

# Management and Prevention of Hereditary Angioedema Attacks

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**H**ereditary angioedema (HAE) is a rare autosomal dominant genetic disorder caused by a deficiency of C1 inhibitor that results in recurrent episodes of non-pruritic subcutaneous and mucosal swellings usually localized to the extremities, face, bowels, genitalia, or upper respiratory tract.<sup>1,2</sup> Attacks follow a fairly predictable clinical course—symptoms gradually worsen over the first 24 hours, then subside—but may vary considerably in frequency and severity.<sup>1,2</sup> Abdominal attacks may be accompanied by severe pain, nausea, and vomiting.<sup>1,2</sup> Laryngeal edema, though relatively rare compared with abdominal and skin swellings, is the most clinically significant manifestation of HAE; death may result from airway obstruction and asphyxiation.<sup>3,4</sup>

The rarity of HAE—an estimated 1 in 50,000 individuals are affected (range: 1 in 10,000–1 in 150,000)<sup>5</sup>—and the fact that symptoms can mimic a variety of other conditions means that diagnosis often lags behind the first appearance of symptoms by a few years to a decade or more.<sup>6,7</sup> The differential diagnosis of HAE is particularly challenging for physicians in the primary care setting who may have limited awareness of the disease and minimal exposure to patients with HAE. Further, the pattern of HAE management in the United States differs from that in several European countries and Canada, where patients are generally referred to specialized treatment centers; in the United States, by contrast, people with HAE receive treatment in more diverse settings, including group and solo physician practices.<sup>8</sup>

Once an HAE diagnosis is confirmed, the patient should be referred to a specialist experienced in the management of the disorder, and a treatment plan should be created and individualized for the patient's medical situation and preferences.<sup>4</sup> The goal of effective HAE management is to restore a normal quality of life for the patient.<sup>4</sup> While this would have been largely unthinkable (and unattainable) just a decade ago, there has been tremendous progress in the treatment and prevention of HAE attacks in recent years, with several effective HAE therapies now available.<sup>9</sup> The following sections review the current treatment options for HAE, side effects of therapy, and issues related to the treatment of special patient populations.

## Treatment of HAE

Contemporary medical management of HAE is divided between treatment of swelling attacks, short-term prophylaxis to avoid

### Abstract

Hereditary angioedema (HAE) is a rare genetic syndrome caused by a deficiency in functional C1 inhibitor that results in recurrent episodes of nonpruritic swelling of the hands, feet, arms, legs, trunk, face, genitalia, bowels, and larynx beginning in childhood or adolescence and continuing throughout the patient's lifetime. Treatment for acute HAE attacks in the United States has been transformed by new therapies that inhibit the underlying mechanisms of angioedema— notably ecallantide, a potent and specific inhibitor of plasma kallikrein, and icatibant, a selective bradykinin receptor antagonist. These treatments, combined with safer formulations of plasma-derived C1 esterase inhibitor concentrate for HAE prophylaxis and acute treatment, have greatly improved the quality of life for people with HAE, many of whom can now lead fairly normal lives. This article reviews the current therapeutic landscape for HAE, including treatment for acute angioedema attacks, short- and long-term HAE prophylaxis, and home-based therapy.

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For author information and disclosures, see end of text.

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attacks during times of increased risk (eg, after medical or dental procedures), and long-term prophylaxis to reduce both the frequency and severity of attacks.<sup>17</sup>

### **Management of Acute Attacks.**

**Purified C1 Esterase Inhibitor.** Purified, plasma-derived C1 inhibitor (C1INH) has been the standard of care for management of acute HAE attacks in Europe for several decades.<sup>2,10</sup> In the United States, concerns about the potential for virus transmission and a lack of prospective, randomized clinical studies meant that C1INH replacement therapy was unavailable until quite recently.<sup>2,9</sup> In October 2009, the US Food and Drug Administration (FDA) approved a purified, pasteurized esterase C1INH concentrate (Berinert) for the treatment of adults and adolescents experiencing acute episodes of abdominal, facial, or laryngeal edema associated with HAE.<sup>10,11</sup> The efficacy of Berinert was established in the randomized, double-blind, placebo-controlled clinical study, IMPACT (International Multicenter Prospective Angioedema C1-INH Trial) 1, conducted in 125 patients with type I or II HAE.<sup>12</sup> Study participants were randomly assigned to receive Berinert (10 or 20 U/kg) or placebo for single attacks of acute abdominal or facial edema.<sup>12</sup> Patients who received Berinert at the 20-U/kg dose had a significantly shorter time to onset of symptom relief compared with placebo (0.5 vs 1.5 hours;  $P = .0025$ ); those who received the 10 U/kg dose had only slight improvement that did not reach statistical significance.<sup>12</sup> The FDA-approved dose of Berinert is therefore 20 U/kg of body weight.<sup>11</sup>

Subsequently, a prospective, nonrandomized, open-label extension study (IMPACT-2) evaluated Berinert for treating HAE attacks affecting any body site.<sup>13</sup> During a median follow-up of 24 months, 57 patients experiencing a total of 1085 attacks were treated with single infusions of Berinert 20 U/kg.<sup>13</sup> The median time to onset of symptom relief was 0.46 hours, while the median time to complete resolution of HAE symptoms was 15.5 hours.<sup>13</sup> Sixteen patients (28.1%) experienced 48 episodes of laryngeal edema, with a median time to onset of symptom relief of 0.25 hours (0.10-1.25 hours).<sup>13</sup> No patients treated with Berinert for laryngeal attacks required intubation, emergency procedures, or additional medication. Adverse events, reported in 25 patients (43.9%), were generally mild or moderate; 1 patient dropped out of the study due to an infusion-related reaction.<sup>13</sup> In January 2012, the FDA granted a label expansion for Berinert to include treatment of laryngeal attacks and intravenous self-administration by properly trained patients.<sup>14</sup>

Cinryze, a pasteurized, nanofiltered C1INH formulation, has been approved for HAE prophylaxis since 2008.<sup>15</sup> A ran-

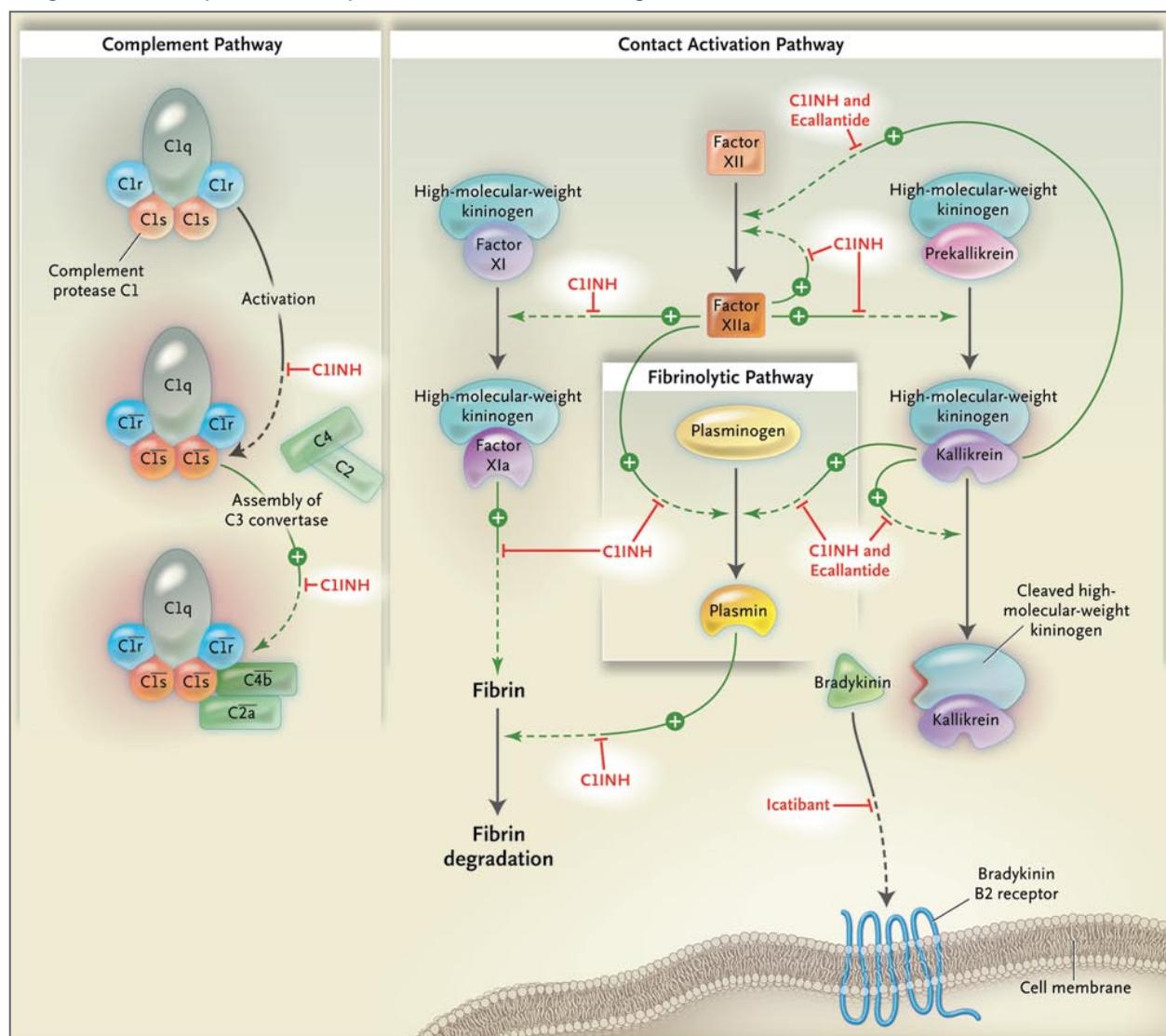
domized, double-blind, placebo-controlled trial demonstrated efficacy of this agent for treatment of attacks, although it is approved for this indication only in Europe.<sup>16</sup> A total of 68 patients (35 in the C1INH group and 33 in the placebo group) were given 1 or 2 intravenous injections (1000 units each) of Cinryze or placebo within 4 hours of onset of an attack (laryngeal attacks were excluded).<sup>16</sup> The median time to onset of unequivocal symptom relief, the study's primary end point, was more than halved in the Cinryze arm compared with placebo (2 hours vs more than 4 hours;  $P = .02$ ).<sup>16</sup> In an open-label extension part of the trial, the median time to response was 30 minutes among 82 patients who experienced 447 separate attacks.<sup>16</sup>

**Ecallantide (Kalbitor).** Ecallantide is a potent and specific inhibitor of plasma kallikrein, a contact system protease that cleaves kininogen, a high-molecular-weight protein, to release bradykinin (see [Figure 1](#)).<sup>1</sup> Bradykinin is the primary mediator of angioedema in HAE through its binding to the bradykinin B2 receptor on the surface of vascular endothelial cells.<sup>17,18</sup> In December 2009, the FDA approved ecallantide for the treatment of HAE attacks in patients 16 years or older based on results from 2 randomized, double-blind, placebo-controlled phase 3 trials (EDEMA3 and EDEMA4) conducted in 168 patients with HAE.<sup>19,20</sup>

In EDEMA3, 72 individuals with HAE who presented with an acute swelling attack were randomized to receive ecallantide 30 mg administered subcutaneously or placebo.<sup>21</sup> Patients in the ecallantide group had significantly greater improvements versus placebo in 2 patient-reported symptom severity and outcome measurements—the treatment outcome score ( $P = .004$ ) and the mean symptom complex severity score ( $P = .01$ )—at 4 hours posttreatment.<sup>21</sup> The estimated time to significant improvement was 165 minutes versus 240 minutes in the ecallantide and placebo groups, respectively ( $P = .14$ ).<sup>21</sup> In EDEMA4, 96 patients with acute HAE attacks were randomized to treatment with ecallantide (30 mg) or placebo.<sup>22</sup> As in EDEMA3, ecallantide-treated patients in EDEMA4 had significant improvement in both treatment outcome ( $P = .003$ ) and symptom severity scores ( $P = .01$ ) versus placebo at 4 hours after dosing.<sup>22</sup>

The most common adverse events associated with ecallantide therapy were headache, nausea, diarrhea, pyrexia, injection-site reactions, and nasopharyngitis.<sup>19,23</sup> In the EDEMA trials, 3 patients in the ecallantide group experienced injection-site reactions versus 1 patient in the placebo group.<sup>23</sup> The rate of seroconversion to both anti-ecallantide antibodies and to neutralizing antibodies was 1.6%; while seroconversion did not appear to affect the efficacy or safety

■ **Figure 1.** Pathways Inhibited by C1 Inhibitor and New Drugs<sup>1</sup>



In the classic complement pathway, the complement protease C1 is activated and then assembles the C3 convertase. (Activation is indicated by horizontal bars over the complement names.) In the contact activation pathway, trace amounts of factor XIIa activate additional factor XII, as well as prekallikrein. Activated factor XIIa activates factor XI to factor XIa, leading to enhanced fibrin formation. Activated factor XIIa and kallikrein activate each other, and then plasma kallikrein cleaves high-molecular-weight kininogen to release bradykinin. In the fibrinolytic pathway, plasminogen is activated to plasmin, which cleaves fibrin. Proteolytic activities are indicated with green arrows and point toward the steps they catalyze. Steps inhibited by C1 inhibitor (C1INH), through conventional or new types of therapy, or by 2 other new drugs being investigated for the treatment of hereditary angioedema are shown with red T bars. Reprinted with permission from Zuraw BL. *N Engl J Med.* 2008;359:1027-1036.

of ecallantide, the sample size was too small to be conclusive.<sup>23</sup> Additionally, the ecallantide package insert contains a boxed warning for the potential for anaphylaxis. Among 255 patients treated in the ecallantide clinical studies, 10 (3.9%) experienced anaphylaxis; for the 187-patient subgroup that received subcutaneous ecallantide, anaphylaxis was reported in 5 patients (2.7%).<sup>19</sup> For this reason, ecallantide should be administered by a healthcare professional trained in recognition and treatment of hypersensitivity reactions, and is not recommended for self-administration.

*Icatibant (Firazyr)*. Icatibant, a selective bradykinin B2 receptor antagonist, is indicated for the treatment of HAE attacks in patients at least 18 years of age.<sup>24</sup> Three randomized, controlled clinical trials (For Angioedema Subcutaneous Treatment [FAST]-1-3) involving a total of 223 patients with HAE evaluated icatibant (30-mg subcutaneous injection) for the treatment of cutaneous, abdominal, or mild-to-moderate laryngeal attacks (patients with severe laryngeal attacks received open-label icatibant).<sup>24,25</sup> Icatibant was compared with placebo in FAST-1 and FAST-

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3, and with tranexamic acid, an oral antifibrinolytic agent, in FAST-2.<sup>25,26</sup>

In FAST-3, icatibant-treated patients ( $n = 43$ ) had significant improvement in 3 main outcome measures compared with placebo ( $n = 45$ ): time to at least a 50% reduction in symptom severity (2.0 vs 19.8 hours;  $P < .001$ , primary end point); onset of symptom relief (1.5 versus 18.5 hours;  $P < .001$ ); and time to almost complete symptom relief (8.0 versus 36 hours;  $P = .012$ ).<sup>26</sup> Median time to onset of symptom relief was 2.5 hours for icatibant versus 4.6 hours for placebo ( $P = .14$ ) in FAST-1, and 2 hours for icatibant versus 12 hours for tranexamic acid ( $P < .001$ ) in FAST-2.<sup>25</sup> The median time to nearly total symptom relief was 8.5 hours for icatibant and 19.4 hours for placebo ( $P = .08$ ), and 10 hours for icatibant versus 51 hours for tranexamic acid ( $P < .001$ ) in FAST-1 and FAST-2, respectively.<sup>25</sup> No icatibant-treated patients in the FAST1-3 trials with nonlaryngeal symptoms required rescue medication.<sup>25,26</sup>

Ten patients in the intent-to-treat population in FAST-3 received icatibant for laryngeal attacks: 5 patients with mild-to-moderate attacks (3 icatibant, 2 placebo) and 5 with severe attacks (open-label icatibant).<sup>26</sup> The median time to onset of symptom relief was 2.5 hours in patients treated with double-blind icatibant, and 2.3 hours for those treated with open-label icatibant.<sup>26</sup> Of the 2 patients in the laryngeal attack group randomized to placebo, 1 received icatibant as rescue medication 3.4 hours after receiving placebo, while the other patient had severe laryngeal symptoms and received open-label icatibant before placebo was administered.<sup>26</sup> In a post hoc analysis of 21 icatibant-treated patients in FAST-3 who experienced laryngeal edema as their first attack, the median time to at least 50% symptom relief was 2 hours.<sup>26</sup>

**Supportive Therapy.** The recent approvals of plasma-derived C1INH concentrate and the newer targeted agents have dramatically altered emergent care for HAE attacks by allowing physicians to administer effective treatment within minutes of a patient's arrival at the hospital. Nonetheless, these swelling attacks can still present significant challenges, particularly in patients not previously diagnosed with HAE—such patients may be misdiagnosed as suffering from an allergic reaction and thus receive ineffective treatments (eg, epinephrine, corticosteroids, antihistamines).<sup>27</sup>

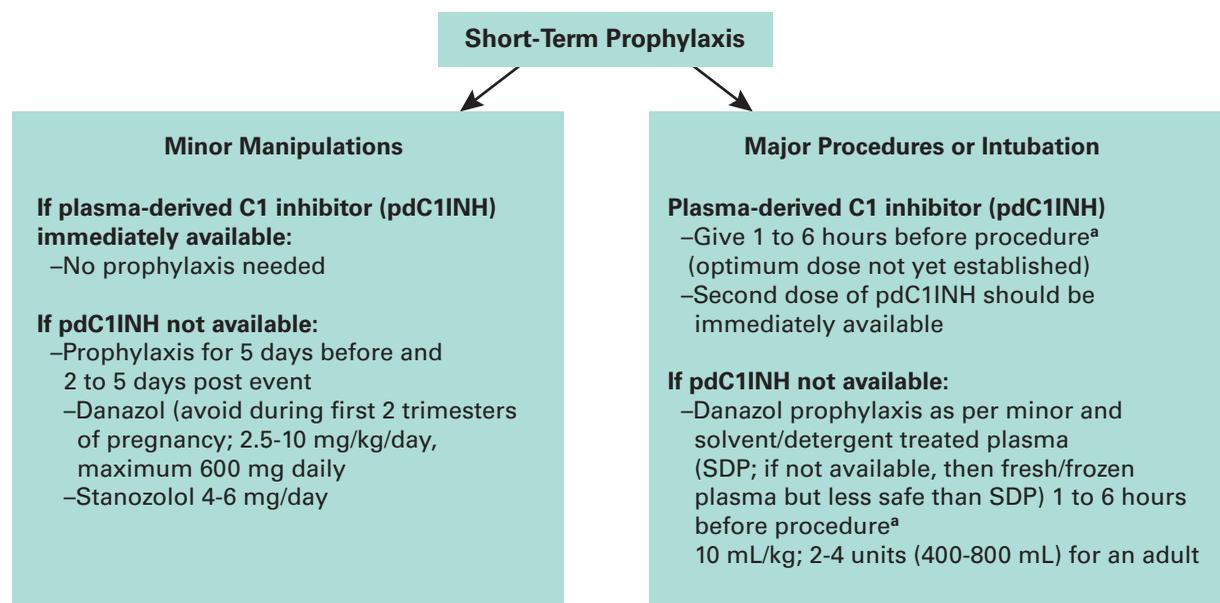
For patients in whom a diagnosis of HAE has been confirmed, supportive therapy may be required for laryngeal or severe abdominal attacks. Maintaining an open upper airway is the primary goal for patients with laryngeal edema.<sup>7</sup> Intubation or, as a last resort, emergent cricothyrotomy, may be necessary in patients with HAE who experience progres-

sively worsening laryngeal swelling. The patient should be transferred to an intensive care unit with personnel experienced in airway management.<sup>27</sup> Patients who self-treat a laryngeal attack should, after treatment, proceed to an emergency medical facility where their airway can be protected if necessary. Severe abdominal attacks may be accompanied by intractable pain, vomiting, and/or diarrhea, which can result in hypovolemic shock due to a combination of fluid loss, extravasation, and vasodilation.<sup>7,28</sup> Intravenous fluid replacement, narcotics, and medications for nausea and cramping can be used in patients with severe abdominal symptoms.

**Short-Term Prophylaxis.** Short-term prophylactic therapy is recommended prior to exposure to a potential trigger for an HAE attack, particularly dental work or invasive medical or surgical procedures.<sup>1</sup> As shown in **Figure 2**, plasma-derived C1INH, if readily available, is the preferred short-term preventive therapy for patients with HAE undergoing minor dental manipulation, but pretreatment may be reserved for those in whom dental procedures have previously precipitated an attack.<sup>29</sup> If C1INH is not available, 17- $\alpha$ -alkylated anabolic androgen (eg, danazol, 200 mg 2-3 times per day) for 5 days before the procedure and 2 to 5 days after is recommended.<sup>1,29</sup> Alternately, antifibrinolytic prophylaxis (eg, tranexamic acid) may be considered; tranexamic 5% mouthwash has been shown to decrease bleeding associated with dental work and suppress bradykinin in the saliva.<sup>29</sup> For patients undergoing major surgery with endotracheal intubation, international consensus guidelines recommend C1INH 10 to 20 U/kg administered as close to surgery as possible (1 to no more than 6 hours preprocedure).<sup>29</sup> Solvent/detergent-treated plasma (considered safer than fresh frozen plasma, but unavailable in the United States) or danazol can be used if C1INH is not available.<sup>29</sup>

**Long-Term Prophylaxis.** Development of agents for the long-term prevention of HAE angioedema attacks has lagged behind that of acute therapy. Presently, only Cinryze and danazol are FDA approved for the routine prophylaxis of HAE.<sup>30,31</sup> The safety and efficacy of Cinryze for routine HAE prophylaxis was demonstrated in a randomized, double-blind, placebo-controlled crossover study in 24 patients with HAE who had a history of at least 2 angioedema attacks per month.<sup>30</sup> Patients were randomized to either Cinryze prophylaxis for 12 weeks (1000 U every 3-4 days) followed by placebo for 12 weeks or the reverse treatment schedule. Both treatment groups were treated with Cinryze for breakthrough HAE attacks.<sup>30</sup> Among the 22 patients who completed the study, those treated with Cinryze had an

■ **Figure 2.** Short-Term Prophylaxis Algorithm for Hereditary Angioedema<sup>29</sup>



<sup>a</sup>As close to procedure as feasible.

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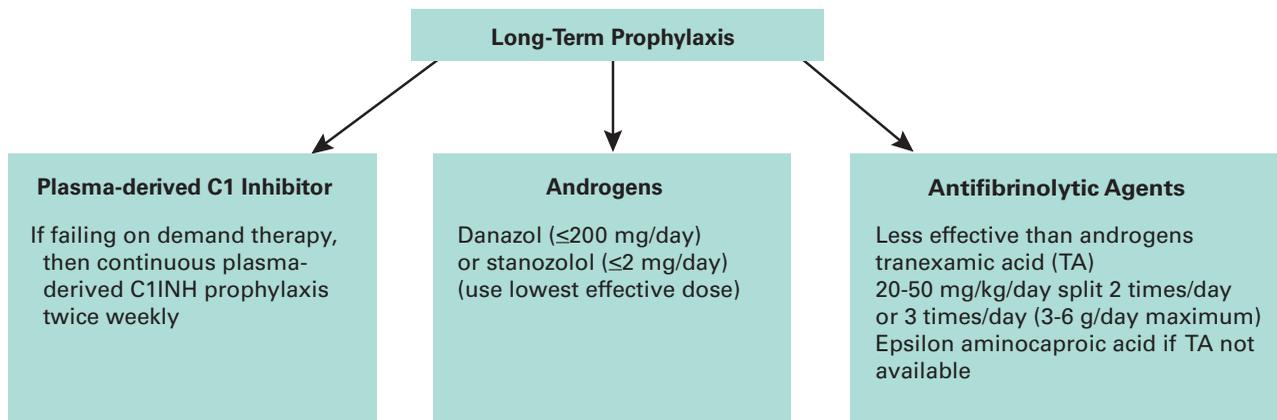
average 66% reduction in the frequency of days with angioedema attacks compared with placebo ( $P < .0001$ ), as well as significant reductions in the average severity ( $P = .0006$ ) and average duration ( $P = .0023$ ) of attacks.<sup>30</sup> The most common adverse reactions were rash, headache, nausea, and vomiting. The approved dose of Cinryze for routine HAE prophylaxis is 1000 U every 3 to 4 days.<sup>30</sup> A recent study by Bernstein et al, presented at the 2012 annual meeting of the American College of Allergy, Asthma & Immunology, demonstrated that select patients may require up to 2500 U of Cinryze every 3 to 4 days to achieve adequate control of their symptoms.<sup>31</sup>

Attenuated androgens such as danazol first demonstrated efficacy for preventing HAE attacks in the 1970s, and have been widely used for that purpose ever since.<sup>7</sup> Danazol therapy is typically initiated at a dose of 200 mg taken orally 2 to 3 times per day; the dose is then gradually decreased by 50% or less every 1 to 3 months or longer if the patient responds favorably.<sup>32</sup> The patient should be monitored closely during dose adjustment, particularly if he or she has a history of laryngeal attacks.<sup>31</sup> A retrospective analysis of 118 patients with HAE receiving danazol for long-term HAE prophylaxis reported an 83.8% reduction in the average number of attacks per year compared with the pretreatment period; 23.7% of patients were symptom free during danazol therapy; 22% had no more than 1 attack per year; and 27.1% had 1 to 5 attacks annually.<sup>33</sup> However, 17 of the 118 patients had

at least 11 attacks per year despite therapy, and 30 patients withdrew from the study before completion due to intolerable side effects.<sup>33</sup> The most common adverse events reported with danazol in the retrospective analysis were weight gain, menstrual irregularities, virilization in women, headache, amenorrhea, myalgia, depression, and acne.<sup>33</sup> Cardiovascular events were reported in 3 different patients—myocardial infarction, stroke, and deep venous thrombosis in the leg. There was also 1 case of acute pancreatitis and 3 cases of liver-cell adenoma.<sup>33</sup> Overall, 78.8% of patients experienced 1 or more adverse event, and 25.4% discontinued danazol therapy—most for clinical reasons, but 5 patients due to laboratory abnormalities (eg, elevated liver enzymes and elevated cholesterol).<sup>33</sup> Patients receiving androgens should be routinely monitored for hepatic abnormalities with liver function tests and abdominal ultrasound every 6 to 12 months.<sup>4,5</sup>

Antifibrinolytic agents, primarily tranexamic acid and aminocaproic acid, though generally considered less effective than androgens, can be used as an alternative for long-term HAE prophylaxis in certain patient groups for whom androgens are contraindicated (eg, pregnant or lactating women, children; see Special Populations below).<sup>1,29</sup> Side effects associated with antifibrinolytics include abdominal discomfort, diarrhea, nausea, headache, myalgia, muscle weakness, hypotension, and fatigue.<sup>7,29</sup> Figure 3 shows the basic treatment algorithm for routine HAE prophylaxis.

■ **Figure 3.** Long-Term Prophylaxis Algorithm for Hereditary Angioedema<sup>29</sup>



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**Special Populations.** Because randomized, controlled clinical trials of HAE therapies have generally not included pregnant or lactating women and children with HAE, these patient populations require special treatment considerations.

**Pregnant or Lactating Women.** As mentioned, the use of attenuated androgens (ie, danazol) for long-term HAE prophylaxis is contraindicated in pregnant or lactating women.<sup>32,34</sup> Plasma-derived C1INH is the treatment of choice for both long-term and short-term HAE prophylaxis and the management of swelling attacks in pregnant and lactating women, although no controlled studies have been conducted in these populations.<sup>34</sup> Antifibrinolytics are indicated only if C1INH is not available.<sup>34</sup> Although most pregnant women with HAE experience uncomplicated deliveries, they may be at increased risk for an acute attack during labor and delivery, and therefore require meticulous monitoring and care by an HAE expert.<sup>34,35</sup> While prophylaxis for uncomplicated, natural deliveries is not recommended, C1INH should be on hand and a physician with experience in the management of HAE available for consultation.<sup>35</sup> Short-term prophylaxis with C1INH is recommended for delivering women with a history of severe HAE attacks or attacks during the third trimester; in cases of mechanical intervention (ie, forceps delivery or vacuum extraction); or prior to cesarean section, as intubation and surgical stress may trigger an attack.<sup>34</sup>

**Pediatric Patients.** The approach to medical management of HAE in children is similar to that of adults with the same condition. Drug prophylaxis is rare in children under the age of 6 years, as HAE symptoms usually don't first appear until later.<sup>36</sup> Consensus statements advocate the use of antifibrino-

lytic agents (eg, tranexamic acid) for long-term prophylaxis in children.<sup>36</sup> Androgens should generally be avoided until children have stopped growing,<sup>29</sup> although danazol has been used safely in pediatric patients for long-term HAE prophylaxis.<sup>36</sup> Danazol should be titrated to the lowest dose possible for achieving symptom control (2.5 mg/kg/day; 50 mg/day initial daily dose).<sup>36</sup>

Presently, clinical data on the use of the newer HAE therapies in pediatric patients are limited. Only 3 patients in the registration trial for Cinryze were under 18 years of age.<sup>30</sup> Icatibant has been evaluated only in patients over the age of 18 years. Results were recently presented from a pooled analysis of 29 pediatric HAE patients (aged 9-17 years) treated with ecallantide (30 mg subcutaneously) for acute angioedema attacks in 4 randomized, controlled trials (EDEMA2, EDEMA3, EDEMA4, and DX-88/19).<sup>37</sup> Twenty-five patients received ecallantide for 62 total HAE attacks, and 10 received placebo for 10 total attacks.<sup>37</sup> Consistent with the findings in adults, pediatric patients treated with ecallantide had greater reductions in symptom severity, greater symptom improvement, and shorter median time to improvement than placebo-treated patients.<sup>36</sup> One serious adverse event—staphylococcal cellulitis—was reported in the ecallantide group, but was not deemed to be associated with the treatment.<sup>37</sup>

**Managing HAE: A Comprehensive Approach.** Effective management of HAE requires a comprehensive approach to care and prevention. All patients with HAE should have an individualized treatment and action plan developed in close collaboration with their physician that address both acute (on demand) treatment needs and long-term prevention.<sup>35</sup> Patients should carry an HAE identification card with clear

■ **Table.** Procedures Recommended During Long-Term Care for Patients With Hereditary Angioedema<sup>35</sup>

Procedures	Timing
Develop action plan	When diagnosed and reviewed annually
Provide with HAE emergency card	When diagnosed and reviewed annually
Provide with 2 doses of on-demand therapy	When diagnosed
Screen family	When diagnosed
Hepatitis C, B and HIV screening	When diagnosed and annually if receiving blood products
Hepatitis A and B vaccine	When diagnosed
Assessment by an HAE specialist	Annually
Influenza vaccine	Annually
If long-term androgens are used	
LFT, CBC, LP, UA	At start and every 6 months
Assess cardiac risk factors	At start and every 6 months
Ultrasound liver	At start and every 12 months

CBC indicates complete blood count; HAE, hereditary angioedema; HIV, human immunodeficiency virus; LFT, liver function test; LP, lipid profile; UA, urine analysis.  
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instructions on how to use on-demand medication in the event of an attack, which treatments to use, and in what circumstances.<sup>35</sup>

Home-based management of HAE prophylaxis and acute attacks (discussed in greater detail in the third article in this supplement) is becoming an increasingly important component of the care of patients with HAE, and is now formally endorsed by international consensus documents.<sup>35,38</sup> Access to self-administered or assisted infusion of C1INH reduces the frequency and severity of attacks, improves quality of life, reduces sick time, is well tolerated, and is popular with patients.<sup>38</sup> All patients diagnosed with type I/II HAE should be considered for at-home self-administration of HAE therapies approved for the treatment of acute angioedema attacks.<sup>35,38</sup> The notable exception to this is ecallantide, which must be administered by a trained health professional because of the risk for anaphylaxis.<sup>19,34</sup>

Good health practices and preventive care should also be incorporated into every HAE management plan (Table). When possible, patients should avoid potential attack triggers, such as emotional stress and certain medications (eg, oral contraceptives, hormone replacement therapy, angiotensin-converting enzyme inhibitors).<sup>5,35</sup> All patients with HAE should have a medical evaluation at least annually, and newly diagnosed patients or those on long-term prophylaxis with attenuated androgens should have a medical evaluation more often.<sup>35</sup> Good dental care and oral hygiene can reduce the need for aggressive dental procedures and prevent acute or chronic intraoral inflammation, which are known triggers

for angioedema attacks.<sup>35</sup> Because patients with HAE may receive human blood products during their care, they should be screened for HIV and hepatitis B and C.<sup>35</sup> Although the risk for viral transmission is quite low, vaccination for hepatitis A and B is suggested.<sup>35</sup> Finally, family members of patients with HAE, including siblings, parents, grandparents, and grandchildren, should be screened for the condition.<sup>35</sup>

## Conclusion

New treatments for HAE are highly effective and should be accessible to all patients diagnosed with the condition. The third article in this supplement reviews the economic burden of HAE, barriers to treatment, and trends in treatment and prevention that may improve economic outcomes in the managed care setting.

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