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Guideline: Hereditary angioedema due to C1 inhibitor deficiency

S1 Guideline of the German Society for Angioedema (*Deutsche Gesellschaft für Angioödeme, DGA*), German Society for Internal Medicine (*Deutsche Gesellschaft für Innere Medizin, DGIM*), German Society for Otorhinolaryngology (*Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, DGHNO*), German Society for Allergology and Clinical Immunology (*Deutsche Gesellschaft für Allergologie und klinische Immunologie, DGAKI*), German Society for Child and Adolescent Medicine (*Deutsche Gesellschaft für Kinder- und Jugendmedizin, DGKJ*), German Dermatological Society (*Deutsche Dermatologische Gesellschaft, DDG*), German Society for Pediatric Allergology and Environmental Medicine (*Gesellschaft für Pädiatrische Allergologie und Umweltmedizin, GPA*), German Association of ENT Surgeons (*Deutscher Berufsverband der Hals-Nasen-Ohren-Ärzte, BVHNO*), and the German HAE Patient Association (*HAE-Vereinigung, Selbsthilfegruppe, HAE-SHG*)

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Abbreviations

ACE	Angiotensin converting enzyme
C1-INH	C1 esterase inhibitor
EACA	Epsilon-aminocaproic acid
FFP	Fresh frozen plasma
HAE	Hereditary angioedema
IU	International unit
IgE	Immunoglobulin E
KKS	Kallikrein-kinin system
rh	Recombinant human

Objective of the guideline

This guideline is based on an informal consensus of experts that have been working in Germany for a considerable time with patients with hereditary angioedema (HAE) due to a genetic C1 inhibitor (C1-INH) deficiency (HAE-C1-INH) and a non-systematic literature search. The guideline is an update of the 2012 German Association of Scientific Medical Societies' (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*, AWMF) guideline on "Hereditary angioedema due to C1 inhibitor deficiency." This updated version includes new developments in the field, taking into account publications published between 2012 and 2018 that were relevant to the guideline. A number of consensus papers and guidelines were also taken into consideration, including the 2017 update of the World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI) guideline on the treatment of HAE [1–4].

The guideline is primarily aimed at physicians treating patients with HAE-C1-INH. In Germany, these generally include dermatologists, internists, pediatricians, as well as ear, nose, and throat (ENT) specialists. However, the guideline is also aimed at physicians coming into less frequent contact with HAE-C1-INH. This applies to many physicians in the above-mentioned specialties, as well as to general practitioners, internists (including gastroenterologists), emergency physicians, anesthetists, dentists, and physicians that deal specifically with rare diseases.

General remarks

Angioedema, formerly often referred to as Quincke edema, is localized edema persisting for 1–3 (maximum 7) days that recurs at irregular intervals. Affected organs include the skin, gastrointestinal tract, and more rarely also the tongue, larynx, and pharynx, as well as other soft tissue organs. The same clinical symptom of "angioedema" is seen in several disease entities [5] of varying etiology. Some of them

are significantly more common than is HAE-C1-INH. HAE-C1-INH is of particular relevance, since fatalities due to asphyxiation can occur, and the quality of life of some patients is significantly impaired due to frequent and severe edema attacks. Therefore, this guideline focuses on HAE-C1-INH.

Epidemiology

The precise incidence of HAE-C1-INH is not known. It is likely to be around 1:50,000 [6]. There are no known differences in various ethnic groups. Men and women are equally affected.

Pathogenesis

Genetics

HAE-C1-INH is inherited in an autosomal dominant fashion; however, the percentage of spontaneous mutations (new mutations) is high at approximately 20%. The gene that codes for C1-INH is located on the long arm of chromosome 11 in the subregion q11.2–q13 and is made up of eight exons and seven introns. Thanks to new techniques to identify mutations, numerous mutations are now known—more than 450 to date [7–9]. All patients are heterozygous for the C1-INH defect. In type I HAE-C1-INH patients, the abnormal or deleted gene is not expressed. In patients with type II HAE-C1-INH, the abnormal gene is expressed and causes the synthesis of dysfunctional C1-INH. The heterozygous presence of one of these mutations results in the development of one of two possible C1-INH deficiencies: approximately 85% of patients have type I HAE-C1-INH. One sees impaired synthesis of C1-INH, which is quantitatively and functionally strongly reduced in plasma. The second form, type II HAE-C1-INH, is seen in around 15% of patients and is caused by a functional deficiency of C1-INH, which, however, is found at normal or even elevated levels in plasma.

Functional C1-INH deficiency and its effects

C1-INH is a glycoprotein with a molecular weight of 105,000 dalton. It is a single-chain protein made up of 478 amino acids and is produced predominantly in hepatocytes and to a small extent in blood monocytes, skin fibroblasts, and umbilical cord endothelial cells. C1-INH derives its name from the control of spontaneous autoactivation of the first complement component (C1) and the activated C1. Therefore, a functional deficiency of C1-INH leads to activation of the first steps of the complement cascade, which explains why the complement factor C4 is almost always permanently lowered in C1-INH deficiency.

Furthermore, C1-INH controls the kallikrein-kinin system (KKS) or contact system. C1-INH is responsible for the inhibition of the majority of plasma kallikrein and factor XIIa and, as such, is the most important regulator of KKS activation. In acute at-

tacks of HAE-C1-INH, kallikrein is not adequately inhibited due to C1-INH deficiency and increased bradykinin ensues locally at the end of the kallikrein-kinin cascade, which causes swelling. However, the precise pathogenesis of HAE-C1-INH has not been fully elucidated as yet. There are a number of indications that bradykinin is fundamentally involved in the development of edema in HAE due to C1-INH deficiency:

- Increased plasma bradykinin is found during acute HAE-C1-INH attacks [10].
- The plasma bradykinin level is higher in the drainage area of angioedema compared with the systemic circulation [11].
- A knock-out mouse model in mice deficient for C1-INH and the bradykinin B2 receptor revealed reduced vessel permeability compared with those that were not C1-INH-deficient [12], suggesting that the combination of bradykinin and the bradykinin B2 receptor mediates the development of angioedema.
- Icatibant, a bradykinin B2 receptor antagonist, is therapeutically effective in acute attacks of HAE due to C1-INH deficiency [13].

Clinical symptoms

From a clinical perspective, HAE-C1-INH is characterized by episodes of edema (edema attacks, attacks), which resolve spontaneously. These attacks affect the skin, gastrointestinal tract, and—more rarely—the respiratory tract. Types I and II HAE-C1-INH do not differ in terms of their clinical symptoms.

Prodrome Fatigue, exhaustion, increased thirst, aggressiveness, depressive mood, and erythema marginatum may precede symptoms.

Skin swelling This usually occurs in the face, extremities, and genital region. Skin swelling in HAE is virtually never associated with pruritus, but rather with a more or less pronounced feeling of tightness—in the advanced stage occasionally also with pain and burning. Pronounced skin swelling can be extremely painful. Swelling persists on average for 1–3 days, but can also resolve after several hours or persist for as long as 7 days. Although the occurrence of urticarial wheals does not belong to the clinical picture of HAE, it does not rule it out.

Gastrointestinal attacks In addition to skin symptoms, most patients experience irregularly alternating gastrointestinal symptoms [14, 15], with massive cramp-like abdominal pain and nausea being the most common, often accompanied by nausea and vomiting. Over the course of these attacks, which usually last 2–7 days, it is not uncommon to see concomitant ascites, which resolves completely after several days. Watery diarrhea due to fluid accumu-

lation in the lumen of the edematous intestine is also common. Together with the accompanying ascites, this can lead to substantial fluid loss and thus to hemoconcentration and, consequently, to clinical circulatory symptoms, including shock [15].

In some patients, the abdominal symptoms can occur in isolation, i.e., without skin symptoms, which, due to severe pain and acuteness of their condition, has occasionally led in the past to unnecessary explorative laparotomies being undertaken for suspected “acute abdomen” or appendicitis.

Laryngeal edema Some patients report involvement of the upper respiratory tract, i.e., laryngeal edema (more precisely, supraglottic edema) [16, 17]. The most frequent cause of death is asphyxiation due to laryngeal edema [18], which frequently follows trauma to the oral cavity or pharynx, particularly after dental surgery/tooth extraction or tonsillectomy [19]. Laryngeal edema can also occur up to 24 h following the intervention.

Asphyxiation due to laryngeal edema Deaths due to laryngeal edema are rare [18–20]. Patients whose disease was undiagnosed prior to asphyxiation are often affected. In other cases, although the diagnosis and required treatment were known, asphyxiation occurred nevertheless for a variety of reasons [18, 20].

Other organs In rarer cases, other organs may be affected by edema attacks, including the hypopharynx, the oropharynx with the soft palate and uvula, as well as the tongue and other organs [21]. Swelling of the urinary tract can imitate an infection.

Disease course

HAE-C1-INH onset occurs in the first or second decade of life—in some patients even later—on average around the age of 11 years. Recurrent edema attacks may be seen in the further course, usually consisting of cutaneous swelling and painful gastrointestinal attacks. The frequency and intensity of edema attacks vary considerably from patient to patient and may change over the course of the patient's life. They range from no attacks to attacks at intervals of a few days. Even within the same family, patients are affected to varying degrees. On average, women are more affected compared to men [21]. During pregnancy, attacks may be more frequent, rarer, or remain unchanged in their frequency [22, 23]. Swelling is rare during and shortly before birth. Laboratory values for C1-INH do not allow conclusions to be drawn on the frequency or severity of attacks.

In advanced age, disease flares in HAE-C1-INH are generally characterized by somewhat milder symptoms in some patients; however, edema attacks rarely cease completely.

Trigger factors for edema attacks

Most edema attacks appear spontaneously without an identifiable trigger. Factors that can trigger an attack primarily include trauma such as blows or pressure, psychologically stressful situations, and infectious diseases such as colds or flu. Iatrogenic trauma such as surgical procedures in the head region (dental surgery, tonsillectomy) and intubation can cause angioedema [24, 25]. It is important to note that edema attacks do not usually occur during the surgical procedure, but with a delay of 4–36 (on average 14) h following the intervention [24]. Menstruation or ovulation is responsible for edema attacks in some patients.

The tendency to develop edema attacks can be massively increased by the use of angiotensin converting enzyme (ACE) inhibitors; therefore, ACE inhibitors are contraindicated in HAE. It would appear that the use of angiotensin (ATII) receptor blockers (sartans) can sometimes also increase the tendency to develop edema attacks. Estrogen-containing contraceptives, as well as estrogens in hormone replacement therapy, can exacerbate the disease [26, 27].

Diagnosis

Biochemical diagnostic methods

Biochemical diagnostic tests (laboratory diagnostic tests in plasma) include the following parameters in the case of clinical suspicion of HAE-C1-INH:

- C1-INH activity
- C1-INH concentration
- C4 concentration

These values are reduced in plasma in type I HAE-C1-INH patients during an attack and in symptom-free intervals. Values of less than 50% for C1-INH activity and less than 50% for C1-INH concentration compared to normal are evidence of C1-INH deficiency. In isolated cases, plasma C4 levels may be normal. In type II HAE C1-INH, C1-INH activity and C4 are permanently reduced; C1-INH concentration, however, is normal or even elevated.

A “screening test” with only one of these parameters can neither prove nor exclude HAE-C1-INH.

The diagnosis of type I or II HAE-C1-INH is established on the basis of:

Diagnostic recommendation

C1-INH activity, C1-INH concentration, and C4 should be determined by means of laboratory tests in all cases of suspected HAE-C1-INH. “Screening tests” with only one of these parameters should not be performed. In the case of pathological levels, follow-up testing should be performed, preferably at a center with an experienced laboratory.

- Recurrent peripheral swelling of the skin and/or attacks of abdominal pain and possibly laryngeal edema
- The associated laboratory findings, i.e., reduced C1-INH activity with or without reduced plasma C1-INH concentration
- Where applicable, a positive family history (negative in the case of new mutations; see above)

Genetic diagnostic testing

In the case of unequivocal clinical and laboratory findings, genetic testing for HAE-C1-INH is unnecessary. The molecular genetic tests used today have a detection rate of 90–95%, making false negative findings not that rare. As such, they are less reliable than laboratory findings. However, they are recommended for patients in whom—despite testing—no precise diagnosis is possible due to contradictory plasma test results (e.g., C1-INH activity between 50–70% and corresponding symptoms). In the case of such patients, it is advisable to contact a treatment center (see below) and let them establish the indication for genetic testing. Mutation searches in the C1-INH gene are carried out commercially at a number of genetic laboratories in Germany.

Prenatal diagnostic testing

In principle, prenatal diagnosis is possible by means of genetic testing of chorionic villi or amniotic fluid. A prerequisite of this is that a causal mutation in the C1-INH gene in the family with HAE-C1-INH is known. Testing of this kind should only be performed on the basis of strict indication criteria.

Postnatal diagnostic testing in children

Due to fluctuating complement values in the first year of life, the three above-mentioned diagnostic plasma parameters are not reliable until the age of 1 year at the earliest [4]. Despite limited reliability, diagnostic testing before the age of 1 year can provide an indication of the presence of HAE.

Family testing

Family testing, i.e., testing blood relatives for the three parameters mentioned above, is required. It is of particular importance since it can help to avoid cases of asphyxiation in undiagnosed patients. New muta-

Recommendation for family testing

In the case of proven C1-INH deficiency, all blood-related family members should be tested for C1-INH deficiency.

tions (see above) are possible, in which case parents and siblings exhibit normal plasma parameters.

Differential diagnosis

The differential diagnosis includes acquired angioedema due to C1-INH deficiency (AAE-C1-INH; no familial occurrence, possible lymphoproliferative diseases or autoimmune diseases as underlying diseases, C1q often reduced in plasma, in some cases autoantibodies against C1-INH present), as well as types of hereditary HAE with normal C1-INH (HAEnCI, type III HAE; normal values for C1-INH activity, C1-INH level, and C4 in plasma; to date, diagnosis only possible using genetic testing [28–30]), as well as other acquired forms of angioedema [5] that are not due to C1-INH deficiency. The most common differential diagnoses include chronic urticaria (with or without wheals) and ACE inhibitor-mediated angioedema. Abdominal attacks of HAE-C1-INH may be misdiagnosed as appendicitis.

Treatment

Treatment goals

Treatment goals include preventing asphyxiation, preventing attacks, or reducing disease activity (frequency, severity, and duration of attacks) and, as a result, normalizing quality of life.

General measures

Patient information

Due to the severe symptoms (gastrointestinal attacks, risk of asphyxiation), managing and treating patients with HAE-C1-INH represents a considerable responsibility. It is mandatory to provide patients with comprehensive and detailed information on symptoms, in particular initial symptoms of laryngeal edema, as well as trigger factors. The patient information session should be documented. The patient must be provided with an individual plan of how to respond in the case of these symptoms. Likewise, family members must be informed about the disease and the necessary measures to be taken. Affected patients should be provided with an emergency medical ID card (see below). Since all these measures are extremely important and also time-consuming, it is advisable to make use of the

many years of experience that an HAE treatment center has and to refer the patient there. There are several treatment centers of this kind in Germany with experienced specialists that treat large numbers of HAE-C1-INH patients. Angioedema outpatient clinics can be found, e.g., at the following centers in Germany: Department of Dermatology, University Hospital Mainz; Department of Pediatrics, University Hospital Frankfurt; Department of Dermatology, Charité Berlin; ENT Department of the TU Munich; ENT Department, University Hospital Ulm; and Department of Dermatology and Allergy, Hannover Medical School (see below for addresses).

Ideally, patients are treated close to where they live by their family physician or treating physician in close cooperation with an HAE treatment center.

Discontinuation of drugs that heighten disease activity

Estrogens (oral contraceptives, hormone replacement therapy) and ACE inhibitors can significantly increase the frequency and severity of attacks in HAE-C1-INH patients. They should be discontinued and avoided in the future. Data in the literature on sartans are conflicting in this regard. As a precaution, they should also be avoided.

Drug treatment

There are essentially two different therapeutic strategies that are used: either the attacks are treated as soon as they become apparent to the patient (on-demand therapy) or long-term treatment is performed with the aim of preventing the attacks (prophylaxis). All patients should be provided with drugs for on-demand therapy and ideally be able to use these themselves. Early administration of on-demand medication promotes early-stage resolution of swelling. Prophylaxis has the advantage that the majority of (and in the ideal case all) attacks can be prevented. Since attacks can occur despite prophylactic measures, all patients should be provided with on-demand medication.

On-demand therapy for acute attacks is considered particularly appropriate in patients with rare attacks. It has the advantage that the patient is able to manage with less medication compared to long-term prophylactic treatment.

Recommendation on patient information

Once the diagnosis of HAE-C1-INH has been confirmed, the patient and his family should be provided with detailed information on the disease. This includes explaining the possible consequences of laryngeal edema (death by asphyxiation, permanent disability).

Treatment recommendation

Taking the individual patient's situation into account, the decision should be taken at regular intervals as to whether on-demand therapy or prophylaxis should be undertaken. The option, advantages, and risks of self-administration should be elucidated.

Treatment of acute edema attacks

General remarks

The severity of attacks ranges from mild to life-threatening. It is not always possible to predict how severe an attack will be from the initial symptoms. Mild swelling of the hands and feet do not necessarily require treatment if it affects only one finger or the back of the hand. In general, swelling of the hands or feet can lead to massive occupational impairment and disability, depending on the type of occupation. This should be borne in mind when establishing the indication for treatment. Irrespective of the selected on-demand therapy, it has been shown that early administration of the on-demand medication reduces the severity and duration of attacks more effectively compared to administration of on-demand medication at a later time [31–33]. It is advisable to avoid, by means of timely treatment, extensive or functionally restrictive swelling, e.g., of an entire limb, or swelling regularly followed by swelling of other parts of the body. Facial swelling in HAE-C1-INH should always be treated, since laryngeal edema may ensue, as was the case in 28.5% of patients in a case series [21]. The majority of abdominal attacks are so painful that drug treatment with the on-demand medication is necessary. Patients with pharyngeal or laryngeal angioedema always constitute an emergency due to the imminent danger of asphyxiation and should be immediately treated and monitored in the nearest hospital. The reader is also referred to the German-language website run by the German Society for Angioedema (*Deutsche Gesellschaft für Angioödeme*)—www.hae-notfall.de—which provides information on how to respond in such situations.

Treatment of laryngeal edema in the setting of HAE-C1-INH depends on how advanced laryngeal edema is. In the case of life-threatening respiratory distress, immediate intubation should be carried out, including the use of fiber optics, or in extreme emergencies, cricothyrotomy or tracheotomy should be performed. Whatever the case may be, immediate treatment with C1-INH concentrate or icatibant is the drug therapy of first choice.

Recommendation on treating attacks

Patients should be informed about the advantages, as well as the potential risks, of on-demand therapy. Appropriate medication should be recommended. This should be based on a joint decision taken by the physician and the patient.

Treatment recommendation

Patient information on how to respond to, and on the treatment of, laryngeal edema should be provided as a matter of urgency.

Drug treatment of acute attacks

C1-INH concentrate

Efficacy The administration of C1-INH concentrate, i.e., substitution of the deficient or dysfunctional protein during the attack, restores the inhibitory control of the kallikrein-kinin cascade (see above).

Human C1-INH concentrate has proven to be highly effective in the treatment of acute attacks. A concentrate of this kind was approved for intravenous injection in Germany in 1979 as C1 Inactivator (Behringwerke), in 1985 in pasteurized and virus-inactivated form as C1 Inactivator (Behring), in 2001 as Berinert® P, and in 2011 as additionally nanofiltered Berinert® (CSL Behring GmbH, Marburg, Germany). Therefore, more than 30 years of experience has been gained in Germany in the treatment of acute HAE-C1-INH attacks with this concentrate [34]. A series of non-placebo-controlled studies demonstrated its efficacy in the treatment of laryngeal edema [16, 35], abdominal attacks [31], and skin swelling [36] in HAE-C1-INH. As part of the approval of Berinert® in the US, a randomized controlled (RCT) study on 125 patients with type I or type II HAE-C1-INH was conducted between 2005 and 2007; the study showed Berinert® (20IU/kg body weight (BW)) to be statistically significantly superior compared to placebo [37]. At this dosage, symptom improvement was seen on average after 30 min, irrespective of the severity of edema in the facial or abdominal region. In June 2011, the C1-INH concentrate Cinryze® (Shire, UK) was also approved in Europe for the treatment of HAE attacks.

One should strive to initiate treatment as early as possible, i.e., at an early stage of the attack [31, 38]. What is termed as a rebound phenomenon, i.e., the short-term recurrence of swelling following an injection, is virtually non-existent with C1-INH concentrate treatment.

Dosage Berinert® 500 and Berinert® 1500 are approved for the treatment of attacks in type I and II HAE-C1-INH in adults, adolescents, and children. The above-mentioned RCT study [37] with Berinert® showed the treatment of acute attacks in the facial and abdominal region with 20IU/kg BW to be statistically significantly superior compared to placebo. Although treatment with 10IU/kg BW was effective compared to placebo, the difference failed to meet statistical significance. This study outcome contrasts with previous practical and published results with C1-INH concentrate in numerous patients and thousands of attacks. According to these studies, 500IU

were highly effective in the vast majority of patients. However, some attacks and patients required 1000 IU, but virtually never more than this dose. In an observational study on 61 patients, 500 IE Berinert® P was needed in 468 attacks and 1000 IU in only nine attacks (2%) [39]. In other studies, 500 IU was sufficient for the effective treatment of 68.6% of the 4834 abdominal attacks in 75 patients [31], 81% of the 2104 cases of skin swelling in 47 patients [36], and 24.9% of the 193 laryngeal edemas in 18 patients [35]. Why the results of the RCT study contradict all previous results is ultimately unclear. The results of the RCT study published in 2009 led in many countries to the approval of a dosage of 20 IU/kg BW (i. e., 1400 IU, almost three Berinert® vials (à 500 IU each) or one Berinert® 1500 vial for the treatment of an acute attack in a 70-kg patient).

The recommended Berinert® dose of 20 IU/kg BW recommended in the product information should always be used to treat angioedema in the head or neck region, since laryngeal edema is per se life-threatening. In the case of non-life-threatening swelling, i. e., hand, foot, or genital swelling, as well as abdominal attacks, which account for approximately 99% of acute attacks, one is entirely justified to adapt the dose to the needs of the patient and, where appropriate, select a lower initial dose of 500 IU or 1000 IU.

The manufacturer of Cinryze® recommends a dose of 1000 IU for the treatment of an acute attack in adults and adolescents.

Safety The safety profile of C1-IHN concentrate (Berinert®) is extremely favorable. Anaphylactic reactions have been observed in extremely rare cases. An unexpected increase in disease activity has been reported in the case of frequent administration of C1-INH concentrate in the long-term treatment in a few patients [40, 41]. Virus transmission has not been observed. The safety profile of Cinryze® is similarly favorable. Berinert® and Cinryze® undergo pasteurization and filtration during production. As in all patients receiving (or who could receive) plasma derivatives, hepatitis B immunization (active immunization) is advised.

Time of injection Early injection is recommended in acute attacks. Initial improvement usually begins on average 30–60 min following intravenous injection.

Self-administration, self-treatment at home Berinert®, Cinryze®, and Ruconest® (see below) are approved in Germany for self-treatment at home, to date only for intravenous administration. Some patients in Germany (and many other countries) now inject themselves with one of the C1-INH preparations, or let a close family member or employee of a commercial home-care company perform the injection. The advantages for the patient of self-treatment at home are enormous, particularly for patients that suffer

regular attacks. Self-treatment at home enables early injection, i. e., as soon as the attack begins, thereby shortening the attack and preventing a full-blown attack with all its negative effects.

The selection of patients for self-treatment at home with intravenous injections is based on the following criteria: proven C1-INH deficiency, motivation and compliance regarding home self-treatment, written consent, access to a telephone during self-treatment, suitable venous access, presence of a partner during self-treatment at home.

Patients require appropriate prior training for self-administration—where necessary, in the presence of family members. The training is comprehensive and covers information on: the basics of anatomy, compliance with hygiene measures, preparing the injection solution, intravenous injection technique, how to respond in the case of complications or inadequate effect, and documentation according to the German Transfusion Law, among many other points. Relevant online material is available on the websites of the pharmaceutical companies that offer the products.

This type of training program can be provided by physicians or medically supervised assistants, as well as by a commercial home-care service. Success needs to be determined by a physician and regularly monitored [42]. The treating physician is not permitted to delegate the responsibility for home self-treatment.

Icatibant

Efficacy Icatibant is a synthetic decapeptide with a structure similar to that of bradykinin. However, it contains five non-proteinogenic amino acids (D-Arg, L-Hyp, L-Thi, D-Tic, and L-Oic). It is possible to treat an HAE-C1-INH attack by antagonizing the binding of bradykinin to the bradykinin B2 receptor. Icatibant is injected subcutaneously. A phase-II study showed that icatibant is effective in acute attacks of HAE-C1-INH [13]. Three extensive multicenter RCT studies (FAST-1, FAST-2, and FAST-3) also showed icatibant to be effective and safe in skin swelling and abdominal attacks in HAE compared to placebo or tranexamic acid [43, 44]. The primary endpoint was not achieved in the FAST-1 study; the significance in abdominal attacks was insufficient. Icatibant was also shown to be effective in laryngeal edema. According to the results of the FAST-1 and FAST-2 studies, a recurrence of swelling appeared after 6 or more hours following injection (rebound phenomenon) in about 10% of the treated attacks, and a second or (extremely rarely) third icatibant injection was required. Icatibant has been approved for the symptomatic treatment of acute HAE-C1-INH attacks in adults since July 2008, under the trade name Firazyr® (Shire, UK).

Dosage Firazyr® is approved for the treatment of acute HAE-C1-INH attacks in adults, adolescents, and children. Firazyr® is injected subcutaneously. A 3-ml pre-filled syringe contains 30 mg icatibant—the

dosage approved for adults. One pre-filled Firazyr® syringe is usually sufficient. In the case of insufficient relief or recurrence of symptoms (see above), a second injection can be administered 6 h later. If relief is still insufficient or symptoms recur following the second injection, a third injection can be administered after a further 6 h. The maximum dose within 24 h is three subcutaneous injections of 30 mg icatibant each. Dosage is weight-adjusted for children.

Safety According to experience to date, the safety profile of icatibant is highly favorable. It is common for erythema, wheal formation, and burning pain to occur at the injection site. Systemic side effects include, e. g., fatigue and a feeling of weakness.

Time of injection Early injection is recommended in acute attacks. Initial improvement usually begins on average 30–60 min following injection. Attack duration is significantly shorter and milder in the case of early injection compared to later injection of icatibant [33].

Self-administration Icatibant has been approved for self-injection by patients since March 2011. The responsibility for home self-treatment by the patient must remain with the treating physician.

Conestat alfa

Efficacy Conestat alfa (Ruconest®, Pharming Group, The Netherlands) is a recombinant human (rh) C1 inhibitor developed for the treatment of HAE-C1-INH attacks. Ruconest® is produced by recombinant DNA technology in the milk of transgenic rabbits. Three RCT studies and one open-label extension study showed Ruconest® to be highly effective [45–48]. Differences in posttranslational glycosylation result in a distinctly shortened half-life compared to C1-INH in human plasma. Ruconest® was licensed for the treatment of acute HAE-C1-INH attacks in Europe in October 2010.

Dosage Ruconest® is approved in Europe for use in adolescents and adults and, since 2017, also approved for self-administration. It is injected intravenously. According to the manufacturer, adults up to 84 kg BW receive 50 IU/kg BW, and adults with higher BW 4200 IU (two vials, each reconstituted in 14 ml sterile water).

Safety The safety profile for Ruconest® is highly favorable according to experience to date. The commonest side effect of Ruconest® is headaches. Since one healthy volunteer with an unreported rabbit allergy developed an anaphylactic reaction following administration of rh-C1-INH, the European Medicines Agency (EMA) decided that, due to the risk of allergic reactions, Ruconest® is contraindicated in patients with known or suspected rabbit allergy.

Fresh frozen plasma

Due to its C1-INH content, fresh frozen plasma (FFP) is also effective in acute HAE-C1-INH attacks. There are no controlled studies on this, but rather a series of individual observations of the efficacy of 500 ml FFP. However, in addition to coagulation factors, FFP also contains kallikrein-kinin system proteins, meaning that more bradykinin may be produced by these, potentially leading to a worsening of acute attacks [49]. FFP is not virus-inactivated. The use of FFP in HAE-C1-INH attacks should only be considered if none of the above-mentioned approved drugs is available.

Ineffective drugs

Corticosteroids, antihistamines, adrenaline, and adrenaline-derivatives are not effective in HAE-C1-INH attacks.

Which drug to use for attacks?

At present, five drugs are available in Germany for the treatment of acute attacks in adults: Berinert® (C1-INH concentrate), Firazyr® (icatibant), Cinryze® (C1-INH concentrate), Ruconest® (rh C1-INH), and FFP. All are highly effective. Head-to-head comparative studies are not available to date. The advantages and disadvantages of the drugs are discussed above. FFP should only be used in emergencies, if Berinert®, Firazyr®, Cinryze®, or Ruconest® is unavailable. Androgens and tranexamic acid (see below) are not suitable for the treatment of acute attacks due to their delayed onset of action.

Treatment of acute attacks during pregnancy and lactation

Berinert® is well-suited for the treatment of acute attacks during pregnancy and lactation, as demonstrated in several observational studies [22, 23]. Cinryze® has also been successfully used in pregnancy. The treatment of acute attacks in pregnancy with Firazyr® has not been recommended to date. Sufficient experience with its use in humans is not available as yet, despite several case studies [50–52]. It is not known whether Firazyr® passes into human breast milk. There is no data as yet on the use of Ruconest® in pregnancy and lactation. Use during pregnancy or lactation is not recommended, unless the treating physician deems the benefit to be greater than the possible risks.

Drug treatment of attacks in childhood

Berinert® is approved for the treatment of acute attacks in childhood. Children receive the same weight-adjusted dosage as adults. Cinryze® is approved for children over the age of 2 years. Children aged be-

Recommendation on prophylaxis

Patients should be informed about the option of prophylaxis. Prophylaxis should not be initiated until such time as on-demand therapy for attacks is no longer sufficiently effective.

tween 2 and 11 years with a BW of between 10 and 25 kg receive an intravenous dose of 500 IU when required, and 1000 IE at a BW of over 25 kg. Firazyr® (weight-adjusted) has been approved for the subcutaneous treatment of attacks in children and adolescents (2–17 years old). In an uncontrolled study with 32 patients aged between 2 and 17 years, more than 90% of patients showed improvement 2 h following Firazyr® injection [53]. The weight-adjusted dosage in children and adolescents is 1–3 ml. Ruconest® is approved for children aged over 12 years and adolescents. The safety and efficacy of Ruconest® in children aged 0–12 years have not been demonstrated as yet.

Long-term drug prophylaxis

All HAE-C1-INH patients should initially receive on-demand treatment for individual attacks. If it is not possible to achieve adequate symptom control despite appropriate on-demand therapy, long-term prophylaxis should be considered. This would be the case if, e.g., >12 severe attacks per year or >24 days with HAE-related symptoms still occur despite optimal on-demand therapy.

C1-INH concentrate

C1-INH concentrate can be used not only for acute treatment, but also for long-term prophylaxis. The first HAE-C1-INH patient was treated in this manner in 1989, with considerable success [54]. Further studies demonstrated good results with respect to efficacy and safety [41, 55, 56]. The weekly dose is 2 × 500 IU of C1-INH concentrate or more. In a randomized, controlled cross-over study (22 patients in two 12-week periods), the nanofiltered C1-INH concentrate Cinryze®, at a dose of 2 × 1000 IU/week, reduced the number of HAE attacks from 12.7 to 6.3. The severity and duration of remaining attacks were significantly decreased [57]. Cinryze® was approved for long-term prevention in the US in October 2008, as well as in Europe (Shire, UK) in June 2011. Cinryze® has also been approved for the prophylaxis of HAE-C1-INH in children—from the age of 6 years—in the EU since 2017.

Despite many years of experience with long-term intravenous prophylaxis with Berinert® in Germany, Berinert® is currently not approved for this indication in Europe. Its good efficacy is documented in case reports and patient series [58]. In an uncontrolled study, 14 patients were treated with one or more Berinert® injections per week for 9 years on average. Prior to

treatment, 93.3% of attacks were severe, while under prophylaxis this was the case in only 3.8% [41].

In some patients with frequent injections of C1-INH concentrate, even those under long-term prophylaxis, an increase in disease activity is seen, indicated by an increased number of attacks, greater C1-INH concentrate requirements, and/or the occurrence of rapidly developing multilocular attacks [41].

The majority of patients who undergo long-term prophylaxis with C1-INH concentrate inject the drug themselves or let a family member or employee of a commercial home-care company perform the injection (see above, “Self-treatment at home”). Patients should be suited to, and trained for, this type of treatment involving multiple intravenous injections (see above, “Self-treatment at home”). Regular follow-up checks are also required, at least once a year. These are designed to review efficacy on the one hand, and, on the other, assess whether it is necessary to continue long-term prophylaxis or whether the switch to on-demand therapy can be made.

Treatment and possible break-through attacks need to be documented in a “swelling calendar.” According to the German Transfusion Law, plasma products are subject to documentation requirements; consequently, this also applies to C1-INH concentrates from human plasma.

Attenuated androgens

Attenuated androgens have been used for long-term prophylaxis since 1976; as such, there is plenty of data on their efficacy and safety. Danazol and oxandrolone are used; stanozolol is no longer available. The efficacy of androgens is high. In a double-blind randomized cross-over study with danazol (600 mg/day) vs. placebo in a total of nine patients, danazol significantly reduced the number of attacks (2.2% vs. 93.6%) [59]. Although all patients in this study gained weight and all five women reported menstrual disorders, including amenorrhea (four out of five), side effects were described as “minimal.” However, such a high dose of danazol is no longer recommended today, with 200 mg/day now being the maximum dose. In a study published in 2008, 46% of patients using danazol were either completely symptom-free or had one or fewer attacks per year [60]. The attacks during danazol treatment were significantly milder compared to before or after treatment. Not all patients respond to androgen treatment. Efficacy can decline in some patients after several years [61]. Possible side effects include, e.g., weight gain, menstrual disorders, and virilization in women, as well as hepatotoxicity, depression, and arterial hypertension, and hemorrhagic cystitis in the case of long-term use [60, 62, 63]. Isolated cases of hepatocellular adenoma have been reported [64, 65], as well as hepatocellular carcinoma in a small number of patients. A long-term observational study found only 21% of danazol patients to be free

of side effects and 30 out of 118 patients discontinued danazol treatment due to side effects [60].

Monitoring includes:

- Prior to therapy and at 6-month intervals: blood pressure monitoring and laboratory tests including blood count with hemoglobin, liver enzymes, lipid levels, glucose, creatinine kinase, and thyroid tests
- Every 12 months: alpha-fetoprotein and ultrasound scan of the liver [60]

Attenuated androgens are not approved in Germany and need to be obtained via an international pharmacy. Anyone performing androgen treatment in HAE-C1-INH patients is also responsible for ensuring that the necessary monitoring of adverse side effects is carried out.

For all these reasons, and since androgens have often been used in the past on the basis of an incorrect indication and at excessively high doses with the resultant sequelae, it is advisable for this form of treatment—if considered at all—to be carried out at an HAE treatment center (see below). The indication for long-term drug prophylaxis must take into consideration the approved treatment alternatives, the risks of androgens, and the patient's personal situation. The number of patients treated with danazol has declined significantly in Germany.

Danazol dosage 200 mg or less per day. Individual dose adjustment until the lowest possible dose at which symptoms are suppressed is reached.

Contraindications Pregnancy (virilization of the female fetus is possible), lactation, childhood, prostate cancer, porphyria, severe heart, liver, and renal failure, active thrombosis or thromboembolic events, even in the patient history, and androgen-dependent tumor. Interactions are numerous and must be taken into account prior to prescription (carbamazepine, phenytoin, barbiturates, oral anticoagulants, sex hormones, antihypertensive drugs, antidiabetic agents, cyclosporine, tacrolimus, ethyl alcohol, alphacalcidol, statins).

Tranexamic acid

Two antifibrinolytic agents have proven effective in HAE-C1-INH: epsilon-aminocaproic acid (EACA) and tranexamic acid. A double-blind placebo-controlled cross-over study with 16 g EACA daily vs. placebo demonstrated significant efficacy for EACA in four patients [66]. Another placebo-controlled cross-over study with tranexamic acid showed a marked improvement in HAE-C1-INH in the majority of patients [67]. Tranexamic acid has been used for the long-term treatment of HAE-C1-INH since 1972 [68]; it is better tolerated than is EACA. In general, the efficacy of tranexamic acid (Cyklokapron® [MEDA Pharma, Bad Homburg, Germany]) in adults is distinctly lower compared to attenuated androgens. Since it has fewer

adverse effects, it is often used in children with HAE-C1-INH.

Dosage An initial dose of 20–50 mg/kg BW up to a maximum of 3 g in adults should be used. The daily dose should then be titrated down to the lowest effective dose.

Contraindications Pregnancy, renal insufficiency, and acute thrombosis or thromboembolic events. Its use is highly limited in the case of a positive family history of thrombophilia or active thromboembolic events. According to the product information, patients with a history of thromboembolic disorders or with a conspicuous frequency of thromboembolic disorders in their family history (high-risk thrombophilic patients), Cyklokapron® film-coated tablets may only be used on the basis of strict indication criteria following consultation with a physician experienced in hemostaseology and under careful medical supervision.

Possible side effects Possible side effects include gastrointestinal symptoms, myalgia involving elevated creatinine kinase and (at least on the basis of theoretical considerations) thrombosis. Patients predisposed to thrombosis should not be treated with tranexamic acid. Since impaired sense of color can also develop, regular ocular fundus examinations are necessary in the case of long-term treatment.

Progestins

Progestins can be helpful in the treatment of women with HAE-C1-INH. Although they are not approved and there are no RCT on their use, there are reports on treatment success in case series [69, 70]. Desogestrel is a progestin-only pill (POP). Approximately two thirds of women reported symptom improvement on progestin. In contrast, seven out of 31 women experienced more pronounced HAE-C1-INH symptoms [70, 71]. Dosage is the same as recommended for contraception. Weight gain and intermenstrual bleeding, among others, are possible side effects. Progestin treatment should not be combined with androgen treatment or tranexamic acid treatment. In general, the beneficial effects of progestin treatment are significantly more modest compared to prophylaxis with a C1-INH concentrate or attenuated androgens.

Short-term drug prophylaxis

Where possible, HAE-C1-INH patients should receive C1-INH concentrate for short-term prophylaxis 1 h prior to all interventions associated with mechanical effects on the upper respiratory and digestive tracts, e.g., dental surgery, tooth extractions, other surgical procedures in the mouth and throat area, as well as intubation [24] (When using Berinert®, the manufacturer recommends the administration of 1000 IU

for adults and 15–30 IU/kg BW for children and adolescents within 6 h prior to surgery, and when using Cinryze®, the manufacturer recommends short-term prophylaxis with 1000 IU within 24 h prior to surgery). Since not all attacks can be avoided despite short-term prophylaxis of this kind, further medication should be available over the subsequent 24 h [24].

Future developments

Work is underway to develop new treatment options in order to achieve the goal whereby HAE-C1-INH patients can lead as normal a life as possible. These potential new developments primarily relate to drugs intended for long-term prophylaxis. Developments are at various stages. Two developments are already well advanced:

- The subcutaneous administration of C1-INH concentrate [72]. Subcutaneous treatment with the Berinert derivative Haegarda® for long-term prophylaxis, which has been approved in the US since 2017, has proven to be highly effective. Similarly, “Berinert 2000IU” and “Berinert 3000IU” will be available in Europe for subcutaneous use.
- Subcutaneous or oral treatment with novel kallikrein inhibitors [73, 74].

Particularly in the case of long-term prophylaxis in hereditary angioedema, i.e., regular exposure of the patient to the drug over years or decades, long-term safety is especially important alongside efficacy.

Prognosis

Mortality due to HAE-C1-INH has diminished in recent years, not least due to numerous patient-information campaigns, transparent communication methods, and worldwide activity by patient organizations. It was particularly high in the past due to a lack of suitable diagnostic and therapeutic options. In some families, the mortality rate reached 25–50%. The cause of death is virtually always asphyxiation due to laryngeal edema. This disease can still cause death today, albeit rarely [18, 20]. Undiagnosed patients that develop edema of the upper respiratory tract in a manner that is unexpected both for themselves and those around them are at greatest risk. If the diagnosis and thus the risk it poses are known, suitable preventive measures can be taken, particularly in the form of detailed information on the disease and especially on the initial symptoms of edema, trigger factors, and emergency measures.

Irrespective of mortality, patients with HAE-C1-INH are often also affected by severe impairments in their daily and professional lives [75–77]. These can be significantly improved by means of adequate and effective treatment of symptoms or prophylactic treatment.

Recommendation on stocking drugs for emergency treatment

All patients should have sufficient drugs for at least two attacks available at home and when traveling.

Practical recommendations

All HAE-C1-INH patients should be issued with an emergency medical ID card. ID cards of this kind (multilingual) are available from the treatment centers and the German self-help group listed below.

HAE-C1-INH patients should have an adequate amount of Berinert®, Firazyr®, Cinryze®, or Ruconest® to treat two attacks available at home and with them when traveling. The patient and their disease should be known to the nearest hospital.

In the case of schoolchildren, teachers should be informed about the fact that attacks may occur, how these manifest, and what action needs to be taken. This information should be provided in written form.

Addresses of treatment centers, specialist societies, and patient self-help groups

Treatment centers with particular experience in this field and which can be consulted by colleagues include:

- Angioedema Outpatient Clinic, Department of Dermatology, University Medical Center Mainz, Germany (Tel.: +49(0)6131-177290; email: konrad.bork@unimedizin-mainz.de, petra.staubach@unimedizin-mainz.de)
- Angioedema Outpatient Clinic, Hemophilia Center Rhein Main, Mörfelden-Walldorf, Germany (Tel.: +49(0)6105-9638900; email: inmaculada.martinez@hzrm.de, info@hzrm.de)
- Comprehensive Care Center for Hereditary Angioedema, Department of Pediatrics, University Hospital Frankfurt, Germany (Tel.: +49(0)69-63016432, -6312; email: aygoeren@em.uni-frankfurt.de)
- Angioedema Outpatient Clinic, Charité Allergy Center, Department of Dermatology, Venereology, and Allergology, Charité University Hospital, Berlin, Germany (Tel.: +49(0)30-450518043; email: marcus.maurer@charite.de, markus.magerl@charite.de)
- Angioedema Outpatient Clinic, ENT Department of the Technical University of Munich, Germany (Tel. +49(0)89-41405380; email: u.strassen@tum.de, m.bas.hno@gmail.com)
- Angioedema Outpatient Clinic, Department of Oto-Rhino-Laryngology, Head and Neck Surgery, University Hospital Ulm, Germany

(Tel. +49(0)731-50059501; email: jens.greve@uniklinik-ulm.de)

- Angioedema Outpatient Clinic, Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany
(Tel. +49(0)511-5327650; email: wedi.bettina@mh-hannover.de)

In Germany, there is a specialist medical society that focuses specifically on hereditary and acquired angioedema:

German Society for Angioedema (*Deutsche Gesellschaft für Angioödeme*, DGA)

Chairman: Prof. Dr. Konrad Bork

Department of Dermatology, University Medical Center Mainz

Langenbeckstraße 1

Email: konrad.bork@unimedizin-mainz.de

Web: www.angioedema.de

There is a German self-help group for patients with hereditary angioedema:

HAE Association (*HAE-Vereinigung e. V.*)

Chairwoman: Lucia Schauf

Mühlenstraße 42 c

52457 Aldenhoven, Germany

Web: www.hae-online.de

Details of the international patient self-help organization are provided below:

HAEi—International Patient Organization for C1 Inhibitor Deficiencies

Kirstinelundsvej 7

8660 Skanderborg, Denmark

Email: info@haei.org

Web: www.haei.org

Participating societies

- German Society for Angioedema (*Deutsche Gesellschaft für Angioödeme e. V.*, DGA,) (Prof. Dr. Konrad Bork, in charge; Prof. Dr. Petra Staubach)
- German Society for Internal Medicine (*Deutsche Gesellschaft für Innere Medizin e. V.*, DGIM) (Dr. Emel Aygören-Pürsün)
- German Society for Otorhinolaryngology (*Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde e. V.*, DGHNO) (Prof. Dr. Murat Bas)
- German Society for Allergy and Clinical Immunology (*Deutsche Gesellschaft für Allergologie und klinische Immunologie e. V.*, DGAKI) (Prof. Dr. Tilo Biedermann, Prof. Dr. Karin Hartmann, Prof. Dr. Bettina Wedi)
- German Dermatological Society (*Deutsche Dermatologische Gesellschaft e. V.*, DDG) (Prof. Dr. Markus Magerl, Prof. Dr. Marcus Maurer)

- German Society for Child and Adolescent Medicine (*Deutsche Gesellschaft für Kinder- und Jugendmedizin e. V.*, DGKJ) (Dr. Inmaculada Martinez-Saguer)
- German Society for Pediatric Allergology and Environmental Medicine (*Gesellschaft für Pädiatrische Allergologie und Umweltmedizin e. V.*, GPA) (PD Dr. Hagen Ott)
- German Association of ENT Surgeons (Deutscher Berufsverband der Hals-Nasen-Ohren-Ärzte, BVHNO)
- German HAE Patient Association (HAE-Vereinigung, HAE-SHG)

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