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2022 Brazilian guidelines for hereditary angioedema – Part 2: therapy

Diretrizes brasileiras de angioedema hereditário 2022 – Parte 2: terapêutica

Régis A. Campos[1], Faradiba Sarquis Serpa[2], Eli Mansour[3], Maria Luiza Oliva Alonso[4], Luisa Karla Arruda[5], Marcelo Vivolo Aun[6,7], Maine Luellah Demaret Bardou[8], Ana Flávia Bernardes[3], Fernanda Lugão Campinhos[2], Herberto Jose Chong-Neto[9], Rosemeire Navickas Constantino-Silva[10], Jane da Silva[11], Sérgio Duarte Dortas-Junior[4], Mariana Paes Leme Ferriani[5], Joanemile Pacheco de Figueiredo[12], Pedro Giavina-Bianchi[6], Lais Souza Gomes[6], Ekaterini Goudouris[13], Anete Sevciovic Grumach[8], Marina Teixeira Henriques[8], Antônio Abilio Motta[6], Therezinha Ribeiro Moyses[2], Fernanda Leonel Nunes[5], Jorge A. Pinto[14], Nelson Augusto Rosario-Filho[9], Norma de Paula M. Rubini[15], Almerinda Maria do Rêgo Silva[16], Dirceu Solé[17], Ana Júlia Ribeiro Teixeira[6], Eliana Toledo[18], Camila Lopes Veronez[19], Solange Oliveira Rodrigues Valle[4]

ABSTRACT

The treatment of hereditary angioedema begins with the education of patients and their families about the disease, as it is essential to know the unpredictability of attacks as well as their triggering factors. Drug treatment is divided into attack therapy and prophylaxis of clinical manifestations. Attacks should be treated as early as possible with the bradykinin receptor antagonist icatibant or C1-inhibitor concentrate. An action plan needs to be established for all patients with attacks. Long-term prophylaxis of symptoms should preferably be performed with first-line drugs such as C1-inhibitor concentrate or the anti-kallikrein monoclonal antibody lanadelumab. Attenuated androgens are the second line of treatment. In short-term prophylaxis, before procedures that can trigger attacks, the use of C1-inhibitor concentrate is recommended. There are some restrictions for the use of these treatments in children and pregnant women that should be considered. New drugs based on advances in knowledge of the pathophysiology of hereditary angioedema are under development and are expected to improve patient quality of life. The use of standardized tools for monitoring quality of life and controlling disease activity is essential in the follow-up of these patients. The creation of associations of patients and families of patients with

RESUMO

O tratamento do angioedema hereditário tem início com a educação dos pacientes e familiares sobre a doença, pois é fundamental o conhecimento da imprevisibilidade das crises, assim como os seus fatores desencadeantes. O tratamento medicamentoso se divide em terapia das crises e profilaxia das manifestações clínicas. As crises devem ser tratadas o mais precocemente possível com o uso do antagonista do receptor de bradicinina, o icatibanto ou o concentrado de C1-inibidor. É necessário estabeler um plano de ação em caso de crises para todos os pacientes. A profilaxia de longo prazo dos sintomas deve ser realizada preferencialmente com medicamentos de primeira linha, como concentrado do C1-inibidor ou o anticorpo monoclonal anti-calicreína, lanadelumabe. Como segunda linha de tratamento temos os andrógenos atenuados. Na profilaxia de curto prazo, antes de procedimentos que podem desencadear crises, o uso do concentrado de C1-inibidor é preconizado. Existem algumas restrições para uso desses tratamentos em crianças e gestantes que devem ser consideradas. Novos medicamentos baseados nos avanços do conhecimento da fisiopatologia do angioedema hereditário estão em desenvolvimento, devendo melhorar a qualidade de vida dos pacientes. O uso de ferramentas padronizadas para

1. Faculdade de Medicina da Bahia, Universidade Federal da Bahia, Department of Internal Medicine and Diagnostic Support, Postgraduate Program in Health Sciences - Salvador, BA, Brazil.
2. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória, Reference Service in Asthma, Allergy and Immunology - Vitória, ES, Brazil.
3. Faculdade de Ciências Médicas, Universidade Estadual de Campinas, Division of Allergy and Clinical Immunology, Department of Internal Medicine - Campinas, SP, Brazil.

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hereditary angioedema has played a very important role in the care of these patients in Brazil.

Keywords: Hereditary angioedema, therapeutics, emergency treatment, quality of life, biological therapy.

monitorização da qualidade de vida, do controle e da atividade da doença são fundamentais no acompanhamento destes pacientes. A criação de associações de pacientes e familiares de pacientes com angioedema hereditário tem desempenhado um papel muito importante no cuidado destes pacientes no nosso país.

Descritores: Angioedema hereditário, tratamento farmacológico, tratamento de emergência, qualidade de vida, tratamento biológico.

4. Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Immunology Service - Rio de Janeiro, RJ, Brazil.
5. Faculdade de Medicina de Ribeirão Preto - Universidade de São Paulo, Discipline of Allergy and Clinical Immunology, Department of Internal Medicine - Ribeirão Preto, SP, Brazil.
6. Faculdade de Medicina da Universidade de São Paulo, Discipline of Allergy and Clinical Immunology - São Paulo, SP, Brazil.
7. Faculdade Israelita de Ciências da Saúde Albert Einstein, Discipline of Host Agent - São Paulo, SP, Brazil.
8. Centro Universitário Faculdade de Medicina do ABC, Discipline of Clinical Immunology - Santo André, SP, Brazil.
9. Federal University of Paraná, Service of Allergy and Immunology, Department of Pediatrics - Curitiba, PR, Brazil.
10. Centro Universitário Faculdade de Medicina do ABC, Laboratory of Clinical Immunology - Santo André, SP, Brazil.
11. Hospital Universitário Prof. Polydoro Ernani de São Thiago, Department of Internal Medicine, Universidade Federal de Santa Catarina - Florianópolis, SC, Brazil.
12. Faculdade de Medicina da Bahia, Universidade Federal da Bahia, Department of Internal Medicine and Diagnostic Support - Salvador, BA, Brazil.
13. Faculdade de Medicina da Universidade Federal do Rio de Janeiro, Department of Pediatrics - Rio de Janeiro, RJ, Brazil.
14. Hospital das Clínicas, Faculty of Medicine, Universidade Federal de Minas Gerais, Clinical Immunology Service - Belo Horizonte, MG, Brazil.
15. Escola de Medicina e Cirurgia da Universidade Federal do Estado do Rio de Janeiro - UNIRIO, Allergy and Immunology Department - Rio de Janeiro, RJ, Brazil.
16. Universidade Federal de Pernambuco, Academic Area of Pediatrics, Center for Medical Sciences - Recife, PE, Brazil.
17. Escola Paulista de Medicina, Universidade Federal de São Paulo, Department of Pediatrics, Division of Allergy, Clinical Immunology and Rheumatology - São Paulo, SP, Brazil.
18. Faculdade de Medicina de São José do Rio Preto, Allergy and Clinical Immunology Service of the Department of Pediatrics and Pediatric Surgery - São José do Rio Preto, SP, Brazil.
19. University of California, Division of Rheumatology, Allergy and Immunology, Department of Medicine - San Diego, California, USA.

How to treat patients with hereditary angioedema?

The treatment of hereditary angioedema (HAE) involves multiple aspects related to health education, pharmacotherapy and the use of tools to assess the control, disease activity and quality of life of the patient. These actions provide individualized treatment plans that contribute to achieving the main objective of treatment, which is to fully control the disease and provide a normal life.[1]

The strategy involving the careful treatment of crises and their prevention is essential for the adequate management of patients, seeking to reduce the significant morbidity and mortality associated with HAE. The drug treatment of HAE consists of the use of drugs for crises and short- or long-term prophylaxis.[2,3] In recent decades there has been a better understanding of the pathophysiology of the disease, which has led to the development of new therapies.[4] However, access to these therapies in Brazil is still restricted, and patients continue to use inappropriate treatments, both for crises and for prophylaxis, which contributes to unfavorable outcomes.

What are the actions related to health education?

Appropriate education can provide patients and/or their families with HAE management skills. Once diagnosed, patients and family members should be oriented about the disease, with the objective of helping them in the best decisions to be made.[3,5,6] During childhood, guidance is also necessary for teachers, caregivers, as well as family doctors and pediatricians.[7-9] Clarifications about the course of HAE and the triggering factors of the crises are the most important initial measures for the patient and his family to have a better quality of life and to prevent serious complications. Other aspects that deserve attention

due to the possibility of affecting the severity of the disease are psychosocial issues.[10-13]

Health professionals involved in monitoring patients with HAE can help them make decisions about treatment and other conditions that deserve special attention, using a process called "shared decision-making" (CDT).[6,13,14] In line with the BDD concept, the latest international HAE guidelines consider the use of this process mainly with regard to the choice of therapy, making HAE management sensitive to the preferences of patients and family members.[2,3] The information shared with the patient must be impartial and balanced, insofar as it includes the reasons why or not to use a certain treatment.[6]

The patient must receive a written document with information about the disease and the conduct to be adopted in case of a crisis[10] (Appendix 1). A report on the disease, therapeutic options, monitoring, prohibited drugs and contact of the specialist physician in HAE must be provided to other assistant physicians and emergency teams.[2,3,15] Sports and hobbies with impactful movements and risk of trauma should be avoided. Regular dental follow-up can avoid extractions and surgical procedures, which are important triggers of crise.[10]

Immunizations are indicated for the prevention of infections that are also potential triggers of crises.[3,16] Considering that HAE is classified as a primary immunodeficiency, that is, an innate error of immunity (ICD10: D84.1), patients can have access to the vaccination schedule administered by the Special Immunobiological Centers (CRIEs) of the Ministry of Health.[17]

Influenza vaccination should be indicated annually, as some patients may have attacks triggered by respiratory infections. Vaccines against hepatitis A and B viruses (HAV and HBV) should be indicated to reduce the chance of infections and the theoretical risk of transmission of HBV by blood products, used in the treatment of HAE crises. Thus, serology for HBV, HCV and HIV is recommended, especially in patients who have been exposed to blood products. Vaccination against COVID-19 should be performed, although there are recent reports of angioedema attacks after the administration of these vaccines.[3,16,18,19]

Another relevant issue is the need to research the disease in family members and provide guidance on the pattern of inheritance and genetic counseling.[10] All first-degree relatives, even if asymptomatic, should be investigated for the possibility of HAE.[10,12,20]

How should long-term prophylaxis be performed?

The objective of long-term prophylaxis is to reduce the frequency and severity of crises with the main focus on improving the patient's quality of life and reducing mortality.[1,3] Treatment must always be personalized, and the indication must be based on the frequency and severity of crises, quality of life and access to medication.[21] There is no established limit for the number of attacks that would indicate the need for continued use of medication. It should be considered that an attack with upper airway obstruction in one patient may have a different weight than a greater number of mild attacks involving extremities in another patient.

Long-term prophylaxis does not necessarily imply permanent uninterrupted use. Dose adjustments and frequency of use must be individualized, guided by the clinical evolution of the patient.[3]

The drugs currently available in Brazil for long-term prophylactic treatment are: attenuated androgens, plasmin inhibitors (antifibrinolytic agents), C1 inhibitor concentrate (C1-INH) and kallikrein inhibitors (Table 1). The most recent international consensus established as first-line drugs for the long-term treatment of HAE, C1-INH concentrates and kallikrein inhibitors.[2,3,15,22] However, in Brazil, these drugs are not yet available in the Unified Health System (SUS), which offers access only to the attenuated androgen danazol, nor incorporated in the List of Procedures of the National Health Agency (ANS), which regulates supplementary health.

Attenuated androgens (AA) used for long-term prophylaxis include danazol and oxandrolone, which increase plasma levels of C1-INH and C4, being effective in reducing the frequency of angioedema attacks.[3] The most relevant adverse effects of AA and usually dose-dependent are hepatotoxicity, virilization and alteration of the plasma lipid profile. Virilizing effects include menstrual cycle irregularity, voice changes, and hirsutism. Psychological effects such as mood swings, loss of libido, anxiety and depression can occur. Other adverse reactions described include weight gain, acne, myopathies, arterial hypertension and hematuria. These adverse effects are reversible when the drug is discontinued.[23-25] Danazol is the only AA registered with the National Health Surveillance Agency (ANVISA), the optimal dose to minimize adverse effects being ≤ 200 mg/day.[3,15,26] Patients using AA should be monitored with blood count,

Table 1
Drugs available in Brazil for long-term treatment of patients with hereditary angioedema[2-4,15]

Drug	Mechanism of action	Half life	Way of use	Dose (adult)	Dose (child)	Comments
Tranexamic acid	Inhibits plasminogen activation	2-8 hours	VO, IV	1000-6000 mg/day	30-50 mg/kg/day	It does not work in crises. Effective in 1/3 of patients
Danazol	Increases hepatic synthesis of C1-INH; enhances aminopeptidase function	7-12 hours	VO	200 mg/day (maximum)[a]	2.5 mg/kg/day	See drug interactions and contraindications. It does not work in crises.
pdC1-INH	Replacement of C1-INH	32.7-62 hours	IV	1000 IU or 20 IU/kg[b]	1000 IU or 20 IU/kg	Approved ≥ 12 years
pdC1-INH	Replacement of C1-INH	50-70 hours	SC	60 IU/kg, 2x/week	60 IU/kg, 2x/wk	Approved ≥ 8 years
Lanadelumab	Kallikrein inhibition	2 weeks	SC	300 mg/2 weeks for 6 months. Space for 4 weeks with improvement	Same as adults	Approved ≥ 12 years

[a] TheMaximum dose established by consensus.
[b] Fixed dose according to pivotal study and variable dose according to studies published later.

liver function, lipid profile, creatine phosphokinase, alpha-fetoprotein, and urinalysis every six months and abdominal ultrasound annually to screen for hepatocellular adenoma or carcinoma. AAs are contraindicated during pregnancy and breastfeeding, before puberty, and in patients with prostate cancer or liver, kidney or heart failure.[25]

The literature is scarce on the use of the antifibrinolytic tranexamic acid in the long-term prophylaxis of AEH.[27-29] This drug competitively inhibits plasminogen activation, with a reduction in the transformation of plasminogen to plasmin and a decrease in fibrinolysis. It has lower efficacy than danazol and less toxicity, and its use is reserved for patients with intolerance or contraindication to danazol, as well as in patients younger than 12 years.[4] Tranexamic acid is used at a dose of 30-50 mg/kg/day, divided into 2-3 doses, with a maximum dose of 6.0 g/day.[3] The main concern with the use of antifibrinolytics is the risk of thrombosis, although this adverse reaction has not been reported.[28,29] The onset of the therapeutic effect is approximately 48 hours after its administration.[27]

Plasma-derived (pdC1-INH) or human recombinant (rhC1-INH) C1 inhibitor concentrates are drugs used to replace C1-INH deficiency. They act on all systems regulated by this glycoprotein, controlling the production of bradykinin.[3,4] pdC1-INH is obtained by separating C1-INH from purified human plasma by a combination of processes such as cryoprecipitation, ion exchange chromatography, ultrafiltration, nanofiltration, polyethylene glycol precipitation,

pasteurization and, finally, lyophilization.[3,30] This process guarantees the safety of the treatment in relation to the transmission of infectious diseases such as hepatitis and acquired immunodeficiency syndrome.[30-37] The plasma half-life of pdC1-INH is greater than 30 hours, therefore, it is safe and effective for long-term prophylaxis, with few adverse events.[32,38-40]

In Brazil, two products are approved by ANVISA: Berinert SC® (subcutaneous use) and Cinryze® (intravenous use). Randomized double-blind studies of Cinryze® have demonstrated its efficacy and safety.[30,41,42] The pivotal study with Cinryze® used a fixed dose of 1,000 IU intravenous (IV) every 3-4 days, however, later, another retrospective study showed better efficacy with the use of doses according to the patient's weight (20 IU/ kg/dose).[30,41,42] The risk of thromboembolism resulting from the prophylactic use of pdC1-INH was observed by the FDA (US Food and Drug Administration).[43] Later studies did not confirm this occurrence, suggesting that patients could have other associated predisposing factors.[44,45]

The prophylactic use of Berinert SC®, twice a week, significantly reduced the frequency of seizures.[46] The most frequent adverse effect was a mild reaction at the application site. The subcutaneous (SC) use of pdC1-INH facilitates self-administration and is available as Berinert® SC 2000/3000 IU (ANVISA).[47] The SC formulation contains 1500 IU in 3 mL of solution, compared to the IV formulation which contains 500 IU in 10 mL. SC administration results in more consistent plasma levels between applications compared to IV administration.[39] The recommended dose is 60 IU/kg of weight, for patients over eight years of age, twice a week (every three or four days), to be applied to the abdomen.[46,48]

Not yet available in our country, rhC1-INH (Ruconest®) is obtained from the milk of transgenic rabbits and, therefore, is contraindicated in patients with known or suspected allergy to rabbits or products derived from them.[32,49] Clinical studies have demonstrated the efficacy and safety of rhC1-INH, without thrombotic adverse events.[49,50] The plasma half-life is shorter due to its glycosylation, approximately 3 hours, which makes its use in long-term prophylaxis difficult, however, a study demonstrated this possibility when administered once a week for eight weeks.[40,51] The recommended dose is 50 U/kg IV for adults weighing less than 84 kg, and a dose of 4200 U (two vials) for adults weighing more.[50] Patients who do not wish to be treated with blood products for religious, moral or other reasons may receive recombinant C1-INH.[52]

Lanadelumab (Takhzyro®) is part of the group of kallikrein inhibitor drugs and is an anti-plasma kallikrein monoclonal antibody for SC use, released for patients over 12 years of age.[53] The pivotal phase 3 (HELP), double-blind, randomized, placebo-controlled study evaluated the drug administered subcutaneously at three different doses (150 mg every four weeks; 300 mg every four weeks and 300 mg every two weeks) or placebo. There was a significant difference in the reduction of seizures for the three doses used in relation to placebo, with better results when used at a dose of 300 mg every two weeks.[53] It is worth noting that the therapeutic effect occurred after the first dose and remained throughout the clinical trial.[54] This study was followed by an open-label phase with a dose of 300 mg, which proved the long-term efficacy and safety of the drug when in 97.7% of the treatment days there were no angioedema attacks.[14] The most frequently reported adverse events were local reactions and dizziness, with no serious events being reported.[14,54] A dose of 300 mg SC every 14 days is recommended and after six months without crises, the interval between doses can increase to four weeks.[55] A recent real-life study showed that the administration interval can be gradually increased before reaching this six-month period, always verifying the clinical response.[56]

The safety profile of the different drugs should always be considered when choosing long-term prophylaxis in the treatment of HAE-C1-INH (Table 2).

Long-term prophylaxis for patients with HAE-nC1-INH has not been studied in randomized, placebo-controlled clinical trials.[2] However, smaller open-label studies and case series reports have suggested strategies that can be used. The two main therapies used are antifibrinolytics and hormone therapy. There are reports for long-term prophylaxis in HAE-nC1-INH using pdC1-INH and lanadelumab, but only in specific situations, usually in the absence of response to other options.[2] Some women with HAE-nC1-INH with worsening symptoms during pregnancy benefited from the use of pdC1-INH.[57]

The first step in the treatment of AEH-nC1-INH consists of suspending the use of exogenous estrogens, which is often enough to make the patient asymptomatic.[58] Other options include the use of progestins or even AA.[59-61] Tranexamic acid has been used with good response, probably due to the inhibition of plasmin formation.[61]

How should short-term prophylaxis be performed?

Short-term prophylaxis is indicated for patients undergoing medical or surgical procedures that mainly involve the cervicofacial region, at risk of angioedema of the upper respiratory tract, such as more invasive dental treatment (tooth extraction), tonsillectomy, facial surgery, endoscopy, bronchoscopy and surgical procedures that require tracheal intubation.[54,62-65] It was found that among patients diagnosed with AEH-C1-INH who underwent tooth extraction, 21% developed local angioedema after the procedure.[65] Dentists are unaware of the AEH and patients face difficulties in obtaining dental care.[66]

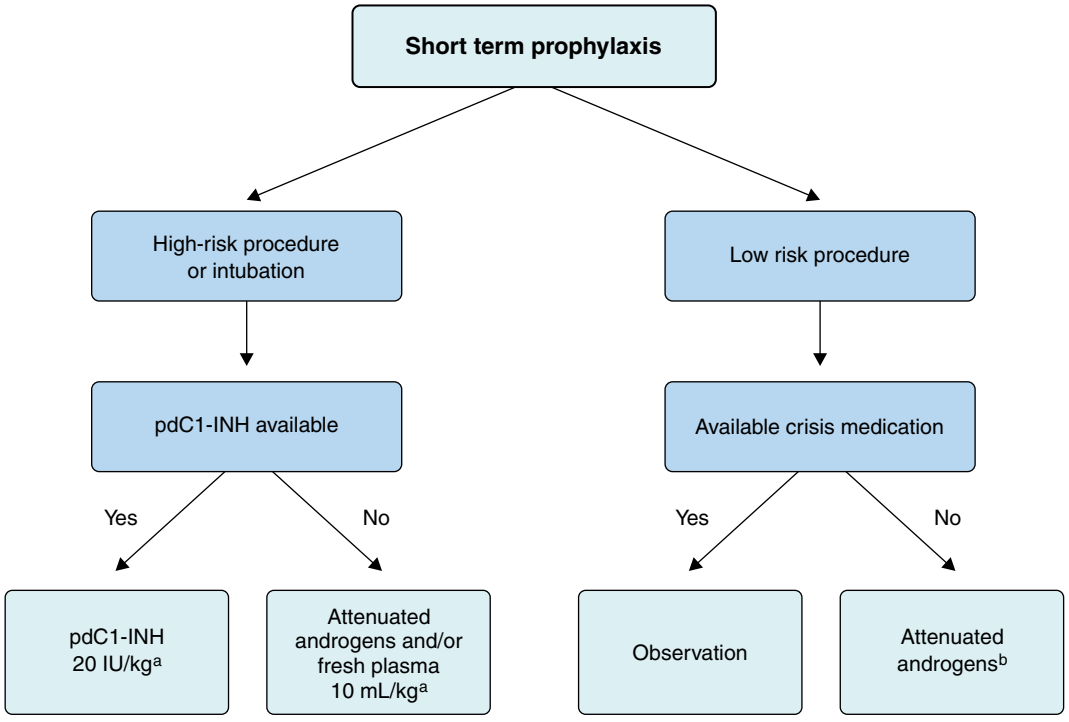
Table 2
Adverse effects and contraindications of prophylactic drugs for hereditary angioedema available in Brazil[2-4,15]

Medication	Adverse effects	Contraindications	Comments
Danazol	Hormonal: seborrhea, acne, hirsutism, menstrual irregularity, virilization, libido alteration, voice alteration. Alkylation at position 17 alpha: hepatotoxicity, increased transaminases, hepatic adenoma, hepatocarcinoma. Others: weight gain, change in lipoprotein profile, increased risk of atherogenesis, increased blood pressure, epiphyseal closure	Children (Tanner I-IV), pregnancy, breast cancer, prostate cancer, nephrotic syndrome, and changes in liver function	Interaction with other drugs: statins (rhabdomyolysis), increases carbamazepine concentration, increases insulin resistance, increases prothrombin time in warfarin users
Tranexamic acid	Muscle necrosis (asthenia, myalgia, increased CPK, increased aldolase), dizziness and postural hypotension, nausea, diarrhea and abdominal pain, muscle cramps, dysmenorrhea, pruritus, theoretical risk of thrombosis	Thrombophilia	Increased risk of thrombosis
Plasma-derived C1 inhibitor (pdC1-INH)	Theoretical risk of transmission of infectious agents, thrombosis (extremely high off-label doses), anaphylaxis (very rare), neutralizing anti-C1-INH antibodies		
Lanadelumab	Mild local reactions, hypersensitivity reactions, interference with clotting tests (APTT prolongation)		

CPK = creatine phosphokinase.

For minor dental procedures, no routine prophylaxis is necessary if crisis treatment is immediately available.[66] In non-dental surgeries, the risk of perioperative crisis varies from 5.7 to 30.5%.[63] The unpredictability of HAE crises triggered by procedures makes the current international consensus suggest that short-term prophylaxis should be considered individually.[2,15] The risk associated with the procedure to be performed, the availability of crisis treatment and the occurrence of a previous episode in similar circumstances should be verified.[15,21] In some situations, when the risk of the procedure to be performed is minimal and there is availability of crisis treatment, one may choose not to indicate short-term prophylaxis. In these cases, at the slightest sign of the onset of symptoms, crisis treatment should be instituted[21] (Figure 1).

pdC1-INH is the first-line treatment for short-term prophylaxis, and should be used one to six hours before the procedure, at a dose of 20 U/kg.[33,41,67,68] Fresh plasma can be used in procedures with high risk or need for intubation, when pdC1-INH is not available, however, there are no comparative studies evaluating the different drugs.[69] The suggested dose of fresh plasma is 10 mL/kg (2-4 units for an adult), one to six hours before the procedure[70] (Figure 1). AAs can also be used when the risk related to the surgery is relatively low.[71] Danazol is administered orally, three times a day, at a dose of 2.5 to 10 mg/kg/day with a maximum of 600 mg/day, starting 5 to 7 days before and maintaining it for 2 to 3 days after the procedure.[2,15,71-73] AEH crisis was found in 12% of patients after tooth extraction, even when receiving short-term prophylaxis,[65] which reinforces the need for



pdC1-INH = plasma-derived C1-INH concentrate.

[a] 1 to 6 hours before the procedure.

[b] For danazol 2.5 to 10 mg/kg, up to 200 mg/ 8-12 hours 5 days before and 2-3 days after the procedure.

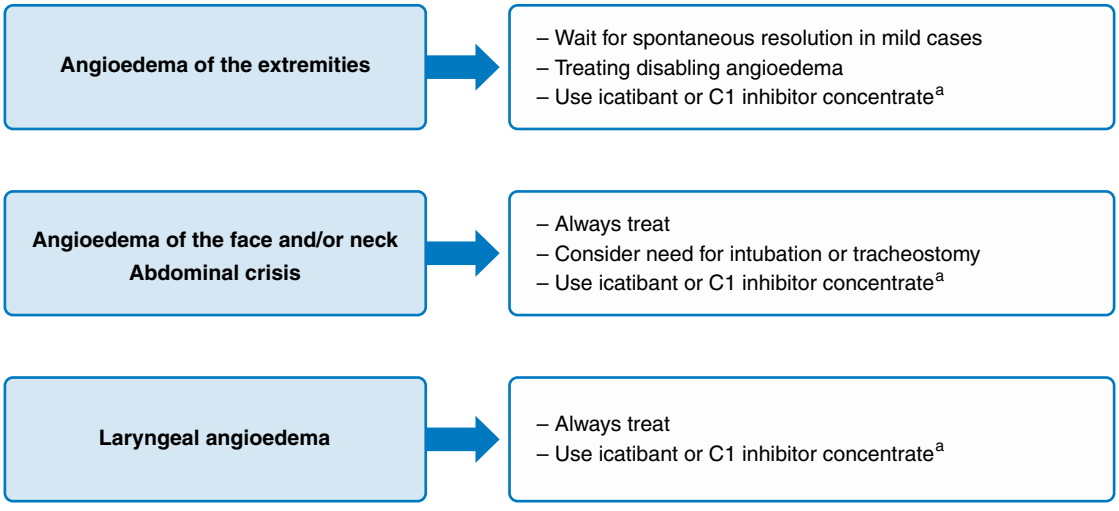
Figure 1
Short-term prophylaxis of hereditary angioedema with C1-INH deficiency[21]

crisis medication availability. There are no published data on short-term prophylaxis in AEH-nC1-INH. Therefore, the same protocol used in the AEH-C1-INH is recommended.[2]

How should hereditary angioedema attacks be treated?

The patient and/or caregiver should be instructed to treat the crisis, considering the potential for severity/location and possible disability. Early treatment of crises is essential and patients must have access to therapy and be trained to self-administer the medication.[2,3,15,74] Treating the crisis only in the medical service requires displacement and results in delayed initiation of therapy, which can contribute to inappropriate approaches and unfavorable outcomes. Although there is a consensus that attacks of abdominal, facial, labial and upper respiratory tract location should be treated early due to their potential for severity, when disabling extremity attacks also deserve attention and rapid treatment[2] (Figure 2). In case of an attack involving the larynx, delay in treatment can be fatal.[75] Thus, it is recommended that HAE patients have at least two doses of the drug to use at home in cases of eventual crises.[3,10,76,77]

In the emergency room, the first step in approaching patients with HAE crisis affecting the upper airways, tongue and/or uvula is to maintain a patent airway. In unstable patients, with imminent risk of asphyxia, orotracheal intubation (OTI) should not be delaye.[78] It is important to emphasize that, in the initial phase of airway obstruction, no drop in oxygen saturation is observed. Emergency room monitoring is indicated and, in cases of hypotension or dehydration, fluid replacement should be applied. When patients present with severe abdominal crises, in addition to specific therapy, symptomatic treatment with administration of fluids, antiemetics and analgesics is indicated. Antispasmodics and narcotics may be needed to treat severe pain.[79]



[a] Available in Brazil: C1-INH concentrate and icatibant (Fyrazyr®). In all situations, if C1 inhibitor concentrate or icatibant is not available, use fresh frozen plasma.

Figure 2
Recommendations for the treatment of hereditary angioedema crisis, according to the affected area[18]

The drugs used for the treatment of crises act by preventing the action of bradykinin on endothelial cells or increasing the levels of C1-INH, and, consequently, reducing the levels of bradykinin.[21] For crisis management, four types of treatments can be used: pdC1-INH, rhC1-INH, bradykinin B2 receptor antagonist (icatibant) and kallikrein inhibitor (ecalantide).[2,3,50,80] In Brazil, so far, there are three products approved by ANVISA for use in HAE crises: two pdC1-INH (Berinert® and Cinryze®)[47,81] and icatibant (Firazyr®)[82] (Table 3).

PdC1-INH and rhC1-INH are effective and safe for the treatment of HAE attacks in all age groups.[42,67,80] Berinert® is a pasteurized and nanofiltered product, indicated for IV administration at a dose of 20 IU/kg, regardless of the severity of the crisis.[42] In pivotal studies, the median time to onset of symptom relief was 0.46 hours and to complete resolution 15.5 hours. In addition, only 1.1% of patients required a second dose to control symptoms, with a time of four hours between the first and second doses, if necessary.[42] The other nanofiltered pdC1-INH concentrate (Cinryze®) was used at fixed doses (500 U or 1,000 U) in patients with angioedema of the extremities and in abdominal crises.[83] As with Berinert®, Cinryze® self-administration significantly reduced the duration and severity of attacks, in addition to the need for analgesics. A dose of 1000 U is recommended for the treatment of crises and can be repeated one hour later, if necessary.[41,49] However, there is evidence that fixed doses may not be sufficient to control seizures, and a dose of 20 IU/kg is more effective.[83] Additional dose was required in more than 60% of patients with laryngeal edema crisis who received fixed doses of pdC1-INH.[83]

RhC1-INH (Ruconest®) is not approved for self-administration, as it is not available in Brazil. The recommended dose is an IV injection of 50 U/kg for adults weighing less than 84 kg and at a dose of 4200U (two vials) for those weighing 84 kg or more.[84]

Icatibant acetate (Firazyr®) is a synthetic molecule, similar to bradykinin, which acts as a competitive and selective antagonist of the bradykinin B2 receptor.[85,86] HAE attacks resolve more quickly with early use of icatibant compared to late use, therefore, administration within the first six hours after the onset of symptoms is recommended.[87] In Brazil, icatibant acetate is licensed for home self-administration. Home use is safe, and the most common adverse events are erythema and pain at the injection site, with spontaneous resolution.[88] The recommended dose is 30 mg for adults and 0.4 mg/kg in the age group from 2 to 17 years, subcutaneously, exclusively in the abdominal region, with additional injections being possible every 6 hours, up to a maximum of three times in 24 hours.[85]

Ecallantide (Kalbitor®) is a kallikrein inhibitor approved for use in the United States and not available in Brazil. The recommended dose is 30 mg SC, and it is not approved for self-administration at home, as anaphylaxis has been observed in approximately 3% of patients.[89]

The use of fresh frozen plasma should be reserved for situations in which no other seizure drugs are available. This treatment strategy has only been used in observational studies and has not been tested in clinical trials for efficacy and safety in HAE attacks. In addition, the administration of plasma offers not only the replacement of C1-INH, but also the substrates on which this inhibitor acts, which may not have adequate efficacy and even worsen the condition. Other risks of the use of plasma consist of the occurrence of transfusion reactions, transmission of pathogens, in addition to volume overload.[90] The recommended dose is two to four units for adults and 10 to 15 mL/kg for children.[21]

The need to seek a health service for plasma administration makes it impossible for many patients to receive rapid treatment.[90] In some situations, the angioedema crisis can be very serious and require rapid response therapy and, in addition, in some regions of Brazil, access to plasma transfusion is not possible, which emphasizes the need to provide an effective therapy. and capable of self-administration.

To date, there are no studies comparing the efficacy of drugs used to treat HAE crisis in randomized clinical trials. Therefore, we suggest using the available option, in the shortest possible time between the beginning of the crisis and its application to obtain better effectiveness.

How should hereditary angioedema in childhood and adolescence be managed?

About 90% of patients present their first HAE symptoms before the age of 20 years.[91] A recent Brazilian multicenter study evaluated 95 pediatric patients with HAE-C1-INH and showed a lower mean age at onset of symptoms (3.3 years), with almost all symptomatic patients (96.2%) having their first symptoms. before age 12.[92] AEH-nC1-INH

generally begins in adolescence or adulthood, and its manifestation before the first decade of life is rare.[93]

In the pediatric age group, there is an average delay of four to eight years in the diagnosis of HAE.[91,92] Some of the main factors involved in this delay include: difficulty for the child to verbalize their symptoms, misdiagnosis of symptoms (eg, recurrent abdominal pain is common in childhood), symptoms may be less intense than in adults, delay in the investigation by parents due to denial of their own disease or fear of the result, screening tests with C4 with low accuracy in the pediatric age group, absence of family history and little

Table 3
Characteristics and guidelines for the drugs available in Brazil for the treatment of hereditary angioedema crisis[4,47,82]

Features/guidelines	Medication	
	Icatibant (Firazyr®)	**Plasma-derived C1-INH concentrate (Cinryze® / Berinert®)**
Age group	≥ 2 years	≥ 12 years / No age limit
Presentation	10 mg/mL of icatibant (syringe with 3 mL of the solution)	500 IU lyophilized powder/ 500 IU lyophilized powder
Dose	0.4 mg/kg up to 18 years 30 mg over 18 years or 65 kg	1,000 IU / 20 IU/kg
Route of administration	Subcutaneously, slowly. Preferably in the abdominal region	Intravenous / Slow intravenous or infusion (4 mL/minute)
Self administration	Yes	Yes / Yes
Solution appearance	Colorless and clear	Colorless to slightly blue / Colorless and clear
Storage temperature	2 °C to 8 °C	2 °C to 8 °C / Ambient (15 °C to 30 °C)
Storage after fractionated dose use or reconstitution	Not recommended	Not recommended / After reconstitution, only in the vial
Storage time	Not recommended	Immediate use after reconstitution / Maximum 8 hours at room temperature
Adverse effects	Local reactions (itching, pain, swelling, and erythema in active ischemic heart disease acetate to administration area)	Theoretical risk of transmission of infectious agents to thrombosis (very high off-label doses). Anaphylaxis (very rare). Formation of anti-C1-INH neutralizing antibodies

recognition of the disease by pediatricians. In general, pediatricians are the first physicians to evaluate a child with HAE, however they are responsible for only 3% of diagnoses of this disease.[94] Thus, it is very important to educate these professionals, highlighting warning signs for the diagnosis of HAE in children: positive family history, presence of recurrent abdominal pain and trauma as a triggering factor for angioedema crises.[95]

The drug treatment of HAE in childhood and adolescence uses the same strategies as adults, however, it is important to note that few clinical trials specifically target the pediatric age group, particularly in children under 12 years of age.[9]

In Brazil, so far, there are three products approved by ANVISA for the treatment of angioedema crises in this age group: two pdC1-INH (Berinert® and Cinryze®) and icatibant (Firazyr®).

pdC1-INH for IV use is effective and safe in the treatment of all forms of HAE attacks due to C1-INH deficiency in children and adolescents. Recent research with the use of pdC1-INH in the pediatric age group for a prolonged period has confirmed its efficacy and safety.[96] Berinert® is indicated for IV administration at a dose of 20 IU/kg, regardless of the severity of the crisis and without age restrictions. Another nanofiltered pdC1-INH, Cinryze® is approved for adolescents over 12 years of age at fixed doses (500 U or 1000 U).[10,97]

The safety and efficacy of icatibant (Firazyr®) have been studied in children.[98] Most patients started to resolve symptoms within an hour and the most common adverse event was reaction at the application site with spontaneous resolution. The recommended dose is 0.4 mg/kg in the age group from 2 to 17 years, over 12 kg, subcutaneously, exclusively in the abdominal region, with additional injections being possible every 6 hours, up to a maximum of three injections within 24 hours. It is presented in 3 mL pre-filled syringes containing 10 mg/mL icatibant. Doses can be adapted by weight [12 to 25 kg = 10 mg (1 mL); 26 to 40 kg = 15 mg (1.5 mL); 41 to 50 kg = 20 mg (2 mL); 51 to 65 kg = 25 mg (2.5 mL); >65 kg = 30 mg (3 mL)].

Fresh frozen plasma should be used at a dose of 10 mL/kg IV, only in emergency situations and in the absence of licensed drugs for crisis, due to side effects and its low efficacy with risk of paradoxical worsening.[98] Other options not available in Brazil, but used in other countries for the treatment of crises, include ecallantide (SC kallikrein inhibitor, over 12 years old) and Ruconest® (intravenous recombinant C1-INH concentrate, over 12 years old).[15,99]

Therefore, for the treatment of seizures in patients under 12 years of age, pdC1-INH for IV use (Berinert®), icatibant (Firazyr®) may be used in patients over two years of age, and fresh plasma in any age.

Tranexamic acid is indicated for long-term prophylaxis of children with HAE under 12 years of age, despite its low efficacy, given the impossibility of treatment with more effective drugs in use in adolescents and adults.[3,100] Lanadelumab (Takhzyro®) is currently only approved in patients over 12 years of age, showing high efficacy and a good safety profile, as demonstrated in the extension study in which 21 patients under 18 years of age were evaluated.[14] AAs should not be used in the pediatric age group, especially before puberty.[25,101] Other options approved by ANVISA with high efficacy and good safety profile include: IV pdC1-INH (Cinryze®, ≥ 12 years) and SC (Berinert® SC, ≥ 8 years) (Table 1). Adolescents with HAE may benefit from the use of continuous progestin from menarche, as it can help in the control of crises, since they inhibit the endogenous estrogen cycle, particularly in the HAE-nC1-INH.[101]

pdC1-INH (Berinert SC®) and lanadelumab (Takhzyro®) have significantly changed long-term prophylaxis as they are both safe, self-administered and released by subcutaneous infusion, which is an important advantage for use in children and teenagers.[2] However, additional studies are still needed to assess efficacy and safety in younger children.

Thus, for long-term prophylaxis in children under 8 years of age, tranexamic acid is currently available. Patients between 8 and 12 years of age can receive pdC1-INH SC (Berinert®), and those 12 years and older can receive long-term prophylaxis like adult patients, considering AA in those with Tanner stage V.

For short-term prophylaxis, the same pharmacotherapy strategies used in adults are recommended. It is important to point out that AA are not indicated for long-term prophylaxis in children before puberty, but they can be used for a short period before risky procedures.[3]

How should HAE be addressed during pregnancy, delivery, postpartum and lactation?

Anatomy, physiology and hormonal changes caused by pregnancy can influence the manifestations

and affect the course and treatment of HAE.[3] Estrogen is a trigger for seizures because it is related to the control of bradykinin production.[102] Thus, symptoms can become more frequent and more severe during pregnancy, after delivery and lactation.[8,59,103,104] During pregnancy, the disease may improve, worsen or there may be no impact on the frequency and severity of attacks, which makes it difficult to predict the evolution of patients.[105-107] Despite the divergent results, the tendency is for symptoms to worsen during the first trimester of pregnancy, when serum estrogen levels are higher and long-term prophylaxis with drugs contraindicated in pregnancy has to be discontinued. The second trimester has been described as the period of lowest disease activity due to permanently high levels of the other hormones. In the third trimester, increased production of placental estrogens and prolactin can increase the frequency and intensity of seizures.[103]

The frequency of seizures during previous pregnancies has no predictive value for the evolution of HAE in later pregnancies. Symptomatic patients are more likely to have premature labor or miscarriage due to bradykinin activity, which leads to uterine smooth muscle contraction.[103] An increase in the frequency and severity of seizures has been described in pregnant women with early onset of symptoms or who present trauma as an important triggering factor.[107] Pregnant women with HAE-C1-INH whose fetus has the same deficiency have a higher frequency of seizures in the gestational period than those whose fetuses are healthy.[108] It is believed that other factors not yet determined may lead to angioedema crises in pregnant women.[108] Pregnant women with AEH-nC1-INH generally have a greater number of seizures during pregnancy, particularly in AEH-FXII.[57,109-111]

The main triggers of crises in this period are stress and physical trauma.[112,113] The seizures occur in a location similar to that of the non-gestational period, and there may be a predilection for the abdomen, which makes the differential diagnosis difficult.[103] In these situations, abdominal ultrasound is useful in the diagnostic evaluation. In general, seizures are mild and rarely life-threatening.[113]

As for the mode of delivery, vaginal delivery is preferable to cesarean section. When there is an obstetric indication for cesarean delivery, epidural anesthesia is the best choice.[114] It is highly recommended that the hospital where the delivery will take place has trained personnel to care for HAE patients and that medication is available, both for prophylaxis and for the management of a possible crisis.[103]

Genetic counseling should be offered to patients with HAE, since there is a 50% chance that the offspring will also have the disease.[103]

When planning pregnancy, women who have been using long-term AA prophylaxis should discontinue treatment at least one month before conception. Androgens are not recommended during pregnancy, as they cross the placental barrier and can result in fetal virilization, leading to female pseudohermaphroditism.[3,15] It is recommended to carry out a beta-HCG measurement before starting AA administration in women of childbearing age.[15] Tranexamic acid also crosses the placental barrier and can cause side effects for the fetus, but to a lesser extent than those caused by AA.[3,8,15,103]

The treatment of crises during pregnancy includes the prescription of symptomatic drugs (analgesics), hydration and use of specific medication, when indicated.[103] The therapy of choice in the management of crises during pregnancy, childbirth, postpartum and breastfeeding is pdC1-INH in the same dosage as non-pregnant women.[2,3,15] Other drugs effective in crisis management, such as icatibant and recombinant C1-INH, were used during this period, with a good safety and efficacy profile.[115-117] There are no data on the use of ecallantide, and this drug is classified as Category C in pregnancy by the FDA.[103] Fresh frozen plasma can be administered in cases of severe crisis where pdC1-INH is not available.

In cases of HAE-C1-INH, when long-term prophylaxis is necessary, the first-line drug is pdC1-INH IV at a dose similar to that of non-pregnant women.[3,15,46,118] The pdC1-INH has been used for over two decades, with evidence of efficacy and safety in this population, being classified as category C by the FDA.[2] In women with HAE-nC1-INH, there are isolated reports that show efficacy and safety of pdC1-INH concentrate.[57,119] The SC administered pdC1-INH has not yet been sufficiently evaluated, but there are reported cases of use in pregnant women, with no evidence of risk to the fetus.[120,121]

When pdC1-INH is not available, tranexamic acid may be indicated, but its effectiveness has not been proven.[3] The dosage is similar to that prescribed for non-pregnant women. Although there are no data that corroborate a greater risk due to the prothrombotic effect, it is recommended to use it with caution in patients with a personal and/or family history of

thromboembolism.[122] There are currently no data available on the use of lanadelumab during pregnancy and therefore it should not be used.

Short-term prophylaxis during pregnancy should be considered in any procedure performed, particularly in interventions with risk of crises such as chorionic villus sampling, amniocentesis and surgically induced abortion.[3] The first-choice treatment is also the administration of pdC1-INH, 1 to 6 hours before the procedure, at a dose of 20 U/kg of weight or 1000 IU, depending on the drug.[15,103] The need for short-term prophylaxis for delivery is unclear. Most international consensuses suggest that prophylaxis should be indicated in cesarean delivery, but that in vaginal delivery, just having crisis medication available in the delivery room would be enough.[2,3,15] Prophylactic administration of pdC1-INH concentrate is also indicated in cases of need for intubation and for difficult deliveries requiring forceps or in patients without disease control during the third trimester.[2,3,103] There are isolated reports showing the efficacy of using pdC1-INH for short-term prophylaxis in the delivery of women with AEH-nC1-INH.[123] When short-term prophylaxis is indicated and pdC1-INH is not available, fresh frozen plasma and/or tranexamic acid can be administered.[3]

In the puerperium, crises usually occur immediately after delivery or within 48 hours after delivery, and can have serious consequences.[103,123] During this period, some women may experience angioedema of the vulva and infusion sites, as well as urethral obstruction and abdominal crises, and observation of the patient is recommended for 72 hours after delivery.[32,103,123] Studies show that, regardless of the type of delivery, crises are rare, even in the absence of prophylaxis.[106,107] After hospital discharge, the recommendations for home follow-up of postpartum women are the same as those given to non-pregnant women with HAE.[103]

During lactation, there may be an increase in the frequency and severity of HAE crises, interfering with breastfeeding.[124] Higher concentrations of prolactin appear to be responsible for the temporary increase in seizures after delivery.[107] AA and antifibrinolytics are excreted in human milk and, therefore, should be avoided during this period.[46,90] Even so, we can consider the use of tranexamic acid in the absence of pdC1-INH as prophylaxis.[32,90] Another therapeutic option for prophylaxis during lactation is the use of progesterone alone, without estrogen.[102] Even at low doses, progesterone alone is the contraceptive of choice during lactation, even in the early postpartum period[125] and has prophylactic potential in the management of AEH.[114]

The use of available drugs for the treatment of HAE with or without C1-INH deficiency is limited during pregnancy, childbirth, postpartum and lactation, but there are safe and available options. The pdC1-INH is the recommended first-line option in the management of these patients, both in prophylaxis and in the treatment of crises.[3]

Drugs for the therapeutic approach of HAE in pregnancy according to FDA categorization are summarized in Table 4.

Therefore, according to the latest international consensus, the treatment of AEH-C1-INH, including special groups (children, pregnant women and nursing mothers), includes first and second choice therapeutic options (Table 5).

What are the prospects in the treatment of hereditary angioedema?

In the last decades, the treatment of HAE has evolved from the use of nonspecific drugs for prophylaxis and treatment of crises (such as attenuated androgens, tranexamic acid and frozen plasma) to the use of specific drugs considered first-line. First-line drugs target the replacement of C1-INH and, more recently, molecules aimed at controlling plasma kallikrein-kinins system proteins.[1-3,15]

With the availability of effective and safe drugs for the treatment of angioedema attacks, most drugs under development work for long-term prophylaxis. Several studies are also being conducted with the aim of expanding the age group and adding other indications for existing products. Most new drugs in development currently target factor XII, plasma kallikrein and the B2 kinin receptor (B2R). The new prophylactic therapies aim to provide greater dosage convenience, with an increase in the interval between IV or SC applications, and to develop drugs for oral administration.

Among the new drugs already available in other countries, berotralstat (BCX7353) (BioCryst Pharmaceuticals, Inc) has been approved by the FDA and EMA (European Medicines Agency). It is a small synthetic molecule that inhibits plasma kallikrein, administered orally, which has been shown to be safe and effective in long-term prophylaxis. In the latest international consensus on hereditary angioedema,

together with the plasma-derived C1-INH concentrate and lanadelumab, this molecule was considered one of the first options for long-term prophylaxis due to its efficacy and its oral administration.[3] Some side effects have been described: abdominal pain, vomiting, diarrhea and low back pain.[127] These reactions occur soon after the start of treatment, becoming less frequent with time and are usually self-limiting.[128]

At least six new drugs intended for HAE prophylaxis or treatment of seizures are in phase 1, 2 and 3 clinical trials (Table 6). Among these medications, three act by inhibiting plasma kallikrein, with oral administration, two of which are intended for long-term prophylaxis and one for the treatment of angioedema crises.[129-134] Donidarsolen (IONIS PKK-LRx) is a new drug for the treatment of AEH-C1-INH based on the use of a second-generation antisense oligonucleotide, which targets the gene encoding plasma prekallikrein with significant clinical efficacy, safety and tolerance in long-term prophylaxis.[135-137] Garadacimab® (CSL312, CSL Behring) is a subcutaneously administered monoclonal antibody that targets factor XIIa, in development for long-term prophylaxis in HAE-C1-INH, showing an average reduction of monthly HAE attacks above 90%.[138] The drug PHA-022121® (Pharvaris) proved to be a potent antagonist of the bradykinin B2 receptor (B2R) with oral administration and is currently being evaluated for the treatment of seizures and long-term prophylaxis in patients with HAE-C1-INH.[139-141]

The perspectives of gene therapy for AEH-C1-INH have become closer using adenoviral vectors (AAV) in the expression of normal copies of the gene encoding C1-INH.[142-144] In another innovative approach, NTLA-2002®, still in the pre-clinical phase, was based on the use of the "clustered regularly interspaced short palindromic repeats" (CRISPR)/Cas^9 system in the in vivo edition of the prekallikrein gene, generating a process of gene knockout.[145]

Considering the new treatments already approved and some of the perspectives of therapy for HAE-C1-INH, most of the contact pathway and fibrinolysis can

Table 4
Medications used in the approach tohereditary angioedemaduring pregnancy[126]

Scientific name	Commercial name	Indication in the HAE	Category (FDA)
Danazol	Ladogal®	Prophylaxis	X
Tranexamic acid	Transamin®	Prophylaxis	B
	Hemoblock®	Prophylaxis	
pdC1-INH	Berinert®	Crisis	C
pdC1-INH	Cinryze®	Prophylaxis	C
rhC1-INH [a]	Ruconest®	Prophylaxis	B
		Crisis	
Icatibanto	Firazyr®	Crisis	C
Ecalantid [a]	Kalbitor®	Crisis	C
Lanadelumab	Takhzyro®	Prophylaxis	Not defined

[a] Medicines not approved by ANVISA for use in Brazil.
HAE = hereditary angioedema, FDA = Food and Drug Administration, pdC1-INH = plasma-derived C1 inhibitor concentrate, rhC1-INH = recombinant C1 inhibitor.

Table 5
AEH-C1-INH treatment strategies approved in Brazil for different patient populations according to the recommendations of the latest international consensus[2,3,15]

Population	Treatment line	Treatment strategies		
		Prophylaxis		Crisis
		Long term	Short term	
Adults and elderly	First	pdC1-INH (SC, EV) Lanadelumab Berotralstat [a]	pdC1-INH EV	pdC1-INH EV Icatibanto
	Second	Attenuated androgens [b] Tranexamic acid	Attenuated androgens Plasma	Plasma
Children and teenagers	First	pdC1-INH EV pdC1-INH SC > 8 years Lanadelumab > 12 years	pdC1-INH EV	pdC1-INH EV Icatibanto > 2 years
	Second	Tranexamic acid Attenuated androgens after puberty	Attenuated androgens Plasma	Plasma
Pregnant women	First	pdC1-INH (SC [a], EV)	pdC1-INH EV	pdC1-INH EV
	Second	Tranexamic acid	Plasma	Plasma

[a] Not approved in Brazil.
[b] Maximum dose of 200 mg (danazol).
pdC1-INH = plasma-derived C1 inhibitor concentrate, IV = intravenous, SC = subcutaneous.

now be controlled, which may result in a lower action of bradykinin, with improvement or prevention of attacks of angioedema (Figure 3).

What are the tools for monitoring the quality of life, activity and control of hereditary angioedema?

HAE crises can cause not only physical damage, but also psychological damage, such as fear of death from asphyxia during laryngeal crises, fear of not having the specific medication in case of crisis, fear of not having a doctor who knows your disease in case of care of urgency, guilt for transmitting the disease to their children, among many others.[146] In addition, the unpredictable and potentially fatal aspect of the disease often leads to anxiety, depression, stress or the risk of other mental disorders, with marked impairment of the quality of life of patients and their families.[147-156]

In the last three decades, it has become common to objectively assess quality of life (QoL) in various diseases, but the impact of HAE on the QoL of affected patients has only recently been studied.[157,158]

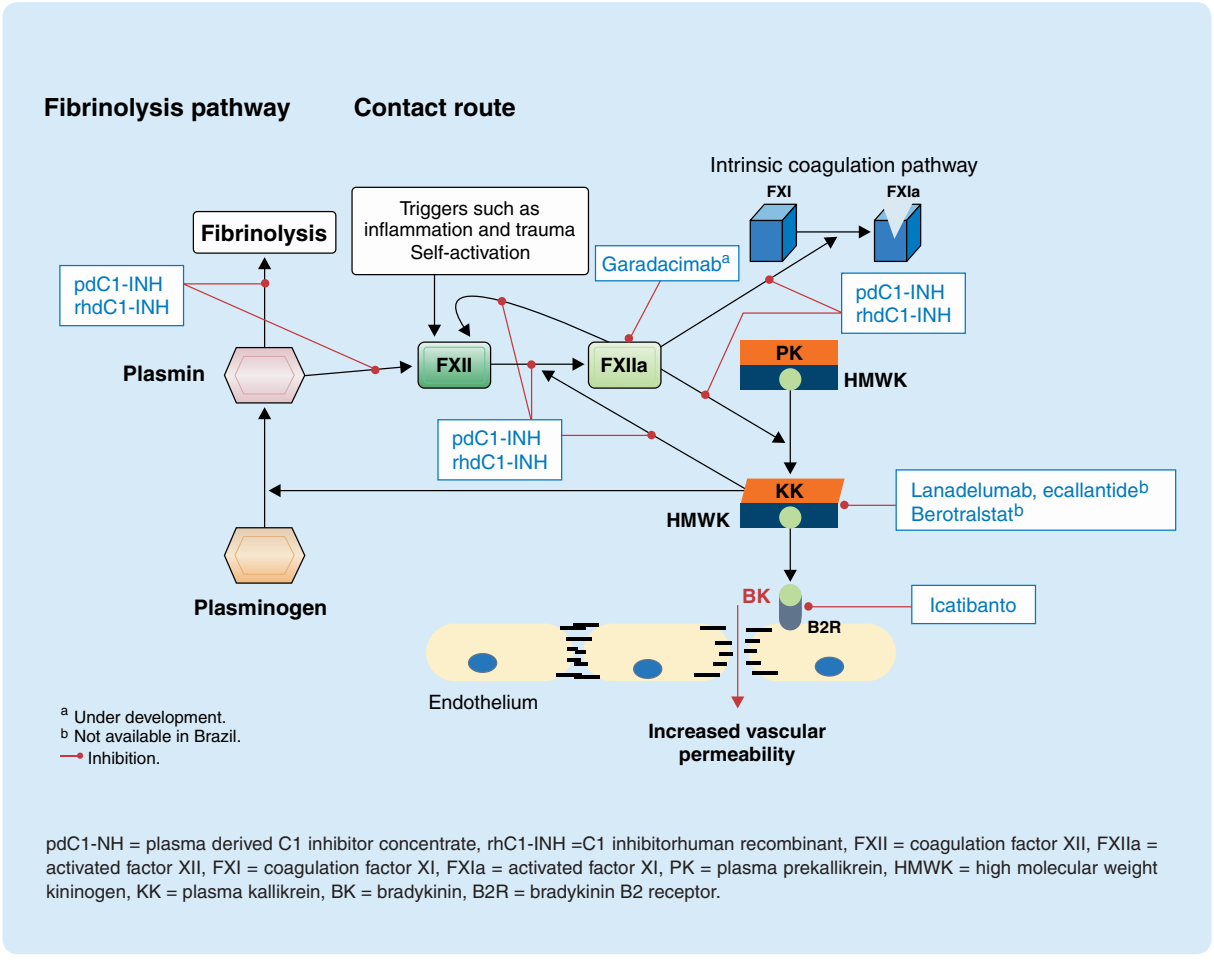
It is well established that HAE profoundly affects the quality of life of those affected, both in the physical, psychological and social spheres.[22] Objectively measuring the QoL of these patients can contribute to improve the therapeutic approach and assess the response to the instituted treatment.

There are two questionnaires to assess the QoL of HAE patients over 18 years of age. The Hereditary Angioedema Quality of Life questionnaire (HAE-QoL) addresses seven domains: physical and health aspects, disease-related stigmas, social and emotional aspects, concern for offspring, perceived control over the disease, mental health and treatment difficulties, with score from 25 to 135, where 25 is the worst general health status, and 135 the best.[119-161] The Angioedema Quality of Life questionnaire (AE-Qol) is a symptom-specific questionnaire for any type of recurrent angioedema, and covers four dimensions:

Table 6
New treatments for hereditary angioedema in phase 1, 2 and 3 clinical studies*

Treatment	Administration	Name	Mechanism	Study phase
PLP	Oral	ATN-249® (Attune Pharmaceuticals)	CP inhibitor	Phase 1 completed[a]
		KVD824® (KalVista Pharmaceuticals)	CP inhibitor	Phase 1 completed[a]
	Subcutaneous	Garadacimab® (CSL Behring)	Anti-factor XII monoclonal antibody	Phase 2 finished and phase 3 recruiting[b]
		IONIS-PKK-LRx® (IONIS Pharmaceuticals)	Antisense oligonucleotide for CP	Phase 2 finished and phase 3 recruiting[b]
PLP and crisis	Oral	PHA-022121® (Pharvaris)	Antagonist B2 receptor	Phase 2 recruiting[b]
Crisis	Oral	KVD900® (Kalvista Pharmaceuticals)	CP inhibitor	Phase 2 completed[b]

* Second access in February/2022.
[a] Registered with the Australian New Zealand Clinical Trials Registry.
[b] Source: US National Library of Medicine – ClinicalTrials.gov.
B2R = bradykinin B2 receptor, PLP = long-term prophylaxis, CP = plasma kallikrein.



pdC1-NH = plasma derived C1 inhibitor concentrate, rhC1-INH =C1 inhibitorhuman recombinant, FXII = coagulation factor XII, FXIIa = activated factor XII, FXI = coagulation factor XI, FXIa = activated factor XI, PK = plasma prekallikrein, HMWK = high molecular weight kininogen, KK = plasma kallikrein, BK = bradykinin, B2R = bradykinin B2 receptor.

Figure 3
Site of action in the fibrinolysis and contact pathways of different therapies for hereditary angioedema with C1-INH2-4 deficiency

functional capacity, fatigue, fear and eating, with a score from 0 to 100, where zero corresponds to the best general health status, and 100 for the worst.[162] The AE-QoL has been used in clinical studies to evaluate the effect of new therapies for AEH.[163]

The Angioedema Activity Score (AAS) was the first instrument developed to assess angioedema activity. It is validated for all forms of recurrent angioedema, including HAE, where patients document the presence or absence of angioedema in the last 24 hours. If angioedema is present, five additional questions must be answered, each with a score of 0 to 3 points. According to the period of time the symptoms were recorded, the minimum and maximum scores for AAS consist of: 0 to 15 (AAS: daily); 0 to 105 (AAS7: weekly) and 0 to 420 (AAS28: monthly).[164]

Recently, the Angioedema Control Test (AECT) was developed, which is the first tool to assess disease control in patients with any type of recurrent angioedema.[165] It consists of four questions, related to frequency, quality of life, unpredictability of the disease, and treatment, with a score from 0 to 16, where 16 is total control, with a score ≥ 10 meaning good control, and < 10 the lack of control. In Brazil, the EGTC is in the process of validation.

All these tools make it possible to measure the quality of life, activity and control of the HAE and help in the management of the disease, as they allow a broader and more objective understanding, helping to adjust the treatment of patients with HAE. However, there is a need to standardize the use of these tools in children and their caregivers.

How do hereditary angioedema patient associations work and what are the functions?

The first associations of patients with chronic diseases appeared in the 1950s and, since then, there has been a growing movement to strengthen these institutions. In the last decades, this movement was based on the assertions that these patients are a group that faces similar obstacles, the shared experiences constitute a different knowledge from that of health professionals and that it was legitimate for the patient to have the right to have an opinion in decisions about his illness. Strategies to value patients and caregivers can improve health outcomes, leading to effective decision making, management of disease complications, better health behavior, strengthening of support groups and efficient use of health services.[166]

In this context, associations of patients with hereditary angioedema (HAE) were created in several countries, with the aim of giving greater visibility and disseminating information about the existence of this disease, offering broad support to patients, family members and caregivers of patients with HAE. These institutions defend the idea that, in all parts of the world, patients with HAE should have access to all the necessary resources to control their symptoms, and with that, guarantee an adequate quality of life that allows them to carry out their activities in work, school and the improvement of interpersonal relationships.[3]

Internationally, Hereditary Angioedema International (HAEi) is a global, non-profit network of patient associations that was created with the aim of improving the lives of individuals with HAE. HAEi, which currently has 93 member countries, provides its member organizations with specially designed tools and technical assistance to promote disease education and support activities that meet the unique needs of HAE patients and their families. In addition, it also works to encourage clinical research in the generation of several new drugs for the treatment of HAE, in partnership with Angioedema Reference and Excellence Centers (ACARE) to further improve the quality of clinical care and patient care.[13]

In Brazil, the Brazilian Association of Hereditary Angioedema (Abranghe) was founded in April 2010 through the initiative of HAE patients. Abranghe has also been working to provide support and represent the interests of HAE carriers. This association offers information about the disease, main reference centers specializing in HAE in the country, provides educational materials and participates in national and international events. In addition, it registers patients with a confirmed diagnosis of the disease and provides them with an identification card. Contact with Abranghe can be made by phone, email or social media.[167]

It should be noted that an important role of patient associations is to raise awareness among managers regarding the recognition of HAE as a disabling and potentially fatal chronic condition. Therefore, these entities can assist in the elaboration of public policies to improve access to diagnostic and therapeutic means, thus aiming to reduce morbidity and mortality and provide a more dignified life to these patients. As an example of these policies, Ordinance GM/MS n°199 of 01/30/2014 instituted the national policy of comprehensive care for people with rare diseases, approved the guidelines for comprehensive care for people with rare diseases in the SUS and instituted financial incentives for funding the diagnosis of these diseases.[168]

Access to treatment, considered expensive, has still been a major challenge faced by associations that fight for the rights of HAE patients. Within the scope of the SUS, in almost all Brazilian states, access to medicines occurs most of the time, by judicialization. In the private service, health operators rarely release the drugs indicated for prophylaxis and for crisis. This demonstrates that these policies still need to be improved so that everyone is guaranteed access to treatment.

It is the role of HAE patient associations to educate patients and caregivers, inform the general population about the disease and raise awareness of HAE-related problems, in order to gain social legitimacy and give visibility to their demands. It is also vitally important that leaders and associations understand the complexities, laws, guidelines and processes involved in accessing medicines, as this will lead to immeasurable benefits for patients with this disease.[169]

Final considerations

Specialists from the Brazilian Association of Allergy and Immunology (ASBAI) and the Brazilian Study Group on Hereditary Angioedema (GEBRAEH) have updated these guidelines for HAE therapy, with the aim of helping health professionals in the identification and management of this disease. The HAE is currently less neglected, but it is still necessary to continue progressing with a critical eye on the new challenges and striving for better care for HAE patients.

All medicines approved for HAE in Brazil so far can be self-administered at home, which is a fundamental aspect in our country, because in many places access to health units is precarious, and early treatment of a crisis is very important, whether for presenting better results, as well as reducing the patient's suffering.

New drugs for long-term prophylaxis such as pdC1-INH SC and lanadelumab, with specific actions on the kinin-kallikrein system, have the potential to significantly reduce the number of seizures, in addition to being administered subcutaneously, contributing to significant improvement in the quality of life of patients. Although the cost of these drugs is high, some patients with severe and very frequent attacks, and who do not improve even with the use of attenuated androgens, need access to them. It should be emphasized that the use of preventive therapies for seizures does not replace the need for access to medication for the treatment of seizures.

Other drugs will emerge with the potential to further improve the care of these patients. The specialist in Allergy and Immunology plays a key role in this process, requiring a more up-to-date and comprehensive knowledge of hereditary angioedema.

Important challenges remain patient access to the newest and most effective drugs, and drug release to pediatric patients.

Final guidelines for the treatment of hereditary angioedema with C1 inhibitor deficiency are summarized in Table 7.

Table 7
Guidelines for the treatment of hereditary angioedema with C1-INH deficiency in Brazil

Treatment strategies	Prevent seizures, prescribe medication for prophylaxis (short and long term) and treatment of seizures (on demand).
Crisis prevention	Treat infections early, control stress, provide guidance on the use of drugs that can trigger crises, prescribe vaccination to prevent infections, among others.
Short term prophylaxis	Indicate before procedures such as dental treatment or endoscopy. Plasma-derived C1 inhibitor concentrate (first-line treatment) may be used. If there is no access, attenuated androgens (second-line treatment) are suggested. In the absence of concentrateC1 inhibitorderived from plasma, fresh frozen plasma may be prescribed.
Long term prophylaxis	Indicate the C1 inhibitor concentrate, subcutaneously (preferably) or intravenously to be applied every 3 or 4 days, or the antikallikrein monoclonal antibody (lanadelumab) to be applied subcutaneously every 2 weeks (treatments of first line). In Brazil, first-line drugs are approved by ANVISA. However, only the attenuated androgen danazol (second-line treatment) is available in the SUS, which should be prescribed at the maximum recommended dose (200 mg/day) as suggested by international consensus.

Table 7 *(continuation)*
Guidelines for the treatment of hereditary angioedema with C1-INH deficiency in Brazil

Choice of long-term prophylactic treatment strategy	Evaluate clinical and laboratory criteria. Consider contraindications to the use of attenuated androgens, such as pregnancy, breastfeeding, severe liver, kidney or heart failure; porphyria; androgen-dependent tumor; abnormal vaginal bleeding not yet diagnosed, active thrombosis or thromboembolic disease, history of both events and concomitant use with simvastatin.
Sustainability of the Brazilian Health System for long-term prophylaxis	Indicate the use of androgen – at the maximum recommended dose (200 mg/day) as suggested by international consensus (second-line treatments). According to the response to treatment, contraindication or adverse events to the use of androgens, which must be evaluated by reference centers, the use of C1 inhibitor and lanadelumab (first-line treatments) is considered. Response to treatment is evaluated by disease control, time to reduction of signs and symptoms, quality of life and adverse events.
Crisis treatment	Indicate icatibant (bradykinin B2 receptor antagonist) or plasma-derived C1 inhibitor concentrate (first-line treatments). In Brazil, these two drugs are approved by ANVISA, but not available in the SUS. In the absence of first-line drugs, fresh frozen plasma may be prescribed. All seizures must be treated, however, seizures that affect the extremities are at lower risk. Despite advances in HAE treatment in recent years, access to treatment is very limited in Brazil.

ACTION PLAN FOR PATIENTS WITH HEREDITARY ANGIOEDEMA

_____has a diagnosis of hereditary angioedema.

Hereditary angioedema (HAE) is characterized by recurrent episodes of edema in different parts of the body, which may occur simultaneously or not, such as lips, eyelids, larynx, hands, and feet, as well as bouts of abdominal pain, with or without nausea, vomiting, and diarrhea due to intestinal loop edema. Abdominal pain is typically intense and may simulate acute abdomen.

SIGNS AND SYMPTOMS OF HAE:

Cutaneous edema	Typically involves feet and hands.
Abdominal edema	Characterized by severe abdominal pain, nausea, vomiting, and diarrhea.
Glottic/airway edema	Compromises breathing and requires immediate medical evaluation. The following may be present: voice alteration and difficulty swallowing.
Prodromes (warning signs of HAE attack onset)	Tingling sensation, redness, tiredness, or nausea.

This type of angioedema is non-allergic and therefore does not respond to antihistamines, corticosteroids, and adrenaline.

If a patient experiencing a HAE attack arrives at your health center, **one** of the following medications should be administered:

Medication	Dosage and administration	Storage and handling	When to re-treat
Icatibant injection (Firazyr®) Patients ≥ 2 years	Dose:_____ (_____) Route: subcutaneous. Region: abdomen.	Storage: 2ºC to 8ºC. Do not freeze.	Additional doses may be administered at intervals of at least 6 hours. Do not administer more than 3 doses in 24 hours.
Plasma-derived human C1-inhibitor – pdC1INH (Berinert®) No age restrictions.	Dose: 20 UI/kg Route: intravenous. Flow rate: 4 mL/min. 1 vial/ampoule: 500 UI.	Storage: 15ºC to 30ºC. Do not freeze. The vial should be stored in the original package to protect from light.	An additional dose may be administered after 1 hour.
Plasma-derived human C1-inhibitor – pdC1INH (Cinryze®) Patients ≥ 12 years	Dose: 1,000 UI Route: intravenous. Flow rate: 4 mL/min. 1 vial/ampoule: 500 UI.	Storage: 2ºC to 8ºC. Do not freeze. The vial should be stored in the original package to protect from light.	An additional dose may be administered after 1 hour. In laryngeal attacks, a second dose may be administered before 1 hour, if necessary.

If none of these medications are available, supportive care should be conducted, and frozen fresh plasma (FFP) should be administered – 10 mL/kg, maximum of 2 to 4 units of FFP, which contains approximately 200 mL/unit.

If the patient shows signs of upper airway obstruction and asphyxia (dyspnea, stridor, hoarseness, difficulty swallowing, sensation of tightness in the throat, drop in O2 saturation level), early orotracheal or nasopharyngeal intubation should be strongly considered.

For questions, please contact us via phone: (__).

Sincerely,
Physician's name and regional medical board number:
Name of follow-up health center:

Observations:_____
_____
_____

Appendix 1
Action plan for patients with hereditary angioedema

References

1. Maurer M, Aygören-Pürsün E, Banerji A, Bernstein JA, Balle Boysen H, Busse PJ, et al. Consensus on Treatment Goals in Hereditary Angioedema: A Global Delphi Initiative. J Allergy Clin Immunol. 2021;148(6):1526-32. doi: 10.1016/j.jaci.2021.05.016.
2. Busse PJ, Christiansen SC, Riedl MA, Banerji A, Bernstein JA, Castaldo AJ, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. J Allergy Clin Immunol Pract. 2021;9(1):132-50.e3. doi: 10.1016/j.jaip.2020.08.046.
3. Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, et al. The International WAO/EAACI Guideline for the Management of Hereditary Angioedema - The 2021 Revision and Update. Allergy. 2022. doi: 10.1111/all.15214.
4. Caballero T. Treatment of Hereditary Angioedema. J Investig Allergol Clin Immunol. 2021;31(1):1-16. doi: 10.18176/jiaci.0653.
5. Riedl MA. Creating a Comprehensive Treatment Plan for Hereditary Angioedema. Immunol Allergy Clin North Am. 2013;33(4):471-85. doi: 10.1016/j.iac.2013.07.003.
6. Settipane RA, Bukstein DA, Riedl MA. Hereditary Angioedema and Shared Decision Making. Allergy Asthma Proc. 2020;41(Suppl 1):S55-S60. doi: 10.2500/aap.2020.41.200057.
7. Campos R de A, Valle SOR, Toledo EC. Hereditary Angioedema: A Disease Seldom Diagnosed by Pediatricians. J Pediatr (Rio J) 2021;97 Suppl 1:S10-S16. doi: 10.1016/j.jped.2020.10.011.
8. Farkas H, Martinez-Saguer I, Bork K, Bowen T, Craig T, Frank M, et al. International Consensus on the Diagnosis and Management of Pediatric Patients with Hereditary Angioedema with C1 Inhibitor Deficiency. Allergy. 2017;72(2):300-13. doi: 10.1111/all.13001.
9. Pancholy N, Craig T. Hereditary Angioedema in Children: A Review and Update. Curr Opin Pediatr. 2019;31(6):863-8. doi: 10.1097/MOP.0000000000000832.
10. Craig T, Aygören-Pürsün E, Bork K, Bowen T, Boysen H, Farkas H, et al. WAO Guideline for the Management of Hereditary Angioedema. World Allergy Organ J. 2012;5(12):182-9. doi: 10.1097/WOX.0b013e318279affa.
11. Dagen C, Craig TJ. Treatment of Hereditary Angioedema: Items that need to be addressed in practice parameter. Allergy Asthma Clin Immunol. 2010;6(1):11. doi: 10.1186/1710-1492-6-11.
12. Valle SOR, França AT, Campos RA, Grumach AS. Angioedema Hereditário. Rev bras alerg imunopatol. 2010;33(3):80-7.
13. Paige D, Maina N, Anderson JT. Hereditary Angioedema: Comprehensive Management Plans and Patient Support. Allergy Asthma Proc. 2020;41(Suppl 1):S38-S42. doi: 10.2500/aap.2020.41.200059.
14. Banerji A, Anderson J, Johnston DT. Optimal Management of Hereditary Angioedema: Shared Decision-Making. J Asthma Allergy. 2021;14:119-25. doi: 10.2147/JAA.S284029.
15. Betschel S, Badiou J, Binkley K, Borici-Mazi R, Hébert J, Kanani A, et al. The International/Canadian Hereditary Angioedema Guideline. Allergy Asthma Clin Immunol. 2019;15(1):72. doi: 10.1186/s13223-019-0376-8.
16. Caballero T, Baeza ML, Cabañas R, Campos A, Cimbollek S, Gómez-Traseira C, et al. Consensus Statement on the Diagnosis, Management, and Treatment of Angioedema Mediated by Bradykinin. Part I. Classification, Epidemiology, Pathophysiology, Genetics, Clinical Symptoms, and Diagnosis. J Investig Allergol Clin Immunol. 2011;21(5):333-47.
17. Brasil. Ministério da Saúde. Manual dos Centros de Referência para Imunobiológicos Especiais. 5th ed., 2019.
18. Serpa FS, Mansour E, Aun MV, Giavina-Bianchi P, Chong HJ, Arruda LK, et al. Hereditary Angioedema: How to Approach It at the Emergency Department? Einstein (São Paulo). 2021;19:eRW5498. doi: 10.31744/einstein_journal/2021RW5498.
19. Fijen LM, Levi M, Cohn DM. COVID-19 Vaccination and the Risk of Swellings in Patients with Hereditary Angioedema. J Allergy Clin Immunol Pract. 2021;9(11):4156-8. doi: 10.1016/j.jaip.2021.08.039.
20. Valle SOR, Alonso MLO, Tortora RP, Abe AT, Levy SAP, Dortas SD. Hereditary Angioedema: Screening of First-Degree Blood Relatives and Earlier Diagnosis. Allergy Asthma Proc. 2019;40(4):279-81. doi: 10.2500/aap.2019.40.4213.
21. Giavina-Bianchi P, Arruda LK, Aun MV, Campos RA, Chong-Neto HJ, Constantino-Silva RN, et al. Diretrizes brasileiras para o diagnóstico e tratamento do angioedema hereditário - 2017. Arq Asma Alerg Imunol. 2017;1(1):23-48. doi: 10.5935/2526-5393.20170005.
22. Bork K, Anderson JT, Caballero T, Craig T, Johnston DT, Li HH, et al. Assessment and Management of Disease Burden and Quality of Life in Patients with Hereditary Angioedema: A Consensus Report. Allergy Asthma Clin Immunol. 2021;17(1):40. doi: 10.1186/s13223-021-00537-2.
23. Cicardi M, Castelli R, Zingale LC, Agostoni A. Side Effects of Long-Term Prophylaxis with Attenuated Androgens in Hereditary Angioedema: Comparison of Treated and Untreated Patients. J Allergy Clin Immunol. 1997;99(2):194-6. doi: 10.1016/s0091-6749(97)70095-2.
24. Füst G, Farkas H, Csuka D, Varga L, Bork K. Long-Term Efficacy of Danazol Treatment in Hereditary Angioedema. Eur J Clin Invest. 2011;41(3):256-62. doi: 10.1111/j.1365-2362.2010.02402.x.
25. Riedl MA. Critical Appraisal of Androgen Use in Hereditary Angioedema: A Systematic Review. Ann Allergy Asthma Immunol. 2015;114(4):281-288.e7. doi: 10.1016/j.anai.2015.01.003.
26. Cicardi M, Bork K, Caballero T, Craig T, Li HH, Longhurst H, et al. Evidence-Based Recommendations for the Therapeutic Management of Angioedema Owing to Hereditary C1 Inhibitor Deficiency: Consensus Report of an International Working Group. Allergy. 2012;67(2):147-57. doi: 10.1111/j.1398-9995.2011.02751.x.
27. Sheffer AL, Austen KF, Rosen FS. Tranexamic Acid Therapy in Hereditary Angioneurotic Edema. N Engl J Med. 1972;287(9):452-4. doi: 10.1056/NEJM197208312870907.
28. Wintenberger C, Boccon-Gibod I, Launay D, Fain O, Kanny G, Jeandel PY, et al. Tranexamic Acid as Maintenance Treatment for Non-Histaminergic Angioedema: Analysis of Efficacy and Safety in 37 Patients. Clin Exp Immunol. 2014;178(1):112-7. doi: 10.1111/cei.12379.
29. Tengborn L, Blombäck M, Berntorp E. Tranexamic Acid – an Old Drug Still Going Strong and Making a Revival. Thromb Res. 2015;135(2):231-42. doi: 10.1016/j.thromres.2014.11.012.
30. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 Inhibitor Concentrate for Treatment of Hereditary Angioedema. N Engl J Med. 2010;363(6):513-22. doi: 10.1056/NEJMoa0805538.
31. Terpstra FG, Kleijn M, Koenderman AHL, Over J, van Engelenburg FAC, Schuitemaker H, et al. Viral Safety of C1-Inhibitor NF. Biologicals. 2007;35(3):173-81. doi: 10.1016/j.biologicals.2006.08.005.
32. Maurer M, Magerl M, Ansotegui I, Aygören-Pürsün E, Betschel S, Bork K, et al. The International WAO/EAACI Guideline for the Management of Hereditary Angioedema-The 2017 Revision and Update. Allergy. 2018;73(8):1575-1596. doi: 10.1111/all.13384.
33. Bork K, Hardt J. Hereditary Angioedema: Long-Term Treatment with One or More Injections of C1 Inhibitor Concentrate per Week. Int Arch Allergy Immunol. 2011;154(1):81-8. doi: 10.1159/000319213.
34. Waytes AT, Rosen FS, Frank MM. Treatment of Hereditary Angioedema with a Vapor-Heated C1 Inhibitor Concentrate. N Engl J Med. 1996;334(25):1630-4. doi: 10.1056/NEJM199606203342503.
35. Tallroth GA. Long-Term Prophylaxis of Hereditary Angioedema with a Pasteurized C1 Inhibitor Concentrate. Int Arch Allergy Immunol. 2011;154(4):356-9. doi: 10.1159/000321830.

36. Kreuz W, Martinez-Saguer I, Aygören-Pürsün E, Rusicke E, Heller C, Klingebiel T. C1-Inhibitor Concentrate for Individual Replacement Therapy in Patients with Severe Hereditary Angioedema Refractory to Danazol Prophylaxis. Transfusion. 2009;49(9):1987-95. doi: 10.1111/j.1537-2995.2009.02230.x.

37. Frank MM. Hereditary Angiodema: A Current State-of-the-Art Review, VI: Novel Therapies for Hereditary Angioedema. Ann Allergy Asthma Immunol 2008;100(1 Suppl 2):S23-29. doi: 10.1016/s1081-1206(10)60583-2.

38. Bernstein JA, Ritchie B, Levy RJ, Wasserman RL, Bewtra AK, Hurewitz DS, et al. Population Pharmacokinetics of Plasma-Derived C1 Esterase Inhibitor Concentrate Used to Treat Acute Hereditary Angioedema Attacks. Ann Allergy Asthma Immunol. 2010;105(2):149-54. doi: 10.1016/j.anai.2010.06.005.

39. Zuraw BL, Cicardi M, Longhurst HJ, Bernstein JA, Li HH, Magerl M, et al. Phase II Study Results of a Replacement Therapy for Hereditary Angioedema with Subcutaneous C1-Inhibitor Concentrate. Allergy. 2015;70(10):1319-28. doi: 10.1111/all.12658.

40. Reshef A, Moldovan D, Obtulowicz K, Leibovich I, Mihaly E, Visscher S, et al. Recombinant Human C1 Inhibitor for the Prophylaxis of Hereditary Angioedema Attacks: A Pilot Study. Allergy. 2013;68(1):118-24. doi: 10.1111/all.12060.

41. Farkas H, Varga L. Human Plasma-Derived, Nanofiltered, C1-Inhibitor Concentrate (Cinryze®), a Novel Therapeutic Alternative for the Management of Hereditary Angioedema Resulting from C1-Inhibitor Deficiency. Biol Ther. 2012;2:2. doi: 10.1007/s13554-012-0002-5.

42. Craig TJ, Bewtra AK, Bahna SL, Hurewitz D, Schneider LC, Levy RJ, et al. C1 Esterase Inhibitor Concentrate in 1085 Hereditary Angioedema Attacks - Final Results of the I.M.P.A.C.T.2 Study. Allergy. 2011;66(12):1604-1611. doi: 10.1111/j.1398-9995.2011.02702.x.

43. Gandhi PK, Gentry WM, Bottorff MB. Thrombotic Events Associated with C1 Esterase Inhibitor Products in Patients with Hereditary Angioedema: Investigation from the United States Food and Drug Administration Adverse Event Reporting System Database. Pharmacotherapy. 2012;32(10):902-9. doi: 10.1002/j.1875-9114.2012.01126.

44. Farkas H, Kohalmi KV, Veszeli N, Zotter Z, Várnai K, Varga L. Risk of Thromboembolism in Patients with Hereditary Angioedema Treated with Plasma-Derived C1-Inhibitor. Allergy Asthma Proc. 2016;37(2):164-70. doi: 10.2500/aap.2016.37.3933.

45. Crowther M, Bauer KA, Kaplan AP. The Thrombogenicity of C1 Esterase Inhibitor (Human): Review of the Evidence. Allergy Asthma Proc. 2014;35(6):444-53. doi: 10.2500/aap.2014.35.3799.

46. Longhurst H, Cicardi M, Craig T, Bork K, Grattan C, Baker J, et al. Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. N Engl J Med. 2017;376(12):1131-40. doi: 10.1056/NEJMoa1613627.

47. Brasill. Ministério Da Saúde. Agência Nacional de Vigilância Sanitária (ANVISA). Bulário Eletrônico. Berinert: Pó Liofilizado Para Solução Injetável. Bula Profissional do Medicamento [Internet]. Brasília (DF): ANVISA; 2021. Available from: https://Consultas.Anvisa.Gov.Br/#/Bulario/q/?NomeProduto=berinert. 2021.

48. Craig T, Zuraw B, Longhurst H, Cicardi M, Bork K, Grattan C, et al. Long-Term Outcomes with Subcutaneous C1-Inhibitor Replacement Therapy for Prevention of Hereditary Angioedema Attacks. J Allergy Clin Immunol Pract. 2019;7(6):1793-1802.e2. doi: 10.1016/j.jaip.2019.01.054.

49. Zuraw B, Cicardi M, Levy RJ, Nuijens JH, Relan A, Visscher S, et al. Recombinant Human C1-Inhibitor for the Treatment of Acute Angioedema Attacks in Patients with Hereditary Angioedema. J Allergy Clin Immunol. 2010;126(4):821-7.e14. doi: 10.1016/j.jaci.2010.07.021.

50. Riedl MA, Bernstein JA, Li H, Reshef A, Lumry W, Moldovan D, et al. Recombinant Human C1-Esterase Inhibitor Relieves Symptoms of Hereditary Angioedema Attacks: Phase 3, Randomized, Placebo-Controlled Trial. Ann Allergy Asthma Immunol. 2014;112(2):163-9.e1. doi: 10.1016/j.anai.2013.12.004.

51. Farrell C, Hayes S, Relan A, van Amersfoort ES, Pijpstra R, Hack CE. Population Pharmacokinetics of Recombinant Human C1 Inhibitor in Patients with Hereditary Angioedema. Br J Clin Pharmacol. 2013;76(6):897-907. doi: 10.1111/bcp.12132.

52. Hemperly SE, Agarwal NS, Xu Y-Y, Zhi Y-X, Craig TJ. Recent Advances in the Management of Hereditary Angioedema. J Am Osteopath Assoc. 2013;113(7):546-55. doi: 10.7556/jaoa.2013.006.

53. Banerji A, Riedl MA, Bernstein JA, Cicardi M, Longhurst HJ, Zuraw BL, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018;320(20):2108-21. doi: 10.1001/jama.2018.16773.

54. Riedl MA, Maurer M, Bernstein JA, Banerji A, Longhurst HJ, Li HH, et al. Lanadelumab Demonstrates Rapid and Sustained Prevention of Hereditary Angioedema Attacks. Allergy 2020;75(11):2879-2887. doi: 10.1111/all.14416.

55. Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária (ANVISA). Bulário Eletrônico. Takhzyro: Solução Injetável. Bula Profissional do Medicamento [Internet]. Brasília (DF): ANVISA; 2021. Available from: https://Consultas.Anvisa.Gov.Br/#/Bulario/q/?NomeProduto=TAKHZYRO. 2021.

56. Buttgereit T, Vera C, Weller K, Gutsche A, Grekowitz EM, Aykanat S, et al. Lanadelumab Efficacy, Safety, and Injection Interval Extension in HAE: A Real-Life Study. J Allergy Clin Immunol Pract. 2021;9(10):3744-51. doi: 10.1016/j.jaip.2021.04.072.

57. Garcia JFB, Takejima P, Veronez CL, Aun MV, Motta AA, Kalil J, et al. Use of PdC1-INH Concentrate for Long-Term Prophylaxis during Pregnancy in Hereditary Angioedema with Normal C1-INH. J Allergy Clin Immunol Pract. 2018;6(4):1406-8. doi: 10.1016/j.jaip.2017.12.022.

58. Bork K. Diagnosis and Treatment of Hereditary Angioedema with Normal C1 Inhibitor. Allergy Asthma Clin Immunol. 2010;6(1):15. doi: 10.1186/1710-1492-6-15.

59. Bork K, Wulff K, Hardt J, Witzke G, Staubach P. Hereditary Angioedema Caused by Missense Mutations in the Factor XII Gene: Clinical Features, Trigger Factors, and Therapy. J Allergy Clin Immunol. 2009;124(1):129-34. doi: 10.1016/j.jaci.2009.03.038.

60. Saule C, Boccon-Gibod I, Fain O, Kanny G, Plu-Bureau G, Martin L, et al. Benefits of Progestin Contraception in Non-Allergic Angioedema. Clin Exp Allergy. 2013;43(4):475-82. doi: 10.1111/cea.12055.

61. Bork K, Wulff K, Witzke G, Hardt J. Treatment for Hereditary Angioedema with Normal C1-INH and Specific Mutations in the F12 Gene (HAE-FXII). Allergy. 2017;72(2):320-4. doi: 10.1111/all.13076.

62. Bernstein JA. Managing Hereditary Angioedema Patients Undergoing Otolaryngeal Procedures. Am J Rhinol Allergy. 2013;27(6):522-7. doi: 10.2500/ajra.2013.27.3964.

63. Aygören-Pürsün E, Martinez Saguer I, Kreuz W, Klingebiel T, Schwabe D. Risk of Angioedema Following Invasive or Surgical Procedures in HAE Type I and II - the Natural History. Allergy. 2013;68(8):1034-9. doi: 10.1111/all.12186.

64. Jurado-Palomo J, Muñoz-Caro JM, López-Serrano MC, Prior N, Cabañas R, Pedrosa M, et al. Management of Dental-Oral Procedures in Patients with Hereditary Angioedema Due to C1 Inhibitor Deficiency. J Investig Allergol Clin Immunol. 2013;23(1):1-6.

65. Bork K, Hardt J, Staubach-Renz P, Witzke G. Risk of Laryngeal Edema and Facial Swellings after Tooth Extraction in Patients with Hereditary Angioedema with and without Prophylaxis with C1 Inhibitor Concentrate: A Retrospective Study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;112(1):58-64. doi: 10.1016/j.tripleo.2011.02.034.

66. Zanichelli A, Ghezzi M, Santicchia I, Vacchini R, Cicardi M, Sparaco A, et al. Short-Term Prophylaxis in Patients with Angioedema Due to C1-Inhibitor Deficiency Undergoing Dental Procedures: An Observational Study. PLoS One. 2020;15(3):e0230128. doi: 10.1371/journal.pone.0230128.

67. Bork K. Pasteurized and Nanofiltered, Plasma-Derived C1 Esterase Inhibitor Concentrate for the Treatment of Hereditary Angioedema. Immunotherapy. 2014;6(5):533-51. doi: 10.2217/imt.14.33.

68. Magerl M, Frank M, Lumry W, Bernstein J, Busse P, Craig T, et al. Short-Term Prophylactic Use of C1-Inhibitor Concentrate in Hereditary Angioedema: Findings from an International Patient Registry. Ann Allergy Asthma Immunol. 2017;118(1):110-2. doi: 10.1016/j.anai.2016.10.006.

69. Navarro Ruiz A, Crespo Diz C, Poveda Andrés JL, Cebollero de Torre A. Algoritmo de diagnóstico y tratamiento del angioedema hereditario como herramienta para su manejo. Farmacia Hospitalaria. 2013;(6):521-9. doi: 10.7399/FH.2013.37.6.980.

70. Galan HL, Reedy MB, Starr J, Knight AB. Fresh Frozen Plasma Prophylaxis for Hereditary Angioedema during Pregnancy. A Case Report. J Reprod Med. 1996;41(7):541-4.

71. Bhardwaj N, Craig TJ. Treatment of Hereditary Angioedema: A Review (CME). Transfusion. 2014;54(11):2989-96. doi: 10.1111/trf.12674.

72. Lumry WR. Management and Prevention of Hereditary Angioedema Attacks. Am J Manag Care. 2013;19(7 Suppl):s111-8.

73. Farkas H, Gyeney L, Gidófalvy E, Füst G, Varga L. The Efficacy of Short-Term Danazol Prophylaxis in Hereditary Angioedema Patients Undergoing Maxillofacial and Dental Procedures. J Oral Maxillofac Surg. 1999;57(4):404-8. doi: 10.1016/s0278-2391(99)90280-x.

74. Vázquez DO, Josviak DO, Fantini CA, Fili NL, Berardi AM, Zwiener RD, et al. Consenso argentino de diagnóstico y tratamiento del angioedema hereditario. Revista Alergia México. 2021;68(Suplemento 2):s1-s22. doi: 10.29262/ram.v68i6.914.

75. Longhurst HJ, Bork K. Hereditary Angioedema: An Update on Causes, Manifestations and Treatment. Br J Hosp Med. 2019;80(7):391-8. doi: 10.12968/hmed.2019.80.7.391.

76. Banerji A, Busse P, Christiansen SC, Li H, Lumry W, Davis-Lorton M, et al. Current State of Hereditary Angioedema Management: A Patient Survey. Allergy Asthma Proc 2015;36(3):213-217. doi: 10.2500/aap.2015.36.3824.

77. Christiansen SC, Bygum A, Banerji A, Busse P, Li H, Lumry W, et al. Before and after, the Impact of Available on-Demand Treatment for HAE. Allergy Asthma Proc. 2015;36(2):145-50. doi: 10.2500/aap.2015.36.3831.

78. Moellman JJ, Bernstein JA, Lindsell C, Banerji A, Busse PJ, Camargo CA, et al. A Consensus Parameter for the Evaluation and Management of Angioedema in the Emergency Department. Acad Emerg Med. 2014;21(4):469-84. doi: 10.1111/acem.12341.

79. Bork K, Staubach P, Eckardt AJ, Hardt J. Symptoms, Course, and Complications of Abdominal Attacks in Hereditary Angioedema Due to C1 Inhibitor Deficiency. Am J Gastroenterol. 2006;101(3):619-7. doi: 10.1111/j.1572-0241.2006.00492.x.

80. Cicardi M, Bellis P, Bertazzoni G, Cancian M, Chiesa M, Cremonesi P, et al. Guidance for Diagnosis and Treatment of Acute Angioedema in the Emergency Department: Consensus Statement by a Panel of Italian Experts. Intern Emerg Med. 2014;9(1):85-92. doi: 10.1007/s11739-013-0993-z.

81. Brasil. Ministério Da Saúde. Agência Nacional de Vigilância Sanitária (ANVISA). Bulário Eletrônico. Cinryze: Pó Liofilizado. Bula Profissional do Medicamento [Internet]. Brasília (DF): ANVISA; 2022. Available from: https://consultas.anvisa.gov.br/#/bulario/q/?nomeProduto=Cinryze . 2022.

82. Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária (ANVISA). Bulário Eletrônico. Firazyr: Solução Injetável. Bula Profissional do Medicamento [Internet]. Brasília (DF): ANVISA; 2019 [citado 2022 Mar 29]. Available from: http://www.Anvisa.Gov.Br/Datavisa/Fila_bula/Index.Asp. 2019.

83. Bork K, Bernstein JA, Machnig T, Craig TJ. Efficacy of Different Medical Therapies for the Treatment of Acute Laryngeal Attacks of Hereditary Angioedema Due to C1-Esterase Inhibitor Deficiency. J Emerg Med. 2016;50(4):567-80.e1. doi: 10.1016/j.jemermed.2015.11.008.

84. Valerieva A, Staevska MT, Grivcheva-Panovska V, Jesenak M, Kohalmi KV, Hrubiskova K, et al. Recombinant Human C1 Esterase Inhibitor for Hereditary Angioedema Attacks: A European Registry. World Allergy Organ J. 2021;14(4):100535. doi: 10.1016/j.waojou.2021.100535.

85. Cicardi M, Banerji A, Bracho F, Malbrán A, Rosenkranz B, Riedl M, et al. Icatibant, a New Bradykinin-Receptor Antagonist, in Hereditary Angioedema. N Engl J Med. 2010;363(6):532-41. doi: 10.1056/NEJMoa0906393.

86. Lumry WR, Li HH, Levy RJ, Potter PC, Farkas H, Moldovan D, et al. Randomized Placebo-Controlled Trial of the Bradykinin B_2 Receptor Antagonist Icatibant for the Treatment of Acute Attacks of Hereditary Angioedema: The FAST-3 Trial. Ann Allergy Asthma Immunol. 2011;107(6):529-37. doi: 10.1016/j.anai.2011.08.015.

87. Maurer M, Aberer W, Bouillet L, Caballero T, Fabien V, Kanny G, et al. Hereditary Angioedema Attacks Resolve Faster and Are Shorter after Early Icatibant Treatment. PLoS One. 2013;8(2):e53773. doi: 10.1371/journal.pone.0053773.

88. Aberer W, Maurer M, Reshef A, Longhurst H, Kivity S, Bygum A, et al. Open-Label, Multicenter Study of Self-Administered Icatibant for Attacks of Hereditary Angioedema. Allergy. 2014;69(3):305-14. doi: 10.1111/all.12303.

89. Cicardi M, Levy RJ, McNeil DL, Li HH, Sheffer AL, Campion M, et al. Ecallantide for the Treatment of Acute Attacks in Hereditary Angioedema. N Engl J Med. 2010;363(6):523-31. doi: 10.1056/NEJMoa0905079.

90. Jindal AK, Reshef A, Longhurst H; GEHM workgroup (Global Equity in HAE Management). Mitigating Disparity in Health-Care Resources Between Countries for Management of Hereditary Angioedema. Clin Rev Allergy Immunol. 2021;61(1):84-97. doi: 10.1007/s12016-021-08854-5.

91. Christiansen SC, Davis DK, Castaldo AJ, Zuraw BL. Pediatric Hereditary Angioedema: Onset, Diagnostic Delay, and Disease Severity. Clin Pediatr (Phila). 2016;55(10):935-42. doi: 10.1177/0009922815616886.

92. Araújo-Simões J, Boanova AGP, Constantino-Silva RN, Fragnan NTML, Pinto JA, Minafra FG, et al. The Challenges in the Follow-Up and Treatment of Brazilian Children with Hereditary Angioedema. Int Arch Allergy Immunol. 2021;182(7):585-91. doi: 10.1159/000512944.

93. Bork K, Gül D, Hardt J, Dewald G. Hereditary Angioedema with Normal C1 Inhibitor: Clinical Symptoms and Course. Am J Med. 2007;120(11):987-92. doi: 10.1016/j.amjmed.2007.08.021.

94. Johnston DT, Smith RC. Hereditary Angioedema: Special Considerations in Children. Allergy Asthma Proc. 2020;41(Suppl 1):S43-S46. doi: 10.2500/aap.2020.41.200042.

95. Ocak M, Nain E, Sahiner ÜM, Akin MS, Karabiber E, Sekerel BE, et al. Recurrent Angioedema in Childhood: Hereditary Angioedema or Histaminergic Angioedema? Pediatr Dermatol. 2021;38(1):143-8. doi: 10.1111/pde.14467.

96. Farkas H, Kohalmi KV, Visy B, Veszeli N, Varga L. Clinical Characteristics and Safety of Plasma-Derived C1-Inhibitor Therapy in Children and Adolescents with Hereditary Angioedema-A Long-Term Survey. J Allergy Clin Immunol Pract. 2020;8(7):2379-83. doi: 10.1016/j.jaip.2020.02.043.

97. Aygören-Pürsün E, Soteres D, Moldovan D, Christensen J, Van Leerberghe A, Hao J, et al. Preventing Hereditary Angioedema Attacks in Children Using Cinryze®: Interim Efficacy and Safety Phase 3 Findings. Int Arch Allergy Immunol. 2017;173(2):114-9. doi: 10.1159/000477541.

98. Farkas H, Reshef A, Aberer W, Caballero T, McCarthy L, Hao J, et al. Treatment Effect and Safety of Icatibant in Pediatric Patients with Hereditary Angioedema. J Allergy Clin Immunol Pract. 2017;5(6):1671-8.e2. doi: 10.1016/j.jaip.2017.04.010.

99. Fijen LM, Bork K, Cohn DM. Current and Prospective Targets of Pharmacologic Treatment of Hereditary Angioedema Types 1 and 2. Clin Rev Allergy Immunol. 2021;61(1):66-76. doi: 10.1007/s12016-021-08832-x.

100. Cancian M, Perego F, Senter R, Arcoleo F, De Pasquale T, Zoli A, et al. Pediatric Angioedema: Essential Features and Preliminary Results from the Hereditary Angioedema Global Registry in Italy. Pediatr Allergy Immunol. 2020;31 Suppl 24:22-24. doi: 10.1111/pai.13170.

101. Wahn V, Aberer W, Aygören-Pürsün E, Bork K, Eberl W, Faßhauer M, et al. Hereditary Angioedema in Children and Adolescents - A Consensus Update on Therapeutic Strategies for German-Speaking Countries. Pediatr Allergy Immunol. 2020;31(8):974-89. doi: 10.1111/pai.13309.

102. Gompel A, Fain O, Boccon-Gibod I, Gobert D, Bouillet L. Exogenous Hormones and Hereditary Angioedema. International Immunopharmacology. 2020;78:106080. doi: 10.1016/j.intimp.2019.106080.

103. Caballero T, Farkas H, Bouillet L, Bowen T, Gompel A, Fagerberg C, et al. International Consensus and Practical Guidelines on the Gynecologic and Obstetric Management of Female Patients with Hereditary Angioedema Caused by C1 Inhibitor Deficiency. J Allergy Clin Immunol. 2012;129(2):308-20. doi: 10.1016/j.jaci.2011.11.025.

104. Zuraw BL, Bork K, Binkley KE, Banerji A, Christiansen SC, Castaldo A, et al. Hereditary Angioedema with Normal C1 Inhibitor Function: Consensus of an International Expert Panel. Allergy Asthma Proc. 2012;33 Suppl 1:S145-56. doi: 10.2500/aap.2012.33.3627.

105. Martinez-Saguer I, Rusicke E, Aygören-Pürsün E, Heller C, Klingebiel T, Kreuz W. Characterization of Acute Hereditary Angioedema Attacks during Pregnancy and Breast-Feeding and Their Treatment with C1 Inhibitor Concentrate. Am J Obstet Gynecol. 2010;203(2):131.e1-7. doi: 10.1016/j.ajog.2010.03.003.

106. Bouillet L, Longhurst H, Boccon-Gibod I, Bork K, Bucher C, Bygum A, et al. Disease Expression in Women with Hereditary Angioedema. Am J Obstet Gynecol. 2008;199(5):484.e1-4. doi: 10.1016/j.ajog.2008.04.034.

107. Czaller I, Visy B, Csuka D, Füst G, Tóth F, Farkas H. The Natural History of Hereditary Angioedema and the Impact of Treatment with Human C1-Inhibitor Concentrate during Pregnancy: A Long-Term Survey. Eur J Obstet Gynecol Reprod Biol. 2010;152(1):44-9. doi: 10.1016/j.ejogrb.2010.05.008.

108. Debreczeni ML, Németh Z, Kajdácsi E, Farkas H, Cervenak L. Molecular Dambusters: What Is Behind Hyperpermeability in Bradykinin-Mediated Angioedema? Clin Rev Allergy Immunol. 2021;60(3):318-47. doi: 10.1007/s12016-021-08851-8.

109. Bork K, Wulff K, Witzke G, Hardt J. Hereditary Angioedema with Normal C1-INH with versus without Specific F12 Gene Mutations. Allergy. 2015;70(8):1004-12. doi: 10.1111/all.12648.

110. Feray S, Fain O, Kayem G, Sabourdin N, Constant I, Rigouzzo A. Repeated Attacks of Type III Hereditary Angioedema with Factor XII Mutation during Pregnancy. Int J Obstet Anesth. 2018;36:114-8. doi: 10.1016/j.ijoa.2018.07.003.

111. Veronez CL, Moreno AS, Constantino-Silva RN, Maia LSM, Ferriani MPL, Castro FFM, et al. Hereditary Angioedema with Normal C1 Inhibitor and F12 Mutations in 42 Brazilian Families. The Journal of Allergy and Clinical Immunology: In Practice. 2018;6(4):1209-16.e8. doi: 10.1016/j.jaip.2017.09.025.

112. Machado AM, Pires RM, Martins RO, Grumach AS. Pregnancy and Postpartum in Hereditary Angioedema With C1 Inhibitor Deficit in Women Who Have No Access to Therapy. J Investig Allergol Clin Immunol. 2017;27(5):322-3. doi: 10.18176/jiaci.0175.

113. González-Quevedo T, Larco JI, Marcos C, Guilarte M, Baeza ML, Cimbollek S, et al. Management of Pregnancy and Delivery in Patients With Hereditary Angioedema Due to C1 Inhibitor Deficiency. J Investig Allergol Clin Immunol. 2016;26(3):161-7. doi: 10.18176/jiaci.0037.

114. Yakaboski E, Motazedi T, Banerji A. Hereditary Angioedema: Special Considerations in Women. Allergy Asthma Proc. 2020;41(Suppl 1):S47-S50. doi: 10.2500/aap.2020.41.200077.

115. Moldovan D, Bernstein JA, Hakl R, Porebski G, Poarch K, Lumry WR, et al. Safety of Recombinant Human C1 Esterase Inhibitor for Hereditary Angioedema Attacks during Pregnancy. J Allergy Clin Immunol Pract. 2019;7(8):2938-40. doi: 10.1016/j.jaip.2019.05.042.

116. Hakl R, Kuklínek P, Krcmová I, Králícková P, Freiberger T, Janku P, et al. Treatment of Hereditary Angioedema Attacks with Icatibant and Recombinant C1 Inhibitor During Pregnancy. J Clin Immunol. 2018;38(7):810-5. doi: 10.1007/s10875-018-0553-4.

117. Kaminsky LW, Kelbel T, Ansary F, Craig T. Multiple Doses of Icatibant Used during Pregnancy. Allergy Rhinol (Providence). 2017;8(3):178-81. doi: 10.2500/ar.2017.8.0210.

118. Brooks JP, Radojicic C, Riedl MA, Newcomer SD, Banerji A, Hsu FI. Experience with Intravenous Plasma-Derived C1-Inhibitor in Pregnant Women with Hereditary Angioedema: A Systematic Literature Review. J Allergy Clin Immunol Pract. 2020;8(6):1875-80.e3. doi: 10.1016/j.jaip.2020.03.009.

119. Gibbons KR, Abraham T, Sandhu M, Peppers BP, Girzhel JF, Hostoffer RW. Successful Perinatal Management of Hereditary Angioedema with Normal C1 Esterase Inhibitor and Factor XII Mutation Using C1 Esterase Inhibitor Therapy. Ann Allergy Asthma Immunol. 2017;119(6):558-9. doi: 10.1016/j.anai.2017.08.015.

120. Levy DS, Farkas H, Riedl MA, Hsu FI, Brooks JP, Cicardi M, et al. Long-Term Efficacy and Safety of Subcutaneous C1-Inhibitor in Women with Hereditary Angioedema: Subgroup Analysis from an Open-Label Extension of a Phase 3 Trial. Allergy Asthma Clin Immunol. 2020;16:8. doi: 10.1186/s13223-020-0409-3.

121. Andarawewa S, Aygören-Pürsün E. Subcutaneous C1-Inhibitor Concentrate for Prophylaxis during Pregnancy and Lactation in a Patient with C1-INH-HAE. Clin Case Rep. 2021;9(3):1273-5. doi: 10.1002/ccr3.3743.

122. Gompels MM, Lock RJ, Abinun M, Bethune CA, Davies G, Grattan C, et al. C1 Inhibitor Deficiency: Consensus Document. Clin Exp Immunol. 2005;139(3):379-94. doi: 10.1111/j.1365-2249.2005.02726.x.

123. Moraes CG de FB de, Mikami LR, Ferrari LP, Pesquero JB, Chong-Neto HJ, Rosario Filho NA. Short-Term Prophylaxis for Delivery in Pregnant Women with Hereditary Angioedema with Normal C1-Inhibitor. Rev Bras Ginecol Obstet. 2020;42(12):845-8. doi: 10.1055/s-0040-1718955.

124. Chinniah N, Katelaris CH. Hereditary Angioedema and Pregnancy. Aust N Z J Obstet Gynaecol. 2009;49(1):2-5. doi: 10.1111/j.1479-828X.2008.00945.x.

125. Bhardwaj NR, Espey E. Lactation and Contraception. Curr Opin Obstet Gynecol. 2015;27(6):496-503. doi: 10.1097/GCO.0000000000000216.

126. Pregnancy and Breastfeeding Warnings. Drugs.com [Internet]. [Cited 2022 Apr 03]. Available from: Available in: https://www.drugs.com/pregnancy/

127. Aygören-Pürsün E, Magerl M, Maetzel A, Maurer M. Epidemiology of Bradykinin-Mediated Angioedema: A Systematic Investigation of Epidemiological Studies. Orphanet J Rare Dis. 2018;13(1):73. doi: 10.1186/s13023-018-0815-5.

128. Farkas H, Stobiecki M, Peter J, Kinaciyan T, Maurer M, Aygören-Pürsün E, et al. Long-Term Safety and Effectiveness of Berotralstat for Hereditary Angioedema: The Open-Label APeX-S Study. Clin Transl Allergy. 2021;11(4):e12035. doi: 10.1002/clt2.12035.

129. Hofman ZLM, Clark CC, Hack CE, de Maat S, Maas C. Detecting Oral Kallikrein-Targeting Therapy through Triggered Contact Activation: A Phase I Study. J Allergy Clin Immunol. 2020;146(6):1446-9.e5. doi: 10.1016/j.jaci.2020.03.038.

130. ANZCTR - Australian New Zealand Clinical Trials Registry. Registration. n.d. [Internet]. [Cited 2022 Apr 03]. Available from: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=375857&isReview=true.

131. KalVista Pharmaceuticals, Inc. KVD824 for HAE. [Internet]. [Cited 2022 Apr 03]. Available from: https://www.kalvista.com/products-pipeline/kvd824-hae.

132. A Phase II, Cross-over Clinical Trial Evaluating the Efficacy and Safety of KVD900 in the On-Demand Treatment of Angioedema Attacks in Adult Subjects With Hereditary Angioedema Type I or II - Tabular View - ClinicalTrials.Gov. [Internet]. [Cited 2022 Apr 03]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT04208412.

133. Duckworth EJ, Murugesan N, Li L, Rushbrooke LJ, Lee DK, De Donatis GM, et al. Pharmacological Suppression of the Kallikrein Kinin System with KVD900: An Orally Available Plasma Kallikrein Inhibitor for the on-Demand Treatment of Hereditary Angioedema. Clin Exp Allergy. 2022. doi: 10.1111/cea.14122.

134. Maetzel A, Smith MD, Duckworth EJ, Hampton SL, De Donatis GM, Murugesan N, et al. KVD900, an Oral on-Demand Treatment for Hereditary Angioedema: Phase 1 Study Results. J Allergy Clin Immunol. 2022;S0091-6749(21)02666-X. doi: 10.1016/j.jaci.2021.10.038.

135. Cohn DM, Viney NJ, Fijen LM, Schneider E, Alexander VJ, Xia S, et al. Antisense Inhibition of Prekallikrein to Control Hereditary Angioedema. N Engl J Med. 2020;383(13):1242-7. doi: 10.1056/NEJMoa1915035.

136. Ferrone JD, Bhattacharjee G, Revenko AS, Zanardi TA, Warren MS, Derosier FJ, et al. IONIS-PKKRx a Novel Antisense Inhibitor of Prekallikrein and Bradykinin Production. Nucleic Acid Ther. 2019;29(2):82-91. doi: 10.1089/nat.2018.0754.

137. Fijen LM, Riedl MA, Bordone L, Bernstein JA, Raasch J, Tachdjian R, et al. Inhibition of Prekallikrein for Hereditary Angioedema. N Engl J Med. 2022;386(11):1026-33. doi: 10.1056/NEJMoa2109329.

138. Craig T, Magerl M, Levy DS, Reshef A, Lumry WR, Martinez-Saguer I, et al. Prophylactic Use of an Anti-Activated Factor XII Monoclonal Antibody, Garadacimab, for Patients with C1-Esterase Inhibitor-Deficient Hereditary Angioedema: A Randomised, Double-Blind, Placebo-Controlled, Phase 2 Trial. The Lancet. 2022;399(10328):945-55. doi: 10.1016/S0140-6736(21)02225-X.

139. Lesage A, Gibson C, Marceau F, Ambrosi H-D, Saupe J, Katzer W, et al. In Vitro Pharmacological Profile of a New Small Molecule Bradykinin B2 Receptor Antagonist. Front Pharmacol. 2020;11:916. doi: 10.3389/fphar.2020.00916.

140. ClinicalTrials.gov. [Internet]. Pharvaris Netherlands B.V. A Phase II, Double-Blind, Placebo-Controlled, Randomized, Dose-Ranging, Parallel Group Study to Evaluate the Safety and Efficacy of PHA-022121 Administered Orally for Prophylaxis Against Angioedema Attacks in Patients With Hereditary Angioedema Due to C1-Inhibitor Deficiency (Type I or Type II). Clinical trial registration; 2022.

141. ClinicalTrials.gov. [Internet]. Dose-Ranging Study of Oral PHA-022121 for Acute Treatment of Angioedema Attacks in Patients with Hereditary Angioedema - Tabular View. [Cited 2022 Apr 03]. Available from: https://clinicaltrials.gov/ct2/show/record/NCT04618211.

142. Biomarin. BMN 331 for Hereditary Angioedema (HAE). [Internet]. [Cited 2022 Apr 03]. Available from: https://www.biomarin.com/our-treatments/pipeline/bmn-331-for-hae/.

143. Qiu T, Chiuchiolo MJ, Whaley AS, Russo AR, Sondhi D, Kaminsky SM, et al. Gene Therapy for C1 Esterase Inhibitor Deficiency in a Murine Model of Hereditary Angioedema. Allergy. 2019;74(6):1081-9. doi: 10.1111/all.13582.

144. REGENXBIO Expands Pipeline Using NAV Vectors to Deliver Therapeutic Antibodies for the Treatment of Hereditary Angioedema and Neurodegenerative Diseases | REGENXBIO Inc. n.d. [Cited 2022 Apr 03]. Available from: http://ir.regenxbio.com/news-releases/news-release-details/regenxbio-expands-pipeline-using-nav-vectors-deliver-therapeutic/.

145. Forget AL. A Modular CRISPR/Cas9 Genome Editing Platform for Durable Therapeutic Knockout and Targeted Gene Insertion Applications. 16th Annual Meeting of the Oligonucleotide Therapeutics Society. [Internet]. [Cited 2022 Apr 03]. Available from: https://3o5c4w3neipl16yvhj3nfqam-wpengine.netdna-ssl.com/wp-content/uploads/Intellia-Therapeutics_Tony-Forget_OTS-2020_final_092920.pdf.

146. Crochet J, Lepelley M, Yahiaoui N, Vermorel C, Bosson J-L, Pralong P, et al. Bradykinin Mechanism Is the Main Responsible for Death by Isolated Asphyxiating Angioedema in France. Clin Exp Allergy. 2019;49(2):252-4. doi: 10.1111/cea.13297.

147. Banerji A. The Burden of Illness in Patients with Hereditary Angioedema. Ann Allergy Asthma Immunol. 2013;111(5):329-36. doi: 10.1016/j.anai.2013.08.019.

148. Longhurst H, Bygum A. The Humanistic, Societal, and Pharmaco-Economic Burden of Angioedema. Clin Rev Allergy Immunol. 2016;51(2):230-9. doi: 10.1007/s12016-016-8575-2.

149. Savarese L, Bova M, De Falco R, Guarino MD, De Luca Picione R, Petraroli A, et al. Emotional Processes and Stress in Children Affected by Hereditary Angioedema with C1-Inhibitor Deficiency: A Multicenter, Prospective Study. Orphanet J Rare Dis. 2018;13(1):115. doi: 10.1186/s13023-018-0871-x.

150. Savarese L, Bova M, Maiello A, Petraroli A, Mormile I, Cancian M, et al. Psychological Processes in the Experience of Hereditary Angioedema in Adult Patients: An Observational Study. Orphanet J Rare Dis. 2021;16(1):23. doi: 10.1186/s13023-020-01643-x.

151. Arce-Ayala YM, Diaz-Algorri Y, Craig T, Ramos-Romey C. Clinical Profile and Quality of Life of Puerto Ricans with Hereditary Angioedema. Allergy Asthma Proc. 2019;40(2):103-10. doi: 10.2500/aap.2019.40.4200.

152. Farkas H. Hereditary Angioedema: Examining the Landscape of Therapies and Preclinical Therapeutic Targets. Expert Opin Ther Targets. 2019;23(6):457-9. doi: 10.1080/14728222.2019.1608949.

153. Kuman Tunçel Ö, Gökmen NM, Demir E, Gülbahar O, Pırıldar. The Impact of Hereditary Angioedema on Quality of Life and Family Planning Decisions. Int J Psychiatry Med. 2019;54(6):377-94. doi: 10.1177/0091217419837068.

154. Liu S, Xu Y, Liu Y, Zhi Y. Hereditary Angioedema: A Chinese Perspective. Eur J Dermatol. 2019;29(1):14-20. doi: 10.1684/ejd.2018.3487.

155. Germenis AE, Margaglione M, Pesquero JB, Farkas H, Cichon S, Csuka D, et al. International Consensus on the Use of Genetics in the Management of Hereditary Angioedema. The Journal of Allergy and Clinical Immunology: In Practice. 2020;8(3):901-11. doi: 10.1016/j.jaip.2019.10.004.

156. Caballero T, Prior N. Burden of Illness and Quality-of-Life Measures in Angioedema Conditions. Immunol Allergy Clin North Am. 2017;37(3):597-616. doi: 10.1016/j.iac.2017.04.005.

157. Sirgy MJ, Michalos AC, Ferriss AL, Easterlin RA, Patrick D, Pavot W. The Quality-of-Life (QOL) Research Movement: Past, Present, and Future. Social Indicators Research. 2006;76(3):343-466. doi: 10.1007/s11205-005-2877-8.

158. Sirgy MJ, Reilly NP, Wu J, Efraty D. A Work-Life Identity Model of Well-Being: Towards a Research Agenda Linking Quality-of-Work-Life (QWL) Programs with Quality of Life (QOL). Applied Research in Quality of Life. 2008;3(3):181-202. doi: 10.1007/s11482-008-9054-6.

159. Prior N, Remor E, Pérez-Fernández E, Caminoa M, Gómez-Traseira C, Gayá F, et al. Psychometric Field Study of Hereditary Angioedema Quality of Life Questionnaire for Adults: HAE-QoL. J Allergy Clin Immunol Pract. 2016;4(3):464-73.e4. doi: 10.1016/j.jaip.2015.12.010.

160. Nunes FL, Ferriani MPL, Moreno AS, Langer SS, Maia LSM, Ferraro MF, et al. Decreasing Attacks and Improving Quality of Life through a Systematic Management Program for Patients with Hereditary Angioedema. Int Arch Allergy Immunol. 2021;182(8):697-708. doi: 10.1159/000513896.

161. Squeglia V, Barbarino A, Bova M, Gravante C, Petraroli A, Spadaro G, et al. High Attack Frequency in Patients with Angioedema Due to C1-Inhibitor Deficiency Is a Major Determinant in Switching to Home Therapy: A Real-Life Observational Study. Orphanet J Rare Dis. 2016;11(1):133. doi: 10.1186/s13023-016-0518-8.

162. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development and Construct Validation of the Angioedema Quality of Life Questionnaire. Allergy. 2012;67(10):1289-98. doi: 10.1111/all.12007.

163. Lumry WR, Weller K, Magerl M, Banerji A, Longhurst HJ, Riedl MA, et al. Impact of Lanadelumab on Health-Related Quality of Life in Patients with Hereditary Angioedema in the HELP Study. Allergy. 2021;76(4):1188-98. doi: 10.1111/all.14680.

164. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development, Validation, and Initial Results of the Angioedema Activity Score. Allergy. 2013;68(9):1185-92. doi: 10.1111/all.12209.

165. Weller K, Donoso T, Magerl M, Aygören-Pürsün E, Staubach P, Martinez-Saguer I, et al. Development of the Angioedema Control Test-A Patient-Reported Outcome Measure That Assesses Disease Control in Patients with Recurrent Angioedema. Allergy. 2020;75(5):1165-77. doi: 10.1111/all.14144.

166. Aymé S, Kole A, Groft S. Empowerment of Patients: Lessons from the Rare Diseases Community. Lancet. 2008;371(9629):2048-51. doi: 10.1016/S0140-6736(08)60875-2.

167. Abranghe [Internet]. [Cited 2022 Apr 03]. Available from: https://www.abranghe.org.br.

168. Brasil. Ministério da Saúde. Portaria Nº 199, de 30 de janeiro de 2014. Institui a Política Nacional de Atenção Integral às Pessoas com Doenças Raras, aprova as Diretrizes para Atenção Integral às Pessoas com Doenças Raras no âmbito do Sistema Único de Saúde (SUS) e institui incentivos financeiros de custeio. [Cited 2022 Apr 03]. Available from: https://bvsms.saude.gov.br/bvs/saudelegis/gm/2014/prt0199_30_01_2014.html .

169. Pharma Boardroom [Internet]. The Role of Patient Associations in Rare Disease Drug Development. [Cited 2022 Apr 03]. Available from: https://pharmaboardroom.com/articles/patient-associations-role-in-rare-disease-drug-development/ .

Conflict of interests

Régis A. Campos, Faradiba S. Serpa, Maria Luisa O. Alonso, Herberto J. Chong-Neto, Pedro Giavina-Bianchi, Anete S. Grumach, Eli Mansour, Eliana Toledo and Solange O. R. Valle received financial and/or honorary support from Takeda and CSL Behring. Anete S. Grumach is a CNPq productivity fellow and has also consulted for Catalyst. The following authors received financial and/or honorary support from Takeda: L. Karla Arruda, Marcelo V. Aun, Jane da Silva and Camila L. Veronez. The authors Maine L. D. Bardou, Ana Flávia Bernardes, Fernanda L. Campinhos, Rosemeire N. Constantino-Silva, Sérgio D. Dortas-Junior, Mariana P. L. Ferriani, Joanemile P. de Figueiredo, Lais S. Gomes, Ekaterini Goudouris, Marina T. Henriques, Antônio A. Motta, Therezinha R. Moyses, Fernanda L. Nunes, Jorge A. Pinto, Ana Júlia R. Teixeira, Nelson A. Rosario-Filho, Norma de Paula M. Rubini, Almerinda Maria do Rêgo Silva and Dirceu Solé deny conflicts of interest.

Corresponding author:
Régis A. Campos
E-mail: regiscampos@ufba.br