**Hereditary Angioedema Type I (HAE-I)**

- **Type**: Represents approximately 80 to 90% of HAE cases. C1 inhibitor is considerably below normal due to a defective gene on chromosome 11. There is usually a family history of angioedema, but a number of cases are due to spontaneous mutation or recombination. Does not respond to antihistamines and corticosteroids.

- **Common Symptoms (1)**: Swelling can occur in the extremities, abdomen, throat, and other organs. Swelling of the airway can be fatal. Abdominal swelling usually involves pain, vomiting and diarrhea. Symptoms may be spontaneous or triggered by physical trauma or emotional stress.

- **Compartment System**: Low levels of C1 inhibitor. C4 is almost always low, C1, C3 and C1q are normal. Abnormal complement component (above) is the same as the condition is hereditary or spontaneous.

- **Possible Treatment**: None. Swelling and/or hives persist beyond 6 weeks. Primarily antihistamines. DH EA. 1-thyroxine for thyroid dysfunction.

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**Hereditary Angioedema with Normal C1-Inhibitor**

- **Type**: Represents approximately 15 to 20% of HAE cases. Similar to Type I, but C1 inhibitor does not function properly. Does not respond to antihistamines and corticosteroids.

- **Common Symptoms (1)**: Swelling may occur just about anywhere and may increase in severity after puberty. Episodes may be spontaneous or triggered by physical trauma or emotional stress.

- **Compartment System**: Number of years ago. Familial history may be present. C1 inhibitor levels and function are normal. A minority of cases associated with mutations in the C1 inhibitor gene. This mutation has not been shown to be the cause of the condition. Predominantly reported in women, but affected male family members have also been identified. Swelling is usually associated with pregnancy and the use of estrogen containing oral contraceptives. Does not respond to antihistamines and corticosteroids.

- **Possible Treatment**: Similar to HAE-I and HAE-II. Normal. Research continues. Published cases document response to FDA approved HAE therapies.

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**Acquired Angioedema Type I (HAE-I)**

- **Type**: Involves complement that is usually looked at under a microscopic slide. Compromises the C1 inhibitor. Angioedema can be triggered by a number of conditions or a genetic defect. There is an absence of a family history of symptoms.

- **Common Symptoms (1)**: Similar to HAE. The symptoms typically appear in the fourth and fifth decades of life. Because acquired angioedema is not related to a genetic defect, there may be no family history of symptoms. Low levels of C1 inhibitor and C4 are usually low, but C1, C3 and C1q are normal.

- **Compartment System**: Diagnosis and treatment of underlying lymphoproliferative disease often eliminates the cause. Antifibrinolytics such as tranexamic acid and epsilon-amino caproic acid for possible prevention of episodes. Angiotensin therapy may help.

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**Acquired Angioedema Type II (HAE-II)**

- **Type**: Involves complement that is usually looked at under a microscopic slide. Compromises the C1 inhibitor. Angioedema can be triggered by a number of conditions or a genetic defect. There is an absence of a family history of symptoms.

- **Common Symptoms (1)**: Similar to HAE-I and HAE-II. Normal. Research continues. Published cases document response to FDA approved HAE therapies.

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**Nonthrombogenic Inherited (NAT)**

- **Type**: Occurs in about 7 out of 20 cases of angioedema. Angioedema without urticaria (usually not responsive to H1 antihistamines block).

- **Common Symptoms (1)**: Swelling may occur anywhere. Antihistamines may be appropriate. Antifibrinolytics such as tranexamic acid and epsilon-amino caproic acid for possible prevention of episodes. Angiotensin therapy may help.

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**Hereditary Angioedema:**

- **Type**: Hereditary Angioedema (HAE) or HAE, is a rare, potentially disabling and life-threatening genetic disease that involves attacks of swelling (doctors call it angioedema) in various body parts including the hands, feet, genitals, stomach, face and/or throat.

- **Common Symptoms (1)**: Swelling in the hands and feet can be painful and interfere with daily activities. HAE attacks that involve the face or throat are a medical emergency and anyone with swelling in these areas requires immediate medical treatment. Without treatment, throat or tongue swelling can cause death by blocking air from getting to the lungs. The symptoms of throat swelling may include difficulty swallowing and a change in how the voice sounds. Stomach attacks can cause severe pain, throwing up, dehydration and diarrhea. Because the pain of a stomach attack is similar to conditions that require emergency stomach surgery, many HAE patients have been exposed to unnecessary operations.

- **Possible Treatment**: Untreated, an HAE attack often lasts for 3 days, sometimes even longer. Because HAE is so rare, the average patient may not receive an accurate diagnosis for as long as 9 years after first experiencing symptoms.

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**For more information about HAE and the US HAE Association, please email us at info@haea.org or call us toll free at 866-798-5598. Please visit our website at www.haea.org**

The US HAE Angioedema Center at UCSD can be contacted at 858-657-6871 or by email at angioedema@ucsd.edu

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**What is Hereditary Angioedema?**

Hereditary Angioedema, or HAE, is a rare, potentially disabling and life-threatening genetic disease that involves attacks of swelling (doctors call it angioedema) in various body parts including the hands, feet, genitals, stomach, face and/or throat.
What Causes HAE Swelling Attacks? Most people with HAE have a defect in the gene that controls an important blood protein called C1-Inhibitor. Because of this genetic defect, the C1-inhibitor protein in people with HAE does not do its job, which is to control complex biological interactions that occur in blood. Left uncontrolled, these interactions produce a biochemical substance called bradykinin that causes swelling by allowing certain blood-fluids to be released into the body’s soft tissues.

Most HAE attacks happen without any apparent cause. Many patients, however, report that illnesses or colds, stress, anxiety, physical activities, and injuries often trigger HAE swelling. Dental work can cause swelling in the mouth and the throat. Some patients feel a tingling or tightness in the area where swelling will occur. About one fourth of HAE patients get a flat, red blotchy rash that does itch both before and during an HAE attack. Some women experience an increase in the number or severity of their HAE attacks during menstrual periods, when they are pregnant, or while taking oral contraceptives and hormone replacement therapy.

Can My Children Get HAE? HAE is called hereditary because the gene defect can be handed down in families. There is a 50 percent chance that a child of a parent who has HAE will inherit the disease. Scientists have found, however, that about 25 percent of patients have no family history of HAE, which means neither their mother nor father had a genetic defect in their C1 inhibitor genes. Instead, the C1 inhibitor gene in these patients became defective spontaneously when they were conceived. Regardless of how a patient obtains the genetic defect, each of their children has a 50 percent chance of inheriting HAE. HAE does not skip generations. Therefore, if you did not inherit HAE, your children will not have HAE.

How is HAE Diagnosed? Most people with swelling symptoms have an underlying allergy problem and do not have HAE. But the only way to determine if HAE is the cause of swelling is through laboratory testing. There are three specific blood tests that doctors use to diagnose HAE: 1) C4 2) C1-Inhibitor quantitative 3) C1-Inhibitor functional

Most HAE patients simply do not produce enough C1-inhibitor protein. This form of the disease is seen in B5 percent of HAE cases and is called HAE Type I. The remaining 15 percent of HAE cases—which call HAE Type II—consists of patients who produce sufficient or even higher than normal levels of the C1-inhibitor protein. The problem, however, is that the protein is defective and does not perform its intended function.

There is a group of patients who have swelling symptoms similar to HAE, but do not have a genetic defect in the C1-inhibitor gene and therefore have normal C1 inhibitor. This form of angioedema is called HAE with Normal C1 inhibitor and is yet to be fully understood. In women, this type of angioedema has been tied to pregnancy or the use of oral contraceptives; however, male family members may also experience this kind of swelling. The HAEA convened a meeting of specialists who published a medical journal article on this form of HAE: Hereditary angioedema with normal C1 inhibitor function: Consensus of an international expert panel. Research on this form of HAE is on-going to identify the cause and treatments for HAE with Normal C1-inhibitor.

At What Age Do HAE Attacks Start? The age that their patients' first HAE attack varies greatly, but one survey showed that 50 percent of all patients had swelling by the age of seven, and over two thirds had symptoms by age thirteen. There also seems to be an increase in the number of HAE attacks during puberty or obesity.

HAE Patients Now Have A Choice Among A Variety of Treatments Before new treatments were FDA-approved, there were two types of HAE medications available in the United States, and both were prescribed to prevent HAE attacks: (1) anabolic steroids (also known as androgens) such as danazol, stanozolol, and oxandrolone; and (2) antifibrinolytics, such as amicar, which were not as effective as androgens and prescribed less frequently. While antifibrinolytic drugs have been shown to be effective, they are male hormones that can cause unacceptable side effects, problems with the liver, and an increase in cholesterol levels. These drugs are not recommended for treating children or pregnant women. Antifibrinolytics have potential side effects that include low blood pressure, abnormal heartbeat, muscle weakness, and blood clots.

According to HAEA specialists, medicines used to treat swelling due to allergies or inflammation, such as corticosteroids (prednisone), antihistamines, and epinephrine, are not effective for HAE attacks.

Available Treatment Options The US HAEA recommends that patients work with their HAE treating physician to create an individualized treatment plan that provides the best opportunity for leading a normal life. Below is a list of the FDA-approved treatment options:

Cinryze™ brand of C1-inhibitor has been FDA-approved for preventing HAE attacks. Cinryze™ is delivered intravenously and approved for home infusion.

Berinert® brand of C1-inhibitor has been FDA-approved for treating acute abdominal, facial or laryngeal HAE attacks. Berinert® is delivered intravenously and is approved for on-demand treatment through self-administration.

Kalbitor® brand of plasma kallikrein inhibitor has been FDA-approved to treat acute HAE attacks in patients 12 years of age and older. Kalbitor® is delivered through subcutaneous injections.

 Firazyr® brand of bradykinin receptor antagonist has been FDA-approved for treating acute HAE attacks in patients 18 years and older. Firazyr® is delivered by subcutaneous injection and is approved for self-administration.

Rucinostat® brand of C1-inhibitor (recombinant) has been FDA-approved for treating acute HAE attacks in adults and adolescents. Rucinostat® is delivered intravenously and is approved for self-administration.

Patients should discus HAE treatment options with their doctor before surgery or dental procedures. HAEA specialists recommend that patients facing surgery receive an FDA medicine approved for attack prevention. We encourage you to contact our regional HAEA Patient Services Team Member (see list to the right) with any question or concern that relates to HAE. These dedicated and experienced staff members are either HAE patients or care givers who have real world insight into understanding and helping to solve an HAE-related challenges.

Treatments on The Horizon Many new treatments are under development. Please contact your Patient Services Team Member for more information and for the most recent information on clinical trials for new HAE therapies, please contact John Williamson.

What Treatments Can Be Given To Children Who Have HAE? The HAEA recommends that parents work with their child's HAE specialist to prepare an individualized HAE treatment plan. Are There Any Medicines That HAE Patients Should Avoid? Estrogen-derived medications [birth control pills and hormone replacement therapies (HRT)] and blood pressure medicines, called ACE inhibitors, have been known to increase the frequency and/or severity of HAE attacks and should be avoided. Below is a list of some of the ACE inhibitors licensed in the US.

• captopril (Capoten)
• enalapril (Vasotec)
• fosinopril (Monopril)
• perindopril (Aceon)
• moexipril (Univasc)

• benzapril (Lotensin)
• lisinopril (Prinivil, Zestril)
• ramipril (Altace)
• quinapril (Accupril)
• and trandolapril (Mavik)