

POSITION ARTICLE AND GUIDELINES

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# The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update

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## Abstract

Hereditary Angioedema (HAE) is a rare and disabling disease. Early diagnosis and appropriate therapy are essential. This update and revision of the global guideline for HAE provides up-to-date consensus recommendations for the management of HAE. In the development of this update and revision of the guideline, an international expert panel reviewed the existing evidence and developed 20 recommendations that were discussed, finalized and consented during the guideline consensus conference in June 2016 in Vienna. The final version of this update and revision of the guideline incorporates the contributions of a board of expert reviewers and the endorsing societies. The goal of this guideline update and revision is to provide clinicians and their patients with guidance that will assist them in making rational decisions in the management of HAE with deficient C1-inhibitor (type 1) and HAE with dysfunctional C1-inhibitor (type 2). The key clinical questions covered by these recommendations are: 1) How should HAE-1/2 be defined and classified?, 2) How should HAE-1/2 be diagnosed?, 3) Should HAE-1/2 patients receive prophylactic and/or on-demand treatment and what treatment options should be used?, 4) Should HAE-1/2 management be different for special HAE-1/2 patient groups such as pregnant/lactating women or children?, and 5) Should HAE-1/2 management incorporate self-administration of therapies and patient support measures? This article is co-published with permission in *Allergy* and the *World Allergy Organization Journal*.

**Keywords:** Hereditary angioedema, C1-inhibitor, Diagnosis, Therapy, Management, Individualized therapy, GRADE, Guideline, Prophylaxis, Quality of life, Recommendations, Self-administration

## Introduction

Hereditary angioedema (HAE) is a rare disease and a serious health problem, globally and for affected patients and their families. The pathophysiological background is primarily a vascular reaction to an overshooting local production of bradykinin. Evidence-based recommendations are needed to inform and guide clinical decision makers. This is the first revision and update of the global guideline for the diagnosis and management of HAE [1]. It was

developed by the World Allergy Organization (WAO) in collaboration with the European Academy of Allergy and Clinical Immunology (EAACI). This revised and updated WAO/EAACI guideline on the diagnosis and management of HAE differs from previous consensus reports and position papers [2–16]. It results from a complete review of the underlying evidence based on systematic and transparent assessments of the quality of this evidence. We used an approach oriented along the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for the revision and update of the recommendations provided by this guideline [17]. GRADE is recommended by the World Health Organization (WHO)

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and takes into account that evidence alone is insufficient, and that values and preferences, clinical circumstances as well as clinical expertise inevitably influence decisions.

During the planning of the WAO HAE International Guideline, Dr. Richard Lockey, then President of the WAO, and Dr. Timothy Craig, Chair of the steering committee, requested nominations from WAO Affiliated Allergy and Immunology Associations to appoint members to the steering committee. For this update and revision of the guideline, the guideline's expert panel and author group was complemented by additional HAE experts to account for the global reach of the guideline.

In the development of this update and revision of the guideline, working groups were assigned to review and assess the evidence available to answer the questions, for which the guideline provides recommendations ([1]), and to raise new clinical questions to be addressed by the guideline [18]. Based on the assessment of the evidence the panel members, in a consensus conference at the EAACI annual meeting in June 2016 in Vienna, Austria, developed the following recommendations. Using the approach outlined below, recommendations made are strong or weak. Strong recommendations indicate that most physicians would want and only few would not want the recommended course of action, that adherence to the recommendation in clinical practice could be used as a quality criterion and that the recommendation can be adapted as policy in most situations and countries. Weak recommendations should be interpreted to indicate that most but not all physicians would want the suggested course of action, that in clinical practice, different choices will be appropriate for individual patients, and that policy making will require substantial debate and the involvement of various stakeholders [19]. Understanding the interpretation of these two grades of strengths of recommendations (either strong or weak/conditional) is essential for clinical decision-making.

This guideline is unique in that global involvement was ensured by the participation of international experts from many different countries. Most of these experts were nominated by Allergy and Immunology Associations of different countries affiliated to the WAO.

The goal of this guideline is to provide clinicians and their patients with guidance that will assist them in making rational decisions in the management of HAE with deficient C1-inhibitor (type 1) and HAE with dysfunctional C1-inhibitor (type 2, in this consensus the abbreviation HAE-1/2 will be utilized). To this end, 20 recommendations (numbered and given in framed boxes) were developed. The key clinical questions covered by these recommendations are: 1) How should HAE-1/2 be defined and classified?, 2) How should HAE-1/2 be diagnosed?, 3) Should HAE-1/2 patients receive prophylactic and/or on-demand treatment and what treatment options should be

used?, 4) Should HAE-1/2 management be different for special HAE-1/2 patient groups such as pregnant/lactating women or children?, and 5) Should HAE-1/2 management incorporate self-administration of therapies and patient support measures?

It is important to mention that the array of available therapies for HAE patients is limited in certain areas of the world, but the intent of this guideline is to help change this and to encourage the use of recommended therapies for all patients.

## Methods

### Nomination of experts

Physicians were nominated to the expert panel and group of authors by the steering committee nominated by WAO and/or EAACI. At least one of the following criteria had to be fulfilled: 1) Extensive clinical experience in the treatment of HAE, 2) Relevant publications in the field of HAE, 3) Relevant experience in evidence-based medicine. Emphasis was placed on selecting a representative panel of experts from throughout the world to ensure global expertise. In addition, the WAO requested a representative from the international HAE patient association (HAEi) to participate as an author group member. One patient representative was nominated by HAEi and participated in the process (selection of key questions).

### Funding and support

Funding of the development of this update and revision of the guideline including for the Guideline Conference was done through the WAO and the EAACI. No company or company representative was present during the meeting, had input into the manuscript, or was allowed to provide feedback. The pharmaceutical companies were not allowed to view the document before publication. This was essential to prevent bias and real or perceived commercial influence on the outcomes. All participants were required to submit conflict of interest statements to participate as expert panel members and authors.

### Selection of key questions, wording of recommendations, and literature research

All authors were assigned to one of 5 working groups: 1) diagnostic work-up, 2) on demand therapy, 3) prophylaxis, 4) special populations, 5) clinical management of HAE-1/2. First, the teams were asked to review the existing recommendations from the WAO/EAACI guideline 2012 [1] in their subject area and to assess these recommendations for accuracy and relevance to current practice. The groups were asked to critically review the wording and to reword if necessary. A standardized wording was used to phrase the recommendations (Table 1).

Second, the teams were asked to consider if new recommendations were needed or useful and agree on the

generation of new recommendations and wording. Third, the teams were prompted to search the literature (database MEDLINE and COCHRANE) that supports each recommendation.

For the update and revision of recommendations from the previous version of the guideline, an incremental systematic search from September 2010 (end of search of the WAO/EAACI guideline 2012 [1]) to current (2016/05/31) was performed (Table 2). For new and additional recommendations, a complete search from 1985 to current (2016/05/31) was performed.

Fourth, the teams evaluated the publications found in their search using a standardized worksheet (Figs. 1 and 2). Each manuscript/trial included in the guideline was evaluated with regard to its methodological quality and assigned a grade of evidence according to the grading system used in the previous version of this guideline (Table 3).

#### Consensus conference, drafting of the manuscript, and review by the review board

The open consensus conference was held in Vienna on 11th of June 2016. Based on the assessment of the evidence, the expert panel reviewed the existing recommendations and developed new recommendations. The expert teams were asked to present a summary of the evidence on each revision and update of existing recommendations as well as on each new recommendation to all conference participants and to give their assessment of the quality of evidence expressed by the “evidence grade” (Table 3).

During the consensus conference, the nominal group technique was used as the formal consensus methodology [20]. All expert panel members were entitled to vote on the recommendations. The nominal group technique was moderated by Alexander Nast, MD, certified moderator for the German Association of Scientific Medical Societies (AWMF). All consented recommendations are highlighted throughout the guideline document (grey boxes). In order to avoid ambiguity, a standardized language was used to classify the direction and strength of each recommendation (Table 1).

The participants of the consensus conference were asked to discuss and vote whether they agreed with recommendations and other specific parts of the text. In statements not receiving  $\geq 90\%$  approval during the first voting, the recommendation was re-discussed, rephrased, and voted on and passed by majority vote. This was a minimum of  $\geq 75\%$  agreement unless stated otherwise. All voting results were documented (% agreement).

International HAE experts (the Review Board Consultation Group) were requested to review the guideline and provide feedback and suggestions for changes. The guideline was then reviewed by the

**Table 1** Wording of recommendations used in this guideline

Strong recommendation	We recommend
Weak recommendation	We suggest
Strength of recommendation, standardized wording	

WAO and EAACI and the other endorsing societies for content and the document was approved as “The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update”.

#### Definitions, nomenclature, and classification

Angioedema is defined as a vascular reaction of deep dermal/subcutaneous tissues or mucosal/submucosal tissues with localized increased permeability of blood vessels resulting in tissue swelling [21–25]. Angioedema can be mediated by bradykinin and/or mast cell-mediators including histamine (Tables 4 and 5) [13, 26]. Bradykinin-mediated angioedema can occur either on a hereditary or acquired basis, due to a deficiency/defect of C1 inhibitor (C1-INH) or other mechanisms (Table 4) [27, 28]. Different forms of hereditary angioedema (HAE) are currently recognized and genetically identifiable: 1) HAE due to C1-INH deficiency (Type 1 HAE, HAE-1), characterized by low antigenic and functional C1-INH levels; 2) HAE due to C1-INH dysfunction (Type 2 HAE, HAE-2), characterized by normal (or elevated) antigenic but low functional C1-INH levels [29, 30], 3) HAE with mutation in the F12 gene (HAE-FXII) [31]; 4) HAE with mutation in the angiotensin-converting enzyme 1 gene (HAE-ANGPT1) [32]; and 5) HAE with mutation in the plasminogen gene (HAE-PLG) [33]. In addition, some patients have HAE due to unknown mutations (HAE-UNK). Different forms of HAE with normal C1-INH (HAE-FXII, HAE-ANGPT1, HAE-PLG, HAE-UNK) share some clinical features and, possibly, therapeutic options.

Acquired angioedema with low C1-inhibitor, henceforth called AAE-C1-INH, refers to patients with angioedema due to C1-INH deficiency on an acquired basis (Table 4) [34–36]. There are a variety of acquired types of angioedema not due to C1-INH deficiency, and these may be bradykinin-mediated (e.g. ACE inhibitor induced angioedema, ACEI-AE) or due

**Table 2** Example of search strategy and identified hits incremental search

Step	Search terms	Hits
1	“Hereditary angioedema” OR “Hereditary angiooedema” OR “Hereditary angio-oedema” OR “Hereditary angioneurotic oedema” OR “Hereditary angioneurotic edema”	2063
2	Limit to yr. = 2010/09/01 - current (2016/05/31)	718
3	Limit to “Clinical Trial”	51

Recommendation No: \_\_\_\_\_  new recommendation

\_\_\_\_\_

Reference: Title, Authors, Journal

<b>Randomization</b>
yes <input type="radio"/> no <input type="radio"/> not sure <input type="radio"/>
<b>Blinded</b>
double <input type="radio"/> single <input type="radio"/> not blinded <input type="radio"/> not sure <input type="radio"/>
<b>Controlled</b>
yes <input type="radio"/> no <input type="radio"/> not sure <input type="radio"/>
if yes: placebo <input type="radio"/> active control <input type="radio"/> other type of control <input type="radio"/>
<b>Sample size</b>
Number of patients after randomisation (n) = .....
Number of arms = .....
<b>Grade of evidence</b>
A      Randomized, double-blind clinical trial of high quality (for example, sample-size calculation, flow chart of patient inclusion, intention-to-treat (ITT) analysis, sufficient sample size)
B      Randomized clinical trial of lesser quality (for example, only single-blind, limited sample size: at least 15 patients per study arm)
C      Comparative trial with severe methodological limitations (for example, not blinded, very small sample size, no randomization) or large retrospective observational studies.
D      Adapted from existing consensus document or statement based on expert opinion voting during consensus conference

**Fig. 1** Literature evaluation form

to mast cell mediators (e.g. urticarial angioedema, anaphylactic angioedema) [27, 37].

This guideline only refers to HAE-1/2.

**Pathophysiology**

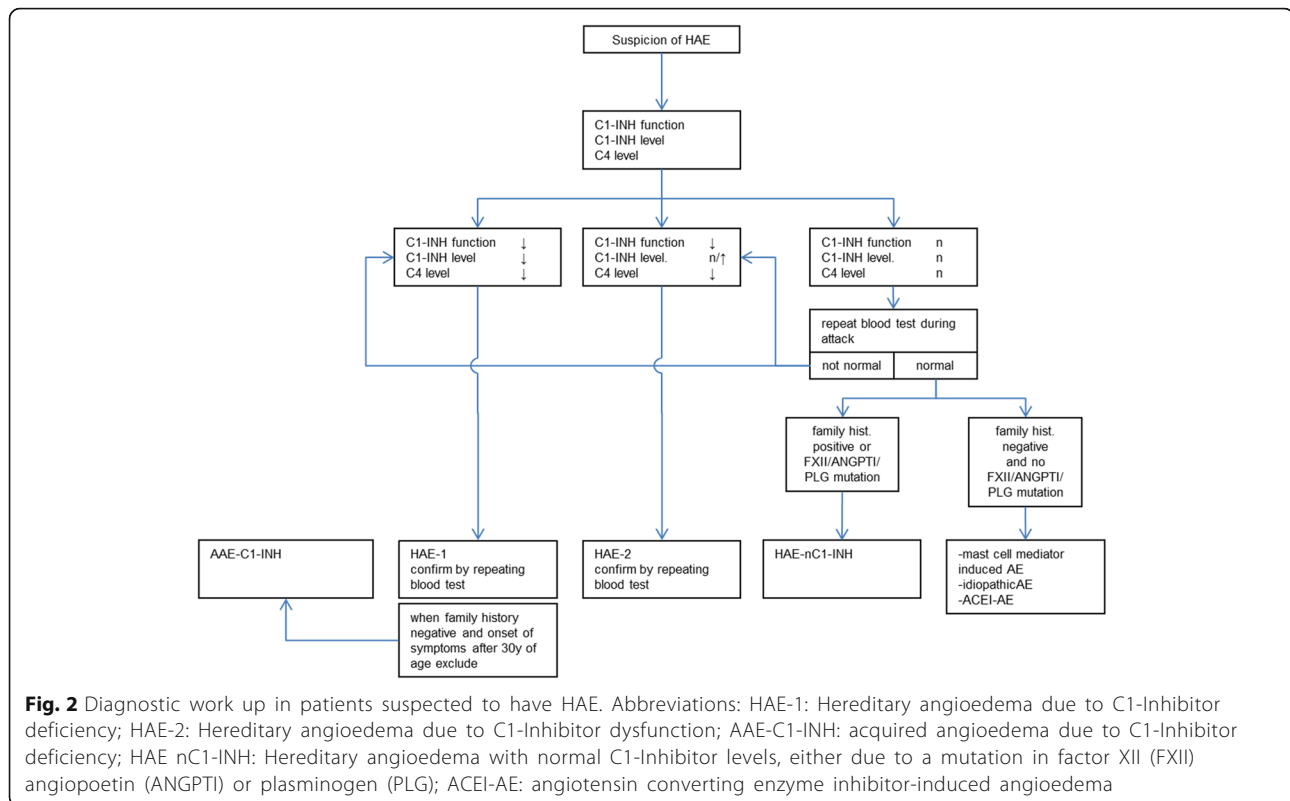
**HAE-1 and HAE-2**

HAE-1/2 is a rare autosomal dominant condition affecting an estimated 1 in 50,000 individuals [38, 39] although this may vary in different regions. HAE-1/2 is caused by one of more than 450 different mutations in the SERPING1 gene, which codes for C1-INH [40]. In approximately 20–25% of patients, a de novo mutation of SERPING1 is responsible for the disease [41, 42].

C1-INH is a serine protease inhibitor (SERPIN) and the major inhibitor of several complement proteases

(C1r, C1s, and mannose-binding lectin-associated serine protease [MASP] 1 and 2) and contact-system proteases (plasma kallikrein and coagulation factor XIIa) as well as a relatively minor inhibitor of the fibrinolytic protease plasmin [43, 44].

The primary mediator of swelling in HAE-1/2 is bradykinin [28]. Bradykinin is a low molecular weight nonapeptide, which is generated when active plasma kallikrein cleaves high molecular weight kininogen (HMWK). Bradykinin is rapidly metabolized by endogenous metalloproteases including angiotensin-converting enzyme (ACE) [45]. Plasma kallikrein is activated from its inactive zymogen prekallikrein by the protease factor XII, which can easily autoactivate upon contact with negatively-charged



surfaces. Both, plasma kallikrein and factor XII are inhibited by C1-INH. Increased vascular permeability induced by the liberation of bradykinin in angioedema is primarily mediated through the bradykinin B2 receptor [46–51].

#### HAE with normal C1 inhibitor

HAE with normal C1-INH (HAE nC1-INH) is a very rare disease. Its clinical appearance largely resembles that of HAE-1/2. In a subgroup of patients, HAE nC1-INH is associated with mutations of the factor XII (FXII-HAE) gene. Recently, two new mutations in - (ANGPT1) and plasminogen (PLG) were reported in HAE nC1-INH [32, 33]. However, in most patients with HAE nC1-INH, no gene mutation can be found, and the pathogenesis

**Table 3** Evidence grades (based on the previous guideline version [1])

A Randomized, double-blind clinical trial of high quality (for example, sample-size calculation, flow chart of patient inclusion, intention-to-treat (ITT) analysis, sufficient sample size)

B Randomized clinical trial of lesser quality (for example, only single-blind, limited sample size: at least 15 patients per study arm)

C Comparative trial with severe methodological limitations (for example, not blinded, very small sample size, no randomization) or large retrospective observational studies.

D Adapted from existing consensus document or statement based on expert opinion voting during consensus conference

remains to be characterized in detail. However, there is clinical evidence that bradykinin may play a major role in some types of HAE nC1-INH, primarily in patients with a FXII-mutation [52–54]. Although HAE nC1-INH shares some clinical features and, possibly, therapeutic options with HAE-1/2, this guideline is for HAE-1/2.

#### Diagnosis

HAE-1/2 should be suspected when a patient presents with a history of recurrent angioedema attacks. This suspicion is further substantiated when patients report: 1) a positive family history (although this may not be present in up to 25% of patients), 2) onset of symptoms in childhood/adolescence, 3) recurrent and painful abdominal symptoms, 4) occurrence of upper airway edema, 5) failure to respond to antihistamines, glucocorticoids, or epinephrine, 6) presence of prodromal signs or symptoms before swellings, and/or 7) the absence of urticaria (wheals). Suspicion of HAE-1/2 should prompt laboratory investigations to support the diagnosis of HAE-1/2 (Fig. 2) [5, 7, 13, 55].

#### Recommendation 1

We recommend that all patients suspected to have HAE-1/2 are assessed for blood levels of C1-INH function, C1-INH protein, and C4. If any of the levels are abnormally low, the tests should be repeated to confirm the diagnosis of HAE-1/2.

Evidence grade: D; Strength of recommendation: Strong,  $\geq 90$  agreement.

**Table 4** Classification of angioedema

Bradykinin-induced AE				Mast Cell Mediator induced AE		Unknown mediator
C1-INH deficiency/defect		C1-INH normal		IgE mediated	non-IgE mediated	
Inherited	Acquired	Inherited	Acquired			
HAE-1	AAE-C1-INH	HAE nC1-INH (HAE-FXII, HAE-ANGPTI, HAE-PLG, HAE-UNK)	ACEI-AE	Angioedema with Anaphylaxis/Urticaria	Angioedema with urticaria	Idiopathic AE
HAE-2						

*HAE-1* hereditary angioedema due to C1-inhibitor deficiency, *HAE-2* hereditary angioedema due to C1-inhibitor dysfunction, *AAE-C1-INH* acquired angioedema due to C1-inhibitor deficiency, *HAE nC1-INH* hereditary angioedema with normal C1-inhibitor levels, either due to a mutation in FXII, ANGPTI, PLG or unknown (HAE-FXII, HAE-ANGPTI, HAE-PLG, HAE-UNK), *ACEI-AE* angiotensin converting enzyme inhibitor-induced angioedema

Measurements of serum/plasma levels of C1-INH function, C1-INH protein, and C4 are used to diagnose HAE-1/2. In HAE-1, which comprises about 85% of patients, both, the concentration and function of C1-INH are low (Table 4). In HAE-2, C1-INH concentrations are either normal or elevated, whereas C1-INH function is reduced. C4 levels are usually low in HAE-1/2 patients, but its sensitivity and specificity are limited [56–59]. Abnormal results should be confirmed. Complement C3 and CH50 levels are expected to be normal in HAE, and testing is usually not helpful. Sequencing of the SERPING1 gene can be supportive in the diagnostic workup of some HAE-1/2 patients (including prenatal diagnosis); however, biochemical C1-INH testing is effective and less expensive than genetic testing [59]. DNA sequencing may miss mutations such as those creating cryptic splice sites. Genetic testing may be relevant in particular cases such as mosaicisms in order to allow for correct genetic counselling [60].

### Differential diagnosis

The differential diagnoses of HAE-1/2 include the other forms of HAE as mentioned above, AAE-C1-INH, ACEI-AE, mast cell-mediated angioedema (e.g. angioedema in patients with chronic spontaneous urticaria without wheals, allergic angioedema), and idiopathic angioedema (Table 4). Because the pathophysiology and the management of these diseases are different from those of HAE-1/2, it is important to determine the correct diagnosis [1, 7, 13, 61].

Recurrent mast cell-mediated angioedema (in the past sometimes referred to as idiopathic angioedema)

**Table 5** Typical diagnostic laboratory profile of HAE-1 and HAE-2 patients

	C1-INH function	C1-INH protein level	C4 protein level
HAE-1	↓	↓	↓
HAE-2	↓	N/↑	↓

is frequently associated with intensely pruritic wheal and flare skin reactions, (hives), in patients with chronic spontaneous urticaria (CSU). Some CSU patients do not show wheals and exclusively develop angioedema. On the other hand, CSU is a common disease, which can also affect HAE patients. The occurrence of wheals, therefore, does not necessarily exclude HAE, and the absence of wheals does not exclude mast cell-mediated angioedema [62]. Non-sedating antihistamines, at standard or higher-than-standard doses, alone or in combination with omalizumab or immune modulators such as cyclosporine are capable of preventing wheals and angioedema in CSU patients [37, 63]. Because mast cell-mediated angioedema is far more common than HAE-1/2, on demand therapy with antihistamines and, if necessary, with epinephrine and corticosteroids, is indicated when the diagnosis is not yet determined and the history seems to be inconsistent with HAE [37, 64, 65].

Angioedema attacks in patients with HAE nC1-INH and in patients taking ACE inhibitors are thought to be bradykinin-mediated [66–75].

AAE-C1-INH, i.e. recurrent angioedema due to acquired C1-INH deficiency, occurs less frequently than HAE-1/2. AAE-C1-INH symptoms are similar to those of HAE-1/2 and the basic diagnostic laboratory profile (C1-INH function, C1-INH protein and C4) is indistinguishable from HAE-1. Differences include onset at later age, underlying diseases such as lymphoma or benign monoclonal gammopathy (MGUS), occasional constitutional symptoms (B symptoms), and often depressed C1q levels. C1q level measurements should be obtained to investigate patients for AAE-C1-INH, especially those with new onset of angioedema after the age of 40 years and a negative family history. C1q is nearly always normal in HAE [36]. C1q is low in 75% of patients with AAE-C1-INH [36, 76]. C1q may be normal in AAE-C1-INH particularly in patients taking anabolic androgens. Many patients with AAE-C1-INH have autoantibodies that inactivate C1-INH [13, 77–79].

## Therapy

### On-demand treatment

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#### *Recommendation 2*

We recommend that all attacks are considered for on-demand treatment. We recommend that any attack affecting or potentially affecting the upper airway is treated.

Evidence grade: D; Strength of recommendation: Strong, 100% agreement.

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Attacks of the upper airways can result in asphyxiation [80, 81]. Abdominal attacks are painful and debilitating. Peripheral attacks such as those of hands or feet result in impaired function. All of these consequences of HAE attacks can be minimized by on-demand treatment [82–88].

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#### *Recommendation 3*

We recommend that attacks are treated as early as possible.

Evidence grade: B; Strength of recommendation: Strong, 100% agreement.

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Early treatment with C1-INH concentrate, ecallantide, or icatibant provides a better treatment response than late treatment. Early treatment is associated with a shorter time to resolution of symptoms and shorter total attack duration regardless of attack severity [89–92]. As early treatment is facilitated by self-administration, all patients with HAE-1/2 should be considered for home therapy and self-administration training [6, 90, 93–95]. All C1-INH concentrates and icatibant are licensed for self-administration, although approved product indications vary around the world.

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#### *Recommendation 4*

We recommend that HAE attacks are treated with either C1-INH, ecallantide, or icatibant. (18/20).

Evidence grade: A; Strength of recommendation: Strong, 90% agreement.

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If a C1-INH concentrate, ecallantide, or icatibant are not available, attacks should be treated with solvent detergent-treated plasma (SDP). If SDP is not available, then attacks should be treated with fresh frozen plasma (FFP), where safe supply is available. We do not advise using antifibrinolytics (e.g. tranexamic acid) or androgens (e.g. danazol) for on-demand treatment of HAE attacks [96], as these drugs show no or only minimal effects when used for on-demand treatment.

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#### *Recommendation 5*

We recommend that intubation or surgical airway intervention are considered early in progressive upper airway edema.

Evidence grade: C, Strength of recommendation: Strong; 100% agreement.

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The clinical course of HAE attacks is unpredictable. Mortality due to laryngeal angioedema can occur, and

extreme caution is essential [81]. Laryngeal attacks should be considered as medical emergencies. Rapid treatment with an effective HAE acute medication is essential in addition to preparing for emergency airway management procedures if respiratory compromise develops.

#### **Treatment with C1-INH concentrate**

Treatment with plasma-derived C1-INH concentrate or recombinant C1-INH-concentrate replaces the deficient/dysfunctional protein in HAE-1/2 patients. Exogenous C1-INH concentrate acts on the same targets as endogenous C1-INH. Treatment results in an increase of the plasma levels of C1-INH and helps to regulate all cascade systems involved in the production of bradykinin during attacks [88, 97–100]. One unit of C1-INH-concentrate corresponds to the mean quantity of C1-INH present in 1 mL fresh normal plasma.

**Plasma-derived C1-INH** Plasma-derived C1-INH concentrate (pdC1-INH) is obtained by separating C1-INH from cryodepleted human plasma by adsorption and precipitation, purification, pasteurization, and virus filtration. Two pdC1-INH concentrates are available for on-demand treatment of HAE-1/2, Berinert (CSL Behring) and Cinryze (Shire HGT). Approved product indications vary around the world. The mean plasma half-life of pdC1-INH is longer than 30 h [101–105]. The safety and tolerability of all available pdC1-INH are good, and few adverse events have been reported. The risk of allergic reactions is negligible. Modern pdC1-INH use has not been associated with transmission of hepatitis B nor C nor human immunodeficiency viruses [106–108].

**Recombinant C1-INH** Ruconest (Pharming) is the only available recombinant human C1-INH (rhC1-INH). The mode of action is identical to that of pdC1-INH. RhC1-INH is indicated for on-demand treatment of all types of HAE attacks in adults and adolescents. It is derived from the milk of transgenic rabbits using a 3-step purification procedure including cation exchange chromatography, anion exchange chromatography, and affinity chromatography. It appears that differential glycosylation of Ruconest relative to the human protein decreases the plasma half-life to approximately 3 h [109–111]. It is contraindicated in patients with known or suspected allergy to rabbits or rabbit-derived products [112]. Safety data from controlled and uncontrolled studies with rhC1-INH support a favorable safety profile. Transmission of human viruses is not a concern [113–115].

#### **Kallikrein-inhibitor**

**Ecallantide** The kallikrein inhibitor ecallantide (Kalbitor; Shire) is licensed only in the US for the on-demand

treatment of all types of HAE attacks in HAE-1/2 patients aged 12 years and older [116, 117]. Inhibition of kallikrein activity inhibits the cleavage of high-molecular weight kininogen to bradykinin as well as the further activation of FXIIa, halting the positive feedback mechanism leading to additional kallikrein production. Ecallantide is a 60-amino acid recombinant protein produced by expression in the yeast *Pichia pastoris*, and has a plasma half-life of 2 h. The main safety concern is potentially serious hypersensitivity reactions, including anaphylaxis, which was reported in 3% to 4% of treated patients. The drug, therefore, should only be administered by a health care professional with appropriate medical support to manage anaphylaxis [85, 116, 118–120].

### **Bradykinin-receptor antagonist**

**Icatibant** Bradykinin binds to and stimulates the bradykinin B2 receptor, thereby mediating vasodilatation and increased capillary permeability [121–123]. Icatibant (Firazyr; Shire HGT), a 10-amino acid synthetic peptide, is a specific and selective competitive antagonist of the bradykinin B2 receptor and prevents binding of bradykinin to its receptor. Icatibant is indicated for self-administered on-demand treatment of all types of HAE attacks in adults (> 18 years). It has a plasma half-life of 1 to 2 h. The safety and tolerability of icatibant are good, although transient local injection site reactions (erythema, wheal, pruritus, and burning sensation) occur. Allergic reactions have not been reported [84, 124, 125].

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#### *Recommendation 6*

We recommend that all patients have sufficient medication for on-demand treatment of two attacks and carry on-demand medication at all times.

Evidence grade: D, strength of recommendation: Strong. 100% agreement.

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### **Pre-procedural (short-term) prophylaxis**

With surgical trauma, dental surgery and other interventions associated with mechanical impact to the upper aerodigestive tract (e.g. endotracheal intubation, bronchoscopy or esophagogastroduodenoscopy), swellings may occur near the site of intervention. Swellings associated with these procedures usually occur within 48 h. Following tooth extraction, more than one third of patients without pre-procedural prophylaxis may develop local angioedema, and 50% of the swellings occur within 10 h and 75% start within 24 h [126–133]. Pre-procedural prophylaxis reduces the risk of angioedema after above mentioned interventions.

Despite the perceived benefits of pre-procedural prophylaxis with C1-INH concentrate, evidence for its efficacy is scarce. Case reports and series suggest that despite prophylaxis, swellings may occur even after relatively minor procedures [127, 132]. However, several reports document a reduction in the incidence of swelling for both adults and

children with preprocedural prophylaxis, and the response appears to be dose related [126, 127, 134, 135]. Preprocedural prophylaxis with C1-INH concentrate is therefore recommended for all medical, surgical and dental procedures associated with any mechanical impact to the upper aerodigestive tract.

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#### *Recommendation 7*

We recommend short-term prophylaxis before procedures that can induce an attack.

Evidence grade: C, strength of recommendation: Strong. 100% agreement.

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C1-INH concentrate should be used for pre-procedural prophylaxis, as close as possible to the start of the procedure. Dosage has yet to be fully established. Product approved indication may vary by country [136, 137]. Most experts use either 1000 units or a dose of 20 units/kg of pdC1-INH. Fresh frozen plasma (FFP) may be used for short-term prophylaxis and on-demand therapy, but is not as safe as C1-INH concentrate and is a second-line agent because of the greater risk of blood borne disease transmission, and allosensitization. [2–5, 9, 134].

Attenuated androgens (e.g. danazol) have been recommended in the past for pre-procedural prophylaxis as an alternative to C1-INH concentrates [134]. Pre-procedural prophylaxis with attenuated androgens is even considered to be safe in children, but C1-INH concentrate is considered the prophylaxis of choice [127]. Very frequent short courses may lead to side effects associated with long-term use. For scheduled pre-procedural prophylaxis, androgens are used for 5 days before and 2 to 3 days post event. Tranexamic acid (TA) has been used for pre-procedural prophylaxis in the past, but is not recommended by most experts in attendance at the guideline meeting [2–5, 127, 134].

With all pre-procedural prophylactic treatments, break-through attacks can occur, so patients should remain under observation, and on demand treatment needs to be available [2–5, 126, 127, 129].

### **Long-term Prophylaxis (LTP)**

Long-term prophylaxis of HAE refers to the use of regular medication to reduce the burden of the disease by preventing/attenuating attacks in patients with confirmed HAE-1/2. Long-term prophylaxis should be individualized, and considered in all severely symptomatic HAE-1/2 patients taking into consideration the activity of the disease, frequency of attacks, patient's quality of life, availability of health-care resources, and failure to achieve adequate control by appropriate on-demand therapy. As all of these factors can vary over time, all patients should be evaluated for long-term



prophylaxis at every visit, at least once a year. Successful long-term prophylaxis requires a high degree of compliance; therefore the patient's preferences should be taken into consideration. Patients with ongoing long-term prophylaxis should be assessed regularly for efficacy and safety of the therapy, and dosage and/or treatment interval should be adapted according to the clinical response. Upper airway edema and other attacks may occur despite the use of long-term prophylaxis. Therefore, all patients using long-term prophylaxis should also have on-demand medication (C1-INH concentrate, ecallantide, or icatibant) as per recommendation 6 [1, 2, 4, 5, 61, 138–140].

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#### *Recommendation 8*

We recommend prophylaxis be considered for patients who face events in life that are associated with increased disease activity. Grade of evidence: D, strength of recommendation: Strong,  $\geq 90$  agreement.

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#### *Recommendation 9*

We recommend that patients are evaluated for long-term prophylaxis at every visit. Disease burden and patient preference should be taken into consideration. Grade of evidence: D, strength of recommendation: Strong, 100% agreement.

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### **Plasma-derived C1-INH**

Plasma-derived C1-INH is currently the preferred long-term prophylaxis for the prevention of HAE attacks. Approved product indications vary around the world. Dosing should be twice a week based upon the half-life of pdC1-INH. Dose and/or frequency may need adjustment for optimum efficacy [86, 141].

Recent studies show that subcutaneous twice-weekly administration of pdC1-INH at doses of 40 U per kilogram or 60 U per kilogram bodyweight provided very good and dose-dependent preventive effects on the occurrence of HAE attacks [142]. The subcutaneous route may provide more convenient administration as well as maintain improved steady-state plasma concentrations of C1INH compared to IV C1INH prophylaxis.

Appropriate vaccination for hepatitis A and B should be generally considered for patients in regular/repeated administration of human plasma-derived products [86, 143–146]. Routine prophylaxis with pdC1-INH has been shown to be safe and effective, and it improves quality of life in patients with relatively frequent HAE attacks compared with acute treatment of individual HAE attacks [86, 143–145].

Thromboembolic events due to C1-INH concentrate use in HAE are rare, and patients who experience such events often have underlying thromboembolic

risk factors (e.g. implanted central venous catheters [147–151]). There are no known interactions with other medicinal products. Tachyphylaxis seems rare with only one report of increasing doses required to prevent attacks when C1-INH concentrate is used regularly for prophylaxis [152].

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#### *Recommendation 10*

We recommend use of C1-inhibitor for first line long term prophylaxis. Grade of evidence: A, strength of recommendation: Strong, 50–75% agreement (majority vote).

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#### *Recommendation 11*

We suggest to use androgens as second-line long-term prophylaxis. Grade of evidence: C, strength of recommendation: Weak, 50–75% agreement (majority vote).

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#### *Recommendation 12*

We suggest adaptation of long-term prophylaxis in terms of dosage and/or treatment interval as needed to minimize burden of disease. Grade of evidence: D, strength of recommendation: Weak, 100% agreement.

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### **Androgens**

Attenuated androgens are traditionally used for long-term prophylaxis of HAE-1/2 [153–162]. Androgen derivatives have been demonstrated to be effective in HAE-1/2, and the oral administration facilitates their use [154, 156, 158]. However, androgens must be regarded critically, especially in light of their adverse androgenic and anabolic effects, drug interactions, and contraindications. Side effects are numerous and involve the majority of patients; in other words, the absence of side effects is exceptional [156, 163]. Side effects appear to be dose related. Virilization is the most feared complication in women; menstrual disorders and even amenorrhea as well as diminished libido and hirsutism are also common [164], as are weight gain, headache, myalgia, depression, and acne. Androgens may lead to virilization of the female fetus and are, therefore, absolutely contraindicated during pregnancy [165, 166]. In children and adolescents, therapy with androgens may interfere with the natural growth and maturation process. In addition, androgens are subject to numerous contraindications and show interactions with many other drugs (e.g. statins). Careful surveillance is imperative in long-term prophylaxis with androgens. In addition to clinical tests and examinations and questioning of the patient, semiannual blood and urine tests (standard urine test strip) are needed, and at least once a year, an ultrasound of the liver should be performed. It is unclear if stopping long term prophylaxis with attenuated androgens should be done by tapering off gradually over time [167, 168].

The dose of androgens needed to control HAE attacks can vary between the equivalent of 100 mg every other day and 200 mg of danazol 3 times a day. The minimal effective dose should be used. Dosages above 200 mg of danazol daily for extended periods of time are not recommended, because of side effects. The response to androgens varies considerably, and the dose required for long-term prophylaxis is variable. For this reason, the dosage should be adjusted according to clinical response and not adjusted based on C4 and C1-INH results [2, 4, 5, 10].

#### **Anti-fibrinolytics**

Antifibrinolytics are not recommended for long-term prophylaxis. Data for their efficacy are largely lacking, but some patients may find them helpful. They are primarily used when C1-INH concentrate is not available and androgens are contraindicated. Side effects are usually minor. They include gastrointestinal upsets (can be reduced by taking the drug with food), myalgia/creatine kinase elevation, and a theoretical risk of thrombosis. Contraindications/precautions include the presence of thrombophilia or increased thrombotic risk or acute thrombosis, e.g. deep venous thrombosis, pulmonary embolism. The doses of Tranexamic Acid (TA) used range from 30 to 50 mg/kg to 6 g daily. Dose ranging studies and comparisons with other prophylactic medications have not been performed [2, 4, 5, 9, 84, 169–171].

### **Management of HAE-1/2 in children**

#### **Course of disease and clinical picture**

The gene defect (SERPING1 mutation) of HAE-1/2 is already present at birth, but symptoms are uncommon during neonatal age or infancy. The symptoms may occur at any age, but usually begin in childhood or adolescence. The median age of symptom onset is approximately 12 years of age. At the age of 12 years, 50% of all female patients are symptomatic and at the age of 23 years, 90% are symptomatic. In males, 50% are symptomatic by the age of 13 years and 90% by the age of 25 [172]. Subcutaneous edema is the most common and the earliest symptom. However, abdominal symptoms may be an unrecognized and often overlooked symptom of HAE-1/2 in infancy. Asphyxia may ensue rapidly in children, probably because of smaller airway diameter [80]. The earliest occurrence was described in a 4-week-old boy [173]. Estimating the prevalence of abdominal attacks in the pediatric population is difficult as abdominal pain is common in childhood. The frequency and the severity of symptoms may increase during puberty and adolescence. The earlier the onset of symptoms,

the more severe the subsequent course of HAE-1/2 [174, 175]. *Erythema marginatum* as a prodromal sign is more frequent in the pediatric population. It has been observed in 42% to 58% of cases and is often mistaken for urticaria. Misdiagnosis of prodromal erythema marginatum can lead to incorrect or insufficient treatment [9, 15, 62, 102, 169, 176–180].

#### **Diagnosis**

With autosomal dominant inheritance, the offspring of a patient with HAE-1/2 stands a 50% chance of inheriting the disease. Therefore, it is important to establish the diagnosis as early as possible, ideally before the onset of clinical manifestations. Until a full investigation for HAE-1/2 is complete, all offspring should be considered to have HAE-1/2.

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#### *Recommendation 13*

We recommend testing children from HAE-affected families be done as soon as possible and all offspring of an affected parent be tested.

Evidence grade: D, strength of recommendation: Strong, 100% agreement.

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Complement concentrations measured in umbilical cord blood of full-term neonates are lower than maternal levels. Antigenic and functional C1-INH levels correspond to 70% and 62% of adult values respectively [15, 181, 182]. Therefore, using umbilical cord blood for complement measurements may produce false positive (low) results. The assessment of complement in peripheral venous blood (serum/plasma) in children lacks reference values. However, with exceptions, in HAE 1/2 aged less than 1 year, C1-INH antigenic level and/or functional activity are low [59, 183]. The measurement of C4, however, was found not to be useful for diagnosing of HAE-1/2 in children below the age of 12 month, as C4 levels are frequently low in healthy infants [59, 183]. Genetic testing increases the diagnostic reliability in children and may be helpful in cases in which biochemical measurements are inconclusive and the genetic mutation of the parent is known [15, 59, 183]. All early complement testing performed in offspring of HAE-1/2 patients should be repeated after the age of 1 year [9, 15, 59, 183, 184].

Prenatal diagnosis of HAE-1/2 has not become widespread in clinical practice. Reasons include (1) mutations in affected parent C1-INH gene are not detected in 8% to 10% of cases, (2) identical mutations may be associated with substantially different phenotypes, and (3) advances in therapy have significantly improved quality of life of patients with HAE-1/2 [9, 40, 185, 186].

Measurements of C1-INH antigen (protein) level, C1-INH functional (activity) level, and C4 level are advisable in all children with angioedema without urticaria.

## Therapy

Similar to adults, all pediatric HAE-1/2 patients need to have a treatment action plan (see below) and on-demand therapy.

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### Recommendation 14

We recommend C1-INH be used for treatment of HAE attacks in children under the age of 12.

Evidence grade: C, strength of recommendation: strong, > 90% agreement.

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### On-demand treatment

Plasma-derived C1-INH concentrate is the only approved drug for HAE-1/2 on-demand treatment in childhood [15]. Treatment with pdC1-INH concentrate is effective, well tolerated and shows a good safety profile in pediatric patients. During abdominal attacks, par-enteral fluid replacement may be required in view of the increased susceptibility of children to hypovolemia and dehydration, because extravasation into the peritoneal cavity and the intestinal lumen can be substantial. When pdC1-INH concentrate is not available SDP is preferred over FFP, but both are considered second-line treatment. Recombinant C1-INH and ecallantide are licensed for the use in adolescents in some countries. In 2017, icatibant was licensed for the use in children or adolescents in some countries. Clinical trials to investigate the efficacy and safety of rhC1-INH and icatibant in children are ongoing [12, 15, 102, 177, 180, 187–190].

### Pre-procedural prophylaxis

As in adults, pre-procedural prophylaxis is recommended for medical, surgical and dental procedures associated with any mechanical impact to the upper aerodigestive tract [126, 127]. Plasma-derived C1-INH is the first-line pre-procedural option, but short courses of attenuated androgens can be used as second line when C1-INH concentrate is not available. With either option, on-demand therapy should be available because short-term prophylaxis is not 100% effective.

### Long-term prophylaxis

The indications for long-term prophylaxis in adolescents are the same as in adults (see above). The preferred therapy for long-term prophylaxis is pdC1-INH. The dosing interval and dose may need to be adjusted according to the individual response.

When C1-INH concentrate is not available for long-term prophylaxis, antifibrinolytics (i.e. Tranexamic acid 20–40 mg/kg) are preferred to androgens because of their better safety profile; however, efficacy is questioned by many, and data are not available supporting its use. Epsilon aminocaproic acid is less well tolerated than

tranexamic acid. Androgens are not recommended for long-term prophylaxis in children and adolescents prior to Tanner Stage V, however, long-term use has been reported, and in some cases, the benefits may outweigh the risks. The administration of androgens requires careful safety monitoring. The continued need for regular prophylaxis with androgens and the dosing should be reviewed on a regular basis. Initial danazol dose for children is 2.5 mg/kg per day with subsequent adjustment, until symptom suppression or the maximum tolerated or maximum recommended dose is reached, with a maximum single dose of 200 mg per day. Androgens result in masculinization and hypogonadism in boys and menstruation irregularities in girls. Unfavourable effects on behaviour are possible. Reduction in ultimate body height may occur owing to the premature closure of epiphyseal growth plates [2–5, 10, 12, 15, 180, 191, 192].

### Primary prevention

As in adults, most attacks in children occur without a obvious trigger [193]. Infections and mechanical trauma seem to be more common trigger factors during childhood. Compulsory and recommended vaccinations for children are safe and the prevention of infections may reduce the frequency of attacks (i.e. throat infections). Medicinal products, which can cause edema as an adverse effect are less frequently used in children. Treatment with ACE-I is less often necessary during childhood. However, early initiation of oral estrogen containing contraceptives is increasingly common and may trigger attacks. These agents should be avoided. Hormonal contraception with progesterone-only pills may turn out to be beneficial for many young women with HAE-1/2 [9, 194, 195], or at least should not increase attack frequency. Other triggers like strenuous physical activities involving mechanical trauma and emotional challenges (stress) are essential elements of childhood and adolescence [193]. Restrictions of suspected triggers will result in a restriction of activities and lifestyle, and should, therefore, be individualized and sensibly applied. The aim of HAE-1/2 management at all ages should be to normalize life activities and lifestyle whenever possible [15].

### Other management considerations

Providing pediatric patients and their families with appropriate information is indispensable to support them to adopt a suitable lifestyle and to avoid complications. Educators, teachers, and health care personnel responsible for the child at daycare or school should receive written information on the disease, with advice on management of HAE attacks, including the urgency of treatment for airway attacks. C1-INH concentrate for emergency use should be available at home,

school, and travel including school field trips. As noted above, an action plan is necessary and the family and local hospital should have therapies available for emergency treatment and this should be included in the treatment plan. All HAE patients have a potential for receiving human blood products. Because of this, HAE patients should be screened for hepatitis B and C and HIV. Vaccinations for hepatitis A and B are recommended by many experts [15, 177]. All patients should be considered to receive influenza vaccine and other routine vaccinations.

## Management of HAE-1/2 during pregnancy and lactation

### Course of disease and clinical picture

The anatomical, physiological and hormonal changes during pregnancy may influence the manifestations and affect the course and treatment of HAE-1/2. Pregnancy can mitigate, aggravate, or have no effect. Infrequently, the manifestations of HAE-1/2 first occur during pregnancy [196–198]. Attack frequency observed during previous pregnancies is only in part predictive of that in subsequent pregnancies [9, 196, 198]. Pregnant HAE-1/2 patients require vigilant care and meticulous monitoring by an HAE expert. Patients should be managed in close cooperation by professionals from relevant medical specialties. Labour and delivery only rarely induce an attack, which may occur either during labour or within 48 h of delivery. Close follow-up is recommended for at least 72 h postpartum after uncomplicated vaginal delivery. Breastfeeding may be associated with an increased number of maternal attacks, with abdominal symptoms and facial edema, but is still recommended based on benefits provided to the infant [9, 196, 197, 199]. Care for C-section, especially if intubation is necessary, should proceed as in any other surgical procedure performed on a patient with HAE-1/2 and is covered below.

### Diagnosis

In healthy women, the plasma levels of C1-INH decrease during pregnancy, and return to normal after delivery [200, 201]. Therefore, measurements of levels of C1-INH function, C1-INH protein and C4 for the purpose of diagnosing HAE-1/2 during pregnancy should be interpreted with caution. It is recommended to repeat the measurements after childbirth to confirm the diagnosis of HAE [9, 199].

### Therapy

C1-INH concentrate is recommended as first-line therapy for pregnant or breast-feeding HAE-1/2 patients as it is safe and effective [202]. No published experience is available for ecallantide. Although contraindicated by label, there are

isolated case reports about the administration of icatibant during pregnancy with no maternal or fetal adverse effects reported [203–205]. SDP may be used when C1-INH concentrate is not available and fresh frozen plasma when SDP is not available [196–198, 206–210].

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#### *Recommendation 15*

We recommend C1-INH as the preferred therapy for HAE attacks during pregnancy and lactation.

Evidence grade: D, strength of recommendation: strong, 100% agreement.

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Pre-procedural prophylaxis is recommended, preferably with C1-INH concentrate, before any intervention such as chorionic villus sampling, amniocentesis, and induced surgical abortion. Alternatively, C1-INH concentrate should be available and administered immediately at the onset of an attack. It is recommended to manage childbirth in the hospital setting, unless robust measures for prompt treatment HAE attacks are available. Although mechanical trauma and stress are known to trigger attacks, few women have developed angioedema during labour and delivery [9, 198]. Therefore, routine administration of pre-procedural prophylaxis before uncomplicated natural delivery is not mandatory, but C1-INH concentrate should be immediately available for on-demand use. However, administering C1-INH concentrate as pre-procedural prophylaxis is recommended before labour and delivery when symptoms have been recurring frequently during the third trimester and the patient's history includes genital edema caused by mechanical trauma, during forceps delivery or vacuum extraction. Vaginal delivery is preferred because surgery or general anaesthesia may involve endotracheal intubation. Pre-procedural prophylaxis with C1-INH concentrate and epidural anaesthesia is recommended before a caesarean section, and intubation should be avoided if possible. If intubation is required, pre-procedural prophylaxis is mandatory [2–5, 9, 10].

LTP may become indicated during pregnancy, especially in women experiencing an increase of attack frequency. In these women, C1-INH concentrate is considered a safe and effective treatment option [197]. Antifibrinolytics may be considered if C1-INH concentrate is unavailable, but efficacy is not proven [9, 209, 211].

Androgens are contraindicated, as these drugs cross the placenta. Their adverse effects include masculinization of the female fetus, placental insufficiency, and fetal growth retardation. Breast-feeding should be discontinued before androgens are introduced. Terminating lactation itself may reduce attack frequency [165, 166].

Plasma-derived C1-INH concentrate is considered the best therapy for on-demand treatment, short-term

prophylaxis and long-term prophylaxis when indicated during lactation. Androgens and antifibrinolytics are secreted in breast milk. In contrast to androgens, tranexamic acid was found to be safe during breastfeeding [212].

### **Patient support, home therapy and self-administration, and other management considerations**

#### **Patient support**

Patient organizations and support groups provide help and support for HAE patients, caregivers, and family members. They endorse the philosophy that all patients worldwide should have sufficient resources to control their HAE symptoms and fulfil their potential at school, at work, and in their relationships. HAEi, the international umbrella organization for the world's Hereditary Angioedema (HAE) patient groups, and national HAE associations have active informative web sites for patients and health care providers. HAEi has launched a "call to action" aimed at increasing the awareness and knowledge on HAE with governments, health authorities, and health care professionals and to achieve recognition of HAE as a serious, disabling, potentially life-threatening, and chronic condition that must receive timely accurate diagnosis and effective treatment.

Patient organizations also work toward identifying and addressing unmet needs in HAE management, which include the development of safe and well-tolerated new prophylactic and on-demand therapies, the optimization of existing long-term prophylactic and on-demand therapies (e.g., by dose-ranging studies, paediatric studies), increasing the availability of modern treatment options worldwide, emphasizing the need for self-care, individual action plans, early therapy, and gene therapy research. As with most diseases, information obtained from the internet is not always accurate and reliable; however, HAEi provides reviewed, updated, and scientifically sound information and is considered to be a quality source for patient education.

#### **Individualized patient action and treatment plans**

Because HAE-1/2 is an unpredictable, painful, and life-threatening condition that incurs a huge stressful burden on patients and their families, an individualized treatment plan should be carefully developed in partnership between the physician and each patient. Individualized treatment plans should address preventive measures and home care and self-administration. It should include an effective emergency (on-demand) treatment plan, with clear instructions on how to best use medications to treat HAE attacks. Patients should

carry on-demand medication and an HAE identification card with instructions on how to manage an HAE attack. Patients on long-term prophylaxis also require an action plan and available therapy for on-demand use [213–216].

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#### Recommendation 16

We recommend that all patients have an action plan.  
Evidence grade: D, strength of recommendation: Strong, 100% agreement.

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#### Recommendation 17

We suggest that HAE specific comprehensive, integrated care is available for all patients.  
Evidence grade: D, strength of recommendation: Weak, 100% agreement.

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### **Home therapy and self-administration**

Self-administration is crucial for an effective on-demand therapy as early treatment in the course of an attack has been shown to be more effective and may prevent complications. This effect is independent of the on-demand medication used (see recommendation 3 and text) and facilitated by the skill of the self-administrator or home therapy partner [6, 90, 93–95]. Similarly, self-administration facilitates long-term prophylaxis. Every patient should be considered for home therapy and self-administration. Having to attend a medical facility to receive acute medication may result in delayed on-demand treatment, prolonged observation or inappropriate therapy. Self-administration training should include a home therapy partner (family member or friend who can provide support, advice, and administration of therapy when the patient is compromised or unable or uncomfortable with self-treatment. Home therapy decreases the severity and duration of HAE attacks, reduces morbidity and disability, and can improve quality of life and productivity. In addition, the cost of care is reduced considerably by the use of home and self-therapy [6, 139, 189, 215, 217–223].

C1-INH concentrate home therapy is also suitable for children with frequent or disruptive attacks, where a responsible adult is available and willing to undertake training. Experience with hemophilia suggests that it is beneficial for children to be encouraged to take an active part early in their treatment, and even at the age of 8, IV self-administration has been proven possible and safe [189, 224]. Advanced age is not a contraindication for home therapy, provided that patients and/or home therapy partners can safely and effectively administer the treatment. The subcutaneous route may provide more convenient administration in all age groups covered by the license. As pdC1-INH concentrate is a blood derivative, tracking for

home use is important in the event of recall, as well as to make sure that the product is being used as directed.

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#### Recommendation 18

We recommend that all patients who are provided with on-demand treatment licensed for self-administration should be taught to self-administer. Evidence grade: C, strength of recommendation: Strong, 100% agreement.

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Early treatment is crucial in cases of upper airway involvement (tongue, uvula, larynx). Patients should self-administer treatment while awaiting transfer to hospital. It is extremely important to encourage all patients to seek further care immediately after administration of therapy. Upper airway swelling may progress or rebound, and repeat dosing may be necessary. Seeking emergency care after therapy is essential to reduce the risk of suffocation.

#### Avoidance of triggers

A variety of conditions and events are known to trigger HAE attacks. Trauma, whether accidental or associated with dental, medical, and surgical procedures, may result in a swelling attack. The use of estrogen-containing oral contraceptive agents and hormone replacement therapy may trigger attacks. These agents should be avoided. Hormonal contraception with progesterone-only pills may turn out to be beneficial for many women with HAE-1/2 [9, 194, 195]. Antihypertensive agents containing ACE inhibitors may increase the frequency or precipitate HAE attacks and should therefore be avoided strictly.

Other reported triggers include psychological stress, fatigue, febrile illness, possibly *Helicobacter pylori* infection, and the menstrual cycle. Patients should be made aware of potentially relevant triggers of symptoms to reduce precipitation of attacks. Many of these latter triggers are only suspected triggers and of limited significance. Most attacks in most patients are unpredictable. Therefore, physicians should not support excessive avoidance of suspected triggers, in order not to limit the patient's normal life. Influenza vaccine may reduce upper airway infections and possibly reduce upper airway swelling. Good dental care can reduce extractions, need for aggressive dental procedures, and prevent acute or chronic intraoral inflammation, which might reduce the threshold for attacks. Monitoring for side effects of medications is important and is outlined above [129, 130, 193, 225–227].

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#### Recommendation 19

We recommend that all patients with HAE should be educated about possible triggers which may induce HAE attacks. Evidence grade: C, strength of recommendation: strong, 100% agreement.

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#### Expert involvement and follow-up

HAE-1/2 patients are encouraged to find a health care provider with knowledge and interest in the disease.

When and where possible, care should be provided by comprehensive care clinics with expertise in HAE.

It is recommended that HAE patients have a medical evaluation at least annually. Newly diagnosed patients and those on long-term prophylaxis with attenuated androgens should be seen in a shorter interval. Those on androgens should continue to be seen twice a year. Evaluation at follow-up visits should include recording of type and frequency and severity of symptoms, frequency of use, and effectiveness of treatments for swelling attacks. A physical examination and appropriate laboratory evaluation should be conducted [228, 229].

#### Family screening

HAE-1/2 is a genetic disorder with autosomal dominant transmission. Family members including grandparents, parents, siblings, children, and grandchildren of HAE-1/2 patients should be screened for C1-INH function, C1-INH protein, and C4 plasma levels. Delayed diagnosis leads to morbidity and decreased quality of life due to delayed introduction of appropriate therapy. There is a risk that the first HAE attack might affect the airway and could be fatal.

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#### Recommendation 20

We recommend that family members of individuals with HAE should be screened for the condition based on:  
 -autosomal dominant inheritance.  
 -delayed diagnosis leads to morbidity and decreased quality of life without appropriate therapy.  
 -risk of the first angioedema event being fatal due to airway involvement without appropriate therapy.  
 Evidence grade: D, strength of recommendation: strong, 100% agreement.

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#### Abbreviations

AAE-C1-INH: Acquired angioedema with low C1-inhibitor; ACE: Angiotensin-converting enzyme; ACE-I: ACE inhibitor; ACEI-AE: ACE inhibitor-induced angioedema; ANGPT1: Angiotensin 1; AWMF: German Association of Scientific Medical Societies; B symptoms: Occasional constitutional symptoms; B2 receptor: Bradykinin 2 receptor; C1-INH: C1-inhibitor; CSU: Chronic spontaneous urticaria; EAACI: European Academy of Allergy and Clinical Immunology; FFP: Fresh frozen plasma; FXIIa: Factor XIIa; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HAE nC1-INH: HAE with normal C1-INH; HAE: Hereditary angioedema; HAE-ANGPT1: HAE due to mutation in the angiotensin-1 gene; HAE-FXII: HAE due to mutation in the F12 gene; HAEi: International HAE patient association; HAE-PLG: HAE due to mutation in the plasminogen gene; HAE-UNK: HAE due to unknown mutations; HMWK: High molecular weight kininogen; ITT: Intention-to-treat; LTP: Long-term prophylaxis; MASP: Mannose-binding lectin-associated serine protease; MGUS: Monoclonal gammopathy; pdC1-INH: Plasma-derived C1-INH concentrate; PLG: Plasminogen; rhC1-INH: Recombinant human C1-INH; SDP: Solvent detergent-treated plasma; TA: Tranexamic Acid; WHO: World Health Organization

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**Endorsing societies**

*Founder societies:* WAO (World Allergy Organization), EAACI (European Academy of Allergy and Clinical Immunology).

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