Consensus Statement on the Diagnosis, Management, and Treatment of Angioedema Mediated by Bradykinin. Part II. Treatment, Follow-up, and Special Situations

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Abstract

Background: There are no previous Spanish guidelines or consensus statements on bradykinin-induced angioedema.
Aim: To draft a consensus statement on the management and treatment of angioedema mediated by bradykinin in light of currently available scientific evidence and the experience of experts. This statement will serve as a guideline to health professionals.
Methods: The consensus was led by the Spanish Study Group on Bradykinin-Induced Angioedema, a working group of the Spanish Society of Allergology and Clinical Immunology. A review was conducted of scientific papers on different types of bradykinin-induced angioedema (hereditary and acquired angioedema due to C1 inhibitor deficiency, hereditary angioedema related to estrogens, angioedema induced by angiotensin-converting enzyme inhibitors). Several discussion meetings were held to reach the consensus.
Results: Treatment approaches are discussed, and the consensus reached is described. Specific situations are addressed, namely, pregnancy, contraception, travelling, blood donation, and organ transplantation.
Conclusions: A review of and consensus on treatment of bradykinin-induced angioedema is presented.

Key words: Angioedema. C1-inhibitor. Bradykinin. Estrogens. ACE inhibitors.

■ **Resumen**

Introducción: No existen guías previas españolas sobre el manejo del angioedema mediado por bradicinina.
Objetivos: Alcanzar un consenso sobre el manejo y tratamiento del angioedema mediado por bradicinina a la luz de la evidencia científica disponible y la experiencia de los expertos, que sirva como guía para los profesionales de la salud.
Métodos: SGBA/GEAB, un grupo de trabajo de la SEAIC dirigió el consenso. Se realizó una revisión de los documentos científicos publicados sobre los diferentes tipos de angioedema mediado por bradicinina [angioedema hereditario o adquirido por deficiencia de inhibidor de la C1 esterasa, angioedema hereditario relacionado con estrógenos (AEH tipo III, AEH-FXII), angioedema inducido por IECA (inhibidores del enzima convertidor de angiotensina]. Hubo varias reuniones del SGBA/GEAB para alcanzar el consenso.
Resultados: Se revisan y discuten los diferentes tratamientos disponibles y se describe el consenso alcanzado. Se abordan situaciones específicas (embarazo, anticoncepción, viajes, hemodonación, trasplante de órganos).
Conclusiones: Se presenta una revisión del tratamiento del angioedema mediado por bradicinina y un consenso sobre su tratamiento en España.

Palabras clave: Angioedema. C1 inhibidor. Bradicinina. Estrógenos. Inhibidores de la ECA.

Introduction

This is the second in a series of 2 papers that describe the consensus reached on the management and treatment of angioedema (AE) induced by bradykinin (BK).

Epidemiology, classification, genetics, pathophysiology, clinical symptoms, and diagnosis are addressed in Part 1 [1]. Part II addresses treatment, follow-up, and special situations.

A summary of the classification and nomenclature of the different types of bradykinin-induced angioedema (BK-AE) can be seen in Table 1.

Table 1. Classification of Bradykinin-Induced Angioedema

Bradykinin-induced AE	With C1-INH deficiency	Hereditary	Type I (HAE-C1-INH type I)
			Type II (HAE-C1-INH type II)
		Acquired (AAE-C1-INH)	
	With normal C1-INH	Hereditary (estrogen-related) (HAE type III)	With *F12* mutation (HAE-FXII)
			Without *F12* mutation (HAE-unknown)
		Associated with ACEi (AE-ACEi)	

Abbreviations: AE, angioedema; ACEi, angiotensin-converting enzyme inhibitors; C1-INH, C1 esterase inhibitor.

Methods

The methodology is described in Part I [1].

Treatment

A schematic approach to treatment is shown in Table 2.

A. Hereditary Angioedema With C1 Esterase Inhibitor Deficiency (HAE-C1-INH Types I and II)

1. Secondary prevention

1.1 Avoid precipitating factors

Early identification of precipitating factors is important (see Table 3).

1.1.1. Infectious processes: If infectious bacterial foci are detected (oral, sinus, respiratory, or digestive), antibiotic treatment (or surgery, if necessary) should be initiated.

In frequently recurring attacks that are mainly, but not exclusively, located in the abdomen, *Helicobacter pylori* infection should be investigated and eradication therapy should be administered if detected [2-4].

1.1.2. Trauma: It is advisable to avoid trauma, especially in dental operations and in those medical and surgical interventions that carry a risk for AE (see short-term prophylaxis).

1.1.3. Mental stress: Situations of mental stress should be identified and the need for psychotherapy or psychoactive drug treatment evaluated [5,6].

1.1.4. Drugs: Drugs that can increase the frequency and severity of AE attacks (Table 3) should be avoided.

1.1.4.1 Angiotensin-converting enzyme inhibitors (ACEi): ACEi should be strictly avoided [7,8].

1.1.4.2. Angiotensin II receptor blockers (ARB): ARBs have not been shown to trigger AE episodes in patients with HAE-C1-INH and can be used with care [7].

1.1.4.3. Estrogens: Estrogens must be avoided in oral contraceptives, hormone replacement therapy, and estrogenically active drugs [8,9].

1.2 Vaccination recommendations

1.2.1. Vaccination against hepatitis B virus is recommended

Table 2. Schematic Approach to Treatment

A. Hereditary angioedema with C1 esterase inhibitor deficiency or dysfunction
- *1. Secondary prevention*
  - 1.1. Avoidance of precipitating factors
    - 1.1.1. Infectious processes
    - 1.1.2. Trauma
    - 1.1.3. Mental stress
    - 1.1.4. Drugs
      - 1.1.4.1. Angiotensin-converting enzyme inhibitors
      - 1.1.4.2. Angiotensin receptor blockers
      - 1.1.4.3. Estrogens
  - 1.2. Vaccination recommendations
    - 1.2.1. Hepatitis B virus vaccination
- *2. Drug treatment and support*
  - 2.1. Treatment for angioedema episode or acute attack
    - 2.1.1. Plasma-derived C1 esterase inhibitor concentrate
    - 2.1.2. Icatibant acetate
    - 2.1.3. Other drugs
      - 2.1.3.1. Ecallantide
      - 2.1.3.2. Fresh frozen plasma
      - 2.1.3.3. Intravenous tranexamic acid
    - 2.1.4. Support treatment
    - 2.1.5. Other medicines under development: recombinant human C1-INH (rhC1INH) (Ruconest)
  - 2.2. Maintenance therapy or long-term prophylaxis
    - 2.2.1. Attenuated androgens: danazol, stanozolol, oxalandrone
    - 2.2.2. Antifibrinolytic agents
      - 2.2.2.1. Epsilon-aminocaproic acid
      - 2.2.2.2. Tranexamic acid
    - 2.2.3. Plasma-derived C1 esterase inhibitor concentrate
  - 2.3. Short-term prophylaxis
    - 2.3.1. Plasma-derived C1 esterase inhibitor concentrate
    - 2.3.2. Fresh frozen plasma
    - 2.3.3. Attenuated androgens
    - 2.3.4. Antifibrinolytic agents
    - 2.3.5. Icatibant acetate
    - 2.3.6. Ecallantide
  - 2.4. Peculiarities of treatment in children and adolescents
    - 2.4.1. Treatment of acute episodes
    - 2.4.2. Long-term prophylaxis
    - 2.4.3. Short-term prophylaxis
    - 2.4.4. Educating patients and their families

B. Acquired angioedema with C1 esterase inhibitor deficiency

C. Hereditary angioedema related to estrogens, including hereditary angioedema associated with a mutation in *F12*
- *1. Secondary prevention:* withdrawal of exogenous estrogens
- *2. Drug treatment*
  - 2.1. Treatment of acute attack
  - 2.2. Maintenance therapy or long-term prophylaxis
  - 2.3. Short-term prophylaxis

D. Angioedema induced by angiotensin-converting enzyme inhibitors

Table 3. Trigger Factors of Acute Edema in Patients With HAE-C1-INH

Psychological	Emotional stress, anxiety
Trauma (even minimal)	Especially important are those affecting the oral cavity (dental manipulations, gastroscopy, bronchoscopy, orotracheal intubation)
Hormonal	Menses, pregnancy, and puberty
Drugs	Estrogen-containing drugs (oral contraceptives, hormonal replacement therapy) and ACEi
Infections	Upper respiratory track infections, *Helicobacter pylori* infection

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; HAE-C1-INH, hereditary angioedema with C1 esterase inhibitor deficiency.

for nonimmunized patients when the diagnosis for the disease is made, since these patients might have to receive plasma derivatives [9,10].

2. Drug treatment and support

Treatment is usually considered at 3 different levels [8]:

2.1. Treatment of acute AE attacks

2.2. Maintenance therapy (long-term prophylaxis)

2.3. Short-term prophylaxis

2.1 Treatment of an acute AE episode

It is important not to delay the administration of treatment, especially if the location of the attack is life-threatening [11,12].

Indications for treatment of acute episodes depend on the severity and location of the AE episodes. One should treat all episodes of glottic edema and also those that affect the cervicofacial or pharyngolaryngeal region, as well as most abdominal episodes. Peripheral episodes should be treated based on the impact on the patient's quality of life (Table 4).

Table 4. Indications for Long-term Prophylaxis, Short-term Prophylaxis and Symptomatic Treatment of Acute Edema Attacks

	Indication
Acute treatment	Edema of the glottis Pharyngolaryngeal edema Cervicofacial edema Abdominal edema Moderate to severe peripheral edema
Long-term prophylaxis (maintenance treatment)	Edema of the glottis More than 1 edema episode per month More than 1 severe abdominal attack More than 1 severe cervicofacial attack Altered quality of life
Short-term prophylaxis	Odontological manipulations Endoscopy, bronchoscopy Surgical wound infection

Table 5. Comparative Table of Approved and Investigational New Drugs for Treatment of Acute Edema Attacks in Patients With HAE-C1-INH

Drug	Trade Name	Company	Drug Description	Mechanism of Action	Administration Route	Doses in HAE-C1-INH	Half-life	Storage	Shelf Life	Adverse Events	Marketed in Spain
Human plasma derived C1-INH	Berinert	CSL-Behring	Human plasma-derived C1-enterase inhibitor	C1-INH replacement	Intravenous	20 U/kg	32-47 h	Room temperature (2-25ºC)	30 mo	Theoretical risk for transmission of infectious agents Allergic reactions (rare) Thrombosis (with much higher doses)	August 2009
Human plasma derived C1-INH	Cetor	Sanquin	Human plasma-derived C1-enterase inhibitor	C1-INH replacement	Intravenous	20 U/kg	48±10 h	2-8ºC	3 y	Theoretical risk for transmission of infectious agents Thrombosis (with much higher doses)	No
Human plasma derived C1-INH	Cinryze[a]	Viropharma	Human plasma-derived C1-esterase	C1-INH replacement	Intravenous	1000 U	56±36 h	Room temperature	18 mo	Theoretical risk for transmission of infectious agents Thrombosis (with much higher doses)	No
Recombinant human C1-INH produced in transgenic rabbits (Conestat alfa)	Rhucin/ Ruconest[b]	Pharming NV	Recombinant human inhibitor of C1-esterase (produced in transgenic rabbits)	C1-INH replacement	Intravenous	50 U/kg	3 h	≤25ºC	36 mo	Allergic reactions in patients with rabbit allergy Theoretical thrombotic risk with high doses	No
Icatibant acetate	Firazyr	JeriniAG/ Shire	Synthetic peptide (10 aa)	Blockage of B2R	Subcutaneous	30 mg	1-2 h	Room temperature (2-25ºC)	24 mo	Local reactions	March 2009
Ecallantide	Kalbitor	Dyax Corp	Synthetic protein (60 aa)	Selective inhibitor of pasma kallikrein	Subcutaneous	30 mg	20±0.5 h	Refrigerated (2-8ºC) It can be stored up to 30ºC for 14 days	36 mo	Drug hypersensitivity reactions (eg. anaphylaxis)	No

Abbreviations: B2R, B2 receptor; C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema
[a]Cynrize is similar to Cetor, but with an added step: 2 nanofiltrations.
[b]Conestat alfa will be marketed as Ruconest in Europe and Rhucin in other parts of the world.

It is important to point out that this type of edema, which is triggered by an increase in BK levels, does not respond to therapy with antihistamines, corticosteroids, or adrenaline [8,13].

2.1.1. Plasma-derived C1 esterase inhibitor concentrate (pdhC1INH) (C1 esterase inhibitor replenishment or replacement therapy): pdhC1INH has proven effective in the resolution of acute AE attacks, both in uncontrolled studies of large series of patients and in placebo-controlled randomized clinical trials [11,14-22]. It comes in several pharmaceutical presentations: Berinert (CSL-Behring GmbH, Marburg, Germany), Cetor/Cebitor (Sanquin, Amsterdam, The Netherlands), and Cinryze (Viropharma Inc, Exton, Pennsylvania, USA) (see Table 5 for a comparison of available and investigational new drugs for acute treatment).

For more than 20 years, Berinert-P (CSL-Behring GmbH) has been available in Spain through the "Medicamentos Extranjeros" (Foreign Medications) office. Berinert-P is a purified and pasteurized pdhC1INH [23,24], which has an excellent postlaunch record for effectiveness and safety [23,24]. It was finally marketed in Spain in August 2009 as Berinert lyophilized in 500-U vials for intravenous administration. It can be preserved at 2ºC-25ºC [25].

The manufacturing process of another C1-esterase inhibitor formulation, Cinryze, has incorporated a nanofiltration step through 2 serial 15-nm filters to reduce transmission of enveloped and nonenveloped viruses and possible prions [22,26].

Dose: We recommend an intravenous dose of 20 U/kg, which proved effective in the IMPACT1 study [21]. Before randomized controlled clinical trials were conducted, the dose varied with body weight, according to an international agreement [7]. The drug should be administered intravenously, as follows: patients weighing ≤50 kg, 500 U; patients weighing 50-100 kg, 1000 U; and patients weighing >100 kg, 1500 U [7]. The dose may be repeated if there has been no response or if the response is incomplete, usually after 1 hour. It begins to act around 30 minutes after injection, and its effect lasts 2 to 4 days [7,8,11,27].

In some case series, the doses that led to improvement were lower [11,17-20].

Possible side effects: pdhC1INH is purified from human plasma; therefore, there is a theoretical risk of transmission of infectious agents. However, the safety of the products currently available on the market (Berinert, Cetor, Cebitor, Cinryze) is ensured by a series of protective measures, and there have been no demonstrated cases of viral transmission [8,18-24,28].

A procoagulant effect has been reported with doses above 200 U/kg [29,30], which are much higher than those used for HAE-C1-INH [21]. However, these effects have not been observed when pdhC1INH is used at recommended doses in patients with HAE-C1-INH or acquired angioedema (AAE-C1-INH) or in studies conducted with doses of 100 U/kg in infants operated on to correct transposition of the great arteries [31,32].

2.1.2. Icatibant acetate (HOE-140, JE-049) (BK type 2 receptor blocker) (Firazyr, Jerini AG, Berlin, Germany): Icatibant acetate is a synthetic decapeptide, a highly specific second-generation antagonist of the BK B2 receptor (B2R), which inhibits the vasodilation produced by BK [33-35]. Its effectiveness has been shown in clinical trials [33,36-38] and in patient series [39]. No serious adverse reactions have been reported, the only significant side effect being injection site reactions (in more than 95% of cases) consisting of self-limiting erythema, edema, pruritus, and pain [33,36-38]. Icatibant acetate has recently been approved by the European Medicines Agency (EMA), which granted marketing authorization in July 2008 [40], and has been available in Spain since March 2009.

There is no information about its efficacy and safety profile in patients younger than 18 years or in women who are pregnant or breastfeeding. It should not be used in patients with active ischemic heart disease or those who have had ischemic stroke in the preceding 2 weeks [41].

Icatibant acetate comes in prefilled syringes with the dose that should be administered subcutaneously (30 mg in 3 mL). It is stored at room temperature (2ºC-25ºC). Currently, it is only approved for symptomatic treatment of acute AE attacks in adult patients with HAE-C1-INH. If an adequate response does not occur, re-injection is indicated after 6 hours have elapsed. In 85%-92% of cases, 1 dose is sufficient, in 7%-12% of cases a second dose is necessary, and in 1%-3% a third dose is required [37,38]. The administration of more than 3 doses within a 24-hour period or more than 8 doses in 1 month is not recommended [41].

It is essential that patients have medication (eg, pdhC1INH [Berinert], icatibant acetate, or any other approved drug) available at all times, so that emergencies can be managed quickly and effectively at home or at a health center. In this way, autonomy and quality of life are increased [10,42,43].

In cases of frequent or more severe AE episodes, training programs can be given for self-administration of intravenous pdhC1INH [8,42-45]. In the case of icatibant acetate, subcutaneous administration may facilitate self-administration (authorized by the EMA in March 2011).

2.1.3. Other drugs

2.1.3.1. Ecallantide (DX-88, EPI-KAL-2)(Kalbitor)(Dyax Corp, Cambridge, Massachusetts, USA)

Ecallantide is a very potent, reversible, and highly specific human plasma kallikrein inhibitor, whose half-life is 2.0±0.5 hours [46]. Its effectiveness has been demonstrated in various clinical trials [46-50]. Anaphylactic reactions have been reported [51,52], as have other acute allergic reactions [53]. The United States Food and Drug Administration approved its use in December 2009 for treatment of acute AE episodes in patients aged 16 years and older. It is administered subcutaneously at 30 mg (divided into 3 doses). This drug should be stored refrigerated [54].

2.1.3.2. Fresh frozen plasma

In countries where pdhC1INH, icatibant, and ecallantide are not available, fresh frozen plasma (FFP) can be used instead, as long as it undergoes viral inactivation, preferably with solvents and detergents [5,55-60]. FFP works by supplying C1-INH. Although a theoretical risk of aggravating AE symptoms exists, because, in addition to C1-INH, FFP also supplies substrates (FXII, prekallikrein, high-molecular-weight kininogen), which can in turn lead to an increase in BK levels before the C1-INH can act [55,56,60-62], there are no scientific data linking exacerbation of the disease with this treatment [55].

The dosage has not been studied and is generally the same as that used in coagulation disorders: 2 units of 200 mL each [7].

Possible side effects include alloimmunization, anaphylactic or allergic reactions, transmission of infectious diseases (viruses, Creutzfeldt-Jakob disease), and excessive intravascular volume with risk of hypervolemia and heart failure [62].

2.1.3.3. Tranexamic acid

Tranexamic acid (Amchafibrin, Rottapharm Madaus, Milan, Italy) competitively inhibits activation of plasminogen, which, under normal conditions, is inhibited by C1-INH, thus reducing the conversion of plasminogen to plasmin (fibrinolysis) [63]. In patients with HAE-C1-INH, this could prevent the development of AE attacks by inhibiting the activation of the first component of the complement induced by plasmin [8].

There are no data based on controlled clinical trials. High intravenous or oral doses have been used (15 mg/kg every 4 hours), although this has only proven effective in prodromal phases of the attack [7,64].

2.1.4. Support treatment

Associated symptoms such as pain, nausea and/or vomiting, or hypotension symptoms caused by third-space phenomena (in abdominal attacks) should receive symptomatic treatment with analgesics, antispasmodics, antiemetics, and fluid replacement [8,65].

The angioedema attack should be closely monitored, especially in pharyngolaryngeal episodes, until stable remission of signs and symptoms has been verified. If necessary, the patient should be referred to the intensive care unit [65], since intubation or tracheotomy could become necessary at any time [67].

2.1.5. Other medicines under development: Recombinant human C1-INH (rhC1INH) (Ruconest, Pharming Technologies BV, Leiden, The Netherlands).

This rhC1INH is produced in transgenic rabbits in which the human C1NH gene has been inserted. rhC1INH is excreted in milk, which is then purified. It has the advantages of being a C1-INH replacement therapy without the risk of transmitting blood-borne human infections and is suitable for large-scale production. The active substance is called Conestat alfa, which has proven effective in the treatment of acute AE attacks [68-74]. It can be kept at room temperature, although it should be refrigerated during summer. It is administered intravenously and the doses used in clinical trials range from 50 U/kg to 100 U/kg [73]. The 50-U/kg dose was approved by the EMA in October 2010 [75].

Recombinant products are potentially immunogenic and carry a risk of producing neutralizing antibodies, allergic reactions, or both [76,77]. Data on immunological safety are encouraging, with no antibody production and no adverse immunological effects observed, except for an anaphylactic reaction in 1 patient with undisclosed rabbit allergy [76].

There are no studies comparing the efficacy, safety, and tolerance of pdhC1INH, icatibant acetate, ecallantide, and rhC1INH.

2.2. Maintenance therapy or long-term prophylaxis

This kind of treatment aims to reduce the frequency, severity, and length of acute AE crises [8,65,78]. The goal of treatment is to reduce the number and severity of AE attacks to 2 or fewer minor episodes a year [79].

Indications for establishing long-term prophylaxis are shown in Table 4 and vary depending on patient access to adequate acute treatment [8-10,66,78,80,81].

Attenuated androgens (AA) are much more effective than antifibrinolytic agents (AF) (97% vs 28%) [78] and are the treatment of choice [7,8,27,78], except when there are contraindications (Table 6) [82].

The drugs and doses for long-term prophylaxis are summarized in Table 7.

Table 6. Contraindications for the Use of Attenuated Androgens

– Children
– Pregnant women
– Breast cancer
– Prostate carcinoma
– Nephrotic syndrome
– Significant alterations of hepatic function

2.2.1.Attenuated androgens

17-α-Alkylated synthetic derivatives (danazol, stanozolol) are very effective and have fewer associated side effects than other androgens [79,83,84].

The mechanism of action of AAs in HAE-C1-INH is not clear, although various effects may contribute to their effectiveness, for example, a significant increase in C1-INH plasma levels with high doses [84], an increase in the expression of C1-INH mRNA in mononuclear cells with the minimum effective dose [85], and an increase in plasma

Table 7. Long-term Prophylaxis: Drugs and Doses

Pharmacological Group	Drug	Doses in Adults	Doses in Children
Attenuated androgens	Danazol	Induction: 400 mg/d 600 mg/d Maintenance: 100 mg/48-72 h	2.5 mg/kg/d
	Stanozolol	Induction: 6-12 mg/d Maintenance: 2 mg/72 h	
	Oxandrolone	0.1 mg/kg	
Antifibrinolytics	EACA Traneamic acid	1 g/6-8 h 1000-3000 mg/d	0.17-0.43 g/kg/d 20-40 mg/kg/d
C1-INH replacement	pdhC1INH	1000-1500 U 1-3 times a week	20 U/kg/1-3 times a week

Abbreviation: C1-INH, C1 esterase inhibitor; EACA, ε-aminocaproic acid.

levels of aminopeptidase P, an enzyme that participates in the catabolism of kinins [86].

Danazol is a potent gonadotropic inhibitor with partial antigestagenic, anabolic, and androgenic activity [84,87,88]. An initial induction dose (400-600 mg/day) is given until the patient is asymptomatic. It is then slowly reduced to the minimal effective maintenance dose, which can be as low as 50-100 mg every other day [5,7,8,27]. An alternative consists of starting with low doses of danazol and increasing them as needed [7,27,89].

Stanozolol is an anabolic steroid with certain anticoagulant properties [90]. An initial induction dose (6 mg/day in 3 doses) is prescribed until the patient is asymptomatic, with subsequent reductions every 2 months, depending on symptom severity, until the minimal effective maintenance dose is reached (which may be as low as 2 mg twice a week) [91,92].

Stanozolol has been shown to be more effective than danazol, with a lower frequency of side effects (menstrual irregularities and weight gain) [79].

Oxandrolone has also been used, although to a lesser extent [93]. It is not available in Spain, but it is available elsewhere (eg, USA, Brazil). The dosage used is 0.1 mg/kg (2.5 to 20 mg/day), taken in 2 to 4 doses [94-97].

The goal is to reach the lowest effective dose that controls symptoms without the need to normalize C4 or C1-INH levels. Alternate-day or rotating schedules can be used to reduce side effects [84].

Concentrated attacks are common during menstruation [98,99]; therefore, doubling the dose of AA during menstruation may be useful [100].

Doubling the AA dose for 3-7 days is also recommended when patients present infections or if a prodrome is noted [7].

The main side effects are disorders of libido, impotence, weight gain, menstrual irregularities, breast atrophy/hypotrophy, acne, voice changes, increased atherogenic index, polycythemia, hypertension, hematuria, transient increases in transaminases, hepatic necrosis, cholestatic hepatitis, hepatosplenic peliosis, transient increases in muscle enzymes (creatine phosphokinase and aldolase), and rhabdomyolysis [82] (Table 8). There have also been documented cases of hepatic adenoma in patients who received danazol in doses greater than 200 mg/day for more than 10 years [101-105] and adenocarcinoma [106].

Table 8. Secondary Effects of Attenuated Androgens

Residual hormonal activity	Seborrhea Acne Hirsutism Voice deepening Decrease in breast size Vasomotor symptoms Menstrual irregularities (amenorrhea, oligomenorrhea, menorrhagia) Decreased libido Virilization of fetus, children, and women Increase in body weight
Alkylation in 17-α position	Hepatotoxicity: necrosis, hepatic peliosis, cholestasis, hepatocellular neoplasm
Other	Lipoprotein alterations: increased risk of atherogenesis Increased creatine phosphokinase Arterial hypertension Premature closure of epiphyseal plates: decreased growth rate Increased hematocrit

An increased risk of early atherosclerosis has been reported in patients with HAE-C1-INH treated with danazol when compared to those not treated with danazol and healthy subjects. In addition, serum high-density lipoprotein cholesterol and apolipoprotein A-I are decreased and low-density lipoprotein cholesterol and apolipoprotein B-100 increased [89]. However, a subsequent study did not find differences between patients who were treated with danazol and those who were not [107].

The risk of rhabdomyolysis is increased after coadministration of danazol and high doses of statins [108-111].

2.2.2.Antifibrinolytic agents

2.2.2.1. ε-Aminocaproic acid

ε-Aminocaproic acid (EACA) is effective in preventing AE attacks [112-114]. Generally, the dose used is 1 g every 6-8 hours [115], although this can be increased to 12 g/day divided into 4 doses [8].

The main side effects are thrombosis, extensive muscle necrosis, and, more frequently, transient increases in creatine phosphokinase and aldolase associated with muscle pain, weakness, and fatigue [113,114].

EACA is less effective than tranexamic acid and can cause muscle necrosis.

2.2.2.2. Tranexamic acid

Tranexamic acid is a cyclic derivative of EACA and has proven effective in preventing AE attacks [64,116].

The dose is 1000-3000 mg/day (divided into 3-4 doses).

Possible side effects include muscle cramps, nausea, diarrhea, hypotension, dizziness, and fatigue [64,116] (Table 9). Retinal and liver disorders have been reported in laboratory animals; therefore, periodic funduscopy is recommended [64].

AFs should be discontinued before surgery, as they may theoretically promote thromboembolic events [117].

2.2.3.Human plasma–derived C1 esterase inhibitor concentrate (pdhC1INH)

Regular administration of intravenous pdhC1INH at different intervals may prevent the development of acute

Table 9. Side Effects of Antifibrinolytics

- Muscle necrosis: asthenia, myalgia, increase in CPK and aldolase
- Dizziness, postural hypotension
- Nausea, diarrhea, abdominal pain
- Muscle cramps
- Dysmenorrhea
- Pruritus
- Thrombosis

Abbreviation: CPK, creatine phosphokinase.

AE attacks [15,22,44,118,119]. The FDA approved Cinryze in October 2008 for prophylactic or long-term treatment of adolescent patients (older than 9 years) and adults. The effective dose was 1000 U twice a week [22]. However, dose and frequency must be adjusted on an individual basis, between 500 and 1000 U from once to 3 times a week.

pdhC1INH is indicated for severe attacks that occur despite prophylactic treatment with high doses of AAs or when it is necessary to discontinue AAs due to their side effects or contraindications [8,42,44,118,119].

The arguments against its use include the risk of developing allergic reactions, the risk of transmitting new infectious diseases, and the possibility of diminished effectiveness if administered on a continuous and prolonged basis [119,120].

Some European centers have developed training programs to teach patients intravenous self-administration of this drug [8,42-45].

2.3. Short-term prophylaxis

Short-term prophylaxis is indicated for patients who undergo surgical or medical procedures that may involve trauma to the cervicofacial region with a risk of laryngeal edema. These procedures include dental operations, tonsillectomy, maxillofacial surgery, digestive endoscopy, bronchoscopy, and surgical interventions that require intubation [8,27,78,121]. Short-term prophylaxis may also be indicated during surgery to prevent local edema from altering the surgeon's work area and affecting the outcome of surgery.

During surgery, it is advisable, whenever possible, to use regional anesthetic techniques to avoid trauma resulting from oropharyngeal intubation [8,27,122].

The information available in the international literature is limited to case reports and small series. Moreover, as not all patients develop AE attacks after surgery, it is difficult to assess the effectiveness of premedication in small series.

Short-term prophylactic treatment was successful using AAs [123], AFs (EACA [124], tranexamic acid [125,126]), FFP [127], and pdhC1INH [128,129]). Although there are no efficacy data for pdhC1INH compared to other treatments, pdhC1INH is the treatment of choice in countries where it is available, especially if intubation is required or surgery is major [7,8,9,27].

The risk of developing secondary AE attacks due to dental or oral operations and to surgical interventions cannot be completely avoided with preoperative prophylaxis [130-132]; therefore, acute treatment should always be available and the patient should be monitored after surgery. In addition, the patient should be informed about the possibility of developing edema, with instructions on what to do should the case arise.

Drugs and doses for short-term prophylaxis are shown in Table 10.

2.3.1.Human plasma-derived C1 inhibitor concentrate

The dose is 500 to 1000 U (<50 kg, >50 kg) 1 to 4 hours before surgery. The effect lasts 2 to 4 days. A second dose of pdhC1INH should be on hand throughout the operation.

2.3.2 Fresh frozen plasma

If pdhC1INH is not available (as is still the case in some countries), 2 units of FFP (treated with detergents) can be administered 1 hour before the procedure [9].

2.3.3. Attenuated androgens

AAs take about 5 days to produce an effect; therefore, they cannot be used in emergency situations.

Danazol (Danatrol, Sanofi-Aventis) can be administered at a dose of 400-600 mg/day, 5-7 days before and up to 2-3 days after the intervention. Stanozolol (Winstrol, Desma Laboratorio Farmacéutico SL, Madrid, Spain) can be administered at a dose of 4-6 mg/day, 5-7 days before and up to 2-3 days after the intervention [10].

This agent may have to be continued for more than 5 days in the case of postoperative complications, especially infection [98].

2.3.4. Antifibrinolytic agents (EACA [124] and tranexamic acid [125,126])

The dose of tranexamic acid is 1 g 4 times a day or 75 mg/kg/day divided into 2-3 doses from 5 days before until 2 days after surgery [125,126]. AFs are seldom used in countries where other treatments are available.

2.3.5.Icatibant acetate

An isolated case of prophylaxis with icatibant acetate (Firazyr) prior to thyroid biopsy without local edema developing has been published [133]. However, controlled studies are necessary. The short half-life (1-2 hours) of this agent and the fact that it blocks B2R but does not diminish BK

Table 10. Short-term Prophylaxis

Pharmacological Group	Drug	Adults	Children
C1-INH replacement	pdhC1INH	500-1500 U 1-4 h before the event	20 U/kg 1 h before the event
	Fresh frozen plasma	2 U (400 mL) 1 h before the procedure	10 mL/kg 1 h before procedure
Attenuated androgens	Danazol	400-600 mg/24 h for 5-7 d before the event and 2-3 d after the event	10 mg/kg/d for 5-7 d before to 2-3 d after the event
	Stanozolol	4-6 mg/24 h for 5 d before the event and 3 d after the event	
Antifibrinolytics (seldom used)	Tranexamic acid	1 g/6 h for 5 d before the event and 2 d after the event	500 mg/6 h for 2 d before the event and 2 d after the event

production [33] may restrict its use in short-term prophylaxis, as there is a theoretical risk of late local edema. The trauma may result in an increase in local BK through FXII activation [8,134]. While B2R blockage continues, no edema is produced, but when B2R are released (after icatibant is eliminated from the body), an edema episode could develop 6-8 hours after surgery if BK remains high.

2.3.6. Ecallantide

One anecdotal case of short-term prophylaxis with 10 mg of ecallantide that did not result in edema has been reported [135]. However, it is worth noting that the case was a single uncontrolled case in which FFP was also administered. Moreover, the short half-life of ecallantide (2.0 ± 0.5 h) could restrict its use as short-term prophylaxis. It is necessary to carry out controlled studies or gain more experience in order to recommend its use in this indication.

2.4. Peculiarities in the treatment of children and adolescents

2.4.1. Treatment of acute episodes

The indications are the same as in adults [98,100,114].

The treatment of choice is pdhC1INH [7,96,98] at 20-25 U/kg [20,114]. If the response is insufficient, the dose may be repeated, usually an hour later [114].

There is no experience with icatibant acetate or ecallantide in children. In countries where pdhC1INH is not available, FFP can be used instead. The dosage has not been studied, although it is generally the same as that used in coagulation disorders (10 mL/kg) [98].

Due to the small diameter of children's airways, mild edema in the laryngeal mucosa can cause a major obstruction, which would rapidly compromise breathing and provoke asphyxiation [100,136,137]. Therefore, treatment and support measures must be applied quickly where required.

2.4.2. Long-term prophylaxis

The indications are the same as in adults.

AFs are the treatment of choice in children and adolescents (before Tanner stage V) [27], given their better safety profile than that of AA [10,114]. Good control has been achieved with tranexamic acid at 20-40 mg/kg/day (divided into 3-4 doses) [100,138] and with EACA at 0.17-0.43 g/kg/day [100]. Children had more side effects with EACA [10], leading this agent to fall into disuse; however, it should be considered in patients with lactose intolerance. The dose should be tailored to the minimal effective dose and adjusted for growth [10,134].

If AFs are not effective or contraindicated, they can be replaced with AAs. AAs have been associated with androgenization, premature puberty, delayed menarche, irregular menstruation, accelerated bone fusion resulting in limited growth, liver disorders, atherogenesis, and changes in behavior [10,87,88,139-142]. It is advisable to use the lowest effective maintenance dose of danazol. A dose of 2.5 mg/kg/day can be used, starting generally at 50 mg/day and increasing to a maximum of 200 mg/day if necessary [100]. Intermittent dosage regimens are preferred for reducing side effects (ie, doses repeated every other day or at 3-day intervals) [100]. Several cases have revealed the effectiveness and good safety profile of oxandrolone in children [95]. As this agent cannot be aromatized to estrogen, estrogen-dependent epiphyseal bone closure is minimal. Oxandrolone may be more indicated for children. The recommended dosage is 0.1 mg/kg (2.5 to 20 mg/day) divided into 2 to 4 doses [94-97].

If treatment with AFs and AAs fails, regular infusions of pdhC1INH every 72 hours should be considered [10,26,114].

2.4.3 Short-term prophylaxis

The agent of choice is pdhC1INH, especially if the patient has a history of severe attacks precipitated by similar procedures, at a dose of 25 units/kg 1 hour before the procedure [98]. If pdhC1INH is not available, it may be replaced with FFP 10 mL/kg to be infused 1 hour before the procedure [98].

If there is enough time, AAs can be used (minimal side effects when used over a short period). Danazol 10 mg/kg/day (maximum, 600 mg/day) for 5-7 days can be administered before and up to 2-3 days after the procedure. If androgens are contraindicated, tranexamic acid can be used (20-40 mg/kg/day divided into 3-4 doses) [100, 138] during the 2 days before and after the procedure. This agent may have to be continued for more than 5 days in patients with postoperative complications, especially infection [98].

2.4.4 Educating patients and their families

It is very important to educate children and their parents on the specific characteristics of the disease, potential triggers, how to recognize symptoms early, and the need for preventive treatment in special situations (eg, dental procedures). Timely health education and close monitoring during early childhood can increase the patient's quality of life, autonomy, safety, and self-confidence, as well as prevent stigmatization and provide a high quality of life as an adult [8].

B. Acquired Angioedema With C1 Esterase Inhibitor Deficiency (AAE-C1-INH)

Control of the underlying disease generally results in reduced symptom severity [143,144].

Treatment of acute AE attacks is as for HAE-C1-INH, although the dose of pdhC1INH needed may be higher [12], because of the presence of anti-C1-INH autoantibodies. Clinical response to the infusion of pdhC1INH varies significantly, probably as a result of varying affinity of the autoantibodies for C1-INH and, consequently, of a differing rate of C1-INH consumption [12,145]. There is little experience with icatibant acetate [146-148], although this agent could be used in cases of resistance to pdhC1INH. Ecallantide may also be effective, because of its mechanism of action. Antihistamines, corticosteroids, and adrenaline are ineffective [149].

Regarding long-term prophylaxis, there are significant individual variations, but AFs are the treatment of choice, since they are more effective than AAs [143,144]. Their effectiveness seems to reside in their antiplasmin and plasminogen activator inhibitor effect [150].

Plasmapheresis followed by cyclophosphamide in a patient with autoantibodies against C1-INH and no underlying disease proved successful in 1 case [151]. The anti-CD20 monoclonal antibody rituximab has also been successful [152-154].

To prevent thrombotic complications in patients at risk, some authors recommend low-dose oral anticoagulants [12]. Potential prothrombotic risk factors need to be assessed individually.

C. Hereditary Angioedema Related to Estrogens (HAE type III) Including Hereditary Angioedema Associated With a Mutation in F12 (HAE-FXII)

There are no controlled studies with placebo, only case studies and small series.

1. Secondary prevention: withdrawal of exogenous estrogens

The main therapeutic measure is to avoid estrogens [155-158]. In a subgroup of patients, symptoms disappear when situations involving increased exogenous estrogens (eg, oral contraceptives, hormone replacement therapy) or pregnancy are avoided; however, in other patients these symptoms persist, although milder [158,159].

ACEis should also be avoided [157], and the introduction of ARBs should be monitored [157].

2. Drug treatment

2.1. Treatment of acute attacks

Acute attacks do not respond to antihistamines or corticosteroids [157,158].

There is no consensus on treatment, with isolated cases or small series in which tranexamic acid (1-2 g/6 hours) [158, 160], pdhC1INH [157,158], and icatibant acetate [158,161] have been used off-label. Ecallantide may also be effective due to its mechanism of action.

2.2. Long-term prophylaxis or maintenance therapy

In those patients in whom AE attacks do not disappear after withdrawing exogenous estrogens or normalizing endogenous estrogens, the indications for starting maintenance treatment are the same as in HAE-C1-INH.

There are no controlled studies with placebo. Most series describe the effectiveness or lack of effectiveness of various drugs administered empirically; therefore, all these drugs should be used off-label. The effectiveness of oral tranexamic acid [157,158,162], oral progesterone [156], and oral danazol [157,163] has been described. The initial dose of tranexamic acid is 1 g every 8 hours, which should be reduced to the minimum effective dose based on clinical improvement [158,162].

2.3. Short-term prophylaxis

Although no published data are available, it might be necessary to premedicate the patient prior to risky interventions in those cases where the disease continues to be active after avoiding estrogens or during pregnancy (see Pregnancy section). The therapeutic possibilities are limited (tranexamic acid, pdhC1INH, and icatibant acetate) and their actual effectiveness is unknown. If premedication is not administered, acute treatment should be available for immediate use.

D. Angioedema Induced by Angiotensin-Converting Enzyme Inhibitors (AE-ACEi)

Antihypertensives from the ACEi group should be strictly avoided [164].

There are few reports of AE associated with ARBs, which does not seem to share the same mechanism as AE-ACEi [165-167]. A low percentage of patients with AE-ACEi develop AE when the ACEi is replaced by an ARB [164,166]. However, in a recent meta-analysis, the prevalence of ARB-induced AE in patients with AE-ACEi was 1.5% (95% CI, 0%-5.1%), with no significant difference with placebo [168,169]. Therefore, ARBs should not be systematically avoided in patients with AE-ACEi, although their use should be monitored.

AE episodes that occur during treatment with ACEi do not respond to treatment with antihistamines, corticosteroids, or adrenaline [170]. Tranexamic acid may be effective, just as with other types of BK-AE [162,171]. The effectiveness of pdhC1INH has been described in 1 case [172] and that of icatibant acetate in a recently published series [170,173], although more studies are needed to confirm this beneficial effect.

Follow-up

The frequency of follow-up visits and the type of complementary examinations depend on the intensity and frequency of symptoms, as well as the type of treatment received (Table 11).

At diagnosis and before starting treatment, biochemical and serological analysis and abdominal ultrasound should be performed [8-10,27,174,175].

In patients on long-term prophylaxis with AAs, follow-up should preferably be every 6 months. A physical examination is necessary to look for signs of virilization and to monitor weight and blood pressure. Analytical checks should also be carried out, including a complete blood count, lipid profile, liver function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), and elementary urinalysis [8-10,27,82,174,175]. An annual measurement of α-fetoprotein is also recommended [9]. In order to make an early diagnosis of possible liver adenomas, abdominal ultrasound should be performed at baseline and at least every year and every 6 months if the dose exceeds 200 mg/day of danazol or 2 mg/day of stanozolol and with any dose if the patient has been treated for more than 10 years with AAs [7-10,27,174-176]. Patients undergoing prophylactic antifibrinolytic treatment should receive serum muscle enzyme and undergo liver function testing every year, as well as ophthalmologic examinations [9,10,177]. Thrombosis has been reported in patients with hypercoagulable states [178]; therefore, it is advisable to perform a hypercoagulability study prior to administration in patients with a family history of thrombophilia or active thromboembolic disease.

Due to the potential theoretical risk of transmission of infectious agents, serology testing should be performed for HCV, HBV, HIV, and parvovirus B19 [10,22,23,174,179,180].

Persons with C1-INH deficiency should be considered patients, even if they are asymptomatic, and actively monitored.

Table 11. Follow-up and Complementary Tests[a]

Treatment	Baseline Visit	6-Month Visit	Annual Visit
Androgen	• Abdominal ultrasound • Hemogram • Liver function tests • Lipid profile • Urinalysis	• Physical examination: – *Virilization signs* – *Weight* – *Blood pressure* • Hemogram • Liver function tests • Lipid profile • Urinalysis • Abdominal ultrasound[b]	• α-Fetoprotein • Abdominal ultrasound
Antifibrinolytic agents	Hypercoagulability study[c]	• Muscle enzyme testing (aldolase, creatine phosphokinase) • Liver and renal function • Urinalysis	• Ophthalmology checkup
pdhC1INH (hemovigilance required)	Serological test: • HCV • HBV • HIV • Parvovirus B19 *Vaccination hepatitis B*		Serology testing[d] • HCV • HBV • HIV • Parvovirus B19

[a]Monitoring varies according to long-term prophylaxis (androgens vs antifibrinolytics); hemovigilance should be performed in all patients because of pdhC1INH treatment.
[b]In patients treated for >10 years or receiving >200 mg/day danazol or 2 mg/day stanozolol or prepuberal patients.
[c]In patients with family history of thrombophilia or active thromboembolic disease.
[d]In cases where the patient has received pdhC1INH since the last visit.

Special Situations

Contraception

Contraceptives that contain estrogens are contraindicated in patients with HAE-C1-INH and HAE type III (including HAE-FXII), given that these drugs can produce an increase in the frequency and severity of AE episodes [99,155-157,181]. As an alternative, patients can use continuous low doses of oral progestogen (mini-pill), such as desogestrel, norgestrel, levonorgestrel, lynestrenol, and ethynodiol diacetate. One retrospective study revealed that 64.3% of women with HAE-C1-INH who took progestogens as contraceptives improved during the course of their AE [155]. In Spain, the only marketed oral progestogen for contraceptive use is desogestrel (Cerazet, Schering-Plough, Madrid, Spain).

As for the intrauterine device (IUD), there is little published data on its safety. However, one European retrospective study showed good tolerance [155]. No short-term prophylaxis is needed for insertion, although acute treatment should be available. There is an IUD with progesterone (levonorgestrel-releasing IUD: Mirena, Bayer, Barcelona, Spain), which could be specifically indicated for patients with HAE-C1-INH.

Finally, condoms and other barrier methods are an alternative with no contraindications.

As for emergency contraceptives (morning after pill), there is no theoretical risk of worsening as long as the patient uses only those with high doses of progestogens. If the patient uses those with high doses of estrogens, acute treatment must be on hand in case of exacerbations. Another alternative is implantation of an emergency IUD within the first 72 hours [182].

Secure contraception must be ensured when the patient is being treated with androgens, which carry a high teratogenic risk.

Pregnancy and Childbirth

• *Pregnancy and HAE-C1-INH and HAE type III*

Pregnancy may improve, worsen, or have no impact on the course of HAE-C1-INH attacks, which may vary from one pregnancy to another in the same patient [78,155,183-188].

Pregnancy is one of the known exacerbating factors in HAE type III [157,160,163,189,190].

• *C1-INH levels during pregnancy*

HAE-C1-INH should not be diagnosed during pregnancy, since transient low levels of C1-INH have been reported in women with or without HAE-C1-INH, although these levels return to normal values after delivery [191-193]. This could be associated with increased circulating plasma volume [194].

• *Scheduled pregnancy*

Androgens should be discontinued before pregnancy, since

they can cross the placental barrier and produce virilization of the fetus, in turn leading to female pseudohermaphroditism [195-198].

Since the elimination half-life of danazol is 9.44±2.74 hours [199], avoidance of danazol 1 month prior to conception should be sufficient.

If the pregnancy test is positive, androgen treatment should be discontinued immediately.

Although tranexamic acid also crosses the placental barrier [200], there are no known significant side effects for the fetus; therefore, this treatment can be continued, bearing in mind its controversial prothrombotic effects.

The half-life of tranexamic acid is approximately 2 hours [201]; therefore, discontinuing its use a few days before conception is sufficient.

Ecallantide, icatibant acetate, and rhC1INH have not been used during pregnancy and should be avoided before conception. As their half-lives are short, avoiding them a few days before conception is sufficient.

pdhC1INH should not be avoided prior to conception.

• *Treatment of HAE-C1-INH during pregnancy*

The treatment of choice for AE attacks during pregnancy is pdhC1INH (20 U/kg) [186,188]. Icatibant acetate, ecallantide, and rhC1INH have not been used in pregnancy, and their safety profile is unknown.

As for short-term prophylaxis, pdhC1INH is also preferred over other options.

Regarding long-term prophylaxis, the use of androgens is contraindicated throughout pregnancy, due to their virilizing effects on the fetus [197,198]. There are no controlled data on the use of AFs during pregnancy, and there is no consensus on the need to monitor other prothrombotic factors. In studies of pregnant women with hemorrhaging, coagulation was not significantly affected [202-204]. However, if the patient has a family or medical history of prothrombotic events, then AFs should be administered with caution, and a prior hypercoagulability study should be performed.

There are few controlled data on the use of pdhC1INH during pregnancy, although most experts have extensive experience with this agent. Several series have recently been published on the efficacy and safety of pdhC1INH in pregnancy [186,188,205].

• *Treatment of AEH type III during pregnancy*

Currently, there are no clear therapeutic alternatives to pdhC1INH, although successful isolated experiences have been reported with tranexamic acid and pdhC1INH [158]. As there is no experience with icatibant acetate or ecallantide during pregnancy, these agents are not recommended, except under life-threatening AE attacks that do not respond to other treatments.

Regarding short-term prophylaxis, it might be necessary to premedicate the patient with pdhC1INH or tranexamic acid prior to risky interventions during pregnancy, although the real effectiveness of these agents is unknown. Acute treatment should be available.

• *Childbirth (HAE-C1INH)*

Although a significant trauma, childbirth has not been shown to be a trigger for AE. It is generally well tolerated without prior prophylaxis with pdhC1INH [155]. However, in recent years, a significant bias has been generated with the publication of isolated cases in which pdhC1INH was administered as prophylaxis [206-210]. Nevertheless, larger series show that spontaneous vaginal deliveries tend to be well tolerated [188]. Therefore, an observational approach should be adopted with this type of delivery, and at least 1 dose of pdhC1INH (20 U/kg) should be kept in the delivery room. For complicated childbirths that require vacuum or forceps, prior administration of purified plasma pdhC1INH is recommended. In patients with no control of the disease and frequent acute outbreaks, prophylactic pdhC1INH should be administered before delivery. The dose can be adjusted according to the patient's weight (50 kg, 500 U; 50-100 kg, 1000 U; >100 kg, 1500 U). The patient should be closely monitored during the postpartum, in case complications arise [208,209,211].

If a cesarean section is required, local anesthesia is preferable in order to avoid the risk of laryngeal edema secondary to endotracheal intubation. pdhC1INH (500-1500 U) must be administered prior to the procedure, with a treatment dose (20 U/kg) on hand in case of complications.

• *Childbirth (HAE type III)*

For patients with HAE type III, delivery may pose a risk of AE; therefore, some authors recommend administering pdhC1INH prior to delivery [158]. Acute treatment should be available for immediate use.

• *Genetic counseling*

Adult patients and/or their family must be informed of the possibility of transmitting HAE-C1-INH and HAE-FXII to offspring. They should also be informed about available treatments and the fact that it is impossible to predict severity in offspring. When permitted by law, the patient should be informed of the possibility of performing prenatal diagnosis or in vitro fertilization with preimplantation genetic diagnosis and selection of healthy embryos. Preimplantation genetic diagnosis is a complicated technique with a low success rate. This approach is more complicated in women with HAE-C1-INH or HAE-FXII, since it can worsen AE through estrogenic stimulation during in vitro fertilization techniques.

Organ Donation and Blood Transfusion

HAE-C1-INH is a genetic disease caused by a deficiency or alteration in the function of C1-INH. This protein is synthesized and expressed mainly in the liver (http://biogps.gnf.org/ Accessed November 19, 2010). For this reason, patients with HAE-C1-INH can donate all of their organs except the liver [212].

However, according to exclusion criteria for blood and blood component donors in Royal Decree 1088/2005, patients with HAE-C1-INH and HAE-FXII may not donate blood [213].

Advice to Patients Before Traveling

Long-term prophylactic treatment should be adjusted. A written medical report may be necessary for the medication to pass airport security. The report must detail the characteristics of the disease and the pertinent instructions for emergency treatment or short-term prophylaxis.

Both pdhC1INH and icatibant acetate must be declared at the check-in desk and carried by hand in a refrigerated bag (only if temperatures are expected to be above 25ºC). Patients should be advised to carry the materials needed for administration of the medication (a syringe and a needle for intravenous administration of pdhC1INH) in case they suffer an attack and have no access to a health center where medication can be administered.

Patients are recommended to carry a card that identifies this disease and its treatment. The Spanish Association of Family Angioedema (AEDAF) has a card written in 4 languages for this very purpose.

AEDAF's website (http://www.angioedema-aedaf.org) provides extensive information on the Spanish hospitals and health centers that are familiar with this disease and have emergency treatment available. It may also be useful for patients to consult the websites of the patient associations of the various countries they intend to travel to.

Other Situations

Coordination With Primary Care

Liaising closely with the patient's primary care physician is recommended. Telephone or email contacts for the unit that cares for the patient should be provided.

Patient Booklet

The patients and their family should have access to a simple publication that provides basic relevant information on self-care and monitoring.

Personal Availability of Acute Treatment

Based on current information, patients at risk of life-threatening outbreaks must have personal access to acute treatment. The health care system should provide patients with pdhC1INH or icatibant acetate and their replacement once these drugs have been used up or have expired.

Patient Associations

Patients and their families should be provided with the means to contact patient associations or social organizations for support (http://www.angioedema-aedaf.org).

Disease Records

Considering the rarity of this type of disorder, a disease registry can be useful, bearing in mind the confidentiality issues outlined by Spanish legislation.

Individualized Clinical Report

Every patient with BK-AE should have a clinical report, especially when the diagnosis is made. At least every 2 years, the report should be revised to include the latest details on the patient's condition.

It may be useful to have a "rapid medical alert" in the form of a bracelet/necklace or electronic device that contains information on diagnosis, emergency treatment, and ineffectiveness of drugs (antihistamines, corticosteroids, and adrenaline).

Document Review

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The final version has been read and approved by all the authors.

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