REVIEW

Brazilian guidelines for the diagnosis and treatment of hereditary angioedema

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Hereditary angioedema is an autosomal dominant disease characterized by edema attacks with multiple organ involvement. It is caused by a quantitative or functional deficiency of the C1 inhibitor, which is a member of the serine protease inhibitor family. Hereditary angioedema is unknown to many health professionals and is therefore an underdiagnosed disease. The causes of death from hereditary angioedema include laryngeal edema with asphyxia. The estimated mortality rate in patients in whom the disease goes undetected and who are therefore incorrectly treated is 25-40%. In addition to edema of the glottis, hereditary angioedema often results in edema of the gastrointestinal tract, which can be incapacitating. Patients with hereditary angioedema may undergo unnecessary surgical interventions because the digestive tract can be the primary or only organ system involved, thus mimicking acute surgical abdomen. It is estimated that patients with hereditary angioedema experience some degree of disability 20-100 days per year. The Experts in Clinical Immunology and Allergy of the ''Associação Brasileira de Alergia e Imunopatologia - ASBAI'' developed these guidelines for the diagnosis, therapy, and management of hereditary angioedema.

KEYWORDS: Hereditary angioedema; C1 inhibitor; Asphyxia; Acute surgical abdomen; Guidelines; Consensus.

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DEFINITION

What is hereditary angioedema?

Hereditary angioedema (HAE) is an autosomal dominant disease that is characterized by edema attacks with multiple organ involvement. It is caused by quantitative or functional deficiency of the C1 inhibitor (C1-INH), which is a member of the serine protease inhibitor family.

INTRODUCTION

Why should we study HAE?

HAE was first described as a clinical entity by Quincke in 1882, and its hereditary nature was established by Osler in 1888.[1,2] The biochemical change associated with HAE, C1-INH deficiency, was not identified until 75 years later, in 1963.[3]

Sir William Osler (1849-1919), a Canadian physician who lived in the United States and England, was renowned for his many contributions to medicine, including his participation in the description of HAE and for stating that ''Medicine is both a Science and an Art''. To develop evidence-based guidelines is to practice medicine as a science. To follow such guidelines and consensuses while treating patients and their various phenotypes in a personalized manner is to practice medicine as an art.

HAE is a disease that is unknown to many health professionals and is therefore underdiagnosed. The prevalence of HAE is approximately 1:50,000 (with estimates ranging from 1:10,000 to 1:150,000); the disease affects various ethnic groups and accounts for 2% of all cases of angioedema.[4-7]

As is true for other autosomal dominant diseases, the children of a patient with HAE have a 50% chance of carrying the anomalous gene. Although a family history is characteristic of the disease and should alert physicians to a possible diagnosis of HAE, in 20-25% of cases, a family history of disease is absent, and new, spontaneous mutations can be observed.[8] Approximately 200 HAE-associated mutations have been identified to date. Although genetic defects are found in patients of both genders with equal

frequency, the phenotype is more common in female patients, for whom the disease is more severe.[9]

The time elapsed between the onset of symptoms and diagnosis, as well as the time between diagnosis and the initiation of treatment, play important roles in HAE-related morbidity and mortality.[10-13] Therefore, physicians should be aware of the clinical profile and laboratory tests that confirm a diagnosis of HAE and inform decisions regarding its treatment.

The cause of death from HAE is laryngeal edema with asphyxia, and the estimated mortality rate in patients in whom the disease goes undetected and who are therefore incorrectly treated is 25-40%.[7,10-15] Patients with HAE are commonly hospitalized and admitted to intensive care units, and the disease accounts for 15,000-30,000 emergency room visits per year in the United States.[16]

The two most severe clinical manifestations of HAE are edema of the larynx and edema of the bowel wall. Delayed diagnosis increases morbidity, thereby affecting the quality of life of patients and their families.[17,18] A study involving two families showed that nine out of ten family members who were hospitalized for symptoms of HAE were discharged with diagnoses other than HAE.[19]

In addition to life-threatening edema of the glottis, HAE often results in edema of the gastrointestinal tract, which can be incapacitating. Patients with HAE may undergo unnecessary surgical interventions because the digestive tract can be the primary or only organ system involved, thus mimicking acute surgical abdomen.[20,21] It is estimated that patients with HAE experience some degree of disability 20-100 days per year.[17]

PATHOPHYSIOLOGY

What is the cause of HAE?

Patients with HAE present with a quantitative or qualitative deficiency of C1-INH, which is a serine protease inhibitor. This enzyme inhibits the C1r and C1s esterases, which bind to and activate C1q. Without such inhibition, the complement system becomes excessively activated.[22,23]

C1-INH also inhibits the lectin pathway of complement system activation and participates in the regulation of the contact, coagulation, and fibrinolysis systems. Deficiency of C1-INH results in increased bradykinin production.

Episodes of angioedema were initially attributed to factors that were formed during complement system activation, including a C2 fragment (C2 kinin) that is associated with vasodilation and increased vascular permeability.[24] Recent evidence has shown that bradykinin is one of the principal mediators of HAE.[25-27]

It has been shown that bradykinin levels are higher in blood drawn from angioedematous sites than in blood drawn from the systemic circulation.[25] Knockout mice with concomitant deficiencies of C1-INH and bradykinin receptor B2 (BDKRB2) display decreased vascular permeability, which demonstrates that the bradykinin/BDKRB2 pathway plays an important role in the development of angioedema.[26]

CLASSIFICATION

What are the types of HAE?

Currently, HAE is divided into three groups (Table 1). Most patients (80-85%) present with type I HAE, with reduced C1-INH synthesis (a quantitative defect).[28] Low serum levels of C1-INH trigger the attacks.

In patients who present with type II HAE (15-20%), adequate quantities of C1-INH are produced, although the functional capacity of the protein is partially diminished.[29] Therefore, the enzyme has a qualitative (i.e., functional) defect.

Type III HAE is rarer than types I and II and principally affects females. It is characterized by normal C1-INH levels and activity.[30] This group includes diseases that vary in their etiopathogenesis; coagulation disorders and links to the endocrine system have been identified in this group.[9,31,32]

Acquired angioedema (AAE), which has a manifestation similar to that of HAE, is noteworthy among the differential diagnoses of HAE.[33] AAE is characteristically associated with lymphoproliferative and autoimmune diseases in which there is consumption of C1-INH, which is caused by the activation of C1-INH or by the production of anti-C1-INH autoantibodies.[34]

DIAGNOSIS

What is the typical clinical manifestation of HAE?

The patient's clinical history is the principal component of an HAE diagnosis. Patients with HAE present with attacks of nonpruritic edema of the skin and submucosa that affects various organs.[11-13] The most commonly affected sites are the face, extremities, genitalia, oropharynx, larynx, and digestive system. However, rarer clinical manifestations, including intense headaches caused by brain edema, urinary retention, and acute pancreatitis, can also occur.[12,35]

The incidence and severity of the clinical manifestations of HAE vary among individuals. It has been reported that 5% of patients with HAE are asymptomatic, and 25% develop sporadic symptoms.[6,11,12,36-38] A retrospective study analyzing 131,110 attacks in 221 patients with HAE reported that laryngeal edema occurred in less than 1% of the attacks, although over 50% of the patients had previously experienced that symptom at least once.[12]

Left untreated, HAE attacks typically last 48-72 h. Although many attacks occur spontaneously, a number of triggering factors have been identified, including minor trauma, stress, infection, menstruation, pregnancy, alcohol consumption, a change in temperature, exercise, the use of angiotensin-converting enzyme (ACE) inhibitors, and the use of estrogen (including contraceptives and hormone replacement therapy).[6,11,12,36-39]

Serpiginous erythema can occur as a prodromal manifestation that precedes angioedema in some patients; however, the concomitant presence of pruritic urticaria makes the diagnosis of HAE unlikely.[6,11,12,36-38] However, some cases of HAE coexisting with urticaria have been reported.[40]

A family history of clinical manifestations that are similar to those seen in the patient supports a diagnosis of HAE, although this type of family history is absent in approximately 25% of cases.[8]

In children, the clinical manifestations of HAE generally develop before six years of age. However, the onset of clinical manifestations in infants is rare, and few cases have been described. Attacks of laryngeal edema are particularly rare before three years of age and tend to occur later than other manifestations. During adolescence, there are substantial changes in disease activity, particularly in girls, for

Table 1 - Classification of hereditary angioedema.

TYPE	DEFECT
Type I – Quantitative	Decreased C1 inhibitor synthesis
Type II - Functional; Qualitative	Decreased C1 inhibitor function
Type III	Normal C1 inhibitor levels and function
	A- Estrogen-dependent or estrogen-related
	B- Mutation of factor XII (Hageman factor)
	C- Idiopathic

whom disease progression is worse because of their menstrual cycles and their use of contraceptives containing estrogen.[6,11,12,36-38]

Although the manifestations of type III HAE are similar to those of the other HAE types, there are certain features unique to this type. Symptom onset generally occurs later in life, the course of the disease tends to be more benign, and tongue involvement is common. Purpura is occasionally seen at sites that are affected by angioedema. However, the most striking characteristic of type III HAE is a personal and family history of associations between the disease and female gender and between the disease and estrogen administration.

In AAE, the onset of symptoms also occurs later, there is no family history of angioedema, and the associations between AAE and lymphoproliferative diseases and between AAE and autoimmune diseases should be investigated.[33,34]

How can laboratory tests confirm the diagnosis of HAE?

Individuals who are clinically suspected of having HAE and individuals with a family history of HAE should be investigated (Table 2). The principal screening test is the determination of serum levels of C4.[6,36-38]

Quantitative or qualitative C1-INH deficiency leads to the permanent activation of the complement system, accompanied by C4 consumption, even when patients are not experiencing an angioedema attack. In 2-5% of cases, C4 levels normalize during the intercrisis period.[41]

C3 turnover is greater than C4 turnover. In addition, there are other proteins that, together with C1-INH, regulate the consumption of C3, the levels of which are generally normal in HAE patients. Therefore, the determination of C3 levels is unnecessary except in patients who are suspected of having AAE, principally in the presence of autoimmune diseases.[6,36-38] In AAE, there is activation and consumption of complement components, and 75% of patients present with reduced serum levels of C1q.[42] Therefore, the determination of C1q levels can aid in the differentiation between HAE and AAE.

Following (or concomitant with) the determination of serum levels of C4, quantitative and qualitative determinations of C1-INH should be performed. All health professionals and family members who are involved in providing care for patients with HAE must ensure that such tests are available. Although the quantitative determination of C1-INH is a relatively easy test to perform, the determination of functional enzymatic activity (qualitative test) should be performed at a referral laboratory.[6,36-38] Importantly, the determination of functional activity is only necessary when C1-INH levels are normal (Figure 1).

If clinical suspicion remains despite normal C4 levels and normal (quantitative/qualitative) C1-INH levels, these tests should be performed again during an angioedema attack.[6,36-38] If the test results are again normal, a diagnosis of type III HAE is suggested.[30]

What are the diagnostic criteria for HAE?

Criteria to standardize the diagnosis of HAE have been proposed (Table 3).[36] According to these criteria, the presence of HAE is confirmed when patients meet one major clinical criterion and one biochemical criterion.

It should be noted that those criteria are not absolute and that the patient's clinical history takes precedence, principally in locations where the laboratory tests are not available and in suspected cases of type III HAE. In selected cases, we can presume a diagnosis of HAE and perform a therapeutic test.

TREATMENT

Guidance

To improve the quality of life of patients and their families and to avoid severe complications, the most important initial measure is to provide guidance regarding the course of HAE and the triggering factors for attacks. Patients should be given relevant information (in writing) regarding the disease and the steps that must be taken in the case of an attack (an action plan). There are nonpharmacological approaches that can reduce HAE severity and therefore merit attention.

Table 2 - Laboratory diagnosis of angioedema.

Type of Angioedema	C1-INH level	C1-INH function	C4	C3	C1q
Type I HAE	Low	Low	Low	Normal	Normal
Type II HAE	Normal	Low	Low	Normal	Normal
Type III HAE	Normal	Normal	Normal	Normal	Normal
AAE	Low	Low	Low	Normal/Low	Low
ACE inhibitor	Normal	Normal	Normal	Normal	Normal
Idiopathic	Normal	Normal	Normal	Normal	Normal

C1-INH: C1 inhibitor, HAE: hereditary angioedema, AAE: acquired angioedema, ACE: angiotensin-converting enzyme.

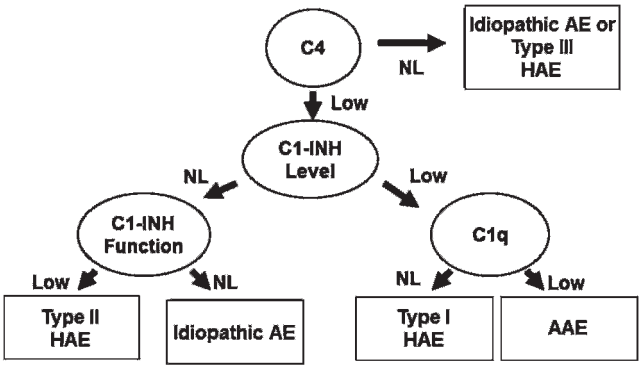

Figure 1 - Diagnostic algorithm of hereditary angioedema. C1-INH: C1 inhibitor, HAE: hereditary angioedema, AAE: acquired angioedema, NL: normal.

Because of the significant morbidity and mortality associated with HAE, a strategy involving careful treatment and prevention of attacks is essential for appropriate patient management (Table 4). The experience at large centers has demonstrated that 25-40% of patients can develop asphyxia and die if they are left untreated.[7,10-15]

Prevention of attacks

The risk of attacks can be reduced by identifying and eliminating the factors that trigger them. Stress and trauma are clearly triggering factors for edema in HAE, so patients should monitor those factors. High-impact sports and hobbies that pose a risk of trauma should be avoided. To prevent infections, which constitute a trigger of attacks, immunization is indicated. Hepatitis B vaccination is recommended because blood products might be used during the treatment of HAE attacks.[43]

Drugs that can worsen or prolong an HAE attack

The drugs that most commonly worsen or prolong the clinical profile of HAE or AAE are ACE inhibitors, angiotensin II receptor antagonists, medications containing estrogen, and certain oral hypoglycemic agents.

Because ACE inhibitors increase the half-life of bradykinin, their use should be avoided.[44] Angiotensin II receptor antagonists can also worsen the clinical profile of HAE, although they do so less commonly than ACE inhibitors.[45]

Contraceptives containing progesterone should be preferentially prescribed over those containing estrogen.[16,46]

Sitagliptin phosphate, which is an oral hypoglycemic agent indicated for the treatment of type 2 diabetes, belongs to a class of oral hypoglycemic agents designated dipeptidyl peptidase-4 inhibitors, which can worsen the clinical profile of HAE.[47]

Table 3 - Diagnostic criteria for hereditary angioedema.[36]

I - Primary clinical criteria
a) Non-inflammatory subcutaneous angioedema lasting longer than 12 h
b) Abdominal pain of undefined organic etiology lasting longer than 6 h
c) Recurrent laryngeal edema
II - Secondary clinical criteria
a) Family history of hereditary angioedema
III - Biochemical criteria
a) Quantitative C1 inhibitor <50% in two distinct samples
b) Functional C1 inhibitor <50% in two distinct samples
c) Mutation in the C1 inhibitor gene

Table 4 - General recommendations for the medical treatment of attacks of hereditary angioedema.

Take a personal and family history of the acute attack profile
Use oxygenation and pulse oximetry
Hydrate
Use antispasmodics and analgesics as needed
Avoid the use of angiotensin-converting enzyme inhibitors
Increase the dose of chronic medication to control the attack
Use acute phase control agents (fresh plasma, C1 inhibitor, bradykinin receptor antagonist, or kallikrein inhibitor) if available

Genetic screening of family members

All first-degree relatives of patients with HAE should be screened for HAE. In pediatric patients with a family history of HAE, the HAE diagnostic tests should be performed at six months of age and repeated at one year.[48]

Patients and their families should receive genetic counseling and guidance regarding the inheritance pattern of the disease.[49]

Pharmacological treatment

The pharmacological treatment of HAE can be divided into three modalities: long-term prophylaxis, short-term prophylaxis, and treatment of attacks.

The therapies recommended here were classified according to the strength of the recommendation, which is based on the level of scientific evidence supporting such a recommendation (Table 5).

How should long-term prophylaxis be performed?

The objective of long-term prophylaxis in HAE is to reduce the frequency and severity of attacks. These two variables can vary widely. Patients may be asymptomatic or experience attacks twice per week with symptoms that are practically continuous. Therefore, the first question regarding long-term prophylaxis should be whether patients actually require this type of treatment.

In general, individuals with frequent symptoms or a history of angioedema attacks involving the upper airways should be treated prophylactically. Patients who are candidates for this type of treatment are those who present with more than one severe attack per month or those who experience more than five attacks per month.[6,36-38]

Although the number and severity of angioedema attacks play important roles in this evaluation, the impact of angioedema episodes on the patient's quality of life is a decisive aspect. Another important point to be considered is whether patients have access to appropriate medical care in the case of a severe episode of angioedema.[50]

In Brazil, two treatment modalities are available for long-term prophylaxis: attenuated androgens and antifibrinolytic agents.

The most effective and best tolerated therapy for long-term prophylaxis of HAE is attenuated androgens that increase the levels of C1-INH and C4 and reduce the number of attacks of angioedema (grade B recommendation).[51] The drugs used include danazol, stanozolol, and oxandrolone, which are less virilizing than methyltestosterone. Oxandrolone is especially recommended for use in children.[52]

Table 5 - Evidence levels and degrees of recommendation for therapies.

Levels of evidence	
Level	**Meaning**
1	One or more randomized controlled clinical trials of sufficient sample size with a narrow confidence interval Meta-analysis of randomized controlled clinical trials
2	Good quality cohort study Low-quality randomized clinical trial (small sample size and >20% lost to follow-up)
3	Case-control studies Meta-analysis of case-control studies
4	Case series Low-quality cohort studies Low-quality case-control studies
5	Based on expert opinions, experimental studies or physiology
Grade/Strength of recommendation	
Grade	**Meaning**
A	Corresponding to level of evidence 1
B	Corresponding to level of evidence 2 or 3 Extrapolated from level 1 studies involving populations other than the current population
C	Corresponding to level of evidence 4 Extrapolated from level 2 or 3 studies involving populations other than the current population
D	Corresponding to level of evidence 5

Adapted from: Levels of evidence and grades of recommendation, Oxford Center for Evidence-Based Medicine, May 2001. http://www.cebm.net/levels_of_evidence.

In Brazil, the most widely used attenuated androgen is danazol, which is also the most widely available (its availability is guaranteed by the High-Cost Drug Program); in addition, well-controlled studies have demonstrated the clinical efficacy of this drug and have shown that it improves biochemical parameters.[51,53,54]

Treatment with danazol can be started at high doses (600 mg/day), which can later be reduced. Another option is to start at a low dose (50-200 mg) and increase the dose as needed. Therefore, two protocols have been established: [6]

a) ***Milan Protocol***—Initiation at a high dose with a subsequent reduction:

- 400-600 mg/day of danazol for one month
- Wean by 1/3, or 100 mg, every month
- At 200 mg/day, taper by 50 mg every two months
- At 100 mg/day, taper by 50 mg every three months
- Minimum dose of 50 mg/day, five days per week
- If the symptoms recur, re-induce remission with the initial dose and wean to a higher maintenance dose than the previously administered dose.

b) ***Budapest Protocol***—Initiation at a low dose with a subsequent increase:

- 2.5 mg/kg of danazol (maximum of 200 mg) administered daily for one month
- If there is no response, increase to 300 mg/day for two-four weeks
- If there is no response, increase to 400 mg/day for two-four weeks
- If controlled at 200 mg, reduce to 100 mg/day for one month
- If controlled at 100 mg, reduce to 50 mg/day or 100 mg on alternate days
- If there are prodromal symptoms of attack, double the dose for several days.

The best strategy should be chosen based on the patient's clinical status. Therefore, we should consider whether it is more important to control the angioedema attacks as fast as possible or to minimize the potential adverse effects of the drug. In both protocols, the final dose should be the lowest dose that provides adequate prophylaxis, generally ranging from the administration of 50 to 200 mg/day or on alternate days.

Although androgens increase the levels of C1-INH and C4, symptomatic benefits are generally achieved at doses lower than those required to significantly alter the levels of complement components. Therefore, it is important that the drug dosage is based on the patient's clinical symptoms rather than his or her biochemical parameters. It should be emphasized that androgens are ineffective in controlling attacks of HAE because it takes approximately 48 h for the drugs to begin to take effect.[55]

Most patients tolerate androgens at the aforementioned doses. However, sustained use at higher doses generally results in significant adverse effects. The adverse effects of androgens are related to the dosage, with the major adverse effects being hepatotoxicity and virilization.[56]

Other adverse reactions include weight gain, headache, menstrual changes, acne, changes in libido, anxiety, mood disorders, hypertension, myopathy, changes in lipid profiles, and hematuria.[57] Although there is evidence of changes in patients' lipid profiles, the association between danazol and atherosclerosis is controversial.[57-59] Danazol-induced hematuria results from mild cystitis or bladder telangiectasia.[60] These adverse effects tend to disappear after the discontinuation of the drug.

In individuals receiving androgens, the hepatic enzyme levels should be evaluated every six months. If liver damage develops, the dose should be reduced or the drug should be discontinued until these tests yield normal results.

Because hepatic adenomas and hepatocellular carcinoma have previously been reported as consequences of the use of androgens, liver ultrasounds should also be routinely performed every six months.[61,62] The development of liver tumors in patients who are using danazol has been associated with the use of higher doses (400-800 mg), a longer duration of administration, and the lack of monitoring for liver injury.[63]

Although many patients complain of androgen-induced adverse events, most patients with HAE can benefit, at least moderately, from androgen use, and the risk profile is acceptable.

Danazol is contraindicated during pregnancy because there have been documented cases of virilization in female neonates. However, discontinuation of the drug by gestational week eight has been shown to avert that alteration.[64-66] Other contraindications for danazol use include breastfeeding and prostate cancer, as well as kidney, liver, and heart failure.

Antifibrinolytic agents (epsilon-aminocaproic acid and tranexamic acid) are generally effective (grade B recommendation) in preventing HAE attacks.[67-71] These drugs antagonize the fibrinolytic system by blocking plasmin formation and inhibiting the proteolytic activity of plasminogen activators and, consequently, clot dissolution. The mechanism by which antifibrinolytic agents prevent HAE attacks remains unknown. Unlike attenuated androgens, antifibrinolytic agents do not increase the serum levels of C1-INH or C4.

The therapeutic dose of epsilon-aminocaproic acid is 1 g, administered orally three to four times per day, and it can be as high as 8 g/day.[55] Tranexamic acid should be administered at a dose of 0.5-0.75 mg/kg two to three times per day; the drug is more potent than aminocaproic acid and has a lower incidence of adverse effects.[72] The side effects of antifibrinolytic agents include nausea, diarrhea, vertigo, postural hypotension, fatigue, muscle weakness, cramps, and increased muscle enzyme levels.[50] Other adverse effects that are associated with the inhibition of plasmin include the increased occurrence of thrombosis and increased tumor growth. Because of the risks of teratogenicity, the use of antifibrinolytic agents during pregnancy is restricted.[50]

As occurs with attenuated androgens, the time of onset of the therapeutic effects of antifibrinolytic agents is approximately 48 h after administration. Therefore, both classes of drugs are of little use in providing immediate symptom relief. Because anabolic androgens are more effective in controlling HAE, they generally constitute the treatment of choice (grade C recommendation). Antifibrinolytic agents should be reserved for patients who do not tolerate anabolic androgens or for cases in which anabolic androgens are contraindicated. In severe cases for which the maximum dose of androgen is not sufficient to control the attacks, antifibrinolytic agents can be used in combination with androgens.

Long-term prophylaxis of HAE is satisfactory for most patients but has the disadvantage of requiring daily medication. In some patients, the use of androgens or antifibrinolytic agents is impractical because of the adverse reactions that they provoke (principally in females) or because of a lack of response. In addition, neither class of drugs is safe for use during pregnancy.

Although they are still unavailable in Brazil, C1-INH concentrates, which have a grade B recommendation, have been used elsewhere for the long-term prophylaxis of HAE.[73-75] Administered intravenously at regular intervals, approximately three times per week, C1-INH concentrates constitute a viable therapeutic alternative for individuals in whom other therapies cannot be used or are ineffective.

Regardless of the drug chosen, the effectiveness of each drug depends on treatment adherence, which must be encouraged and evaluated.

How should short-term prophylaxis be performed?

Short-term prophylaxis is indicated for patients undergoing major surgical procedures (e.g., surgery with orotracheal intubation), other surgical procedures (principally craniofacial procedures), invasive diagnostic procedures (e.g., endoscopy), or major dental procedures (all patients should be informed of the higher risk of attacks during major dental procedures).

In addition to prophylaxis, patients should remain under observation for 36 h and should have easy access to rescue medication.[5]

Therapeutic intervention should be performed before the occurrence of events that can provoke HAE attacks. Favorable results have been obtained with the use of attenuated androgens, antifibrinolytic agents, fresh frozen plasma, and C1-INH concentrates (Table 6).

Fresh frozen plasma can be administered intravenously at a dose of 2 U the night before surgery or on the day of surgery (grade D recommendation). Epsilon-aminocaproic acid is effective when it is administered several days before the triggering event (grade C recommendation). Androgens, which have a grade C recommendation, are used three-five days before surgery at doses of 10 $mg \cdot kg^{-1} \cdot day^{-1}$, with a maximum dose of 600 mg/day.[76] For prophylaxis in adults and children, C1-INH concentrates are safe and effective at doses of 500-1,000 U when administered intravenously (grade C recommendation). Some of these products have also been tested and are currently used in pregnant women.

Initially, in the 1970s, C1-INH concentrate was established as the emergency treatment for HAE. With the introduction of viral inactivation processes, C1-INH concentrate also became a first-line drug for the prophylaxis of acute HAE attacks. There are two C1-INH concentrates currently in use in the United States: Cinryze® and Berinert®. Because of regulatory issues, Cinryze® is indicated for short-term prophylaxis of HAE but not for the treatment of attacks, and Berinert® is indicated for the treatment of acute HAE attacks.

How should HAE attacks be treated?

The treatment of acute HAE attacks depends on their severity (Table 7). Severe attacks and attacks involving the respiratory tract require urgent treatment because of the potential for morbidity and mortality.

Although episodes of peripheral edema rarely require treatment, the early administration of danazol can shorten the duration of attacks and uncomfortable symptoms (grade D recommendation). Patients who are taking attenuated androgens prophylactically should double the dose for a few days after identifying an attack in any part of the body.[76] Therapy with antifibrinolytic agents, such as tranexamic acid administered orally every 3-4 h, has also been recommended for mild crisis periods (grade C recommendation).

Abdominal attacks are extremely painful and can be accompanied by vomiting, diarrhea, or both. When patients present with severe abdominal attacks, symptomatic treatment with the administration of fluids, antiemetics, and analgesics is indicated. Antispasmodics and narcotics may be required to treat intense pain.[37]

Dysphonia and dysphagia are indicative of progression to a severe laryngeal attack. Such attacks develop slowly over the course of approximately 8 h on average, and dysphagia and voice changes generally precede laryngeal obstruction.[16] However, there have been reports of rapid-onset laryngeal edema, and physicians should bear this in mind when evaluating such patients.

More severe cases require immediate intubation. In such cases, oxygen therapy is indicated, and pulse oximetry should be monitored. During laryngoscopy and intubation, the need for tracheostomy should be evaluated.[77] In cases of laryngeal edema, it may be prudent to perform prophylactic

Table 6 - Drugs used for the short-term prophylaxis and treatment of acute attacks of hereditary angioedema.

Short-term prophylaxis	Trade name	Dose	Adverse events
Tranexamic acid	Transamin® Hemoblock®	1 g administered orally every 4 h (or 0.5 g administered intravenously every 4 h) for 18 h	Diarrhea
High-dose attenuated androgens	Danazol Oxandrolone	10 mg • kg^{-1} • day^{-1} with a maximum dose of 600 mg/day for 3-5 days before the procedure	Weight gain, voice changes, increased hair growth, and menstrual irregularity
C1-INH concentrate* and recombinant C1-INH*	Berinert® Cinryze®	500-1,000 U on the day before the procedure or on the day of the procedure	-
Fresh plasma	-	10 ml/kg	Hyperosmolarity
Treatment of acute attacks			
C1-INH concentrate* and recombinant C1-INH*	Berinert® Cinryze®	1,000 U administered intravenously or 10-20 U/kg	-
Fresh plasma	-	10 ml/kg	Hyperosmolarity
Bradykinin receptor Antagonist	Icatibant (Firazyr®)	30 mg/dose and repeat an initial dose and a second dose if the attack persists	Local hyperemia
Kallikrein inhibitor*	Ecallantide (Kalbitor®)	20 U/kg or 30 mg/dose and repeat the second dose if the attack persists	Hypersensitivity reactions

*Drugs that have not yet been approved in Brazil.

intubation as an early measure to maintain airway patency and avoid tracheostomy (grade D recommendation).[77]

In cases of severe acute attacks, the treatment of choice is C1-INH replacement therapy, which can be achieved by the intravenous infusion of 1,000 U of a C1-INH concentrate (grade A recommendation), by the infusion of recombinant C1-INH, or, as reported recently, by a kallikrein inhibitor or a BDKRB2 antagonist (grade B recommendation).

In countries where the aforementioned drugs are not available, fresh plasma or solvent/detergent-treated plasma, which contains C1-INH, can be used (grade D recommendation). However, this type of treatment can worsen HAE attacks because fresh plasma also contains the remaining complement, coagulation, and contact system components. In addition, there are concerns regarding the safety of fresh plasma (e.g., transfusion-related acute lung injury, anaphylaxis, and viral transmission), and the need for a relatively large volume of plasma might be problematic in an emergency setting or in patients who cannot tolerate significant volume expansion. Therefore, when C1-INH concentrate, or bradykinin receptor antagonist, or kallikrein inhibitor are available, they are preferred over plasma transfusion.[37,78,79]

The symptoms generally improve 30-40 min after the infusion of C1-INH concentrate. A second, identical, dose can be administered if necessary.

The fractional catabolic rate of C1-INH is 2.5% of the plasma pool per hour. However, in patients with HAE, the half-life of C1-INH is longer than predicted by the fractional catabolic rate (>48 h *vs.* 28 h). This difference is probably attributable to the observation that exogenous C1-INH reduces the consumption of endogenous C1-INH, preventing C1 autoactivation.[50,79,80]

Rhucin®, which was developed recently, is a recombinant C1-INH derived from the milk of transgenic rabbits.[75] Although its half-life is only 3 h, Rhucin® has been shown to produce a response similar to that produced by other commercially available C1-INH preparations in the treatment of HAE attacks (grade B recommendation).[75,81] Further studies are needed to assess the effects of Rhucin.

In addition to C1-INH replacement therapy, blocking the synthesis and effects of bradykinin constitute other pharmacological approaches to HAE attacks. Recent studies have confirmed the efficacy of a kallikrein inhibitor and a BDKRB2 antagonist.

The BDKRB2 antagonist, icatibant, is highly specific for BDKRB2, binding to it with the same affinity as bradykinin and inhibiting a variety of BDKRB2-mediated effects.[82] The drug is administered subcutaneously, and its plasma half-life is 2-4 h. Icatibant is degraded by peptidases, and the products of icatibant degradation are excreted by the

Table 7 - Parameters for the treatment of acute attacks in patients with hereditary angioedema.[6,38]

Treatment	Edema of the skin		Abdominal attack	Laryngeal edema
	Torso and extremities	Face and neck region		
Wait and see (spontaneous resolution)	±	−	−	−
Tranexamic acid	+	+	+	+
C1-INH concentrate, bradykinin receptor antagonist, kallikrein inhibitor	±	+	+	+
ICU (intubation/tracheostomy)	−	−	−	+

C1-INH: C1 inhibitor, ICU: intensive care unit.
+ indicated.
± consider indication.
− contraindicated.

kidneys. Icatibant was initially shown to be effective in treating seasonal allergic rhinitis and asthma. Subsequently, two double-blind, randomized, multicenter trials (the For Angioedema Subcutaneous Treatment trial, parts 1 and 2) found that a single dose of icatibant was effective in 90% of the attacks of HAE (grade B recommendation).[83] One perspective that merits investigation is the home treatment of HAE attacks with icatibant. Icatibant has been approved in Brazil, and its use is indicated for the treatment of HAE attacks. Although the drug can be stored at room temperature, in Brazil, it is suggested that the drug be stored at 4℃.

Ecallantide is a high-potency recombinant protease inhibitor that binds to and inhibits kallikrein, thus decreasing bradykinin production. Because of its short half-life when it is administered subcutaneously, ecallantide has been evaluated for use in acute HAE attacks only. Multicenter phase III clinical trials have found a significant reduction in the severity of acute attacks after ecallantide administration compared to a placebo (grade B recommendation).[84] Side effects were rare and included dyspnea, oropharyngeal edema, and prolonged prothrombin and thrombin times. There have also been isolated reports of anaphylactic reactions following ecallantide administration; therefore, the use of the drug is restricted to hospital environments.[85]

To date, no studies been conducted to compare the efficacy of C1-INH concentrate, icatibant, and ecallantide in the treatment of HAE attacks.[86]

Regarding pharmacological treatment, it should be highlighted that, unlike anaphylaxis and edemas associated with the degranulation of mast cells and basophils, C1-INH deficiency-induced angioedema does not respond significantly to the administration of antihistamines, glucocorticoids, or epinephrine.[77]

SPECIAL SITUATIONS

Pediatric patients

In pediatric patients, antifibrinolytic agents are the drugs of choice for long-term prophylaxis because of their safety profiles (grade C recommendation). Studies have reported that tranexamic acid is better tolerated than epsilon-aminocaproic acid. When these agents are not sufficient, attenuated androgens may be required. The use of minimum maintenance doses for control has been found to have no negative impact on growth, and the only adverse effect that was observed was late menarche with subsequent menstrual irregularity, which was attributed to the use of danazol (200 mg/day).[87]

During the first two years of prophylaxis, it is recommended that laboratory tests be performed every three-four months and that abdominal ultrasounds be performed every six months. The clinical course of HAE should be monitored, as should any adverse effects of treatment.

Pregnancy and delivery

During pregnancy and, if possible, even before conception, the ideal situation is that no prophylactic drug be used. Attenuated androgens are contraindicated, and tranexamic acid can be used if it is administered with caution (grade C recommendation).

The treatment of HAE attacks does not change during pregnancy. Attacks during vaginal delivery are rare. However, when they do occur, they are severe. Regional analgesia is recommended for surgical delivery; general anesthesia and orotracheal intubation should be avoided (grade C recommendation).

Suspected cases of acute abdomen

Some HAE attacks mimic acute surgical abdomen, and negative exploratory laparotomy results are common in such patients.[20,21] However, a diagnosis of HAE raises the concern that if there is a true abdominal emergency requiring surgery, the timing of the surgical procedure may be delayed.

CONCLUSION

The Experts in Clinical Immunology and Allergy of the ''Associação Brasileira de Alergia e Imunopatologia - ASBAI'' developed these guidelines for the diagnosis, therapy, and management of hereditary angioedema. We hope that these guidelines will aid readers in the diagnosis and treatment of HAE, which is a neglected disease. A Portuguese version of this consensus is published in the ''Revista Brasileira de Alergia e Imunopatologia''. [88]

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