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International Guideline on the Diagnosis and Management of Pediatric Patients With Hereditary Angioedema

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ABSTRACT

Hereditary angioedema (HAE) with C1 inhibitor deficiency is a rare disease characterized by unpredictable episodes of tissue swelling (angioedema), which, in most cases, occur first under the age of 18 years, and entail a significant burden of disease not only for the patients but also for their families. Clinical symptoms of HAE are not specific, which may cause difficulties in differential diagnosis. Additionally, if not appropriately treated, HAE attacks can be life-threatening. The international HAE guidelines published so far have focused mainly on adults. A guideline that refers to the age-specific characteristics of pediatric patients, both in terms of diagnosis and management, was therefore needed. The International Steering Committee and Taskforce developed recommendations and provided evidence-based grading based on expert opinion and strength of evidence. Recommendations were presented to, discussed, and electronically voted by healthcare professionals during the 14th C1 Inhibitor Deficiency and Angioedema Workshop in Budapest, Hungary, 2025. This international guideline will ensure early diagnosis, standardized and up-to-date treatment, and promote the availability of effective therapies for all

Abbreviations: AA, attenuated androgens; ACARE, Angioedema Center of Reference and Excellence; ACEI, angiotensin converting enzyme inhibitor; AE, angioedema; AE-MC, mast cell-mediated angioedema; BDKRB2, bradykinin B2 receptor; BK, bradykinin; C1INH, C1 inhibitor protein; CARE, Chronic Angioedema Registry; CCC, Comprehensive Care Center; CPK, creatine phosphokinase; DBS, dried blood spot; ECOCs, estrogen-containing oral contraceptives; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; FFP, fresh frozen plasma; FXIIa, activated factor XII; HAE, hereditary angioedema; HAE-C1INH, hereditary angioedema due to C1 inhibitor deficiency; HAE-C1INH-Type1, hereditary angioedema due to decreased production of C1 inhibitor; HAE-C1INH-Type2, hereditary angioedema due to production of dysfunctional C1 inhibitor; HAEi, Hereditary Angioedema International; HAE-nC1INH, hereditary angioedema with normal C1 inhibitor; HAWK Group, Hereditary Angioedema Working Group; HK, high molecular weight kininogen; HR-QoL, health-related quality of life; ITF, International Taskforce; IV, intravenous; LMIC, low- to middle-income country; LTP, long-term prophylaxis; MOA, mode of action; pdC1INH, human plasma-derived C1 inhibitor concentrate; ped-HAE-C1INH, pediatric patients with HAE-C1INH; PedP, pediatric patient; P-GM, Pediatric HAE Guideline Meeting; PKa, plasma kallikrein; PO, *per os* (oral administration); QoL, quality of life; rhC1INH, recombinant human C1 inhibitor concentrate; ROA, route of administration; SAE, serious adverse event; SC, subcutaneous; SDP, solvent detergent plasma; SERPING1, Serine Protease Inhibitor Gene 1; StCom, Steering Committee; STP, short-term prophylaxis; TEAE, treatment-emergent adverse event; TXA, tranexamic acid; UAAE, upper airway angioedema.

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pediatric patients affected with this rare disease. It also draws attention to the importance of establishing HAE centers and registries, which solicit specialist care and research of the disease.

1 | Introduction

Hereditary angioedema (HAE) is a rare disease characterized by recurrent, unpredictable swelling episodes (angioedema, AE) most commonly caused by bradykinin release. The burden of HAE is substantial; therefore, several special factors should be considered, particularly when managing pediatric patients (PedPs). The most prevalent form of HAE (estimated prevalence is 1:50,000 [1]) is associated with inborn deficiency, or dysfunction of C1 inhibitor (C1INH) (HAE-C1INH). Since the publication of the first international pediatric HAE-C1INH consensus in 2017 [2], significant advancements have been made in the diagnosis and management of PedPs with HAE-C1INH (ped-HAE-C1INH). There is a current unmet need for updated, evidence-based practice parameters to guide clinical care.

New emerging HAE types with normal C1INH (HAE-nC1INH) have been described in the last 25 years, with a much lower prevalence than HAE-C1INH, but their true prevalence is unknown. In these HAE types, the first clinical symptoms usually occur in adulthood, the pathophysiology remains poorly understood, there are no approved treatments, and no clinical trials have been conducted [3]. Therefore, the authors agreed that HAE-nC1INH would not be included within the scope of this guideline; however, the available literature is summarized in Data S1: Section 1. Throughout this guideline, HAE refers to all types of HAE, including HAE-nC1INH, while HAE-C1INH is used when a statement is only true for this endpoint.

2 | Scope and Purpose

The objective of this guideline is to provide evidence-based recommendations for the management of ped-HAE-C1INH. This includes diagnosis, treatment of HAE attacks, short-term (STP) and long-term prophylaxis (LTP), and recommendations for self-administration, individualized therapy, quality of life (QoL), and comprehensive care. It is anticipated that this guideline will provide practicing physicians (especially pediatricians) with valuable information about the management of HAE and promote knowledge transfer to non-specialist clinicians.

3 | Intended Audience

The intended target users of this pediatric guideline are healthcare providers caring for patients with AE. Since HAE is often managed by multidisciplinary teams, the providers who may use this guideline are: pediatricians, allergists, immunologists, internists, dermatologists, otolaryngologists, surgeons, dentists, emergency department physicians, nurses, pharmacists, policy makers, hospital administrators,

genetic counselors, and payers. This guideline is intended for a global audience, and its recommendations were synthesized with the aim of supporting equitable care and outcomes across diverse populations and healthcare settings with variable resources.

4 | Methods

4.1 | Steering Committee, International Taskforce, and the HAWK Group

The Steering Committee (StCom) was composed of the authors of the previous international consensus on the management of ped-HAE-C1INH², all experienced HAE specialists, and expanded by three additional experts. They defined the scope and purpose of the guideline and selected the members of the International Taskforce (ITF). The Hereditary Angioedema Working Group (HAWK Group) consisted of the representatives of Hereditary Angioedema International (HAEi) and healthcare professionals who attended the Pediatric HAE Guideline Meeting (P-GM), held during the 14th C1 Inhibitor Deficiency and Angioedema Workshop on May 30, 2025, in Budapest, Hungary, <https://2025.haenetworkshop.hu> (Data S1: Section 2).

4.2 | Identifying the Evidence

Literature search was performed with a focus on articles published from January 1, 2016, to January 14, 2025. PubMed and OVID-Medline databases were searched (Data S1: Section 3). Later, newly published articles were monitored, and relevant information was incorporated into the guideline.

4.3 | Summarizing and Evaluating the Evidence

The level of evidence was decided based on the quality of articles supporting the recommendation (Table 1 [4]), and the strength of recommendation based on the GRADE recommendations (Table 2 [5]).

4.4 | Recommendation Development and Approval

Experts from the StCom and ITF reviewed the published evidence and developed recommendations based on the aforementioned criteria (Tables 1 and 2) through multiple rounds of deliberation. The recommendations were presented with the proposed level of evidence and strength of recommendation to the attendees of the P-GM. Attendees then voted anonymously via electronic voting. 80% consensus was acceptable (Figure S1).

5 | Results

5.1 | Nomenclature, Definitions

Classification and nomenclature of HAE in PedPs do not differ from that of adults [6, 7]. Information on specific age groups within the HAE pediatric population differs from country to country; PedPs are underrepresented in HAE registries (Data S1: Section 5 and Table S1). Only a handful of PedPs have been included in the recently established International Chronic Angioedema Registry (CARE) [8].

Although the pediatric population is biologically heterogeneous [9], pediatric sections of the international HAE guidelines and pediatric consensus documents [2, 4, 10] address

ped-HAE-C1INH under 18 years of age and do not specify age groups (Data S1: Section 6).

Consistent with the International Council for Harmonization guidelines, we are proposing four pediatric age groups as suggested by the FDA, with slight modifications [11]:

- *Age category I. Neonates:* birth through younger than one month
- *Age category II. Infants:* one month to younger than two years
- *Age category III. Children:* 2 years to younger than 12 years
- *Age category IV. Adolescents:* 12 years to younger than 18 years

RECOMMENDATION 1

We recommend that future clinical studies consider the dynamic development milestones of pediatric patients with hereditary angioedema and stratify them accordingly.

91% agreement	Level of evidence: consensus
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RECOMMENDATION 2

We recommend that national and international hereditary angioedema repositories report pediatric patient census periodically.

92% agreement	Level of evidence: consensus
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TABLE 1 | Level of evidence.

Quality of evidence	Meaning
High	Randomized, double-blind clinical trial of high quality (e.g., sample size calculation, flow chart of patient inclusion, intention-to-treat (ITT) analysis, and sufficient sample size)
Moderate	Randomized clinical trial of lesser quality (e.g., only single-blind, limited sample size: at least 15 patients per study arm)
Low	Comparative trial with severe methodological limitations (e.g., not blinded, very small sample size, and no randomization) or large retrospective observational study, large open-label study, registry data
Consensus	Adapted from existing consensus document or statement based on expert opinion voting during consensus conference, evidence not in the previous groups

Note: Table adapted from Maurer et al. [4].

5.2 | Pathophysiology of HAE-C1INH

HAE-C1INH is caused by C1INH deficiency resulting from pathogenic variants in the *SERPING1* gene [12]. To date, more than 800 variants have been described that are considered pathogenic/likely pathogenic [13]. They result in impaired synthesis of C1INH (HAE-C1INH-Type1) or synthesis of dysfunctional C1INH (HAE-C1INH-Type2) [14]. C1INH is a protein responsible for inhibiting numerous proteases, mainly in

TABLE 2 | Strength of recommendation.

Strength of recommendation	Wording	Meaning
Strong recommendation for	We recommend...	We believe that all or almost all informed people would make a choice in favor of using this intervention.
Weak recommendation for	We suggest...	We believe that most informed people would make a choice in favor of using this intervention, but a substantial number would not.
No recommendation	We cannot make a recommendation with respect to...	Currently, a recommendation in favor of or against using this intervention cannot be made due to certain circumstances (eg, unclear or balanced benefit-risk ratio, no data available).
Weak recommendation against	We suggest against...	We believe that most informed people would make a choice against using this intervention, but a substantial number would not.
Strong recommendation against	We recommend against...	We believe that all or almost all informed people would make a choice against using this intervention.

Note: Table adapted from Andrews et al. [5].

the complement (C1r, C1s, mannose-associated serine protease 1 and 2), contact (plasma kallikrein (PKa), factor XIIa), fibrinolysis pathway (plasminogen-plasmin), and intrinsic coagulation (factor XIa) systems [15]. Reciprocal activation of factor XII and plasma prekallikrein results in active PKa, which cleaves high molecular weight kininogen (HK), releasing bradykinin (BK) [16]. This cascade is not sufficiently inhibited in C1INH deficiency. As a result, BK is produced in excess, binds to its bradykinin B2 receptor (BDKRB2), which is constitutively present on vascular endothelial cells and is considered to be responsible for mediating endothelial hyperpermeability and angioedema in HAE-C1INH [17]. Activation by BK triggers intracellular signaling mechanisms that ultimately lead to the opening of cadherin endothelial junctions, increased vascular permeability, and AE formation [12] (Figure 1).

5.3 | Diagnosis of HAE-C1INH

5.3.1 | Clinical Symptoms

The characteristic symptoms of HAE-C1INH in PedPs (similarly to adults) include recurrent swelling of the subcutaneous and/or submucosal tissues. Although the genetic variant is present from conception, clinical symptoms are extremely uncommon (but have been reported) in utero and during infancy [18]. The usual age of onset of attacks varies from 4.4 to 18 years with a mean age of first attack at the age of 10, with no difference between boys and girls [19–22]. Early onset of symptoms may predict a more severe subsequent course of disease [20, 21, 23, 24]. The frequency and severity of the symptoms show intra- and inter-individual variability. Symptoms often worsen during puberty most likely due to hormonal changes [22, 25, 26].

Subcutaneous AE (of the extremities, face, trunk, and genitals) without wheals or itching is the most common and often the earliest symptom in PedPs. It may last 1 to 5 days before resolving spontaneously [27]. Erythema marginatum, a map-like rash, is reported as a prodromal symptom in 42%–58% of PedPs [23]. Facial AE may extend to the upper airway mucosa [19, 20, 28].

AE of the submucosal tissue of the *intestinal wall* can cause abdominal tenderness, colicky abdominal pain, nausea with vomiting, diarrhea, and hypovolemia. Cases of intestinal obstruction (ileus) and intussusception have also been described [19, 20, 23, 28]. As abdominal pain is frequent in the general pediatric population, abdominal attacks may be an unrecognized symptom of HAE-C1INH [29–31].

Symptoms of *upper airway angioedema (UAAE)* include lump sensation, dysphagia, hoarseness, aphonia, tachypnea, dyspnea, and stridor [32]. In general, UAAE first occurs after the age of 11 and is life-threatening, often causing death from asphyxiation if left untreated. Compared to adults, death by asphyxiation is less common in ped-HAE-C1INHS [33], however, upper airway obstruction may develop quickly in children due to smaller airway diameters, necessitating immediate medical attention [34–38].

5.3.2 | Laboratory Testing

5.3.2.1 | Complement Testing. The diagnosis of HAE-C1INH is easily established by the biochemical evaluation of quantitative (antigenic) and/or functional (activity) C1INH. HAE-C1INH-Type1 and HAE-C1INH-Type2 can be differentiated based on these measurements [4, 39]. C4 levels are low in HAE-C1INH due to the activation of the classical pathway of the complement system. Consequently, C4 levels are used as a screening test in resource-limited settings. Specific biochemical analysis of quantitative and functional C1INH and C4 is mandatory for a definitive diagnosis (Table 3).

The accurate performance of plasma complement tests requires careful sample collection, freezing, and storage [40, 41]. Recently, dry blood spot (DBS) sampling was introduced for complement testing, making sample handling easier [42, 43].

Early identification of ped-HAE-C1INH is essential; however, some aspects must be considered regarding the levels of complement system proteins in the first year of life [2]. Complement levels in the umbilical cord blood of full-term neonates can be lower than maternal levels due to the immaturity of the complement system [44–49].

Both antigenic and functional C1INH levels in newborns correspond to approximately 60% to 70% of adult values [50–52]. Premature babies have lower quantitative and functional C1INH than full-term newborns [51, 53]. C1INH reaches adult levels in most cases at 6 months to 1 year of age. Therefore, complement tests performed before this period should be repeated after one year of age [54, 55].

The use of C4 levels for screening could also lead to misdiagnosis if performed early in life, and cases of congenital C4 deficiency may obscure proper diagnosis [46, 56] (Figure 2).

5.3.2.2 | Genetic Testing. Genetic testing is not required to confirm the diagnosis of HAE-C1INH, unless preimplantation diagnosis or prenatal testing is considered, or in cases where biochemical tests are uncertain, as is the case in neonates and early infancy. Genetic analysis can be of significant assistance in instances where biochemical analyses are not feasible locally. Genetic testing can be performed on blood from the umbilical cord, peripheral blood, or buccal swab [2, 45, 57]. However, in case of a buccal swab, a proper sampling method should be used to ensure the sufficient quality and quantity of the acquired DNA.

Genetic diagnosis may be helpful in cases where the disease-causing gene variant in the family is known. However, the gene variant responsible for C1INH deficiency (*SERPING1*) is only identified in 90% to 92% of patients with HAE-C1INH [58, 59]. Thus, in cases where the disease-causing gene variant in the family is not known, a negative genetic test does not totally exclude the diagnosis of HAE-C1INH. Pathogenic and non-pathogenic *SERPING1* mutations have been recorded in genetic repositories [60] (Figure 2).

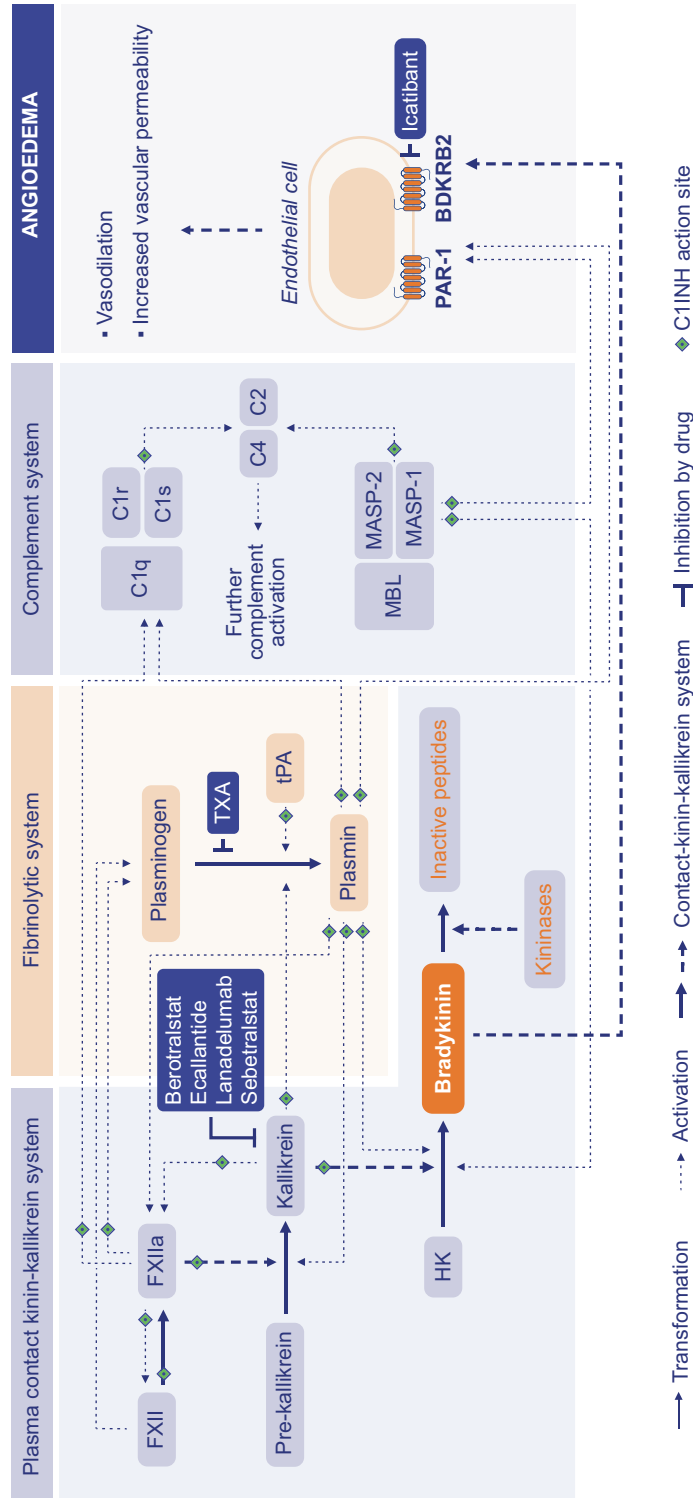


FIGURE 1 | Pathomechanism of hereditary angioedema due to C1INH deficiency and mechanism of action of current treatment options. Continuous arrows represent the transformation; dashed arrows represent the activation; bolded arrows highlight the contact-kinin-kallikrein system; T-shaped lines represent inhibition by drugs; the green rectangles highlight the sites of action of C1INH. The figure only presents drugs that were approved for pediatric patients at the time of the Pediatric HAE Guideline Meeting. Attenuated androgens are not presented in the figure because their exact mechanism of action is not known. Abbreviations: BDKRB2, Bradykinin B2 receptor; C1INH, C1 inhibitor protein; HK, High molecular weight kininogen; MASP, Mannose-associated serine protease; MBL, Mannose-binding lectin; PAR, Protease-activated receptor.

TABLE 3 | Biochemical analysis of complement parameters in different types of HAE.

	C4	C1INH antigenic level	C1INH functional activity	C1q
HAE-C1INH-Type1	↓	↓	↓	Normal
HAE-C1INH-Type2	↓	Normal/↑	↓	Normal
HAE-nC1INH	Normal	Normal	Normal	Normal

Note: C1q is not mandatory for the diagnosis but can be useful for differential diagnosis.

Abbreviations: C1INH, C1 inhibitor protein; HAE-C1INH-Type1, Hereditary angioedema due to decreased production of C1 inhibitor; HAE-C1INH-Type2, Hereditary angioedema due to production of dysfunctional C1 inhibitor; HAE-nC1INH, Hereditary angioedema with normal C1 inhibitor.

Genetic analysis allows the identification of a pathogenic gene variant in the embryo during the gestational period [61]. The decision whether to perform prenatal diagnosis should be made by the parents after receiving appropriate counseling and careful evaluation of the benefits and risks.

5.3.3 | Family History/Family Screening, Newborn Screening

Early identification of HAE in PedPs through family and newborn screening can improve access to life-saving treatments, reduce the burden of disease, and minimize parental anxiety [45, 62, 63]. Inheritance of HAE is autosomal dominant, meaning that screening first-degree relatives carries a high yield. Family history of HAE-C1INH can be absent in 25% of cases (*de-novo* pathogenic variants). Recent studies highlight that the implementation of family screening programs exhibits considerable global variability, influenced by factors such as healthcare infrastructure, cultural attitudes, and health literacy [62, 64, 65].

Establishing family-based outreach screening programs and culturally sensitive education could improve acceptance of family screening and detection rates [40, 66]. The increasing availability and improved affordability of genetic testing will also ensure more equitable access to family and newborn screening strategies [67]. When the family genetic variant is known, genetic testing can be a convenient and accurate method of neonatal testing (Figure 2A).

5.3.4 | Differential Diagnosis of HAE-C1INH

Angioedema attacks in patients with HAE-C1INH can mimic several conditions, potentially leading to delayed and misdiagnosis [68]. Since the clinical manifestation of HAE-nC1INH is almost the same as that of HAE-C1INH, this disorder is one of the most important differential diagnostic options [3].

Clinicians evaluating attacks of AE in patients suspected of having HAE-C1INH without a family history of HAE should consider a wider differential of medical conditions depending on clinical presentations, such as upper airway obstruction, abdominal pain syndromes, and subcutaneous swelling, pain, or rash [69].

Subcutaneous AE of the extremities, trunk, and face might mimic allergic or immunoregulatory diseases, such as systemic lupus erythematosus, juvenile dermatomyositis, orofacial granulomatosis (Melkersson-Rosenthal Syndrome), hypocomplementemic urticarial vasculitis syndrome,

capillary-leak syndrome (Clarkson's disease), cellulitis, ethmoiditis, and contact dermatitis, or post-traumatic swelling [68]. *Genital AE* may be misdiagnosed as orchitis or testicular torsion [23]. *Erythema marginatum* is often misdiagnosed as urticaria [70, 71].

As unexplained *abdominal pain* is very common in infants and children, a number of causes should be considered, such as colic, constipation, viral gastroenteritis, acute appendicitis, intussusception, and volvulus, among other less common conditions [69]. In contrast, children presenting with a history of recurrent relentless episodes of colicky abdominal pain should be screened for HAE-C1INH, regardless of family history of this disease [72]. During abdominal AE attacks, intestinal-wall edema and free peritoneal fluid (ascites) should be looked for by abdominal ultrasound, CT scan, or MRI in the emergency department [29, 30, 73–80]. Complete blood count and blood chemistry are often not helpful because neutrophilia and a mild increase in CRP and D-dimer may occur secondary to an HAE attack [81–85]. Clinical response to HAE-specific acute medications helps to confirm abdominal HAE attack in cases of high suspicion of HAE.

The differential diagnosis of *UAAE* in pediatrics includes allergic food reactions, croup, pseudocroup, foreign body aspiration, and acute epiglottitis [23].

Progression of symptoms and treatment response can help narrow the differential diagnosis. In clinical practice, differentiation of mast cell-mediated AE (AE-MC) and BK-mediated AE is the primary focus, as there is limited data regarding other types of AE in the pediatric population. AE-MC, such as in the case of anaphylaxis, with or without urticaria (hives), is associated with a rapid onset and progression (within minutes to a few hours), good response to antihistamines, glucocorticoids, or epinephrine, and resolution within 12 to 24 h from the onset. Wheezing, hypotension, and nausea/vomiting may be associated and exposure to a known trigger (i.e., allergen) can support this diagnosis [86]. In contrast, HAE attacks tend to peak at 12 to 24 h from onset and may persist up to several days; they do not respond to epinephrine, H1-antihistamines, or glucocorticoids—all of which are clues to help clinicians differentiate between BK- and MC-mediated AE [86, 87].

RECOMMENDATION 3

We suggest clinicians evaluating a pediatric patient presenting with recurrent peripheral edema and/or upper airway edema and/or recurrent abdominal pain of unknown origin to consider hereditary angioedema and to perform laboratory testing for the diagnosis of hereditary angioedema regardless of family history of angioedema.

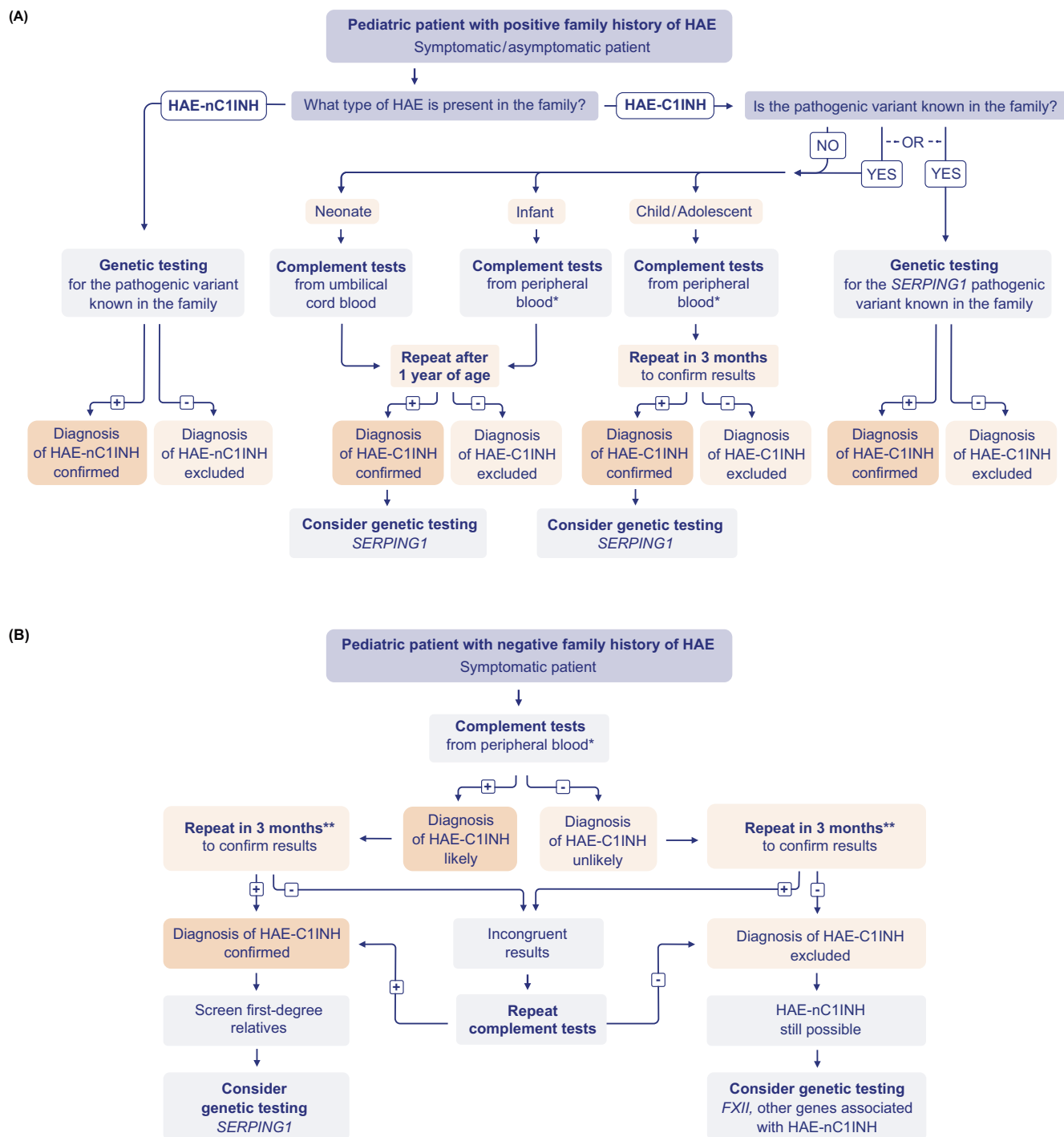


FIGURE 2 | Diagnostic algorithm of hereditary angioedema with (A) or without (B) positive family history of hereditary angioedema. *Also possible from dried blood samples. **Second test should be after one year of age. +: Positive complement tests (decreased C1INH functional activity). -: Negative complement test (normal C1INH functional activity and antigenic concentration, normal C4 levels). Abbreviations: HAE, Hereditary angioedema; HAE-C1INH, Hereditary angioedema due to C1 inhibitor deficiency; HAE-nC1INH, Hereditary angioedema with normal C1 inhibitor.

96% agreement Level of evidence: consensus

96% agreement Level of evidence: high

RECOMMENDATION 4

We recommend that all first-degree relatives of hereditary angioedema patients be considered to be at risk of this disease and should be tested as early as possible.

RECOMMENDATION 5

We recommend performing biochemical analysis of C4 level, C1 inhibitor antigenic and functional levels in pediatric patients who are suspected to have hereditary angioedema. Two congruent

results are required for the confirmation or exclusion of the diagnosis of hereditary angioedema with C1 inhibitor deficiency.

89% agreement	Level of evidence: high
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RECOMMENDATION 6

We recommend that pediatric patients who are first-degree relatives of patients with hereditary angioedema with normal C1 inhibitor, are screened for the pathogenic variant known in the family.

83% agreement	Level of evidence: consensus
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RECOMMENDATION 7

We recommend that pediatric patients who have symptoms characteristic of hereditary angioedema without a family history of hereditary angioedema and with normal C4, C1 inhibitor antigenic and functional levels, are assessed for the known pathogenic variants.

85% agreement	Level of evidence: consensus
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RECOMMENDATION 8

We recommend screening newborns with a positive family history of hereditary angioedema with complement testing (C4 level, C1 inhibitor antigenic and functional levels) and/or genetic tests if the pathogenic variant is known in the family. Complement tests should be repeated after one year of age.

81% agreement	Level of evidence: moderate
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5.4 | Management of HAE

5.4.1 | Comprehensive Care Centers, Transition Process From Pediatric to Adult Care

Comprehensive care centers (CCCs) are an important resource in the management of HAE, as the multi-faceted nature of the disease requires the availability of specialized resources in terms of diagnostics and therapy, as well as coordinated care by various specialists throughout the patient's lifetime [88–90]. Where a CCC cannot provide its own pediatric care by an expert, close cooperation with the associated pediatric department is essential. To ensure the quality of care provided by a CCC on a sustained basis, regular auditing by an external institution should be considered.

In the majority of ped-HAE-C1INHs, other family members are also affected. This allows centers in which pediatric and adult patients are treated under one roof to implement a family-centered approach. The transition from pediatric to adult services must be prepared early (at approximately 12–15 years of age) and in a structured manner [89, 91] (Data S1: Section 7).

RECOMMENDATION 9

We recommend the follow-up of pediatric patients with hereditary angioedema to be done by experienced clinicians at a specialized comprehensive care center.

94% agreement	Level of evidence: consensus
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RECOMMENDATION 10

We recommend ensuring the transition of hereditary angioedema patients from pediatric to adult care for continuous patient care by starting discussions with patients, caregivers, and their future physicians at an early stage

88% agreement	Level of evidence: consensus
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5.4.2 | Education, Counseling

HAE imposes a pervasive burden upon affected PedPs and their family [92–94]. Fortunately, the available options for acute and prophylactic treatments provide an optimistic prospect for PedPs to enjoy a future free of disease-related restrictions.

HAE-specific education is essential for PedPs, family members, and caregivers [23, 44, 95, 96] (Data S1: Section 8). Patient organizations serve as resources for management insights, care guidelines, and support networks. Written information detailing the nature of HAE, potential triggers, identification of early attack signs and symptoms, treatments, action plans, and acute and prophylactic therapy should be available to PedPs and all responsible caretakers. Medication self-administration techniques, storage, refill processes, emergency and expert physician contacts must be clearly delineated. Emergency Cards and multilingual action plans are recommended. The action plan contains what medication to use, how and when to use it in case of an HAE attack, and when further medical care is necessary. The overarching goal of childhood management is to coordinate a therapeutic plan designed to enable PedPs' full engagement in social, academic, or physical activities of their choice [97, 98].

RECOMMENDATION 11

We recommend regular education about the course of the disease, early recognition of angioedema symptoms, treatment administration training of children/adolescents, and multidisciplinary counseling services of pediatric patients with hereditary angioedema and their families.

96% agreement	Level of evidence: consensus
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RECOMMENDATION 12

We recommend contacting and educating teachers, coaches, physicians, and others who have care or supervision of pediatric patients with hereditary angioedema and providing them with written information about the disease and treatment,

especially the acute treatment of hereditary angioedema attacks. Educational material should be developed with the local community, accessible in preferred languages, to ensure effective communication.

95% agreement	Level of evidence: consensus
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RECOMMENDATION 13

We recommend that all pediatric patients with hereditary angioedema and their caregivers be informed about national patient organizations and HAE International

93% agreement	Level of evidence: consensus
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5.4.3 | Trigger Factors/Primary Prevention

5.4.3.1 | Trigger Factors. A multitude of factors may trigger HAE attacks at any age; however, most attacks occur spontaneously [99–101]. Mechanical trauma, physical exertion, dental and surgical procedures, weather changes, airway infections, drugs, and occasionally, mental stress and food may provoke HAE attacks [23, 102–108]. Dental eruption is not a frequent trigger, but could also act as a provoking factor [109]. In adolescent girls, menstruation, ovulation, and estrogen-containing contraceptives (ECOCs) are additional triggers [25, 110–112].

5.4.3.2 | Primary Prevention. The aim of primary prevention is to avoid trigger factors to prevent HAE attacks. However, the activities and lifestyle of patients should be kept as normal as possible. Physical activity, which is beneficial to the healthy development of children and adolescents, should be encouraged individually, and unjustified restrictions on activity should be avoided. However, physical sports should be considered carefully [109, 113]. Dental, surgical procedures, and endoscopy may provoke HAE attacks [114] (see the section on STP). Upper airway infections are common triggers of HAE attacks in ped-HAE-C1INH; therefore, their prevention can reduce HAE's impact on patients' lives. Mandatory and non-mandatory vaccinations are recommended as they have proven to be both safe and effective [2, 4]. There is no relationship between duration of breastfeeding, timing of cow's milk introduction, age at symptom onset, and localization of the attacks [115].

Angiotensin converting enzyme inhibitors (ACEIs) and ECOCs, which may initiate or aggravate HAE attacks, should be avoided in pediatric HAE patients whenever possible. Although ACEIs are less often needed during childhood, early initiation of ECOCs in girls is increasingly common. Hormonal contraception with progestin-only pills may be beneficial [23, 25, 55, 101, 102, 105, 116].

RECOMMENDATION 14

We recommend against the use of estrogen-containing oral contraceptives in adolescent patients with hereditary angioedema.

89% agreement	Level of evidence: moderate
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RECOMMENDATION 15

We suggest against the use of angiotensin-converting enzyme inhibitors in pediatric patients with hereditary angioedema.

88% agreement	Level of evidence: low
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RECOMMENDATION 16

We recommend that all pediatric patients with hereditary angioedema receive regular immunizations according to the national vaccination schedule.

96% agreement	Level of evidence: consensus
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RECOMMENDATION 17

We suggest that pediatric patients with hereditary angioedema should have no limitation to physical activity including all sports, provided they have rapid access to their acute treatment. If necessary, prophylaxis may be introduced.

86% agreement	Level of evidence: moderate
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5.4.4 | Treatment of HAE-C1INH

The goal of treatment is to alleviate the burden of disease, restore the patient's quality of life, and prevent HAE attacks. Medications differ in their mode of action, production methods, and mode of administration. They act through supplementation of C1INH, inhibition of the pathways leading to the release of BK, or blockage of the effect of BK on the vascular endothelium (Figure 1).

5.4.4.1 | Acute Treatment. The aim of acute treatment of HAE attacks is to prevent mortality and to minimize morbidity by decreasing the duration and severity of symptoms. Treatment outcomes have been shown to improve with earlier treatment administration as compared to later-stage treatment [117–119]. Early treatment is supported by home treatment or self-injection after appropriate training of patients/caregivers [118, 120] (see the section on home treatment). Acute treatment should be immediately available under every circumstance, including at home, kindergarten, school, and while traveling. If an abdominal HAE attack does not improve on HAE treatment, further investigation is required urgently to rule out an acute abdomen. UAAs require emergency admission to a hospital where airway management is available. Hospital or other point-of-care should also be considered in case of other forms of severe attacks. Well-known secondary effects of HAE attacks, like anxiety, depression, and loss of productivity, will likely be prevented or minimized by the availability and timely administration of acute treatment [121–125].

An overview of approved drugs for acute treatment is outlined in Table 4 (data on randomized clinical trials are provided in

Table S2). Options include replacement of low levels of C1INH with intravenous (IV) plasma-derived (pdC1INH) or recombinant human (rhC1INH) C1INH concentrate [22, 118, 126–131], BDKRB2-blockade with subcutaneously (SC) administered icatibant [132–136], inhibition of PKa with SC administered ecallantide [137], or with orally used sebetralstat [138, 139]. Only IV pdC1INH is registered for *neonates and infants*, while *children* can use icatibant, IV pdC1INH, and rhC1INH. *Adolescents* can be treated with these medications and also with sebetralstat. Given the favorable safety profiles and demonstrated efficacy, each of these treatments is considered a first-line therapeutic option.

RECOMMENDATION 18

We recommend creating an action plan for acute treatment of angioedema attacks in pediatric patients with hereditary angioedema, considering availability of medications and patient/caregiver preferences.

96% agreement	Level of evidence: consensus
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RECOMMENDATION 19

In **neonates and infants with hereditary angioedema due to C1 inhibitor deficiency between birth and 2 years**, we recommend the use of intravenous plasma-derived C1 inhibitor concentrate as first-line therapy for acute treatment of angioedema attacks.

87% agreement	Level of evidence: moderate
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RECOMMENDATION 20

In **children with hereditary angioedema due to C1 inhibitor deficiency aged between 2 and 12 years**, we recommend the use of icatibant, intravenous plasma-derived C1 inhibitor concentrate, or intravenous recombinant human C1 inhibitor as first-line therapy for acute treatment of angioedema attacks.

97% agreement	Level of evidence: high
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RECOMMENDATION 21

In **adolescents with hereditary angioedema due to C1 inhibitor deficiency aged 12 years or older**, we recommend the use of ecallantide, icatibant, intravenous plasma-derived C1 inhibitor concentrate, intravenous recombinant human C1 inhibitor, or sebetralstat as first-line therapy for acute treatment of angioedema attacks.

92% agreement	Level of evidence: high
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RECOMMENDATION 22

We recommend acute treatment of angioedema attacks in pediatric patients with hereditary angioedema as early as possible.

96% agreement	Level of evidence:	Neonates: consensus Infants: consensus Children: moderate Adolescents: moderate
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RECOMMENDATION 23

We recommend home treatment of angioedema attacks to ensure early treatment in pediatric patients with hereditary angioedema.

89% agreement	Level of evidence:	Neonates: consensus Infants: consensus Children: moderate Adolescents: moderate
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RECOMMENDATION 24

We recommend considering treatment of all angioedema attacks in pediatric patients with hereditary angioedema.

89% agreement	Level of evidence: consensus
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RECOMMENDATION 25

We recommend that upper airway, facial, and neck edema should always be treated. In case of upper airway edema, pediatric patients with hereditary angioedema should also have an emergency referral to a hospital where airway management is available.

99% agreement	Level of evidence: consensus
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RECOMMENDATION 26

We recommend supplying all pediatric patients with hereditary angioedema with acute treatment for at least two angioedema attacks even if they are on long-term prophylaxis.

95% agreement	Level of evidence: consensus
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RECOMMENDATION 27

We recommend ensuring the availability of appropriate medication for acute treatment of angioedema attacks at any time and anywhere

92% agreement	Level of evidence: consensus
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TABLE 4 | Acute therapy in pediatric patients with hereditary angioedema due to C1INH deficiency.

	Drug name	Brand name	Dosage and age-related approval status ^a		ROA	MOA	Side-effects
First-line options	Human plasma-derived C1INH	Berinert	- FDA - Some European and other countries	All ages, 20 IU/kg ^b All ages, 20 IU/kg ^b	IV	Replacement of the missing functional C1INH	Headaches, nausea, fever, rare risk of anaphylaxis, thrombosis, and the theoretical risk of viral transmission associated with all plasma products
		Cinryze	- FDA - EMA	N.A. 2–11 years, 10–25 kg: 500 IU ^C 2–11 years, > 25 kg: 1000 IU ^d 12–17 years: 1000 U ^d	IV	Replacement of the missing functional C1INH	Headaches, nausea, fever, rare risk of anaphylaxis, thrombosis, and the theoretical risk of viral transmission associated with all plasma products
	Recombinant human C1INH	Ruconest	- FDA - EMA	≥12 years, < 84 kg: ^e 50 IU/kg ≥12 years, ≥ 84 kg: ^e 4200 IU ≥ 2 years, < 84 kg: 50 IU/kg ≥ 2 years, ≥ 84 kg: 4200 IU	IV	Replacement of the missing functional C1INH	Nausea, abdominal pain, diarrhoea, sensation of tingling, prickling or numbness in the mouth, headache, dizziness, throat irritation, hives, allergic shock, hypersensitivity reactions
	Icatibant	Firazyr ^f	- FDA - EMA	N.A. ≥ 2 years and ≥ 12 kg 12 – 25 kg: 10 mg (1,0 ml) 26 – 40 kg: 15 mg (1,5 ml) 41 – 50 kg: 20 mg (2,0 ml) 51 – 65 kg: 25 mg (2,5 ml) > 65 kg: 30 mg (3,0 ml)	SC	BDKRB2-antagonism	Injection site reactions, dizziness, headache, nausea, rash, erythema, pruritus, pyrexia, transaminases increased
	Ecallantide ^g	Kalbitor	- FDA - EMA	≥ 12 years: 30 mg (3 mL) in three 10 mg (1 mL) injections ^h N.A.	SC	PKa inhibition	Black box warning of anaphylaxis, headache, nausea, fatigue, diarrhea, upper respiratory tract infection, injection site reactions, nasopharyngitis, vomiting, pruritus, upper abdominal pain and pyrexia.
	Sebetralstat	Ekterly	- FDA - EMA	≥ 12 years: 300mg Tablet ≥ 12 years: 300mg Tablet	Oral	PKa inhibition	Dyspepsia, nausea, fatigue

(Continues)

TABLE 4 | (Continued)

Drug name	Brand name	Dosage and age-related approval status ^a	ROA	MOA	Side-effects
Second-line options	Fresh frozen plasma	10–20 ml/kg (maximum starting dose: 2 units)	IV	Replacement of the missing functional CIINH	Infusion reactions, anaphylaxis, risk of volume overload, risk of blood-borne viral transmission, theoretical risk of aggravation of an acute attack
	Solvent-detergent plasma	10–20 ml/kg (maximum starting dose: 2 units)	IV	Replacement of the missing functional CIINH	Infusion reactions, anaphylaxis, risk of volume overload, theoretical risk of aggravation of an acute attack, less risk of viral transmission

Abbreviations: BDKRB2: Bradykinin B2 receptor; CIINH: C1 inhibitor protein; EMA: European Medicines Agency; FDA: U.S. Food and Drug Administration; IU: International unit; IV: Intravenous; MOA: Mode of action; N.A.: Not applicable; PKa: Plasma kallikrein; PO: Per os; ROA: Route of administration; SC: Subcutaneous.

^aApproval status with regard to age may vary between countries.

^bRounded to the nearest 500 IU vial (for weight ≥ 12.5 kg).

^cAnother 500 IU can be applied in case of insufficient symptom relief within 60 min, laryngeal attacks, or delayed treatment.

^dAnother 1000 IU can be applied in case of insufficient symptom relief within 60 min, laryngeal attacks, or delayed treatment.

^eEffectiveness not established in HAE patients with laryngeal attacks.

^fGeneric versions available.

^gBlack box warning of anaphylaxis.

^hIf attack persists an additional dose of 30 mg may be administered within a 24 h period.

5.4.5 | Short-Term Prophylaxis (STP)

STP is necessary for all ped-HAE-C1INHs, even in those who have never had an HAE attack. STP is essential for preparation before surgery, intubation, interventional medical procedures, endoscopy, and dental work, especially when the procedure approximates the upper airway [4, 98, 140, 141].

The preferred therapy for STP in all ages is IV pdC1INH 1–6 h before the procedure. Pharmacokinetics suggests a rapid effect and confers protection for approximately 3 days. Weight-based dosing, especially for children, allows the individualization of STP [114, 142–144] (Table 5).

Due to a lack of controlled studies with LTP medications, experts suggest STP even for patients who are currently on LTP. Acute treatment should always be available during and after the intervention [140].

RECOMMENDATION 28

We recommend that short-term prophylaxis be considered in pediatric patients with hereditary angioedema due to C1 inhibitor deficiency before medical, dental, and surgical procedures and any angioedema-inducing event, especially when procedures involve the upper airway.

96% agreement	Level of evidence: moderate
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RECOMMENDATION 29

We recommend that acute treatment of angioedema attacks is available during medical, dental, and surgical procedures in pediatric patients with hereditary angioedema.

99% agreement	Level of evidence: consensus
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RECOMMENDATION 30

We suggest that short-term prophylaxis should be considered even in pediatric patients with hereditary angioedema due to C1 inhibitor deficiency on long-term prophylaxis.

83% agreement	Level of evidence: low
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RECOMMENDATION 31

We recommend intravenous plasma-derived C1 inhibitor as the first-line treatment for short-term prophylaxis in pediatric patients with hereditary angioedema due to C1 inhibitor deficiency.

93% agreement	Level of evidence:	Neonates: consensus
		Infants: consensus
		Children: moderate
		Adolescents: moderate

TABLE 5 | Short-term prophylaxis in pediatric patients with hereditary angioedema due to C1INH deficiency.

	Drug name	Brand Name	Dosage	Timing of administration	ROA	MOA	Side Effects
First-line options	Human plasma-derived CIINH	Berinert	• FDA • EMA 15–30 IU/kg	within 6 h before a medical, dental, or surgical procedure.	IV	Replacement of the missing functional CIINH	Headaches, nausea, fever, rare risk of anaphylaxis, thrombosis, and the theoretical risk of viral transmission associated with all plasma products
		Cinryze	• FDA • EMA 2 to 11 years, 10 – 25 kg: 500 IU 2 to 11 years, > 25 kg: 1000 IU ≥ 12 years: 1000 IU	within 24 h before a medical, dental, or surgical procedure.	IV	Replacement of the missing functional CIINH	Headaches, nausea, fever, rare risk of anaphylaxis, thrombosis, and the theoretical risk of viral transmission associated with all plasma products
Second-line options	Attenuated androgens Danazol Stanozolol	Danol	3–5 mg/kg/day (maximum dose is 200 mg TID)	5–7 days prior to the procedure and 3 days following the procedure	PO	Increase in the production of CIINH in the liver	Short term therapy (1–2 weeks) usually well tolerated; Headache, myopathy, anxiety, abnormal liver function test, hair loss
		Danogen Danatrol	0.05 – 0.06 mg/kg/day (maximum dose is 2 mg BID)				
		Menabol					
	Tranexamic acid	Exacyl Trenaxa	50 mg/kg/day divided BID or TID (maximum dose is 1000 mg TID)	5 days prior to the procedure and 2 days following the procedure	PO	Inhibition of the plasminogen-plasmin transformation	Headache, anaphylaxis, syncope, myalgia, elevated CPK and aldolase, AMS, nausea, emesis, and diarrhea
		Fresh frozen plasma	10–20 ml/kg (maximum: 2 units)	1–2 h prior to the procedure (repeat the dose if needed)	IV	Replacement of the missing functional CIINH	Infusion reactions, anaphylaxis, risk of volume overload, allo sensitization, risk of blood-borne viral transmission
		Solvent-detergent plasma	10–20 ml/kg (maximum: 2 units)	1–2 h prior to the procedure (repeat the dose if needed)	IV	Replacement of the missing functional CIINH	Infusion reactions, anaphylaxis, risk of volume overload, allo sensitization, less risk of blood-borne viral transmission,

Abbreviations: AMS, Altered mental status; BID, Two times a day; CIINH, C1 inhibitor protein; CPK, Creatine phosphokinase; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; IU, International unit; IV, Intravenous; MOA, Mode of action; N.A., Not applicable; PO, Per os; ROA, Route of administration; SDP, Solvent-detergent plasma; TID, Three times a day.

5.4.6 | Long-Term Prophylaxis (LTP)

The primary goal of long-term treatment in HAE-C1INH is to achieve full disease control and restore patients' lives to normal. Today, this is only possible through LTP—the regular use of medications designed to prevent attacks [4].

LTP is rarely needed in *children under 6 years of age*. If, however, LTP is required, then subcutaneously administered, prefilled lanadelumab injection (a fully human IgG1 monoclonal antibody inhibiting PKa) is the only approved treatment option for this indication between 2 and 6 years of age [145]. IV pdC1INH concentrate may also be considered for LTP in this population intermittently, although its use is off-label, as it is approved for patients aged 6 years and older [22].

In *children aged between 6 and 12 years*, lanadelumab and IV pd-C1INH can be used [145, 146].

Wider therapeutic choices for LTP are available for *adolescents*. These treatments include garadacimab, a fully human IgG4 monoclonal antibody inhibiting factor XIIa, administered subcutaneously with an autoinjector [147], lanadelumab [148], IV or SC pdC1INH concentrate [149, 150], or berotralstat, a selective oral plasma kallikrein inhibitor [151]. The recommended dosages for this population are consistent with those established for adult patients. Given the favorable safety profiles and demonstrated efficacy, each of these treatments is considered a first-line therapeutic option. Note: Berotralstat and lanadelumab have a delayed onset of a few weeks until optimal protective effect is achieved, which should be considered when initiating prophylaxis [152, 153] (Table 6, Table S3).

RECOMMENDATION 32

We recommend evaluating frequency and location of angioedema attacks, burden of disease, quality of life, patients' and caregivers' preferences, and availability of medications when considering long-term prophylaxis.

96% agreement	Level of evidence: consensus
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RECOMMENDATION 33

In **children with hereditary angioedema due to C1 inhibitor deficiency aged between 2 and 6 years**, we recommend the use of lanadelumab or plasma-derived C1 inhibitor as first-line long-term prophylaxis.

84% agreement	Level of evidence:	Lanadelumab: moderate Plasma-derived C1 inhibitor: consensus
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RECOMMENDATION 34

In **children with hereditary angioedema due to C1 inhibitor deficiency aged between 6 and 12 years**, we recommend

the use of lanadelumab or plasma-derived C1 inhibitor as first-line long-term prophylaxis.

82% agreement	Level of evidence: moderate
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RECOMMENDATION 35

In **adolescents with hereditary angioedema due to C1 inhibitor deficiency aged 12 years or older**, we recommend the use of any of the following treatments: berotralstat or garadacimab or lanadelumab or plasma-derived C1 inhibitor, as first-line long-term prophylaxis.

91% agreement	Level of evidence: high
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RECOMMENDATION 36

We recommend evaluating efficacy and safety of the long-term prophylactic agent in pediatric patients with hereditary angioedema due to C1 inhibitor deficiency at least three and six months after initiation, then at least annually.

92% agreement	Level of evidence: consensus
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5.4.7 | Home-Treatment

Self-administration of medications shortens time to treatment, resulting in less severe attacks and faster resolution. It also reduces family disruption and distress associated with emergency hospital visits. PedPs can be involved in self-administering treatments, potentially taking full responsibility from their early teens, with exact timing depending on individual maturity [118, 154–156]. Parenteral treatments can be technically challenging [157], therefore, home care nurse support can be invaluable in facilitating self-administration training for both carer and child. Since almost everyone with HAE will experience attacks at some point, even asymptomatic PedPs should be trained in self-management when developmentally appropriate.

Self-management of prophylactic medications is also important and appears safe [92].

Self-administration confers generic benefits, namely [158]:

- An increase in understanding of their medication and wider health needs
- Improved adherence to medication regimens in the longer term.
- Enhancing independence and autonomous self-care.
- Facilitating the transition from pediatric to adult care.

RECOMMENDATION 37

We suggest that children and adolescents with hereditary angioedema should be encouraged to take an active role in their

TABLE 6 | Long-term prophylaxis in pediatric patients with hereditary angioedema due to C1INH deficiency.

Drug name	Brand name	Dosage and age-related approval status		ROA	MOA	Side-effects
First-line options						
Berotrastat	Orladeyo	FDA EMA	≥ 12 years ≥ 12 years	150 mg once daily with food	PO	Abdominal pain, vomiting, diarrhea, back pain, heartburn; QT prolongation at supratherapeutic exposures
Garadacimab	Andembry	FDA EMA	≥ 12 years ≥ 12 years	Initial: 400 mg, then 200 mg monthly	SC	Injection-site reactions (redness/itching/bruising), nasopharyngitis, abdominal pain, headache
Human plasma- derived C1INH	Cinryze	FDA EMA	6–11 years: ≥ 12 years: 6–11 years: ≥ 12 years:	500 IU every 3–4 days ^a 1000 IU every 3–4 days ^b 500 IU every 3–4 days 1000 IU every 3–4 days	IV	Headache, nausea, rash; infusion-site reactions
Human plasma- derived C1INH	Berinert	FDA EMA	N.A. Adolescents	40 IU/kg or 60 IU/ kg every 3–4 days	SC	Injection-site reactions, pruritus, headache
Human plasma- derived C1INH	Haegarda	FDA EMA	≥ 6 years N.A.	60 IU/kg every 3–4 days	SC	Injection-site reactions, hypersensitivity; dizziness.
Lanadelumab	Takhzyro	FDA EMA	2 to 5 years 6 to 11 years ≥ 12 years ≥ 2 years ^d 10–19 kg: 20–39 kg: ≥ 40 kg: ≥ 12 years	150 mg every 4 weeks 150 mg every 2 weeks ^c 300 mg every 2 weeks ^c 150 mg every 4 weeks 150 mg every 2 weeks ^c 300 mg every 2 weeks ^c 300 mg every 2 weeks ^c	SC	Injection-site pain/redness, URIs, headache, dizziness
Second-line options						
Attenuated androgens Danazol Stanozolol	Danogen Danatrol Menabol	Indications and approval status may vary according to countries and according to manufacturers	Age is not specified in the prescribing information	3–5 mg/kg/day (maximum dose is 200 mg TID) 0.05–0.06 mg per kg per day (maximum dose is 2 mg BID)	PO	Weight gain, hyperlipidemia, hypertension, hyperglycemia, psychological changes such as aggressive behavior, liver enzyme abnormalities, hepatocellular adenoma, effect on growth (in pre-pubertal children), acne, headache, myalgia, hair loss, diminished libido Specific side effects in females: Hirsutism, menstrual irregularities, voice change, precocious puberty

(Continues)

TABLE 6 | (Continued)

Drug name	Brand name	Dosage and age-related approval status	ROA	MOA	Side-effects		
Tranexamic acid	Exacyl Trenaxa	Indications and approval status may vary according to countries and manufacturers	Age is not specified in the prescribing information.	50 mg/kg/day divided BID or TID (maximum dose is 1000 mg TID)	PO	Inhibition of the plasminogen-plasmin transformation	Headache, anaphylaxis, syncope, myalgia, elevated CPK and aldolase, AMS, nausea, emesis, and diarrhea, theoretical risk of thrombosis

Abbreviations: C1INH, C1 inhibitor protein; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; FXIIa, Activated factor XII; IU, International unit; IV, Intravenous; MOA, Mode of action; N.A., Not applicable; PKa, Plasma kallikrein; PO, Per os; ROA, Route of administration; SC, Subcutaneous.

^aMay increase to 1000 IU if needed.

^bCan increase up to 2000 IU or 80 IU/kg if needed.

^cCan extend to every 4 weeks if well-controlled for more than 6 months (FDA)/stably attack-free (EMA).

^dAutoinjector only in ≥ 12 years.

own care, with the aim of self-administration of medication from early adolescence.

97% agreement	Level of evidence: consensus
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RECOMMENDATION 38

We suggest that caregivers of pediatric patients with hereditary angioedema should be educated about the administration of medications for hereditary angioedema.

99% agreement	Level of evidence: consensus
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5.4.8 | Monitoring, Quality of Life

At least an annual (or every 3–6 months if the ped-HAE-C1INH is on LTP) follow-up at an HAE CCC is important, together with ongoing communication with the family practitioner or pediatrician. Growth and development should be closely monitored as in other chronic conditions. Between visits, clinical support should be accessible via phone or email.

At follow-up visits, clinicians should assess attack frequency and location, response to treatment, side effects, disease burden, HR-QoL, patient and caregiver preferences, medication availability, adverse events, treatment burden, and concomitant diseases to guide the therapy. Patient data can be recorded using paper-based or electronic patient records (mobile tools) developed in each country, but HAE TrackR, developed by HAEi, is also available in many languages [159]. Presently, AE- and HAE-specific patient-reported outcome measures are validated only for adults. Few studies have assessed illness burden in ped-HAE-C1INH, reporting slight HR-QoL impairment using generic pediatric questionnaires (i.e., KIDSCREEN 27, KINDL, PedsQL™), dermatology tools (i.e., CDLQI), a non-validated HAE-specific questionnaire, and/or a visual analogue scale [93, 113, 124, 160–163].

HR-QoL is influenced by age at symptom onset (positively correlated with physical well-being, negatively with self-esteem) [113], attack frequency [160, 163], and abdominal attack location [162].

RECOMMENDATION 39

We suggest regularly monitoring health-related quality of life of children and adolescents with hereditary angioedema.

81% agreement	Level of evidence: consensus
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RECOMMENDATION 40

We recommend monitoring pediatric patients with hereditary angioedema regularly at least once a year, in close collaboration with their primary care providers, even if they are asymptomatic.

87% agreement	Level of evidence: consensus
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5.4.9 | Individualized Therapy

Ped-HAE-C1INHs can present with a wide range of disease severity, and they and their families can have different feelings about approaches to HAE therapy. Therefore, an individualized therapeutic strategy is required. Shared decision making is an appropriate process for decisions and outlining a treatment plan [89, 112, 155, 164, 165]. In addition, ped-HAE-C1INHs without a family history are likely to need more education about the disease and treatment options. Prior to puberty, disease activity is often lower, so acute therapy alone may be preferable. Other considerations include needle-phobia, distance from medical care, and participation in activities that can potentially induce attacks [166, 167]. Finally, caregivers and patients vary in their comfort with administering injectable therapies at home [168]. In-depth education for patients and their family members on the treatment options available and strategies for avoiding triggers should be personalized, proactive, and reviewed regularly, particularly when there are significant changes in the child or adolescent's life [169].

RECOMMENDATION 41

We recommend that clinicians who care for pediatric patients with hereditary angioedema individualize the treatment plans for patients and their family through shared decision making, which takes their preferences and values into account.

94% agreement	Level of evidence: consensus
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5.4.10 | Variation in the Availability of Healthcare Options and Levels of Healthcare Services

Lack of awareness of HAE among healthcare providers, lack of diagnostic facilities, insufficient availability or access to first-line treatment options, and health insurance coverage are the major challenges in resource-limited settings in high-income countries as well as in low-to-middle-income countries (LMICs) [170–172]. In LMICs, a large proportion of patients remain undiagnosed, and HAE still remains a fatal disease, associated with a poor QoL [124, 173–175]. In LMICs (with a lack of access to C1INH levels and C1INH function), C4 levels may be used as an initial screening test (sensitivity up to 80%–85%) for suspected patients with HAE [176].

There is also a remarkable disparity in availability and access to treatment options in LMICs for ped-HAE-C1INHs, highlighting opportunities to expand equitable care and innovative use of available resources to provide quality care [177, 178]. Here, second-line treatment options are often used in PedPs (Tables S4–S6).

In emergency situations (AE involving the upper airway, gastrointestinal tract, neck, or face), when none of the first-line treatment options are available, solvent detergent treated or fresh frozen plasma (SDP/FFP) can be considered for acute treatment of AE attacks. These agents are associated with a risk of anaphylactic reaction and transmission of blood-borne infections [179, 180] (Table 4).

For STP, when IV pdC1INH is not available, attenuated androgens (AAs) or tranexamic acid (TXA) can be used 5 days before and continued for 2 days post procedure. SDP or FFP can be an alternative option 1–6 h before the procedure [140, 179, 181–186] (Table 5).

For LTP, AAs or TXA could be considered in the pediatric population. AAs, such as danazol, stanozolol, and oxandrolone, have historically been utilized for LTP but only with caution. Their use is associated with significant adverse effects [187–199] (Table 6). If targeted therapies are unavailable, and the need for LTP is high, then AAs could be considered only in adolescents with Tanner stage V and higher, with careful surveillance [176]. Although a few older studies suggested a moderate effect of TXA, an oral antifibrinolytic agent, these findings have not been confirmed in larger-scale analyses. Although TXA is safe, it is less efficacious than AAs, and a large proportion of patients require either a switch to or the addition of AAs. A few recent studies on ped-HAE-C1INH reported the use of AAs, TXA or a combination of these two drugs for LTP [62, 108, 200, 201] (Table 6).

There is an urgent unmet need to increase awareness among healthcare providers, expand access to diagnostic facilities, and improve the availability and access to first-line treatment options for ped-HAE-C1INHs in LMICs. Patient support groups play a crucial role in this endeavor [202].

RECOMMENDATION 42

We suggest, when none of the first-line treatment options are available, using fresh frozen or solvent detergent plasma for acute treatment of angioedema attacks involving the upper airway, gastrointestinal tract, neck, or face in pediatric patients with hereditary angioedema due to C1 inhibitor deficiency.

86% agreement	Level of evidence: low
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RECOMMENDATION 43

We suggest, when none of the first-line treatment options are available, to consider using attenuated androgens, antifibrinolytics, fresh frozen or solvent detergent plasma for short-term prophylaxis in pediatric patients with hereditary angioedema due to C1 inhibitor deficiency.

81% agreement	Level of evidence: consensus
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RECOMMENDATION 44

We suggest, when none of the first-line treatment options are available, to consider the use of antifibrinolytics for long-term prophylaxis in children and adolescents with hereditary angioedema due to C1 inhibitor deficiency.

83% agreement	Level of evidence: consensus
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TABLE 7 | Emerging therapies in pediatric patients with hereditary angioedema due to C1INH deficiency.

Drug name [Clinical trial]	ROA	MOA	Age Range	Pediatric/Adolescent Trial(s)	Primary Outcomes	Safety Highlights	Anticipated No. of patients
Acute							
Sebetralstat (Ektely) KONFIDENT- KID [NCT06467084]	PO	PKa inhibition	2–11 years	Oral On-Demand Treatment of Angioedema Attacks Open- Label Safety, Pharmacokinetic, and Efficacy in pediatric patients with HAE-C1INH-Type 1 or 2	experience any adverse event(s) (including fatal adverse events) during the study, irrespective of uses of other medications and sebetralstat discontinuations for any reason.	Pending	36
Deucritibant RAPIDe-3 [NCT06343779]	PO	BDKRB2- antagonism	12–75 years	Soft Capsule for On-Demand Treatment of Angioedema Attacks in Adolescents and Adults With HAE-C1INH-Type 1 or 2, or HAE-nC1INH	Time to onset of symptom relief, defined as Patient Global Impression of Change rating of at least “a little better” for 2 consecutive timepoints within 12 h post-treatment.	Pending	Number of adolescent subjects not specified
Long-term prophylaxis							
Berotrastat (Orladeyo) APEX-P [205] [NCT05453968]	PO	PKa inhibition	2–<12 years	A Phase 3 Study to Evaluate the Safety and Pharmacokinetics of Berotrastat Prophylaxis in Children With HAE	Median (range) HAE attack rate during SOC was 0.96 (0–5.0) attacks per 4-week period. Median (range) HAE attack rates for each 4-week period from Day 1 to Week 48 were 0 (Week 4: 0–4.0; Week 48: 0–1.7).	Most common TEAEs were nasopharyngitis, upper respiratory tract infection, and headache. No drug-related Grade 3/4 or SAEs, deaths, or discontinuations related to adverse events.	29
Garadacimab (Andembry)	SC	Factor XIIa Inhibitor	2–11 years	A Phase 3 Open-label Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of CSL312 (Garadacimab) in the Prophylactic Treatment of Hereditary Angioedema in Pediatric Subjects 2 to 11 Years of Age	Number of subjects with treatment emergent adverse events (TEAEs), Percent of subjects with TEAEs, Number of TEAEs, TEAE rates per injection, TEAE rates per subject year at least 14 months Maximum concentration (Cmax) of CSL312 at steady-state, Trough concentration (C _{trough}) of CSL312 at steady-state, Time to maximum concentration (Tmax) of CSL312 at steady-state at least 12 months	Garadacimab (Andembry) [NCT05819775]	20

(Continues)

TABLE 7 | (Continued)

Drug name [Clinical trial]	ROA	MOA	Age Range	Pediatric/Adolescent Trial(s)	Primary Outcomes	Safety Highlights	Anticipated No. of patients
Deucricitabant CHAPTER-3 [NCT06669754]	PO	BDKRB2- antagonism	> 11 years	Phase 3, multicenter, randomized, double-blind, placebo- controlled study to evaluate the efficacy and safety of once-daily orally administered deucricitabant extended-release tablet compared to placebo	Time-normalized (per 4 weeks) number of Investigator-confirmed HAE attacks during the 24- week Treatment Period	Pending	Number of adolescent subjects not specified
Donidalorsen (Dawnzera) OASIS-HAE [206] [NCT05139810]	SC	Prekallikrein mRNA degradation ^a	> 11 years	phase 3, double-blind, randomized trial of donidalorsen or placebo	Mean attack rate from week 1 to week 25 was 81% lower (95% CI, 65–89) in the 4-week group than in the placebo group ($p < 0.001$) and 55% lower (95% CI, 22–74) in the 8-week group than in the placebo group ($p = 0.004$)	Most common adverse events were erythema at the injection site, headache, and nasopharyngitis 98% of adverse events were mild or moderate.	7 adolescent subjects
Navenibart ALPHA-ORBIT [NCT06842823]	SC	PKa inhibition	> 11 years	Phase 3 multicenter, randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of subcutaneous administration of navenibart in participants with HAE-C1INH-Type 1 or 2	Number of time-normalized investigator-confirmed HAE attacks during the 6- month Treatment Period.	Pending	Number of adolescent subjects not specified.

Abbreviations: BDKRB2, Bradykinin B2 receptor; CI, Confidence interval; HAE, Hereditary angioedema; HAE-C1INH, Hereditary angioedema due to C1 inhibitor deficiency; HAE-nC1INH, Hereditary angioedema with normal C1 inhibitor; MOA, Mode of action; No.: Number; PKa, Plasma kallikrein; PO, Per os; ROA, Route of administration; SAE, Serious adverse event; SC, Subcutaneous; TEAE, Treatment-emergent adverse event.
^a Antisense oligonucleotide.

RECOMMENDATION 45

We suggest, when none of the first-line treatment options are available, the use of attenuated androgens for long-term prophylaxis in adolescents with hereditary angioedema due to C1 inhibitor deficiency with Tanner stage V, administering the lowest effective dose.

81% agreement	Level of evidence: low
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RECOMMENDATION 46

We recommend the monitoring of blood pressure, weight, height, lipid profile, liver function, and fasting blood sugar and performing liver ultrasonography in all adolescents with hereditary angioedema due to C1 inhibitor deficiency receiving long-term prophylaxis with attenuated androgens. Follow-up should be conducted three and six months after the introduction of treatment, then every six months.

82% agreement	Level of evidence: consensus
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5.4.11 | Registries and Biobanks

A key tool for optimizing the management of HAE is the use of disease registries [203]. Several national registries for HAE are active today (Data S1: Section 12). Additionally, the Angioedema Center of Reference and Excellence (ACARE) [204] Network promoted an international registry, CARE [8].

Ideally, disease registries should be associated with biobanks, defined as any systematic, collaboration-ready repository of biological specimens intended for clinical research, with a specific focus on rare diseases.

RECOMMENDATION 47

We suggest establishing and maintaining registries with biobanking capabilities for hereditary angioedema, which include pediatric patients, allow patients and clinicians to enter high-quality data, and ensure data protection.

82% agreement	Level of evidence: consensus
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5.4.12 | Emerging Therapies

Several trials are either recently completed or being conducted in pediatric HAE patients. These studies and their details are outlined in Table 7.

Currently, two trials are evaluating acute therapies. KONFIDENT-KID is evaluating an oral PKa inhibitor (sebetralstat) in subjects aged 2–11 years [207] and RAPIDE-3 is evaluating an oral BDKRB2 antagonist (deucricitbant) in adolescent and adult patients [208].

Two phase 3 LTP trials have been recently published. APEX-P evaluated an oral PKa inhibitor (berotralstat) in subjects aged 2–11 years [205] and OASIS-HAE evaluated a SC prekallikrein mRNA silencing therapy (donidalorsen) in adults and adolescents [206].

There are two ongoing phase 3 LTP trials in adolescents and adults. CHAPTER-3 is evaluating an oral BDKRB2 antagonist (deucricitbant) [209] and ALPHA-ORBIT is evaluating an SC extended half-life monoclonal antibody inhibitor of PKa (navenibart) [210].

Although one study (OASIS-HAE) was published before the P-GM, it does not provide sufficient data to make a specific recommendation [206]. In the meantime, the FDA approved donidalorsen (Dawnzera) for LTP in adolescent and adult patients [211]. Additionally, APEX-P, an interim analysis on berotralstat in children, was published after the P-GM [205], and as such, no specific recommendation could be made at this time for this drug in children.

6 | Conclusions and Future Perspectives

Ped-HAE-C1INHs deserve special attention in the diagnosis and management of their disease. Early diagnosis, family screening, education and counseling of patients and their caregivers, selection of appropriate individualized therapy, development of a therapeutic strategic plan with shared decision making, centralized care, and regular follow-up of patients are essential to reach the goal of ensuring that these young patients can lead normal lives similar to their peers. Future goals include spreading knowledge about the disease, ensuring correct diagnosis, and ensuring that targeted therapies are available to all PedPs, conducting clinical trials of new therapies in children, developing HAE centers, and collecting and publishing as much real-world data as possible.

Author Contributions

H.F., I.M.-S., K.B., A.E.G., A.S.G., H.R.H., A.L., A.Z., M.M., S.B., T.Cr. conceptualized the manuscript. Literature review and material preparation was performed as follows: “Introduction” H.F. “Scope and purpose, Intended audience, Steering Committee, International Taskforce, and the HAWK Group” S.B., S.C., “Identifying the evidence and Summarizing and evaluating the evidence” H.R.H., “Recommendation development and approval” S.B., S.C., “Nomenclature, definitions” A.R., “Pathophysiology of HAE-C1INH” G.P., B.Z., “Clinical symptoms” K.B., I.M.-S., A.Z., “Complement testing” A.S.G., “Genetic testing” A.E.G., “Family history/family screening, newborn screening” J.P., “Differential diagnosis” J.A.B., “Comprehensive care centers, transition process from pediatric to adult care” M.M., “Education, counseling” S.C., C.I., “Trigger factors/primary prevention” I.B.-G., “Acute treatment” C.H.K., E.A.-P., “Short-term prophylaxis” T.Cr., “Long-term prophylaxis” D.M.C., F.C., A.L., “Home-treatment” H.J.L., “Monitoring, quality of life” T.C., “Individualized therapy” A.M., “International variation in availability of healthcare options and levels of healthcare, services” A.J., D.V.N., “Registries and biobanks” M.C., “Emerging therapies” S.B., M.C., “Conclusions and future perspectives” H.F. The first draft of the complete manuscript was compiled by H.F. and H.R.H., who oversaw revisions. All authors reviewed and/or contributed critical revisions during the manuscript development. All authors approved the manuscript.

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Glossary

Hereditary angioedema (HAE) A rare, heritable disease characterized by unpredictable, recurrent submucosal and/or subcutaneous swelling episodes (HAE attacks) that do not respond to conventional treatment with antihistamines, corticosteroids, and epinephrine

Hereditary angioedema due to C1 inhibitor deficiency (HAE-C1INH) The most frequent subtype of HAE, caused by pathogenic variants in the *SERPING1* gene, leading to a decrease in C1 inhibitor functional activity

Plasma contact-kinin-kallikrein system An enzyme cascade system that is initiated by activated factor XII. This system is responsible for the production of bradykinin, the main vasoactive mediator of HAE

Complement system An enzyme cascade system, which is part of the innate immune system and enhances cell lysis and phagocytic function of different immune cells

Complement test Laboratory measurements to determine serum levels of complement proteins, including C1 inhibitor antigenic concentration and functional activity, C4, and C1q levels. It is the diagnostic test for HAE-C1INH

Treatment of hereditary angioedema The goals of treatment are to relieve and prevent HAE attacks, thus reducing disease burden. Medications differ in their pharmacologic properties, mode of action, production methods, and mode of administration

Acute treatment The aim of acute treatment of HAE attacks is to prevent mortality and to minimize morbidity by decreasing the duration and severity of symptoms

Short-term prophylaxis (STP) Refers to the use of medication shortly before known triggers of HAE attacks (i.e., interventional medical procedures, contact sports, stressful situations) to protect the patients from the occurrence of swelling

Long-term prophylaxis (LTP) Refers to the regular use of medications designed to prevent HAE attacks, to achieve full disease control and restore patients' lives to normal

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Conflicts of Interest

H. Farkas has received research grants from CSL Behring and Pharvaris; speaker fees from Biocryst, CSL Behring, Pharming, Pharvaris, and Takeda; travel grants from Astria, Biocryst, CSL Behring, Intellia, Ionis, KalVista, ONO Pharmaceutical, Pharming, Pharvaris, and Takeda; and served as an advisor/consultant for Astria, Biocryst, CSL Behring, Intellia, Ionis, KalVista, ONO Pharmaceutical, Pharming, Pharvaris, and Takeda. I. Martinez-Saguer has received honoraria, research funding, and travel grants from BioCryst, CSL Behring, Pharming, Octapharma, KalVista, and Takeda/Shire, and/or has served as a consultant and/or participated in advisory boards for these companies. K. Bork has received research grants and/or lecture fees from CSL Behring and Takeda for unrelated projects. A.E. Germenis has received honoraria and travel support from CSL Behring and Swixx BioPharma, and he is President of the Hellenic Society of Angioedema. A.S. Grumach has received speaker/consultancy fees from Catalyst, CSL Behring, KalVista Pharmaceuticals, Multicare Pharma, Pharvaris, Pint Pharma, AstraZeneca, and Takeda; a scholarship from the Brazilian Council of Research (CNPq); and a grant of researcher initiative from Takeda. H.R. Horváth has received travel grants from CSL Behring and Takeda. A. Zanichelli has received honoraria, meeting/travel support, and/or served on advisory boards for Astria, BioCryst, CSL Behring, KalVista, Otsuka, Pharvaris, and Takeda. M. Magerl has received speaker/advisor fees and/or research funding from Argo, Astria, Biocryst, CSL Behring, Intellia, Ionis/Otsuka, KalVista, Medscape, Octapharma, Pharvaris, Takeda/Shire. S. Betschel has received consulting fees and speaker honoraria not related to this study from Astria, Biocryst, KalVista, CSL Behring, and Takeda; and grants or contracts from Astria, Ionis, Biocryst, KalVista, CSL Behring, Pharvaris, and Takeda. E. Aygören-Pürsün has received speaker/consultancy fees personally or to the institution and/or grants from Astria, Biocryst, CSL Behring, Intellia, Otsuka, Pharming, Pharvaris, and Takeda. J.A. Bernstein has served as an investigator and consultant for ADARx, Ajou University, Allergy therapeutics, Amgen, Apogee, Areteia, ARS, Astra Zeneca, Astria, Biocryst, Blueprint Medicine, Celldex, Cogent, CSL Behring, Eli Lilly, Escient, Evommune, Fresenius Kabi, Genentech, GSK Incyte, Intellia, Ionis, Japan Tobacco Company, Jasper, KalVista, Kenvue, Kymeria, Kyowa Kirin, Medscape, Merck, Novartis, Opella, Pharming, Pharvaris, Proctor and Gamble, Regeneron, Sanofi, Takeda/Shire, Telios, Teledoc, TEVA, Yuhan, WebMD news; as a consultant for Enanta, Pfizer, RAPT; and as a speaker for Pharming, KalVista, CSL Pharming. I. Boccon-Gibod is or recently was a speaker, advisor, and engaged in research and educational projects for, and/or received research and consultancy grants from, BioCryst, CSL Behring, KalVista Pharmaceuticals, Novartis, Pharming, Pharvaris, Otsuka, and Takeda. T. Caballero has received grant research support and/or speaker/consultancy fees from AEDAF, Astria, BioCryst, CSL Behring, Ionis, KalVista, Novartis, Otsuka, Pharvaris, and Takeda. She has also received funding to attend conferences/educational events from BioCryst, CSL Behring, Novartis, and Takeda. T. Caballero is/has been a clinical trial/registry investigator for Biocryst, Biomarin, CSL Behring, Ionis, KalVista, Novartis, Pharvaris, and Takeda. She is a researcher on the IdiPAZ program for promoting research activities. M. Cancian has received grant research support and/or speaker/consultancy fees from BioCryst, CSL Behring, KalVista, Novartis, Otsuka, Pharming, Pharvaris, Sanofi, SOBI, and Takeda. S. Christiansen served as a consultant for BioCryst, CSL, and KalVista and is a member of the Medical Advisory Board US HAEA. D.M. Cohn has received consulting and/or speaking fees from Astria, BioCryst, CSL Behring, Intellia Therapeutics, Ionis Pharmaceuticals,

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** all70207-sup-0001-DataS1.docx. **Figure S1:** all70207-sup-0002-FigureS1.pdf.

Appendix A

Members of the HAWK Group

Last name	First name	Country
Adatia	Adil	Canada
Adrianzen	Fiorella	Spain
Andarawewa	Shimalee	Germany
Andrejevic	Sladjana	Serbia
Arce-Estrada	Gabriel Emmanuel	Mexico
Ay	Ecem	Turkey
Bahadir	Adil	Turkey
Bara	Noemi Anna	Romania
Barešić	Marko	Croatia
Baynova	Krasimira	Spain
Benor	Shira	Israel
Besson	Juliette	France
Bhattarai	Dharmagat	Nepal
Bigas	Patricia	Spain
Bocquet	Alexis	France
Bouillet	Laurence	France
Brodzski	Nicholas	Sweden
Buttgereit	Thomas	Germany
Cabañas	Rosario	Spain
Campos	Regis	Brazil
Çamyar	Asuman	Turkey
Chol	Orlane	France
Cimbollek	Stefan	Spain
Colque Bayona	Monica	Spain
Day	Cascia	South Africa
de Lange	Mats	Netherlands
Fam	Alex	Bulgaria

Last name	First name	Country
Firinu	Davide	Italy
Freiberger	Tomas	Czech Republic
Gil-Serrano	Johana	Spain
Gobert	Delphine	France
Goodyear	Dawn	Canada
Guilarte Clavero	Maria del Mar	Spain
Hadvabova	Svetlana	Slovakia
Hagin	David	Israel
Hakl	Roman	Czech Republic
Harmat	George	Hungary
Hasanhodzic	Mensuda	Bosnia Herzegovina
Jacek	Gocki	Poland
Jacobs	Joshua	United States
Jain	Rashmi	United Kingdom
Jesenak	Milos	Slovakia
Kanani	Amin	Canada
Kapustová	Daniela	Slovakia
Karanovic	Boris	Croatia
Keith	Paul	Canada
Kinaciyar	Tamar	Austria
Kralickova	Pavlina	Czech Republic
Kurowski	Marcin	Poland
Kuziemski	Krzysztof	Poland
Laurel-Laurel	Rolando	Mexico
Leibovich- Nassi	Iris	Israel
Leon Zambrana	Gabriela	Spain
Lleonart	Ramon	Spain
Lorenzo	Lorena	UK
Maksudov	Ferhat	Bulgaria
Manson	Ania	United Kingdom
Markovic	Dusanka	Serbia
McGucken	Jayne	United Kingdom
Mete Gokmen	Nihal	Turkey
Mijanovic	Radovan	Serbia
Miranda Saavedra	Vania Maria	Guatemala
Modestou	Irene	Greece
Nieto	Sandra	Mexico
Nilsson	Nora	Sweden
Nordenfelt	Patrik	Sweden
Perego	Francesca	Italy
Petraroli	Angelica	Italy
Phillips-Angles	Elsa	Spain

Last name	First name	Country
Prieto-García	Alicia	Spain
Raguet	Michel	France
Riedl	Marc	United States
Rijavec	Matija	Slovenia
Rodrigues Valle	Solange	Brazil
Romanyshyn	Yaryna	Ukraine
Saut	Antoine	France
Senter	Riccardo	Italy
Šlenker	Branislav	Slovakia
Sobotkova	Marta	Czech Republic
Spaeth	Peter J	Switzerland
Stobiecki	Marcin	Poland
Sundler Björkman	Linda	Sweden
Suttle	Mireille-Maria	Finland
Szilágyi	Agnes	Hungary
Triggianese	Paola	Italy
Tzeli	Kassiani	Greece
Vachová	Martina	Czech Republic
Valerieva	Anna	Bulgaria
Valle	Solange	Brazil
Varga	Lilian	Hungary
Wuillemin	Walter A.	Switzerland
Yong	Patrick	United Kingdom
Yuxiang	Zhi	China
Zabrodska	Liudmyla	Ukraine
Zachova	Radana	Czech Republic
Zharankova	Julia	Belarus