PROFESSOR VOLKER WAHN (Orcid ID : 0000-0003-1218-2940)
DR RENATE KRÜGER (Orcid ID : 0000-0001-8728-9385)

Article type : Original

Hereditary angioedema in children and adolescents – A consensus update on therapeutic strategies for German-speaking countries

V. Wahn[1], W. Aberer[2], E. Aygören-Pürsün[3], K. Bork[4], W. Eberl[5], M. Faßhauer[6], R. Krüger[1], M. Magerl[7], I. Martinez-Saguer[8], P. Späth[9], P. Staubach-Renz[4], C. Weber-Chrysochoou[10]

(1) Department of Pediatric Pneumology, Immunology, and Intensive Care Medicine, Charité Universitätsmedizin, Berlin, Germany
(2) Department of Dermatology and Venereology, Medical University, Graz, Austria
(3) Center for Children and Adolescents, University Hospital, Frankfurt, Germany
(4) Department of Dermatology, Johannes Gutenberg University, Mainz, Germany
(5) Department of Pediatrics, City Hospital, Braunschweig, Germany
(6) Department of Pediatric Rheumatology, Immunology and Infectiology, Municipal Hospital St. Georg, Leipzig, Germany
(7) Department of Dermatology and Allergy, Charité Universitätsmedizin, Berlin, Germany
(8) Hemophilia Centre Rhine Main, Mörfelden-Walldorf, Germany
(9) Institute of Pharmacology, University, Bern, Switzerland
(10) Allergology Unit, Department of Dermatology, University Hospital, Zürich, Switzerland

Corresponding author:
Prof. Dr. Volker Wahn
Campus Virchow-Klinikum, Charité Centrum 17
Klinik für Pädiatrie (Pneumologie, Immunologie und Intensivmedizin)
Augustenburger Platz 1
D-13353 Berlin

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/PAI.13309

Telephone: +49 30 450 566 131
Fax: +49 30 450 566 931
E-mail: Volker.Wahn@charite.de

All authors contributed equally to this work.

Conflicts of interest

VW received a honorarium from CSL Behring for preparation of and participation in the meeting as well as repeated corrections of the manuscript. In addition, he was paid for chairing a session at the German Allergy Congress 2019.

WA has collaborations with BioCryst, CSL Behring, Pharming, and Shire/Takeda.

EA reports personal fees from Adverum, BioCryst, Kalvista and Pharming, and grants and personal fees from CSL Behring and Shire/Takeda.

KB received speaker honoraria from CSL Behring and Shire/Takeda.

WE received speaker / consultancy fees from Bayer, CSL Behring, and Shire/Takeda.

MF received honoraria for lectures from CSL Behring, Shire/Takeda, and travel grants from Octapharma.

RK received speaker honoraria and travel grants from CSL Behring.

MM is or was speaker and/or advisor for Attune, BioCryst, CSL Behring, Kalvista, Octapharma, Pharming, and Shire/Takeda.

IM received research funding and / or speaker / consultancy fees from BioCryst, CSL Behring, Kalvista, Octapharma, Pharming, and Shire/Takeda.

PS received an honorarium from CSL Behring providing expertise in the meeting as well as repeated corrections of the manuscript. From his former employment, PS holds shares of CSL Ltd.

PSR received honoraria and travel grants from BioCryst, CSL Behring, Octapharma, Pharming, Shire/Takeda, Viropharma.

CW received honoraria from CSL Behring and Shire/Takeda.

All authors declare that their recommendations are solely based on scientific evidence and approval status and are not influenced by the sponsor.

Financial support

The consensus meeting was sponsored by CSL Behring GmbH (Hattersheim, Germany). Medical writing services were performed on behalf of CSL Behring GmbH.

Abstract

Background/Methods: At a consensus meeting in August 2018, pediatricians and dermatologists from German-speaking countries discussed the therapeutic strategy for the treatment of pediatric patients with types I and II hereditary angioedema due to C1 inhibitor deficiency (HAE-C1-INH) for Germany, Austria, and Switzerland, taking into account the current marketing approval status. HAE-C1-INH is a rare disease that usually presents during childhood or adolescence with intermittent episodes of potentially life-threatening angioedema. Diagnosis as early as possible and an optimal management of the disease are important to avoid ineffective therapies and to properly treat swelling attacks. This article provides recommendations for developing appropriate treatment strategies in the management of HAE-C1-INH in pediatric patients in German-speaking countries. An overview of available drugs in this age group is provided, together with their approval status, and study results obtained in adults and pediatric patients.

Results/Conclusion: Currently, plasma-derived C1 inhibitor concentrates have the broadest approval status and are considered the best available option for on-demand treatment of HAE-C1-INH attacks and for short- and long-term prophylaxis across all pediatric age groups in German-speaking countries. For on-demand treatment of children over 2 years of age, bradykinin-receptor icatibant is an alternative. For long-term prophylaxis in adolescents, the parenteral kallikrein inhibitor lanadelumab has recently been approved and can be recommended due to proven efficacy and safety.

Keywords: C1-INH (C1 inhibitor), hereditary angioedema, consensus, treatment, pediatric.

Abbreviations:

BK	bradykinin
C1-INH	C1 inhibitor (C1-esterase inhibitor)
CHMP	Committee for Medicinal Products for Human Use
EAACI	European Academy of Allergy and Clinical Immunology
FXII(a)	Factor XII (activated)
HAE	hereditary angioedema
HAE-C1-INH	hereditary angioedema due to C1 inhibitor deficiency
IU	international unit
pdC1-INH	plasma-derived C1 inhibitor concentrate
rhC1-INH	recombinant C1 inhibitor concentrate
SERPING1	serine protease inhibitor, clade G, member 1
SmPC	Summary of Product Characteristics

Introduction

Hereditary angioedema (HAE) due to C1 inhibitor (C1-INH) deficiency (HAE-C1-INH) is a rare disease that usually first manifests itself during childhood or adolescence as recurrent spontaneous swellings of the skin and mucosal tissues, resulting in skin disfigurement, colicky abdominal pain, or obstruction of the upper airways. There is no cure for HAE-C1-INH but effective treatments are on the market to manage the symptoms. Current guidelines for treatment and management include an international guideline with the focus in adult patients and only two recommendations specifically for children not taking into account the regulatory status of products and clinical praxis in specific countries[1], an international consensus on the diagnosis and management of pediatric patients,[2] and a guideline aimed at physicians treating patients with HAE-C1-INH in Germany.[3]

Our first consensus specifically tailored to pediatric patients in German-speaking countries was issued in 2012.[4] At a consensus meeting, experts from Germany, Austria, and Switzerland formulated recommendations for developing appropriate treatment strategies. To update these recommendations, taking into account changes in marketing approval, recent research, and new therapeutic options, another meeting was held in August 2018.

The resulting consensus intends to provide physicians in German-speaking countries with a guideline to achieve optimal management of HAE-C1-INH in pediatric patients. The recommendations provided cannot be the sole basis for a treatment decision, but the individual course of disease, life circumstances, and wishes of the patients must be considered.

These recommendations correspond to the high standard of drug availability in German-speaking countries. As it would be desirable to have these conditions also in countries outside Central Europe, an additional aim is to promote medical awareness across countries by publishing this consensus.

Pathophysiology of hereditary angioedema

The various known forms of HAE have a bradykinin (BK)-mediated pathophysiology. In the majority of cases, patients have either insufficient levels of C1-INH protein (type I) or normal or elevated levels along with reduced function (type II). Both forms result from mutations in the gene encoding C1-INH (*SERPING1)*. C1-INH is the main inhibitor of the active contact system proteases, plasma kallikrein and coagulation factor XII (FXII). Deficiency of C1-INH therefore leads to dysregulation of the contact and kinin systems, resulting in overproduction of BK that causes an increase in vascular permeability and thus promotes angioedema formation.[5] In 75% to 80% of patients, HAE-C1-INH is inherited as an autosomal dominant trait[1] and occurs de novo in the remaining patients.

HAE forms other than HAE-C1-INH involve edema formation in patients with normal C1-INH. They are caused by mutations in other genes, such as *F12*, resulting in enhanced activation of FXII, or the genes for plasminogen and angiopoetin-1.[5] Recently, a mutation in the gene encoding kininogen 1 that changes the N-terminal cleavage site of BK has been associated with HAE.[6] These other forms only rarely affect children,[7] which is why HAE with normal C1-INH (formerly named HAE type III) is not further discussed here.

The network for genetic control of BK metabolism is just evolving and genetic studies may elucidate unknown aspects of angioedema pathogenesis and heterogeneity[5] by identifying further genes potentially involved in the regulation of BK production, its cleavage, and edema formation.[8]

Recommendations for diagnosis

How to recognize HAE-C1-INH

In the majority of patients, first symptoms of HAE-C1-INH occur during childhood or early adolescence,[2] often as recurrent abdominal pain caused by swelling of the intestinal wall.[9] Being only rarely seen in other types of angioedema, this may be a distinguishing feature. Other common symptoms include swelling of the extremities, face, thoracic wall and genital region, and life-threatening edemas in the upper airways.

Delays of several years until a diagnosis is established, during which patients suffer from wrong diagnoses, treatments, and unnecessary surgical interventions, are not uncommon.[10,11] This is partly because the disease is rare and not well known among physicians, but also because symptoms are ambiguous and resemble those of other diseases. Particularly abdominal attacks are sometimes accompanied by vomiting and diarrhea, both frequent symptoms in childhood. In cases of recurrent, unclear abdominal pain, we therefore strongly recommend sonography during an acute phase, whereby a thickening of the bowel wall in particular is a sign of HAE-C1-INH.[12] However, mild intestinal edema may be overlooked on imaging even in symptomatic patients[13] so that negative scans do not necessarily exclude a diagnosis of HAE-C1-INH.

External swelling sites are pale, hard, and doughy, sometimes causing considerable tension-induced pain. They mimic mast cell-mediated angioedema, but are not accompanied by pruritic wheals. Accordingly, HAE-C1-INH is unlikely with recurrent itching urticarial wheals, whereas erythema marginatum, a non-itching sharply defined rash, is a prodromal symptom that has also been reported in very young children.[14,15]

Triggers of an attack cannot always be determined. However, known potential triggering factors such as emotional distress, physical trauma, infection, changes in estrogen levels, and certain food[16,17,18] should be explained to the patient.

Testing procedure

For an accurate diagnosis of types I or II HAE-C1-INH, determination of C1-INH antigen concentration and function (with a chromogenic substrate assay) in plasma are usually sufficient. Genetic testing for *SERPING1* mutations is not indicated for routine diagnosis and should only be done in special cases when all other values are within the normal ranges.

As most patients have persistently low antigen C4 levels,[3] C4 testing, having a high level of specificity and sensitivity for HAE-C1-INH,[19] can provide clarity in cases with unclear findings.[3] C4 testing alone with unknown C1-INH concentration and function is not sufficient for diagnosis, because normal C4 levels do not necessarily exclude HAE-C1-INH and low C4 levels may be caused by other conditions.[20,21]

Because C1-INH is an acute phase protein, blood sampling for laboratory diagnostics should primarily be performed during attack-free periods and in the absence of inflammatory processes. Diagnostics should always be done in accredited laboratories using validated assays. Commercially available tests with positive, negative, and calibration samples are recommended. Interpretation of results should take into account age-dependent normal values. Especially before the age of 1 year, antigenic and functional C1-INH levels are often lower than in adults.[2]

Time of diagnosis

All patients with suspected HAE-C1-INH, whether due to conspicuous symptoms or a known family history, should be tested. Because of the considerable consequences of a diagnosis, a positive test should be repeated and confirmed.

Newborns with a positive family history are considered potentially affected until HAE-C1-INH is excluded and must be well observed and tested as early as possible, to ensure optimal management of the disease. This is particularly important in view of the potentially fatal outcome of upper airway attacks.[1] A valid diagnosis based on C1-INH activity, C1-INH antigen concentration, and C4 testing can be performed from the age of 4 weeks on and is to be verified at the age of 1 year. It is important that physicians mention, if necessary repeatedly, that other family members ought to be tested for their disease status.[2]

Prenatal testing is not recommended because a diagnosis at this time has no direct consequences for mother or child and there are no known cases of in utero symptoms.[2] Likewise, testing umbilical cord blood is not recommended as even in unaffected children, antigenic and functional C1-INH cord blood levels are only approximately 70% and 62% of adult normal values.[2]

Therapeutic options and clinical evidence

HAE-C1-INH therapeutics are described below, their approval status summarized in **Table 1**, and their mechanisms of action shown in **Figure 1**. An overview of specific risks is provided in **Table 2**.

Data from studies in pregnant and nursing mothers are not considered.

Human plasma-derived C1-INH concentrates

Human plasma-derived C1-INH (pdC1-INH) concentrates replace and take over the function of the missing or nonfunctional protein in inhibiting contact activation and the kallikrein-kinin system (**Figure 1**). Currently, two pdC1-INH products, Berinert® (CSL Behring GmbH, Marburg, Germany) and Cinryze® (Shire Services BVBA, Bruxelles, Belgium [part of Takeda Pharmaceutical Company Limited]) are available for pediatric patients (**Table 1**). See **Table 2** for specific risks.

pd C1-INH (Berinert)

pdC1-INH (Berinert) is available as a 500 international unit (IU) application set for intravenous injection, and a reduced-volume formulation (1500 IU vial) enabling shorter treatment time.[22] It is also available as sets of 2000 or 3000 IU for subcutaneous application.

See **Table 1** for the approval status.

On-demand treatment with intravenous pdC1-INH (Berinert):

Efficacy and safety of 20 IU/kg pdC1-INH (Berinert) have been shown in the pivotal randomized, double-blind, placebo-controlled study I.M.P.A.C.T.1 in 124 patients, including pediatric patients,[23] and were confirmed for long-term therapy in the open-label extension I.M.P.A.C.T.2 in 57 patients, also including pediatric patients.[24]

For 20 pediatric patients, efficacy and safety were confirmed in a retrospective observational study on on-demand home therapy, which concluded that, as in adults, home therapy with pC1-INH is effective and safe in the treatment of HAE-C1-INH attacks in pediatric patients.[25]

See **Table 3** for a short summary of studies.

Short-term prophylaxis with intravenous pdC1-INH (Berinert):

No specific results are available for short-term prophylaxis in children and adolescents but efficacy and safety were confirmed in a patient survey of 171 patients[26] and the Berinert registry[27] of 79 patients, which also included pediatric patients. See **Table 3** for a short summary.

Long-term prophylaxis with subcutaneous pdC1-INH (Berinert):

Efficacy and safety of twice weekly 40 or 60 IU/kg subcutaneous pdC1-INH (Berinert) (HAEGARDA® in the United States) were shown in the randomized, double-blind COMPACT study for 90 patients. No specific results have been reported for pediatric patients, the study included patients from the age of 17 years.

Similarly, the randomized, open-label extension of COMPACT, including pediatric patients from the age of 8 years, demonstrated that long-term replacement therapy with subcutaneous pdC1-INH (Berinert) is safe with a substantial and sustained prophylactic effect.[29]

See **Table 3** for a short summary.

A subgroup analysis of COMPACT showed that switching from intravenous to subcutaneous long-term prophylaxis may result in a significant benefit for patients.[30] Additional clinical experience and further studies are needed to confirm these observations.

Additional safety information for pdC1-INH (Berinert):

For intravenous pdC1-INH (Berinert), the product information leaflets state that there are no very common, common, or uncommon adverse reactions from postmarketing experience and scientific literature.

For subcutaneous pdC1-INH (Berinert), nasopharyngitis (runny or stuffy nose, sneezing, watery eyes) and injection site reactions are listed as very common, hypersensitivity (itching and rash) and dizziness are common.

pdC1-INH (Cinryze)

The other approved pdC1-INH, pdC1-INH (Cinryze), is available as a 500 IU application set for intravenous injection.

See **Table 1** for the approval status.

On-demand treatment with pdC1-INH (Cinryze):

A randomized, double-blind, placebo-controlled study showed good efficacy and safety for on-demand 1000 IU pdC1-INH (Cinryze) in 68 adult patients, including 12 children from the age of 6 years.[31] This benefit was confirmed for repeated treatment in an open-label extension in 113 patients, including 22 children from the age of 2.[32]

In an open-label study in 9 children <12 years, on-demand treatment with either 500 IU, 1000 IU, or 1500 IU pdC1-INH (Cinryze) was safe and effective.[33] It was therefore concluded that doses of <1000 IU may be appropriate in some pediatric patients.

See **Table 3** for a short summary of studies.

Long-term prophylaxis with pdC1-INH (Cinryze):

Of the patients in the acute-treatment study described above, 22 were treated in a long-term prophylaxis study, which included 4 patients ≤18 years of age and confirmed efficacy of pdC1-INH.[31]

The open-label extension in 146 patients, included 23 children from the age of 3.[34] The study showed that at 1000 IU twice weekly, pdC1-INH (Cinryze) was highly effective and safe in the majority of patients.

Likewise, in 12 children, routine prophylaxis was efficacious and safe in a randomized, single-blind Phase III study.[35]

See **Table 4** for a short summary of studies.

Additional safety information for pdC1-INH (Cinryze):

In the current E.U. Summary of Product Characteristics [SmPC] and Swiss product information, headache and nausea are listed as very common (in ≥1/10 cases), indicated by data from clinical studies and postmarketing reports. Hypersensitivity, dizziness, vomiting, rash, erythema, pruritus, injection site reactions, and pyrexia are common (≥1/100 to <1/10).

Recombinant human C1-INH concentrate

The active ingredient of recombinant human C1-INH concentrate (rhC1-INH) (Ruconest®, Pharming Group NV, Leiden, the Netherlands), conestat alfa, is a recombinant analog of pdC1-INH, produced in transgenic rabbits and purified from their milk. Its glycosylation is not identical to that of human C1-INH, which is presumably the reason for its shorter half-life of approximately 2 hours (current E.U. SmPC) but its function is the same (**Figure 1**).

rhC1-INH is available as a 2100 IU application set for intravenous injection.

See **Table 1** for the approval status.

On-demand treatment with rhC1-INH:

Two randomized, double-blind, placebo-controlled studies were conducted in 70 patients (from 17 years on), that showed good efficacy and safety for 50 IU/kg rhC1-INH.[36]

For 20 pediatric patients, the favorable results were confirmed in an open-label, single-arm Phase II study.[37]

So far, no head-to-head comparison with pdC1-INH concentrates has been published.

See **Table 3** for a short summary of studies.

Additional safety information for rhC1-INH:

The most common (in ≥1/100 to <1/10 cases) adverse reaction across clinical studies was headache (current E.U. SmPC). Other adverse reactions, mostly mild or moderate, occurred in <1/100 patients. Efficacy and safety in adolescent patients were consistent with those seen in adults. See **Table 2** for specific risks.

Bradykinin-receptor antagonist icatibant

Icatibant (Firazyr®, Shire Orphan Therapies GmbH, Berlin [part of Takeda Pharmaceutical Company Limited]) is a chemically synthesized decapeptide with a BK-like structure rendering the molecule resistant to enzymatic degradation. It is a selective antagonist of the BK B2 receptor that inhibits the interaction of BK with endothelial cells (**Figure 1**).

Icatibant is available as a 30 mg solution for subcutaneous injection in a pre-filled syringe.

See **Table 1** for the approval status.

On-demand treatment with icatibant:

In adult patients, the FAST study program, including 3 randomized double-blind studies, showed superiority of icatibant: in FAST-1 versus placebo for 56 patients[38] followed by an open-label extension period[39], in FAST-2 versus tranexamic acid for 74 patients[38] also followed by an open-label extension period[40], and in FAST-3 versus placebo for 88 patients, with efficacy and safety being confirmed for multiple attacks during an open-label extension period.[42]

For 11 children and 11 adolescents, a non-randomized, open-label Phase III study, confirmed efficacy of a single dose of icatibant (0.4 mg/kg; maximum 30 mg).[43]

During FAST-1 and FAST-2, there was evidence that a single dose of icatibant was not sufficient in some patients. This observation is supported by real-life data from the Icatibant Outcome Survey, which reports that 81% of 652 attacks resolved with a single injection of icatibant, compared with 19% that required one or more additional injections of icatibant and/or C1-INH rescue medication.[44]

See Table 3 for more details on the studies.

Additional safety information for icatibant:

Across clinical studies, for adult patients, the current E.U. SmPC and Swiss product information list injection site reactions as very common (in ≥1/10 cases) and the following adverse reactions as common (≥1/100 to <1/10): dizziness, headache, nausea, rash, erythema pruritus, pyrexia, and increased transaminases. See **Table 2** for specific risks.

Kallikrein inhibitors

Lanadelumab

Parenteral kallikrein inhibitor lanadelumab (Takhzyro®, Shire Pharmaceuticals Ireland Limited [part of Takeda Pharmaceutical Company Limited]), with its active substance lanadelumab, is a monoclonal antibody inhibiting the increased plasma kallikrein proteolytic activity that leads to angioedema attacks through proteolysis of high-molecular-weight kininogen to generate BK (**Figure 1**). Lanadelumab is available as a 300 mg solution for subcutaneous injection. See **Table 1** for the approval status.

Long-term prophylaxis with lanadelumab:

Efficacy and safety of long-term prophylaxis with different doses of lanadelumab were shown in the randomized, double-blind, placebo-controlled HELP study in 125 patients, including 10 adolescents ≥12 years of age.[45] Results for adolescents are not explicitly reported.

Additional safety information for lanadelumab:

In the current E.U. SmPC the following adverse events are listed as being very common (≥1/10): injection site reactions; and common (≥1/100 to <1/10): hypersensitivity, dizziness, maculo-papular rash, myalgia, and increased alanine and aspartate aminotransferases.

Safety of lanadelumab in a subgroup of 23 patients between 12 and <18 years was consistent with overall study results. See **Table 2** for specific risks.

Ecallantide

The active substance in Kalbitor® (Dyax Corp., Cambridge, MA, USA) is ecallantide (DX-88), a 60-amino-acid recombinant protein, which blocks kallikrein and is thereby expected to help reduce swelling attacks (**Figure 1**). Impaired control of kallikrein activity results in increased circulating BK levels, leading to increased endothelial permeability and leaking of fluid into the tissue, which in turn causes swelling.

During the submission process to receive marketing authorization from the European Medicines Agency, Dyax S.A. withdrew its application. Based on review of the submitted data and the company's response to the Committee for Medicinal Products for Human Use (CHMP) list of questions, the CHMP had concerns about hypersensitivity reactions, which were seen at a higher rate in patients treated with ecallantide, and about effectiveness of the proposed doses in heavier patients. Therefore, the CHMP concluded that the benefits of ecallantide did not outweigh its risks. Ecallantide is thus not approved in the European Union or any of the German-speaking countries (**Table 1**). In the United States, ecallantide has a boxed warning, highlighting the risk of anaphylaxis, see **Table 2**.

Attenuated androgens

In many parts of the world, attenuated androgens are used for short- and long-term prophylaxis in HAE-C1-INH, causing an increase in C1-INH plasma levels. They are not approved anymore in German-speaking countries (**Table 1**) and guidelines explicitly do not recommend androgens for long-term prophylaxis in young children.[1,2] For short-term prophylaxis, attenuated androgens (e.g., danazol) have been recommended in the past, even in children. Recent guidelines, however, recommend pdC1-INH concentrate as prophylaxis of choice.[1]

Because androgens may interfere with the natural growth, bone maturation, and sexual development of children[46] and have numerous other side effects, see **Table 2**, we consider their use contraindicated in pediatric patients and do not recommend this option. No appropriate clinical studies have been performed in children and adolescents with HAE-C1-INH and only a small case series provides some data on the efficacy and tolerability at low doses.[47]

Antifibrinolytics

Antifibrinolytics (ε-aminocaproic acid or tranexamic acid [cyclic analog of ε-aminocaproic acid]), such as Cyklokapron® (Meda Pharma, Bad Homburg, Germany), are chemically synthesized and exert their action in HAE-C1-INH by inhibiting the conversion of plasminogen to plasmin, and thereby activation of FXII (**Figure 1**). Antifibrinolytics are available as tablets for oral application. See **Table 1** for the approval status.

Antifibrinolytics are used to treat HAE-C1-INH in many parts of the world for lack of better alternatives. They are less effective than attenuated androgens but due to their good safety profile, see **Table 2**, they are sometimes propagated as a possible option for prophylaxis in children.[48] Two early double-blind, placebo-controlled studies (in 5 and 18 patients) showed a reduction in attack frequency.[49,50] A more recent prospective study comparing long-term prophylaxis in patients with and without tranexamic acid did not demonstrate any effect.[51] As more effective options are available, we do not recommend tranexamic acid for pediatric patients despite an existing approval.

Experimental approaches

A variety of experimental approaches have been discussed for HAE-C1-INH management, none of which can be recommended from today's perspective. These include antisense-mediated inhibition of either activated FXII or prekallikrein, which alleviated the effects of C1-INH depletion in a mouse model.[52]

A case of severe HAE in a previously HAE-negative subject after having received a liver transplant from a HAE-positive donor has been reported. Conversely, it is discussed whether HAE could be cured by transplanting a healthy liver.[53] To date, no such case is known.

Somatic gene therapy using an adenoviral vector carrying wildtype *SERPING1* gene provided sustained increase of human C1-INH activity levels in a mouse model and could potentially provide long-term protection from HAE-C1-INH attacks.[54] No data are yet available in humans.

General recommendations

All of the approved drugs are generally effective. In case of several possible treatment options, the choice should be discussed and advantages and disadvantages of therapies weighed up. The current drug approvals in the individual countries must be taken into account before deciding on an off-label treatment in carefully selected cases.

The following general recommendations are intended to provide guidance and simplify disease management. The individual clinical picture, external circumstances, and patient wishes must also be taken into account when establishing a therapy.

Patient care

Cooperation with a dedicated HAE center is essential to provide patients with access to disease-specific comprehensive care.

An action plan shows the patient and parents how to act in certain situations for optimal disease management at home and at daycare/school. This includes learning how to recognize prodromal signs and being sensitized to possible triggers.

An emergency medical card with the diagnosis and recommended treatment may prevent treatment delay and wrong medication.

The patient should keep a diary where each swelling is documented together with the medication used (for blood products including the batch number) and, if possible, trigger factors.

In general, a weight-dependent dosage is desirable for children and adolescents.

Self-administration

Home self-treatment under medical supervision is feasible for many patients, including children and adolescents. Patients, parents, and caregivers must be sufficiently trained in self-administration techniques and made aware of special precautions with respect to storage and handling.

Hormones for contraception

It is well known that sexual hormone fluctuations can influence attack frequency, and menstruation has long been recognized as a trigger in some women.[2] Puberty has also been reported to exacerbate the disease, as have been estrogen-containing contraceptives which should therefore be avoided.[55] Progestin-containing contraceptives may alleviate HAE-C1-INH symptoms, which is why, if well tolerated, these can be taken from the time of menarche.

Recommendations for on-demand therapy

With regard to the safety of the child, there is agreement that in very young patients under the age of 6, every attack should be treated. The recommended medications are safe and the benefits of treatment outweigh the risks. If there is no symptom relief upon self-treatment, an experienced physician must be consulted immediately.

In general, this also applies to children over 6 years. However, it is acceptable in certain situations with mild peripheral and gastrointestinal attacks without any progression or interference with everyday activities, to follow a wait-and-see approach.

It is strongly recommended to always treat attacks affecting the neck and head area, in particular if the upper respiratory tract is involved. Hospital admission may be necessary. Treatment of an attack in this area should start as soon as possible to stop further edema formation and promote its rapid regression.[56]

Recurrent abdominal attacks or attacks for which an otherwise effective treatment remains ineffective should be confirmed sonographically to rule out other possible causes.

Emergency HAE-specific medicine for the treatment of at least two attacks must be available to patients and within easy reach at all times.

In general, pdC1-INH concentrates and icatibant are recommended for on-demand treatment in children (**Table 4**). For dosing see **Table 1**. Icatibant is injected subcutaneously, and is a stable ready-to-use product with no need for reconstitution that can be easily taken along. Sustainability of the treatment effect is somewhat lower than of pdC1-INH. According to the current E.U. SmPC and Swiss product information, in case of insufficient relief or symptom recurrence, adults can administer a second injection after 6 hours and a third after a further 6 hours. For children, no details are given. pdC1-INH concentrates have the advantage of proven sustained efficacy, as in most cases they require only one application, and the disadvantage of intravenous administration (for on-demand treatment).

As no head-to-head comparative studies are available for pdC1-INH and icatibant, priority for one of the products cannot be determined but has to be agreed upon between physician and patient; a treatment decision must be based on individual factors such as product availability, patient's tolerance and possibility for easy venous access, adverse effects, and need for re-dosing with a product.

Recommendations for short-term prophylaxis

There are reports on patients who died of laryngeal attacks after dental treatment.[26] Therefore, short-term prophylaxis is recommended before procedures such as dental treatment with significant traumatization of the gums (with and without intubation), procedures requiring endotracheal intubation, surgical interventions in the neck and head area, and other essential surgical procedures. Even with short-term prophylaxis, emergency medication (pdC1-INH or icatibant) must be available for immediate use in case of breakthrough attacks.

Short-term prophylaxis is also recommended for stressful life events that may trigger an attack. In cases where it is unclear whether short-term prophylaxis should be given, the attending physician should contact the HAE center to achieve a decision.

We recommend to administer short-term prophylaxis as close as possible (30 minutes to 1 hour) to the planned procedure to ensure high plasma levels.

Only intravenous pdC1-INH concentrates are recommended for short-term prophylaxis in pediatric patients (Table 4). For dosing see **Table 1**. Previous recommendations of androgens and tranexamic acid are outdated due to the reasons described above.

Recommendations for long-term prophylaxis

The decision whether long-term prophylaxis is indicated must primarily be made by the physician. If the medical prerequisites are met, the patient should be involved in the decision process as to whether and how prophylaxis is to be established. Dosage and treatment interval should be adjusted so that the patient's individual burden of disease is minimized and costs are reasonable. We do not recommend long-term prophylaxis in patients with less than two attacks per month. Potential candidates are those with more frequent attacks, high disease burden, and severe impairment of everyday life, who cannot sufficiently control their HAE-C1-INH with on-demand therapy.

Attenuated androgens cannot be recommended for long-term prophylaxis in children due to the risks involved. We also do not recommend tranexamic acid because of doubts about its efficacy in HAE-C1-INH.[52]

Long-term prophylaxis cannot be recommended in patients younger than 2 years of age. For children younger than 6 years, there is no sufficient evidence available and no medication is approved. Options for older children and adolescents include pdC1-INH concentrates and lanadelumab, see Table 4 and **Table 1** for dosing.

As no head-to-head comparative studies are available for pdC1-INH and lanadelumab, priority for one of the products cannot be set. For a treatment decision, factors such as product availability, patient's tolerance and possibility for easy venous access, and treatment frequency must be taken into account. A decision on which drug to use should be made between physician and patient after weighing up all advantages and disadvantages.

Future perspectives

Oral kallikrein inhibitors

A potent small molecule inhibitor of plasma kallikrein, BCX7353, significantly lowered the attack rate compared with placebo when administered once daily at doses of at least 125 mg.[57]

On-demand treatment with 750 mg of the same compound had superior efficacy compared with placebo and was safe in a double-blind, placebo-controlled, randomized, crossover study in adults with HAE-C1-INH.[58]

A third potent selective small molecule plasma kallikrein inhibitor, KVD900, with pharmacokinetic properties well suited for rapidly-acting treatment of attacks, is currently being tested in a randomized, double-blind, placebo-controlled, Phase II, crossover study.[59]

Oral drugs for treatment of attacks in HAE-C1-INH patients, especially children, are highly desirable. We look forward to publication of appropriate clinical studies.

Factor XII antibodies

A humanized anti-FXIIa monoclonal antibody is in development for use in multiple indications including subcutaneous HAE-C1-INH therapy.[60,61] A randomized, placebo-controlled, parallel-arm, Phase II study is currently ongoing to investigate the clinical efficacy, pharmacokinetics, and safety of CSL312 prophylaxis to prevent attacks in adult patients.

Acknowledgments

We thank Eva Kestner (Trilogy Writing & Consulting GmbH) for medical writing services.

References

1. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema - the 2017 revision and update. Allergy 2018;73(8):1575-1596.
2. Farkas H, Martinez-Saguer, Bork K, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. Allergy 2017;72(2):300-313.
3. Bork K, Aygören-Pürsün E, Bas M, et al. Guideline: hereditary angioedema due to C1 inhibitor deficiency. Allergo J Int 2019;28:16-29.
4. Wahn V, Aberer W, Eberl W, et al. Hereditary angioedema (HAE) in children and adolescents -- a consensus on therapeutic strategies. Eur J Pediatr 2012;171(9):1339-1348.
5. Cicardi M, Zuraw BL. Angioedema due to bradykinin dysregulation. J Allergy Clin Immunol Pract 2018;6:1132-1141.
6. Bork K, Wulff K, Rossmann H, et al. Hereditary angioedema cosegregating with a novel kininogen 1 gene mutation changing the N-terminal cleavage site of bradykinin. Allergy 2019. doi: 10.1111/all.13869. [Epub ahead of print]
7. Magerl M, Germenis AE, Maas C, Maurer M. Hereditary angioedema with normal C1 inhibitor: update on evaluation and treatment. Immunol Allergy Clin North Am 2017;37(3):571-584.
8. Castellano G, Divella C, Sallustio F, et al. A transcriptomics study of hereditary angioedema attacks. J Allergy Clin Immunol 2018;142(3):883-891.
9. Busse P, Baker J, Martinez-Saguer I, et al. Safety of C1-inhibitor concentrate use for hereditary angioedema in pediatric patients. J Allergy Clin Immunol Pract 2017;5(4):1142-1145.
10. Zanichelli A, Magerl M, Longhurst H, et al. Hereditary angioedema with C1 inhibitor deficiency: delay in diagnosis in Europe. Allergy Asthma Clin Immunol 2013;9:29.
11. Martinez-Saguer I, Escuriola Ettingshausen C. Delayed diagnosis of hereditary angioedema: Thirty-nine years of inadequate treatment. Ann Allergy Asthma Immunol 2016;117(5):554-556.
12. Gakhal MS, Marcotte GV. Hereditary angioedema: imaging manifestations and clinical management. Emerg Radiol 2015;22(1):83-90.
13. Jalaj S, Scolapio JS. Gastrointestinal manifestations, diagnosis, and management of hereditary angioedema. J Clin Gastroenterol 2013;47(10):817-823.

14. Magerl M, Doumoulakis G, Kalkounou I, et al. Characterization of prodromal symptoms in a large population of patients with hereditary angio-oedema. Clin Exp Dermatol 2014;39(3):298-303.
15. Martinez-Saguer I, Farkas H. Erythema marginatum as an early symptom of hereditary angioedema: case report of 2 newborns. Pediatrics 2016;137(2):e20152411.
16. Caballero T, Maurer M, Longhurst HJ, et al. Triggers and prodromal symptoms of angioedema attacks in patients with hereditary angioedema. J Investig Allergol Clin Immunol 2016;26(6):383-386.
17. Savarese L, Bova M, De Falco R, et al. Emotional processes and stress in children affected by hereditary angioedema with C1-inhibitor deficiency: a multicenter, prospective study. Orphanet J Rare Dis 2018;13(1):115.
18. Steiner UC, Kölliker L, Weber-Chrysochoou C, et al. Food as a trigger for abdominal angioedema attacks in patients with hereditary angioedema. Orphanet J Rare Dis 2018;13(1):90.
19. Ohsawa I, Honda D, Nagamachi S, et al. Clinical and laboratory characteristics that differentiate hereditary angioedema in 72 patients with angioedema. Allergol Int 2014;63(4):595-602.
20. Karim Y, Griffiths H, Deacock S. Normal complement C4 values do not exclude hereditary angioedema. J Clin Pathol 2004;57(2):213-214.
21. Aabom A, Bygum A, Koch C. Complement factor C4 activation in patients with hereditary angioedema. Clin Biochem 2017;50(15):816-821.
22. Dempster J. Practicalities of a reduced volume formulation of a C1-INH concentrate for the treatment of hereditary angioedema: real-life experience. Allergy Asthma Clin Immunol 2018;14:44.
23. Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attack. J Allergy Clin Immunol 2009;124(4):801-808.
24. Craig TJ, Bewtra AK, Bahna SL, et al. C1 esterase inhibitor concentrate in 1085 hereditary angioedema attacks – final results of the I.M.P.A.C.T.2 study. Allergy 2011;66(12):1604-1611.
25. Kreuz W, Rusicke E, Martinez-Saguer I, et al. Home therapy with intravenous human C1-inhibitor in children and adolescents with hereditary angioedema. Transfusion 2012;52(1):100-107.
26. Bork K, Hardt J, Staubach-Renz P, Witzke G. Risk of laryngeal edema and facial swellings after tooth extraction in patients with hereditary angioedema with and without

prophylaxis with C1 inhibitor concentrate: a retrospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112(1):58-64.

27. Magerl M, Frank M, Lumry W, et al. Short-term prophylactic use of C1-inhibitor concentrate in hereditary angioedema: findings from an international patient registry. Ann Allergy Asthma Immunol 2017;118(1):110-112.
28. Longhurst H, Cicardi M, Craig T, et al. Prevention of hereditary angioedema attacks with a subcutaneous C1 Inhibitor. N Engl J Med 2017;376(12):1131-1140.
29. Craig T, Zuraw B, Longhurst H, et al. Long-term outcomes with subcutaneous C1-inhibitor replacement therapy for prevention of hereditary angioedema attacks. J Allergy Clin Immunol Pract 2019;7(6):1793-1802.
30. Craig TJ, Lumry W, Cicardi M, et al. Treatment effect of switching from intravenous to subcutaneous C1-inhibitor for prevention of hereditary angioedema attacks: COMPACT subgroup findings. J Allergy Clin Immunol Pract 2019;7(6):2035-2038.
31. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med 2010;363(6):513-522.
32. Riedl MA, Hurewitz DS, Levy R, et al. Nanofiltered C1 esterase inhibitor (human) for the treatment of acute attacks of hereditary angioedema: an open-label trial. Ann Allergy Asthma Immunol 2012;108(1):49-53.
33. Lumry W, Soteres D, Gower R, et al. Safety and efficacy of C1 esterase inhibitor for acute attacks in children with hereditary angioedema. Pediatr Allergy Immunol 2015;26(7):674-680.
34. Zuraw BL, Kalfus I. Safety and efficacy of prophylactic nanofiltered C1-inhibitor in hereditary angioedema. Am J Med 2012;125(9):938.e1-7.
35. Aygören-Pürsün E, Soteres DF, Nieto-Martinez SA, et al. A randomized trial of human C1 inhibitor prophylaxis in children with hereditary angioedema. Pediatr Allergy Immunol 2019;30(5):553-561.
36. Zuraw B, Cicardi M, Levy RJ, et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. J Allergy Clin Immunol 2010;126(4):821-827.
37. Reshef A, Grivcheva-Panovska V, Kessel A, et al. Recombinant human C1 esterase inhibitor treatment for hereditary angioedema attacks in children. Pediatr Allergy Immunol 2019;30(5):562-568.
38. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N Engl J Med 2010;363(6):532-541.

39. Malbrán A, Riedl M, Ritchie B, et al. Repeat treatment of acute hereditary angioedema attacks with open-label icatibant in the FAST-1 trial. Clin Exp Immunol 2014;177(2):544-553.
40. Baş M, Greve J, Hoffmann TK. Repeat treatment with icatibant for multiple hereditary angioedema attacks: FAST-2 open-label study. Allergy 2013;68(11):1452-1459.
41. Lumry WR, Li HH, Levy RJ, et al. Randomized placebo-controlled trial of the bradykinin B_2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. Ann Allergy Asthma Immunol 2011;107(6):529-537.
42. Lumry WR, Farkas H, Moldovan D, et al. Icatibant for multiple hereditary angioedema attacks across the controlled and open-label extension phases of FAST-3. Int Arch Allergy Immunol 2015;168(1):44-55.
43. Farkas H, Reshef A, Aberer W, et al. Treatment effect and safety of icatibant in pediatric patients with hereditary angioedema. J Allergy Clin Immunol Pract 2017;5(6):1671-1678.
44. Longhurst HJ, Aberer W, Bouillet L, et al. Analysis of characteristics associated with reinjection of icatibant: results from the icatibant outcome survey. Allergy Asthma Proc 2015;36(5):399-406.
45. Banerji A, Riedl MA, Bernstein JA, et al. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. JAMA 2018 27;320(20):2108-2121.
46. Frank MM, Zuraw B, Banerji A, et al. Management of children with hereditary angioedema due to C1 inhibitor deficiency. Pediatrics 2016;138(5).
47. Farkas H, Harmat G, Gyeney L, Füst G, Varga L. Danazol therapy for hereditary angio-oedema in children. Lancet 1999;354(9183):1031-1032.
48. Longhurst H, Zinser E. Prophylactic therapy for hereditary angioedema. Immunol Allergy Clin North Am 2017;37(3):557-570.
49. Frank MM, Sergent JS, Kane MA, Alling DW. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema. A double-blind study. N Engl J Med 1972;286(15):808-812.
50. Sheffer AL, Austen KF, Rosen FS. Tranexamic acid therapy in hereditary angioneurotic edema. N Engl J Med 1972;287(9):452-454.
51. Zanichelli A, Vaccini R, Badini M, Penna V, Cicardi M. Standard care impact on angioedema because of hereditary C1 inhibitor deficiency: a 21-month prospective study in a cohort of 103 patients. Allergy 2011;66(2):192-196.

52. Bhattacharjee G, Revenko AS, Crosby JR, et al. Inhibition of vascular permeability by antisense-mediated inhibition of plasma kallikrein and coagulation factor 12. Nucleic Acid Ther 2013;23(3):175-187.
53. Ameratunga R, Bartlett A, McCall J, Steele R, Woon ST, Katelaris CH. Hereditary angioedema as a metabolic liver disorder: novel therapeutic options and prospects for cure. Front Immunol 2016;7:547.
54. Qiu T, Chiuchiolo MJ, Whaley AS, et al. Gene therapy for C1 esterase inhibitor deficiency in a murine model of hereditary angioedema. Allergy 2019;74(6):1081-1089.
55. Bork K, Fischer B, Dewald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy. Am J Med 2003;114(4):294-298.
56. Maurer M, Aberer W, Bouillet L, et al. Hereditary angioedema attacks resolve faster and are shorter after early icatibant treatment. PLoS One 2013;8(2):e53773.
57. Aygören-Pürsün E, Bygum A, Grivcheva-Panovska V, et al. Oral plasma kallikrein inhibitor for prophylaxis in hereditary angioedema. N Engl J Med 2018;379(4):352-362.
58. Longhurst H, Moldovan D, Bygum A, et al. Oral plasma kallikrein inhibitor BCX7353 is safe and effective as an on-demand treatment of angioedema attacks in hereditary angioedema (HAE) patients: results of the ZENITH-1 trial. J Allergy Clin Immunol 2019;143(2):Suppl.AB36.
59. Hampton SL, De Donatis GM, Murugesan NI, et al. KVD900 as a single dose, rapid, oral plasma kallikrein inhibitor for the on-demand treatment of hereditary angioedema attacks: pharmacokinetic and pharmacodynamic results from a Phase 1 single ascending dose study. J Allergy Clin Immunol 2019;143(2):Suppl.AB39.
60. Cao H, Biondo M, Rayzman V, et al. Development and characterization of an anti-FXIIa monoclonal antibody for the treatment of hereditary angioedema. J Allergy Clin Immunol 2015;135(2):Suppl.AB194.
61. Cao H, Biondo M, Lioe H, et al. Antibody-mediated inhibition of FXIIa blocks downstream bradykinin generation. J Allergy Clin Immunol 2018;142(4):1355-1358.
62. Schneider L, Hurewitz D, Wasserman R, et al. C1-INH concentrate for treatment of acute hereditary angioedema: a pediatric cohort from the I.M.P.A.C.T. studies. Pediatr Allergy Immunol 2013;24(1):54-60.
63. Lumry W, Manning ME, Hurewitz DS, et al. Nanofiltered C1-esterase inhibitor for the acute management and prevention of hereditary angioedema attacks due to C1-inhibitor deficiency in children. J Pediatr 2013;162(5):1017-22.

Tables

Table 1: Approval status and dosing of products for the treatment of HAE-C1-INH in German-speaking countries (as of September 2019)

Products (application mode)	**Countries**	**Home therapy**	**Dosing per age group** On demand	Short-term prophylaxis	Long-term prophylaxis
pdC1-INH					
Berinert® 500/1500 [a] *(i.v.)*	Germany + Austria [b]	possible	**≥0 y:** 20 IU/kg	**0-<18 y:** 15-30 IU/kg **≥18 y:** 1000 IU	—
	Switzerland	possible	**≥0 y:** 20 IU/kg	**≥0 y:** 20 IU/kg	—
Berinert® 2000/3000 *(s.c.)*	Germany + Austria	possible	—	—	**≥12 y:** 60 IU/kg 2x/week
	Switzerland	—	—	—	—
Cinryze® *(i.v.)*	E.U.	possible	**2-11 y (10-25 kg):** 500 IU **≥2 y (>25 kg):** 1000 IU	**2-11 y (10-25 kg):** 500 IU **≥2 y (>25 kg):** 1000 IU	**6-11 y:** 500 IU every 3-4 days **≥12 y:** 1000 IU every 3-4 days
	Switzerland	possible	**≥6 y:** 1000 IU	**≥6 y:** 1000 IU	**≥6 y:** 1000 IU every 3-4 days
rhC1-INH					
Ruconest® *(i.v.)*	E.U.	possible	**≥12 y:** **<84 kg:** 50 IU/kg **≥84 kg:** 4200 IU	—	—
	Switzerland	—	—	—	—
Icatibant					

Firazyr® *(s.c.)*	E.U. + Switzerland	possible	**2 -<18 y:** **12-25 kg:** 10 mg **26-40 kg:** 15 mg **41-50 kg:** 20 mg **51-65 kg:** 25 mg **>65 kg:** 30 mg **≥18 y:** 30 mg	—	—
Lanadelumab					
Takhzyro® *(s.c.)*	E.U. + Switzerland	possible	—	—	**≥12 y:** 300 mg/2 weeks[c]
Tranexamic acid					
Cyklokapron® *(oral)*	Germany	possible	—	up to 3x1.5 g	up to 50 mg/kg daily[d]
	Austria	possible	—	2-3x500 mg 2-3x/day[e]	2-3x500 mg 2-3x/day[e]
	Switzerland	possible	—	25 mg/kg daily[e]	25 mg/kg daily[e]

HAE-C1-INH=hereditary angioedema due to C1 inhibitor deficiency; IU=international unit; i.v.=intravenous; pdC1-INH=plasma-derived C1 inhibitor concentrate; rhC1-INH=recombinant human C1 inhibitor concentrate; s.c.=subcutaneous; SmPC=Summary of Product Characteristics; y=years.

Note: Authorities responsible for approval are: in Germany the Paul Ehrlich Institut (PEI), in Austria the Bundesamt für Sicherheit im Gesundheitswesen (BASG), in Switzerland Swissmedic, and for central approval across the E.U. the European Medicines Agency (EMA).

a. In Switzerland, only 500 IU are approved.

b. Approved in Austria but not marketed so far.

c. May be reduced to every 4 weeks if attack free for a long period, especially for low body weight patients.

d. For children 1 to 2 g daily are recommended in the product information.

e. No age restriction according to product information.

Sources: Berinert Austrian, German, and Swiss product information; Cinryze E.U. SmPC, Swiss product information; Firazyr E.U. SmPC, Swiss product information; Ruconest E.U. SmPC; Takhzyro E.U. SmPC, Swiss product information.

Table 2: Specific risks and adverse events of products (approved and off-label) for the treatment of HAE-C1-INH

Active ingredient / trade name	Risks and adverse events
Human plasma-derived C1 inhibitor concentrates	
Berinert®, Cinryze®	The theoretical risk of pathogen transmission associated with all plasma products is minimized during manufacturing by dedicated virus reduction steps. No such transmissions have thus far been described for these products. In this respect, Berinert and Cinryze can be judged to be safe. For patients who regularly take preparations from human blood or plasma, a vaccination against hepatitis A and B is generally recommended.
Recombinant human C1 inhibitor concentrate	
Ruconest®	A potential risk of allergic reactions and formation of neutralizing antibodies is associated with recombinant products. Therefore, Ruconest is contraindicated in patients with rabbit allergy. Hypersensitivity reactions cannot be excluded. Patients must be closely monitored and carefully observed for any symptoms of hypersensitivity throughout the administration period. The risk is considered to be very low. To the best of our knowledge and based on published data, this has been sufficiently studied and is not a practical problem.
Bradykinin-receptor antagonist	
Icatibant / Firazyr®	From the theoretical perspective, caution is advised in patients with ischemic heart disease, unstable angina pectoris, and in the first weeks following a stroke. Clinically relevant problems in this regard have not been observed to date, especially not in children. Injection site reactions (skin irritation, swelling, pain, itchiness, erythema, burning sensation) are frequently reported.
Kallikrein inhibitors	
Lanadelumab / Takhzyro®	Mild hypersensitivity reactions have been observed.
Ecallantide / Kalbitor® (not licensed outside	Worth mentioning is the risk of anaphylactic reactions (frequency according to the boxed warning in the U.S. full prescribing information: 4%). Kalbitor may only be

U.S.)	administered by healthcare professionals with appropriate medical support.
Attenuated androgens	
e.g., Danazol, Danocrine™ (not licensed outside U.S.)	Adverse events are numerous and include weight gain, acne, edema, hair loss, voice change, menstrual disturbances, amenorrhea, flushing, sweating, emotional lability, and hepatic dysfunction in the case of long-term treatment. In children, adverse effects on bone maturation, sexual development, and growth have been reported.
Antifibrinolytics	
Tranexamic acid / Cyklokapron®	The most common adverse effects are dose-dependent gastrointestinal symptoms (nausea, vomiting, diarrhea). There is a hypothetical risk of arterial or venous thromboses. The frequency of these is not known.

HAE-C1-INH=hereditary angioedema due to C1 inhibitor deficiency, smPC=Summary of Product Characteristics.

Note: In general, product availability depends on the capacities of validated production facilities approved by (local) authorities. Furthermore, plasma products are dependent on the availability of donated blood.

Sources: Berinert Austrian, German, and Swiss product information; Cinryze E.U. SmPC, Swiss product information; Cyklokapron Austrian, German, and Swiss product information; Danocrine U.S. package insert; Firazyr E.U. SmPC, Swiss product information; Frank et al. 2016; Kalbitor U.S. prescribing information; Ruconest E.U. SmPC; Takhzyro E.U. SmPC, Swiss product informationTakhzyro.

Table 3: Study summaries

Product Study	Patient details	Dosing	Short summary of key efficacy results	Short summary of safety results
pdC1-INH				
Berinert			**On-demand (intravenous)**	
I.M.P.A.C.T.1[23,62] NCT00168103 (randomized, double-blind, placebo-controlled, Phase III)	124 patients, ***including 7 children ≥6 years***	20 IU/kg i.v. vs. placebo	With pdC1-INH, shorter median time to onset of relief (0.5 vs. 1.5 h; p=0.0025), secondary outcomes supported efficacy; ***pediatric patients: median time to onset of relief: 0.42 h, to complete resolution: 8.08 h***	4 h after treatment: no SAEs, AEs leading to discontinuation, or seroconversions
I.M.P.A.C.T.2[24,62] NCT00292981 (open-label extension)	57 patients, ***including 9 children ≥10 years***	20 IU/kg i.v.	Single dose sufficient in 99% of 1085 attacks at any body location; ***pediatric patients: median time to onset of symptom relief: 0.4 h, to complete resolution: 14.1 h***	Mainly mild or moderate AEs, 1 discontinuation due to AE, no related SAEs, inhibitory ABs, or viral transmissions

Retrospective, observational study[25]	***20 pediatric patients (7-18 years)***	500 / 1000 IU i.v. physician-based vs. home therapy	***Median time to initial symptom relief: 40 min (home therapy), 60 min (physician-based)***	***No AEs or seroconversions***
			Short-term prophylaxis (intravenous)	
Patient survey[26]	171 patients	500 / 1000 IU i.v. vs. no prophylaxis	With prophylaxis, 44% reduction of attacks (per-patient), 42% (per-attack) ***No details reported for pediatric patients***	No drug-related AEs
Berinert registry[27] NCT01108848	79 patients, ***including children ≥8 years***	Median dose (range) per i.v. infusion: 14.6 IU/kg (3.6-33.9 IU/kg) or 1,000 IU (500-3,500 IU)	Cumulative attack rates (CI) within days after treatment: 1 day: 0.04 (0.015-0.088) 2 days: 0.06 (0.028-0.115) 3 days: 0.11 (0.061-0.174) 4 days: 0.23 (0.158-0.319) ***No details reported for pediatric patients***	6 AEs in 6.3% of patients, 2 related AES
			Long-term prophylaxis (subcutaneous)	
COMPACT[28] NCT01912456 (randomized, double-blind, Phase III)	90 patients, ≥12 years	40 / 60 IU/kg s.c. twice weekly followed by placebo or vice versa	Median reduction in normalized number of attacks vs. placebo: 89% (40 IU), 95% (60 IU) ***No details reported for pediatric patients***	AEs were mainly mild, transient local site reactions, similar in all groups
NCT02316353[29] (randomized open-label extension)	126 patients, ***including children ≥8 years***	40 / 60 IU/kg s.c. twice weekly	Median annualized attack rates: 1.3 (40 IU/kg), 1.0 (60 IU/kg); median rescue medication use: 0.2, 0.0 times/year; 54% of 63 patients (60 IU/kg) symptom free during Months 1-6, 83% of 23 during Months 25-30 ***No details reported for pediatric patients***	Low incidence of AEs, similar in both dose groups, 12 SAEs, 1 discontinuation due to an AE
Cinryze			**On-demand**	
LEVP2005-1/A[31,63] NCT00289211 (randomized double-blind, placebo-controlled, Phase III)	68 patients, ***including 12 children ≥6 years***	1000 IU i.v. vs. placebo	With pdC1-INH, shorter median times to onset of unequivocal relief (all patients 2 vs. 4 h, p=0.02; ***pediatric patients 0.5 vs. 2 h***) and complete resolution of symptoms (12 vs. 25 h, p=0.004)	No related SAEs, discontinuations due to AEs, viral transmissions, or ABs
CHANGE2[32,63] NCT00438815 (prospective, open-label extension)	113 patients, ***including 22 children ≥2 years***	1000 IU i.v.	609 treated attacks in 101 patients: 68% achieved unequivocal relief within 1 h, 87% in 4 h; ***pediatric patients (121 attacks): 79% within 1 h, 89% in 4 h***	Mainly mild or moderate TEAEs, no related SAEs, discontinuations due to AEs, viral transmissions, or ABs

Open-label study[33]	***9 pediatric patients <12 years***	i.v. 500 IU (10-25 kg) / 1000 IU (>25 kg) / 1500 IU (>25 kg)	***Median time (range) to unequivocal symptom relief: was 0.5 h (0.25-2.5)***	***Treatment with all doses was well tolerated***
			Long-term prophylaxis	
LEVP2005-1/B[31,63] CHANGE1 NCT01005888 (randomized double-blind, placebo-controlled)	22 patients, ***including 4 patients ≤ 18 years***	1000 IU i.v. vs. placebo every 3-4 days (crossover after 12 weeks)	With prophylaxis, shorter average normalized attack rates (6.26 vs. 12.73); ***pediatric patients: lower mean number of attacks (7.0 vs. 13.0)***	88% of patients had AEs, no related SAEs, discontinuations due to AEs, viral transmissions, or ABs
CHANGE3[34,63] NCT00462709 (open-label extension)	146 patients, ***including 23 children ≥3 years***	1000 IU i.v. every 3-7 days	With prophylaxis, median monthly attack rate decreased from 3.0 to 0.19 ($p<0.001$); ***pediatric patients: 3.0 to 0.39***	No related SAEs, discontinuations due to AEs, viral transmissions, or ABs
NCT02052141[35] (randomized, single-blind study Phase III)	***12 pediatric patients (7-11 years)***	500 / 1000 IU i.v. twice weekly (crossover after 12 weeks)	***With prophylaxis, reduced mean monthly normalized number of attacks (SD) by 71% (27%) with 500 IU and 85% (20%) with 1000 IU***	***No SAEs, discontinuations, or ABs***
rhC1-INH			**On-demand**	
NCT00225147 NCT00262301[36] (randomized, double-blind, placebo-controlled)	70 patients, ≥12 years	50 / 100 IU/kg i.v. vs. placebo	Median time to beginning of symptom relief faster with 50 IU/kg (122 min; $p=0.013$) and 100 IU/kg rhC1-INH (66 min; $p<0.001$) vs. placebo (495 min) ***No details reported for pediatric patients***	No related SAEs, discontinuations due to AEs, rhC1-INH ABs, or host-related impurities
Open-label, single-arm Phase II study[37]	***20 pediatric patients (5-14 years)***	50 IU/kg i.v.	***Efficacious and safe, overall median time to beginning of symptom relief: 60 min***	***No related SAEs, hypersensitivity reactions, or neutralizing ABs***
Icatibant			**On-demand**	
FAST-1[38] NCT00097695 (randomized, double-blind, placebo-controlled, Phase II/III)	56 adult patients	30 mg s.c. vs. placebo	With icatibant, shorter median times to first symptom improvement (1.0 vs. 5.7 h; $p<0.001$) and significant symptom relief (2.5 vs. 4.6 h; $p=0.14$), rescue therapy: 11% (icatibant) vs. 45% (placebo) of patients ***No pediatric patients included in the study***	No SAEs, discontinuations due to AEs
Open-label extension[39] NCT00097695	72 adult patients	30 mg s.c.	1 injection sufficient in 88% of 340 attacks, 2 in 11%, 3 in 1% ***No pediatric patients included in the study***	

FAST-2[38] NCT00500656 (randomized, double-blind, controlled, Phase III)	74 adult patients	30 mg icatibant s.c. + placebo p.o. vs. 3 g tranexamic acid p.o. + placebo s.c.	With icatibant, shorter median times to first symptom improvement (1.5 h vs. 6.9 h; p<0.001) and significant symptom relief (2.0 h vs. 12.0 h; p<0.001) ***No pediatric patients included in the study***	No related SAEs, discontinuations due to AEs
Open-label extension[40] NCT00500656	54 adult patients	30 mg s.c.	Median time to onset of symptom relief: 2.0 h, second injection for 10% of 374 attacks ***No pediatric patients included in the study***	No related SAEs
FAST-3[41] NCT00912093 (randomized, double-blind, placebo-controlled, Phase III)	88 adult patients	30 mg s.c. vs. placebo	With icatibant, shorter median times to ≥50% reduction in symptom severity (2.0 vs. 19.8 h; p<0.001), onset of primary symptom relief (1.5 vs. 18.5 h; p<0.001), almost complete symptom relief (8.0 vs. 36.0 h; p=0.012), no need for rescue medication ***No pediatric patients included in the study***	No related SAEs, discontinuation due to AE
Open-label extension[42] NCT00912093	82 adult patients	30 mg s.c.	Similar median times to onset of primary symptom relief and almost complete symptom relief as in FAST-3 ***No pediatric patients included in the study***	6 related SAEs, 1 leading to discontinuation
NCT01386658[43] Open-label Phase III study	***11 children, 11 adolescents***	0.4 mg/kg s.c. ; max: 30 mg	***Median time to onset of symptom relief: 1.0 h***	***TEAEs were mild or moderate, no related serious TEAEs***
Lanadelumab			**Long-term prophylaxis**	
HELP[45] NCT02586805 (randomized, double-blind, placebo-controlled Phase III)	125 patients, ***including 10 patients ≥12-<18 years***	150 mg every 4 weeks, 300 mg every 4 weeks, or 300 mg s.c. every 2 weeks, vs. placebo for 26 weeks	With lanadelumab, lower mean monthly attack rate (0.26-0.53 vs. 1.97 attacks; p<0.001), higher number of attack-free patients (31%-44% vs. 2%; p<0.001) and attack-free days/month (26.9-27.3 vs. 22.6 days; p<0.001), lower need of C1-INH on-demand medication (20% vs. 66%) ***No details reported for pediatric patients***	Mostly mild or moderate TEAEs, most common related TEAE: injection site pain (41.7%), no related serious TEAEs

AB=antibody; AE=adverse event; CI=confidence interval; IU=international unit; i.v.=intravenous; pdC1-INH=plasma-derived C1-INH inhibitor concentrate; p.o.=oral; rhC1-INH=recombinant C1 inhibitor concentrate; SAE=serious adverse event; s.c.=subcutaneous; TEAE=treatment-emergent adverse event.

Table 4: Recommendations by age groups (as of September 2019)

	Age groups			
Therapy	**0-<2 y**	**2-<6 y**	**6-<12 y**	**≥12 y**
On demand				
Products	• Berinert (i.v.)	• Berinert (i.v.) • Cinryze (i.v.)[a] • Firazyr (s.c.)	• Berinert (i.v.) • Cinryze (i.v.) • Firazyr (s.c.)	• Berinert (i.v.) • Cinryze (i.v.) • Ruconest (i.v.) • Firazyr (s.c.)
General	• Always treat attacks affecting the neck and head area • Treat as early as possible • Children <6 y: also treat attacks at all other body locations • Children ≥6 y: consider attacks at all other body locations for on-demand treatment • Keep emergency medicine available and within easy reach at all times			
Short-term prophylaxis				
Products	• Berinert (i.v.)	• Berinert (i.v.) • Cinryze (i.v.)	• Berinert (i.v.) • Cinryze (i.v.)	• Berinert (i.v.) • Cinryze (i.v.)
General	• Recommended for all medical procedures with significant tissue traumatization and surgical interventions in neck and head area • For procedures where short-term prophylaxis is not given, keep emergency C1-INH concentrate available • Administer as shortly as possible before the planned procedure			
Long-term prophylaxis				
Products	• Not recommended	• None approved	• Cinryze (i.v.)	• Berinert (s.c.) • Cinryze (i.v.) • Takhzyro (s.c.)
General	• For long-term prophylaxis treatment decision, consider frequency of attacks, disease burden, and impairment of everyday life			

i.v.=intravenous; s.c.=subcutaneous; y=years.

Note: See **Table 1** for the approved dosing for each age group.

a. In Switzerland, Cinryze is not approved for children under 6 years of age.

Figure legend

Figure 1: Pathogenesis of hereditary angioedema and possible points of action for therapeutics

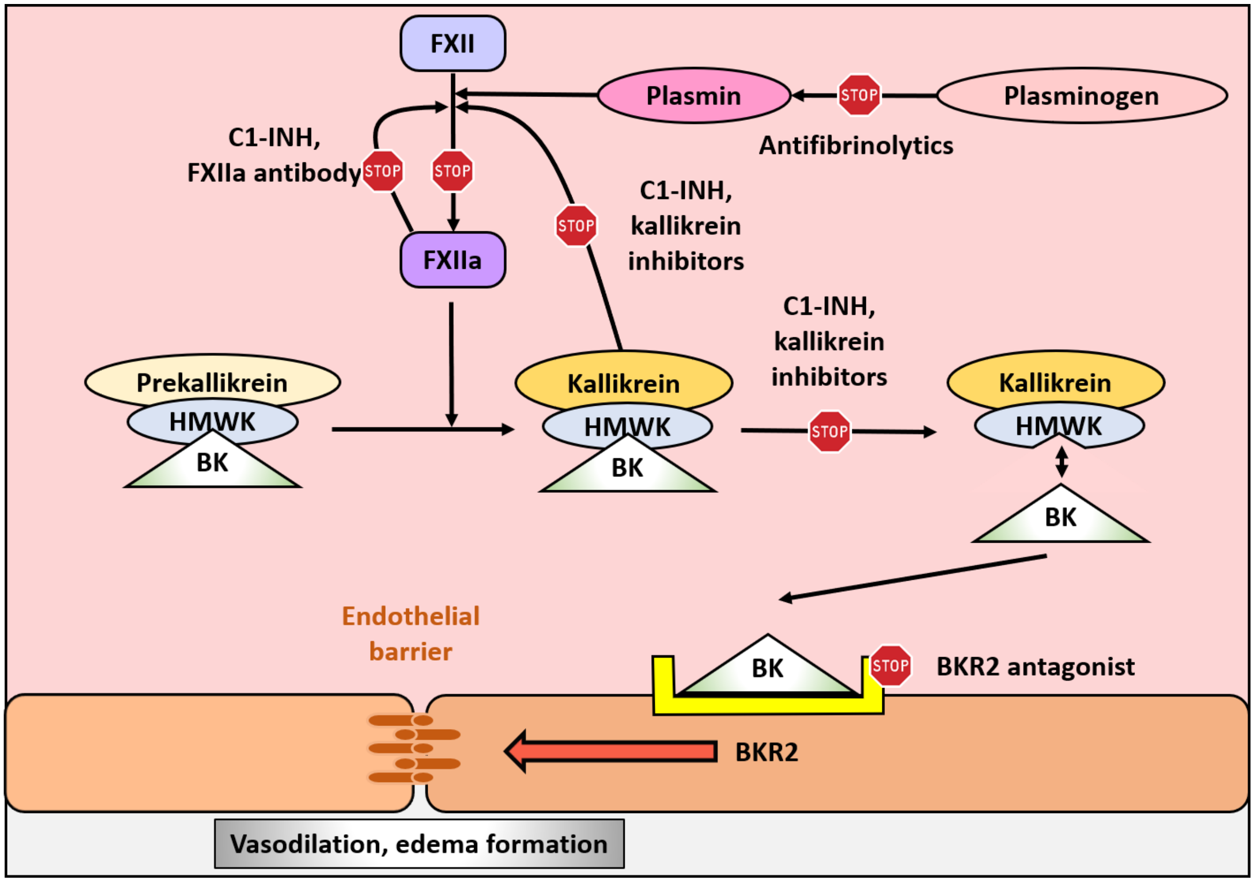
BK=bradykinin; BKR2=bradykinin receptor 2; C1-INH=C1 inhibitor; FXII(a)=(activated) Factor XII; (c)HMWK=(cleaved) high-molecular-weight kininogen.

Note: FXII is activated to FXIIa, e.g. by plasmin derived from plasminogen. FXIIa converts prekallikrein, which is in complex with HMWK, to kallikrein. Kallikrein can enhance FXII activation via positive feedback in addition to FXII autoactivation. Kallikrein also cleaves HMWK to cHMWK and releases BK. Reaction of BK with BKR2, induces increased endothelial permeability, resulting in the formation of tissue edema. Possible points of action for approved drugs are indicated by a "STOP" sign.

The degradation of BK is not shown here: BK is either inactivated by angiotensin converting enzyme (ACE) or is transformed by carboxypeptidase N to its des-Arg-metabolite, which can react with BKR1 and, to a much lesser extent, with BKR2, thereby also inducing vasodilation and edema formation.

Modified from Busse P and Christiansen C;N Engl J Med 2020;382(12):1136-1148 and Cicardi M, Zuraw BL;J Allergy Clin Immunol Pract 2018;6:1132-1141.

Figure 1: Pathogenesis of hereditary angioedema and possible points of action for therapeutics



BK=bradykinin; BKR2=bradykinin receptor 2; C1-INH=C1 inhibitor; FXII(a)=(activated) Factor XII; (c)HMWK=(cleaved) high-molecular-weight kininogen.
Note: FXII is activated to FXIIa, e.g. by plasmin derived from plasminogen. FXIIa converts prekallikrein, which is in complex with HMWK, to kallikrein. Kallikrein can enhance FXII activation via positive feedback in addition to FXII autoactivation. Kallikrein also cleaves HMWK to cHMWK and releases BK. Reaction of BK with BKR2, induces increased endothelial permeability, resulting in the formation of tissue edema. Possible points of action for approved drugs are indicated by a "STOP" sign.
The degradation of BK is not shown here: BK is either inactivated by angiotensin converting enzyme (ACE) or is transformed by carboxypeptidase N to its des-Arg-metabolite, which can react with BKR1 and, to a much lesser extent, with BKR2, thereby also inducing vasodilation and edema formation.
Modified from Busse P and Christiansen C;N Engl J Med 2020;382(12):1136-1148 and Cicardi M, Zuraw BL;J Allergy Clin Immunol Pract 2018;6:1132-1141.