REVIEWS

Evolution of Guidelines for the Management of Hereditary Angioedema due to C1 Inhibitor Deficiency

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Abstract

Hereditary angioedema (HAE) is a severe and disabling condition characterized by recurrent episodes of subcutaneous or mucosal swelling in the skin and respiratory and gastrointestinal tracts. HAE due to C1-esterase inhibitor deficiency (C1-INH-HAE) is the most prevalent subtype. The present Iberian study compared C1-INH-HAE treatment guidelines published between 2010 and 2022 to identify the main differences in therapeutic approaches for on-demand treatment and short- and long-term prophylaxis (LTP).

HAE guidelines evolved with the availability of new treatments and with a change in the management paradigm towards an individualized, patient-centered approach, where quality of life (QOL) is central. A parallel trend was observed towards increasingly frequent home-based treatment, which potentially facilitates timely interventions, provides greater flexibility and convenience, and is associated with increased QOL, enabling patients to lead more normal lives.

Most innovations over the years were made for LTP, together with the advent of new therapies and awareness of patients' needs. Several prophylactic therapies with a high level of evidence became available, although formal head-to-head comparisons are lacking. The treatment goals became more ambitious, ranging from a reduction in the frequency, severity, and duration of attacks to achieving total disease control and normalization of patients' lives. The document also addresses relevant items such as changes in terminology (eg, the introduction of designations as "first-line") and the introduction of patient-reported outcome measures to assess patients' perceptions of their self-experienced QOL and well-being. Unmet needs in the management of C1-INH-HAE are identified.

Key words: C1 inhibitor deficiency. Consensus document. Guideline. Hereditary angioedema treatment.

Resumen

El angioedema hereditario (AEH) es una enfermedad grave e incapacitante, caracterizada por episodios recurrentes de edema subcutáneo en la piel o en las mucosas de los tractos respiratorio y gastrointestinal. El AEH por déficit del C1-inhibidor (AEH-C1-INH) es el subtipo más prevalente. En el presente estudio ibérico se han comparado las guías/recomendaciones de tratamiento del AEH-INH-C1, publicadas entre 2010 y 2022 para identificar las principales diferencias en cuanto a los enfoques terapéuticos para el tratamiento a demanda y la profilaxis a corto y largo plazo (PLP).

A nivel mundial, las directrices sobre el AEH evolucionaron con la disponibilidad de nuevos tratamientos y con un cambio en el paradigma de gestión hacia un enfoque individualizado y centrado en el paciente en el que la calidad de vida (CdV) es fundamental. En consonancia con ello, se observó una tendencia creciente hacia el tratamiento domiciliario, ya que facilita potencialmente las intervenciones precoces, proporciona mayor flexibilidad y comodidad, y se asocia a una mayor calidad de vida, permitiendo a los pacientes llevar una vida normal. La PLP es el indicador que más innovaciones ha experimentado a lo largo de los años, paralelamente a la disponibilidad de nuevas terapias y a la toma de conciencia de las necesidades de los pacientes. Se dispone de varias terapias profilácticas con un alto nivel de evidencia, aunque faltan estudios específicos de comparaciones directas entre ellas. Los objetivos del tratamiento se han ido haciendo más ambiciosos, desde la reducción de la frecuencia, gravedad y duración de los ataques, hasta lograr el control total de la enfermedad y la normalización de la vida de los pacientes en la actualidad. Los cambios en la terminología, como la introducción de designaciones como "primera línea" y la introducción de medidas de resultados comunicados por los pacientes ("PROM") para evaluar las percepciones de los pacientes sobre su calidad de vida y bienestar auto experimentados, también son relevantes y se abordan en el documento, junto con las necesidades aún no cubiertas en el tratamiento de la AEH-C1-INH.

Palabras clave: Deficiencia de C1-inhibidor. Documento de consenso. Guía. Tratamiento del angioedema hereditario.

Introduction

Hereditary angioedema (HAE) is a severe, disabling, and rare autosomal dominant condition characterized by recurrent episodes of bradykinin-mediated subcutaneous or mucosal swelling of the tissues of the skin and respiratory and gastrointestinal tracts [1,2]. HAE can be broadly divided into 2 main types with a similar clinical phenotype: HAE due to C1-esterase inhibitor (C1-INH) deficiency (C1-INH-HAE) and HAE with normal C1-INH protein levels and function (nC1-INH-HAE) [3,4]. C1-INH-HAE is more prevalent, ranging between 1:50 000 and 1:100 000 according to the region, while the prevalence of nC1-INH-HAE is unknown but likely much lower [5,6].

C1-INH-HAE results from mutations in the gene *SERPING1*, which codes for C1-INH. This protein is responsible for regulating several proteases implicated in the complement, coagulation, contact-system, and fibrinolytic pathways [4,7]. It has a mostly autosomal dominant inheritance pattern [8]. There are 2 C1-INH-HAE classes: type I, the most frequent, is attributable to insufficient C1-INH synthesis, while type II is due to nonfunctional C1-INH [9].

The condition usually develops in childhood and worsens during puberty [10,11], with earlier onset frequently associated with more severe disease [12]. Symptoms include recurrent, unpredictable, asymmetric, nonpruritic, nonpitting episodes of cutaneous edema without urticaria usually lasting for 2 to 5 days and/or episodes of gastrointestinal wall edema with severe abdominal pain that can mimic acute abdomen, sometimes associated with diarrhea and vomiting [10,11,13,14]. Besides cutaneous and abdominal attacks, which are clearly the most common disease features, patients may also experience attacks of the upper airway (eg, tongue, pharynx, larynx) that can cause asphyxiation, with more than 50% of patients experiencing a laryngeal attack during their lifetime [1,15-17]. Genital swelling and, more rarely, bladder, muscle, or joint swelling may also be present [10,11,13]. Therefore, HAE attacks may be life-threatening and are associated with clinically significant morbidity [18].

The main triggers of an attack in patients with C1-INH-HAE are stress, trauma, infections, fatigue, angiotensin-converting enzyme inhibitors, exogenous estrogens, drugs affecting bradykinin metabolism, surgery, and dental or endoscopic procedures [10,19-21]. The frequency of attacks varies significantly between patients and over time [22,23]. Altogether, the disease represents a substantial burden for patients and significantly impairs their quality of life (QOL) [24].

Diagnosis of C1-INH-HAE requires a high index of suspicion regarding the above-mentioned symptoms, together with an assessment of the patient's family history, followed by laboratory confirmation [11]. This involves determination of low serum antigenic C4 levels and assessment of C1-INH levels and plasma functional C1-INH [10,11,13]. Genetic testing may confirm the *SERPING1* gene mutation and should be performed in de novo cases without affected relatives and in cases with clinical suspicion in which the complement study is inconclusive [11]. Approximately 25% of cases correspond to de novo *SERPING1* gene mutations [13]. Gene sequencing is usually unnecessary, except for establishing a diagnosis in rare cases [25-27].

There have been remarkable improvements in HAE management over the past decade. Since the advent of antifibrinolytic agents (AFs) and attenuated androgens (AAs [eg, danazol]), several therapeutic options have been approved, with the subsequent impact on patients' prognosis and QOL. Therapeutic approaches for HAE include acute treatment (on-demand) and prophylactic treatment. While acute treatment intends to mitigate symptoms during an attack, prophylaxis aims to reduce the likelihood of swelling in the presence of a triggering factor (short-term prophylaxis) or to reduce the recurrence of attacks (long-term prophylaxis) [28-30].

Scientific and clinical progress, together with the emergence of novel therapeutic options, have driven significant changes in the treatment recommendations and guidelines for C1-INH-HAE over the last decade. However, documented inequities exist in the provision of HAE services and treatments between countries, and these are related to limited access to acute life-saving treatments and highly effective prophylactic medications and absence of specialized HAE services or diagnostic facilities in low-income countries [31]. Standardizing management recommendations and guidelines and practices across countries is an unmet need in HAE and has the potential to improve patient outcomes. With this in mind, the present Iberian study aimed to compare C1-INH-HAE treatment guidelines published globally over the last decade and to identify their main differences regarding the therapeutic approach for on-demand treatment and short- and long-term prophylaxis.

Methodology

A group of experts from Portugal and Spain with extensive clinical experience in the treatment of HAE convened to retrieve and analyze guidelines on the treatment of C1-INH-HAE published between 2010 and 2022 and to identify changes in treatment patterns over the last 12 years.

A literature search was conducted on PubMed to identify documents in English published between 2010 and 2022 by committees, consortia, and working groups and providing recommendations and guidelines on the treatment of C1-INH-HAE. The documents retrieved were then individually screened to determine eligibility for inclusion based on their methodologic validity. Formal clinical practice guidelines were included directly in the study. These comprised documents with recommendations and guidelines intended to optimize patient care that were informed by a systematic review of the available evidence and followed by a set of recommendations based on the evidence retrieved and on an assessment of risks and benefits of the various care options. We also included documents that were not strict guidelines according to the previous criteria but were considered relevant for this analysis, either because they were from the Iberian peninsula and aimed to guide medical actions in the respective countries or because they included recommendations based on evidence and were informed by the strength of those recommendations. In cases where an issuing body published guidelines and the respective update during the considered 12-year study period, both documents were considered for analysis. Documents addressing specific issues, such as self-administration and disease management in women and children, were not included.

The documents included were analyzed and compared with respect to on-demand treatment and short- and long-term prophylaxis.

Results

The literature search returned 17 records with treatment recommendations on C1-INH-HAE. Of these, 8 were excluded because they did not meet guideline criteria, and 9 were included in the analysis. Of the 9 documents included, 5 corresponded to formal clinical practice guidelines, and 4 were not strict guidelines (Table 1). Despite not being an English-language document or PubMed-indexed, the Portuguese Standard (Norma Clínica da Direção-Geral da Saúde 009/2019; 2019 PT DGS) was included in the analysis because it is an Iberian document and because of its strength as a reference document guiding medical actions in Portugal.

Tables 2-4 depict the main considerations and therapeutic options for on-demand treatment and prophylaxis of adult, pediatric, and pregnant/breastfeeding patients with C1-INH-HAE retrieved from the 9 documents.

Discussion

The present study aimed to review Iberian and international guidelines for the management of C1-INH-HAE published over the last decade, seeking to identify the main differences regarding on-demand treatment and short-term prophylaxis (STP) and long-term prophylaxis (LTP) during that period.

Globally, HAE guidelines have evolved with the availability of new treatments and with a change in the management paradigm of the disease towards an individualized, patient-centered approach, where QOL is central. In close association with that, an increasing trend has been observed towards home-based treatment, as this potentially facilitates timely interventions, provides greater flexibility and convenience, and is associated with increased QOL, thus enabling patients to lead more normal lives.

On-Demand Treatment

The indications for on-demand (or acute) treatment of angioedema attacks have evolved over time. In the 2011 Spanish Study Group on Bradykinin-Induced Angioedema (SGBA) Consensus Statement, the authors state that treatment of acute episodes should be provided depending on the severity and location of episodes. However, the indication evolved to recommend treating any angioedema attack regardless of the location and as early as possible (2013 US Hereditary Angioedema Association [HAEA] Recommendations), and that recommendation remains in place in the latest 2022 World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EACCI) Guidelines.

The guidelines have also evolved in their terminology. The concept of "first-line therapy" in the setting of on-demand treatment was introduced in the 2012 WAO Guidelines but not subsequently addressed until the 2018 WAO/EACCI Guidelines, being adopted from then on.

In addition, the term "specific therapy" in the setting of on-demand treatment changed over time. The concept was introduced in the 2012 WAO guidelines, which stated that "attacks should be treated as early as possible, using specific therapies without delay when indicated". The term was subsequently adopted and referred to in several guidelines. The 2014 Canadian Hereditary Angioedema Network (CHAEN) Guidelines stated that "All patients should be trained on self-administration of HAE-specific therapies if they are suitable candidates", the 2019 Portuguese Health Authority (Direção-Geral da Saúde; PT DGS) Recommendation sustained that "Patients should always carry specific acute treatment medication and be trained in self-administration of specific therapies," and the 2021 HAEA Recommendations referred to the development and approval of specific products for on-demand treatment of HAE attacks.

Four specific drugs are used in the treatment of acute angioedema attacks in patients with C1-INH-HAE: intravenous (IV) plasma-derived C1-inhibitor concentrate (pdC1-INH), IV recombinant human C1-inhibitor concentrate (rhC1-INH), subcutaneous (SC) icatibant acetate, and SC ecallantide. Acute treatments evolved from the use of mainly pdC1-INH and fresh frozen plasma (FFP) prior to 2011 to include the use of icatibant and ecallantide in the treatment armamentarium of affected patients in the 2011 SGBA Consensus Statement. Acute treatment later went on to include rhC1-INH in the 2012 WAO Guidelines, with these therapies remaining as options for on-demand treatment of C1-INH-HAE over the years and until the present.

In children and adolescents, icatibant only started to be considered as of the 2018 WAO/EACCI Guidelines, when it was approved for use in this age range in some countries. At that time, the benefit of icatibant in the pediatric population was still under assessment, and experience with its use was very limited, with no specific dose recommended. In the following guidelines (2019 International/Canadian Hereditary Angioedema Network [ICHAEN] Guidelines), icatibant was already considered an effective therapeutic option in children aged ≥2 years at the dose of 0.4 mg/kg and up to 30 mg. As evidence continued to mount on the drug's efficacy and safety, it moved to be considered a first-line option in the 2019 PT DGS Recommendations and remains so today. Ecallantide was included in the guidelines as on-demand treatment for pediatric patients in the 2013 HAEA recommendations and has thenceforth been kept as a therapeutic option.

Disease management decisions in pregnancy and breastfeeding are more complex and require additional considerations to reduce the disease burden and risk of fetal harm. Data on the safety and efficacy of (on-demand or prophylactic) therapeutic options during pregnancy, labor, delivery, and lactation are generally limited, and except for pdC1-INH, which has a long history of clinical use and well-established safety profile in this patient population, the data available for most drugs come mainly from case reports and have a low level of evidence. pdC1-INH has been the treatment of choice for on-demand treatment of angioedema attacks in pregnant and breastfeeding women since the SGBA Consensus Statement of 2011. Ecallantide has not been studied in this group of patients and is not considered a therapeutic option in any of the guidelines. The same is true for icatibant, as only anecdotal reports of its use during pregnancy are available in the literature, despite the absence of documented maternal or fetal adverse effects [32-36]. The only exception is the 2019 ICHAEN guidelines, which consider icatibant an option in pregnancy and lactation when pdC1-INH is not available or has not been efficacious in a specific patient, with no other guidelines endorsing this recommendation.

The recommendation for availability of and patients' access to emergency medication for acute attacks was already in place in the 2011 SGBA Consensus Statement, which has been maintained in succeeding guidelines as a way of preserving patients' autonomy and QOL and ensuring early treatment. The concept of self-administration and respective training was introduced in the 2012 WAO Guidelines, and all drugs except ecallantide are currently recommended for home self-administration by the patient or a relative after appropriate training. The administration of ecallantide is reserved for health care providers owing to the risk of anaphylactic reactions. In the same 2012 WAO Guidelines, the experts introduced the recommendation that patients should have sufficient medication for the treatment of 2 attacks and carry on-demand medication at all times, even if using LTP. The indication for carrying 2 doses of an approved on-demand medication for acute HAE attacks was maintained until the current 2022 WAO/EACCI Guidelines.

Short-Term Prophylaxis

The definition of STP, also referred to as preprocedure prophylaxis, has changed over the years, as reflected in the guidelines. In guidelines prior to 2014, STP was described as the treatment administered before medical or surgical procedures to prevent angioedema episodes [37]. However, in the 2014 CHAEN Guidelines, the recommendation evolved to include preventive treatment before life events (eg, examinations, weddings) and during particularly stressful life periods (such as a divorce or other emotional stressors) because of their potential to elicit angioedema episodes. This extended recommendation was adopted and included in subsequent guidelines.

Although IV pdC1-INH, AAs, AFs, and FFP represented options for STP of C1-INH-HAE in the 2011 SGBA Consensus Statement, IV pdC1-INH was the treatment of choice in countries where it was available, despite the lack of efficacy

Table 1. Guidelines for the Management of C1-INH-HAE Included in the Study.

Issuing body	Reference	Comments
Spanish Study Group on Bradykinin-Induced Angioedema (SGBA) - 2011	Caballero et al. J Investig Allergol Clin Immunol. 2011;21(6):422-41; quiz 442-3 [38]	Consensus Statement – Part II Although it is not a guideline, it intends to guide medical actions in the respective country and hence must be considered in this Iberian document.
World Allergy Organization (WAO) - 2012	Craig et al. World Allergy Organ J. 2012 Dec;5(12):182-99 [75]	Guidelines
US Hereditary Angioedema Association (HAEA) Medical Advisory Board - 2013	Zuraw et al. J Allergy Clin Immunol Pract. 2013 Sep-Oct;1(5):458-67 [28]	2013 Recommendations Although methodologically it is not strictly a guideline, it includes recommendations based on evidence as well as strength of recommendations.
Canadian Hereditary Angioedema Network (CHAEN) Guideline - 2014	Betschel et al. Allergy Asthma Clin Immunol. 2014 Oct 24;10(1):50 [76]	Guidelines
World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EACCI) - 2018	Maurer et al. Allergy. 2018 Aug;73(8):1575-96 [29]	Guidelines
International/Canadian Hereditary Angioedema Network (ICHAEN) Guideline - 2019	Betschel S et al. Allergy Asthma Clin Immunol. 2019 Nov 25;15:72 [77]	Guidelines
Direção-Geral da Saúde (DGS; Portuguese Health Authority) - 2019	Portuguese Standard (Norma Clínica): 009/2019 [78]	Clinical Practice Recommendations Although it is not a guideline, it intends to guide medical actions in the respective country and hence must be considered in this Iberian document.
US Hereditary Angioedema Association (HAEA) Medical Advisory Board - 2020	Busse et al. J Allergy Clin Immunol Pract. 2020 Sep 6:S2213-2198(20)30878-3 [36]	2020 Recommendation update Although methodologically not strictly a guideline, it includes recommendations based on evidence as well as strength of recommendations.
World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EACCI) - 2022	Maurer et al. Allergy. 2022 Jan 10. Online ahead of print [79]	Guidelines

Table 2. On-demand Treatment for C1-INH-HAE.

	SGBA Consensus Statement	WAO Guidelines	HAEA Recommendations	CHAEN Guidelines	WAO/EACCI Guidelines	ICHAEN Guidelines	PT DGS Recommendation	HAEA Recommendations	WAO/EACCI Guidelines
Year	**2011**	**2012**	**2013**	**2014**	**2018**	**2019**	**2019**	**2021**	**2022**
General Considerations					**General Considerations**				
Indication	Indications for treatment of acute episodes depend on the severity and location of the episodes. All episodes of glottic edema, pharyngo-laryngeal edema, and cervicofacial edema, as well as most episodes of abdominal edema, should be treated. Peripheral episodes should be treated based on the impact on the patient's quality of life.	All attacks that result in debilitation/ dysfunction and/or involve the face, the neck, or the abdomen should be treated. Treatment of attacks affecting the upper airways is mandatory	All attacks, irrespective of location, should be considered for treatment as soon as they are clearly recognized. All abdominal, facial, oral, and upper respiratory attacks should be treated as early as possible. Treatment of attacks involving the extremities can be left to the patient's sense of whether the swelling location is likely to result in disability.	Effective therapy should be used to treat acute attacks of angioedema to reduce duration and severity of attacks. All attacks of angioedema involving the upper airway are medical emergencies and must be treated immediately.	All attacks should be considered for on-demand treatment. Any attack affecting or potentially affecting the upper airway should be treated.	Effective therapy should be used for the acute treatment of angioedema attacks to reduce the duration and severity of attacks. All angioedema attacks involving the upper airway are medical emergencies and must be treated immediately.	All acute attacks that interfere with the patient's quality of life should be treated, regardless of their location. Absolute indication: All episodes of laryngeal edema, edema with involvement of the face or neck, abdominal crises, and disabling attacks with impact on school, leisure, occupational, or professional activity or interfering with the patient's quality of life should be treated. Upon individual assessment: Mild-to-moderate abdominal pain lasting longer than 48 h; mild-to-moderate. mucocutaneous edema lasting longer than 48 h; polytrauma, burn, or localized trauma (to minimize future risk); and prodromic symptoms (extreme fatigue, sudden mood changes, abdominal, muscle or joint pain, erythema marginatum, or paresthesia) should be treated.	All attacks, irrespective of location, should be considered for treatment as soon as they are clearly recognized. All abdominal, facial, oral, and upper respiratory attacks should be treated as early as possible, as should attacks affecting the extremities.	All attacks should be considered for on-demand treatment, including all abdominal, peripheral (hand and feet), and upper airway attacks. Treatment of any attack affecting or potentially affecting the upper airway is mandatory.
Timing	The administration of treatment should not be delayed, especially if the location of the attack is life-threatening.	Attacks should be treated as early as possible, using specific therapies without delay when indicated	Treatment should be administered early in the attack. Patients should be counseled to treat as soon as the attack is clearly recognized. Treatment should be administered only when the patient can identify that an attack has begun.	Attacks should be treated early to reduce morbidity and mortality. Attacks involving the upper airway should be treated immediately.	Attacks should be treated as early as possible.	Attacks should be treated early to reduce morbidity and mortality. Attacks involving the upper airway should be treated immediately.	Treatment should be promptly administered at symptom onset.	Treatment should be administered early after attack onset.	Attacks should be treated as early as possible. Early treatment is crucial in cases of upper airway involvement (eg, tongue, posterior pharyngeal, uvula, larynx, and vocal cords).
Home therapy	It is essential that patients have medication (eg, pdhC1-INH, icatibant acetate, or any other approved drug) available at all times, so that emergencies can be managed quickly and effectively at home or at a health center. This way, autonomy and quality of life are increased.	All patients should be considered for home therapy and self-administration training. All patients should have on-demand treatment for 2 attacks and carry their on-demand treatment at all times.	All patients should have access to at least 2 standard doses of an FDA-approved medicine for on-demand treatment of acute HAE attacks. Effective on-demand treatment should be available even for patients on prophylactic treatment regimens.	All patients should be trained in self-administration of HAE-specific therapies if they are suitable candidates, and self-administration should be considered in their overall care plan.	All patients should be considered for home therapy and self-administration. Patients should have sufficient medication for on-demand treatment of 2 attacks and carry on-demand medication at all times	All pediatric patients diagnosed with HAE should have access to acute treatment, including those who are symptom-free	Patients should always carry specific acute treatment medication and be trained in self-administration of specific therapies. All patients should carry 2 therapeutic doses for on-demand treatment of acute HAE attacks.	All patients should have access to at least 2 standard doses of an FDA-approved medicine for on-demand treatment of acute HAE attacks. Effective on-demand treatment should be available even for patients on prophylactic treatment regimens.	Patients should have and carry on-demand medication for the treatment of at least 2 attacks. All patients should be considered for home therapy and self-administration training. In patients with frequent attacks, the time it takes to obtain more on-demand medication should be taken into consideration in the provision of treatment, so that they never run out of on-demand medication.
Go to the ED after treatment?	If necessary, the patient should be referred to the intensive care unit, since intubation or tracheotomy could become necessary at any time	Intubation or tracheotomy is recommended early in progressive upper airway edema.	Most HAE attacks can be treated outside a medical facility. Patients who experience symptoms of laryngeal, tongue, or throat swelling should seek emergency medical care as soon as possible, even after initial self-treatment.	All patients with laryngeal edema, even following self-administered therapy, should be assessed in the emergency department in the event that the angioedema does not respond to therapy. Expertise in airway management is required	Intubation or surgical airway intervention are recommended early in progressive upper airway edema.	All angioedema attacks involving the upper airway are medical emergencies and must be treated immediately.	Patients and/or legal representatives and/or caregivers should seek emergency medical care in cases where the patient does not carry specific on-demand medication for AE attacks, in absence of response to the administered therapy, and in cases of upper airway impairment.	Patients who experience symptoms of laryngeal, tongue, or throat swelling should seek emergency medical care as soon as possible, even after initial self-treatment. Elective intubation should be considered for patients with signs of respiratory distress not improving after treatment.	Intubation or surgical airway intervention should be considered early in progressive upper airway edema. Seeking emergency care after upper airway swelling is essential to reduce the risk of asphyxia.

(continued)

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Table 2. On-demand Treatment for C1-INH-HAE (*continuation*).

	SGBA Consensus Statement	WAO Guidelines	HAEA Recommendations	CHAEN Guidelines	WAO/EACCI Guidelines	ICHAEN Guidelines	PT DGS Recommendation	HAEA Recommendations	WAO/EACCI Guidelines
Year	**2011**	**2012**	**2013**	**2014**	**2018**	**2019**	**2019**	**2021**	**2022**
Options for adults					**Options for adults**				
pdC1-INH	Effective in the resolution of acute attacks. Dose: 20 U/kg IV, administered as follows: patients with ≤50 kg, 500 U; patients with 50-100 kg, 1000 U; patients with >100 kg, 1500 U Dose may be repeated if response is absent or incomplete after 1 hour	First-line therapeutic option Dose: 20 U/kg IV	Therapeutic option Berinert – FDA-approved Dose: 20 U/kg IV Cinryze – Not FDA approved Dose: 1000 U IV	Effective and safe therapeutic option Berinert - Dose: 20 U/kg IV Cinryze – Dose: 1000 U every 3-4 d IV initially. Another dose of 1000 U can be given if no response.	Recommended therapeutic option Dose: NM	Effective and safe therapeutic option Berinert - Dose: 20 U/kg IV Cinryze – Dose: 1000 U IV	First-line therapeutic option Dose: 20 U/kg IV In case of no response within the first hour, a second dose should be given, with 24-hour surveillance	First-line therapeutic option Dose: 20 U/kg IV	First-line therapeutic option Dose: NM, IV
rhC1-INH	Medicine under development. The active substance has proven effective in the treatment of acute attacks. Dose: 50 U/kg IV	First-line therapeutic option Dose: 50 U/kg IV	Non–FDA-approved therapeutic option Dose: 50 U/kg IV	Effective therapeutic option Dose: 50 U/kg IV in people <84 kg and 4200 U IV in people ≥84 kg	Recommended therapeutic option Dose: NM	Effective therapeutic option Dose: 50 U/kg IV in people <84 kg and 4200 U IV in people ≥84 kg	NM	First-line therapeutic option Dose: 50 U/kg up to 4200 U IV Treatment may be repeated during a single attack until the maximum of 2 doses within a 24-h period	First-line therapeutic option Dose: NM, IV
Icatibant	Effective therapeutic option. Dose: 30 mg If an adequate response does not occur, reinjection is indicated after 6 h have elapsed. In most cases 1 dose is sufficient, but a second or third dose may be necessary in some cases. The administration of more than 3 doses within a 24-hour period or more than 8 doses in 1 month is not recommended.	First-line therapeutic option Dose: 30 mg SC	Therapeutic option Dose: 30 mg SC	Effective therapeutic option Dose: 30 mg SC	Recommended therapeutic option. Indicated for self-administered treatment Dose: NM	Effective therapeutic option Dose: 30 mg SC	First-line therapeutic option Dose: 30 mg SC In case of insufficient response, repeat the administration 6 h after the first dose until a maximum of 90 mg/24 h, with 24-h surveillance	First-line therapeutic option Dose: 30 mg SC Treatment may be repeated during a single attack until the maximum of 3 doses within a 24-h period at intervals of at least 6 h.	First-line therapeutic option Dose: NM
Ecallantide	Effective therapeutic option Dose: 30 mg SC divided into 3 doses	First-line therapeutic option Dose: 30 mg SC	Therapeutic option Dose: 30 mg SC	Effective therapeutic option Dose: three 10 mg doses SC (until the total dose of 30 mg) Must only be administered by health care professionals trained and prepared to treat adverse reactions.	Recommended therapeutic option (licensed only in the US) Dose: NM Should only be administered by a health care professional with appropriate medical support to manage anaphylaxis.	Effective therapeutic option Dose: 3 × 10-mg doses SC (until the total dose of 30 mg)	NM	First-line therapeutic option Dose: 30 mg SC Treatment may be repeated during a single attack until the maximum of 2 doses within a 24-h period) Requires administration by a health care provider	First-line therapeutic option Dose: NM, SC Should only be administered by a health care professional with appropriate medical support to manage anaphylaxis.
AF	TXA: No data from controlled clinical trials. Reported use of high IV or oral doses (15 mg/kg every 4 h IV/oral), but have only proven effective in prodromal phases of the attack	Oral AFs are NR IV AFs: NM	NM	TXA - contraindicated	NR	TXA - contraindicated	Therapeutic option when pdC1-INH and icatibant are NA or in case of insufficient response to those therapies. TXA: 0.5-1 g IV, until the maximum dose of 4 g ECA: 100 mg/kg or 3 mg/m^2 IV, until the maximum dose of 600 mg/kg	NR	Contraindicated
SDP/FFP	Option when pdC1-INH, icatibant, and ecallantide are NA Dose: 2 U of 200 mL each	Second-line therapeutic option when recommended therapies (C1-INH concentrate, ecallantide, or icatibant) are NA, starting with SDP and using FFP if SDP is NA Dose: NM	Non–FDA-approved therapeutic option FFP - Dose: 2 U	Option only if other recommended therapies are NA. FFP not as safe as SDP. FFP with low evidence of effectiveness in the treatment of acute attacks Dose: NM	Second-line option when recommended therapies (C1-INH concentrate, ecallantide, or icatibant) are NA, starting with SDP and using FFP if SDP is NA Dose: NM	Option only if other recommended therapies are NA. FFP not as safe as SDP. FFP with low evidence of effectiveness in the treatment of acute attacks Dose: NM	FFP is an option when pdC1-INH, icatibant, and AF are NA Dose: 5-10 mL/kg IV, until the maximum dose of 400 mL	FFP can be used to treat HAE attacks if none of the FDA-approved on-demand medications are available. SDP may be safer than FFP.	Second-line therapeutic option SDP is an option when first-line therapies are NA. If SDP is NA, FFP should be used.

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Table 2. On-demand Treatment for C1-INH-HAE (*continuation*).

	SGBA Consensus Statement	WAO Guidelines	HAEA Recommendations	CHAEN Guidelines	WAO/EACCI Guidelines	ICHAEN Guidelines	PT DGS Recommendation	HAEA Recommendations	WAO/EACCI Guidelines
Year	**2011**	**2012**	**2013**	**2014**	**2018**	**2019**	**2019**	**2021**	**2022**
Options for children					**Options for children**				
pdC1-INH	Is the treatment of choice at 20-25 U/kg. If response is insufficient, the dose may be repeated, usually an hour later.	Preferred (first-line) therapeutic option and the only approved in childhood (in European Union only, ≥12 y in the US) Dose: 20 U/Kg IV	Therapeutic option in adolescents Dose: 20 U/kg IV	Effective and safe therapeutic option Berinert - Dose: 20 U/kg IV Cinryze – Dose: 1000 U every 3-4 d IV initially. Another dose of 1000 U can be given if no response.	Preferred (first-line) therapeutic option and the only approved in childhood Dose: NM	Effective and safe therapeutic option Berinert - Dose: 20 U/kg IV Cinryze - Dose: – 500 U IV for children 10-25 kg – 1000 U IV for children >25 kg	First-line therapeutic option Dose: 20 U/kg IV In case of no response within the first hour, a second dose should be given, with 24-h surveillance.	Effective and safe therapeutic option for children Treatment of choice in the US Dose: 20 U/kg IV Self-administration (by the child or his/her caregiver) of C1-INH recommended for children.	First-line therapeutic option in children aged <12 y Dose: NM
rhC1-INH	NM	Not licensed for use in children. Very limited experience in this patient population.	NM	NM	Licensed for use in adolescents in some countries. Efficacy and safety under investigation. Dose: NM	Effective therapeutic option Dose: 50 U/kg IV in people weighing <84 kg and 4200 U IV in people weighing ≥84 kg	NM	Limited but encouraging data in children Effective and safe therapeutuic option for adolescents Dose: 50 U/kg up to 4200 U IV Treatment may be repeated during a single attack until the maximum of 2 doses within a 24-h period Self-administration (by the child or his/her caregiver) of C1-INH recommended for children.	First-line therapeutic option in children aged <12 y Dose: NM
Icatibant	No information about its efficacy and safety profile in patients aged <18 y. No experience.	Not licensed for use in children. Very limited experience in this patient population.	NM	NM	Licensed for use in children or adolescents in some countries. Efficacy and safety under investigation. Dose: NM	Effective therapeutic option in children aged ≥2 y Dose: 0.4 mg/kg (to a maximum dose of 30 mg) SC	First-line therapeutic option in children aged >2 y and adolescents aged ≥10 y Doses: - 12-25 kg: 10 mg (1.0 mL) SC - 26-40 kg: 15 mg (1.5 mL) SC - 41-50 kg: 20 mg (2.0 mL) SC - 51-65 kg: 25 mg (2.5 mL) SC - >65 kg: 30 mg (3.0 mL) SC In case of insufficient response, repeat the administration 6 h after the first dose until a maximum of 90 mg/24 h, with 24-h surveillance	Effective and safe therapeutic option approved in Europe, New Zealand, and Australia for children aged ≥2 y Dose: - 12-25 kg - 10 mg SC - 26-40 kg - 15 mg SC - 41-50 kg - 20 mg SC - 51-65 kg - 25 mg SC - >65 kg - 30 mg SC Treatment may be repeated during a single attack until the maximum of 3 doses within a 24-h period at intervals of at least 6 h.	First-line therapeutic option in children aged <12 y Dose: NM
Ecallantide	Approved by the FDA for treatment of acute episodes in patients aged ≥16 y. No experience.	Not licensed for use in children. Very limited experience in this patient population. Dose: 30 mg SC in children aged ≥16 y.	Therapeutic option in patients aged ≥16 y	Effective therapeutic option Dose: 3 × 10-mg doses SC (until the total dose of 30 mg) Must only be administered by health care professionals trained and prepared to treat adverse reactions.	Licensed only in the US for use in patients aged ≥12 y Should only be administered by a health care professional with appropriate medical support to manage anaphylaxis.	Effective therapeutic option in adolescents aged ≥12 y Dose: 3 × 10-mg doses SC (until the total dose of 30 mg) Must be administered by health care professionals. Cannot be self-administered.	NM	Effective and safe therapeutic option for children aged ≥12 y Dose: 30 mg SC Treatment may be repeated during a single attack until the maximum of 2 doses within a 24-h period) Requires administration by a health care provider	Therapeutic option in children aged ≥12 y Dose: NM Should only be administered by a health care professional with appropriate medical support to manage anaphylaxis.
AF	NM	NM	NM	TXA - contraindicated	NM	TXA - contraindicated	Therapeutic option when pdC1-INH and icatibant are NA or in case of insufficient response to those therapies. TXA: 7-10 mg/kg IV, until the maximum dose of 20 mg/kg in children aged >1 y and adolescents aged ≥10 y ECA: 100 mg/kg or 3 mg/m^2 IV, until the maximum dose of 600 mg/kg	NR	Contraindicated
SDP/FFP	FFP is an option in countries where pdC1-INH is NA Dose: 10 mL/kg	Second-line option when pdC1-INH is NA. SDP is preferred over FFP. Dose: NM	NM	NM	Second-line option when pdC1-INH is NA SDP is preferred over FFP. Dose: NM	NM	NM	NM	Second-line therapeutic option SDP is an option when first-line therapies are NA. If SDP is NA, FFP should be used.

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Table 2. On-demand Treatment for C1-INH-HAE (*continuation*).

	SGBA Consensus Statement	WAO Guidelines	HAEA Recommendations	CHAEN Guidelines	WAO/EACCI Guidelines	ICHAEN Guidelines	PT DGS Recommendation	HAEA Recommendations	WAO/EACCI Guidelines
Year	**2011**	**2012**	**2013**	**2014**	**2018**	**2019**	**2019**	**2021**	**2022**
Options for pregnancy and breastfeeding					**Options for pregnancy and breastfeeding**				
pdC1-INH	Treatment of choice for angioedema attacks during pregnancy. Dose: 20 U/kg	Recommended first-line therapeutic option. Should be immediately available for on-demand use. Dose: NM	NM	NM	Recommended first-line therapeutic option. Dose: NM C1-INH concentrate should be immediately available for on-demand use.	Therapy of choice Dose: NM	Recommended therapeutic option Dose: 20 U/kg IV, with 24-h surveillance In case of no response within the first hour, repeat dose	Preferred therapeutic option Recommend treatment during breastfeeding Dose: NM	First-line therapeutic option Dose: NM
rhC1-INH	No experience in pregnancy; therefore, the safety profile is unknown.	No experience	NM	NM	NM	Option when pdC1-NH is NA or has not been efficacious for a particular patient Dose: NM	NM	Therapeutic option with limited, but reassuring evidence Recommend treatment during breastfeeding Dose: NM	NM
Icatibant	No information about its efficacy and safety profile in women who are pregnant or breastfeeding. No experience in pregnancy.	No experience	NM	NM	Contraindicated, but with isolated case reports of use during pregnancy with no report of maternal or fetal adverse effects.	Option when pdC1-NH is NA or has not been efficacious for a particular patient Dose NM	NM	NR No safety data during breastfeeding.	Contraindicated by label, but with no maternal or fetal adverse effects reported in isolated case reports
Ecallantide	No experience in pregnancy; therefore, the safety profile is unknown.	No experience	NM	NM	No experience	NR	NM	No safety data from clinical trials. No safety data during breastfeeding.	NR
AF	NM	NR	NM	TXA - contraindicated	NM	TXA - contraindicated	Therapeutic option when pdC1-NH is NA or in case of no response to pdC1-NH (except in the first trimester and breastfeeding) TXA: 0.5-1 g IV, until the maximum dose of 4 g	NR TXA - Contraindicated during breastfeeding	Contraindicated
SDP/FFP	NM	Second-line option when pdC1-INH is NA, starting with SDP and using FFP when SDP is NA Dose: NM	NM	NM	Second-line option when pdC1-INH is NA, starting with SDP and using FFP when SDP is NA Dose: NM	NM	Therapeutic option when pdC1-NH is NA or TXA is contraindicated Dose: 5-10 ml/kg IV, until the maximum dose of 400 mL	NM	Second-line therapeutic option SDP is an option when pdC1-INH is NA If SDP is NA, FFP should be used. Doses: NM
Self-administration					**Self-administration**				
IV or SC drugs	In cases of frequent or more severe AE episodes, training programs can be given for self-administration of IV pdhC1-INH. In the case of icatibant, SC administration may facilitate self-administration	All patients should be considered for home therapy and self-administration training, as it facilitates early treatment. All patients should have on-demand treatment of 2 attacks. All patients carrying on-demand treatment licensed for self-administration should be taught to self-administer. All patients should be provided with an HAE identification card.	Treatment can be self-administered or given by a trained family member or a home health professional. Patients who self-administer treatment should seek medical care if the attack has unusual features, response to self-treatment is inadequate, or the attack involves the airway. The physician should address whether there have been any difficulties in self-administration. Follow-up visits offer opportunities for retraining as well as ensuring that other family members or friends can administer medication in case the patient is unable to do so. There must be a plan for patients who self-administer or receive on-demand medications to report this use in a timely manner.	All patients should be trained in self-administration of HAE-specific therapies if they are suitable candidates. If patients cannot self-administer therapy, provisions should be made to ensure timely access to all appropriate therapies. Therapies for the treatment of HAE attacks that can be self-administered include the following: – Berinert (pdC1-INH) - can be administered either by health care professionals or by patients and caregivers who have been trained in its administration. – Icatibant - is licensed in Europe and the USA for self-administration.	All patients should be considered for home therapy and self-administration training, as this facilitates early treatment. All patients should have sufficient medication for on-demand treatment of 2 attacks and carry on-demand medication at all times. All patients who are provided with on-demand treatment licensed for self-administration should be taught to self-administer. Self-administration training should include a home therapy partner who can provide support, advice, and administration of therapy when the patient is compromised. unable, or uncomfortable with self-treatment.	All patients should be considered for home therapy and self-administration training, as this facilitates early treatment. All patients should have sufficient medication for on-demand treatment of 2 attacks and carry on-demand medication at all times. All patients who are provided with on-demand treatment licensed for self-administration should be taught to self-administer. Self-administration training should include a home therapy partner who can provide support, advice, and administration of therapy when the patient is compromised. unable, or uncomfortable with self-treatment	All patients should be trained in self-administration of HAE-specific therapies if they are suitable candidates. If patients cannot self-administer therapy, provisions should be made to ensure timely access to all appropriate therapies. Therapies for the treatment of HAE attacks that can be self-administered include the following: – pdC1-INH - can be administered either by health care professionals or by patients and caregivers who have been trained in its administration. – Icatibant - can be self-administered or given by a caregiver (particularly in children)	Self-administration enables prompt treatment as soon as the patient recognizes the attack. Treatment should be administered only when the patient can reliably identify that an attack has begun. Patients who self-administer treatment should seek medical care if the features of their attack are unusual, their response to self-treatment is inadequate, or they experience an attack involving the airway. Self-administration (by the Child or his/her caregiver) of C1-INH is recommended for children.	All patients should be considered for home therapy and self-administration training, as this facilitates early treatment. All patients who are provided with on-demand treatment licensed for self-administration should be taught to self-administer. Self-administration training should ideally include a home therapy partner, ie, a 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. Patients should self-administer treatment while awaiting transfer to the hospital. All C1-INH concentrates and icatibant are licensed for self-administration, although approved product indications vary around the world.

Abbreviations: AA, attenuated androgens; AF, antifibrinolytic agents; AMA, aminocaproid acid; C1-INH, C1 esterase inhibitor; EACA, ε-aminocaproic acid; ED, emergency department; FDA, United States Food and Drug Administration; FFP, fresh frozen plasma; IV, intravenous; NA, not available; NM, not mentioned; NR, not recommended; pdC1-INH, plasma-derived C1 esterase inhibitor concentrate; QOL, quality of life; rhC1-INH, recombinant human C1-INH; SC, subcutaneous; SDP, solvent/detergent-treated plasma; TXA, tranexamic acid.

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Table 3. Short-term Prophylaxis for C1-INH-HAE.

	SGBA Consensus Statement	WAO Guidelines	HAEA Recommendations	CHAEN Guidelines	WAO/EACCI Guidelines	ICHAEN Guidelines	PT DGS Recommendation	HAEA Recommendations	WAO/EACCI Guidelines
Year	**2011**	**2012**	**2013**	**2014**	**2018**	**2019**	**2019**	**2021**	**2022**
General Considerations					**General Considerations**				
Indication	In patients who undergo surgical or medical procedures that may involve trauma to the cervicofacial region with a risk of laryngeal edema, including dental operations, tonsillectomy, maxillofacial surgery, digestive endoscopy, bronchoscopy, and surgical interventions that require intubation. During surgery to prevent local edema from altering the surgeon's work area and affecting the outcome of the surgery.	Before surgeries, especially dental/intraoral surgery, where endotracheal intubation is required, where the upper airway or pharynx is manipulated, and before bronchoscopy or endoscopy. Should also be considered to cover periods of high risk for attacks due to either increased likelihood of attack or increased consequence of attack (eg, stressful periods, examinations, or similar). Where available, 2 doses of C1-INH concentrate, ecallantide, or icatibant should be immediately accessible.	Indicated before medical, surgical, or dental procedures, although few data are available on the risk of swelling after these procedures. Patients on prophylactic treatment regimens must also have access to effective on-demand treatment of acute attacks.	Indicated prior to known patient-specific triggers and for any medical, surgical, or dental procedures. HAE-specific acute treatment should be available during and after any procedure. If the decision is made not to administer SDP, all patients should have 2 acute treatment doses of appropriate therapy immediately available.	Before procedures that can induce an attack, namely surgical trauma, dental surgery and other interventions associated with mechanical impact to the upper aerodigestive tract (eg, endotracheal intubation, bronchoscopy, or esophagogastroduodenoscopy). Pregnancy: Recommended before any intervention such as chorionic villus sampling, amniocentesis, and induced surgical abortion. Recommended before labor 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. Recommended before cesarean delivery, avoiding intubation if possible.	Indicated prior to known patient-specific triggers and for any medical, surgical, or dental procedures, particularly near the upper airway. HAE-specific acute treatment should be available during and after any procedure. If the decision is made not to administer STP, all patients should have 2 doses of appropriate on-demand therapy immediately available. Even patients who receive STP should have 2 on-demand treatments available.	Indicated in all patients prior to dental, surgical, endoscopic, and other minimally invasive procedures involving the head and/or neck and before procedures that can induce an attack. Indicated in pregnant women prior to chorionic villus biopsy, amniocentesis, pregnancy termination, cesarean delivery, instrumental vaginal delivery, vaginal delivery with clinical worsening in the third trimester or history of trauma-induced vaginal edema, epidural anesthesia and/or general anesthesia. On-demand treatment should be provided whenever necessary.	Indicated before medical, surgical, or dental procedures, although there are few data on the risk of swelling after these procedures. May also be considered before stressful life events. Effective on-demand treatment should be available even for patients receiving short-term prophylaxis.	Indicated before medical, surgical, or dental procedures as well as exposure to other angioedema attack–inducing events (the identification of which should be based on expert clinical judgement and individualized risk assessment). On demand treatment should be available. Indicated prior to exposure to patient-specific angioedema-inducing situations (eg, emotional stressors).
Options for adults					**Options for adults**				
pdC1-INH	Successfully used as short-term prophylaxis. Treatment of choice in countries where available, especially if intubation is required or surgery is major. Dose: 500-1500 U 1-4 hours IV before the event A second dose should be on hand throughout the operation.	Recommended therapeutic option. Dose: still under investigation. Recommendations vary from 10-20 U/kg or 1000 U, 1-6 h before the procedure. Where available, 2 doses of C1-INH concentrate should be immediately accessible.	Therapeutic option Dose: 1000 U IV administered 1-12 h before the procedure	Recommended therapeutic option Berinert (licensed in Europe) - Dose: 1000 U within 6 h of the procedure Cinryze (licensed in Europe) – Dose: 1000 U within 24 h of the procedure	Recommended therapeutic option. Dose: still to be fully established. Mostly used 1000 U or 20 U/kg IV as close as possible to the start of the procedure.	Recommended therapeutic option Dose: 20 U/kg IV 1 h before the procedure Berinert (licensed in Europe) - Dose: 1000 U within 6 h of the procedure Cinryze (licensed in Europe) – Dose: 1000 U within 24 h of the procedure	First-line therapeutic option Dose: 20 U/kg IV until the maximum dose of 1500 U 1-6 h before the procedure	Therapeutic option Dose: 20 U/kg IV 1-12 h before the procedure	First-line therapeutic option, used as close as possible to the start of the procedure Dose: not fully established yet. Mostly 1000 U or 20 U/kg IV
rhC1-INH	NM	NM	NM	NM	Recommended therapeutic option. Dose: NM	NM	NM	Therapeutic option after pdC1-INH and AA, due to fewer data and less experience Dose: 50 U/kg IV	Option if IV pdC1-INH is NA. Dose: NM
AA	Successfully used as short-term prophylaxis. Not an option in emergency situations as it takes ≈5 days to produce an effect. Danazol: 400-600 mg/24 h for 5-7 d before the event and 2-3 d after the event Stanozolol: 4-6 mg/24h for 5 d before the event and 3 d after the event. May have to be continued for more than 5 d in case of postoperative complications, especially infection.	Option when the surgery-related risk is relatively low and when pdC1-INH is NA. Dose: 5 d before and 2-5 d after the event. Danazol - Dose: 2.5-10 mg/kg/d until a maximum of 600 mg Stanozolol – Dose: 4-6 mg/d	Therapeutic option Danazol: ≤200 mg/d Stanozolol: ≤2 mg/d Oxandralone (not FDA approved): ≤10 mg/d Methyl-testosterone (not FDA approved): ≤10 mg/d Should be started 7-10 d before the procedure. Should not be used in patients who express a preference for an alternative therapy. Failure of androgen therapy should not be a prerequisite for receiving prophylactic C1-INH concentrate.	Therapeutic option when surgery-related risk is considered low and other HAE-specific acute treatments are not immediately available. Danazol: 2.5-10 mg/kg/d until a maximum of 600 mg/day 5 d before and 2-3 d after the procedure or anticipated trigger	Alternative to pdC1-INH concentrate Dose: NM Administration 5 d before and 2-3 d after the procedure	Option when pdC1-INH is NA and particularly when HAE-specific acute therapies are NA. Danazol: 2.5 to 10 mg/kg/d, until the maximum of 600 mg/d, 5 d before the procedure or trigger, and until 2–3 d after the anticipated trigger.	Therapeutic option when pdC1-INH is NA, 5 d before and 3 d after the procedure Danazol: 2.5-10 mg/kg orally until the maximum dose of 600 mg/d	Therapeutic option Danazol - Dose: 400-600 mg/d 5-7 d before the procedure and continued for 2 to 5 d after the procedure	Are used for 5 d before and 2 to 3 d post event as scheduled preprocedural prophylaxis. Dose: NM

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Table 3. Short-term Prophylaxis for C1-INH-HAE (*continuation*).

	SGBA Consensus Statement	WAO Guidelines	HAEA Recommendations	CHAEN Guidelines	WAO/EACCI Guidelines	ICHAEN Guidelines	PT DGS Recommendation	HAEA Recommendations	WAO/EACCI Guidelines
Year	**2011**	**2012**	**2013**	**2014**	**2018**	**2019**	**2019**	**2021**	**2022**
Options for adults					**Options for adults**				
AF	EACA and TXA successfully used as short-term prophylaxis. However, seldom used in countries where other treatments are available. TXA: 1 g 4 times daily or 75 mg/kg/d divided into 2-3 doses from 5 d before until 2 d after surgery	Efficacy in suppressing breakthrough attacks seems to be low. TXA - Dose: not fully established; 25 mg/kg 2-3 times daily until maximum of 3-6 g/d recommended	Therapeutic option EACA (not FDA approved): 1-2 g 3 times daily TXA (not FDA approved): 1 g twice daily	Therapeutic option only if other therapies are NA. TXA - Dose: 25 mg/kg 2-3 times daily to a maximum of 3-6 g/d, 5 d before and 2-5 d after the procedure or anticipated trigger	TXA: NR	TXA: option only if other therapies are NA Dose: 25 mg/kg 2–3 times daily to a maximum of 3–6 g/d, 5 d before and 2–5 d after a procedure or anticipated trigger	Therapeutic option when pdC1-INH is NA, 5 d before and 3 d after the procedure TXA - Dose: 20-40 mg/kg/d orally EACA - Dose: 0.17-0.43 g/kg/d orally		NR
SDP/FFP	Successfully used as short-term prophylaxis. Option when pdC1-INH is NA (as in some countries). Dose: 2 U (400 mL) 1 h before the procedure	Can be used if pdC1-INH is NA	NM	NM	FFP: Second-line option, after C1-INH concentrate	FFP is an option when pdC1-INH is NA and particularly when HAE-specific acute therapies are NA. Optimal dose undetermined. Usually given as 2 U 1-2 h before the procedure.	FFP is an option when C1-INH is NA and in cases of emergency procedures Dose: 10mL/kg IV, until the maximum dose of 400 mL	FFP is an option when pdC1-INH is NA and there is insufficient time for a course of AA Dose: NM	Second-line therapeutic option, when IV pdC1-INH is NA Dose: NM
Options for children					**Options for children**				
pdC1-INH	Agent of choice, especially in patients with a history of severe attacks precipitated by similar procedures Dose: 25 U/kg 1 h before the event	First-line therapeutic option. Still, on-demand therapy should be available, as short-term prophylaxis is not 100% effective.	Therapeutic option in adolescents Dose: NM Administered 1-12 h before the procedure.	NM	First-line therapeutic option. Still, on-demand therapy should be available, as short-term prophylaxis is not 100% effective.	Therapeutic option Cinryze - Dose: 500 U for children 10-25 kg within 24 h of an anticipated procedure Berinert – Dose: 15-30 U/kg within 6 h	Recommended therapeutic option in patients aged ≥10 y Dose: 15-30 U/kg IV until the maximum dose of 1000 U 1-6 h before the procedure	Therapeutic option Dose: 20 U/kg IV 1-12 h before the procedure	First-line therapeutic option Dose: NM
rhC1-INH	NM	NM	NM	NM	NM	NM	NM	Therapeutic option after pdC1-INH and AA, due to fewer data and less experience Dose: 50 U/kg IV	NM
AA	Can be used if there is enough time, given that adverse effects are minimal when used for a short period Danazol - Dose: 10 mg/kg/d (maximum, 600 mg/day) for 5-7 d before to 2-3 d after the event	Second-line option in short courses when pdC1-INH is NA. Still, on-demand therapy should be available, as short-term prophylaxis is not 100% effective.	NM	NM	Second-line option in short courses when pdC1-INH is NA. Still, on-demand therapy should be available, as short-term prophylaxis is not 100% effective.	NM	NM	Therapeutic option Danazol - Dose: 400-600 mg/d 5-7 d before the procedure and continued for 2 to 5 d after the procedure	Second-line therapeutic option, when C1-INH concentrate is NA Dose: NM
AF	TXA can be used if AAs are contraindicated. Dose: 20-40 mg/kg/d divided into 3-4 doses for 2 d before and 2 d after the procedure. May have to be continued for more than 5 d in patients with postoperative complications, especially infection.	NM	NM	NM	NM	NM	Therapeutic option when pdC1-INH is NA, 5 d before and 3 d after the procedure TXA - Dose: 20-40 mg/kg/d orally EACA - Dose: 0.17-0.43 g/kg/d orally	NM	NR
SDP /FFP	Option if pdC1-INH is NA. Dose: 10 mL/kg 1 h before the procedure	NM	NM	NM	NM	Option when pdC1-INH is NA and when HAE-specific acute therapies are NA. Optimal dose undetermined. Usually given as 10 mL/kg 1-2 h before the procedure	NM	FFP is an option when pdC1-INH is NA and there is insufficient time for a course of AA Dose: NM	NM

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Table 3. Short-term Prophylaxis for C1-INH-HAE (*continuation*).

	SGBA Consensus Statement	WAO Guidelines	HAEA Recommendations	CHAEN Guidelines	WAO/EACCI Guidelines	ICHAEN Guidelines	PT DGS Recommendation	HAEA Recommendations	WAO/EACCI Guidelines
Year	**2011**	**2012**	**2013**	**2014**	**2018**	**2019**	**2019**	**2021**	**2022**
Options for pregnancy and breastfeeding					**Options for pregnancy and breastfeeding**				
pdC1-INH	Preferred option Dose: 20 U/kg	Recommended before chorionic villus sampling, amniocentesis, and induced surgical abortion. Recommended before labor and delivery when HAE is severe, if symptoms have been recurring frequently during the third trimester, if the patient's history includes genital edema caused by mechanical trauma, when intubation is required, and when forceps delivery or vacuum extraction is performed. Recommended before cesarean delivery avoiding intubation when possible.	NM	NM	Recommended before chorionic villus sampling, amniocentesis, and induced surgical abortion. Recommended before labor and delivery when HAE is severe, if symptoms have been recurring frequently during the third trimester, if the patient's history includes genital edema caused by mechanical trauma, when intubation is required, and when forceps delivery or vacuum extraction is performed. Recommended before a cesarean delivery, avoiding intubation when possible.	Therapy of choice Dose: NM	Recommended therapeutic option Dose: 20 U/kg IV until the maximum dose of 1500 U 1-6 h before the procedure	Preferred therapeutic option Recommended treatment during breastfeeding Dose: NM	First-line therapeutic option C1-INH should be available for on-demand use and administered immediately at the onset of an attack. Dose: NM
rhC1-INH	NM	NM	NM	NM	NM	NM	NM	Recommend treatment during breastfeeding	NM
AAs	Should be discontinued before pregnancy, NM during pregnancy/ breastfeeding.	NR for pregnant (except last trimester) or breastfeeding women.	NR	NR	Contraindicated	NR	NR in pregnancy and breastfeeding	Contraindicated during breastfeeding	NM
AFs	TXA should be discontinued a few days before conception. NM during pregnancy/ breastfeeding.	NR	NM	NM	TXA safe during breastfeeding	NM	Therapeutic option when pdC1-INH is NA, 5 d before and 3 d after the procedure TXA - Dose: 20-40 mg/ kg/d orally, except in the first trimester or during breastfeeding EACA - NR in pregnancy and breastfeeding	NR TXA - Contraindicated during breastfeeding	NR
SDP /FFP	NM	Second-line option when pdC1-INH is NA, starting with SDP and using FFP when SDP is NA Dose: NM	NM	NM	NM	NM	NM	NM	May be used when IV pdC1-INH is NA Dose: NM

Abbreviations: AA, attenuated androgen; AF, antifibrinolytic agent; AMA, aminocaproic acid; C1-INH, C1 esterase inhibitor; EACA, ε-aminocaproic acid; FFP, fresh frozen plasma; IV, intravenously; NA, not available; NM, not mentioned; NR, not recommended; pdC1-INH, plasma-derived C1 esterase inhibitor concentrate; QOL, quality of life; rhC1-INH, recombinant human C1-INH; SC, subcutaneously; SDP, solvent/detergent-treated plasma; TXA, tranexamic acid.

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data for this agent compared to other therapies at the time. AAs and AFs were mainly used in countries where pdC1-INH was not available. In the 2012 WAO Guidelines, IV pdC1-INH became a recommended therapeutic option for STP of C1-INH-HAE, and in the 2019 PT DGS Recommendation, it was formally referred to as a first-line option. pdC1-INH currently remains the treatment of choice in this setting, while danazol, used for 5 days before and 2-3 days after the procedure, is an option when pdC1-INH is not available. The recent 2022 WAO/EACCI Guidelines also consider rhC1-INH an option if pdC1-INH is not available. Icatibant and ecallantide are not recommended for use as STP owing to their short half-life and lack of evidence [13,38].

Regarding special populations, pdC1-INH has always been the preferred option for STP in the guidelines, either in pediatric or pregnant/breastfeeding populations.

Long-Term Prophylaxis

LTP is the section of the guidelines where most innovations have been made over the years. Also termed routine prophylaxis, LTP refers to ongoing, scheduled therapy to reduce the frequency and/or severity and/or duration of attacks and improve patients' QOL when they are unable to meet their treatment goals with on-demand therapy alone [29].

The criteria for LTP changed over the last 2 decades in parallel with the availability of new therapies and awareness of patients' needs. It moved from being conditional on patients' access to adequate acute treatment and on the severity of disease and frequency of attacks in the 2011 SGBA Consensus Statement to being considered for severely symptomatic patients, but also taking into account patients' QOL, availability of resources, and failure to achieve adequate control with appropriate on-demand therapy in the 2012 WAO Guidelines. It was later recommended in cases in which patients experience an increase in disease activity triggered by specific life events in the 2018 WAO/EACCI Guidelines.

The indication gradually shifted throughout the guidelines towards an individualized treatment approach that reflects the needs of the individual patient and takes his/her preferences into account. The 2012 WAO/EACCI Guidelines already foresaw that all patients with HAE should be routinely evaluated for LTP. However, this recommendation evolved to include assessment of disease burden and need for LTP at each patient visit in the 2022 WAO/EACCI Guidelines, which recommend periodic monitoring of disease activity, impact on QOL, and disease control in patients using validated tools, such as patient-reported outcome measures (PROMs). Factors that should be considered when assessing the needs of the individual patient include the frequency and severity of HAE attacks, as well as significant anxiety, impaired QOL, history of laryngeal attacks, excessive days lost from work or school due to HAE, and/or poor disease control with on-demand therapy [29,39].

Several prophylactic therapies with a high level of evidence have become available over the years. These either replace deficient C1-INH or inhibit the kallikrein-bradykinin cascade, gradually changing the LTP landscape of the disease.

AAs and AFs were historical options for LTP of angioedema. They were the only options available in the 1960s, but while the efficacy of AAs was well established, despite having been based on low-quality evidence, the same was not true for tranexamic acid (TXA), for which there were concerns about lack of efficacy compared to AAs. Regardless of the underlying evidence, the appraisal of these drugs in recent guidelines was influenced by the literature search strategy used. In fact, the literature search conducted by the authors in the 2012 WAO Guidelines started in 1985 and therefore excluded several clinical trials of AAs and TXA that had been published before that period. Although these trials were limited by their low quality and small patient numbers, and studies of AAs reported disparate results and variable treatment effects (with some studies supporting their efficacy [40,41] and others showing suboptimal outcomes [42,43]), AAs were reported to be efficacious in HAE [40,41,44,45]. Back then, the aim was to reduce the frequency and severity of angioedema attacks with a low risk of adverse effects, although as adverse effects were described in approximately 80% of patients in some studies of AAs [29,40,45,46], the use of the minimal effective dose was advised for these drugs. Regarding TXA, the evidence for its use in HAE was derived from studies that were small-scale, noncontrolled [47,48], and, hence, even more limited. Given this bias in the reference search, the authors of the 2012 WAO Guidelines found no evidence of efficacy for AAs or TXA in HAE. This selection bias was repeated in the 2018 WAO/EACCI Guidelines, where the authors again conducted a search starting from 1985 to look for new recommendations published since the prior 2012 version. In contrast, the Canadian guidelines performed a wider literature search. The 2014 CHAEN Guidelines were based on a search with no limits regarding the publication date other than those imposed by the database, which resulted in the inclusion of studies from 1946 onwards. Consequently, the authors found evidence for the benefits of AAs and AFs in HAE (both for TXA and aminocaproic acid), assigning a moderate level of evidence to these agents. In the following 2019 ICHAEN Guidelines, the authors used the same search strategy "to ensure that the most recent evidence was considered" and found a moderate level of evidence for the benefits of AAs and TXA in LTP of HAE-1/2, stating that they should not be used as first-line therapies for LTP in affected patients and instead be reserved for specific patient groups.

With the emergence of effective and better-tolerated targeted options for LTP, the use of AAs and AFs started declining and even began to be discontinued, as reflected in the guidelines. Since the 2018 WAO/EACCI Guidelines, AAs have been formally considered a second-line option for LTP to be used in specific circumstances, for example, when the recommended first-line options are not available or patients are unwilling or unable to use injectable treatment. Given the lack of evidence on efficacy, AFs were excluded from LTP options as from the 2012 WAO Guidelines, with the 2018 WAO/EACCI Guidelines considering them an option for empirical use when first-line options were not available or AAs were contraindicated. These recommendations were maintained in the most recent 2022 WAO/EACCI Guidelines, and, overall, the use of AAs and AFs declined substantially in the past decade simultaneously with the emergence and growing use of more effective, pathway-specific treatments.

New therapies subsequently appeared, supported by a higher level of evidence derived from randomized, controlled trials that was previously missing for AAs and AFs, thus prompting a shift away from these agents in the management of HAE.

Intravenous pdC1-INH was shown to reduce the frequency of acute attacks by 50% compared with placebo in a study from 2010 [49] and was subsequently approved for LTP of HAE and included in the guidelines. In the 2011 SGBA Consensus Statement, it was considered an option when AAs and AFs failed to control the disease or had to be discontinued or were contraindicated, later becoming the preferred option for LTP in the 2012 WAO Guidelines and remaining a first-line therapeutic option until present (2022 EAACI/WAO Guidelines), with dosage and/or treatment interval adjustments as needed to minimize disease burden. In the most recent EAACI/WAO guidelines, failure of AAs is not a requirement for starting new therapies.

SC pdC1-INH was later shown to reduce the frequency of attacks compared with placebo [50-52] and enabled the maintenance of more constant plasma C1-INH activity levels above ~40% of normal [52]. This approach was also approved by regulatory authorities and added to the 2018 EAACI/WAO Guidelines, becoming a preferred option together with its IV counterpart. SC administration of pdC1-INH is more suitable for regular therapy, as it overcomes the potential technical difficulties of constant venous access and the risks associated with the use of indwelling venous catheters, in addition to facilitating patients' acceptance of self-administration [51]. Of note, although the approved dose of SC pdC1-INH is 60 mg/kg twice a week, the Spanish Group for the Study of Bradykinin-mediated Angioedema (GEAB) of the Spanish Society of Allergology and Clinical Immunology (SEAIC) proposed starting treatment with a lower dose, based on personal experience with patients whose disease was controlled at a much lower dose (2000 IU twice a week) and the marked variability of individual patient responses in clinical trials, aiming to achieve a more cost-effective approach [53,54].

Antikallikrein treatments were subsequently shown to be efficacious, and the specific plasma kallikrein inhibitor lanadelumab was first included in the 2019 ICHAEN Guidelines, followed by the second-generation plasma kallikrein inhibitor berotralstat, which was included for the first time in the 2022 WAO/EAACI Guidelines. SC pdC1-INH and lanadelumab achieved higher rates of reduction in the number of angioedema attacks than IV pdC1-INH (84% [51] and 87% [55] vs 51% [49] in the pivotal clinical trials of each drug, respectively), although formal head-to-head comparisons that establish the higher efficacy of one drug over the others are lacking.

After the increase in the availability of more efficacious and safer drugs for LTP, the treatment goals became more ambitious, with the ultimate goals of treatment in the 2022 WAO/EAACI Guidelines being to achieve total disease control and normalize the patient's life. These guidelines further state that treatment goals can only be achieved through the regular use of medications that reduce the burden of the disease by preventing attacks, ie, through long-term prophylactic treatment.

In pediatric patients, although the optimal dose was still under assessment, IV pdC1-INH became an option for LTP in the 2012 WAO Guidelines, gradually being implemented as first-line therapy for this patient subgroup from the 2013 HAEA Recommendations onwards. In addition to IV pdC1-INH, both SC pdC1-INH and lanadelumab were also included as first-line options for LTP in children aged ≥12 years in the 2019 ICHAEN Guidelines.

PdC1-INH is also the recommended first-line option for LTP in the pregnant/breastfeeding patient population, with IV pdC1-INH first included in the 2018 WAO/EACCI Guidelines and SC C1-INH initially included in the 2019 PT DGS Recommendation, with advice for periodic adjustments according to clinical response. Lanadelumab is not recommended in this patient population owing to the lack of data.

The concept of first- and second-line therapy was not always contemplated in the guidelines. In fact, it began to be used in the WAO/EACCI Guidelines for LTP of HAE only as of 2018, being widely adopted from then on.

In contrast to older agents used for LTP of HAE, such as AAs, which are limited by dose-related adverse effects, new agents are not associated with notable safety issues, with the most common adverse events being transient injection site reactions with SC pdC1-INH and injection site reactions or dizziness with lanadelumab [36,51,55]. Thromboembolic events are rare with pdC1-INH and typically develop in patients with pre-existing risk factors or indwelling ports [29]. Therefore, the monitoring requirements for adverse events of LTP agents have not changed significantly throughout the years or in guidelines.

The journey towards disease control in HAE has also come a long way, from the initial treatment goals of reducing the frequency, severity, and length of acute angioedema attacks in the 2011 SGBA Consensus Statement, to a new era where the treatment goals in the 2022 WAO/EACCI Guidelines are no attacks and a normal life. It has been increasingly acknowledged that the management of HAE should focus on individualized patient care and normalization of patients' lives as much as possible, enabling them to fully engage in work, school, family, and leisure activities and that the improvement of quality of life should be a key goal in this context. Such an approach became possible in this century owing to a change in the paradigm of introduction of LTP, to new evidence on disease burden and health care professionals' approach, to new tools to assess treatment effectiveness, and to the availability of new, modern, and disease-specific therapeutic modalities, including protein replacement agents (pdC1-INH, rhC1-INH), kallikrein inhibitors (ecallantide, lanadelumab, berotralstat), and bradykinin antagonists (icatibant) [56,57]. Nevertheless, the 2022 WAO/EACCI Guidelines stress that no treatment is absolutely effective, and even patients receiving LTP should have an adequate supply of on-demand medications available to treat breakthrough attacks at home.

Patients with HAE experience substantial repercussions of the disease on their daily lives. Awareness of the impact of the disease on patients' lives improved in the 2000s, with the recognition of the need to consider the humanistic and economic burden of HAE from a patient perspective [58],

Table 4. Long-term Prophylaxis for C1-INH-HAE.

	SGBA Consensus Statement	WAO Guidelines	HAEA Recommendations	CHAEN Guidelines	WAO/EACCI Guidelines	ICHAEN Guidelines	PT DGS Recommendation	HAEA Recommendations	WAO/EACCI Guidelines
Year	**2011**	**2012**	**2013**	**2014**	**2018**	**2019**	**2019**	**2021**	**2022**
General Considerations					**General Considerations**				
Indications	Depend on patient access to adequate acute treatment and include the following: – edema of the glottis – more than 1 edema episode per month – more than 1 severe abdominal attack – more than 1 severe cervicofacial attack – altered quality of life	Taking into consideration disease severity, frequency of attacks, patient's QOL, availability of resources, and failure to achieve adequate control by appropriate on-demand therapy.	Should reflect the needs of the individual patient, considering attack frequency, and severity, comorbid conditions, access to emergency treatment, patient experience and preference. Should be periodically reviewed.	Recurrent episodes of angioedema when on-demand treatment does not meet patients' treatment requirements. The decision should be made by the patient and an HAE specialist. There is no recommended order or hierarchy for using each therapy. This should be based on efficacy, adverse effects and safety, and patients' preferences.	Should be individualized and considered in all severely symptomatic HAE-1/2 patients based on the activity of the disease, frequency of attacks, patient's QOL and preferences, availability of health-care resources, and failure to achieve adequate control by appropriate on-demand therapy. Recommended for patients who face events in life that are associated with increased disease activity. Should be evaluated in every visit, at least once a year.	Recurrent episodes of angioedema when on-demand treatment does not meet patients' treatment requirements.	In the following cases: – angioedema of the upper airway or laryngeal angioedema – more than 1 episode of mucocutaneous angioedema per month – more than 1 episode of severe abdominal angioedema in the previous year – more than 1 episode of severe cervicofacial angioedema in the previous year – compromised quality of life in the previous year	Decision cannot be made based on rigid criteria but should instead reflect the needs of the individual patient and take into consideration patients' QOL and treatment preferences in the context of attack frequency and severity, comorbid conditions, and access to emergency treatment. Should be periodically reviewed and discussed with the patient.	Should be individualized and considered in all HAE-1/2 patients, taking into account disease activity, patient QOL, availability of health care resources, and failure to achieve adequate control by appropriate on-demand therapy. Patient preference should be considered.
Aims	To reduce the frequency, severity, and length of acute angioedema crises, specifically to reduce to 2 or fewer minor episodes a year	To prevent episodes of angioedema in patients with confirmed HAE-1/2.	To control disease activity and maintain patients' normal QOL using the lowest effective medication dose.	To reduce the frequency, duration, and/or severity of angioedema attacks and minimize the impact of HAE on patients' QOL, enabling them to live normal lives.	To reduce the burden of disease by preventing/attenuating attacks in patients with confirmed HAE-1/2.	To reduce the frequency, duration, and/or severity of attacks and minimize the impact on patients' QOL, enabling them to live normal lives.	To reduce the frequency of episodes, and duration and severity of attacks.	To decrease the overall number, severity, and burden of AE attacks.	To achieve total control of the disease and normalize patients' lives by preventing attacks.
Options for adults					**Options for adults**				
AF	Much less effective than AA. TXA: 1000-3000 mg/d (divided into 3-4 doses) EACA (less effective than TXA): 1 g/6-8 h (up to 12 g/d divided into 4 doses)	NR (lack of efficacy data) Empirical use: TXA: 30-50 mg/kg/d in 2-3 divided doses, to a maximum of 6 g	Option EACA (not FDA approved): 1-2 g × 3 times daily TXA (not FDA-approved): 1 g × 2 times daily	Option TXA: 30-50 mg/kg/d divided in 2 or 3 doses to a maximum of 6 g per day	NR (lack of efficacy data) Empirical use: when C1-INH concentrate is NA and AA are contraindicated TXA: 30-50 mg/kg to 6 g/d	NR as first-line therapy, but may be considered in patients who already obtained a benefit from their use or with difficulty obtaining first-line options TXA: 30-50 mg/kg/d divided in 2 or 3 doses to a maximum of 6 g/d	EACA at the dose of 1.5-12 g/d, orally, every 6-12 h or TXA at the dose of 1-3 g/d, orally, every 6-12 h	Second-line therapeutic option (when first-line options are NA or the patient only accepts oral therapy). Less effective than other therapies. TXA: 1 g twice daily (0.25 g Twice daily to 1.5 g × 3 times daily) EACA: 2 g × 3 times daily (1 g twice/d to 4 g × 3 times daily)	NR (lack of efficacy data) Empirical use: when first-line therapies are NA and AA are contraindicated TXA: 30-50 mg/kg/d divided into 2 or 3 doses to a maximum of 6 g/d
AA	Much more effective than AFs and the therapy of choice. Danazol and stanozolol very effective and with fewer adverse effects than other AAs. Danazol: induction dose of 400-600 mg/d followed by maintenance dose of 100 mg/48-72 h or starting with low doses of danazol and increasing as needed. Stanozolol: induction dose of 6-12 mg/d followed by dose reductions every 2 mo until minimal effective maintenance dose (which can be 2 mg/72 h) Oxandrolone (where available): 0.1 mg/kg (2.5-20 mg/d), taken in 2-4 doses	Recommended The decision to use AA or C1-INH concentrate depends on contraindications, adverse events, risk factors for adverse effects, tolerance, response to intervention, and dose required to control attacks. Danazol: 100 mg every other day-200 mg × 3 times daily Doses >200 mg NR in the long term Suggested dose: 100-200 mg/d, with monthly adjustments	Danazol: ≤200 mg/d Stanozolol: ≤2 mg/d Oxandrolone (not FDA approved): ≤10 mg/d Methyl-testosterone (not FDA approved): ≤10 mg/d Should not be used in patients who express a preference for an alternative therapy.	Danazol: ≤200 mg/d, lowest effective dose	Second-line therapy Danazol: between 100 mg every other day to 200 mg × 3 times daily The minimal effective dose should be used. Doses >200 mg/d NR in the long term. Dose should be adjusted according to clinical response	NR as first-line therapy, but may be considered in patients who already obtained benefit from their use or with difficulty obtaining first-line options Danazol: ≤200 mg/d	Danazol: 200-600 mg/d, orally	Second-line therapy (when first-line therapies are NA or the patient only accepts oral therapy). Should be given at the lowest effective dose. Danazol: 200 mg/d (100 mg every 3 d to 600 mg/d) Stanozolol: 2 mg/d (1 mg every 3 d to 6 mg/d)	Second-line therapy Danazol: between 100 mg every other day to 200 mg of 3 times daily The minimal effective dose should be used. Doses >200 mg/d NR in the long term. Dose should be adjusted according to clinical response and not C4 or C1-INH levels
IV pdC1-INH	Option when severe attacks occur despite treatment with high AA doses or when AAs must be discontinued or are contraindicated Dose: 500-1000 U 1-3 times weekly (dose and interval must be adjusted on an individual basis)	Depends on contraindications, adverse events, risk factors for adverse effects, tolerance, response to intervention, and dose required to control attacks. Dose: twice a week, with adjustment of dose and/or frequency for optimum control.	Dose: 1000 U twice weekly Failure of AA therapy should not be a prerequisite to receiving prophylactic C1-INH concentrate.	Dose: 1000 U once or twice weekly (usually every 3-4 d) Not necessary for other therapies to fail before using pdC1-INH.	First-line therapy IV pdC1-INH: twice a week, with adjustment of dose and/or frequency for optimum efficacy SC pdC1-INH: 40 U/kg or 60 U/kg twice weekly	Effective therapeutic option Dose: 60 U/kg body weight twice weekly (every 3-4 d)	NM	First-line therapeutic option. Should be used without need for AA to have failed Dose: 1000 IU twice weekly Possibility of escalation of dose up to 2500 IU and frequency up to 3 times weekly for patients who continue to have attacks despite receiving the standard dose	First-line therapeutic option Dose: IV twice a week based on pdC1-INH half-life

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Table 4. Long-term Prophylaxis for C1-INH-HAE (*continuation*).

	SGBA Consensus Statement	WAO Guidelines	HAEA Recommendations	CHAEN Guidelines	WAO/EACCI Guidelines	ICHAEN Guidelines	PT DGS Recommendation	HAEA Recommendations	WAO/EACCI Guidelines
Year	**2011**	**2012**	**2013**	**2014**	**2018**	**2019**	**2019**	**2021**	**2022**
Options for adults					**Options for adults**				
SC C1-INH	NA	NA	NA	NA	NA	First-line therapy (dose NM)	In cases of contraindication to AA or AF. Dose of 60 IU/kg twice weekly, adjusting the periodicity according to clinical response.	First-line therapy Dose: 60 IU/kg twice weekly	First- line therapeutic option Dose: 60 U/kg twice a week The SC route may provide more convenient administration and improved steady-state plasma concentrations, allowing for better symptom control compared with IV C1-INH
Lanadelumab	NA	NA	NA	NA	NA	First-line therapy Dose: 300 mg every 2 wk Dosing every 4 wk may be considered if disease is well controlled (eg, attack-free) for >6 mo	In cases of contraindication to AA or AF. Initial dose of 300 mg SC every 2 wk, with possibility of reduction to every 4 wk in patients clinically stable and without acute attacks	First-line therapy Dose: 300 mg every 2 wk A dosing interval of 300 mg every 4 wk may be considered for patients whose disease is well controlled (eg, attack free) for more than 6 mo	First-line therapy Dose: 300 mg every 2 wk A dosing interval of 300 mg every 4 wk may be considered if the disease is well controlled (eg, attack free)
Berotralstat	NA	NA	NA	NA	NA	NA	NA	NA	First-line therapy Dose: 150 mg orally with food, with dose reductions to 110 mg in some regions if there is hepatic impairment, use of P- glycoprotein or BCRP inhibitors (drug interactions), or patients experiencing gastrointestinal symptoms with the 150-mg dose
rhC1-INH	NM	NM	NM	NM	NM	NM	NM	NM	Option for off-label use in the absence of all 3 first-line therapeutic options. Dose: NM
Options for children					**Options for children**				
AF	Treatment of choice (before Tanner stage V) TXA: 20-40 mg/kg/d (divided into 3-4 doses) EACA: 0.17-0.43 g/kg/d	Option when pdC1-INH is NA. TXA: 20-40 mg/kg EACA less well tolerated than TXA (dose NM). Data supporting AF use is NA	NM	May be considered (doses NM)	Second-line therapy TXA: 20-40 mg/kg EACA less well tolerated than TXA (dose NM).	NM	EACA at the dose of 0.17-0.43 g/kg/d, orally, every 6-12 h or TXA at the dose of 20-40 mg/kg/d, orally, every 6-12 h (children >1 y)	TXA: 20 mg/kg twice/d bid (10 mg/kg twice/d to 25 mg/kg × 3 times daily) EACA: 0.05 g/kg twice/d (0.025 g/kg twice daily to 0.1 g/kg twice daily)	Second-line therapy when C1-INH concentrate is NA. TXA: 20-50 mg/kg EACA less well tolerated than TXA (dose NM).
AA	Option when AFs are not effective or contraindicated. Danazol: 2.5 mg/kg/ d, starting at 50 mg/d and increasing to a maximum of 200 mg/d, if necessary, preferably given at intermittent dosages (repeating doses every other day or at 3-d intervals) Oxandrolone: 0.1 mg/kg (2.5 to 20 mg/d) divided into 2-4 doses	NR in prepubertal children. Empirical use: Danazol: 2.5 mg/kg/d; (50 mg/d initial dose with subsequent reduction of the dosage interval to every other day or every third day, with a maximum single dose of 200 mg over 10 years of age). Adjust to the lowest effective dose.	Contraindicated in children aged ≤16 y	Contraindicated before puberty	NR in children and adolescents prior to Tanner stage V Empirical use: 2.5 mg/kg/d with subsequent adjustment until symptom suppression or the maximum tolerated or maximum recommended dose is reached, with a maximum single dose of 200 mg/d.	Contraindicated in pediatric patients before Tanner stage V May be considered once patients have completed puberty, starting at the lowest effective dose.	NR	Contraindicated in patients <16 y Danazol: 50 mg/d (50 mg/wk to 200 mg/d) Stanozolol: 0.5 mg/d (0.5 mg/wk to 2 mg/d)	NR in children and adolescents prior to Tanner stage V Danazol: 2.5 mg/kg/d with subsequent adjustment until symptom suppression or the maximum tolerated or maximum recommended dose is reached. Maximum single dose of 200 mg/d. Continued use and dosing should be reviewed on a regular basis.
IV pdC1-INH	Option when treatment with AFs and AAs fails. Regular infusions every 72 h.	Therapeutic option of choice The optimal dose requires further study. Possible dosage for postpubertal adolescents: 1000 U every 3 or 4 d	Dose: 1000 U twice weekly (adolescents)	NM	First-line therapy IV pdC1-INH: twice a week, with adjustment of dosing interval and dose according to the individual response.	First-line therapy Dose: 1000 U (500 U for children aged 6 to 11 y) every 3 to 4 d	NM	Preferred first-line therapeutic option Dose: 500 IU every 3-4 d in pediatric patients (6-11 y); 1000 U every 3-4 d in adolescents Doses up to 2500 U IV every 3-4 d be considered based on individual patient response	First-line therapy in children aged <12 y. Dose: NM Dosing interval and dose should be adjusted according to individual response

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Table 4. Long-term Prophylaxis for C1-INH-HAE (*continuation*).

	SGBA Consensus Statement	WAO Guidelines	HAEA Recommendations	CHAEN Guidelines	WAO/EACCI Guidelines	ICHAEN Guidelines	PT DGS Recommendation	HAEA Recommendations	WAO/EACCI Guidelines
Year	**2011**	**2012**	**2013**	**2014**	**2018**	**2019**	**2019**	**2021**	**2022**
Options for children					**Options for children**				
SC C1-INH	NA	NA	NA	NA	NA	First-line therapy in children aged ≥12 y	Dose of 60 IU/kg twice weekly, adjusting the periodicity according to clinical response (adolescents aged ≥10 y)	First-line therapy in children aged >12 y	First-line therapy in children aged >12 y
Lanadelumab	NA	NA	NA	NA	NA	First line in children aged ≥12 y	Initial dose of 300 mg SC every 2 wk, with possibility of reduction to every 4 wk in patients who are clinically stable and without acute attacks (adolescents aged ≥12 y).	First line in children aged >12 y	First line in children aged >12 y
Options for pregnancy and breastfeeding					**Options for pregnancy and breastfeeding**				
AF	No controlled data on use during pregnancy, and no consensus on the need to monitor other prothrombotic factors. Should be administered with caution in cases of personal or family history of prothrombotic events, and a prior hypercoagulability study should be performed.	Option when pdC1-INH is NA, only in cases of clear need (efficacy evidence is lacking). Avoid during breastfeeding.	NM	NM	Second-line therapeutic option (doses NM) TXA safe during breastfeeding	NM	EACA NR TXA at the dose 1-3 g/d, orally, every 6-12 h in women after the first pregnancy trimester; NR in breastfeeding	NM	Option when C1-INH concentrate is NA (lack of efficacy data) Dose: NM
AA	Contraindicated	NR	NR	Contraindicated	Absolutely contraindicated	Contraindicated	NR	Contraindicated	Absolutely contraindicated
IV pdC1-INH	Extensive experience with its use, despite few controlled data. Safe and effective in pregnancy	Therapeutic option of choice.	NM	NM	First-line therapeutic option	First-line therapeutic option	NM	First-line therapeutic option	First-line therapeutic option
SC C1-INH	NA	NA	NA	NA	NA	NM	Dose of 60 IU/kg twice weekly, adjusting the periodicity according to clinical response.	First-line therapeutic option	First-line therapeutic option
Lanadelumab	NA	NA	NA	NA	NA	NM	NR	NR (lack of safety data)	NR
Self-administration					**Self-administration**				
IV or SC drugs	Patients and families should have access to a simple publication providing basic relevant information on selfcare and monitoring.	Patients should be considered for home therapy and self-administration once the diagnosis is confirmed. Self-administration training should include the training of a "home therapy partner" who can provide support, advice, and administration of therapy when necessary.	Patients should understand the medication they will use, where and how it is stored, how to use it, who will administer it (self vs health care provider), where it will be administered (home vs health care facility), and how to monitor the need to seek additional assistance or require additional dosing.	All patients should be trained on self-administration of HAE-specific therapies if they are suitable candidates. If patients cannot self-administer therapy, provisions should be made to ensure timely access to all appropriate therapies.	Every patient should be considered for home therapy and self-administration. Patients should have individualized treatment plans addressing preventive measures and home care and self-administration. 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). Also suitable for children.	All HAE patients should be trained on self-administration of HAE-specific therapies if they are suitable candidates. If patients cannot self-administer therapy, provisions should be made to ensure timely access to all appropriate therapies.	Patients should be adequately trained for self-administration of specific therapies at home. C1-INH and icatibant can be used for self-administration, with SC icatibant being the only drug available nationally for self-administration in cases of acute crises.	Patients and caregivers should be encouraged and taught to self-administer HAE medication whenever possible	All patients should be considered for home therapy and self-administration

Abbreviations: AA, attenuated androgens; AF, antifibrinolytic agents; C1-INH, C1 esterase inhibitor; EACA, ε-aminocaproic acid; FFP, fresh frozen plasma; iv, intravenous; NA, not available; NM, not mentioned; NR, not recommended; pdC1-INH, plasma-derived C1 esterase inhibitor concentrate; QOL, quality of life; rhC1-INH, recombinant human C1-INH; SC, subcutaneously; SDP, solvent/detergent-treated plasma; TXA, tranexamic acid.

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development of a specific health-related quality of life questionnaire for adult patients with HAE-C1-INH [59], and acknowledgment that patients experience substantial physical and emotional impairment both during and between attacks [58].

The assessment of treatment effectiveness was also incorporated into management of these patients [60]. Several QOL and PROM tools have been adopted for use in clinical practice. These include the following: generic scores, such as the 36-Item Short Form Health Survey (SF-36 [61] and the EuroQol 5-Dimensions Survey (EQ-5D) [62]; angioedema-specific scores, such as the Angioedema Activity Score (AAS) [63] for the assessment of disease activity, the Angioedema Control Test (AECT) [64] for the assessment of disease control, and the Angioedema Quality of Life (AE-QoL) Questionnaire [65]; and HAE-specific scores, such as the HAE Activity Score (HAE-AS) [66], the Hereditary Angioedema Quality of Life (HAE-QoL) Questionnaire [59], and the United States HAE Association Quality of Life (HAEA-QoL) Survey [67] for the assessment of disease burden/quality of life. These tools were initially mentioned in the 2021 HAEA Recommendations and again in the 2022 WAO/EACCI Guidelines and are currently considered important tools for monitoring the success of LTP. In addition, according to a recent Delphi initiative, patients with HAE should provide input on how they or their treating physician can assess whether HAE is well controlled or their life is normalized [68].

Despite regular updates over the years, guidelines for the management of C1-INH-HAE have unmet needs that should be acknowledged, starting with the cost of new treatments, which is not addressed in the guidelines. The treatment of choice is selected based exclusively on clinical criteria. However, in the real world, access to treatment is governed by clinical as well as economic considerations, with the result that the cost of therapies cannot be separated from their clinical value when making treatment decisions. Although new, disease-specific drugs have been better studied and are more efficacious and safer than older drugs, their cost is much higher and not affordable for many middle- and low-income countries. Even in developed, higher-income countries, new therapies are sometimes only approved for reimbursement for narrow patient populations, as these countries often struggle with affordability issues and tight budget constraints as the main barriers to access to health care. Such is the case of lanadelumab, which has been approved for reimbursement for the treatment of HAE in the UK only for patients with ≥2 clinically significant attacks per week over 8 weeks [69] and in Denmark for patients with ≥4 attacks per month [70]. In Portugal, lanadelumab is funded by the National Health System for the routine prevention of recurrent HAE attacks in patients aged ≥12 years with contraindications, intolerance, or lack of control with AAs and/or AFs [71]. In Spain, there are no national criteria for reimbursement of new drugs. Local criteria are in place in some regions, such as Catalonia and Galicia, where hospital approval is required for the use of new drugs, as their cost is paid through the Catalan and Galician Autonomous Health Services.

Therefore, while not all patients will have access to new drugs approved for LTP, AAs and TXA are cheap and widely available therapies that can be used to treat HAE in settings where more specific therapeutics are unavailable, due to either economic constraints or lack of resources. Although the efficacy of these older agents is limited (AAs) or controversial (TXA), and other treatment options may be preferred, they are currently used to treat HAE in some countries in an effort to optimize available resources. Therefore, the present Iberian working group believes that, besides clinical need, the cost of treatments should also be addressed in the guidelines, with recommendations to select the most cost-effective option that is available in each country in an individualized way for each patient.

In 2004, Agostoni et al [37] suggested, based on clinical experience, that an LTP approach should be considered when patients continue experiencing more than 12 moderate-to-severe attacks per year or more than 24 days per year affected by HAE despite optimal on-demand treatment. However, guidelines over the years have generally been omissive regarding a specific cut-off to start LTP. Most guidelines only state that the decision to start LTP should be individualized, taking into account aspects related to the patient, disease, and availability of resources. The 2021 HAEA Recommendations sustain that the decision on when to use LTP cannot be based on rigid criteria but should reflect the needs of the individual patient, advising to periodically review and discuss with the patient the need to start or continue LTP. However, leaving this cut-off undefined raises a problem for countries with more limited resources, where, even if new drugs are available, not all patients can receive them.

Furthermore, the number of attacks that can be considered a treatment goal in LTP is not clearly defined in most guidelines. Except for the 2011 SGBA Consensus Statement, which specifies the goal of LTP as the reduction in the number of attacks to ≤2 minor episodes a year, and the latest 2022 WAO/EACCI Guidelines, which state that LTP goals in HAE are to normalize patients' lives and achieve full control of the disease, namely, zero attacks. None of the guidelines in between (ie, from 2011 to present) specify the number of episodes that constitute disease control with LTP. Reducing the frequency of attacks to ≤2 minor episodes per year was a treatment goal with AAs back in 1996, with patients considered to be "nearly free of symptoms" this way [72,73].

Nevertheless, with the evolution of the treatment landscape and the incorporation of modern and expensive drugs in the therapeutic armamentarium, for example, lanadelumab and SC pdC1INH, the treatment goals also evolved to become more stringent. Although this working group subscribes to the importance of objectively defining the number of attacks that suggest disease control with LTP, it also acknowledges the difficulty of this endeavor due to the lack of studies specifically addressing the subject and considers that other indicators should be used in clinical practice for this purpose. PROMs are emerging as an important component of angioedema management, enabling patients to provide their perceptions on self-experienced QOL and well-being. This concept has only recently been incorporated in HAE guidelines, specifically in the newest 2022 WAO/EACCI ones, to be used together with disease activity in the assessment of the impact of angioedema on patients' lives and QOL. In the working group's view, the definition of PROM cut-offs can be a valuable tool to indicate when to start LTP and to determine the treatment goal.

The absence of clear criteria for initiation of LTP and of LTP goals in the C1INH-HAE guidelines was recently addressed by a Spanish Treat to Target Delphi consensus [74].

Conclusion

Guidelines for the management of C1-INH-HAE have come a long way. This study sought to highlight the main changes in the guidelines throughout the years, given the marked evolution of concepts and management strategy for the disease, which in turn highlights the need for regularly updating national and international guidelines. We hope that this document will be useful for health care professionals interested in HAE and, taken together with the most recent Portuguese and Spanish guidelines, serve as a tool to guide the management of patients with C1-INH-HAE in both countries.

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Conflicts of Interest

Manuel Branco Ferreira has participated in advisory boards for Takeda, CSL Behring, Bial, and GSK and has received speaker fees from Takeda, CSL Behring, GSK, AstraZeneca, Bial, Jaba Recordati, and Medinfar. He has received funding to attend conferences from Takeda and Bial. He is the President of the Scientific Committee of the Portuguese Hereditary Angioedema Patients' Association.

Maria Luisa Baeza has received speaker and consultancy fees from CSL Behring, Novartis, and Takeda and received funding to attend conferences and educational events from CSL Behring, Novartis, Leti, and Takeda. She has participated as an investigator in clinical trials and registries from CSL Behring, BioCryst, Novartis, Takeda, and Pharvaris and is a researcher in the Instituto de Investigación Sanitaria Gregorio Marañón (IISGM) research program.

Amélia Spínola Santos received speaker and consultancy fees from CSL Behring and Takeda and funding to attend conferences and educational events from CSL Behring and Takeda. She also participated as an investigator in a clinical trial from Takeda.

Alicia Prieto-García has received speaker and consultancy fees from CSL Behring, Novartis, and Takeda and funding to attend conferences and educational events from CSL Behring, Novartis, Takeda, and Pharming. She has also participated as an investigator in clinical trials and registries for CSL Behring, BioCryst, and Pharvaris and is a researcher in the Instituto de Investigación Sanitaria Gregorio Marañón (IISGM) research program.

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Teresa Caballero has participated in advisory boards for Astria, BioCryst, CSL Behring, Novartis, Pharming, and Takeda and is a member of speakers' bureaus for CSL Behring, Novartis, and Takeda. She has received grants and honoraria from BioCryst, CSL Behring, Novartis, Pharming, and Takeda and funding to attend conferences and educational events from BioCryst, CSL Behring, Novartis, Pharming, and Takeda. She has acted as an investigator (clinical trials, registries, studies) for BioCryst, Biomarin, CSL Behring, IONIS, KalVista, Novartis, Pharming, and Takeda and as a researcher in the Instituto de Investigación Hospital Universitario La Paz (IdiPAZ) program for promoting research activities.

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