Type	Description	Common Symptoms (1)	Complement System	Possible Treatment*
Hereditary Angioedema Type I (HAE-I)	Represents approximately 80 to 85% 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 a spontaneous mutation of the gene. Does not respond to antihistamines and corticosteroids.	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 usually appear early in life, most often by age 13 and may increase in severity after puberty. Episodes may be spontaneous or triggered by physical trauma or emotional stress.	Low levels of C1-inhibitor. C4 is almost always low. C1, C3 and C1q are normal. Abnormal complement (above) is the same whether the condition is hereditary or spontaneous.	Anabolic steroids (also known as androgens) such as danazol, oxandrolone and stanozolol have, historically, been the most commonly prescribed preventive HAE therapies. While anabolic steroids have been shown to be useful, they are not well-tolerated by many women, directly linked to liver toxicity and can 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. Four new treatments are now FDA-approved for treating HAE, including two C1-inhibitor products, a kallikrein inhibitor, and a bradykinin receptor antagonist. Patients and their physicians now have options for developing a non-steroidal HAE treatment plan tailored to meet each patient's unique needs. **Cinryze™ brand of C1-inhibitor** The Cinryze™ brand of C1-inhibitor concentrate has been FDA-approved for preventing HAE attacks. Cinryze™ is delivered intravenously and is approved for home infusion. **Berinert® brand of C1-inhibitor** The Berinert® brand of C1-inhibitor concentrate has been FDA-approved for treating acute abdominal, facial and laryngeal HAE attacks. Berinert® is delivered intravenously and is approved for on-demand treatment through self-administration. **Kalbitor® brand of plasma kallikrein inhibitor** 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** Firazyr® brand of bradykinin receptor antagonist has been FDA-approved for treating acute HAE attacks in patients 18 years of age and older. Firazyr® is delivered by subcutaneous injection and is approved for self-administration. **Ruconest® brand of C1-inhibitor concentrate** Ruconest® brand of C1-inhibitor [recombinant] has been FDA-approved for treating acute HAE attacks in adults and adolescents. Ruconest® is delivered intravenously and is approved for self-administration.
Hereditary Angioedema Type II (HAE-II)	Represents approximately 15 to 20% of HAE cases. Similar description to Type I, but C1-inhibitor does not function properly. Does not respond to antihistamines and corticosteroids.	Same as HAE-I.	C1-inhibitor level may be normal or elevated, but it is dysfunctional. C1, C3 and C1q are normal, but C4 is almost always low.	Same as HAE-1
Hereditary Angioedema with Normal C1-Inhibitor	Number of cases unknown. Family history must be present. C1-inhibitor levels and function are normal. A minority of cases associated with mutations in the coagulation factor XII gene, however, 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 sometimes associated with pregnancy and the use of estrogen-containing oral contraceptives. Does not respond to antihistamines and corticosteroids.	Similar to HAE-I and HAE-II.	Normal.	Research continues. Published cases document response to FDA-approved HAE therapies.
Acquired Angioedema Type I (AAE-I) AAE-I & II are considered very rare; there are few reported cases.	Immune complexes that are usually linked to an underlying lymphoproliferative disorder destroy the function of C1-inhibitor. Angioedema can be an indicator that a lymphoproliferative disease is developing, so early detection needs to be emphasized.	Similar to HAE. The symptoms typically appear in the fourth decade of life or later. Because acquired angioedema is not related to a genetic defect there is an absence of a family history of symptoms.	Low level of C1-inhibitor and C4. C1q is usually reduced, but not always.	Diagnosis and treatment of underlying lymphoproliferative disease often eliminates the root cause. Antifibrinolytics such as tranexamic acid and epsilon-aminocaproic acid for possible prevention of episodes. Androgen therapy may help.
Acquired Angioedema Type II (AAE-II) AAE-I & II are considered very rare; there are few reported cases.	Autoantibodies are present and destroy C1-inhibitor function. There is no apparent underlying disorder.	Same as AAE-I.	Same as AAE-I. A lab test for autoantibodies may be appropriate.	Antifibrinolytics such as tranexamic acid and epsilon-aminocaproic acid for possible prevention. It is possible that immunosuppressive therapy might be successful.
Idiopathic	Swelling and/or hives persist beyond 6 weeks. Thyroid dysfunction should be considered.	Swelling may occur just about anywhere and may be accompanied by urticaria (hives).	Normal.	Primarily antihistamines. DHEA. 1-thyroxine for thyroid dysfunction. Prednisone therapy.
Nonhistaminergic (INAE) May occur in about 1 out of 20 cases of angioedema	Angioedema without urticaria (usually not responsive to H1 antihistamine blockers). Parasites, infections and autoimmune diseases are not present.	Swelling may occur anywhere: face, arms, legs, genitalia, throat, abdomen (but abdomen is less frequent than those with HAE). Symptoms do not change due to menstrual period or pregnancy.	Normal.	Antifibrinolytics such as tranexamic acid and epsilon-aminocaproic acid.
Allergic This is the most common form of angioedema.	Swelling and/or hives are a reaction to an outside influence such as food, bee sting, cold, heat, latex or drug. The outside influence provokes a histamine reaction, which leads to swelling and/or the hives.	Swelling occurs most often in the face and throat area. Urticaria (hives) may be present. If condition persists beyond 6 weeks it is considered chronic idiopathic and not an allergic reaction.	Normal.	Avoid the substance or behavior that causes the allergic reaction. Antihistamines. Adrenaline (epinephrine) possibly as autoinjectors (self-injecting pens) containing epinephrine for emergencies.
ACE-Inhibitor (Angiotensin-Converting Enzyme Inhibitor) Possible cause for 4 to 8% of people with angioedema.	Caused by ACE-Inhibitors for high blood pressure (captopril, enalapril, genzapril, quinapril, ramipril). Swelling may commence anywhere from a few hours to years after first starting medication.	Swelling may occur just about anywhere: throat, face, lips, tongue, hands, feet, genitals, intestines. If urticaria is present it reduces the probability of a link to ACE-Inhibitors.	Normal.	Suspension or change of medication

*Patients with the slightest hint of throat swelling should seek immediate treatment to ensure that their airway is not compromised. The medical literature and practitioner experience confirms that corticosteriods (Prednisone), antihistamines, and epinephrine are not effective in treating angioedema created by C1-inhibitor deficiency. However, a recent study noted success using inhaled epinephrine to prevent complete airway closure. **NOTES:** The presence of urticaria associated with angioedema usually suggests a diagnosis other than HAE or AAE.

haea
US Hereditary Angioedema Association

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.

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.

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 HAE symptoms.

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 HAEA Angioedema Center at UCSD can be contacted at **858-657-6871** *or by email at* **angioedema@uscd.edu**

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 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-based fluids to be released into the body's soft tissue.

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 for 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% 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) C-4

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 85 percent of HAE cases and is called HAE Type I. The remaining 15 percent of HAE cases—called 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-Inihibtor 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*[1]. Research on this form of HAE is on-going to identify the cause and the treatments for HAE with Normal C1-Inhibitor.

At What Age Do HAE Attacks Start?

The age that patients have their first HAE attack varies greatly, but one survey showed that half 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 adolescence.

HAE Patients Now Have A Choice Among A Variety of Treatments

Before new treatments were FDA-approved, there were two types of HAE medicines 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 anabolic steroids 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 HAE 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 available FDA-approved treatment options.

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

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

Patients should discuss HAE treatment options with their doctor before surgery or dental procedures. HAE specialists recommend that patients facing surgery receive an FDA medicine approved for attack prevention.

We encourage you to contact your 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 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.

1. *Zuraw BL, Bork K, Binkley K, Banerji A,Christiansen SC, Castaldo A, Kaplan A, Riedl M, Kirkpatrick C, Magerl M, Drouet C, Cacardi M.* Hereditary angioedema with normal C1 inhibitor function: Consensus of an international expert panel. Allergy Asthma Proc. 2012 Dec 13.

Hereditary Angioedema Association Patient Services Team Regional Contact Information

Region - 1 Donna Davis, Assistant Vice President for Patient Services and Clinical Programs (Supervise All Regions)	Urgent Assistance (808) 216-1029 donna-davis@haea.org
(Region 1 includes: Canada, Hawaii, all US Territories (American Samoa, Federated States of Micronesia, Guam, Marshall Islands, Mariana Islands, Midway Islands, Puerto Rico, Palau,Virgin Islands)	
Region - 2 Lois Perry, Director for Patient Services and Clinical Programs	Urgent Assistance (559) 259-0572 loisperry@haea.org
(Region 2 includes: Alaska, California, Colorado, Iowa, Maine, Missouri, Mississippi, Montana, Oregon, South Dakota, Utah, Vermont, Virginia, Washington DC, West Virginia)	
Region - 3 John Williamson, Patient Services Team Member	Urgent Assistance (972) 984-0621 john@haea.org
(Region 3 includes: Arizona, Idaho, North Dakota, Nevada, Pennsylvania, Texas, Wyoming)	
Region - 4 Sally Urbaniak, Patient Services Team Member	Urgent Assistance (904) 826-6700 surbaniak@haea.org
(Region 4 includes: Connecticut, Delaware, Florida, Kentucky, Massachusetts, New Hampshire, New York, Rhode Island)	
Region - 5 Jenny Barnes, Patient Services Team Member	Urgent Assistance (252) 585-0763 jennybarnes@haea.org
(Region 5 includes: Alabama, Arkansas, Georgia, Illinois, Louisiana, Michigan, Minnesota, North Carolina, Oklahoma, South Carolina)	
Region - 6 Sherry Porter, Patient Services Team Member	Urgent Assistance (815) 274-4206 sherryporter@haea.org
(Region 6 includes: Indiana, Kansas, Maryland, Nebraska, New Jersey, New Mexico, Ohio, Tennessee, Washington, Wisconsin)	
For Clinical Trial Referrals, contact Patient Services Team Member, John Williamson	(972) 984-0621 john@haea.org
For assistance with reimbursement and access issues, contact Nurse Reimbursement Manager, Nikia Davis	Urgent Assistance (609) 287-9540 nikiadavis@haea.org

What Treatments Can Be Given To Childen 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)
- benazepril (Lotensin)
- lisinopril (Prinivil, Zestril)
- ramipril (Altace)
- quinapril (Accupril)
- and trandolapril (Mavik)