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Review article

Updates on hereditary angioedema in pediatrics

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Introduction

Angioedema is characterized by an asymmetric nondependent swelling that is generally not pruritic. The pathogenesis of angioedema results from increased vascular permeability, with leakage of plasma into the deeper skin layers in patients with angioedema.[1,2] Hereditary angioedema (HAE) is a rare genetic life-long disabling disease that predisposes an individual to develop vasogenic edema.[3] HAE is an autosomal dominant disease, and most patients with HAE have a positive family history of angioedema.[3] The prevalence of HAE is estimated to be between 1:30,000 and 1:80,000 in the general population, and there is no evidence of sex, ethnic, or racial differences in the prevalence of HAE. [1] Awareness and recognition of this disease is important as HAE is often misdiagnosed as allergic angioedema or acute abdomen (especially acute appendicitis). This may often lead to inappropriate use of antihistamines, corticosteroids, adrenaline and sometimes even surgical interventions.[4]

Etiology and classification

HAE has classically been recognized as resulting from a deficiency of the C1-inhibitor (C1-INH) which is a broad-spectrum serine protease inhibitor and is further subdivided into type I or type II HAE, depending on whether the plasma C1-INH antigenic levels are low or normal, respectively.[5,6] Type I HAE is the most common and accounts for more than 80 % of the cases. It presents with low C1-INH antigenic and functional levels, whereas type II HAE presents with normal C1-INH antigenic levels but decreased C1-INH functional levels. However, there are other rare types of HAE now genetically identified with normal level and function of C1-INH but due to other genetic defects (HAE- nC1-INH). Another form of HAE with unknown genetic mutation has been as well identified. [7]

Genetics

C1-INH gene (now named SERPING1), is located on chromosome 11 (p11.2-q13), contains 8 exons and 7 introns, does not contain a 59 TATA box, and is distinguished by 17 Alu repeats in introns 3 to 7.[8] HAE is an autosomal dominant disease caused by mutations in the SERPING1 gene. Missense mutations constitute approximately 30-40% of all mutations in SERPING1 gene.[9] Each child of an affected patient has a 50% chance of having HAE. Importantly, HAE does not skip generations. However, lack of a positive family history of angioedema cannot be used to exclude the diagnosis as 25% of patients presumably have a de novo mutation of the SERPING1 gene.[10] Genetic defects are identified in the very rare type of HAE nC1-INH including gain of function mutation of factor XII gene (HAE-FXII)[11] which is transmitted as autosomal dominant, missense mutation in the plasminogen gene (HAE-PLG) resulting in increased production of the bradykinin through activation of factor XII[12], and lastly the novel mutation discovered in angiopoietin 1 (ANGPT1) gene (HAE-ANGPTI), the mutant protein is unable to bind to its receptor on endothelial cells to maintain vascular permeability.[13]

Pathophysiology

C1-INH is a member of the serpin (serine protease inhibitor) superfamily with significant homology to a1-antitrypsin. It has important roles in inhibiting several complement proteases (C1r, C1s, and mannose-binding lectin–associated serine protease [MASP] 1 and 2) and contact-system proteases (plasma kallikrein and coagulation factor XIIa) as well as a relatively minor inhibitor of the fibrinolytic protease plasmin.[5, 14]

The primary mediator of swelling in HAE-1/2 is bradykinin. Bradykinin is a low molecular weight nonapeptide, which is generated when active plasma kallikrein cleaves high molecular weight kininogen (HMWK). Plasma kallikrein is activated from its inactive zymogen prekallikrein by the protease factor XII which can easily autoactivate upon contact with negatively charged surfaces. Kallikrein is capable of directly converting plasminogen to plasmin and also with the help of urokinase type plasminogen activator. Plasmin and kallikrein in turn augment Factor XIIa generation thereby creating an auto-activation loop. Bradykinin has a number of important effects on

the body including normal homeostasis, normal immune responses, inflammation, vascular tone, and vascular permeability. The vascular permeability–increasing effect of bradykinin in angioedema is primarily mediated through the bradykinin B2 receptor. Both plasma kallikrein and factor XII are normally inhibited by C1-INH. Bradykinin is rapidly metabolized by endogenous metalloproteases including angiotensin-converting enzyme (ACE).[15,16] On the other hand, the pathogenesis in patients with HAE-nC1-INH remains to be characterized. However, there is clinical evidence that bradykinin may play a major role in some types of HAE nC1-INH, primarily in patients with a F12 gene-mutation.[17]

As HAE-nC1-INH usually presents in the adulthood and may have special characteristics in addition to some features of HAE-type I/II, this review is concerned with HAE-type I/II in pediatrics.

Clinical presentation

The symptoms may occur at any age but uncommon in neonates or during infancy. They usually begin in childhood or adolescence, the median age of symptom onset is approximately 12 years of age and worsens around puberty.[18] However, reports of early onset HAE by the age of 4 weeks[19] and another in one-year infant[20] have been documented. The earlier the onset of symptoms, the more severe the subsequent course of HAE-type I/II. [21]

HAE is characterized by relatively prolonged attacks of angioedema involving the extremities, abdomen, genitourinary tract, face, oropharynx, larynx, or a combination of these areas. skin involvement is the most frequent location of the edema (91% of patients) followed in frequency by abdominal attacks (73%) and upper airway edema (48%). Viewing per-episode, nearly all episodes consisted of skin swellings and abdominal attacks (96.5%) with rare laryngeal events (0.9%), but potentially life threatening. The swelling in patients with HAE is always episodic and not continuous daily swelling. Typical HAE attack tends to progressively worsen for 24 hours and then slowly remit over the following 48 to 72 hours; however, attacks can occasionally last longer, particularly if the swelling moves from site to site.[1,18]

Subcutaneous edema of the extremities is often the earliest and most common swelling site in pediatric

patients. Bowel wall edema and related symptoms of colicky abdominal pain, nausea, vomiting, and postattack watery diarrhea are common (80–90%) in the pediatric patients. Less severe abdominal symptoms may be an unrecognized and often overlooked symptom of HAE in infancy.[18,22,23] Subcutaneous edema is the most common and the earliest symptom. Asphyxia may ensue rapidly in children, probably because of smaller airway diameter.[24]

Several stressors have been associated with precipitating HAE attacks, especially mechanical trauma, emotional stress, and airway infections. [20,22] In adolescent girls, menstruation and ovulation are additional triggers.[25] Other precipitating factors include exercises, and iatrogenic trauma, such as dental work, medical procedures, and surgery. Also, ACE-Is can precipitate attacks of angioedema although uncommonly used in pediatric population.[1,20]

Patients with HAE can experience prodromal manifestations several hours or up to a day before the onset of an attack. The most common prodromal symptoms are an erythematous nonurticarial rash (erythema marginatum), localized tingling, or a sense of skin tightness. Erythema marginatum as a prodromal sign is more frequent in the pediatric population. It has been observed in 42% to 58% of cases and is often mistaken for urticaria. Misdiagnosis of prodromal erythema marginatum can lead to incorrect or insufficient treatment.[26-28] Other prodromal symptoms include fatigue, malaise, flu-like symptoms, irritability, mood changes, hyperactivity, thirst, or nausea. However, these symptoms are less commonly reported by children.[1]

Higher incidence of concomitant celiac disease has been observed in HAE-type I/II pediatric patients. Celiac dietary restriction may reduce abdominal symptoms in these patients.[29]

Diagnosis

HAE-type I/II should be suspected when a child/adolescent presents with a history of recurrent angioedema attacks without urticaria. This suspicion is further substantiated when there is a positive family history (although this may not be present in up to 25% of patients), recurrent and painful abdominal symptoms, occurrence of upper airway edema, failure to respond to antihistamines, glucocorticoids, or epinephrine, and presence of prodromal signs or symptoms before swellings.[7]

Measuring complement C4 levels is recommended as the best initial screening test to exclude a diagnosis of HAE,[30,31] but its sensitivity and specificity are limited.[32,33] The next step should be to measure C1INH antigen (and function if the antigenic level is normal). The functional level

should be less than 50% to 60% of the lower limit of normal to be compatible with HAE. In a patient with a compatible history and clinical course, the combination of low C4 and low C1-INH antigen levels can confirm a diagnosis of type I HAE; the combination of low C4 levels, normal C1-INH antigen levels, and low C1-INH function can confirm a diagnosis of type II HAE.[30,34] A chromogenic functional C1-INH assay appears to be superior to the ELISA-based C1-INH functional assay.[35]

The measurement of C4, however, was found not to be useful for diagnosing of HAE-type I/II in infants below the age of 12 month, as C4 levels are frequently low in healthy infants[36, 37], thus should be repeated after the age of 1 year.[36-38] Abnormal results should be confirmed by repeating once to exclude ex vivo degradation of the sample or laboratory error. Complement C3 and CH50 levels are expected to be normal in HAE, and testing is usually not helpful.[1]

Genetic testing is not required to confirm the diagnosis of C1-INH-HAE unless prenatal testing is considered or in rare cases where biochemical tests are inconclusive and genetic mutation of the parents is known. Taken into considerations that not all of the mutations detected by routine genetic testing are undoubtedly disease causing.[36-39]

It is important to establish the diagnosis as early as possible, ideally before the onset of clinical manifestations. Therefore, family members of HAE-type I/II patients should be screened for C1-INH function, C1-INH protein, and C4 plasma levels. Delayed diagnosis leads to morbidity and decreased quality of life due to delayed introduction of appropriate therapy. There is a risk that the first HAE attack might affect the airway and could be fatal.[1, 7, 38]

Differential diagnosis

This include the other forms angioedema namely acquired angioedema due to C1-Inhibitor deficiency (AAE-C1-INH), angiotensin converting enzyme inhibitor-induced angioedema (ACEI-AE), mast cell-mediated angioedema (e.g. angioedema in patients with chronic spontaneous urticaria without wheals, allergic angioedema), and idiopathic angioedema.[40,41] Basic laboratory profile can distinguish between the two types of HAE and mast cell-mediated angioedema (table 1).

Although symptoms and basic laboratory investigations of AAE-C1-INH are similar to those of HAE-type I, but it occurs at later age, commonly associated with an underlying disease such as lymphoma, and often depressed C1q, and negative family history. Mast cell-mediated angioedema is frequently associated with intensely pruritic wheal and flare skin reactions, however, some patients with chronic spontaneous urticaria do not show wheals and exclusively develop angioedema.[42]

Because mast cell-mediated angioedema is far more common than HAE type I/II, on demand therapy with antihistamines and, if necessary, with epinephrine and corticosteroids, is indicated when the diagnosis is not yet determined, and the history seems to be inconsistent with HAE.[43]

Table 1. Basic complement laboratory profile among patients with HAE-type I and type II and patients with mast cell-mediated angioedema

Type of Angioedema	C4 level	C1-INH level	C1-INH function
HAE-type I	Low	Low	Low
HAE-type II	Low	Normal (may be high)	Low
Mast cell-mediated angioedema	Normal	Normal	Normal

HAE: Hereditary angioedema, C4: complement 4: C1-INH: C1-esterase inhibitor

Treatment

The aim of management of HAE is to prevent the life-threatening and disabling consequences of HAE attacks and to normalize the patients' activities and lifestyle whenever possible. Dosage and mode of administration of drugs used in management of HAE in pediatrics are summarized in table 2. Epinephrine, corticosteroids, and antihistamines are not efficacious and not recommended for the treatment of HAE.[1,7]

A- Pharmacological therapy

I- On demand-treatment:

All of the consequences of HAE attacks can be minimized by using on-demand treatment. Laryngeal attacks should be considered as medical emergencies. Rapid treatment with an effective HAE acute medication is essential in addition to preparing for emergency airway management procedures if respiratory compromise develops.[1] During abdominal attacks, intravenous fluid replacement may be required because of the increased susceptibility of children to hypovolemia and dehydration, since extravasation into the peritoneal cavity and the intestinal lumen can be substantial.[7]

Drugs used in acute attacks include C1-INH concentrate whether plasma-derived or

recombinant, Kallikrein inhibitor (ecallantide) and bradykinin-receptor antagonist (icatibant). Berinert, a plasma-derived C1-INH concentrate (pdC1-INH), is the only FDA-approved drug to be used in all pediatric age groups . However, recombinant C1-INH concentrate, ecallantide and icatibant are recently licensed in some countries for on demand treatment of HAE in older children and adolescents.[38, 44,45]

Treatment with pdC1-INH concentrate is effective, well tolerated and shows a good safety profile in pediatric patients. When pdC1-INH concentrate is not available, solvent detergent-treated plasma (SDP) is preferred over fresh frozen plasma (FFP), but both are considered second-line treatment.[1,7,38]

Antifibrinolytics (e.g. tranexamic acid) or androgens (e.g. danazol) are not recommended for on-demand treatment of HAE attacks, as these drugs show no or only minimal effects when used for on-demand treatment.[46]

a-C1-INH concentrate:

Treatment results in an increase of the plasma levels of C1-INH and therefore helps to inhibit the cascade system involved in the production of bradykinin during attacks. One unit of C1-INH concentrate corresponds to the mean quantity of C1-INH present in 1 mL fresh normal plasma.[47,48]

Plasma-derived C1-INH concentrate:

Two pdC1-INH concentrate are available for on-demand treatment of HAE-type I/II; Berinert and Cinryze. The mean plasma half-life of pdC1-INH is longer than 30 hours.[49,50] The safety and tolerability of pdC1-INH are good, and risk of allergic reactions is negligible. Modern pdC1-INH use has not been associated with transmission of hepatitis B nor C nor human immunodeficiency viruses.[51,52] Cinryze is approved in Europe for ages of 12 years and older by the EMA but not FDA approved for on demand treatment of HAE attacks.[38]

Recombinant C1-INH concentrate:

Ruconest is the only available recombinant human C1-INH (rhC1-INH). The mode of action is identical to that of pdC1-INH. It is derived from the milk of transgenic rabbits and its plasma half-life is approximately 3 hours. It is contraindicated in patients with known or suspected allergy to rabbits or rabbit derived products.[53] It is both FDA and EMA approved for on demand treatment of the patients aged 13 and older.[54] rhC1-INH has a favorable safety profile. Transmission of human viruses is not a concern.[55]

b- Kallikrein inhibitor:

Ecallantide is a 60-amino acid recombinant protein and has a plasma half-life of 2 hours. It inhibits kallikrein and therefore, inhibits the cleavage of high-molecular weight kininogen to bradykinin as well as the further activation of FXIIa, preventing additional kallikrein production. Ecallantide is FDA approved for on demand treatment of patients 12 years and older but not EMA approved.[56] Potentially serious hypersensitivity reactions including anaphylaxis, but no deaths have been reported.[56, 57]

c- Bradykinin-receptor antagonist:

Icatibant is a specific and selective competitive antagonist of the bradykinin B2 receptor and prevents binding of bradykinin to its receptor. It is a 10-amino acid synthetic peptide and has a plasma half-life of 1 to 2 hours. Icatibant is FDA and EMA approved for on demand treatment of patients 18 years and older but clinical trials are ongoing in pediatrics.[58] The safety and tolerability of icatibant are good, although transient local injection site reactions (erythema, wheal, pruritus, and burning sensation) can occur.[59]

II- Pre-procedural (short-term) prophylaxis:

Surgical trauma, dental surgery and other interventions associated with mechanical impact to the upper aerodigestive tract (e.g. endotracheal intubation, bronchoscopy or esophago-gastroduodenoscopy) may lead to swellings near the site of intervention. Swellings usually occur within 48 hours. Preprocedural prophylaxis is recommended for all medical, surgical and dental procedures associated with any mechanical impact to the upper aerodigestive tract.[1,7]

The drugs recommended for short-term prophylaxis include pdC1-INH concentrate as first choice and short course of attenuated androgen as a second line. Antifibrinolytics are not recommended for preprocedural prophylaxis. With all pre-procedural prophylactic treatments, break-through attacks can occur, so patients should remain under observation, and on demand treatment needs to be available.[60-62]

a-Plasma-derived C1-INH concentrate:

pdC1-INH concentrate is the first-line pre-procedural option, the timing of administration varies from during procedure or one or more hours before the procedure but trying to give as close to the procedure as possible.[38] In case pdC1-INH concentrate is not available, 10 mL/kg of SDP or FFP can be used as a second line agent several

hours up to 12 hours before the expected procedure. However, FFP is not as safe as pdC1-INH concentrate because of the greater risk of blood borne disease transmission, and allosensitization.[34]

b-17α-alkylated androgens:

The mechanisms underlying the efficacy of attenuated androgens are uncertain. Although androgens have been reported to result in a small increase in C1-INHmRNA levels in blood monocytes,[63] no evidence of androgen-stimulated C1INH protein synthesis has been reported. Androgens have also been shown to increase levels of kininases that degrade bradykinin, which might contribute to their effectiveness.[64]

Use of short courses of attenuated androgens (e.g. danazol) can be used as second line when pdC1-INH concentrate is not available. For scheduled pre-procedural prophylaxis, androgens can be used with mean dose suggestion of 5 mg/kg/day (2.5-10 mg/kg/day with a maximum of 600 mg daily) for 5 days before and 2 to 3 days post event. Very frequent short course of attenuated androgens may lead to side effects associated with long-term use.[7,38]

III- Long-term prophylaxis:

The aim of long-term prophylaxis (LTP) of HAE is to reduce the burden of the disease by preventing/attenuating attacks in patients with confirmed HAE-type I/II by using regular medication. However, not every patient with HAE-type I/II should receive LTP, this should be individualized, and LTP should be considered in all severely symptomatic patients taking into consideration the frequency and severity of attacks, patient's quality of life, availability of health-care resources, failure to achieve adequate control by appropriate on-demand therapy and patient's compliance. The pattern of HAE type I/II attacks can vary over time in the same patient, therefore, patients should be evaluated for the need of LTP at every visit, at least once a year.[1,7,38]

Patients who are receiving LTP should be evaluated regularly for efficacy and safety of the therapy, and dosage and/or treatment interval should be adapted according to the clinical response rather than the C1-INH plasma level or the C4 level. In general, there is no need to measure C1-INH or C4 levels in a patient with HAE once the diagnosis has been made.[1,38] Upper airway edema and other attacks may occur despite the use of long-term prophylaxis. Therefore, all patients using long-term prophylaxis should also have on-demand medication.[1,7,34,38]

a- Plasma-derived C1-INH

pdC1-INH concentrate is currently the preferred LTP prophylaxis for the prevention of HAE attacks. A dose of 10 to 20 units per kg per dose once or twice weekly with an initial maximum dose of 1000 units is recommended.[38] Recent study in adults shows that subcutaneous twice-weekly administration of pdC1-INH at doses of 40 U per kilogram or 60 U per kilogram bodyweight provided very good and dose-dependent preventive effects on the occurrence of HAE attacks.[65] The subcutaneous route may provide more convenient administration as well as maintain improved steady-state plasma concentrations of C1-INH compared to IV C1-INH prophylaxis. Routine prophylaxis with pdC1-INH has been shown to be safe and effective.[66,67] Tachyphylaxis seems rare with only one report of increasing doses required to prevent attacks when C1-INH concentrate is used regularly for prophylaxis.[68] Thromboembolic events due to pdC1-INH concentrate use in HAE are rare, and patients who experience such events often have underlying thromboembolic risk factors.[69]

b- Antifibrinolytics

Antifibrinolytics (i.e. Tranexamic acid 20–50 mg/kg/day divided in 2-3 doses with dose adjustment in renal impairment) are preferred to androgens for LTP in case pdC1-INH concentrate is not available because of their better safety profile.[38] However, efficacy is questioned by many, and data are not available supporting its use. The mechanism underlying antifibrinolytic agents in the treatment of HAE is unknown. Epsilon aminocaproic acid is less well tolerated than tranexamic acid. Side effects are usually minor and include gastrointestinal upsets (can be reduced by taking the drug with food), myalgia/creatine kinase elevation, and a theoretical risk of thrombosis. Contraindications include the presence of thrombophilia or increased thrombotic risk or acute thrombosis.[34, 38, 70]

c- ***17α-alkylated androgens***

Attenuated androgens are not recommended for LTP in children and adolescents prior to Tanner stage V, however, long-term use has been reported, and in some cases, the benefits may outweigh the risks. Initial danazol dose for children is 2.5 mg/kg per day with subsequent adjustment, until symptom suppression or the maximum tolerated or maximum single dose of 200 mg per day is reached. It is critical that the dosage be adjusted to the lowest dose that provides effective control of HAE. Because the beneficial effects of androgens occur

slowly, it is generally not recommended to change the dosage faster than once every 2 weeks.[1, 15]

Androgens result in masculinization and hypogonadism in boys and menstruation irregularities in girls. Unfavourable effects on behaviour are possible. Reduction in ultimate body height may occur owing to the premature closure of epiphyseal growth plates.[15, 34, 70]

In addition to clinical evaluation of the patient, semiannual blood and urine tests (standard urine test strip) are needed, and at least once a year, an ultrasound of the liver should be performed, and to be seen by endocrinologist at each visit.[7, 15] It is unclear if stopping long term prophylaxis with attenuated androgens should be done by tapering off gradually over time.[71]

B-Non-pharmacological therapy:

Avoidance of triggers

Infections and mechanical trauma seem to be more common trigger factors during childhood. Compulsory and recommended vaccinations for children are safe and the prevention of infections may reduce the frequency of attacks (i.e. throat infections). Medicinal products (ACE-I) which can cause edema as an adverse effect should be avoided although are less frequently used in pediatrics. Other triggers like strenuous physical activities involving mechanical trauma and emotional challenges (stress) are essential elements of childhood and adolescence and should be decreased whenever possible.[1, 7, 15, 72]

Patients and family education

Providing appropriate education to pediatric patients and their families is indispensable to support them to have a suitable lifestyle and to avoid complications. Teachers, and health care personnel responsible for the child at daycare or school should receive written information on the disease, with advice on management of HAE attacks, including the urgency of treatment for airway attacks. Pediatric patients should have an information card containing a description of emergency procedures including on demand treatment for emergency use. Alert devices, including identifying wrist or neck bands with emergency contact information, should also be considered. The pdC1-INH concentrate for emergency use should be available at home, however, it is extremely important to encourage all patients to seek further care immediately after administration of therapy to reduce the risk of potentially fatal complications as in upper airway swelling. [7, 38, 40, 73]

Home therapy and self-/assisted administration

Based on the experience with hemophilia where children are benefited by taking an active part early in their treatment, and even at the age of 8, IV self-administration has been proven possible and safe, C1-INH concentrate home therapy is also suitable for children with frequent or disruptive attacks. Therefore, self-or assisted treatment techniques should be discussed, and training programs should be offered to parents and pediatric patients.[40,74]

Other considerations

All patients should be screened for hepatitis B and C and HIV. Vaccinations for hepatitis A and B are recommended by many experts. All patients should be considered to receive influenza vaccine and other routine vaccinations.[38]

Patient organizations and support groups provide help and support for HAE patients, caregivers, and family members. They endorse the philosophy that all patients worldwide should have sufficient resources to control their HAE symptoms and fulfil their potential at school, at work, and in their relationships. Patient organizations also work toward identifying and addressing unmet needs in HAE management, which include the development of safe and well tolerated new prophylactic and on-demand therapies, the optimization of existing long-term prophylactic and on-demand therapies, increasing the availability of modern treatment options worldwide, emphasizing the need for self-care, individual action plans, early therapy, and gene therapy research. HAEi is the international umbrella organization for the world's Hereditary Angioedema (HAE) patient groups, provide active informative web sites for patients and health care providers.[7]

Burden of HAE

It is impossible to predict the ultimate severity of an attack at the onset of that attack. Swelling of the extremities can result in temporary inability to walk because of swelling of the feet or to use the swollen hand for writing or typing. Subcutaneous swelling is a common cause of school absenteeism and may affect a child's progress in school and participation in sports and other daily activities.[20,22] Genitourinary attacks can cause significant discomfort and lead to a temporary inability to urinate. Abdominal attacks are a frequent cause of morbidity. The angioedema can result in severe abdominal pain with intractable nausea and vomiting and third-space sequestration of fluid that can induce significant hypotension.[7] Moreover, many patients with HAE may undergo unnecessary and inappropriate surgical interventions because of

severe abdominal attacks. Angioedema of the oropharynx in patients with HAE is capable of suffocation and resulting in death.[1] The cost of the disease in developing countries without specific medications for C1-INH-HAE is often excessive absenteeism, significant morbidity, failure to maintain employment, and higher risk of mortality.[75, 76]

Table 2. Doses, mode of administration and indication of drugs used in management of HAE-type I/II

Drug category (trade name)	Dose/mode of administration	Indications	Adverse effects
Plasma derived C1-INH concentrate (Berinert)	10-20 Units /kg with a maximum initial dose of 1000 units-intravenous	On-demand treatment/ STP and LTP	Hypersensitivity reactions-theoretical risk of transmission of blood borne infections
Plasma derived C1-INH concentrate (Cinryze)	10-20 Units /kg - intravenous 1000 units once or twice weekly (LTP)	Children 12 years and older: On demand treatment LTP (mainly)-STP	Hypersensitivity reactions-theoretical risk of transmission of blood borne infections
Recombinant C1-INH (Ruconest)	50 unit /kg -intravenous	On-demand treatment in children 13 years and older	Hypersensitivity reactions in patients with allergy to the rabbit and its products
Kallikrein inhibitor-Ecallantide (Kalbitor)	30 mg subcutaneous	On demand treatment in children 13 years and older	Risk of anaphylaxis, needs medical supervision.
17 α-alkylated androgens (Danazol)	Oral-2.5-10 mg/kg/day (average 5 mg/kg/day) STP: maximum 600 mg daily LTP: maximum 200 mg daily better to titrated to EOD	Second line agent in prophylaxis in patients with Tanner stage V and above.	Weight gain, elevation of the liver enzymes, menstrual irregularities and negative effect on the height
Antifibrinolytics/Tranxamic acid (Cyklocapron)	20-50 mg /kg /day maximum 3-6 gm daily	LTP	GIT upset, increased risk of thrombosis (uncommon)

C1-INH: C1-esterase inhibitor; STP: short-term prophylaxis; LTP: long term prophylaxis; GIT: gastrointestinal; EOD: every other day

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