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# Management of Hereditary Angioedema in Pediatric Patients

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## ABSTRACT

Hereditary angioneurotic edema is a rare disorder caused by the congenital deficiency of C1 inhibitor. Recurring angioedematous paroxysms that most commonly involve the subcutis (eg, extremities, face, trunk, and genitals) or the submucosa (eg, intestines and larynx) are the hallmarks of hereditary angioneurotic edema. Edema formation is related to reduction or dysfunction of C1 inhibitor, and conventional therapy with antihistamines and corticosteroids is ineffective. Manifestations occur during the initial 2 decades of life, but even today there is a long delay between the onset of initial symptoms and the diagnosis of hereditary angioneurotic edema. Although a variety of reviews have been published during the last 3 decades on the general management of hereditary angioneurotic edema, little has been published regarding management of pediatric hereditary angioneurotic edema. Thus, we review our experience and published data to provide an approach to hereditary angioneurotic edema in childhood.

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### Key Words

hereditary angioedema, pediatrics, C1 inhibitor, danazol, tranexamic acid

### Abbreviations

HAE—hereditary angioneurotic edema  
TA—tranexamic acid

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**H**EREDITARY ANGIONEUROTIC EDEMA (HAE) is an uncommon disorder that is caused by the congenital deficiency of C1 inhibitor.<sup>1</sup> Two types of this condition have been identified: type 1 HAE (seen in ~85% of cases), which is characterized by the low antigenic and functional activity of C1 inhibitor in the serum, and type 2 HAE (seen in 15% of cases), which is characterized by normal levels of protein C1 inhibitor but low functional levels of C1 inhibitor.<sup>2</sup> HAE follows a Mendelian autosomal-dominant trait with an estimated prevalence of 1 in 10 000 to 1 in 50 000 births. Recurring angioedematous paroxysms that most commonly involve the subcutis (eg, extremities, face, trunk, and genitals) or submucosa (eg, intestines and larynx) are the hallmarks of HAE. Edema formation is related to reduction or dysfunction of C1 inhibitor, which results in the release of bradykinin and C2-kinin mediators, which in turn enhance vascular permeability and lead to fluid extravasation.<sup>3,4</sup> A variety of reviews have been published during the last 3 decades on the general management of HAE. Although the early manifestations of HAE occur during the initial 2 decades of life, little has been published regarding management of pediatric HAE.<sup>5-8</sup> The first article that discussed the attributes of HAE during childhood determined by long-term follow-up of Hungarian pediatric patients was published in 2002.<sup>9</sup> Consensus documents,<sup>10</sup> an in-depth article,<sup>3</sup> and a review article<sup>11</sup> have separate sections on the properties of pediatric HAE. We review here our experience and published data to provide an approach to managing HAE in childhood.

## DIAGNOSIS

Even today there is a long delay between the onset of initial symptoms and the diagnosis of HAE. In 1975, Frank et al<sup>5</sup> reported the mean duration of this lag period until recognition of the disease to be 21 years. As shown by the results of a Spanish population study, this duration had decreased in some countries to 13.1 years, on average, by 2005, which is an improvement that is probably related to the augmentation of family screening and the increasing awareness of and familiarity with HAE.<sup>11</sup> However, the Italian experience reported by Zingale et al<sup>12</sup> in 2006 (reporting on data collected to the end of 2003) indicated a 21-year lag period. These diagnostic lag times are intolerably long. As demonstrated by reviews of large patient populations, the initial symptoms of HAE appear during the first decade of life in 50%, during the second decade in 35%, and after 20 years of age in the remaining 15% of patients.<sup>7,13</sup> Although the mean age at the onset of initial symptoms is 8 to 12 years, HAE can occur as early as the first year of life.<sup>1,14-17</sup> The large-scale study conducted by Bork et al<sup>13</sup> revealed that the annual number of attacks is almost twice as high in patients with disease onset before age 5 compared with those with HAE manifesting after the age of 15. Early diagnosis, therefore, is important, because disease

severity seems to be inversely correlated to age at onset, and the mortality of undiagnosed HAE can be as high as 50%. The earlier that HAE is identified, the sooner complex management can be initiated, which can afford efficient prevention and appropriate treatment of life-threatening complications.

## Clinical Manifestations

The 3 most common forms of angioedema are subcutaneous edema, abdominal edematous attacks, and laryngeal edema. Attack frequency is highly variable and shows substantial interindividual variation. In severe cases, attacks can occur weekly, but some patients remain symptom free almost throughout their lifetime. Reflecting the hereditary nature of the disorder, family history is positive in 75% of patients. In the remaining 25%, HAE cannot be demonstrated in the parents, which suggests *de novo* mutation of the C1-inhibitor gene in the index cases.<sup>3</sup>

### *Subcutaneous Edema*

Subcutaneous angioedema developing in HAE is circumscribed, nonpruritic, and nonerythematous swelling of the skin. It is not accompanied by urticaria, and it is experienced by almost 100% of symptomatic patients during their life. It is most commonly seen on the extremities (45% of attacks involve extremal edema) but can also develop on the face, neck, genitals, and trunk (skin edema occurs in 50% of all HAE attacks).<sup>13</sup> Subcutaneous angioedema resolves spontaneously, usually within 2 to 4 days. Mechanical trauma and airway infection are common precipitating factors in children.

### *Abdominal Attacks*

Abdominal attacks may mimic an acute abdominal catastrophe and lead to unwarranted surgery. Clinical manifestations include diffuse abdominal pain, vomiting, diarrhea, and ileus and may lead to hypovolemic shock. The absence of fever is an important differential diagnostic clue. Hemoconcentration can result in an elevated white blood cell count, but in contrast to inflammatory disorders, it is associated with a high red blood cell and platelet count, elevated hemoglobin and hematocrit levels, and shortened coagulation time. The abdomen is the second most frequent localization of acute HAE attacks, 48% of which involve the stomach and/or gut. Ninety-seven percent of symptomatic patients experience manifestations that are suggestive of an abdominal attack during their lifetime. The importance of recognizing abdominal HAE attacks in pediatric patients cannot be stressed enough. Abdominal pain, a frequent problem during childhood, is often related to common causes. In a small proportion of cases, however, abdominal pain may reflect the onset of an acute abdominal attack of HAE, and as such, it can be the first and only

manifestation of the disease. Often, it is also accompanied by subcutaneous edema.<sup>18</sup>

### *Laryngeal Edema*

Although angioneurotic edema of the larynx is rare (0.9% of all HAE attacks), it is a life-threatening manifestation of C1-inhibitor deficiency because of the risk of impending suffocation.<sup>13</sup> Usually, it occurs for the first time in patients in their mid-20s, afflicts approximately half of patients with HAE during their lifetime, and has been reported as early as age 3.<sup>19</sup> In children, edema formation has a propensity for the face and neck, and it can progress to involve the uvula, the soft palate, or the larynx. Because of the small diameter of the upper airways in children, relatively mild swelling of the mucosal lining causes substantial obstruction; therefore, suffocation can ensue rapidly.<sup>19,20</sup> Clinical manifestations include hoarseness, stridor, dyspnea, globus sensation, dysphagia, and voice change. Establishing a definitive diagnosis usually requires consultation with an otolaryngologist (ear, nose, and throat specialist). Because indirect laryngoscopy is usually difficult to perform on infants, presence of any of the symptoms listed above should be regarded as evidence of laryngeal edema.

### *Angioedema in Other Locations*

The localization of 2% of HAE attacks is different than those discussed above.<sup>13</sup> This applies also to pediatric patients, in whom edema of atypical location can involve the brain (causing headache), the urinary bladder, the urethra, muscles and joints, and the kidney. The so-called chest episode (accompanying subcutaneous edema of the trunk) with retrosternal pain and dyspnea deserves special mention. Infrequently, pericardiac or pleural effusion can be detected during the attack.

### **Laboratory Diagnosis**

Because the onset of symptoms from HAE can be early, detection of HAE (C1-inhibitor deficiency) as early as possible (ie, before the onset of initial symptoms) by laboratory testing is desirable for families afflicted by HAE. Importantly, the lack of manifestations does not rule out inherited HAE. Because this disease is caused by the hereditary deficiency of C1 inhibitor,<sup>1</sup> diagnosing either type of HAE in children is based on proving the abnormally low concentration of functional C1 inhibitor.<sup>3,10,21</sup> The reduced C1 inhibitor is associated with an increased cleavage of C4 by C1, which results in low C4 levels in patients with HAE; therefore, documenting low C4 levels helps to confirm the diagnosis of HAE. C4 levels are normal between attacks in <1% of patients with HAE.<sup>22,23</sup> In general, C1-inhibitor and C4 levels are related to disease symptoms.<sup>9,24</sup> Normal antigenic activity of the C1-inhibitor protein does not rule out type 2 HAE. If there are normal C1-inhibitor protein levels but HAE is suspected, then C1-inhibitor functional activity should

also be determined to rule out type 2 HAE. Substantial differences exist between the results of various methods used for the measurement of functional C1 inhibitor.<sup>24</sup> Using a chromogenic substrate kit, for example, functional C1-inhibitor levels of patients with HAE are less than half of the normal mean, whereas methods based on C1r or C1s and C1-inhibitor complex formation may yield normal values (especially in symptom-free patients). Thus, chromogenic methods are more suitable for establishing the diagnosis, whereas complex-formation methods may be more appropriate for follow-up purposes.<sup>3</sup> Simultaneous determination of all 3 parameters (ie, functional C1 inhibitor, antigenic C1 inhibitor, and C4 levels) is important for eliminating uncertainty. In pediatric patients, the situation is complicated further by age-dependent changes in the normal values of C1-inhibitor and complement proteins. Serum levels of the latter increase rapidly after birth, and the concentration of individual complement proteins is highly variable. In general, the complement system reaches adult maturity level by the age of 6 to 36 months.<sup>25</sup> In healthy neonates of normal weight, C1-inhibitor concentration in umbilical blood is approximately two thirds that of the adult normal value (although the result is substantially influenced by the maturity of the neonate, the laboratory method used, and the properties of the blood sample<sup>3,26</sup>). Diagnostic uncertainty is still rather high in infants younger than 6 months of age, because C1-inhibitor and C4 concentrations increase to adult levels between 2 and 3 years of age.<sup>27</sup> Therefore, both positive and negative findings should be interpreted with caution and in comparison to age-matched controls, and tests performed before 1 year of age should be confirmed after 1 year of age.<sup>21,24</sup> Furthermore, it is recommended to repeat measurements (possibly with alternative methods) in a sample obtained 4 weeks later. The child should be followed up as a patient with HAE as long as the possibility of the disease cannot be ruled out definitively and if there is a high index of suspicion. Considering its tremendous genetic variability,<sup>28</sup> testing for the C1-inhibitor gene is expensive and labor intensive. Accordingly, genetic screening of DNA is not recommended for initial testing. If complement values are inconsistent, however, molecular genetic tests may be useful and can also be used for prenatal diagnosis. It should be kept in mind that genetic screening fails to yield an accurate diagnosis in ~10% of cases.<sup>29</sup> Clearly abnormal C1-inhibitor and C4 assays, particularly with a positive family history, make genetic confirmation unnecessary. Acquired C1-inhibitor deficiency is unlikely in childhood; consequently, the measurement of C1/C1q levels and the detection of anti-C1-inhibitor antibodies are not necessary.

### **PEDIATRIC PATIENT MANAGEMENT**

Although the algorithm of patient management is similar for children and adults, treatment strategy must be

shaped by taking in consideration age-related anatomic and physiologic differences as well as the age-dependent characteristics of HAE. Management algorithms have essential and indispensable principles. However, treatment should always be individualized.

Management should comprise the following stages (Fig 1):

- information and education;
- treatment (emergency therapy of acute edematous attacks and prophylaxis [elimination of precipitating factors, long-term prophylaxis, and short-term prophylaxis]);
- follow-up; and
- home therapy.

### Information and Education

Providing in-depth and individualized education to the patient and family members on the nature of the disease, as well as giving advice on the most suitable means of lifestyle modification, are indispensable. In addition,

written information should be disseminated among the staff of day nurseries and schools, the professionals of school-based health services, and general practitioners and pediatricians. It is prudent to supply patients with HAE with a medical-information card (wallet card) that summarizes essential knowledge and methods of emergency care in several languages and contains the availability of the attending physician or other medical professional or of a hospital department or hotline service that specializes in the management of HAE (such hotlines can be developed locally, provincially, nationally, and even internationally). This card can prove to be an extremely useful aid for medical professionals who are relatively unfamiliar with HAE, both at home and abroad. At the initial visit, patients should be supplied with C1-inhibitor concentrate to be kept on hand for emergencies and travel. A patient diary should also be furnished for recording the number, location, duration, and precipitating factors of attacks; their treatment; and adverse reactions to medication. Replacement-therapy infusions must be recorded accurately in these diaries to

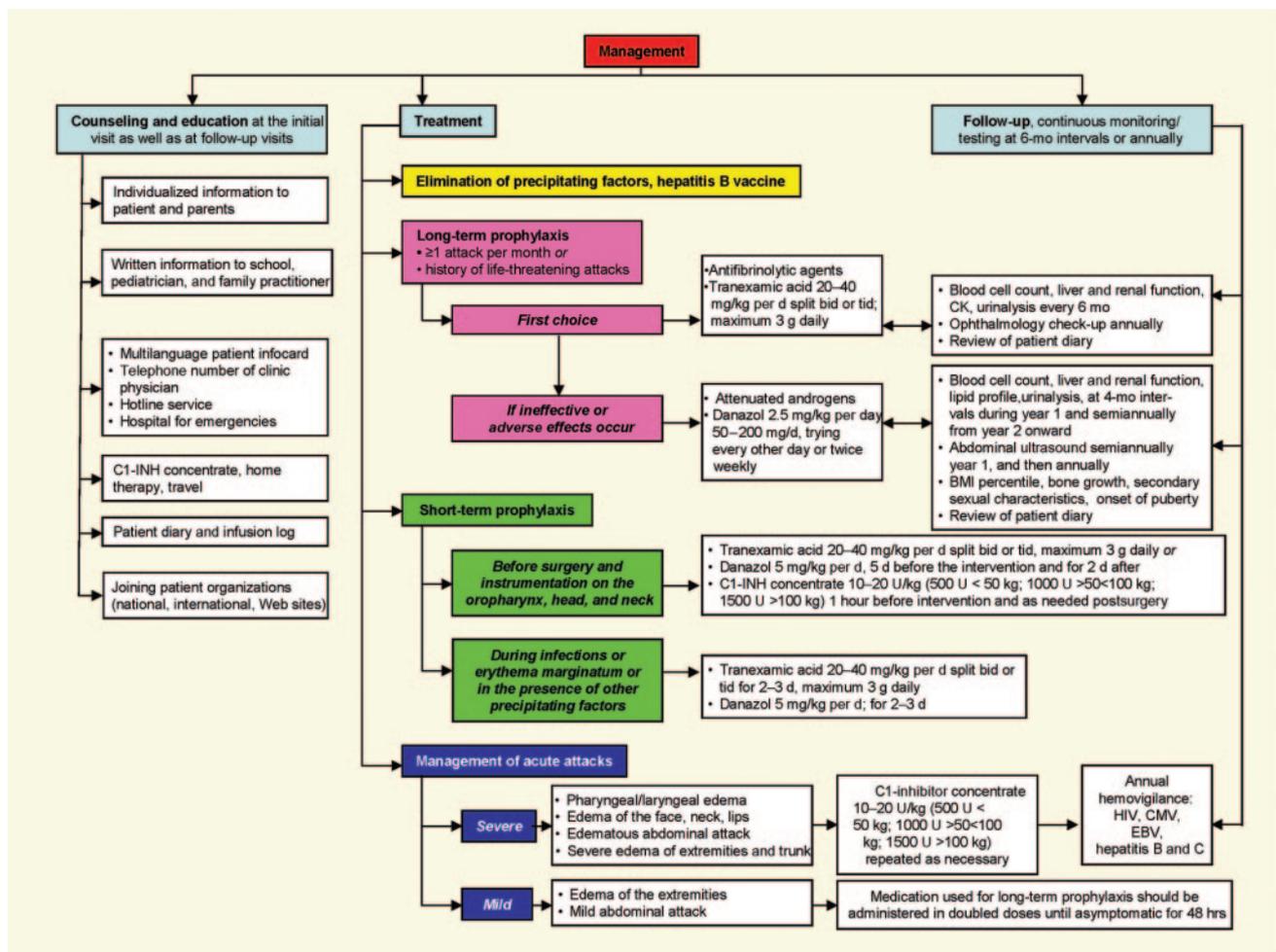


FIGURE 1

Management strategy for pediatric HAE. bid indicates 2 times daily; tid, 3 times daily; CK, creatine kinase; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

allow product lookback and traceback and for patient infusion records. Reviewing and interpreting the data in the patient diary at follow-up visits is extremely useful and instrumental for developing an individualized management protocol. Early health education and meticulous follow-up initiated in childhood can prevent social stigmatization and guarantee an improved quality of life during adulthood. We recommend that children with HAE participate in sports systematically, but sports with direct contact are not recommended. To reduce the risk of infection, pediatric patients with HAE should not go to day care before kindergarten. It is not recommended for adolescent girls to take oral contraceptives. If menstruation worsens HAE symptoms, doubling the dose of long-term prophylactics are useful.

The activity of patients' self-help groups can assist such efforts. If a national HAE organization is active in the country of residence, the physician should notify the patients and relatives of its existence and contact information, including Web-site location. Furthermore, it is important to call attention to Internet Web sites of international self-help organizations, because they communicate useful information for patients who are traveling abroad (HAE International [www.haei.org] and other national organization Web sites [eg, www.haecanada.com]).<sup>3,10,30,31</sup>

## Treatment

### *Emergency Therapy of Acute Edematous Attacks*

The child must be hospitalized if:

1. the edematous attack involves the submucosa (eg, in laryngeal edema): edema of the face and lips has a risk of propagation to the larynx, but if the conditions at home are reliable (close parental control, health care professionals with adequate intervention equipment and drugs immediately available), hospitalization may not be necessary. Laryngeal edema is a medical emergency and is an indication for admission to an ICU with ready access to endotracheal intubation, tracheostomy if needed, and airway management. C1-inhibitor concentrate should be administered at home as early as possible, and the patient should be sent to the emergency department for observation and further concentrate-replacement therapy if needed.
2. a severe abdominal attack has occurred and other acute abdominal pathologies cannot be ruled out with certainty (rapid resolution of symptoms with infusion of C1-inhibitor-replacement therapy is very helpful in sorting things out): the similarity between the clinical manifestations of abdominal HAE attacks and surgical emergencies including appendicitis is an apparent diagnostic pitfall.<sup>13,18,32</sup> Abdominal ultrasound (preferably performed before appropriate

treatment is initiated) is a nonspecific but extremely sensitive and noninvasive method that is particularly advantageous in pediatric practice. The presence of free peritoneal fluid and edematous swelling of the intestinal wall are highly suggestive of an abdominal attack of HAE.<sup>32-34</sup> Evidently, the onset or lack of symptomatic relief after intervention confirms or refutes the tentative diagnosis.

3. the attack is associated with obvious signs of hypovolemia (paleness of skin, prostration, dehydration, tachyarrhythmia).

Currently, the intravenous administration of C1-inhibitor concentrate is the most appropriate therapy for significant acute HAE attacks (laryngeal or diffuse facial edema and severe abdominal attacks).<sup>3,35-39</sup> Similar to that in adults, an intravenous dose of 10 to 20 U/kg (500 U up to 50 kg, 1000 U for weights between 50 and 100 kg, and 1500 U if weight is >100 kg) usually ensures therapeutic effect. This intervention is highly effective in halting the progression of clinical symptoms and achieving improvement within 15 to 60 minutes. A repeat dose may be required if the symptoms are not relieved within 1 hour or progress. C1-inhibitor concentrate may be administered to any pediatric age group and has an excellent safety profile.<sup>40</sup> Volume replacement to correct hypovolemic shock that results from an acute abdominal edematous attack is more frequently necessary in children. However, C1-inhibitor concentrate is unavailable in a number of countries.<sup>41,42</sup> If this is the case, appropriate measures for life-threatening HAE attacks include administering 1 to 2 U of fresh-frozen plasma (10 mL/kg, preferably solvent-detergent treated to reduce viral transmission).<sup>42-45</sup> Mild edematous attacks (eg, edema of the extremities, mild abdominal attack) usually subside spontaneously within a couple of days and often do not require intervention. Doubling the dose of medications administered for long-term prophylaxis for the duration of the attack often prevents the progression of edema and reduces the time required for its resolution.<sup>9</sup>

### *Prophylaxis*

#### *Elimination of Precipitating Factors*

The incidence and severity of characteristic manifestations show substantial interindividual variation, even among patients from the same family. A variety of environmental factors can influence the onset of attacks. Therefore, patient management should start with the identification, elimination, and avoidance of precipitating factors when possible. In the case of children, mechanical trauma is usually the most common precipitating factor. Even dentition or minor mechanical trauma (ie, friction during writing) can induce edema formation and should be recognized by pediatricians and family physicians. Considering the importance of physical ac-

tivity and sports on growth and development, there seems to be little indication for restriction of physical activities, but this must be closely discussed with the family and patient. Upper-airway infection and *Helicobacter pylori* infection are potential triggering factors; the former warrants prompt treatment and the latter warrants eradication of the *H pylori*.<sup>46,47</sup> Psychic stress or excitement in children can also precipitate HAE attacks and, therefore, should be minimized when possible. Adolescence is often associated with substantial changes in the activity of the disease, so close supervision is required during this period. Contraception indications are the same for adults and adolescents. Estrogen contraceptives should be avoided, because they may precipitate acute attacks.<sup>48</sup> Angiotensin-converting enzyme inhibitors also induce edema and, although rarely indicated in the pediatric population, are best avoided.<sup>49</sup> As with other potential recipients of chronic blood-product administration, consideration should be given to vaccinating patients with HAE against hepatitis B (may be combined hepatitis A and B).

#### *Long-term Prophylaxis*

Long-term prophylaxis is seldom necessary for children under the age of 6, because frequent HAE symptoms are rare before this age. The introduction of long-term prophylaxis is recommended if edematous attacks recur frequently ( $\geq 1$  attack per month) or a life-threatening episode can be identified in the patient's history.<sup>21,50</sup> C1-inhibitor-concentrate-replacement therapy on demand has been suggested as an ideal agent for pediatric patients.<sup>51</sup> Unfortunately, short half-life, intravenous administration, and cost of the concentrate often preclude its regular use for long-term prophylaxis. In pediatric patients, antifibrinolytic agents may be the treatment of choice for continuous therapy, because their safety profile is more favorable than that of attenuated androgens.<sup>3,9,52-54</sup> Clinical experience shows that tranexamic acid (TA) at a dosage of 20 to 40 mg/kg per day split 2 or 3 times per day (maximum dose: 3 g/day split 2 or 3 times per day) is better tolerated than  $\epsilon$ -aminocaproic acid (0.17–0.43 g/kg per day), which often causes gastrointestinal discomfort. Muscle weakness, myalgia, elevated creatine kinase activity, vascular thrombosis, postural hypotension, myonecrosis, and retinal changes may occur as adverse effects treatment with of TA.<sup>5,54</sup> TA is contraindicated in active thromboembolic disease or if a family history of thrombophilia (if family history is positive for thrombophilia, we suggest a thrombophilia workup before considering use of TA). If, however, these agents fail to achieve satisfactory improvement, treatment with attenuated androgens may be necessary.<sup>9,55-57</sup> Danazol and stanozolol have been in clinical use for  $>20$  years.<sup>58-60</sup> Stanozolol is not available in many countries,<sup>41,61</sup> and its efficacy seems inferior to that of danazol. Limited experience with pediatric use

has been obtained in patients treated for idiopathic thrombocytopenic purpura.<sup>62</sup> Treatment with the lowest effective maintenance dose of danazol (2.5 mg/kg per day; 50 mg/day starting dose; if necessary, up to a maximum of 200 mg/day) and intermittent dosage regimens (ie, doses repeated every other day or at 3-day intervals) do not interfere with growth and mental development and may prevent potential adverse effects such as hirsutism, virilization, weight gain, myalgia, headache, libido changes, elevation of serum transaminase levels, microhematuria, menstruation irregularities, and lipid-profile changes.<sup>21,52,58,60,63</sup> In recent years, several case reports have been published on the efficacy and favorable safety profile of oxandrolone in pediatric patients.<sup>64</sup>

#### *Short-term Prophylaxis*

Except for children who are undergoing surgical or diagnostic interventions in the head and neck region, short-term prophylaxis is less frequently required in children compared with adults.<sup>65-68</sup> Attenuated androgens such as danazol provide adequate protection when initiated 5 days before and continued 2 days after surgery with double the long-term daily dose (ie, 5 mg/kg per day; maximum of 600 mg/day). Antifibrinolytic agents (TA; see dosage above) are similarly effective for attack prevention.<sup>22,50</sup> Nevertheless, prophylaxis with C1-inhibitor concentrate (10–20 U/kg)<sup>22</sup> 1 hour before the aforementioned procedures is the safest option for patients with a history of severe attacks that are precipitated by similar interventions (particularly if endotracheal intubation or the contemplated surgery is expected to last several hours and involves tissue destruction).<sup>9,10,21,31,69</sup> Fresh-frozen plasma (preferably solvent detergent; 10 mL/kg) is a reasonable alternative if C1-inhibitor concentrate is not available.<sup>6,70,71</sup> Another strategy for short-term prophylaxis involves reserving the administration of agents conventionally used for long-term prophylaxis for the occurrence of prodromal symptoms (eg, generalized nonpruritic skin rash [erythema marginatum]), which can be observed before and during edematous attacks of HAE.<sup>72</sup> Short-term prophylaxis may alleviate the need for continuous prophylaxis and minimize drug exposure and adverse effects. TA or danazol (see short-term dosage above) administered for 2 to 3 days reduces the severity and duration of subcutaneous or gastrointestinal manifestations.

#### **Follow-up**

Given that HAE is a lifelong, currently incurable hereditary disorder with disease activity that varies in response to concomitant diseases, medications, and physiologic influences, lifelong regular monitoring and follow-up of patients in a comprehensive care clinic similar to that in the hemophilia model is of utmost importance. Regular follow-up visits to update medical history, perform physical and laboratory checkups, review the patient diary

and infusion records, and decide on potential changes to the therapeutic strategy are necessary at least once or twice per year.

In patients who are undergoing long-term prophylaxis with attenuated androgens, laboratory tests (complete blood count, liver- and renal-function tests, clotting test, obtain serum lipid levels, and urinalysis) should be repeated initially at 3-month intervals and abdominal ultrasound should be performed semiannually during the first 2 years of treatment. Subsequently, asymptomatic individuals or patients with mild symptoms should be checked every 6 to 12 months to detect potential liver damage. Anthropometric assessment of growth should be done every 6 months. The following studies may be undertaken as necessary: bone-age determination; monitoring the development of secondary sexual characteristics and pubertal changes; and developmental milestones and school performance.<sup>63,73,74</sup>

In patients who are receiving long-term TA prophylaxis, it is recommended to repeat laboratory tests including performing a complete blood count, liver- and renal-function tests, and a clotting test, obtaining the creatine kinase level, and performing urinalysis every 3 months during the first year and then, if asymptomatic, every 6 to 12 months thereafter. Ophthalmology review should be performed semiannually during the first 2 years of treatment and annually thereafter.<sup>75,76</sup>

C1-inhibitor concentrate is a blood product; therefore, appropriate hemovigilance for blood-borne pathogens (viral serology screening for hepatitis B and C, HIV, and parvovirus B19 at baseline and follow-up) should be performed before the first administration and annually, as is done for patients with hemophilia.<sup>9,10,21,40</sup> Serum samples should be stored on an annual basis for look-back and traceback purposes, should a new pathogen be encountered in the blood program, and meticulous blood-product–infusion recording is required to ensure vein-to-vein tracking of blood products.<sup>77</sup> Blood products that include C1 inhibitor that is manufactured by using the pasteurization procedure have an excellent safety profile.<sup>40</sup> Recent findings indicate that administration of C1-inhibitor concentrate is not associated with development of autoantibodies against C1 inhibitor.<sup>78</sup>

Meticulous follow-up in a comprehensive care clinic and registration on an international database registry (the HAE Register, available at [www.haeregister.org](http://www.haeregister.org)) afford timely recognition of therapy-related adverse effects and allow fine-tuning of therapy as necessary. Psychosocial support for the patient and family for this lifelong chronic disease is essential.

### Home Therapy

Similar to the hemophilia model, which is now >30 years old,<sup>79,80</sup> all patients with HAE should be offered home therapy.<sup>10,22</sup> The edematous attacks of HAE can rapidly progress to a life-threatening condition, espe-

cially in children.<sup>19</sup> It is recommended that patients keep a supply of C1-inhibitor–replacement therapy for personal use at home and for travel to be either self-administered or infused by a caregiver (human C1-inhibitor concentrate reconstituted, warmed to room temperature if time permits; 25-gauge butterfly intravenous cannula; over 10 minutes).<sup>10,22</sup> Self-administration on demand allows timely administration of the replacement product, lessens the severity of the event, improves quality of life, hopefully prevents the life-threatening complication of laryngeal edema, and usually prevents hospital emergency department visits. Home therapy should be supervised by the comprehensive care clinic to ensure ongoing competence of the infusers, training updates, infusion guidelines, hemovigilance sampling, and blood-product tracking.<sup>10,22,77</sup> Not all patients are capable of home self-infusion, and sometimes the attack is so severe and sudden that venous access for self-infusion may be difficult (eg, waking with hypovolemia in the middle of the night with an abdominal attack). Patients should not hesitate to seek immediate medical attention if they feel self-administration or infusion-partner administration will not be possible. Self-possession of C1-inhibitor–replacement product reduces the lag time to successful infusion by emergency personnel.<sup>3</sup> The patient should seek immediate medical attention if the episode is not responding to replacement infusion and always if the event has started to involve the larynx. Appropriate carrying cases for infusion supplies and the C1-inhibitor–replacement product to prevent exposure to extremes of heat and cold should be provided.<sup>3,10,22,79</sup> Comprehensive care clinics and their patients should be encouraged to participate with the HAE Register to speed up advances in diagnosis, therapy, and management of this disorder.

### Novel Therapeutic Agents

Novel therapeutic agents such as recombinant C1 inhibitor (Pharming Group, Leiden, Netherlands), the bradykinin B<sub>2</sub>-receptor antagonist icatibant (Jerini AG, Berlin, Germany), and the kallikrein antagonist DX88 (Dyax-Genzyme, Cambridge, MA) are being investigated in phase II/III clinical trials. The introduction of these drugs into clinical practice may expand the options for managing HAE with new treatments with novel modes of action.<sup>3,12,41,61,80</sup>

### Complex Management of HAE: Comprehensive Care Clinic/Angioedema Center

HAE is an uncommon disorder. Accordingly, the majority of medical professionals are unfamiliar with this condition and often do not consider HAE in the differential diagnosis of angioedema.<sup>13</sup> The clinical manifestations of HAE are not exclusively related to any particular organ. Therefore, patients frequently visit different medical outpatient clinics and the emergency department before

their condition is eventually diagnosed. With the autosomal-dominant nature of HAE, a new gene mutation may occur with the family history negative in 25% of cases.<sup>81</sup> Diagnostic workup is further complicated by the lack of ready availability of C1-inhibitor functional levels in the laboratory. The complement laboratory cooperating in the diagnosis of HAE must be competent in performing the whole range of special studies that are necessary, including testing the C1-inhibitor functional level. Genetic testing is indicated in a small proportion of cases and is rarely readily available (with >100 known mutations).<sup>28</sup> Although establishing an accurate diagnosis is a precondition, it is not sufficient for the management of HAE. Once diagnosed, HAE is associated with further difficulties during its management. Available treatment protocols are guidelines only and do not enable the inexperienced physician to fully manage this disorder and deliver optimum and individualized care. C1-inhibitor concentrate is not available everywhere for the treatment of acute, life-threatening attacks. The lack of licensed pharmaceutical products for the treatment of HAE is an important difficulty. Unlicensed medications may require special access processes with arduous paperwork and may delay timely therapy. Prophylactic medication administration must be carefully monitored to minimize adverse events. Establishing and maintaining a database of the clinical and laboratory parameters of patients (ie, the HAE Register) as well as organizing the follow-up care of patients and appropriate inpatient care are demanding challenges that are best undertaken by comprehensive care clinics that specialize in HAE and include appropriate transition from pediatric to adult clinics and require close cooperation with genetics services, diagnostic complement laboratories, and support from patient self-help groups (Table 1).<sup>3,30</sup> Only such comprehensive care clinics are capable of meeting educational, research, and development requirements in addition to delivering state-of-the-art patient care (Table 2). International cooperation between individual HAE centers and national and international organizations affords the most rapid improvement in our knowledge of such an uncommon disease. An international registry has already been established for this purpose with anonymized records of patients from only European countries to date but, hopefully, expanding worldwide as soon as possible.

**TABLE 1** Makeup of the HAE Comprehensive Care Center

HAE comprehensive care clinic staff including physician, nursing, psychosocial support, transfusion medicine
Complement laboratory
HAE hospital for pediatric patients
HAE hospital for adult patients
Molecular genetics laboratory
HAE patient self-help organization

**TABLE 2** Role of the HAE Center

Diagnostic workup
Differential diagnosis
Treatment
Follow-up care
Patient database registry maintenance
Education: community and medical (continuing medical education, graduate and postgraduate courses)
Research
Conference activity
Publications
Participation in international projects (basic science research and clinical trials)

Clinical studies that are necessary for the approval of novel and innovative therapies cannot be implemented effectively without the active contribution of HAE centers. Institutions with substantial experience can assist regions in which a proprietary health care delivery system has not yet been established. This is exemplified by the HAENetwork Project of the Hungarian HAE Center. This 3-phase project endeavors to foster the establishment of similar centers in all countries of Middle Europe over ~3 years. According to this experience, establishing an HAE center for every 10 million inhabitants seems reasonable; more centers may be necessary where populations are spread over larger geographic regions. Detailed information on the project is available at the homepage of the Hungarian HAE Center ([www.haenet.hu](http://www.haenet.hu)).

## CONCLUSIONS

Early diagnosis is the cornerstone of successful management of HAE in pediatric patients. Treatment requires adequate professional experience and lifelong follow-up. Therefore, it is recommended that patients with HAE be cared for in comprehensive care centers that specialize in the management of HAE. Emergency C1-inhibitor-replacement therapy for life-threatening edematous attacks must be made readily available to all patients, with home therapy encouraged and promoted, and the product must be carried for travel to assure the best quality of life and prevention of progression of life-threatening events with early replacement-therapy intervention.

## REFERENCES

1. Donaldson VH, Rosen FS. Hereditary angioneurotic edema: a clinical survey. *Pediatrics*. 1966;37:1017-1027
2. Rosen FS, Pensky J, Donaldson V, Charache P. Hereditary angioneurotic edema: two genetic variants. *Science*. 1965;148:957-958
3. Agostoni A, Aygoren-Pursun E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress—proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004;114(3 suppl):S51-S131
4. Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angio-oedema. *Lancet*. 1998;351:1693-1697
5. Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema:

- the clinical syndrome and its management. *Ann Intern Med.* 1976;84:580–593
6. Sim TC, Grant JA. Hereditary angioedema: its diagnostic and management perspectives. *Am J Med.* 1990;88:656–664
  7. Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore).* 1992;71:206–215
  8. Carugati A, Pappalardo E, Zingale LC, Cicardi M. C1-inhibitor deficiency and angioedema. *Mol Immunol.* 2001;38:161–173
  9. Farkas H, Harmat G, Fust G, Varga L, Visy B. Clinical management of hereditary angio-oedema in children. *Pediatr Allergy Immunol.* 2002;13:153–161
  10. Gompels MM, Lock RJ, Abinun M, et al. C1 inhibitor deficiency: consensus document [published correction appears in *Clin Exp Immunol.* 2005;141:189–190]. *Clin Exp Immunol.* 2005;139:379–394
  11. Roche O, Blanch A, Caballero T, Sastre N, Callejo D, Lopez-Trascasa M. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. *Ann Allergy Asthma Immunol.* 2005;94:498–503
  12. Zingale LC, Beltrami L, Zanichelli A, et al. Angioedema without urticaria: a large clinical survey. *CMAJ.* 2006;175:1065–1070
  13. Bork K, Staubach P, Eckardt AJ, Hardt J. Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. *Am J Gastroenterol.* 2006;101:619–627
  14. Blohmé G, Ysander L, Korsan-Bengtson K, Laurell AB. Hereditary angioneurotic oedema in three families: symptomatic heterogeneity, complement analysis and therapeutic trials. *Acta Med Scand.* 1972;191:209–219
  15. Ohela K. Hereditary angioneurotic oedema in Finland: clinical, immunological and genealogical studies. *Acta Med Scand.* 1977;201:415–427
  16. Zeana C. Hereditary angioedema due to deficit of C1 esterase inhibitor. *Med Interne.* 1989;27:143–147
  17. Nielsen EW, Gran JT, Straume B, Mellbye OJ, Johansen HT, Mollnes TE. Hereditary angio-oedema: new clinical observations and autoimmune screening, complement and kallikrein-kinin analyses. *J Intern Med.* 1996;239:119–130
  18. Foix-L'Hélias L, Weiss L, Mollet-Boudjemline A, Fallik D, Tri-choche-Eberschweiler P, Labrune P. Recurring acute abdominal pains in an adolescent as the presenting manifestations of hereditary angioneurotic oedema. *Acta Paediatr.* 2005;94:1158–1161
  19. Bork K, Hardt J, Schicketanz KH, Ressel N. Clinical studies of sudden upper airway obstruction in patients with hereditary angioedema due to C1 esterase inhibitor deficiency. *Arch Intern Med.* 2003;163:1229–1235
  20. El-Hachem C, Amiour M, Guillot M, Laurent J. Hereditary angioneurotic edema: a case report in a 3-year-old child [in French]. *Arch Pediatr.* 2005;12:1232–1236
  21. Bowen T, Cicardi M, Farkas H, et al. Canadian 2003 international consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *J Allergy Clin Immunol.* 2004;114:629–637
  22. Zuraw BL. Diagnosis and management of hereditary angioedema: an American approach. *Transfus Apher Sci.* 2003;29:239–245
  23. Zuraw BL, Sugimoto S, Curd JG. The value of rocket immunoelectrophoresis for C4 activation in the evaluation of patients with angioedema or C1-inhibitor deficiency. *J Allergy Clin Immunol.* 1986;78:1115–1120
  24. Spath PJ, Wütrich B. Inherited and acquired deficiencies of C1 esterase inhibitor in humans. In: Rother K, Till G, Hansch G, eds. *The Complement System.* Berlin, Germany: Springer; 1998: 353–410
  25. Davis CA, Vallota EH, Forristal J. Serum complement levels in infancy: age related changes. *Pediatr Res.* 1979;13:1043–1046
  26. Nielsen EW, Johansen HT, Holt J, Mollnes TE. C1 inhibitor and diagnosis of hereditary angioedema in newborns. *Pediatr Res.* 1994;35:184–187
  27. Roach B, Kim Y, Jerome E, Michael AF. Influence of age and sex on serum complement components in children. *Am J Dis Child.* 1981;135:918–920
  28. Kalmár L, Hegedus T, Farkas H, Nagy M, Tordai A. HAEdb: a novel interactive, locus-specific mutation database for the C1 inhibitor gene. *Hum Mutat.* 2005;25:1–5
  29. Kalmár L, Bors A, Farkas H, et al. Mutation screening of the C1 inhibitor gene among Hungarian patients with hereditary angioedema. *Hum Mutat.* 2003;22:498
  30. Farkas H, Varga L. The Hungarian HAE experience. *Transfus Apher Sci.* 2003;29:229–233
  31. Boyle RJ, Nikpour M, Tang ML. Hereditary angio-oedema in children: a management guideline. *Pediatr Allergy Immunol.* 2005;16:288–294
  32. Farkas H, Harmat G, Kaposi PN, et al. Ultrasonography in the diagnosis and monitoring of ascites in acute abdominal attacks of hereditary angioneurotic oedema. *Eur J Gastroenterol Hepatol.* 2001;13:1225–1230
  33. Talavera A, Larraona JL, Ramos JL, et al. Hereditary angioedema: an infrequent cause of abdominal pain with ascites. *Am J Gastroenterol.* 1995;90:471–474
  34. Farkas H, Harmat G, Fekete B, Karadi I, Visy B, Varga L. Acute abdominal attack of hereditary angioneurotic oedema associated with ultrasound abnormalities suggestive of acute hepatitis. *Acta Paediatr.* 2002;91:971–974
  35. Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. *N Engl J Med.* 1996;334:1630–1634
  36. Gadek JE, Hosea SW, Gelfand JA, et al. Replacement therapy in hereditary angioedema: successful treatment of acute episodes of angioedema with partly purified C1 inhibitor. *N Engl J Med.* 1980;302:542–546
  37. Agostoni A, Cicardi M, Bergamaschini L, Boccassini G, Tucci A. C1-inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med.* 1980;303:527
  38. Bork K, Barnstedt SE. Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema. *Arch Intern Med.* 2001;161:714–718
  39. Davis AE 3rd. Biological effects of C1 inhibitor. *Drug News Perspect.* 2004;17:439–446
  40. De Serres J, Groner A, Lindner J. Safety and efficacy of pasteurized C1 inhibitor concentrate (Berinert P) in hereditary angioedema: a review. *Transfus Apher Sci.* 2003;29:247–254
  41. Frank MM. Hereditary angioedema. *Curr Opin Pediatr.* 2005;17: 686–689
  42. Bowen TJ, Zuraw B. Treatment of hereditary angioedema: current USA and Canadian studies. Presented at: meeting of the Network of Rare Blood Disorders Organizations; February 3, 2006; Toronto, Ontario, Canada. Available at: [www.hemophilia.ca/nrbdo/pdf/Bowen\\_Zuraw.Treatment.HAE.ppt](http://www.hemophilia.ca/nrbdo/pdf/Bowen_Zuraw.Treatment.HAE.ppt). Accessed May 29, 2007
  43. Hill BJ, Thomas SH, McCabe C. Fresh frozen plasma for acute exacerbations of hereditary angioedema. *Am J Emerg Med.* 2004;22:633
  44. Pickering RJ, Good RA, Kelly JR, Gewurz H. Replacement therapy in hereditary angioedema: successful treatment of two patients with fresh frozen plasma. *Lancet.* 1969;1(7590): 326–330
  45. Lieberman A. The use of fresh-frozen plasma in hereditary angioedema. *JAMA.* 1994;272:518
  46. Farkas H, Fust G, Fekete B, Karadi I, Varga L. Eradication of

- Helicobacter pylori* and improvement of hereditary angioneurotic oedema. *Lancet*. 2001;358:1695–1696
47. Rais M, Unzeitig J, Grant JA. Refractory exacerbations of hereditary angioedema with associated *Helicobacter pylori* infection. *J Allergy Clin Immunol*. 1999;103:713–714
  48. Bouillet L, Ponard D, Drouet C, Jullien D, Massot C. Angioedema and oral contraception. *Dermatology*. 2003;206:106–109
  49. Agostoni A, Cicardi M. Drug-induced angioedema without urticaria. *Drug Saf*. 2001;24:599–606
  50. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med*. 2006;119:267–274
  51. Bork K, Witzke G. Long-term prophylaxis with C1-inhibitor (C1 INH) concentrate in patients with recurrent angioedema caused by hereditary and acquired C1-inhibitor deficiency. *J Allergy Clin Immunol*. 1989;83:677–682
  52. Abinun M. Hereditary angio-oedema in children. *Lancet*. 1999;353:2242
  53. Gwynn CM. Therapy in hereditary angioneurotic oedema. *Arch Dis Child*. 1974;49:636–640
  54. Ritchie BC. Protease inhibitors in the treatment of hereditary angioedema. *Transfus Apher Sci*. 2003;29:259–267
  55. Farkas H, Harmat G, Gyeney L, Fust G, Varga L. Danazol therapy for hereditary angio-oedema in children. *Lancet*. 1999;354:1031–1032
  56. Barakat A, Castaldo AJ. Hereditary angioedema: danazol therapy in a 5-year-old child. *Am J Dis Child*. 1993;147:931–932
  57. Rajagopal C, Harper JR. Successful use of danazol for hereditary angio-oedema. *Arch Dis Child*. 1981;56:229–230
  58. Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol: reversal of clinical and biochemical abnormalities. *N Engl J Med*. 1976;295:1444–1448
  59. Agostoni A, Cicardi M, Martignoni GC, Bergamaschini L, Marasini B. Danazol and stanozolol in long-term prophylactic treatment of hereditary angioedema. *J Allergy Clin Immunol*. 1980;65:75–79
  60. Sheffer AL, Fearon DT, Austen KF. Hereditary angioedema: a decade of management with stanozolol. *J Allergy Clin Immunol*. 1987;80:855–860
  61. Zuraw BL. Current and future therapy for hereditary angioedema. *Clin Immunol*. 2005;114:10–16
  62. Weinblatt ME, Kochen J, Ortega J. Danazol for children with immune thrombocytopenic purpura. *Am J Dis Child*. 1988;142:1317–1319
  63. Cicardi M, Castelli R, Zingale LC, Agostoni A. Side effects of long-term prophylaxis with attenuated androgens in hereditary angioedema: comparison of treated and untreated patients. *J Allergy Clin Immunol*. 1997;99:194–196
  64. Church JA. Oxandrolone treatment of childhood hereditary angioedema. *Ann Allergy Asthma Immunol*. 2004;92:377–378
  65. Maeda S, Miyawaki T, Nomura S, Yagi T, Shimada M. Management of oral surgery in patients with hereditary or acquired angioedemas: review and case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2003;96:540–543
  66. Atkinson JC, Frank MM. Oral manifestations and dental management of patients with hereditary angioedema. *J Oral Pathol Med*. 1991;20:139–142
  67. Farkas H, Gyeney L, Gidofalvy E, Fust G, Varga L. The efficacy of short-term danazol prophylaxis in hereditary angioedema patients undergoing maxillofacial and dental procedures. *J Oral Maxillofac Surg*. 1999;57:404–408
  68. Mohr M, Pollok-Kopp B, Gotze O, Burchardi H. The use of a C1-inhibitor concentrate for short-term preoperative prophylaxis in two patients with hereditary angioedema [in German]. *Anaesthesist*. 1996;45:626–630
  69. Socker M, Boyle C, Burke M. Angio-oedema in dentistry: management of two cases using C1 esterase inhibitor. *Dent Update*. 2005;32:350–352, 354
  70. Jaffe CJ, Atkinson JP, Gelfand JA, Frank MM. Hereditary angioedema: the use of fresh frozen plasma for prophylaxis in patients undergoing oral surgery. *J Allergy Clin Immunol*. 1975;55:386–393
  71. Longhurst HJ. Emergency treatment of acute attacks in hereditary angioedema due to C1 inhibitor deficiency: what is the evidence? *Int J Clin Pract*. 2005;59:594–599
  72. Farkas H, Harmat G, Fay A, et al. Erythema marginatum preceding an acute oedematous attack of hereditary angioneurotic oedema. *Acta Derm Venereol*. 2001;81:376–377
  73. Széplaki G, Varga L, Valentin S, et al. Adverse effects of danazol prophylaxis on the lipid profiles of patients with hereditary angioedema. *J Allergy Clin Immunol*. 2005;115:864–869
  74. Bork K, Pitton M, Harten P, Koch P. Hepatocellular adenomas in patients taking danazol for hereditary angio-oedema. *Lancet*. 1999;353:1066–1067
  75. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. *Drugs*. 1999;57:1005–1032
  76. Snir M, Axer-Siegel R, Buckman G, Yassur Y. Central venous stasis retinopathy following the use of tranexamic acid. *Retina*. 1990;10:181–184
  77. Ritchie BC. Tissue archives to track blood borne pathogens in people receiving blood products. *Transfus Apher Sci*. 2003;29:269–274
  78. Varga L, Széplaki G, Visy B, et al. C1-inhibitor (C1-INH) auto-antibodies in hereditary angioedema: strong correlation with the severity of disease in C1-INH concentrate naive patients. *Mol Immunol*. 2007;44:1454–1460
  79. Strawczynski H, Stachewitsch A, Morgenstern G, Shaw ME. Delivery of care to hemophilic children: home care versus hospitalization. *Pediatrics*. 1973;51:986–991
  80. Bracho FA. Hereditary angioedema. *Curr Opin Hematol*. 2005;12:493–498
  81. Pappalardo E, Cicardi M, Duponchel C, et al. Frequent de novo mutations and exon deletions in the C1 inhibitor gene of patients with angioedema. *J Allergy Clin Immunol*. 2000;106:1147–1154

## Management of Hereditary Angioedema in Pediatric Patients

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