



## HAE Frequently Asked Questions

### **What is Hereditary Angioedema?**

Hereditary Angioedema (HAE) is a very rare and potentially life threatening genetic condition that occurs in about 1/10,000 to 1/50,000 people. HAE symptoms include episodes of edema (swelling) in various body parts including the hands, feet, face, and airway.



In addition, patients often have bouts of excruciating abdominal pain, nausea, and vomiting that is caused by swelling in the intestinal wall. Airway swelling is particularly dangerous and can lead to death by suffocation.



HAE patients have a defect in the gene that controls a blood protein called C1-inhibitor. The genetic defect results in production of either inadequate or nonfunctioning C1-inhibitor protein. Normal C1-inhibitor helps to regulate the complex biochemical interactions of blood based systems involved in disease fighting, inflammatory response, and coagulation. Because defective C1-inhibitor does not adequately perform its regulatory function, a biochemical imbalance can occur and produce unwanted peptides that induce the capillaries to release fluids into surrounding tissues, thereby causing edema.

HAE is called hereditary because the genetic defect is passed on in families. A child has a 50 percent chance of inheriting this disease if one of his or her parents has it. The absence of family history does not rule out the HAE diagnosis, however. Scientists report that as many as 20 percent of HAE cases result from patients who had a spontaneous mutation of the C1-inhibitor gene at conception. These patients can pass the defective gene to their offspring.

Because the disease is very rare, it is not uncommon for patients to remain undiagnosed for many years. Many patients report that their frequent and severe abdominal pain was inappropriately diagnosed as psychosomatic, resulting in referral for psychiatric evaluation. Unnecessary exploratory surgery has been performed on patients experiencing gastrointestinal edema because abdominal HAE attacks mimic a surgical abdomen. Before therapy became available, the mortality rate from airway obstruction was reportedly as high as 30%.

### **What causes Hereditary Angioedema attacks?**

Most attacks occur spontaneously with no apparent reason, however anxiety, stress, minor trauma, surgery, and illnesses such as colds and flu have been cited as triggers. Trauma to the oral cavity caused by dental procedures make HAE patients particularly vulnerable to airway attacks. Patients have also reported swelling in extremities following typing, prolonged writing, pushing a lawn mower, hammering, shoveling, and other physical activities.

In women, menstruation and pregnancy seem to have a major effect on disease activity. Some women patients report a definite increase in the number of attacks during their menstrual periods. During pregnancy, some patients note an increase in the frequency of attacks, while others have reported a decrease. Use of oral contraceptives and hormone replacement therapy is associated with an increase in the frequency and severity of attacks.



### **How is Hereditary Angioedema diagnosed?**

Most cases of angioedema are not HAE because swelling attacks are typically caused by something other than C1-inhibitor deficiency, usually an allergic reaction. Laboratory analysis of blood samples or genetic testing is required to establish the HAE diagnosis. There are two specific blood tests that confirm HAE:

1. C1-inhibitor quantitative (antigenic)
2. C1-inhibitor functional

The most common form of the disease--Type I--is characterized by low quantitative levels of C1-inhibitor and affects about 85% of patients. Type II HAE affects the other 15% of patients who have normal or elevated levels of C1-inhibitor, but the protein does not function properly. Several investigators have noted a familial (and therefore inherited) angioedema in patients with normal levels of C1-inhibitor. Often found under the designation of "HAE Type III", this form of angioedema is yet to be fully understood. In women, swellings have been correlated with pregnancy or the use of oral contraceptives; however, affected male family members have also been identified. Some scientists believe that a mutation in the gene for human coagulation Factor XII may be a potential cause of swelling in these patients.

### **At what age do attacks of Hereditary Angioedema start?**

The age of HAE onset varies considerably, however, in one study, half of the patients reported onset of their symptoms by the age of seven, and over two thirds became symptomatic by the age of thirteen. There also seems to be an increased frequency of attacks during puberty or adolescence.

### **What are the characteristics of an HAE attack?**

Patients often report tingling or tightness at the site where edema then occurs thirty minutes to several hours later. In some cases, this sensation can be present twelve to twenty four hours before the onset of swelling. Approximately one fourth of HAE patients experience a flat, non-itching red blotchy rash both before and during an attack. Swelling of the extremities is uncomfortable and, according to some patients, can be painful and debilitating depending on the location of the edema. Untreated, an average attack lasts for twenty-four to seventy-two hours, but some residual swelling may persist for up to four or more days.



Attacks that involve the face or throat should be considered a medical emergency. They must be taken seriously and medical treatment should be sought without delay. Swelling of the throat can close the air passage and cause death by suffocation. The symptoms of an impending airway obstruction include difficulty swallowing and a change in voice pitch. As noted above, abdominal attacks can mimic a surgical abdomen and many patients have been subjected to unnecessary exploratory surgery.



### **Do newly-approved therapies offer additional treatment options?**

New FDA-approved HAE treatments provide patients and their physicians with choices and an opportunity to develop an HAE treatment plan tailored to meet each patient's unique needs.

- **Cinryze™ brand of C1-inhibitor (approved by the FDA on October 9, 2008)**  
Cinryze™ brand of C1-inhibitor concentrate has been FDA-approved for preventing HAE attacks. The product is delivered intravenously and is approved for home infusion. Contact your HAEA regional Patient Services Representative (see list below) for more information.
- **Berinert® brand of C1-inhibitor has been FDA-approved** for treating acute laryngeal and abdominal HAE attacks. The product is delivered intravenously. Contact your HAEA regional Patient Services Representative (see list below) for more information.
- **Kalbitor®, from Dyax Corp., was approved in December 2009** to treat acute HAE attacks in patients 16 years of age and older. The product is delivered through subcutaneous injections and is estimated to be available in the US in early 2010.

**HAEA Patient Services Representative  
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**For Clinical Trial Referrals, Contact Patient Services/Clinical Programs**

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**Traditional HAE Therapies Including Preventive Care for Dental/Surgical Procedures**

The medical literature and practitioner experience confirms that corticosteroids (prednisone), antihistamines and epinephrine are not effective in treating angioedema caused by C1-inhibitor deficiency.

Prior to the FDA's approval of C1-inhibitor concentrate, anabolic steroids (also known as androgens) such as danazol, oxandrolone and stanozolol were commonly prescribed for treating HAE patients. While anabolic steroids have been shown to be useful, they are not well-tolerated by many women, directly linked to liver toxicity and cause an increase in cholesterol levels. In addition, these drugs should not be used to treat children, some of whom, tragically, are severely affected and suffer frequent attacks.

Research indicates that patients treated with anabolic steroids can experience breakthrough laryngeal or abdominal attacks that require hospitalization. If C1-inhibitor is not immediately available, the physician treating laryngeal edema should focus on maintaining an open airway and providing supportive care. Because abdominal swelling usually involves excruciating pain and frequent vomiting, the treating physician should provide fluid replacement and manage pain aggressively.

Even patients who do not require on-going HAE preventive therapy find it necessary to receive treatment prior to undergoing dental and surgical procedures. C1-inhibitor is the treatment of choice for preventing these trauma-related attacks. Patients should discuss this treatment option with their doctor.

When C1-inhibitor is not available, some physicians may infuse fresh frozen plasma (FFP) or prescribe high-dose androgen therapy for at least five days prior to surgery and four days afterward.



## **Are there any new treatments on the horizon?**

Shire is recruiting HAE patients for an on-going trial testing the safety and effectiveness of its bradykinin receptor antagonist called Firazyr. The product is being investigated for treating acute attacks and is administered through one subcutaneous injection.

Pharming is recruiting HAE patients for an on-going trial testing Rhucin, a recombinant C1-inhibitor derived from the milk of genetically-altered rabbits. The product is being investigated for treating acute attacks and is administered intravenously.

## **What treatments are available for children who have Hereditary Angioedema?**

C1 inhibitor concentrate is the treatment of choice for children with HAE. Parents should discuss getting access to the medicine with their child's pediatrician.

## **What medicine should HAE patients avoid?**

ACE Inhibitors and estrogen-derived medications (birth control pills and hormone replacement drugs) have been known to increase the frequency and intensity of HAE attacks. ACE Inhibitors are often prescribed to treat high blood pressure. Below is a list of some of the ACE Inhibitors licensed in the US:

- captopril (Capoten)
- benazepril (Lotensin)
- enalapril (Vasotec)
- lisinopril (Prinivil, Zestril)
- fosinopril (Monopril)
- ramipril (Altace)
- perindopril (Aceon)
- quinapril (Accupril)
- moexipril (Univasc)
- andtrandolapril (Mavik)

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