mutation in the plasminogen gene. *Allergy*. 2018;73(2):442–450.

42. Bork K, Wulff K, Rossmann H, Steinmüller-Magin L, Braenne I, Witzke G, et al. Hereditary angioedema cosegregating with a novel kininogen 1 gene mutation changing the N-terminal cleavage site of bradykinin. *Allergy*. 2019;74(12):2479–2481.

43. Ariano A, D'Apolito M, Bova M, Bellanti F, Loffredo S, D'Andrea G, et al. A myoferlin gain-of-function variant associates with a new type of hereditary angioedema. *Allergy*. 2020;75(11):2989–2992.

44. Bork K, Wulff K, Möhl BS, Steinmüller-Magin L, Witzke G, Hardt J, et al. Novel hereditary angioedema linked with a heparan sulfate 3-O-sulfotransferase 6 gene mutation. *Journal of Allergy and Clinical Immunology*. 2021;148(4):1041–1048.

45. Banday AZ, Kaur A, Jindal AK, Rawat A, Singh S. An update on the genetics and pathogenesis of hereditary angioedema. *Genes Dis*. 2020;7(1):75–83.

46. Cicardi M, Aberer W, Banerji A, Bas M, Bernstein JA, Bork K, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy*. 2014;69(5):602–616.

47. Proper SP, Lavery WJ, Bernstein JA. Definition and classification of hereditary angioedema. *Allergy and Asthma Proceedings*. 2020;41(6):S03–7.

48. Reshef A, Buttgereit T, Betschel SD, Caballero T, Farkas H, Grumach AS, et al. Definition, acronyms, nomenclature, and classification of angioedema (DANCE): AAAAI, ACAAI, ACARE, and APAAACI DANCE consensus. *J Allergy Clin Immunol*. 2024;154(2):398–411.e1.

49. Vincent D, Parsopoulou F, Martin L, Gaboriaud C, Demongeot J, Loules G, et al. Hereditary angioedema with normal C1 inhibitor associated with carboxypeptidase N deficiency. *J Allergy Clin Immunol Glob*. 2024;3(2), 100223.

50. D'Apolito M, Santacroce R, Vazquez DO, Cordisco G, Fantini CA, D'Andrea G, et al. DAB2IP associates with hereditary angioedema: Insights into the role of VEGF signaling in HAE pathophysiology. *J Allergy Clin Immunol*. 2024;S0091-6749(24):00558-X.

51. Giavina-Bianchi P, Aun MV, Kalil J. Vascular endothelial growth factor (VEGF) emerging as a mediator of hereditary angioedema (HAE). *World Allergy Organ J*. 2024;17(8), 100942.

52. Giavina-Bianchi P, Vivolo Aun M, Giavina-Bianchi M, Ribeiro AJ, Camara Agondi R, Motta AA, et al. Hereditary angioedema classification: Expanding knowledge by genotyping and endotyping. *World Allergy Organ J*. 2024;17(5), 100906.

53. Aygören-Pürsün E, Magerl M, Maetzel A, Maurer M. Epidemiology of Bradykinin-mediated angioedema: a systematic investigation of epidemiological studies. *Orphanet J Rare Dis*. 2018;13(1):73.

54. Lumry WR, Settipane RA. Hereditary angioedema: Epidemiology and burden of disease. *Allergy Asthma Proc*. 2020;41(Suppl 1):S08–S13.

55. Cicardi M, Bellis P, Bertazzoni G, Cancian M, Chiesa M, Cremonesi P, et al. Guidance for diagnosis and treatment of acute angioedema in the emergency department: consensus statement by a panel of Italian experts. *Intern Emerg Med*. 2014;9(1):85–92.

56. Betschel S, Badiou J, Binkley K, Borici-Mazi R, Hébert J, Kanani A, et al. The International/Canadian Hereditary Angioedema Guideline. *Allergy Asthma Clin Immunol*. 2019;15(1):72.

57. Giavina-Bianchi P, Arruda LK, Aun MV, Campos RA, Chong-Neto HJ, Constantino-Silva RN, et al. Brazilian Guidelines for Hereditary Angioedema Management - 2017 Update Part 1: Definition, Classification and Diagnosis. *Clinics (Sao Paulo)*. 2018;73, e310.

58. Bouillet L, Lehmann A, Gompel A, Boccon-Gibod I, Launay D, Fain O, et al. [Hereditary angiœdema treatments: Recommendations from the French national center for angiœdema (Bordeaux consensus 2014)]. *Presse Med*. 2015;44(5):526–532.

59. Vazquez DO, Josviack DO, Fantini CA, Fili NL, Berardi AM, Zwiener RD, et al. [Argentine Consensus of the Diagnosis and Treatment of Hereditary Angioedema]. *Rev Alerg Mex*. 2021;68(Suppl 2):s1–22.

60. Zuraw BL, Banerji A, Bernstein JA, Busse PJ, Christiansen SC, Davis-Lorton M, 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(5):458–467.

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61. Gavorník P, Gašpar Ľ, Dukát A. [Management of angioedema. Guidelines of the Angiology Section of Slovak Medical Chamber (2013)]. *Vnitr Lek*. 2014;60(5–6):490–498.

62. Zanichelli A, Farkas H, Bouillet L, Bara N, Germenis AE, Psarros F, et al. The Global Registry for Hereditary Angioedema due to C1-Inhibitor Deficiency. *Clinic Rev Allerg Immunol*. 2021;61(1):77–83.

63. Zanichelli A, Arcoleo F, Barca MP, Borrelli P, Bova M, Cancian M, et al. A nationwide survey of hereditary angioedema due to C1 inhibitor deficiency in Italy. *Orphanet J Rare Dis*. 2015;10:11.

64. Roche O, Blanch A, Caballero T, Sastre N, Callejo D, López-Trascasa M. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. *Ann Allergy Asthma Immunol*. 2005;94(4):498–503.

65. Caballero T, Aberer W, Longhurst HJ, Maurer M, Zanichelli A, Perrin A, et al. The Icatibant Outcome Survey: experience of hereditary angioedema management from six European countries. *Acad Dermatol Venereol*. 2017;31(7):1214–1222.

66. Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. *Br J Dermatol*. 2009;161(5):1153–1158.

67. Maurer M, Bork K, Martinez-Saguer I, Aygören-Pürsün E, Botha J, Andresen I, et al. Management of patients with hereditary angioedema in Germany: comparison with other countries in the Icatibant Outcome Survey. *J Eur Acad Dermatol Venereol*. 2019;33(1):163–169.

68. Sundler Björkman L, Thulin M, Ekström M, Nordenfelt P, Egesten A. Trends in Treatments With Disease-Specific and Interfering Drugs in Patients With Hereditary Angioedema in Sweden. *The journal of allergy and clinical immunology In practice*. 2023;11(2):621–628.

69. Malbran E, Menendez A, Malbrán A. *Treatment of hereditary angioedema due to c1 inhibitor deficiency in argentina*; 2017 Aug [cited 2023 Sep 2]; Available from: https://ri.conicet.gov.ar/handle/11336/51220.

70. Grumach AS, Valle SOR, Toledo E, de Moraes Vasconcelos D, Villela MMS, Mansour E, et al. Hereditary angioedema: first report of the Brazilian registry and challenges. *Journal of the European Academy of Dermatology and Venereology*. 2013;27(3):e338–e344.

71. Nieto S, Madrigal I, Contreras F, Vargas ME. Real-world experience of hereditary angioedema (HAE) in Mexico: A mixed-methods approach to describe epidemiology, diagnosis, and treatment patterns. *World Allergy Organ J*. 2023;16(9), 100812.

72. Sobotkova M, Zachova R, Hakl R, Kuklinek P, Kralickova P, Krcmova I, et al. Acquired Angioedema with C1 Inhibitor Deficiency: Occurrence, Clinical Features, and Management: A Nationwide Retrospective Study in the Czech Republic Patients. *Int Arch Allergy Immunol*. 2021;182(7):642–649.

73. Perumalla S, Mathew L, Mathew J, Naina P, Joseph AJ, Prakash JAJ, et al. Clinical profile of hereditary angioedema from a tertiary care centre in India. *Indian J Med Microbiol*. 2021;39(4):509–512.

74. Stray-Pedersen A, Abrahamsen TG, Frøland SS. Primary immunodeficiency diseases in Norway. *J Clin Immunol*. 2000;20(6):477–485.

75. Psarros F, Koutsostathis N, Farmaki E, Speletas MG, Germenis AE. Hereditary angioedema in Greece: the first results of the greek hereditary angioedema registry. *Int Arch Allergy Immunol*. 2014;164(4):326–332.

76. Guryanova I, Suffritti C, Parolin D, Zanichelli A, Ishchanka N, Polyakova E, et al. Hereditary angioedema due to C1 inhibitor deficiency in Belarus: epidemiology, access to diagnosis and seven novel mutations in SERPING1 gene. *Clin Mol Allergy*. 2021;19(1):3.

77. Longhurst HJ, Dempster J, Lorenzo L, Buckland M, Grigoriadou S, Symons C, et al. Real-world outcomes in hereditary angioedema: first experience from the Icatibant Outcome Survey in the United Kingdom. *Allergy Asthma Clin Immunol*. 2018;14(1):28.

78. Schöffl C, Wiednig M, Koch L, Blagojevic D, Duschet P, Hawranek T, et al. Hereditary angioedema in Austria: prevalence and regional peculiarities. *J Dtsch Dermatol Ges*. 2019;17(4):416–423.

79. Escobar JJ, Aguirre J, Ibáñez S, Cid BJ, Campillay R, Gallardo AM, et al. Universal Access to On-Demand Treatment of Patients with Hereditary Angioedema, the Chilean Experience. *Pediatr Allergy Immunol Pulmonol*. 2023;2023;36(4):130–132.

80. Lee EY, Hsieh J, Caballero T, McCusker C, Kanani A, Lacuesta G, et al. Demographic and clinical characteristics of patients with hereditary angioedema in Canada. *Ann Allergy Asthma Immunol*. 2022;128(1):89–94.e1.

81. Sánchez MD, Cuervo J, Rave D, Clemen G, Yepes-Núñez JJ, Ortiz-Reyes B, et al. [Hereditary angioedema in Medellín (Colombia): Clinical evaluation and quality of life appraisal]. *Biomedica*. 2015;35(3):419–428.

82. Katelaris CH, Boicos K, Button PH, McCloud PI, Burton PK, Perram FA, et al. Living With Hereditary Angioedema in Australia: Findings From a National Observational Study Using Short Message Service to Monitor the Burden of Disease. *J Allergy Clin Immunol Pract*. 2023;11(8):2457–2467.e1.

83. Iwamoto K, Yamamoto B, Ohsawa I, Honda D, Horiuchi T, Tanaka A, et al. The diagnosis and treatment of hereditary angioedema patients in Japan: A patient reported outcome survey. *Allergol Int*. 2021;70(2):235–243.

84. Varandas C, Esteves Caldeira L, Silva SL, Costa C, Limão R, Silva MI, et al. Hereditary angioedema: 24 years of experience in a Portuguese Reference Center. *Eur Ann Allergy Clin Immunol*. 2022 Dec 14; 2024;56(5):210–218.

85. Lindsay K, Chua I, Jordan A, Stephens S. National audit of a hereditary and acquired angioedema cohort in New Zealand. *Intern Med J*. 2022;52(12):2124–2129.

86. Jung JW, Suh DI, Park HJ, Kim S, Kwon HS, Yang MS, et al. Clinical Features of Hereditary Angioedema in Korean Patients: A Nationwide Multicenter Study. *Int Arch Allergy Immunol*. 2018;176(3–4):272–279.

87. Martinez-Saguer I, Dominas N, Straben U, Greve J, Brehler R, Magerl M, et al. Patients with hereditary angioedema and their treatment patterns in Germany: a Delphi consensus study. *Eur J Dermatol*. 2022;32(4):487–494.

88. Liu S, Xu Y, Liu Y, Zhi Y. Hereditary angioedema: a Chinese perspective. *Eur J Dermatol*. 2019;29(1):14–20.

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89. Tachdjian R, Johnson KE, Casso D, Oliveria SA, Devercelli G, Jain G. Real-world cohort study of adult and pediatric patients treated for hereditary angioedema in the United States. *Allergy Asthma Proc*. 2020;41(3):172–182.

90. Honda D, Li PH, Jindal AK, Katelaris CH, Zhi YX, Thong BYH, et al. Uncovering the True Burden of Hereditary Angioedema due to C1-Inhibitor Deficiency: A Focus on the Asia-Pacific Region. *J Allergy Clin Immunol*. 2023;S0091-6749(23):01381–01387.

91. Van der Poorten M, Schrijvers R, Hermans C, Bartiaux M, Haerynck F, Lapeere H, et al. Hereditary angioedema (HAE) in Belgium: results from a national survey. *Front Allergy*. 2023;4, 1143897.

92. Kanepa A, Nartisa I, Rots D, Gailite L, Farkas H, Kurjane N. National survey on clinical and genetic characteristics of patients with hereditary angioedema in Latvia. Allergy. *Asthma & Clinical Immunology*. 2023;19(1):28.

93. Ahmed A, Fayyaz S. Novel use of fresh frozen plasma in treating hereditary angioedema: A success story from Pakistan. *Cureus*. 2020;12(8), e9669.

94. Valerieva A, Staevska M, Jesenak M, Hrubiskova K, Sobotkova M, Zachova R, et al. Recombinant human C1 esterase inhibitor as short-term prophylaxis in patients with hereditary angioedema. *The Journal of Allergy and Clinical Immunology: In Practice*. 2020;8(2):799–802.

95. Coovadia KM, Chothia MY, Baker SG, Peter JG, Potter PC. Hereditary angio-oedema in the Western Cape Province, South Africa. *S Afr Med J*. 2018;108(4):283.

96. Jolles S, Williams P, Carne E, Mian H, Huissoon A, Wong G, et al. A UK national audit of hereditary and acquired angioedema. *Clin Exp Immunol*. 2014;175(1):59–67.

97. Stipić Marković A, Rožmanić V, Anić B, Aberle N, Račić G, Novak S, et al. SMJERNICE ZA DIJAGNOSTIKU I LIJEČENJE HEREDITARNOG ANGIOEDEMA. *Liječnički vjesnik*. 2014;136(5–6):117–129.

98. Gokmen NM, Gulbahar O, Onay H, Koc ZP, Ozgul S, Kose T, et al. *Deletions in SERPING1 Lead to Lower C1 Inhibitor Function: Lower C1 Inhibitor Function Can Predict Disease Severity*; 2019 [cited 2023 Oct 4]; Available from: http://acikerisim.ege.edu.tr/xmlui/handle/11454/29588.

99. Description of the Hereditary Form of Angioneurotic Edema in a Child (ОШИСАНИЕ НАСЛЕДСТВЕННОЙ ФОРМЫ АНГИОНЕВРОТИцЕСКОГО ОТЕКА У РЕБЕНКА) [Internet]. [cited 2023 Oct 8]. Available from: https://cyberleninka.ru/article/n/opisanie-nasledstvennoy-formy-angionevroticheskogo-oteka-u-rebenka/viewer.

100. Giavina-Bianchi P, Aun MV, Garcia JFB, Gomes LS, Ribeiro AJ, Takejima P, et al. Clinical features of hereditary angioedema and warning signs (H4AE) for its identification. *Clinics (Sao Paulo)*. 2022;77, 100023.

101. Christiansen SC, Wilmot J, Castaldo AJ, Zuraw BL. The US Hereditary Angioedema Association Scientific Registry: hereditary angioedema demographics, disease severity, and comorbidities. *Ann Allergy Asthma Immunol*. 2023;131(6):766–774.e8.

102. Calderón-Llosa OM, Muñoz-Campos D, Olivares-Gómez M. [Registry of Members of the Association of Patients with Hereditary Angioedema of Perú]. *Rev Alerg Mex*. 2024;71(1):62.

103. Hillmeister P, Persson PB. The Kallikrein–Kinin system. *Acta Physiologica*. 2012;206(4):215–219.

104. Shoemaker LR, Schurman SJ, Donaldson VH, Davis AE. Hereditary angioneurotic oedema: characterization of plasma kinin and vascular permeability-enhancing activities. *Clin Exp Immunol*. 1994;95(1):22–28.

105. Marceau F, Bachelard H, Bouthillier J, Fortin JP, Morissette G, Bawolak MT, et al. Bradykinin receptors: Agonists, antagonists, expression, signaling, and adaptation to sustained stimulation. *Int Immunopharmacol*. 2020;82, 106305.

106. Dyga W, Obtulowicz A, Mikolajczyk T, Bogdali A, Dubiela P, Obtulowicz K. The Role of Bradykinin Receptors in Hereditary Angioedema Due to C1-Inhibitor Deficiency. *International Journal of Molecular Sciences*. 2022;23(18), 10332.

107. Kaplan AP, Joseph K. Complement, Kinins, and Hereditary Angioedema: Mechanisms of Plasma Instability when C1 Inhibitor is Absent. *Clin Rev Allergy Immunol*. 2016;51(2):207–215.

108. Cicardi M, Zingale L, Zanichelli A, Pappalardo E, Cicardi B. Cvd1 inhibitor: molecular and clinical aspects. *Springer Semin Immunopathol*. 2005;27(3):286–298.

109. Shamanaev A, Dickeson SK, Ivanov I, Litvak M, Sun MF, Kumar S, et al. Mechanisms involved in hereditary angioedema with normal C1-inhibitor activity. *Front Physiol*. 2023;14, 1146834.

110. Drouet C, López Lera A, Ghannam A, López-Trascasa M, Cichon S, Ponard D, et al. SERPING1 variants and C1-INH biological function: a close relationship with C1-INH-HAE. *Frontiers in allergy*. 2022;(3):1–17.

111. Santacroce R, D'Andrea G, Maffione AB, Margaglione M, d'Apolito M. The Genetics of Hereditary Angioedema: A Review. *JCM*. 2021;10(9):2023.

112. Hintze S, Möhl BS, Beyerl J, Wulff K, Wieser A, Bork K, et al. Mutant plasminogen in hereditary angioedema is bypassing FXII/kallikrein to generate bradykinin. *Front Physiol*. 2022;13, 1090732.

113. D'Apolito M, Santacroce R, Colia AL, Cordisco G, Maffione AB, Margaglione M. Angiopoietin-1 haploinsufficiency affects the endothelial barrier and causes hereditary angioedema. *Clin Exp Allergy*. 2019;49(5):626–635.

114. Bork K, Wulff K, Witzke G, Hardt J. Treatment for hereditary angioedema with normal C1-INH and specific mutations in the F12 gene (HAE-FXII). *Allergy (Copenhagen)*. 2017;72(2):320–324.

115. Bork K, Wulff K, Witzke G, Machnig T, Hardt J. Treatment of patients with hereditary angioedema with the c.988A>G (p.Lys330Glu) variant in the plasminogen gene. *Orphanet J Rare Dis*. 2020;15(1):52.

116. Dickeson SK, Kumar S, Sun MF, Mohammed BM, Phillips DR, Whisstock JC, et al. A mechanism for hereditary angioedema caused by a lysine 311-to-glutamic acid substitution in plasminogen. *Blood*. 2022;139(18):2816–2829.

117. Dickeson SK, Kumar S, Sun MF, Litvak M, He TZ, Phillips DR, et al. A mechanism for hereditary angioedema caused by a methionine-379-to-lysine substitution in kininogens. *Blood*. 2024;143(7):641–650.

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118. Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)*. 1992;71(4):206–215.

119. Pappalardo E, Cicardi M, Duponchel C, Carugati A, Choquet S, Agostoni A, et al. Frequent de novo mutations and exon deletions in the C1inhibitor gene of patients with angioedema. *J Allergy Clin Immunol*. 2000;106(6):1147–1154.

120. Ponard D, Gaboriaud C, Charignon D, Ghannam A, Wagenaar-Bos IGA, Roem D, et al. SERPING1 mutation update: Mutation spectrum and C1 Inhibitor phenotypes. *Hum Mutat*. 2020;41(1):38–57.

121. Loules G, Parsopoulou F, Zamanakou M, Csuka D, Bova M, González-Quevedo T, et al. Deciphering the Genetics of Primary Angioedema with Normal Levels of C1 Inhibitor. *J Clin Med*. 2020;9(11):3402.

122. Manning ME. Hereditary angioedema: Differential diagnosis, diagnostic tests, and family screening. *Allergy Asthma Proc*. 2020;41(Suppl 1):S22–S25.

123. Porebski G, Kwitniewski M, Reshef A. Biomarkers in Hereditary Angioedema. *Clin Rev Allergy Immunol*. 2021;60(3):404–415.

124. As M, Lsm M, Pb P, Mm D, Vf M, Ec C, et al. Genetic Analysis as a Practical Tool for Diagnosis of Hereditary Angioedema With Normal C1 Inhibitor: A Case Report. *J Investig Allergol Clin Immunol*. 2016;26(1):48–72.

125. Atkinson JP. Diagnosis and management of hereditary angioedema (HAE). *Ann Allergy*. 1979;42(6):348–352.

126. Baeza ML, Caballero Molina T, Crespo Diz C, null González-Quevedo, Guilarte Clavero M, Hernández Fernández de Rojas D, et al. [Algorithm for diagnosis and treatment of hereditary angioedema as a tool for management]. *Farm Hosp*. 2013;37(6):521–529.

127. Sinnathamby ES, Issa PP, Roberts L, Norwood H, Malone K, Vemulapalli H, et al. Hereditary Angioedema: Diagnosis, Clinical Implications, and Pathophysiology. *Adv Ther*. 2023;40(3):814–827.

128. Azmy V, Brooks JP, Hsu FI. Clinical presentation of hereditary angioedema. *Allergy and Asthma Proceedings*. 2020;41(6):S18–21.

129. Caballero T, Baeza ML, Cabañas R, Campos A, Cimbollek S, Gómez-Traseira C, et al. Consensus statement on the diagnosis, management, and treatment of angioedema mediated by bradykinin. Part I. Classification, epidemiology, pathophysiology, genetics, clinical symptoms, and diagnosis. *J Investig Allergol Clin Immunol*. 2011;21(5):333–347. quiz follow 347.

130. Cicardi M, Zanichelli A. Diagnosing angioedema. *Immunol Allergy Clin North Am*. 2013;33(4):449–456.

131. Agostoni A, Aygören-Pürsün E, Binkley KE, Blanch A, Bork K, Bouillet L, et al. Hereditary and acquired angioedema: Problems and progress: Proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *Journal of Allergy and Clinical Immunology*. 2004;114(3):S51–131.

132. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med*. 2006;119(3):267–274.

133. Collins-Yoder AS. Angioedema: Clinical Presentations and Pharmacological Management. *Dimens Crit Care Nurs*. 2016;35(4):181–189.

134. Kusuma A, Relan A, Knulst AC, Moldovan D, Zuraw B, Cicardi M, et al. Clinical impact of peripheral attacks in hereditary angioedema patients. *Am J Med*. 2012;125(9):937.e17–937.e24.

135. Lumry W. Overview of epidemiology, pathophysiology, and disease progression in hereditary angioedema. *The American journal of managed care*. 2013;19(7 Suppl).

136. Prematta MJ, Laudadio C, Craig T. Frequency and Types of Hereditary Angioedema Prodromes as Reported by Patients. *Journal of Allergy and Clinical Immunology*. 2010;125(2), AB165.

137. Farkas H. Pediatric hereditary angioedema due to C1-inhibitor deficiency. *Allergy Asthma Clin Immunol*. 2010;6(1):18.

138. Martin L, Renné T, Drouet C. Urticaria as a Presenting Prodromal Manifestation of Attacks of Hereditary Angioedema. *Acta Derm Venereol*. 2016;96(4):574–575.

139. Rasmussen ER, de Freitas PV, Bygum A. Urticaria and Prodromal Symptoms Including Erythema Marginatum in Danish Patients with Hereditary Angioedema. *Acta Derm Venereol*. 2016;96(3):373–376.

140. Xu YY, Jiang Y, Zhi YX, Yin J, Wang LL, Wen LP, et al. Clinical features of hereditary angioedema in Chinese patients: new findings and differences from other populations. *Eur J Dermatol*. 2013;23(4):500–504.

141. Agostoni A, Aygören-Pürsün E, Binkley KE, Blanch A, Bork K, Bouillet L, et al. Hereditary and acquired angioedema: Problems and progress: Proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *Journal of Allergy and Clinical Immunology*. 2004;114(3):S51–131.

142. Cao Y, Liu S, Zhi Y. Recurrent and acute abdominal pain as the main clinical manifestation in patients with hereditary angioedema. *Allergy Asthma Proc*. 2021;42(2):131–135.

143. Lumry WR. Hereditary angioedema: a case of near fatal laryngeal swelling in a 41-year-old woman. *Allergy Asthma Proc*. 2011;32(Suppl 1):13–15.

144. Rajan N, Sharma V, Patro SK, Goyal A. Acute Presentation of Undiagnosed Hereditary Angioedema of the Larynx: Averting Death. *Turk Arch Otorhinolaryngol*. 2020;58(4):279–281.

145. Piotrowicz-Wójcik K, Porebski G. Life-threatening laryngeal attacks in hereditary angioedema patients. *Otolaryngol Pol*. 2020;74(2):1–5.

146. Moldovan D, Bara N, Nădăşan V, Gábos G, Mihály E. Consequences of Misdiagnosed and Mismanaged Hereditary Angioedema Laryngeal Attacks: An Overview of Cases from the Romanian Registry. *Case Rep Emerg Med*. 2018;2018, 6363787.

147. 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(3):692–697.

148. Bork K, Ressel N. Sudden upper airway obstruction in patients with hereditary angioedema. *Transfus Apher Sci*. 2003;29(3):235–238.

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149. Minafra FG, Cunha LAO, Mariano RG de S, Goebel GA, de Lima LS, Pinto JA. Investigation of Mortality of Hereditary Angioedema in a Reference Center in Brazil. *J Allergy Clin Immunol Pract*. 2022;10(7):1805–1812.

150. Magerl M, Germenis AE, Maas C, Maurer M. Hereditary Angioedema with Normal C1 Inhibitor: Update on Evaluation and Treatment. *Immunol Allergy Clin North Am*. 2017;37(3):571–584.

151. 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(4):294–298.

152. Jindal AK, Chiang V, Barman P, Sil A, Chawla S, Au EYL, et al. Screening for type II hereditary angioedema-the "poor man's c1-inhibitor function.". *J Allergy Clin Immunol Glob*. 2024;3(1), 100179.

153. Trainotti S, Johnson F, Hahn J, Hofauer B, Greve J, Wollenberg B, et al. Acquired Angioedema Due to C1-Inhibitor Deficiency (AAE-C1-INH)-A Bicenter Retrospective Study on Diagnosis, Course, and Therapy. *J Allergy Clin Immunol Pract*. 2023;S2213-2198(23):01011–01015.

154. Ebo DG, Verweij MM, De Knop KJ, Hagendorens MM, Bridts CH, De Clerck LS, et al. Hereditary angioedema in childhood: an approach to management. *Paediatr Drugs*. 2010;12(4):257–268.

155. Kiani-Alikhan S, Walker E, Hickey A, Grigoriadou S, Buckland M, Scott C. Measurement of C1-Inhibitor function alone is sufficient for diagnosis of hereditary angioedema. *J Clin Pathol*. 2022;75(11):787–788.

156. Fu LW, Freedman-Kalchman T, Betschel S, Sussman G. Review of hereditary angioedema. *LymphoSign Journal*. 2016;3(2):47–53.

157. Wagenaar-Bos IGA, Drouet C, Aygören-Pursun E, Bork K, Bucher C, Bygum A, et al. Functional C1-Inhibitor diagnostics in hereditary angioedema: Assay evaluation and recommendations. *Journal of Immunological Methods*. 2008;338(1):14–20.

158. Pedrosa M, Phillips-Angles E, López-Lera A, López-Trascasa M, Caballero T. Complement Study Versus CINH Gene Testing for the Diagnosis of Type I Hereditary Angioedema in Children. *J Clin Immunol*. 2016;36(1):16–18.

159. Charest-Morin X, Betschel S, Borici-Mazi R, Kanani A, Lacuesta G, Rivard GÉ, et al. The diagnosis of hereditary angioedema with C1 inhibitor deficiency: a survey of Canadian physicians and laboratories. *Allergy Asthma Clin Immunol*. 2018;14(1):83.

160. Lai Y, Zhang G, Zhou Z, Inhaber N, Bernstein JA, Chockalingam PS, et al. A novel functional C1 inhibitor activity assay in dried blood spot for diagnosis of Hereditary angioedema. *Clin Chim Acta*. 2020;504:155–162.

161. Lai Y, Zhang G, Inhaber N, Bernstein JA, Cwik M, Zhou Z, et al. A robust multiplexed assay to quantify C1-inhibitor, C1q, and C4 proteins for in vitro diagnosis of hereditary angioedema from dried blood spot. *Journal of Pharmaceutical and Biomedical Analysis*. 2021;195, 113844.

162. Iurașcu MI, Balla Z, Pereira C, Andrási N, Varga L, Csuka D, et al. Application of a dried blood spot based proteomic and genetic assay for diagnosing hereditary angioedema. *Clin Transl Allergy*. 2023;13(11), e12317.

163. Karim Y, Griffiths H, Deacock S. Normal complement C4 values do not exclude hereditary angioedema. *J Clin Pathol*. 2004;57(2):213–214.

164. Tarzi MD, Hickey A, Förster T, Mohammadi M, Longhurst HJ. An evaluation of tests used for the diagnosis and monitoring of C1 inhibitor deficiency: normal serum C4 does not exclude hereditary angio-oedema. *Clin Exp Immunol*. 2007;149(3):513–516.

165. Joseph K, Bains S, Tholanikunnel BG, Bygum A, Aabom A, Koch C, et al. A novel assay to diagnose hereditary angioedema utilizing inhibition of bradykinin-forming enzymes. *Allergy*. 2015;70(1):115–119.

166. Johnston DT. Diagnosis and management of hereditary angioedema. *J Am Osteopath Assoc*. 2011;111(1):28–36.

167. Gompels MM, Lock RJ, Unsworth DJ, Johnston SL, Archer CB, Davies SV. Misdiagnosis of hereditary angio-oedema type 1 and type 2. *Br J Dermatol*. 2003;148(4):719–723.

168. Clarke A. *Harper's Practical Genetic Counselling*. Eighth Edition. 8th ed. London: CRC Press; 2019:542.

169. Germenis AE, Margaglione M, Pesquero JB, Farkas H, Cichon S, Csuka D, et al. International Consensus on the Use of Genetics in the Management of Hereditary Angioedema. *The Journal of Allergy and Clinical Immunology: In Practice*. 2020;8(3):901–911.

170. Emelyanov AV, Leshenkova EV, Kameneva GA. [Diagnosis and treatment of hereditary angioedema with normal C1-inhibitor level]. *Ter Arkh*. 2020;92(12):86–90.

171. Bork K, Zibat A, Ferrari DM, Wollnik B, Schön MP, Wulff K, et al. Hereditary angioedema in a single family with specific mutations in both plasminogen and SERPING1 genes. *J Dtsch Dermatol Ges*. 2020;18(3):215–223.

172. Speletas M, Szilagyi A, Psarros F, Moldovan D, Magerl M, Kompoti M, et al. Hereditary angioedema: molecular and clinical differences among European populations. *J Allergy Clin Immunol*. 2015;135(2):570–573.

173. Grombirikova H, Bily V, Soucek P, Kramarek M, Hakl R, Ballonova L, et al. Systematic Approach Revealed SERPING1 Splicing-Affecting Variants to be Highly Represented in the Czech National HAE Cohort. *J Clin Immunol*. 2023;43(8):1974–1991.

174. Rijavec M, Korošec P, Šilar M, Zidarn M, Miljković J, Košnik M. Hereditary angioedema nationwide study in Slovenia reveals four novel mutations in SERPING1 gene. *PloS one*. 2013;8(2):1–6.

175. Johnsrud I, Kulseth MA, Rødningen OK, Landrø L, Helsing P, Waage Nielsen E, et al. A Nationwide Study of Norwegian Patients with Hereditary Angioedema with C1 Inhibitor Deficiency Identified Six Novel Mutations in SERPING1. *PLoS One*. 2015;10(7), e0131637.

176. Andrejević S, Korošec P, Šilar M, Košnik M, Mijanović R, Bonači-Nikolić B, et al. Hereditary angioedema due to C1 inhibitor deficiency in Serbia: two novel mutations and evidence of genotype-phenotype association. *PloS one*. 2015;10(11):1–11.

177. Kalmár L, Bors A, Farkas H, Vas S, Fandl B, Varga L, et al. Mutation screening of the C1 inhibitor gene among Hungarian patients with hereditary angioedema. *Hum Mutat*. 2003;22(6):498.

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178. Faiyaz-Ul-Haque M, Al-Gazlan S, Abalkhail HA, Al-Abdulatif A, Toulimat M, Peltekova I, et al. Novel and recurrent mutations in the C1NH gene of Arab patients affected with hereditary angioedema. *Int Arch Allergy Immunol*. 2010;151(2):149–154.

179. Bafunno V, Bova M, Loffredo S, Divella C, Petraroli A, Marone G, et al. Mutational Spectrum of the C1 Inhibitor Gene in a Cohort of Italian Patients with Hereditary Angioedema: Description of Nine Novel Mutations. *Annals of Human Genetics*. 2014;78(2):73–82.

180. Cagini N, Veronez CL, Constantino-Silva RN, Buzolin M, Martin RP, Grumach AS, et al. New mutations in SERPING1 gene of Brazilian patients with hereditary angioedema. *Biol Chem*. 2016;397(4):337–344.

181. Roche O, Blanch A, Duponchel C, Fontán G, Tosi M, López-Trascasa M. Hereditary angioedema: the mutation spectrum of SERPING1/C1NH in a large Spanish cohort. *Hum Mutat*. 2005;26(2):135–144.

182. Jindal AK, Rawat A, Kaur A, Sharma D, Suri D, Gupta A, et al. Novel SERPING1 gene mutations and clinical experience of type 1 hereditary angioedema from North India. *Pediatr Allergy Immunol*. 2021;32(3):599–611.

183. Speletas M, Boukas K, Papadopoulou-Alataki E, Tsitsami E, Germenis AE. Hereditary angioedema in Greek families caused by novel and recurrent mutations. *Human Immunology*. 2009;70(11):925–929.

184. Wang X, Lei S, Xu Y, Liu S, Zhi Y. Mutation update of SERPING1 related to hereditary angioedema in the Chinese population. *Hereditas*. 2022;159(1):28.

185. Ren Z, Zhao S, Li T, Wedner HJ, Atkinson JP. Insights into the pathogenesis of hereditary angioedema using genetic sequencing and recombinant protein expression analyses. *J Allergy Clin Immunol*. 2023;151(4):1040–1049.e5.

186. Veronez CL, Csuka D, Sheikh FR, Zuraw BL, Farkas H, Bork K. The Expanding Spectrum of Mutations in Hereditary Angioedema. *J Allergy Clin Immunol Pract*. 2021;9(6):2229–2234.

187. Rehm HL, Bale SJ, Bayrak-Toydemir P, Berg JS, Brown KK, Deignan JL, et al. ACMG clinical laboratory standards for next-generation sequencing. *Genet Med*. 2013;15(9):733–747.

188. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405–424.

189. Mendoza-Alvarez A, Muñoz-Barrera A, Rubio-Rodríguez LA, Marcelino-Rodriguez I, Corrales A, Iñigo-Campos A, et al. Interactive Web-Based Resource for Annotation of Genetic Variants Causing Hereditary Angioedema (HADA): Database Development, Implementation, and Validation. *J Med Internet Res*. 2020;22(10), e19040.

190. Hereditary Angioedema Variant Curation Expert Panel - ClinGen | Clinical Genome Resource [Internet]. [cited 2023 Nov 19]. Available from: https://clinicalgenome.org/affiliation/50128/.

191. Verpy E, Biasotto M, Brai M, Misiano G, Meo T, Tosi M. Exhaustive mutation scanning by fluorescence-assisted mismatch analysis discloses new genotype-phenotype correlations in angiodema. *Am J Hum Genet*. 1996;59(2):308–319.

192. Maia LSM, Moreno AS, Ferriani MPL, Nunes FL, Ferraro MF, Dias MM, et al. Genotype-phenotype correlations in Brazilian patients with hereditary angioedema due to C1 inhibitor deficiency. *Allergy*. 2019;74(5):1013–1016.

193. Rijavec M, Karandža-Lapić L, Zidarn M, Šilar M, Korošec P, Cikojević D, et al. High heterogeneity of mutations in the SERPING1 gene and genotype-phenotype correlation in patients with hereditary angioedema due to C1 inhibitor deficiency from Croatia. In: Heiszler Z, Hohol R, eds. *Serbia and Slovenia*40.

194. George R, Kovak K, Cox SL. Aligning policy to promote cascade genetic screening for prevention and early diagnosis of heritable diseases. *J Genet Couns*. 2015;24(3):388–399.

195. Wahn V, Aberer W, Aygören-Pürsün E, Bork K, Eberl W, Faßhauer M, et al. Hereditary angioedema in children and adolescents – A consensus update on therapeutic strategies for German-speaking countries. *Pediatric Allergy and Immunology*. 2020;31(8):974–989.

196. Caballero T, Farkas H, Bouillet L, Bowen T, Gompel A, Fagerberg C, 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(2):308–320.

197. Maskatia ZK, Orson FM. Delayed diagnosis of hereditary angioedema. *Am J Med Sci*. 2010;340(1):82–83.

198. Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. *Ann Intern Med*. 1976;84(5):580–593.

199. Riedl M, Gower RG, Chrvala CA. Current medical management of hereditary angioedema: results from a large survey of US physicians. *Annals of Allergy, Asthma & Immunology*. 2011;106(4):316–322.e4.

200. Gutierrez M, Veronez CL, Rodrigues Valle SO, Gonçalves RF, Ferriani MPL, Moreno AS, et al. Unnecessary Abdominal Surgeries in Attacks of Hereditary Angioedema with Normal C1 Inhibitor. *Clin Rev Allergy Immunol*. 2021;61(1):60–65.

201. Huang SW. Results of an On-Line Survey of Patients with Hereditary Angioedema. *Allergy and Asthma Proceedings*. 2004;25(2):127–131.

202. Sarici G, Koca R, Tekin NS, Altinyalzar HC. *A Family with Hereditary Angioedema Having Been Followed as Familial Mediterranean Fever*; 2019 Dec 23 [cited 2023 Oct 4];(1). Available from: https://acikarsiv.beun.edu.tr/?p=17&modul=yayin&alan=tum_txt&q=%22hereditary+angioedema%22&recordid=2035.

203. Polai Z, Balla Z, Varga L, Benedek S, Farkas H. Long term follow-up of complement parameters to improve the management of acquired angioedema due to C1-inhibitor deficiency. *Heliyon*. 2022;8(11), e11292.

204. Zanichelli A, Azin GM, Wu MA, Suffritti C, Maggioni L, Caccia S, et al. Diagnosis, Course, and Management of Angioedema in Patients With Acquired C1-Inhibitor Deficiency. *J Allergy Clin Immunol Pract*. 2017;5(5):1307–1313.

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205. Veronez CL, Serpa FS, Pesquero JB. A rare mutation in the F12 gene in a patient with ACE inhibitor-induced angioedema. *Ann Allergy Asthma Immunol*. 2017;118(6):743–745.

206. Yakushiji H, Hashimura C, Fukuoka K, Kaji A, Miyahara H, Kaname S, et al. A missense mutation of the plasminogen gene in hereditary angioedema with normal C1 inhibitor in Japan. *Allergy*. 2018;73(11):2244–2247.

207. Balla Z, Zsilinszky Z, Pólai Z, Andrási N, Kőhalmi KV, Csuka D, et al. The Importance of Complement Testing in Acquired Angioedema Related to Angiotensin-Converting Enzyme Inhibitors. *J Allergy Clin Immunol Pract*. 2021 Feb;9(2):947–955.

208. Giavina-Bianchi P, Aun MV, Jares EJ, Kalil J. Angioedema associated with nonsteroidal anti-inflammatory drugs. *Curr Opin Allergy Clin Immunol*. 2016;16(4):323–332.

209. Wong JCY, Cheong N, Lau WCS, Li PH. Prevalence and impact of misdiagnosed drug allergy labels among patients with hereditary angioedema [cited 2023 Sep 5]; Available from: http://hub.hku.hk/handle/10722/316336; 2022.

210. Zanichelli A, Longhurst HJ, Maurer M, Bouillet L, Aberer W, Fabien V, et al. Misdiagnosis trends in patients with hereditary angioedema from the real-world clinical setting. *Annals of Allergy, Asthma & Immunology*. 2016;117(4):394–398.

211. Tadros S, Hayman GR. Chronic spontaneous urticaria and angioedema requiring treatment with omalizumab in a patient with hereditary angioedema. *Ann Allergy Asthma Immunol*. 2019;122(6):666–667.

212. Craig T. Triggers and short-term prophylaxis in patients with hereditary angioedema. *Allergy Asthma Proc*. 2020;41(Suppl 1):S30–S34.

213. Steiner UC, Kölliker L, Weber-Chrysochoou C, Schmid-Grendelmeier P, Probst E, Wuillemin WA, et al. Food as a trigger for abdominal angioedema attacks in patients with hereditary angioedema. *Orphanet Journal of Rare Diseases*. 2018;13(1):90.

214. Serpa FS, Mansour E, Aun MV, Giavina-Bianchi P, Chong HJ, Arruda LK, et al. Hereditary angioedema: how to approach it at the emergency department? *Einstein (São Paulo)*. 2021;19, eRW5498.

215. Aygören-Pürsün E, Martinez Saguer I, Kreuz W, Klingebiel T, Schwabe D. Risk of angioedema following invasive or surgical procedures in HAE type I and II–the natural history. *Allergy*. 2013;68(8):1034–1039.

216. Bork K, Barnstedt SE. Laryngeal edema and death from asphyxiation after tooth extraction in four patients with hereditary angioedema. *J Am Dent Assoc*. 2003;134(8):1088–1094.

217. Savarese L, Bova M, De Falco R, Guarino MD, De Luca Picione R, Petraroli A, 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(1):115.

218. Gröner A, Nowak T, Schäfer W. Pathogen safety of human C1 esterase inhibitor concentrate. *Transfusion*. 2012t;52(10):2104–2112.

219. Simon TL, Kalina U, Laske R, Mycroft S, Widmer E, Roth NJ. Manufacturing of plasma-derived C1-inhibitor concentrate for treatment of patients with hereditary angioedema. *Allergy Asthma Proc*. 2020;41(2):99–107.

220. Bouillet L, Longhurst H, Boccon-Gibod I, Bork K, Bucher C, Bygum A, et al. Disease expression in women with hereditary angioedema. *American Journal of Obstetrics and Gynecology*. 2008;199(5):484.e1-4.

221. Saule C, Boccon-Gibod I, Fain O, Kanny G, Plu-Bureau G, Martin L, et al. Benefits of progestin contraception in non-allergic angioedema. *Clin Exp Allergy*. 2013;43(4):475–482.

222. Zotter Z, Csuka D, Szabó E, Czaller I, Nébenführer Z, Temesszentandrási G, et al. The influence of trigger factors on hereditary angioedema due to C1-inhibitor deficiency. *Orphanet J Rare Dis*. 2014;9:44.

223. Parente R, Sartorio S, Brussino L, De Pasquale T, Zoli A, Agolini S, et al. Multicentric Observational Study on Safety and Tolerability of COVID-19 Vaccines in Patients with Angioedema with C1 Inhibitor Deficiency: Data from Italian Network on Hereditary and Acquired Angioedema (ITACA). *Vaccines (Basel)*. 2023;11(4):852.

224. Asik A, Mete Gokmen N. *COVID-19 Disease and Hereditary Angioedema*; 2020 [cited 2023 Oct 4]; Available from: http://acikerisim.ege.edu.tr/xmlui/handle/11454/70509.

225. Milota T, Sobotkova M, Smetanova J, Bloomfield M, Vydlakova J, Chovancova Z, et al. Risk Factors for Severe COVID-19 and Hospital Admission in Patients With Inborn Errors of Immunity - Results From a Multicenter Nationwide Study. *Front Immunol*. 2022;13, 835770.

226. Olivares MM, Zwiener RD, Panqueva LML, Contreras Verduzco FA, Mansour E, Rodriguez JA, et al. COVID-19 triggers attacks in HAE patients without worsening disease outcome. *J Allergy Clin Immunol Pract*. 2022;10(3):855–858.

227. Szilágyi D, Horváth HR, Andrási N, Kempler MS, Balla Z, Farkas H. The analysis of the effect of the COVID-19 pandemic on patients with hereditary angioedema type I and type II. *Sci Rep*. 2023 Nov;13(1), 20446.

228. Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133(5):1270–1277.

229. Santa C, Valente CL, Mesquita M, Lopes J, Cardoso I, Rodrigues J, et al. Acute urticaria in children: from pediatric Emergency Department to allergology consultation at a Central Hospital. *Eur Ann Allergy Clin Immunol*. 2022;54(4):168–174.

230. Christiansen SC, Bygum A, Banerji A, Busse P, Li H, Lumry W, et al. Before and after, the impact of available on-demand treatment for HAE. *Allergy Asthma Proc*. 2015;36(2):145–150.

231. Zanichelli A, Mansi M, Azin GM, Wu MA, Periti G, Casazza G, et al. Efficacy of on-demand treatment in reducing morbidity in patients with hereditary angioedema due to C1 inhibitor deficiency. *Allergy*. 2015;70(12):1553–1558.

232. Bork K, Barnstedt SE. Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema. *Arch Intern Med*. 2001;161(5):714–718.

233. Craig TJ, Wasserman RL, Levy RJ, Bewtra AK, Schneider L, Packer F, et al. Prospective study of rapid relief provided by C1 esterase inhibitor in emergency treatment of acute

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laryngeal attacks in hereditary angioedema. *J Clin Immunol*. 2010;30(6):823–829.

234. Sheffer AL, MacGinnitie AJ, Campion M, Stolz LE, Pullman WE. Outcomes after ecallantide treatment of laryngeal hereditary angioedema attacks. *Ann Allergy Asthma Immunol*. 2013;110(3):184–188.e2.

235. Banta E, Horn P, Craig TJ. Response to ecallantide treatment of acute attacks of hereditary angioedema based on time to intervention: results from the EDEMA clinical trials. *Allergy Asthma Proc*. 2011;32(4):319–324.

236. Craig TJ, Rojavin MA, Machnig T, Keinecke HO, Bernstein JA. Effect of time to treatment on response to C1 esterase inhibitor concentrate for hereditary angioedema attacks. *Ann Allergy Asthma Immunol*. 2013;111(3):211–215.

237. Maurer M, Aberer W, Bouillet L, Caballero T, Fabien V, Kanny G, et al. Hereditary angioedema attacks resolve faster and are shorter after early icatibant treatment. *PLoS One*. 2013;8(2), e53773.

238. Leibovich-Nassi I, Golander H, Reshef A. Prodromes predict attacks of hereditary angioedema: Results of a prospective study. *Allergy*. 2023;78(2):577–579.

239. Leibovich-Nassi I, Reshef A. The Enigma of Prodromes in Hereditary Angioedema (HAE). *Clin Rev Allergy Immunol*. 2021;61(1):15–28.

240. Magerl M, Doumoulakis G, Kalkounou I, Weller K, Church MK, Kreuz W, et al. Characterization of prodromal symptoms in a large population of patients with hereditary angio-oedema. *Clin Exp Dermatol*. 2014;39(3):298–303.

241. Prematta MJ, Bewtra AK, Levy RJ, Wasserman RL, Jacobson KW, Machnig T, et al. Per-attack reporting of prodromal symptoms concurrent with C1-inhibitor treatment of hereditary angioedema attacks. *Adv Ther*. 2012;29(10):913–922.

242. Cicardi M, Banerji A, Bracho F, Malbran A, Rosenkranz B, Riedl M, et al. Icatibant, a new Bradykinin-receptor antagonist, in hereditary angioedema. *New England journal of medicine*. 2010;363(6):532–541.

243. Craig TJ, Levy RJ, Wasserman RL, Bewtra AK, Hurewitz D, Obtułowicz K, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol*. 2009;124(4):801–808.

244. Levy RJ, Lumry WR, McNeil DL, Li HH, Campion M, Horn PT, et al. EDEMA4: a phase 3, double-blind study of subcutaneous ecallantide treatment for acute attacks of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;104(6):523–529.

245. Riedl MA, Bernstein JA, Li H, Reshef A, Lumry W, Moldovan D, et al. Recombinant human C1-esterase inhibitor relieves symptoms of hereditary angioedema attacks: phase 3, randomized, placebo-controlled trial. *Ann Allergy Asthma Immunol*. 2014;112(2):163–169.e1.

246. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med*. 2010;363(6):513–522.

247. Lunn M, Santos C, Craig T. Cinryze as the first approved C1 inhibitor in the USA for the treatment of hereditary angioedema: approval, efficacy and safety. *J Blood Med*. 2010;1:163–170.

248. Federici C, Perego F, Borsoi L, Crosta V, Zanichelli A, Gidaro A, et al. Costs and effects of on-demand treatment of hereditary angioedema in Italy: a prospective cohort study of 167 patients. *BMJ Open*. 2018;8(7), e022291.

249. Longhurst HJ. Emergency treatment of acute attacks in hereditary angioedema due to C1 inhibitor deficiency: what is the evidence? *Int J Clin Pract*. 2005;59(5):594–599.

250. Sabeen Ahmed A, Fayyaz S. Novel Use of Fresh Frozen Plasma in Treating Hereditary Angioedema: A Success Story From Pakistan. *Cureus*. 2020;12(8), e9669.

251. Wentzel N, Panieri A, Ayazi M, Ntshalintshali SD, Pourpak Z, Hawarden D, et al. Fresh frozen plasma for on-demand hereditary angioedema treatment in South Africa and Iran. *World Allergy Organ J*. 2019;12(9), 100049.

252. Zanichelli A, Vacchini R, Badini M, Penna V, Cicardi M. Standard care impact on angioedema because of hereditary C1 inhibitor deficiency: a 21-month prospective study in a cohort of 103 patients. *Allergy*. 2011;66(2):192–196.

253. Kunschak M, Engl W, Maritsch F, Rosen FS, Eder G, Zerlauth G, et al. A randomized, controlled trial to study the efficacy and safety of C1 inhibitor concentrate in treating hereditary angioedema. *Transfusion*. 1998;38(6):540–549.

254. Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. *N Engl J Med*. 1996;334(25):1630–1634.

255. De Serres J, Gröner A, Lindner J. Safety and efficacy of pasteurized C1 inhibitor concentrate (Berinert P) in hereditary angioedema: a review. jean. *de.serres@aventis.com. Transfus Apher Sci*. 2003;29(3):247–254.

256. Terpstra FG, Kleijn M, Koenderman AHL, Over J, van Engelenburg FaC, Schuitemaker H, et al. Viral safety of C1-inhibitor NF. *Biologicals*. 2007;35(3):173–181.

257. Moldovan D, Reshef A, Fabiani J, Kivity S, Toubi E, Shlesinger M, et al. Efficacy and safety of recombinant human C1-inhibitor for the treatment of attacks of hereditary angioedema: European open-label extension study. *Clin Exp Allergy*. 2012;42(6):929–935.

258. Riedl M. Recombinant human C1 esterase inhibitor in the management of hereditary angioedema. *Clin Drug Investig*. 2015;35(7):407–417.

259. Crowther M, Bauer KA, Kaplan AP. The thrombogenicity of C1 esterase inhibitor (human): review of the evidence. *Allergy Asthma Proc*. 2014;35(6):444–453.

260. Bork K, Hardt J. Hereditary angioedema: increased number of attacks after frequent treatments with C1 inhibitor concentrate. *Am J Med*. 2009;122(8):780–783.

261. Riedl MA, Bygum A, Lumry W, Magerl M, Bernstein JA, Busse P, et al. Safety and Usage of C1-Inhibitor in Hereditary Angioedema: Berinert Registry Data. *J Allergy Clin Immunol Pract*. 2016;4(5):963–971.

262. Farkas H, Kőhalmi KV, Veszeli N, Zotter Z, Várnai K, Varga L. Risk of thromboembolism in patients with hereditary angioedema treated with plasma-derived C1-inhibitor. *Allergy Asthma Proc*. 2016;37(2):164–170.

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263. Longhurst HJ, Aberer W, Bouillet L, Caballero T, Fabien V, Zanichelli A, et al. Analysis of characteristics associated with reinjection of icatibant: Results from the icatibant outcome survey. *Allergy Asthma Proc*. 2015;36(5):399–406.

264. Farkas H. Icatibant as acute treatment for hereditary angioedema in adults. *Expert Rev Clin Pharmacol*. 2016;9(6):779–788.

265. Bork K, Frank J, Grundt B, Schlattmann P, Nussberger J, Kreuz W. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). *J Allergy Clin Immunol*. 2007;119(6):1497–1503.

266. Bygum A, Caballero T, Grumach AS, Longhurst HJ, Bouillet L, Aberer W, et al. *Elderly versus younger patients with hereditary angioedema type I/II: patient characteristics and safety analysis from the Icatibant Outcome Survey*; 2019 [cited 2023 Sep 20]; Available from: https://www.repository.cam.ac.uk/handle/1810/308127.

267. Dyax s.a. withdraws its marketing authorisation application for Kalbitor (ecallantide).

268. Craig TJ, Li HH, Riedl M, Bernstein JA, Lumry WR, MacGinnitie AJ, et al. Characterization of anaphylaxis after ecallantide treatment of hereditary angioedema attacks. *J Allergy Clin Immunol Pract*. 2015;3(2):206–212.e4.

269. Cicardi M, Levy RJ, McNeil DL, Li HH, Sheffer AL, Campion M, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med*. 2010;363(6):523–531.

270. Riedl MA, Farkas H, Aygören-Pürsün E, Psarros F, Soteres DF, Staevska M, et al. Oral Sebetralstat for On-Demand Treatment of Hereditary Angioedema Attacks. *N Engl J Med*. 2024;391(1):32–43.

271. Javaud N, Gompel A, Bouillet L, Boccon-Gibod I, Cantin D, Smaiti N, et al. Factors associated with hospital admission in hereditary angioedema attacks: a multicenter prospective study. *Ann Allergy Asthma Immunol*. 2015;114(6):499–503.

272. Bork K, Bernstein JA, Machnig T, Craig TJ. Efficacy of Different Medical Therapies for the Treatment of Acute Laryngeal Attacks of Hereditary Angioedema due to C1-esterase Inhibitor Deficiency. *J Emerg Med*. 2016;50(4):567–580.e1.

273. Bork K, Siedlecki K, Bosch S, Schopf RE, Kreuz W. Asphyxiation by laryngeal edema in patients with hereditary angioedema. *Mayo Clin Proc*. 2000;75(4):349–354.

274. Javaud N, Fain O, Durand-Zaleski I, Launay D, Bouillet L, Gompel A, et al. Specialist Advice Support for Management of Severe Hereditary Angioedema Attacks: A Multicenter Cluster-Randomized Controlled Trial. *Ann Emerg Med*. 2018;72(2):194–203.e1.

275. Javaud N, Altar A, Fain O, Reuter PG, Desmaizieres M, Petrovic T, et al. Hereditary angioedema, emergency management of attacks by a call center. *European Journal of Internal Medicine*. 2019;67:42–46.

276. Day C, Van der Walt J, Crombie K, Hendrikse C, Peter J. Acute angioedema in Cape Town emergency centres and a suggested algorithm to simplify and improve management. *S Afr Med J*. 2023;113(8):51–57.

277. Berinert Prescribing information. CSL Behring. Accessed November 2024 https://labeling.cslbehring.com/PI/US/Berinert/EN/Berinert-Prescribing-Information.pdf. Available at:.

278. Ruconest prescribing information. Pharming pharmaceuticals. Accessed November 2024 https:// shared.salix.com/shared/pi/ruconest-pi.pdf. Available at:.

279. Cinryze Prescribing information. Shire. Available at: http://pi.shirecontent.com/PI/ PDFs/Cinryze_USA_ENG.pdf. Accessed November 2024.

280. Ecallantide Prescribing information. Takeda. Accessed November 2024 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125277s081lbl.pdf. Available at:.

281. Icatibant Prescribing information. Shire. Accessed November 2024 https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022150s000lbl.pdf. Available at:.

282. Lanadelumab Prescribing information. Takeda. Acccesed November 2024 https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761090s000lbl.pdf. Available at:.

283. Accessed November 2024 Danazol Prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/017557s033s039s040s041s042lbl.pdf.

284. Accessed November 2024 Tranexamic acid Prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212020lbl.pdf.

285. Berotralstat Prescribing information. BioCryst Pharmaceuticals. Accessed November 2024 https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214094s000lbl.pdf. Available at:.

286. Bork K, Wulff K, Witzke G, Hardt J. Hereditary angioedema with normal C1-INH with versus without specific F12 gene mutations. *Allergy*. 2015;70(8):1004–1012.

287. Farkas H, Zotter Z, Csuka D, Szabó E, Nébenfűhrer Z, Temesszentandrási G, et al. Short-term prophylaxis in hereditary angioedema due to deficiency of the C1-inhibitor – a long-term survey. *Allergy*. 2012;67(12):1586–1593.

288. Bork K, Hardt J, Staubach-Renz P, Witzke G. 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(1):58–64.

289. Nanda MK, Singh U, Wilmot J, Bernstein JA. A cross-sectional questionnaire assessing patient and physician use of short-term prophylaxis for hereditary angioedema. *Ann Allergy Asthma Immunol*. 2014;113(2):198–203.

290. Ajewole O, Lanlokun M, Dimanche S, Craig T. Short-term prophylaxis for children and adolescents with hereditary angioedema. *Allergy Asthma Proc*. 2021;42(3):205–213.

291. Magerl M, Frank M, Lumry W, Bernstein J, Busse P, Craig T, 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(1):110–112.

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292. Bernstein JA, Coleman S, Bonnin AJ. Successful C1 inhibitor short-term prophylaxis during redo mitral valve replacement in a patient with hereditary angioedema. *J Cardiothorac Surg*. 2010;5:86.

293. Farkas H, Gyeney L, Gidófalvy E, Füst G, Varga L. The efficacy of short-term danazol prophylaxis in hereditary angioedema patients undergoing maxillofacial and dental procedures. *J Oral Maxillofac Surg*. 1999;57(4):404–408.

294. Jindal AK, Sil A, Aggarwal R, Vinay K, Bishnoi A, Suri D, et al. Management of hereditary angioedema in resource-constrained settings: A consensus statement from Indian subcontinent. *Asia Pac Allergy*. 2023;13(2):60–65.

295. Jindal AK, Singh A, Anjani G, Kaur A, Jaiswal M, Chopra S, et al. Successful perioperative management of three patients with hereditary angioedema without C1 esterase inhibitor therapy: A developing country perspective. *Immunobiology*. 2020;225(6), 152022.

296. Tuncel OK, Gokmen NM, Demur E, Gulbahar O, Pirildar S. *The impact of hereditary angioedema on quality of life and family planning decisions*; 2019 [cited 2023 Oct 4]; Available from: http://acikerisim.ege.edu.tr/xmlui/handle/11454/28561.

297. Nicolas A, Launay D, Duprez C, Citerne I, Morell-Dubois S, Sobanski V, et al. [Impact of disease on daily activities, emotions and quality of life of patients with hereditary angioedema]. *Rev Med Interne*. 2021;42(9):608–615.

298. Caballero T, Prior N. Burden of Illness and Quality-of-Life Measures in Angioedema Conditions. *Immunol Allergy Clin North Am*. 2017;37(3):597–616.

299. Mendivil J, Murphy R, de la Cruz M, Janssen E, Boysen HB, Jain G, et al. Clinical characteristics and burden of illness in patients with hereditary angioedema: findings from a multinational patient survey. *Orphanet J Rare Dis*. 2021;16(1):94.

300. Yamamoto B, Honda D, Ohsawa I, Iwamoto K, Horiuchi T, Fukunaga A, et al. Burden of illness seen in hereditary angioedema in Japanese patients: Results from a patient reported outcome survey. *Intractable Rare Dis Res*. 2023;12(1):35–44.

301. Bork K, Anderson JT, Caballero T, Craig T, Johnston DT, Li HH, et al. Assessment and management of disease burden and quality of life in patients with hereditary angioedema: a consensus report. *Allergy Asthma Clin Immunol*. 2021;17(1):40.

302. Aygören-Pürsün E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, Wait S, et al. Socioeconomic burden of hereditary angioedema: results from the hereditary angioedema burden of illness study in Europe. *Orphanet J Rare Dis*. 2014;9(1):99.

303. Gao Y, Ng S, Al-Shaikhly T, Craig T. Suicide, depression, and anxiety disorders among hereditary angioedema patients. *Journal of Allergy and Clinical Immunology*. 2023;151(2), AB208.

304. Park K, Yeich A, Craig T. Evaluating the Impact of Acute Versus Prophylaxis Therapy in Hereditary Angioedema. *Journal of Allergy and Clinical Immunology*. 2023;151(2):AB135.

305. Medina I, Josviack D, Berardi A, Cavallo C, Chinigo M, Chorzepa G, et al. [Health related to quality life of patients with hereditary angioedema in Argentina. A multicenter study]. *Rev Alerg Mex*. 2023;70(2):64–71.

306. Branco Ferreira M, Baeza ML, Spínola Santos A, Prieto-García A, Leal R, Alvarez J, et al. Evolution of Guidelines for the Management of Hereditary Angioedema due to C1 Inhibitor Deficiency. *J Investig Allergol Clin Immunol*. 2023;33(5):332–362.

307. Buckland Matthew. Putting Guidelines into Practice: Supporting Young People with Hereditary Angioedema to Live Attack-Free. *EMJ*. 2023;8(1):49–53.

308. Jean-Baptiste M, Itzler R, Prusty S, Supina D, Martin ML. The symptom experience of hereditary angioedema (HAE) patients beyond HAE attacks: literature review and clinician interviews. *Orphanet J Rare Dis*. 2022;17(1):232.

309. Maurer M, Aygören-Pürsün E, Banerji A, Bernstein JA, Balle Boysen H, Busse PJ, et al. Consensus on treatment goals in hereditary angioedema: A global Delphi initiative. *Journal of Allergy and Clinical Immunology*. 2021;148(6):1526–1532.

310. Lumry WR, Weller K, Magerl M, Banerji A, Longhurst HJ, Riedl MA, et al. Impact of lanadelumab on health-related quality of life in patients with hereditary angioedema in the HELP study. *Allergy*. 2020;76(4):1188–1198.

311. Lumry WR, Maurer M, Weller K, Riedl MA, Watt M, Yu M, et al. Long-term lanadelumab treatment improves health-related quality of life in patients with hereditary angioedema. *Ann Allergy Asthma Immunol*. 2023;131(1):101–108.e3.

312. Longhurst HJ, Valerieva A. A Review of Randomized Controlled Trials of Hereditary Angioedema Long-Term Prophylaxis with C1 Inhibitor Replacement Therapy: Alleviation of Disease Symptoms Is Achievable. *J Asthma Allergy*. 2023;16:269–277.

313. Hahn J, Trainotti S, Wigand MC, Schuler PJ, Hoffmann TK, Greve J. Prospective Analysis in Patients With HAE Under Prophylaxis With Lanadelumab: A Real-life Experience. *J Drugs Dermatol*. 2020;19(10):978–983.

314. Banerji A, Davis KH, Brown TM, Hollis K, Hunter SM, Long J, et al. Patient-reported burden of hereditary angioedema: findings from a patient survey in the United States. *Ann Allergy Asthma Immunol*. 2020;124(6):600–607.

315. Buttgereit T, Vera C, Weller K, Gutsche A, Grekowitz EM, Aykanat S, et al. Lanadelumab Efficacy, Safety, and Injection Interval Extension in HAE: A Real-Life Study. *J Allergy Clin Immunol Pract*. 2021;9(10):3744–3751.

316. Li HH, Zuraw B, Longhurst HJ, Cicardi M, Bork K, Baker J, et al. Subcutaneous C1 inhibitor for prevention of attacks of hereditary angioedema: additional outcomes and subgroup analysis of a placebo-controlled randomized study. *Allergy Asthma Clin Immunol*. 2019;15:49.

317. Caballero T, Lleonart-Bellfill R, Pedrosa M, Ferrer L, Guilarte M. Expert Review and Consensus on the Treat-to-Target Management of Hereditary Angioedema: From Scientific Evidence to Clinical Practice. *J Investig Allergol Clin Immunol*. 2023;33(4):238–249.

318. Riedl MA, Neville D, Cloud B, Desai B, Bernstein JA. Shared decision-making in the management of hereditary angioedema: An analysis of patient and physician perspectives. *Allergy Asthma Proc*. 2022;43(5):397–405.

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319. Settipane RA, Bukstein DA, Riedl MA. Hereditary angioedema and shared decision making. *Allergy Asthma Proc*. 2020;41(Suppl 1):S55–60.

320. Riedl MA, Craig TJ, Banerji A, Aggarwal K, Best JM, Rosselli J, et al. Physician and patient perspectives on the management of hereditary angioedema: a survey on treatment burden and needs. *Allergy Asthma Proc*. 2021;42(3):S17–25.

321. Banerji A, Anderson J, Johnston DT. Optimal Management of Hereditary Angioedema: Shared Decision-Making. *J Asthma Allergy*. 2021;14:119–125.

322. Maurer M, Magerl M. Long-term prophylaxis of hereditary angioedema with androgen derivates: a critical appraisal and potential alternatives. *J Dtsch Dermatol Ges*. 2011;9(2): 99–107.

323. Frank MM. Update on preventive therapy (prophylaxis) for hereditary angioedema. *Immunol Allergy Clin North Am*. 2013;33(4):495–503.

324. Longhurst H, Cicardi M, Craig T, Bork K, Grattan C, Baker J, et al. Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. *N Engl J Med*. 2017;376(12): 1131–1140.

325. Aygören-Pürsün E, Soteres DF, Nieto-Martinez SA, Christensen J, Jacobson KW, Moldovan D, et al. A randomized trial of human C1 inhibitor prophylaxis in children with hereditary angioedema. *Pediatric Allergy Immunology*. 2019;30(5):553–561.

326. Lumry WR, Martinez-Saguer I, Yang WH, Bernstein JA, Jacobs J, Moldovan D, et al. Fixed-Dose Subcutaneous C1-Inhibitor Liquid for Prophylactic Treatment of C1-INH-HAE: SAHARA Randomized Study. *J Allergy Clin Immunol Pract*. 2019;7(5):1610–1618.e4.

327. Bernstein JA, Manning ME, Li H, White MV, Baker J, Lumry WR, et al. Escalating doses of C1 esterase inhibitor (CINRYZE) for prophylaxis in patients with hereditary angioedema. *J Allergy Clin Immunol Pract*. 2014;2(1):77–84.

328. Krüger R, Dahlinger N, Magerl M, von Bernuth H, Wahn V. Daily subcutaneous administration of human C1 inhibitor in a child with hereditary angioedema type 1. *Pediatr Allergy Immunol*. 2016;27(2):223–224.

329. Weller K, Krüger R, Maurer M, Magerl M. Subcutaneous self-injections of C1 inhibitor: an effective and safe treatment in a patient with hereditary angio-oedema. *Clin Exp Dermatol*. 2016;41(1):91–93.

330. Lumry WR, Craig T, Zuraw B, Longhurst H, Baker J, Li HH, 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(5):1733–1741.e3.

331. Weller K, Maurer M, Fridman M, Supina D, Schranz J, Magerl M. Health-related quality of life with hereditary angioedema following prophylaxis with subcutaneous C1-inhibitor with recombinant hyaluronidase. *Allergy Asthma Proc*. 2017;38(2):143–151.

332. Bernstein JA, Li HH, Craig TJ, Manning ME, Lawo JP, Machnig T, 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.

333. Craig T, Zuraw B, Longhurst H, Cicardi M, Bork K, Grattan C, et al. Long-Term Outcomes with Subcutaneous C1-Inhibitor Replacement Therapy for Prevention of Hereditary Angioedema Attacks. *The Journal of Allergy and Clinical Immunology: In Practice*. 2019;7(6):1793–1802.e2.

334. Craig T, Feuersenger H, Pragst I, Dang J. Prophylactic therapy with subcutaneous C1-inhibitor is associated with sustained symptom control in patients with hereditary angioedema. *Allergy Asthma Proc*. 2022;43(3):202–208.

335. Lumry WR, Zuraw B, Cicardi M, Craig T, Anderson J, Banerji A, et al. Long-term health-related quality of life in patients treated with subcutaneous C1-inhibitor replacement therapy for the prevention of hereditary angioedema attacks: findings from the COMPACT open-label extension study. *Orphanet J Rare Dis*. 2021;16(1):86.

336. Riedl MA, Maurer M, Bernstein JA, Banerji A, Longhurst HJ, Li HH, et al. Lanadelumab demonstrates rapid and sustained prevention of hereditary angioedema attacks. *Allergy*. 2020;75(11):2879–2887.

337. Fain O, Du-Thanh A, Gobert D, Launay D, Inhaber N, Boudjemia K, et al. Long-term prophylaxis with lanadelumab for HAE: authorization for temporary use in France. *Allergy, Asthma and Clinical Immunology*. 2022;18(1):30.

338. Banerji A, Bernstein JA, Johnston DT, Lumry WR, Magerl M, Maurer M, et al. Long-term prevention of hereditary angioedema attacks with lanadelumab: The HELP OLE Study. *Allergy*. 2022;77(3):979–990.

339. Bernstein J, Betschel S, Busse P, Banerji A, Baptist A, Craig T, et al. Long-Term Effectiveness and Safety of Lanadelumab in Patients With Hereditary Angioedema From the United States and Canada: Final Data From the EMPOWER Study. *Journal of Allergy and Clinical Immunology*. 2024;153(2), AB242.

340. Aygören-Pürsün E, Bygum A, Grivcheva-Panovska V, Magerl M, Graff J, Steiner UC, et al. Oral Plasma Kallikrein Inhibitor for Prophylaxis in Hereditary Angioedema. *N Engl J Med*. 2018;379(4):352–362.

341. Kiani-Alikhan S, Gower R, Craig T, Wedner HJ, Kinaciyan T, Aygören-Pürsün E, et al. Once-Daily Oral Berotralstat for Long-Term Prophylaxis of Hereditary Angioedema: The Open-Label Extension of the APeX-2 Randomized Trial. *J Allergy Clin Immunol Pract*. 2024;12(3):733–743.e10.

342. Manning ME, Kashkin JM. Berotralstat (BCX7353) is a novel oral prophylactic treatment for hereditary angioedema: Review of phase II and III studies. *Allergy Asthma Proc*. 2021;42(4):274–282.

343. Beard N, Frese M, Smertina E, Mere P, Katelaris C, Mills K. Interventions for the long-term prevention of hereditary angioedema attacks. *Cochrane Database Syst Rev*. 2022;11(11), CD013403.

344. Watt M, Malmenäs M, Romanus D, Haeussler K. Network meta-analysis for indirect comparison of lanadelumab and berotralstat for the treatment of hereditary angioedema. *J Comp Eff Res*. 2023;12(6), e220188.

345. Mendivil J, Malmenäs M, Haeussler K, Hunger M, Jain G, Devercelli G. Indirect Comparison of Lanadelumab and Intravenous C1-INH Using Data from the HELP and CHANGE Studies: Bayesian and Frequentist Analyses. *Drugs R D*. 2021;21(1):113–121.

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346. Magerl M, Schiffhorst G, Fanter L, Müller G, Hirche C, Berkemeier F, et al. Patient-level indirect treatment comparison of lanadelumab versus pdC1-INH i.v. in hereditary angioedema patients: PATCH study. *Allergy*. 2024;79(1):215–224.

347. Gower RG, Wilber M. Considerations for transition from subcutaneous to oral prophylaxis in the treatment of hereditary angioedema. *Allergy Asthma Clin Immunol*. 2021;17(1):100.

348. Peter JG, Desai B, Tomita D, Collis P, Stobiecki M. Assessment of HAE prophylaxis transition from androgen therapy to berotralstat: A subset analysis of the APeX-S trial. *World Allergy Organ J*. 2023;16(11), 100841.

349. Riedl MA, Soteres D, Sublett JW, Desai B, Tomita D, Collis P, et al. Hereditary angioedema outcomes in US patients switched from injectable long-term prophylactic medication to oral berotralstat. *Ann Allergy Asthma Immunol*. 2024;132(4):505–511.e1.

350. Craig TJ, Reshef A, Li HH, Jacobs JS, Bernstein JA, Farkas H, et al. Efficacy and safety of garadacimab, a factor XIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2023;401(10382):1079–1090. Erratum in: Lancet. 2023;401(10384):1266.

351. Craig TJ, Levy DS, Reshef A, Lumry WR, Martinez-Saguer I, Jacobs JS, et al. Garadacimab for hereditary angioedema attack prevention: long-term efficacy, quality of life, and safety data from a phase 2, randomised, open-label extension study. *Lancet Haematol*. 2024 Jun;11(6):e436–e447, 352. Riedl MA, Tachdjian R, Lumry WR, Craig T, Karakaya G, Gelincik A, et al. Efficacy and Safety of Donidalorsen for Hereditary Angioedema. N Engl J Med. 2024;391(1):21–e447.

352. Riedl MA, Tachdjian R, Lumry WR, Craig T, Karakaya G, Gelincik A, et al. Efficacy and Safety of Donidalorsen for Hereditary Angioedema. *N Engl J Med*. 2024;391(1):21–31.

353. Bouillet L, Boccon-Gibod I, Gompel A, Floccard B, Martin L, Blanchard-Delaunay C, et al. Hereditary angioedema with normal C1 inhibitor: clinical characteristics and treatment response with plasma-derived human C1 inhibitor concentrate (Berinert®) in a French cohort. *Eur J Dermatol*. 2017;27(2):155–159.

354. Kelbel T. A case of normal C1 esterase inhibitor hereditary angioedema successfully treated with berotralstat. *Annals of Allergy, Asthma & Immunology*. 2022;128(4):462–463.

355. Bouillet L, Bocquet A, Belbezier A, Boccon-Gibod I. Effectiveness of lanadelumab in patients with hereditary angioedema with normal C1 inhibitor and FXII mutation. *Ann Allergy Asthma Immunol*. 2021;127(3):391–392.

356. Garcia JFB, Takejima P, Veronez CL, Aun MV, Motta AA, Kalil J, et al. Use of pdC1-INH concentrate for long-term prophylaxis during pregnancy in hereditary angioedema with normal C1-INH. *The Journal of Allergy and Clinical Immunology: In Practice*. 2018;6(4):1406–1408.

357. Riedl MA, Staubach P, Farkas H, Zanichelli A, Ren H, Nurse C, et al. Lanadelumab for prevention of attacks of non-histaminergic normal C1 inhibitor angioedema: results from the randomized, double-blind CASPIAN Study and CASPIAN open-label extension. *Front Immunol*. 2025;16, 1502325.

358. Valerieva A, Caccia S, Cicardi M. Recombinant human C1 esterase inhibitor (Conestat alfa) for prophylaxis to prevent attacks in adult and adolescent patients with hereditary angioedema. *Expert Rev Clin Immunol*. 2018;14(9):707–718.

359. Agostoni A, Cicardi M, Martignoni GC, Bergamaschini L, Marasini B. Danazol and stanozolol in long-term prophylactic treatment of hereditary angioedema. *J Allergy Clin Immunol*. 1980;65(1):75–79.

360. Cicardi M, Bergamaschini L, Cugno M, Hack E, Agostoni G, Agostoni A. Long-term treatment of hereditary angioedema with attenuated androgens: a survey of a 13-year experience. *J Allergy Clin Immunol*. 1991;87(4):768–773.

361. 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(2):153–161.

362. Kesh S, Singh U, Bernstein JA. Longitudinal experience with treatment of acquired angioedema using tranexamic acid. *Allergy Asthma Proc*. 2022;43(5):413–418.

363. Farkas H, Czaller I, Csuka D, Vas A, Valentin S, Varga L, et al. The effect of long-term danazol prophylaxis on liver function in hereditary angioedema-a longitudinal study. *European Journal of Clinical Pharmacology*. 2009;66(4):419–426.

364. Füst G, Farkas H, Csuka D, Varga L, Bork K. Long-term efficacy of danazol treatment in hereditary angioedema. *Eur J Clin Invest*. 2011;41(3):256–262.

365. Riedl MA. Critical appraisal of androgen use in hereditary angioedema: a systematic review. *Annals of Allergy, Asthma & Immunology*. 2015;114(4):281–288.e7.

366. Stankovic I, Vlahovic-Stipac A, Putnikovic B, Cvetkovic Z, Neskovic AN. Concomitant administration of simvastatin and danazol associated with fatal rhabdomyolysis. *Clin Ther*. 2010;32(5):909–914.

367. Bork K, Pitton M, Harten P, Koch P. Hepatocellular adenomas in patients taking danazol for hereditary angio-oedema. *Lancet*. 1999;353(9158):1066–1067.

368. Craig TJ. Appraisal of danazol prophylaxis for hereditary angioedema. *Allergy Asthma Proc*. 2008;29(3):225–231.

369. Sheffer AL, Austen KF, Rosen FS. Tranexamic acid therapy in hereditary angioneurotic edema. *N Engl J Med*. 1972;287(9):452–454.

370. Katelaris CH, Lima H, Marsland A, Weller K, Shah A, Waserman S. How to Measure Disease Activity, Impact, and Control in Patients with Recurrent Wheals, Angioedema, or Both. *J Allergy Clin Immunol Pract*. 2021;9(6):2151–2157.

371. Balla Z, Ignácz B, Varga L, Kőhalmi KV, Farkas H. How Angioedema Quality of Life Questionnaire Can Help Physicians in Treating C1-Inhibitor Deficiency Patients? *Clin Rev Allergy Immunol*. 2021;61(1):50–59.

372. Vanya M, Watt M, Shahraz S, Kosmas CE, Rhoten S, Costa-Cabral S, et al. Content validation and psychometric evaluation of the Angioedema Quality of Life Questionnaire for hereditary angioedema. *J Patient Rep Outcomes*. 2023;7(1):33.

373. Chularojanamontri L, Kulthanan K, Tuchinda P, Rujitharanawong C, Munprom K, Pochanapan O, et al. The validity and reliability of a Thai version of the Angioedema

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Control Test: Which recall period is preferable? *Asian Pac J Allergy Immunol.*. 2023 Jan 3 https://doi.org/10.12932/AP-270822-1442.

374. Kulthanan K, Chularojanamontri L, Rujitharanawong C, Weerasubpong P, Weller K, Maurer M. Angioedema Activity Score (AAS): A Valid and Reliable Tool to Use in Asian Patients. *Biomed Res Int*. 2019;2019, 9157895.

375. Bygum A, Busse P, Caballero T, Maurer M. Disease Severity, Activity, Impact, and Control and How to Assess Them in Patients with Hereditary Angioedema. *Front Med (Lausanne)*. 2017;4:212.

376. Weller K, Donoso T, Magerl M, Aygören-Pürsün E, Staubach P, Martinez-Saguer I, et al. Validation of the Angioedema Control Test (AECT)-A Patient-Reported Outcome Instrument for Assessing Angioedema Control. *J Allergy Clin Immunol Pract*. 2020;8(6):2050–2057.e4.

377. Nordenfelt P, Nilsson M, Lindfors A, Wahlgren CF, Björkander JF. Health-related quality of life in relation to disease activity in adults with hereditary angioedema in Sweden. *Allergy and Asthma Proceedings*. 2017;38(6):447–455.

378. Mansour E, Veronez CL, Craig T, Grumach AS. Hereditary angioedema in children and adolescents. *Allergologia et immunopathologia: International journal for clinical and investigate allergology and clinical immunology*. 2022;50(Extra 1):1–6.

379. Grivcheva-Panovska V, Giannetti B. Hereditary Angioedema Attack in Utero and Treatment of the Mother and Fetus. *Mayo Clin Proc Innov Qual Outcomes*. 2020;4(5):595–600.

380. Christiansen SC, Davis DK, Castaldo AJ, Zuraw BL. Pediatric Hereditary Angioedema: Onset, Diagnostic Delay, and Disease Severity. *Clin Pediatr (Phila)*. 2016;55(10):935–942.

381. Johnston DT, Smith RC. Hereditary angioedema: Special considerations in children. *Allergy Asthma Proc*. 2020;41(Suppl 1):S43–S46.

382. Farkas H, Martinez-Saguer I, Bork K, Bowen T, Craig T, Frank M, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. *Allergy*. 2017;72(2):300–313.

383. Grumach AS, Ceccon ME, Rutz R, Fertig A, Kirschfink M. Complement profile in neonates of different gestational ages. *Scand J Immunol*. 2014;79(4):276–281.

384. Liotti L, Pecoraro L, Mastrorilli C, Castagnoli R, Saretta F, Mori F, et al. Pediatric Angioedema without Wheals: How to Guide the Diagnosis. *Life (Basel)*. 2023;13(4):1021.

385. Aabom A, Andersen KE, Fagerberg C, Fisker N, Jakobsen MA, Bygum A. Clinical characteristics and real-life diagnostic approaches in all Danish children with hereditary angioedema. *Orphanet J Rare Dis*. 2017;12(1):55.

386. Frank MM, Zuraw B, Banerji A, Bernstein JA, Craig T, Busse P, et al. Management of Children With Hereditary Angioedema Due to C1 Inhibitor Deficiency. *Pediatrics*. 2016;138(5), e20160575.

387. Boyle RJ, Nikpour M, Tang MLK. Hereditary angio-oedema in children: a management guideline. *Pediatr Allergy Immunol*. 2005;16(4):288–294.

388. Tachdjian R, Kaplan AP. A Comprehensive Management Approach in Pediatric and Adolescent Patients With Hereditary Angioedema. *Clinical pediatrics*. 2023, 99228231155703.

389. Farkas H, Kőhalmi KV. Icatibant for the treatment of hereditary angioedema with C1-inhibitor deficiency in adolescents and in children aged over 2 years. *Expert Rev Clin Immunol*. 2018;14(6):447–460.

390. Farkas H, Reshef A, Aberer W, Caballero T, McCarthy L, Hao J, et al. Treatment Effect and Safety of Icatibant in Pediatric Patients with Hereditary Angioedema. *J Allergy Clin Immunol Pract*. 2017;5(6):1671–1678.e2.

391. Reshef A, Grivcheva-Panovska V, Kessel A, Kivity S, Klimaszewska-Rembiasz M, Moldovan D, et al. Recombinant human C1 esterase inhibitor treatment for hereditary angioedema attacks in children. *Pediatr Allergy Immunol*. 2019;30(5):562–568.

392. Farkas H, Balla Z. A safety review of prophylaxis drugs for adolescent patients with hereditary angioedema. *Expert Opin Drug Saf*. 2023;22(7):549–561.

393. Norris M, Ashoor Z, Craig T. Management of pediatric hereditary angioedema types 1 and 2: A search for international consensus. *Allergy Asthma Proc*. 2022;43(5):388–396.

394. Lasa EM, Herrero L, Martínez S, Arruti N, Oliver P, Joral A. Use of Concentrated Plasma-Derived Subcutaneous C1 Inhibitor as Long-Term Prophylaxis in an 8-Year- Old Child With Hereditary Angioedema. *J Investig Allergol Clin Immunol*. 2023;33(4):302–304.

395. Hide M, Wang Y, Dote N, Miyakawa K, Sugiura K, Ishida K. Safety, efficacy, and pharmacokinetics of icatibant treatment in Japanese pediatric patients with hereditary angioedema: A phase 3, open-label study. *J Dermatol*. 2023;50(11):1473–1477.

396. Farkas H, Stobiecki M, Peter J, Kinaciyan T, Maurer M, Aygören-Pürsün E, et al. Long-term safety and effectiveness of berotralstat for hereditary angioedema: The open-label APeX-S study. *Clinical & Translational All*. 2021;11(4), e12035.

397. Farkas H, Csuka D, Zotter Z, Varga L, Füst G. Prophylactic therapy in children with hereditary angioedema. *J Allergy Clin Immunol*. 2013;131(2):579–582. e1-2.

398. Farkas H. Pharmacological Management of Hereditary Angioedema with C1-Inhibitor Deficiency in Pediatric Patients. *Paediatr Drugs*. 2018;20(2):135–151.

399. Wahn V, Aberer W, Eberl W, Faßhauer M, Kühne T, Kurnik K, et al. Hereditary angioedema (HAE) in children and adolescents–a consensus on therapeutic strategies. *Eur J Pediatr*. 2012;171(9):1339–1348.

400. Maurer M, Lumry WR, Li HH, Aygören-Pürsün E, Busse PJ, Jacobs J, et al. Lanadelumab in Patients 2 to Less Than 12 Years Old With Hereditary Angioedema: Results From the Phase 3 SPRING Study. *J Allergy Clin Immunol Pract*. 2024;12(1):201–211.e6.

401. Farkas H, Varga L, Széplaki G, Visy B, Harmat G, Bowen T. Management of hereditary angioedema in pediatric patients. *Pediatrics*. 2007;120(3):e713–722.

402. Czaller I, Visy B, Csuka D, Füst G, Tóth F, Farkas H. The natural history of hereditary angioedema and the impact of

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treatment with human C1-inhibitor concentrate during pregnancy: a long-term survey. *Eur J Obstet Gynecol Reprod Biol*. 2010;152(1):44–49.

403. Martinez-Saguer I, Rusicke E, Aygören-Pürsün E, Heller C, Klingebiel T, Kreuz W. Characterization of acute hereditary angioedema attacks during pregnancy and breast-feeding and their treatment with C1 inhibitor concentrate. *Am J Obstet Gynecol*. 2010;203(2):131.e1–131.e7.
404. Satomura A, Fujita T, Nakayama T. Comparison of the Frequency of Angioedema Attack, before and during Pregnancy, in a Patient with Type I Hereditary Angioedema. *Intern Med*. 2018;57(5):751–755.
405. Sankrithi P, Shah K, Bernabe CC. Pregnancy-Induced Exacerbation of Hereditary Angioedema in a Multiparous Caucasian Female. *Cureus*. 2020;12(5), e8006.
406. Caballero T, Canabal J, Rivero-Paparoni D, Cabañas R. Management of hereditary angioedema in pregnant women: a review. *Int J Womens Health*. 2014;6:839–848.
407. Moraes CG de FB de, Mikami LR, Ferrari LP, Pesquero JB, Chong-Neto HJ, Rosario Filho NA. Short-term Prophylaxis for Delivery in Pregnant Women with Hereditary Angioedema with Normal C1-Inhibitor. *Rev Bras Ginecol Obstet*. 2021;42:845–848.
408. Yeich A, Elhatw A, Ashoor Z, Park K, Craig T. Safety of medications for hereditary angioedema during pregnancy and lactation. *Expert Opin Drug Saf*. 2023;22(1):17–24.
409. Évora F, Rodolfo A. Hereditary Angioedema: A Gynecology and Obstetrics Perspective. *Cureus*. 2021;13(11), e19861.
410. Šimac DV, Štimac T, Novak S. Is Icatibant Safe for the Treatment of Hereditary Angioedema During Pregnancy? *Curr Allergy Asthma Rep*. 2022;22(10):135–140.
411. Kaminsky LW, Kelbel T, Ansary F, Craig T. Multiple doses of icatibant used during pregnancy. *Allergy Rhinol (Providence)*. 2017;8(3):178–181.
412. Kardum Ž, Prus V, Milas Ahić J, Kardum D. Successful treatment with Cinryze® replacement therapy of a pregnant patient with hereditary angioedema: a case report. *J Med Case Rep*. 2021;15(1):20.
413. Moldovan D, Bernstein JA, Hakl R, Porebski G, Poarch K, Lumry WR, et al. Safety of recombinant human C1 esterase inhibitor for hereditary angioedema attacks during pregnancy. *J Allergy Clin Immunol Pract*. 2019;7(8):2938–2940.
414. Hakl R, Kuklínek P, Krčmová I, Králíčková P, Freiberger T, Janků P, et al. Treatment of Hereditary Angioedema Attacks with Icatibant and Recombinant C1 Inhibitor During Pregnancy. *J Clin Immunol*. 2018;38(7):810–815.
415. Galan HL, Reedy MB, Starr J, Knight AB. Fresh frozen plasma prophylaxis for hereditary angioedema during pregnancy. A case report. *J Reprod Med*. 1996;41(7):541–544.
416. Hrubišková K, Jeseňák M, Payer J. Initial use of subcutaneous plasma-derived C1 inhibitor in prophylaxis of acute attacks of hereditary angioedema in pregnant patients in Slovakia. *Vnitr Lek*. 2023;69(4):265–268.
417. Caliskaner Z, Ozturk S, Gulec M, Dede M, Erel F, Karaayvaz M. A successful pregnancy and uncomplicated labor with C1INH concentrate prophylaxis in a patient with hereditary angioedema. *Allergol Immunopathol (Madr)*. 2007;35(3):117–119.
418. Farkas H, Csuka D, Tóth F, Kőszegi L, Varga L. Successful pregnancy outcome after treatment with C1-inhibitor concentrate in a patient with hereditary angioedema and a history of four miscarriages. *Eur J Obstet Gynecol Reprod Biol*. 2012;165(2):366–367.
419. Hermans C. Successful management with C1-inhibitor concentrate of hereditary angioedema attacks during two successive pregnancies: a case report. *Archives of gynecology and obstetrics*. 2007;276(3):271.
420. Herraez L, Álvarez Sala P, Mielgo R. Subcutaneous plasma-derived C1 inhibitor for long-term prophylaxis during pregnancy and breast-feeding in a patient with factor XII hereditary angioedema. *J Allergy Clin Immunol Pract*. 2023;11(8):2587–2588.
421. Andarawewa S, Aygören-Pürsün E. Subcutaneous C1-Inhibitor Concentrate for prophylaxis during pregnancy and lactation in a patient with C1-INH-HAE. *Clin Case Rep*. 2021;9(3):1273–1275.
422. Gorman PJ. Hereditary angioedema and pregnancy: a successful outcome using C1 esterase inhibitor concentrate. *Can Fam Physician*. 2008;54(3):365–366.
423. Brunskill PJ. The effects of fetal exposure to danazol. *Br J Obstet Gynaecol*. 1992;99(3):212–215.
424. Wentz AC. Adverse effects of danazol in pregnancy. *Ann Intern Med*. 1982;96(5):672–673.
425. Loli-Ausejo D, Hernández-Martín I, Cabañas R, Entrala A, Gutiérrez-Alvariño M, Martínez-Sánchez N, et al. Tranexamic Acid Plus Bemiparin Sodium as Long- Term Prophylaxis in a Patient With FXII-HAE During Pregnancy: A Case Report. *J Investig Allergol Clin Immunol*. 2020;30(6):464–465.
426. Jindal AK, Barman P, Chawla S, Kaur A, Tyagi R, Sikka P, et al. Management of pregnancy in hereditary angioedema in a resource constrained setting: Our experience at Chandigarh, North India. *Immunobiology*. 2022;227(2), 152175.
427. Gilad O, Merlob P, Stahl B, Klinger G. Outcome following tranexamic acid exposure during breastfeeding. *Breastfeed Med*. 2014;9(8):407–410.
428. Eyice Karabacak D, Can A, Demir S, Yegit OO, Colakoglu B, Buyukozturk S, et al. How Does Pregnancy and Type of Delivery Affect the Clinical Course of Hereditary Angioedema? *Int Arch Allergy Immunol*. 2023;184(12):1216–1224.
429. Wan EL, Elkaim Y, Gao W, Yoon R. Zebras Among Us: Advocating for the 30 Million Americans Living with Rare Disease. *Med Sci Educ*. 2023;33(5):1239–1242.
430. Beaverson KL, Julkowska D, Letinturier MCV, Aartsma-Rus A, Austin J, Bueren J, et al. The IRDiRC Chrysalis Task Force: making rare disease research attractive to companies. *Ther Adv Rare Dis*. 2023;4, 26330040231188979.
431. Wong-Rieger D. Moving from Patient Advocacy to Partnership: A Long and Bumpy Road. Patient 2017;. 2017;10(3):271–276.
432. PlusR. HAE International (HAEi). HAE International [cited 2023 Nov 23] https://haei.org/. Available from:.

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433. Katelaris CH. Self-Management Plans in Patients with Hereditary Angioedema: Strategies, Outcomes and Integration into Clinical Care. *J Asthma Allergy*. 2020;13:153–158.

434. Mühlberg H, Ettl N, Magerl M. An analysis of the teaching of intravenous self-administration in patients with hereditary angio-oedema. *Clin Exp Dermatol*. 2016;41(4):366–371.

435. Zanichelli A, Azin GM, Cristina F, Vacchini R, Caballero T. Safety, effectiveness, and impact on quality of life of self-administration with plasma-derived nanofiltered C1 inhibitor (Berinert®) in patients with hereditary angioedema: the SABHA study. *Orphanet J Rare Dis*. 2018;13(1):51.

436. Aberer W, Maurer M, Reshef A, Longhurst H, Kivity S, Bygum A, et al. Open-label, multicenter study of self-administered icatibant for attacks of hereditary angioedema. *Allergy*. 2014;69(3):305–314.

437. Kreuz W, Rusicke E, Martinez-Saguer I, Aygören-Pürsün E, Heller C, Klingebiel T. Home therapy with intravenous human C1-inhibitor in children and adolescents with hereditary angioedema. *Transfusion*. 2012;52(1):100–107.

438. Bernstein JA, Riedl M, Zacek L, Shapiro RS. Facilitating home-based treatment of hereditary angioedema. *Allergy Asthma Proc*. 2015;36(2):92–99.

439. Abdel-Karim O, Dizdarevic A, Bygum A. Hereditary angioedema: children should be considered for training in self-administration. *Pediatr Dermatol*. 2014;31(6):e132–135.

440. Honda D, Ohsawa I, Mano S, Rinno H, Tomino Y, Suzuki Y. Icatibant promotes patients' behavior modification associated with emergency room visits during an acute attack of hereditary angioedema. *Intractable Rare Dis Res*. 2021;10(2):142–145.

441. Boccon-Gibod I. [Hereditary angioedema: treatment and educational therapeutic program]. *Presse Med*. 2015;44(1):78–88.

442. Nasr IH, Manson AL, Al Wahshi HA, Longhurst HJ. Optimizing hereditary angioedema management through tailored treatment approaches. *Expert Rev Clin Immunol*. 2016;12(1):19–31.

443. Andarawewa S, Aygören-Pürsün E. Individual approach to long-term therapy in patients with hereditary angioedema (HAE-C1-INH): A case series. *Front Allergy*. 2022;3, 949387.

444. Stieber C, Cichon S, Magerl M, Nöthen MM. Clinical Utility Gene Card for hereditary angioedema with normal C1 inhibitor (HAEnC1). *Eur J Hum Genet*. 2017;25(10):e1–4.

445. Williams AH, Craig TJ. Perioperative management for patients with hereditary angioedema. *Allergy Rhinol (Providence)*. 2015;6(1):50–55.

446. Banerji A, Baş M, Bernstein JA, Boccon-Gibod I, Bova M, Dempster J, et al. Expert perspectives on hereditary angioedema: Key areas for advancements in care across the patient journey. *Allergy Rhinol (Providence)*. 2016;7(3):172–181.

447. Ferriani MPL, Eduardo S, Lemos J, Arruda LK, Nunes FL, Dias MM, et al. Insights from the first 820 patients from the Brazilian Multicenter Registry of Hereditary Angioedema: the key role of genetic testing and targeted therapies. *J Allergy Clin Immunol Pract*. 2025. S2213-2198(25)00827-X.

448. Maurer M, Buttgereit T, Magerl M, Schön K, Balla Z, Farkas H. Patient-physician interactions in hereditary angioedema-Key learnings from the coronavirus disease 2019 pandemic. *Clin Transl Allergy*. 2023;13(9), e12300.

449. Riedl MA, Johnston DT, Anderson J, Meadows JA, Soteres D, LeBlanc SB, et al. Optimization of care for patients with hereditary angioedema living in rural areas. *Ann Allergy Asthma Immunol*. 2022;128(5):526–533.

450. Ozturk AB, Baççıoğlu A, Soyer O, Civelek E, Şekerel BE, Bavbek S. Change in Allergy Practice during the COVID-19 Pandemic. *Int Arch Allergy Immunol*. 2021;182(1):49–52.

451. Giavina-Bianchi P, França AT, Grumach AS, Motta AA, Fernandes FR, Campos RA, et al. Brazilian guidelines for the diagnosis and treatment of hereditary angioedema. *Clinics*. 2011;66(9):1627–1636.

452. Caballero T. Treatment of Hereditary Angioedema. *J Investig Allergol Clin Immunol*. 2021;31(1):1–16.

453. Maetzel A, Smith MD, Duckworth EJ, Hampton SL, De Donatis GM, Murugesan N, et al. KVD900, an oral on-demand treatment for hereditary angioedema: Phase 1 study results. *J Allergy Clin Immunol*. 2022;149(6):2034–2042.

454. Aygören-Pürsün E, Zanichelli A, Cohn DM, Cancian M, Hakl R, Kinaciyan T, et al. An investigational oral plasma kallikrein inhibitor for on-demand treatment of hereditary angioedema: a two-part, randomised, double-blind, placebo-controlled, crossover phase 2 trial. *Lancet*. 2023;401(10375):458–469.

455. Riedl M, Aygören-Pürsün E, Lumry W, Farkas H, Zanichelli A, Hao J, et al. Sebetralstat for On-demand Treatment of Hereditary Angioedema Attacks: Results of the Double-blind, Placebo-controlled Phase 3 KONFIDENT Trial. *Journal of Allergy and Clinical Immunology*. 2024;153(2), AB375.

456. Wong JCY, Chiang V, Lam DLY, Lee E, Lam K, Au EYL, et al. Long-term prophylaxis for hereditary angioedema: Initial experiences with garadacimab and lanadelumab. *J Allergy Clin Immunol Glob*. 2023;2(4), 100166.

457. Petersen RS, Bordone L, Riedl MA, Tachdjian R, Craig TJ, Lumry WR, et al. A phase 2 open-label extension study of prekallikrein inhibition with donidalorsen for hereditary angioedema. *Allergy*. 2024;79(3):724–734.

458. Lesage A, Marceau F, Gibson C, Loenders B, Katzer W, Ambrosi HD, et al. In vitro pharmacological profile of PHA-022121, a small molecule bradykinin B2 receptor antagonist in clinical development. *Int Immunopharmacol*. 2022;105, 108523.

459. de Lange M, Petersen RS, Fijen LM, Cohn DM. Long-term prophylactic treatment with deucrictibant for angioedema due to acquired C1-inhibitor deficiency. *J Allergy Clin Immunol*. 2025. S0091-6749(25)00889-9.

460. Riedl MA, Bordone L, Revenko A, Newman KB, Cohn DM. Clinical Progress in Hepatic Targeting for Novel Prophylactic Therapies in Hereditary Angioedema. *J Allergy Clin Immunol Pract*. 2024;12(4):911–918.

461. Lumry W, Gunsior M, Cohen T, Bernard K, Gustafson P, Chung JK, Morabito C. Safety and pharmacokinetics of long-acting plasma kallikrein inhibitor navenibart (STAR-0215) in healthy adults. *Ann Allergy Asthma Immunol*. 2025;135(1):103–111.e2.

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462. Longhurst HJ, Lindsay K, Petersen RS, Fijen LM, Gurugama P, Maag D, et al. CRISPR-Cas9 In Vivo Gene Editing of KLKB1 for Hereditary Angioedema. *N Engl J Med*. 2024;390(5):432–441.

463. Cohn DM, Gurugama P, Magerl M, Katelaris CH, Launay D, Bouillet L, et al. CRISPR-Based Therapy for Hereditary Angioedema. *N Engl J Med*. 2025;392(5):458–467.

464. Chodankar D. Introduction to real-world evidence studies. *Perspect Clin Res*. 2021;12(3):171–174.

465. Jindal AK, Reshef A, Longhurst H. GEHM workgroup (Global Equity in HAE Management). Mitigating Disparity in Healthcare Resources Between Countries for Management of Hereditary Angioedema. *Clin Rev Allergy Immunol*. 2021;61(1):84–97.

466. Gomide MACMS, Toledo E, Valle SOR, Campos RA, França AT, Gomez NP, et al. Hereditary angioedema: quality of life in Brazilian patients. *Clinics*. 2013;68(1):81–83.

467. Liu S, Wang X, Xu Y, Xu Q, Zhi Y. Health-related quality of life and its risk factors in Chinese hereditary angioedema patients. *Orphanet J Rare Dis*. 2019;14(1):191.

468. Ahuja M, Dorr A, Bode E, Boulton APR, Buckland M, Chee S, et al. Berotralstat for the prophylaxis of hereditary angioedema-Real-world evidence data from the United Kingdom. *Allergy*. 2023;78(5):1380–1383.

469. Dorr AD, Chopra C, Coulter TI, Dempster J, Dziadzio M, El-Shanawany T, et al. Lanadelumab for the prevention of hereditary angioedema attacks: A real-world UK audit. *Allergy*. 2023;78(5):1369–1371.

470. Maurer M, Aberer W, Caballero T, Bouillet L, Grumach AS, Botha J, et al. *The Icatibant Outcome Survey: 10 years of experience with icatibant for patients with hereditary angioedema*; 2022 Sep [cited 2023 Sep 20]; Available from: https://www.repository.cam.ac.uk/handle/1810/339925.

471. Kucharczyk A, Matuszewski T, Kurowski M, Juchacz A, Tomasial-Lozowska M, Trębas-Pietraś E, et al. Real-world Treatment Outcomes of Lanadelumab in the Prevention of Hereditary Angioedema Attacks: an Interim Analysis of a Polish, Prospective, Multicenter, Observational Study (CHOPIN). *Journal of Allergy and Clinical Immunology*. 2024;153(2). AB9.

472. Maurer M, Caballero T, Aberer W, Zanichelli A, Bouillet L, Bygum A, et al. Variability of disease activity in patients with hereditary angioedema type 1/2: longitudinal data from the Icatibant Outcome Survey. *J Eur Acad Dermatol Venereol*. 2021;35(12):2421–2430.

473. Mendivil J, DerSarkissian M, Banerji A, Diwakar L, Katelaris CH, Keith PK, et al. A multicenter chart review of patient characteristics, treatment, and outcomes in hereditary angioedema: unmet need for more effective long-term prophylaxis. *Allergy Asthma Clin Immunol*. 2023;19(1):48.

474. Riedl MA, Banerji A, Manning ME, Burrell E, Joshi N, Patel D, et al. Treatment patterns and healthcare resource utilization among patients with hereditary angioedema in the United States. *Orphanet J Rare Dis*. 2018;13(1):180.

475. Anderson J, Levy DS, Lumry W, Koochaki P, Lanar S, Henry Li H. Letting the patients speak: an in-depth, qualitative research-based investigation of factors relevant to health-related quality of life in real-world patients with hereditary angioedema using subcutaneous C1 inhibitor replacement therapy. *Allergy Asthma Clin Immunol*. 2021;17(1):60.

476. Giacomini E, Leogrande M, Perrone V, Andretta M, Bacca M, Chinellato A, et al. Characteristics and Drug Utilization of Patients with Hereditary Angioedema in Italy, a Real-World Analysis. *Healthcare (Basel)*. 2023;11(18):2509.

477. Zanichelli A, Suffritti C, Popescu Janu V, Merlo A, Cogliati C. Real-Life Experience With Subcutaneous Plasma-Derived C1-Inhibitor for Long-Term Prophylaxis in Patients With Hereditary Angioedema: A Case Series. *Front Allergy*. 2022;3, 818741.

478. Bouillet L, Fain O, Armengol G, Aubineau M, Blanchard-Delaunay C, Dalmas MC, et al. Long-term prophylaxis in hereditary angioedema management: Current practices in France and unmet needs. *Allergy Asthma Proc*. 2022;43(5):406–412.

479. Malbrán A, Malbrán E, Menéndez A, Fernández Romero DS. [Hereditary angioedema. Treatment of acute attacks in Argentina]. *Medicina (B Aires)*. 2014;74(3):198–200.

480. Guo Y, Zhang H, Lai H, Wang H, Chong-Neto HJ, Valle SOR, et al. Long-term Prophylaxis with Androgens in the management of Hereditary Angioedema (HAE) in emerging countries. *Orphanet J Rare Dis*. 2022;17(1):399.

481. Yong PFK, Coulter T, El-Shanawany T, Garcez T, Hackett S, Jain R, et al. A National Survey of Hereditary Angioedema and Acquired C1 Inhibitor Deficiency in the United Kingdom. *The Journal of Allergy and Clinical Immunology: In Practice*. 2023;11(8):2476–2483.

482. Giavina-Bianchi P, Giavina-Bianchi M, Oliveira Martins R de, Cristina Fortunato M, Guersoni AC. Unmet needs in the management of hereditary angioedema from the perspective of Brazilian patients. *World Allergy Organ J*. 2024;17(11), 100992.

483. Lumry WR. Pharmacoeconomics of Orphan Disease Treatment with a Focus on Hereditary Angioedema. *Immunol Allergy Clin North Am*. 2017;37(3):617–628.

484. Zozaya N, Caballero T, González-Quevedo T, Gamboa Setien P, González MÁ, Jódar R, et al. A multicriteria decision analysis (MCDA) applied to three long-term prophylactic treatments for hereditary angioedema in Spain. *Grhta*. 2022;9:14–21.

485. Observational real-world evidence update: prophylaxis of hereditary angioedema with Takhzyro and C1 inhibitors : effectiveness and value - Digital Collections - National Library of Medicine [Internet]. [cited 2023 Oct 4]. Available from: https://collections.nlm.nih.gov/catalog/nlm:nlmuid-9918401082906676-pdf.

486. Blasco A, Lázaro P, Caballero T, Guilarte M. Social costs of icatibant self-administration vs. health professional-administration in the treatment of hereditary angioedema in Spain. *Health Economics Review*. 2013;3(1):1–11.

487. Li PH, Pawankar R, Thong BYH, Fok JS, Chantaphakul H, Hide M, et al. *Epidemiology, management and treatment access of hereditary angioedema in the Asia Pacific Region: outcomes from an international survey*; 2022 [cited 2023 Sep 5]; Available from: http://hub.hku.hk/handle/10722/323583.

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488. Mallbris L, Nordenfelt P, Björkander J, Lindfors A, Werner S, Wahlgren CF. The establishment and utility of Sweha-Reg: a Swedish population-based registry to understand hereditary angioedema. *BMC Dermatology*. 2007;7(1):6.

489. Cancian M, Perego F, Senter R, Arcoleo F, De Pasquale T, Zoli A, et al. Pediatric angioedema: Essential features and preliminary results from the Hereditary Angioedema Global Registry in Italy. *Pediatr Allergy Immunol*. 2020;31(Suppl 24): 22–24.

490. Llosa OC, Campos DRM, Sousa JIL, Arruda-Chaves E, Rojas EC, Rojas JRP, et al. Clinical practice guidelines: screening, diagnosis and management of acute events and prophylaxis of hereditary angioedema - Part I: Diagnostic approach. *Arq Asma Alerg Imunol*. 2020;4(4):382–393.

491. Llosa OC, Campos DRM, Sousa JIL, Arruda-Chaves E, Rojas EC, Rojas JRP, et al. Clinical practice guidelines: screening, diagnosis and management of acute events and prophylaxis of hereditary angioedema - Part II: Management and treatment. *Arq Asma Alerg Imunol*. 2020;4(4):394–414.

492. Wong JCY, Chiang V, Lam K, Tung E, Au EYL, Lau CS, et al. Prospective Study on the Efficacy and Impact of Cascade Screening and Evaluation of Hereditary Angioedema (CaSE-HAE). *J Allergy Clin Immunol Pract*. 2022;10(11):2896–2903.e2.

493. Li PH, Pawankar R, Thong BY, Fok JS, Chantaphakul H, Hide M, et al. Epidemiology, Management, and Treatment Access of Hereditary Angioedema in the Asia Pacific Region: Outcomes From an International Survey. *J Allergy Clin Immunol Pract*. 2023;11(4):1253–1260.

494. Wong JCY, Tsui CCW, Lao KCW, Abong J, Ali A, Bhattarai D, et al. Advocacy in Action: International Patient Group Improves Hereditary Angioedema Diagnosis and Care Across the Asia-Pacific. *Clin Exp Allergy*. 2025 Jan 12;55(8): 742–744.

495. Xu Y, Liu S, Wang X, Chen W, Cheng L, Guo Y, et al. Expert Consensus on the Diagnosis and Treatment of Hereditary Angioedema in China (2024 Edition). *Int Arch Allergy Immunol*. 2025 Apr;10:1–13.

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