REVIEW ARTICLE

# Pediatric hereditary angioedema

Andrew J. MacGinnitie[1,2]

[1]Division of Immunology, Boston Children's Hospital, Boston, MA, USA; [2]Department of Pediatrics, Harvard Medical School, Boston, MA, USA

**Correspondence**
Andrew J. MacGinnitie, Division of Immunology, Fegan 6, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115, USA
Tel.: +617-355-6117
Fax: +617-730-0310
E-mail: Andrew.macginnitie@childrens.harvard.edu

**Abstract**

Hereditary angioedema (HAE) is a lifelong illness characterized by recurrent swelling of the skin, intestinal tract, and, ominously, the upper airway. It is caused by inadequate activity of the protein C1-inhibitor, with dysfunction in the kallikrein/bradykinin pathway underlying the clinical symptoms. In addition to the physical symptoms, patients experience significant decrements in vocational and school achievement as well as in overall quality of life. Symptoms often begin in childhood and occur by age 20 in most patients, but life-threatening attacks are uncommon in the pediatric population. The availability of new therapies has transformed the management of HAE.

Hereditary angioedema (HAE) was first described in the 1880s by Quincke (1) and Osler (2). Patients with HAE experience recurrent, unpredictable attacks of edema primarily affecting the skin, intestinal tract, and upper airway (3). Attacks typically develop and resolve slowly, lasting 2–5 days. Significant variability in disease severity is seen, with rare individuals carrying causative mutations but remaining asymptomatic, and other patients experiencing frequent severe attacks (4). The recent approval of safe, effective targeted therapies has revolutionized the treatment of HAE. A plethora of consensus statements and guidelines have been recently promulgated to guide providers in diagnosing and treating HAE, but the evidence supporting many of the recommendations remains at the level of expert opinion (5–9). This review focuses on the presentation, diagnosis, and management of HAE with decreased C1-inhibitor (C1-INH) function in children and adolescents. Both acquired HAE and HAE with normal C1-INH, formerly known as type III HAE, are rare in the pediatric age group and not considered further here

## HAE pathophysiology

C1-INH is a member of the serpin class of protease inhibitors, which act as decoy substrates for proteases (10,11). Protease inhibition by C1-INH results from covalent linkage of the protease to the C1-INH molecule, perhaps explaining why a single functional C1-INH gene is insufficient to prevent HAE symptoms. C1-INH is named for the ability to inhibit C1, the

first component of the classical complement cascade, but it also inhibits a number of other circulating enzymes including kallikrein, activated factors XI and XII, and tissue plasminogen activator (10,11).

Conclusive evidence demonstrates that the recurrent episodes of swelling in HAE are primarily due to increased production of bradykinin secondary to increased activity of plasma kallikrein (10–12), as shown in Fig. 1. Briefly, high-molecular-weight kininogen (HMWK), the precursor of bradykinin, circulates in the bloodstream bound to pre-kallikrein (10,11). Activation of pre-kallikrein to plasma kallikrein, usually by activated factor XII, results in generation of bradykinin from HMWK. Bradykinin then binds to its receptor on endothelial cells, resulting in increased vascular permeability and the swelling typical of HAE (10,11). It is not known why attacks are temporally and anatomically limited, while C1-INH activity is constitutively reduced.

Type I and type II HAE both result from heterozygous mutations in the C1-INH gene and are the result of deficient C1-INH function (13). Decreased levels of C1-INH characterize type I HAE, whereas in type II HAE, C1-INH levels are normal or increased, but activity is decreased (14). Patients with type I or type II HAE have decreased C1-INH activity, typically about 30% of normal. This is less than would be predicted and may be due to increased C1-INH consumption. Patients within a kindred with identical C1-INH mutations can have vastly different courses (4), perhaps because of the effects of modifier genes. As many as one quarter of patients with
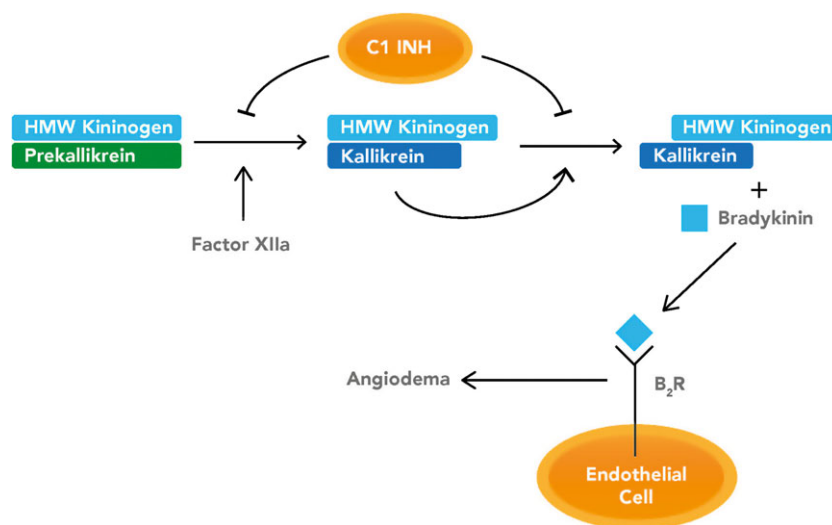
**Figure 1** Pathophysiology of HAE. Decreased C1-INH activity leads to increased production of bradykinin. Bradykinin binds to its receptor on endothelial cells, increasing vascular permeability and leading to the characteristic symptoms of HAE.

HAE have no family history and represent de novo C1-INH mutations (15).

Homozygous missense mutations in C1-INH have been described in sis patients from three kindreds, but reported symptoms were relatively mild and heterozygotes were asymptomatic, suggesting that the mutated C1-INH alleles retain some residual function (16–18).

### Clinical presentation

Hereditary angioedema attacks are characterized by non-pruritic, often painful swelling, with the skin, gastrointestinal (GI) tract, and upper airway the most commonly involved locations (19). Rarely, attacks may involve other sites including the esophagus, brain, kidney, and pancreas (19,20). Attacks typically progress and resolve slowly, with a total attack duration of 2–5 days. Cutaneous attacks localized to the extremities are the most common, but over time, most patients have attacks at multiple locations. Some patients have symptoms limited to the GI tract, complicating recognition of the disease and leading to delayed diagnosis, a problem that is common in HAE.

Attacks are sometimes, but not consistently, preceded by a prodromal phase (21). Patients typically report feeling a sensation of tingling or altered sensation prior to the start of skin swelling. Patients may also experience a rash termed *erythema marginatum*, which is a non-raised, non-pruritic erythematous eruption with central pallor. Urticaria is not associated with HAE, but as hives are common, they may be seen coincidentally in some patients with HAE.

A number of factors can predispose a patient to attacks, including stress and local trauma. Estrogen is a known trigger, and patients with HAE should avoid exposure to exogenous estrogens (19). Angiotensin-converting enzyme (ACE) is the primary enzyme responsible for breakdown of bradykinin, although other peptidases also participate (11,12). ACE inhibitors, frequently prescribed for hypertension and renal disease, can precipitate sudden worsening or even unmask

HAE and should be avoided (22). ACE inhibitors can occasionally trigger angioedema in patients without HAE (9), although this is rare in children, perhaps because these drugs are not frequently used in this population.

The distribution of attacks varies among patients. In one large series, all patients had extremity swelling, 97% had abdominal attacks, and just over half had laryngeal attacks (19). On a per-attack basis, about 50% of attacks affected the skin and just slightly less affected the abdomen (19). Upper airway attacks are potentially fatal. A recent analysis of patients who asphyxiated from HAE demonstrated a significantly elevated risk in those who had undiagnosed HAE, emphasizing the need for prompt diagnosis (23). Abdominal attacks, if not recognized as HAE, can be mistaken for a variety of other intra-abdominal illnesses including appendicitis. Patients may undergo unnecessary surgical intervention (24), although this seems less common with the widespread use of computed tomography and ultrasound for imaging (25).

### HAE in childhood

The onset of HAE symptoms is variable, but occurs in the first or second decade of life in most patients. An early US report revealed nearly half of patients had symptoms by age 6, although severity was typically mild (26). Farkas described a series of children with HAE from Hungary and noted the first attack at a median age of 6.6 yrs, with a range from 4 to 11 yrs (27). Similarly, a series from Germany showed a median first attack at 11 yrs but with a very broad age range (19). Patients experienced attacks as early as the first of life. Importantly, almost 90% of patients (186 of 209) had onset of symptoms before age 20. Median age of first HAE symptoms was 9.5 yrs in a series from Denmark (28) and 12.5 in a series from Spain (29). These series are primarily based on diagnosed cases and so may miss patients with mild or asymptomatic disease, although the Spanish series included a number of asymptomatic individuals. While most patients experience symptoms during childhood and adolescence, a fraction remains asymptomatic

throughout childhood and sometimes adulthood despite carrying a disease-causing mutation (19,26,29). Identification of these asymptomatic carriers is crucial, as initial symptoms can manifest as severe and/or life-threatening edema (23).

While symptoms may start in early childhood, attacks are typically infrequent in prepubertal children. Early onset of symptoms and frequent attacks in childhood predict more severe disease in adulthood (19,28). The number and severity of attacks typically increase in both sexes around puberty. Although this may be due to increased levels of endogenous estrogen in girls, the explanation for the worsening in boys is unknown. The distribution of attacks in adolescent patients typically mirrors that of adults. Nearly half of patients will have an upper airway attack by age 18 (19), and life-threatening attacks have been reported even in young children (23,30). Fatal attacks are rare in childhood, with only 3 of 70 deaths occurring in patients under age 21 in the largest published series (23).

## Quality of life

Besides the burden of the disease itself, HAE causes a significant decrease in quality of life (QOL). Patients with HAE have diminished physical and psychological QOL (31). Decreased QOL is partially due to the unpredictable nature of attacks. In a recent study of more than 450 patients, the majority reported decreased educational and vocational achievement because of HAE (31). Patients reported missing a median of 1.9 days of school (or 3.3 days of work) with their most recent attack (31). Preliminary evidence indicates an improvement in QOL with the availability of effective therapy for treatment of attacks (32).

## Diagnosis

The diagnoses of type I and type II HAE are dependent on demonstration of low levels of C1-INH protein or function, respectively. C4 is low at all times in a large majority of patients and invariably low during attacks. Published algorithms for diagnosis recommend screening with C4 initially, followed by C1-INH level and then activity if required (5). For patients with normal C4 but a history strongly suggestive of HAE, C4 should be rechecked during an attack (33). In practice, many physicians check C1-INH function initially to either establish or exclude the diagnosis of HAE. This may be particularly appropriate in children for whom repeated blood draws are problematic. Traditionally, it was believed that the level of C1-INH function did not predict disease severity; however, a recent report demonstrated that residual C1-INH activity was inversely correlated with disease severity (34). However, this does not imply that monitoring C1-INH levels should be used as part of disease management.

While development of the complement and kallikrein/bradykinin systems have not been well studied, available data suggest that neonates have levels below those seen in adults (35). Therefore, testing for C1-INH function can be deferred until 6 months and then repeated at 1 yr of age (26). Diagnosis of HAE is often delayed, with some patients being symptomatic for 10 or more years before HAE is identified, particularly when a family history of HAE is absent (36).

## Management

### Counseling and prevention of attacks

All patients and families should be educated about the disease, the risk of disease in family members, and factors that can worsen the disease or precipitate attacks (37). Patients should be advised to continue an active lifestyle including regular physical activity. However, as trauma is a frequent attack trigger, some patients may need to avoid contact sports. Estrogen-containing hormones should be avoided for contraception and normalization of menstruation in girls during and after puberty. Although not typically used in childhood, patients and families should know to avoid ACE inhibitors, as these can cause abrupt worsening of disease. Likewise, patients and families should be aware that dental and surgical procedures often precipitate attacks; therefore, prophylaxis or availability of emergency treatment should be arranged.

### Emergency plan

All patients with HAE should have an emergency plan for the treatment of attacks, a recommendation reinforced by a recent series regarding the frequency of laryngeal attacks and asphyxiation (23). This includes patients on long-term prophylaxis who may experience breakthrough attacks. For patients with infrequent attacks, this plan may be as simple as knowing an emergency facility nearby where effective acute therapy is available. The provider can help facilitate availability of one or more of the newer targeted HAE therapies in an emergency department or similar facility close to home and school. Likewise, working on a detailed care plan at a designated medical facility can speed treatment, increase the comfort level of both the patient and providers, and minimize unforeseen problems. For patients with more frequent attacks, on-demand treatment can be available at home or work, including administration by the patient or caregiver if appropriate. However, patients need to seek emergency medical care for upper airway attacks.

### Medication

Antihistamines and steroids are typically ineffective for the bradykinin-mediated swelling of HAE, although they are often tried, particularly in patients with undiagnosed HAE and by providers unfamiliar with the disease. It has been suggested that epinephrine may be successful as a temporizing measure (38), particularly in the setting of laryngeal edema, but no studies show efficacy and it should not be relied on.

### Older treatment options

For many years, there were limited options for the treatment of HAE in the United States, while purified C1-INH (pC1-INH) concentrate was available in Europe and other countries. Danazol was noted to increase the production of C1-INH and decrease the rate and severity of attacks (39). Attenuated

androgens such as stanozolol and danazol have significant adverse effects including hirsutism, acne, weight gain, and psychological changes (40), which can be particularly problematic in women. In addition, androgens have adverse effects on blood lipid profiles and may cause hepatic adenomas and even adenocarcinoma (41).

Androgen use should be avoided in children. By causing premature closure of the growth plate, androgens are associated with a risk of decreased stature when used in childhood. While a small series and case reports indicated efficacy and tolerability in prepubertal children with severe HAE (42–44), the advent of safer, targeted therapies for HAE eliminates the need for attenuated androgens in the pediatric population.

Antifibrinolytic medicines, including tranexamic acid and epsilon-aminocaproic acid, represent an alternative for HAE prophylaxis with a more acceptable adverse-effect profile in the pediatric age group. Initial data showed an improvement in attack frequency and severity in adult patients with HAE (45), but other data suggest marginal benefit, and some guidelines do not recommend use for prophylaxis (7). Data in children are limited; a recent article reported the experience with long-term prophylaxis in pediatric patients, with few patients having an adequate response (46). Furthermore, antifibrinolytics are not without adverse effects, most commonly muscle pain and weakness and/or elevated serum aldolase and creatinine phosphokinase levels. The requirement for divided daily dosing may affect adherence.

Finally, fresh frozen plasma (FFP) contains C1-INH and can be used as prophylaxis prior to dental and surgical procedures. FFP has also been used as therapy for acute attacks (47). However, FFP also contains HMWK, and anecdotal reports of acute worsening after FFP was administered during attacks have limited its use. The advent of more targeted therapies has obviated the need for use of FFP in HAE.

## Newer therapies

A number of new therapies are now available for the prevention and treatment of HAE attacks, although experience in children and adolescents is mostly limited to pC1-INH. These therapies include C1-INH purified from plasma (Cinryze®, ViroPharma Incorporated, Exton, PA; Berinert®, CSL Behring GmbH, Marburg, Germany), recombinant C1-INH (Ruconest®; Pharming, Inc; Leiden, The Netherlands), a kallikrein inhibitor (ecallantide; Kalbitor®, Dyax Corp, Burlington, MA, USA), and a bradykinin receptor antagonist (icatibant; Firazyr®, Shire Human Genetic Therapies, Inc, Lexington, MA, USA). These options are discussed in the following text and summarized in the Table 1.

### Plasma-purified C1-INH

C1-INH can be efficiently purified from donated plasma and used to treat patients with HAE, either prophylactically or to abort attacks. It is the only targeted therapy for which substantial pediatric experience has been published.

Berinert has been studied for treatment of acute attacks. It was effective in alleviating facial and abdominal attacks when given at a dose of 20 U/kg intravenously (IV), with initial improvement within a half hour (48,49). Despite its IV formulation, some patients can either self-administer or have a caregiver administer this medication, eliminating the need for a visit to a medical facility for treatment. While originally approved in the United States for the treatment of abdominal and facial attacks only (48), it was later approved for the treatment of laryngeal attacks (49).

Cinryze has been studied for prevention of attacks in a phase 3, double-blind, cross-over trial in patients with severe HAE (attacks at baseline roughly weekly). Administration of nanofiltered pC1-INH 1000 units IV twice weekly was associated with a roughly 50% decline in the number of attacks compared with placebo. In addition, the severity and duration of attacks in patients receiving nanofiltered pC1-INH were also significantly decreased (50). An open-label follow-up study showed a dramatic reduction in attacks in patients receiving pC1-INH prophylaxis compared with their baseline attack rate. This study suggested that a small number of patients may do well with less frequent dosing. Cinryze is approved for prophylaxis of attacks in adolescents and adults with HAE at the previously mentioned dose and is also approved for self-administration (51).

Farkas described the experience with pC1-INH in a cohort of pediatric patients from Hungary (52). Prior to adulthood, 27 of 50 patients required therapy with pC1-INH (Berinert), for a total of 152 doses. Therapy was well tolerated, with almost all attacks responding and initial improvement starting within 60 min in almost all attacks. As seen in adults, a few patients (3 of 50) required frequent treatment, accounting for more than 40% of the total doses given. Similarly, Schneider et al. (53) described the experience of 15 pediatric patients treated with pC1-INH (Berinert) during two trials of its efficacy for acute HAE attacks. The patients were treated for 122 attacks, the majority receiving open-label therapy. Response to treatment was rapid, with a median time to improvement of 30 min or less under both double-blind and open-label conditions.

Finally, Lumry et al. (54) assessed treatment with nanofiltered pC1-INH (Cinryze) in 46 pediatric patients. The median time to onset of improvement of symptoms during acute attacks in the double-blind phase three study was 30 min, remarkably similar to the data reported in the other studies (52,53). Patients given pC1-INH for prophylaxis showed a decrease in attack rate of nearly 50% in the double-blind study compared with placebo, and approximately 85% in the open-label extension compared with historical attacks prior to study entry (54). Together, these studies indicated that pC1-INH is safe and effective for treatment of HAE attacks in pediatric patients and also effective for prophylaxis in appropriate patients. Of note, most of the children treated in these pediatric studies were 10 yrs of age or older; a few younger children also were treated.

Both formulations of pC1-INH are approved in the United States and Europe for treatment of adolescents and adults (Berinert is approved in the EU for children as well), with adolescents being defined as patients 12 yrs of age and older in the United States. pC1-INH is generally well tolerated, although the requirement for IV infusion may be a barrier

**Table 1** Characteristics of targeted therapies of hereditary angioedema

| Medicine | Brand name | Approval (US) | Age, yr (US) | Approval (EU) | Dosage and route of administration | Advantages | Disadvantages |
|---|---|---|---|---|---|---|---|
| Plasma-purified C1-INH | Cinryze | Prophylaxis | Adolescents and adults, 12+ | Prophylaxis, acute therapy | 1000 U twice weekly IV | Replaces missing C1; potential self-administration, long half-life, stable at room temperature | Requires IV; theoretical risks of viral transmission and thrombosis; expensive |
| Plasma-purified C1-INH | Berinert | Acute therapy | Adolescents and adults, 12+ | Acute therapy | 20 IU/kg IV | Replaces missing C1; potential self-administration, long half-life, stable at room temperature | Requires IV; theoretical risks of viral transmission and thrombosis; expensive |
| Recombinant C1-INH | Ruconest | Not FDA approved | Not applicable | Acute therapy | 50 U/kg IV | Replaces missing C1; no risk of human viral transmission, stable at room temperature | Short half-life; requires IV; hypersensitivity to rabbit proteins; theoretical risk of rabbit viral transmission |
| Ecallantide | Kalbitor | Acute therapy | 16+ | Not approved | 30 mg SC (as 3 injections) | More potent kallikrein inhibitor than C1-INH; route of administration | Short half-life; hypersensitivity; (black box warning for anaphylaxis); only administered by health care professional; expensive |
| Icatibant | Firazyr | Acute therapy | 18+ | Acute Therapy | 30 mg SC (single injection) | Route of administration, prefilled syringe, potential self-administration; stable at room temperature | Short half-life; injection-site reactions; expensive |

C1-INH, C1-inhibitor; FDA, US Food and Drug Administration; IV, intravenous; SC, subcutaneous.
CINRYZE is a registered trademark of ViroPharma Biologics; Berinert is a registered trademark of CSL Behring; Ruconest is a registered trademark of Pharming; Kalbitor is a registered trademark of Dyax Corp; and Firazyr is a registered trademark of Shire Human Genetic Therapies, Inc.

for some patients. While pC1-INH is a blood-derived product, no cases of infection transmitted by C1-INH have been documented. Likewise, concern about increased thrombosis risk appears to be theoretical at the doses used for HAE. In summary, pC1-INH has been demonstrated to be both safe and effective in pediatric patients with HAE and should be considered the targeted therapy of choice.

### Recombinant C1-INH

The amount of C1-INH that can be purified from plasma is limited, and as a blood-derived product, pC1-INH carries a theoretical risk of infection. An alternative is recombinant human C1-INH (rC1-INH). rC1INH (Ruconest) is purified from the breast milk of transgenic rabbits. Owing to differences in glycosylation, the half-life of rC1-INH product is significantly shorter than that of pC1-INH. rC1-INH was found effective for therapy of acute attacks (55,56), although the studies were small. Small amounts of leporine protein are present in the final product, so allergy to rabbit is a contraindication to use (57). It is approved in Europe, but not the United States, for treatment of acute HAE attacks.

### Ecallantide

Ecallantide (Kalbitor) is a potent small peptide kallikrein inhibitor produced in the yeast *Pichia pastoris*. It has increased affinity for kallikrein, compared with C1-INH. Two double-blind, randomized controlled trials showed that ecallantide, when administered subcutaneously, was effective in relieving the symptoms of acute HAE attacks (58,59). Moreover, it retains efficacy when utilized over time for multiple attacks in individual patients (60). While generally well tolerated, hypersensitivity reactions, including anaphylaxis, have been observed in 2.7% of patients treated subcutaneously (61). MacGinnitie et al. (62) reported the efficacy of ecallantide in 25 pediatric HAE patients treated for a total of 62 attacks, mostly open label. Ecallantide showed efficacy equivalent to that seen in adults. Onset of improvement was <1 h, with complete or near complete resolution of symptoms occurring at a median of 180 min. Ecallantide is approved in the United States, but not Europe for the treatment of patients with HAE 16 yrs of age and older, only under the direct supervision of a healthcare professional capable of managing reactions including anaphylaxis.

### Icatibant

Icatibant (Firazyr) is a small peptide containing several synthetic amino acids that block binding of bradykinin to the B2 receptor on endothelial cells, decreasing leakage of fluid across the endothelium and thereby alleviating HAE symptoms. Icatibant's efficacy has been examined in three double-blind randomized trials for the treatment of acute HAE attacks, using either placebo or tranexamic acid as a comparator (63,64). Patients showed prompt improvement of symptoms, although in one trial, this was not significantly better than comparator, likely because of an unexpectedly rapid

improvement in patients who received placebo. Icatibant is approved in the United States and Europe for patients age 18 and older. It is given subcutaneously and is easily self-administered. Patients treated with icatibant often experience symptoms of pain, burning, and redness at the injection site, but these are typically manageable (63,64). Icatibant has a short half-life (approximately 1.5 h), but rebound of symptoms does not seem to be more prevalent than with other acute therapies (63–65).

### Prophylaxis

The ideal treatment for HAE would completely prevent attacks, freeing patients to lead a normal life. Although this has not proven possible in most cases, many patients benefit from long-term therapy to prevent attacks, and almost all patients with HAE can use prophylactic medications before undergoing medical and dental procedures, which commonly trigger attacks.

### Long-term prophylaxis

Three classes of medications can be considered for long-term prophylaxis: attenuated androgens, antifibrinolytics, and pC1-INH. Androgens are effective in preventing attacks, but are associated with significant adverse effects, and many patients require relatively high doses (40). As discussed previously, androgens should be avoided in children who are still growing. Antifibrinolytics were formerly the prophylactic treatment of choice for prepubertal children with HAE, although their efficacy has not been demonstrated. Currently, C1-INH is the safest, most effective therapy for long-term prophylaxis in children and adolescents with HAE and should be considered the best option when indicated. Cinryze is the C1-INH indicated for routine prophylaxis in adolescents and adults with HAE.

The decision to undertake long-term prophylaxis is not an easy one and should be individualized, especially given the cost of newer HAE medicines. Considerations include the frequency and severity of attacks; the degree to which HAE disrupts the patient's lifestyle, especially work and school; and patient and family preferences.

### Short-term prophylaxis

Short-term prophylaxis is recommended for patients prior to undergoing invasive procedures that are likely to generate attacks (5–9). Short courses of androgens are effective in this role and avoid most of the adverse effects associated with long-term use (40). C1-INH has also been utilized to good effect in this role (66). In addition to consideration of prophylaxis, all patients with HAE should have a plan for treatment if an attack occurs.

### Acute therapy

In the United States, C1-INH is approved for treatment of adults and adolescents 12 yrs of age and older, while ecallantide is approved for patients age 16 and older and icatibant for

those 18 and older. C1-INH and icatibant are both approved in Europe. Because each trial used different end-points to judge efficacy and no head-to-head trials have been conducted, it is currently not possible to state that any acute therapy is more or less efficacious than another. However, there is extensive experience with pC1-INH as acute therapy in children and adolescents (52–54), and it represents the current first choice for therapy of attacks in the pediatric population (7,8). It is hoped that analysis of existing data, combined with that from new trials, will extend the age range for other acute therapies, increasing the treatment options for children and adolescents with HAE.

## Conclusions

HAE has been a devastating disease for which few effective treatment options were available until recently, particularly in the United States. This has changed dramatically with the introduction of new therapies for both prevention and treatment of attacks. Because of the risk of severe, life-threatening attacks, testing is recommended for all at-risk individuals so that appropriate therapy can be made available. Although androgens and antifibrinolytics have been used in the past, pC1-INH is both safe and effective for the prevention of attacks in the pediatric population. Likewise, extensive data show that pC1-INH is effective for the treatment of attacks. Data on the efficacy of other targeted therapies in the pediatric population are eagerly awaited.

## Acknowledgments

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