

# Management of Children With Hereditary Angioedema Due to C1 Inhibitor Deficiency

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Hereditary angioedema (HAE) is a potentially life-threatening inherited disease characterized by attacks of skin swelling, severe abdominal pain, and upper airway swelling. Attacks typically begin in childhood, but the appropriate diagnosis is often missed. Attacks do not respond to epinephrine, antihistamines, or glucocorticoids. Recently, many effective drugs have been approved for treatment of adults with HAE, and the Medical Advisory Board of the HAE Patient's Association has developed and reported treatment recommendations for adults. Only 1 medication is approved for treatment of children <12 years of age, and there are no reported consensus recommendations for treatment of young children in the United States. The 11-member Medical Advisory Board, with extensive experience in the treatment of children, in concert with the leaders of the HAE Patient's Association, has developed these consensus recommendations to help in recognition, diagnosis, treatment of attacks, and prophylaxis of children with HAE.

Hereditary angioedema (HAE) is an autosomal dominant disease characterized by recurrent angioedema episodes (circumscribed areas of marked subcutaneous edema) that are nonpruritic, are not associated with hives, and affect the skin, gastrointestinal submucosa, and upper airway.<sup>1-5</sup> The swelling attacks do not respond to epinephrine, glucocorticoids, or antihistamines. Types 1 and 2 HAE are caused by low levels of functional C1 inhibitor (C1 INH) protein that regulates the activity of complement system, the clotting, fibrinolytic, and kinin-generating systems in plasma.<sup>6</sup> Unregulated cleavage of plasma high-molecular-weight kininogen leads to the overproduction of bradykinin, the mediator of angioedema attacks.<sup>7</sup> Prevalence in the United States is

unknown but is estimated at 1 per 50 000 population.<sup>2</sup> Characteristically, disease manifestations begin in childhood. In 1 large series of 211 patients from 102 families, the mean age of symptom onset was 11.2 years (SD  $\pm$  7.7).<sup>8</sup> Onset of clinical symptoms occurred in the first decade of life in 107 patients, in the second decade in 79 patients, and later in 23 patients. Although highly effective medications are currently available, the proper diagnosis is often missed and treatment delayed. In surveys carried out in America, Denmark, and Italy, delay in diagnosis was reported as 8.3 years, 16 years, and 8.5 years.<sup>9-11</sup> Upper airway edema is potentially fatal. Bork et al<sup>12</sup> published a large series of his German cohort on the danger of asphyxiation. Of the 214 of 728 patients in his series

## abstract

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This consensus recommendation was conceptualized at a meeting in May 2014 of the Hereditary Angioedema Medical Board and was further discussed at a meeting in October 2015. A series of conference calls allowed further discussion of the document. Dr Frank drafted the initial manuscript. After the initial draft, all members of the board made corrections, all were recirculated to the board, and again changes were made. The Medical Advisory Board (MAB) revised the draft 3 times. All members of the MAB and the leaders of the Hereditary Angioedema Association (HAEA) approved each item and the final manuscript. The MAB of the HAEA is composed of leading clinicians who have played a major role in the development of new drugs for the treatment of hereditary angioedema (HAE), see many patients, and have published extensively in the field. For example, Frank and colleagues published the first double-blind controlled study of the treatment of HAE with danazol in 1976 and with C1 inhibitor in adults in 1996, both in the *New England Journal of Medicine*. He was senior author on the *New England Journal of Medicine* article that reported the first double-blind study of the drug later marketed as Cinryze. Dr Zuraw was the lead author on that article. Drs Busse, Lumry, Craig, and Bernstein contributed to that paper as well. Dr Li was an

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who died, 70 asphyxiated during a laryngeal attack. Mortality by asphyxiation was higher in patients with undiagnosed HAE C1 INH (63 cases) than in patients with diagnosed HAE C1 INH (7 cases). The life span of asphyxiated patients with undiagnosed HAE C1 INH was on average ~31 years shorter than that of patients with diagnosed HAE C1 INH. Attacks in childhood are generally mild, with subcutaneous swelling of the extremities or severe colicky abdominal pain, but they become more severe at puberty.<sup>5</sup> However, some young children experience severe disease, and treatment is challenging. There are many potential attack triggers, but particularly important in children, dental manipulation may precipitate an oral or laryngeal attack. However, most attacks occur spontaneously and with no known cause.<sup>8,13</sup> There are few reported pediatric double-blind treatment studies, and unlike in Europe there are no US established pediatric treatment guidelines.<sup>14</sup> As in adult patients, for unknown reasons, symptoms of HAE in children vary markedly, even in the same family.<sup>8</sup> It is important that physicians and patient families work together to design individualized treatment plans that optimize patient care.

Two types of HAE, both inherited as autosomal dominant traits and associated with deficiency of circulating levels of functional C1 INH protein, are described.<sup>15</sup> Type I HAE, characterized by low plasma levels of C1 INH, accounts for 85% of cases. Type II HAE, with normal to elevated plasma levels of dysfunctional C1 INH, accounts for the remaining cases; 25% of all cases appear to arise from de novo mutations.<sup>16</sup> Acquired forms of angioedema associated with C1 INH deficiency and a form of HAE associated with normal C1 INH protein level and function have been described but are extremely rare in children.

In 2013 the Medical Advisory Board (MAB) of the US Hereditary Angioedema Association (HAEA) published recommendations for treatment of type I and II HAE in adults.<sup>17</sup> At that time, after double-blind studies the US Food and Drug Administration (FDA) had approved 4 new medications for HAE treatment, 1 for HAE prophylaxis and 3 for the treatment of attacks. Since that time a fourth medication for the treatment of HAE attacks has received FDA approval,<sup>18</sup> and 1 (Berinert) has been approved for treatment of attacks in all children, based on extensive experience with its use.

The HAEA MAB has developed these recommendations to help treating physicians make decisions about preferred treatment of children with HAE types 1 and 2. Lay members of the HAEA had considerable input into their development and approved these recommendations. As with the adult treatment guidelines, the MAB strongly endorses the concept that patients and families have major input into their own treatment decision, because they significantly affect their lives.

The health care system in the United States differs from that in many other countries. For example, in countries with a centralized health care system the government may pay for all medical services including drugs. Available drugs also vary from country to country. Thus, these recommendations outlining our assessment of best practices in the United States may differ from those written for the treatment of children in other countries.<sup>19</sup> As with adults, we believe that a comprehensive individualized management plan developed by an expert HAE physician and the patient, in collaboration with local medical providers and emergency departments, gives patients the best opportunity to lead a normal life.

## METHODS

The HAEA MAB, which has developed these recommendations, consists of 11 clinicians, each of whom treats a large number of patients with HAE. These recommendations include a management plan, treatment of acute angioedema attacks, prophylactic treatment, and patient monitoring. Treatment options are divided into management of attacks, short-term prophylaxis, and long-term prophylaxis. These guidelines were written after 2 conference meetings attended by all the authors and 2 conference calls. Dr Frank wrote the first draft and distributed it to the other members of the Advisory Board. All members corrected the document and resubmitted it to Dr Frank. The draft went through 3 rounds of alterations. The revised final draft of the recommendations reflects the unanimous consensus of the MAB and the HAEA leaders.

## HAE MANAGEMENT RECOMMENDATIONS

### Section 1. Management Plan

An accurate diagnosis of HAE must be established before treatment options are discussed. This diagnosis can usually be accomplished by the measurement of plasma complement protein 4 (C4) and an assessment of quantitative and functional activity of C1 INH.<sup>20</sup> In general the blood levels of complement proteins and C1 INH are low at birth<sup>21</sup>; therefore, we recommend that these studies be delayed for  $\geq 1$  year. If for some reason an earlier diagnosis is needed, sequence analysis of the C1 INH gene will lead to an accurate diagnosis, but usually this more expensive test is not needed<sup>20</sup> and is often not covered by third-party payers. However, if a genetic analysis is pursued, because most children seen will have an affected parent with the same genetic abnormality, the parents' and child's genes should be analyzed simultaneously. It should be

emphasized that HAE is inherited as an autosomal dominant disease, and almost all patients are heterozygous for the gene abnormality. Thus, not only first-degree relatives but second-degree relatives may have the genetic abnormality and the disease. Early recognition is important because the first instance of swelling can be life threatening.<sup>22,23</sup>

The overall goals of HAE treatment are to reduce morbidity and mortality, ensure normal growth and development, and restore a normal quality of life to the affected child and his or her family. To achieve these goals, an individualized comprehensive management plan should be developed and implemented. The elements of such a plan are as follows.

### *1.1. Expert Physician*

Because of the complexity and variability of HAE and treatment, we strongly recommend that every patient with HAE be followed by a physician who is knowledgeable about the condition, experienced in managing patients with HAE, and familiar with all treatment options. This physician must work with the patient's primary health care providers and the local community emergency department or hospital to ensure that components of the treatment plan are clearly communicated.

### *1.2. Patient Education*

It is suggested that affected patients and families be educated about the condition when the diagnosis is made. The HAEA provides appropriate materials. All first-degree family members should be tested for HAE, given the demonstrated mortality risk associated with undiagnosed HAE and the fact that in some patients, manifestations of HAE may appear late in life.<sup>24</sup> Patients should understand the cause of HAE, the inheritance patterns, potential

benefits of family testing, common attack manifestations, potential risks and complications from attacks, possible attack triggers, and treatment options. Given the fact that HAE with appropriate treatment carries little risk, we expect that most family members will favor family testing efforts, but this may not always be the case. In addition to education about HAE, it is important that patients and families be provided guidance on navigating the health care system.

### *1.3. Treatment Options*

Therapeutic approaches for HAE include both on-demand therapy, given at the onset of symptoms to abrogate attacks, and prophylactic treatment to prevent or minimize attack number and severity. These treatments have been studied carefully in adults, but not all have not been investigated with the same level of care in children (Table 1). Nevertheless, all patients need a readily available on-demand treatment to terminate unpredictable angioedema episodes. For some patients, on-demand treatment alone is sufficient; for others, prophylactic treatment is indicated as first-line treatment together with on-demand treatment of breakthrough attacks. There is dramatic intraindividual and interindividual clinical variability of HAE, and treatment strategies must be individualized based on patient- and parent-specific factors. These factors include age, comorbidities, access to emergency medical facilities, and the patient's past clinical experience. It should also be recognized that HAE severity may wax and wane over time.<sup>8</sup> Symptom-free periods may extend at times for years<sup>8</sup> and physicians must periodically review and potentially refine the treatment plan based on clinical course and dynamic patient factors (eg, pregnancy, rural versus urban residence).

### *1.4. Coordination of Care*

Patients with HAE often experience angioedema attacks that warrant intervention by physicians without expertise in HAE. Because these needs are likely to be emergent, local providers, including the local emergency department and primary care clinician, should know about the patient and be educated about HAE treatment options. If the child is in school, teachers and school nurses should be informed about the disease and its treatment. The local providers should also know how to reach the expert physician should they need additional recommendations. All patients with HAE should carry identification that alerts health care providers about their HAE and includes contact information for their expert physician.

### *1.5. Treatment Logistics*

Attacks progress over a period of hours, not minutes. Nevertheless, preplacement of FDA-approved HAE-specific medication for each affected patient is important. Family members should understand which medication they will use to treat an attack, where the medication is stored, when they will use the medication, who will administer it (home, school, or health care provider), where it will be administered (home, school, or health care facility), and how they will determine whether they need additional assistance or additional dosing of medication. Given the unpredictable onset of HAE attacks, patients should also understand the process by which their medication is refilled so that they are appropriately prepared for the next attack. Although in clinical trials these drugs had an efficacy of 60% to 90%, the experience of the MAB suggests that efficacy is closer to 90%.

## **Section 2. Treatment of Acute Angioedema Attacks**

The goal of treatment in pediatric HAE is to prevent mortality, minimize

**TABLE 1** Drugs for Prophylaxis and for Acute Treatment of Hereditary Angioedema

Drug	Type of Evidence (I, Randomized Controlled Trial; II-3, Dramatic Results in Uncontrolled Trial)	Dosage	Administration	Use	Side Effects
Cinryze	I, adults; FDA approved age >18 y; II-3 in children	1000 U in adults	Intravenous	Prophylaxis	Allergic reaction, nausea, diarrhea
Berinert	I, adults; II-3 in children; FDA approved July 2016 for all children	20 U/kg	Intravenous	On demand	Allergic reaction, nausea, diarrhea
Ruconest	I, adults; FDA approved ≥18 y	50 U/kg	Intravenous	On demand	Headache, nausea, diarrhea
Icatibant	I, adults; FDA approved ≥18; II-3 in children	30 mg	Subcutaneous	On demand	Redness, swelling, pain
Ecallantide	I, adults; FDA approved for ≥12; II-3 in children	30 mg	Subcutaneous	On demand	Possible anaphylaxis
Danazol	I, FDA approved for adults; II-3 in children; NOT RECOMMENDED	<200 mg	Oral	Prophylaxis	Androgenic side effects: wt gain, masculinization
Tranexamic acid	II-3 in adults and children	20–40 mg/kg up to 3 g/d	Oral	Prophylaxis	Fibrinolysis inhibitor; clot formation, allergic reaction
Fresh frozen plasma	II-3 in adults	1–2 U	Intravenous	On demand	Infection, hypersensitivity

morbidity, and allow for a normal childhood. Treatment of attacks on demand (ie, whenever they occur) may accomplish this goal. Multiple specific and effective medications are available for the on-demand treatment of attacks in adults, and many have been studied in a limited number of young patients (Table 1). Only 1 of these treatments, a purified C1 esterase inhibitor protein (Berinert), has been approved for children of all ages by the FDA. However, all of these therapies share a common characteristic. They act to prevent the generation or action of bradykinin and thus inhibit the extravasation of fluid into tissue. None of these agents act to hasten the reabsorption of accumulated fluid responsible for disease manifestations. Thus, there is a major advantage in treating early in an attack, before much fluid has accumulated, which emphasizes the importance of home therapy whenever possible.<sup>25,26</sup>

### 2.1. Availability of On-Demand Treatment

Children with HAE should have access to ≥2 standard doses of FDA-approved medicine for on-demand treatment of attacks. As mentioned, in July 2016 the FDA approved intravenous C1 INH (Berinert) as the first on-demand medication

for children of all ages with HAE. In addition, ecallantide and a recombinant C1 INH (Ruconest) are available for use in adolescents.

### 2.2. Existing Management Plan

Patients should have a management plan in place, with easy access to their health care provider during an attack. The management plan should include the names and dosages of the medications and the methods of administration. We assume that most HAE attacks can be treated outside a medical facility. Nevertheless, initial treatments should be administered with the availability of medical personnel. Subsequently, treatment can be rendered by self-administration, a trained family member, a home health professional, or a medical facility. Arrangement for easy access to a medical facility or health care provider is strongly encouraged for all patients, even those who can be treated at home. This recommendation is especially important for any attacks involving the airway, or the neck and above, because swelling can potentially extend to the laryngopharynx, resulting in asphyxia.<sup>12</sup>

### 2.3. Early Treatment

Families should be counseled to treat as soon as the attack is

clearly recognized. In cases where the patient can reliably predict an attack (ie, appearance of erythema marginatum or other prodromes<sup>27</sup>), arrangements for treatment may be initiated during a prodrome.<sup>28,29</sup>

However, treatment should be administered only when the child or family can be certain that an attack has begun. If any features of the attack are unusual, the response to treatment is inadequate, or the attack involves the upper airway, the child should be seen in a medical facility with adequate emergency care.

### 2.4. Attack Location

Decisions about which attacks to treat with on-demand medications should be based on the goals of minimizing morbidity, preventing mortality, and increasing quality of life rather than an arbitrary distinction based on location. There is consensus among the MAB and the HAE Association membership that all attacks, irrespective of location, should be considered for treatment as soon as they are clearly recognized.

### 2.5 Assessment of On-Demand Treatment Efficacy

Realistic expectation of treatment efficacy should be discussed with caregivers. Onset of treatment

effect may take 30 to 60 minutes and complete resolution may take hours. In general, a second dose of the on-demand treatment is not warranted unless the attack begins to worsen.

### 2.5. Agents Available for On-Demand Therapy

#### C1 Inhibitor.

The agent in longest use for treatment of attacks is C1 INH purified from plasma (pC1 INH). Although it has been available in Europe for decades, it was only approved in the United States for intravenous injection in children as Berinert (CSL Behring, Marlberg, Germany) in 2016.<sup>30</sup> Because the fundamental problem in HAE is decreased C1 INH function, this therapy directly addresses the cause of attacks. Both the efficacy and tolerability of pC1 INH in pediatric HAE have been the focus of multiple reports,<sup>25,26,31–36</sup> at the suggested dosage of 20 U/kg.<sup>35</sup> It is now FDA approved for treatment in children of all ages. Cinryze (Shire/Viropharma, Lexington, MA), a similar pC1 INH approved for prophylaxis in adults and adolescents, has also been used for acute management in younger children but is not FDA approved for acute attacks.<sup>37,38</sup> A recombinant form of C1 INH, also given intravenously (Ruconest, Salix, Indianapolis, IN) is also approved for treatment of attacks in adolescents and adults,<sup>39</sup> and like Berinert it has the advantage of weight-based dosing.

#### Ecallantide.

Ecallantide (Kalbitor, Shire, Lexington, MA) is a plasma kallikrein inhibitor currently approved for treatment of HAE attacks in patients aged  $\geq 12$  years. A recent analysis of pooled data suggests that ecallantide is effective for the treatment of HAE attacks in younger patients and has an acceptable safety profile.<sup>40,41</sup> Ecallantide has been associated with hypersensitivity reactions in

a small percentage (3%–4%) of recipients and therefore has a boxed warning that states that it must be administered under the supervision of medical personnel. It can often be arranged for a home health nurse to administer the drug.

#### Icatibant.

Icatibant (Firazyr, Shire, Lexington, MA) is a bradykinin  $B_2$  receptor antagonist currently approved for treatment of HAE attacks in patients  $>18$  years of age. A pharmacokinetic, tolerability, and safety study of icatibant in patients  $<18$  years of age with HAE has been completed, demonstrating its safety and efficacy in children. It is approved to treat children in Europe but not yet in the United States. The dosage is 30 mg subcutaneously in 1 injection in the abdomen and is not weight adjusted.

### Section 3. Prophylactic Treatment

In addition to treatment for attacks of angioedema, patients with HAE may need short-term prophylactic treatment to reduce the likelihood of swelling in the setting of a stressor or procedure that may precipitate an attack, or they may need long-term prophylaxis to decrease the number and severity of attacks. Because there are significant differences in the route of administration and side effect profiles between the prophylactic drugs, patient and family preferences must be considered in the selection of the most appropriate therapy (Table 1).

#### 3.0. Short-Term Prophylaxis

Trauma and stress sometimes induce angioedema attacks. Dental surgery, in particular, is associated with swelling of the oral cavity that can progress and cause airway obstruction.<sup>1,38,42</sup> Depending on the extent of the local trauma, short-term prophylaxis may be indicated before medical, surgical, or dental procedures. Fresh frozen plasma given empirically at 2 U per patient immediately before surgery has been

reported to provide effective short-term therapy in adults and poses little risk.<sup>43</sup> Although it has not been studied in children, one would expect that it will also be effective for them. Purified pC1 INH at 20 U/kg has little risk of containing an infectious agent, is FDA approved in children, and is preferable when available.<sup>35,38,44</sup> It is critically important that effective on-demand treatment be available, whether the patient is given short-term prophylaxis or not.

#### 3.1. Long-Term Prophylaxis

The decision to use long-term prophylactic treatment should take into account attack frequency, attack severity, comorbid conditions, access to emergent treatment, and family experience and preference. Because disease severity may change over time,<sup>8</sup> the need to start or continue long-term prophylaxis should be periodically reviewed.

#### 3.2. Dosing

Neither the optimal dosage nor clinical response to long-term prophylactic treatment is predicted by the complement protein 4 or C1 INH levels but must be determined clinically.<sup>1</sup> Prophylactic medications should be titrated to the lowest effective dosage that controls disease activity and maintains normal quality of life. The half-life of C1 INH is on the order of 30 to 40 hours in adults, and therefore dosing for routine prophylaxis must be fairly frequent.<sup>15</sup> The only C1 INH preparation FDA approved for prophylaxis is Cinryze, administered at 1000 U twice a week in adults of all sizes because there have been no dose response studies.<sup>2,45</sup> The 2 pC1 INH preparations (Berinert and Cinryze) are quite similar. In uncontrolled studies both Cinryze and Berinert have been effective in children, and in emergencies probably either can be used.<sup>5,26,32,38,46,47</sup> It may be appropriate to treat using approved Berinert dosing of 20 U/kg to avoid larger dosages than needed in young

children. Because of the possibility of thrombosis, intravenous ports should be avoided. Patients on a prophylactic treatment regimen must also have access to on-demand treatment of acute breakthrough attacks.

### 3.4. Use of Antifibrinolytics in Children

$\epsilon$ -Aminocaproic acid (EACA), a fibrinolysis inhibitor, was shown to be effective in HAE prophylaxis decades ago,<sup>48</sup> and a cyclic derivative, tranexamic acid (TXA), has been used for adult treatment in Europe for years.<sup>49,50</sup> The precise mechanism of action of antifibrinolytic agents in treating HAE is unclear, but it is assumed that the drug downregulates the action of factor XII in promoting bradykinin generation. Among the antifibrinolytics, TXA has been preferred over EACA for prophylaxis, but there are no head-to-head drug comparisons. In an early double-blinded crossover trial, treatment with EACA resulted in a reduction, but not complete resolution, of attacks in a small number of children.<sup>51</sup> At higher dosages (>12 g/day in adolescents) nausea, dizziness, and myalgias were noted. These are well-known side effects of EACA.<sup>31,52</sup> Long-term use of EACA in childhood is associated with severe fatigue and poor school performance.<sup>31</sup> Both EACA and TXA are ineffective in some children.<sup>31</sup> Although these drugs have been recommended for short-term or perioperative prophylaxis in children, we believe that pC1 INH therapy or androgens are better choices.

### 3.5. Use of Androgens and Estrogens in Children

Anabolic androgens (17- $\alpha$ -alkylated androgens) have been successfully used for prophylaxis in adults for many years.<sup>25,53-56</sup> Although these agents are less costly than the newer agents, over time they cause dose-related side effects that may be significant. Their toxicity in children is

of particular concern, given potential adverse effects on bone maturation, sexual development, and growth, to name a few. It has therefore been a policy in the United States to not recommend their use in children, and the HAEA MAB endorses this policy. Because many FDA-approved agents or agents currently under study for approval are safer, we believe that the danger of potential side effects outweighs the benefit of androgens in the treatment of children with HAE.

Unlike androgens, which clearly reduce the incidence of HAE attacks, estrogens markedly increase the incidence of attacks.<sup>57,58</sup> Estrogens are present in many birth control preparations and should be used only when the benefit far outweighs the risk. In general, progestones decrease the severity of HAE attacks and can be substituted for estrogen-containing preparations if birth control medications are needed.<sup>57</sup>

## Section 4. Patient Monitoring

### 4.1. Monitor Attack Frequency and Severity

HAE disease severity is highly variable, both between patients and also over time in an individual patient.<sup>8</sup> Patients may be symptom free for years and then begin to have attacks.<sup>8</sup>

Therefore, physician knowledge of the patient's attack frequency, severity, and factors that precipitate attacks are critical to successful HAE management. We recommend that patients or families keep a record of all attacks, regardless of severity (mild, moderate, or severe). These records should specifically identify the following 3 domains: description of attack including location and severity, treatment of attack, and response to treatment. Specific issues that relate to a child should be recorded, including time of day, child's activity, and mood at the time of an attack. In adults local trauma

and even psychological factors may trigger attacks, but less is known about factors that trigger attacks in children. In our experience the usual childhood recreational activities, even those with extensive trauma such as football, rarely trigger attacks. We do not limit play unless experience with the individual patient indicates that it triggers attacks. Physician knowledge of the patient's HAE attack frequency, severity, and precipitating factors is therefore critical to determine the ongoing management of HAE.

## CONCLUSIONS

HAE is an autosomal dominant disease that in childhood typically causes localized swelling of an extremity or colicky abdominal pain. Attacks do not respond to epinephrine, antihistamines, or glucocorticoids. When attacks involve the airway they can be life threatening. With a recent understanding of pathophysiology, new and highly effective drugs have been developed. The treating pediatrician with detailed knowledge of the patient and family, attack frequency, precipitating factors, current drugs available, and response to therapy can achieve effective disease control in most children, allowing them to achieve a normal life.

## ABBREVIATIONS

C1 INH: C1 inhibitor  
EACA:  $\epsilon$ -aminocaproic acid  
FDA: US Federal Food and Drug Administration  
HAE: hereditary angioedema  
HAEA: Hereditary Angioedema Association  
MAB: Medical Advisory Board, pC1 INH, C1 inhibitor purified from plasma  
TXA: tranexamic acid

author on the double-blind *New England Journal of Medicine* article that introduced ecallantide. Dr Craig was the first author on the double-blind study published in the *Journal of Allergy and Clinical Immunology* that introduced C1 inhibitor for acute attacks that became Berinert. Dr Bernstein was the senior author on that study. Drs Banerji, Riedl, Lumry, and Bernstein were all authors on the double-blind study reported in the *New England Journal of Medicine* that introduced icatibant.

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