<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Common Symptoms (1)</th>
<th>Complement System</th>
<th>Possible Treatment*</th>
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<tbody>
<tr>
<td>Hereditary Type I (HAE-I)</td>
<td>Represents approximately 80 to 85% of HAE cases. Similar description to Type II. CI-inhibitor does not function properly. Does not respond to antihistamines and corticosteroids.</td>
<td>Swelling can occur in the extremities, abdomen, throat, and other organs. Swelling in the airway is not uncommon. Swelling usually involves pain, vomiting and diarrhea. Symptoms usually appear early in life, most often by age 13 and may increase in severity in later puberty. Episodic swelling is spontaneous or triggered by physical trauma or emotional stress. Low levels of C1-inhibitor C4 is almost always low (C1, C3 and C4 are normal). Abnormal complement (above) is the same whether the condition is hereditary or spontaneous.</td>
<td>Anabolic steroids (also known as androgens) such as danazol, oxandrolone and stanozolol have historically been the most commonly prescribed preventive HAE therapies. While these 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 steroid therapies experience breakthrough lethargy or abnormal 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-interrupted HAE treatment plan tailored to each patient's unique needs.</td>
<td>Cicryza® brand of CI-inhibitor. The Cicryza® brand of CI-inhibitor concentrates has been FDA-approved for preventing HAE attacks. Cicryza® is delivered intravenously and is approved for home infusion. Berinert® brand of CI-inhibitor. The Berinert® brand of CI-inhibitor concentrates has been FDA-approved for treating acute abdominal, facial and laryngeal HAE attacks. Berinert® is delivered intravenously and is approved for on-demand treatments through self-administration. Kallikrein® brand of plasma kallikrein inhibitor. Kallikrein® brand of plasma kallikrein inhibitor has been FDA-approved to treat acute HAE attacks in patients 16 years of age and older. Kallikrein® 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.</td>
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<tr>
<td>Hereditary Type II (HAE-II)</td>
<td>Represents approximately 15 to 25% of HAE cases. Similar description to Type I. CI-inhibitor does not function properly. Does not respond to antihistamines and corticosteroids.</td>
<td>Same as HAE-I. CI-inhibitor level may be normal or elevated, but it is dysfunctional. C1, C3 and C4 are normal, but C4 is almost always low.</td>
<td>Same as HAE-I.</td>
<td>Research continues. Published cases document response to FDA-approved HAE therapies.</td>
</tr>
<tr>
<td>Acquired Type I (AIE-I)</td>
<td>Number of cases unknown. Family history may be present. CI-inhibitor levels and function are normal. A minority of cases associated with mutations in the C1 esterase inhibitor (C1 INH) gene.</td>
<td>Similar to HAE caused by CI-inhibitor deficiency. Normal.</td>
<td>Research continues. Published cases document response to FDA-approved HAE therapies.</td>
<td>Possible Treatment*</td>
</tr>
<tr>
<td>Acquired Type II (AIE-II)</td>
<td>AIE-I &amp; II are considered very rare, there are few reported cases.</td>
<td>Swelling and/or hives persist beyond 6 weeks. Thyroid dysfunction should be considered. Similar to HAE. The symptoms usually 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. C1 is usually reduced, but not always. Diagnosis and treatment of underlying lymphoproliferative disease often eliminates the root cause.</td>
<td>Antifibrinolytics such as tranexamic acid and epsilon-amino-caproic acid for possible prevention of episodes. Angiotensin converting enzyme inhibition (ACE-I) therapy may help.</td>
<td>Protocols for the use of ACE-I in angioedema require close monitoring to ensure that senior is not compromised. The risk of hypertension and proteinuria increases without adequate angiotensin converting enzyme inhibition. ACE-I and angiotensin receptor antagonists (ARBs) are not effective in treating angioedema caused by C1-inhibitor deficiency. However, a recent study found success using an anti-ACE receptor to prevent complete acute attacks.</td>
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<tr>
<td>Idiopathic</td>
<td>Swelling and/or hives persist beyond 6 weeks. Thyroid dysfunction should be considered.</td>
<td>Swelling may occur just about anywhere and may be accompanied by urticaria (hives). Normal.</td>
<td>Swelling may occur anywhere: face, arms, legs, hands, feet, genitals, throat. If urticaria is present it reduces the morbidity of the swelling.</td>
<td>C1-inhibitor helps to regulate the complex biochemical interactions of blood-borne systems involved in normal body function. It controls blood pressure, prevents blood clots and destroys the function of C1-inhibitor. There is no apparent root cause. Antifibrinolytics such as tranexamic acid and epsilon-amino-caproic acid for possible prevention of episodes. Angiotensin converting enzyme inhibition (ACE-I) therapy may help.</td>
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<tr>
<td>Nonbimastocitin (HAE)</td>
<td>May occur in about 1 in 20 of cases of angioedema. Nonbimastocitin (HAE) occurs without urticaria (usualy not responsive to H1 histamine blockers). Parasitic infections and autoimmune diseases are not present.</td>
<td>Swelling may occur anywhere: face, arms, legs, hands, feet, genitals, throat. If urticaria is present it reduces the morbidity of the swelling.</td>
<td>C1-inhibitor is considerably below normal. C1q is usually reduced, but not always.</td>
<td>Antifibrinolytics such as tranexamic acid and epsilon-amino-caproic acid for possible prevention of episodes. Angiotensin converting enzyme inhibition (ACE-I) therapy may help.</td>
</tr>
<tr>
<td>Allergic</td>
<td>Swelling and/or hives persist beyond 6 weeks. Thyroid dysfunction should be considered.</td>
<td>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.</td>
<td>Normal.</td>
<td>Avoid the substance or behavior that causes the allergic reaction.</td>
</tr>
<tr>
<td>ACE-Inhibitor (Angiotensin-Converting Enzyme Inhibitor)</td>
<td>Possible causes for 4 to 8% of people with angioedema.</td>
<td>Swelling may occur anywhere: face, arms, legs, hands, feet, genitals, throat. If urticaria is present it reduces the morbidity of the swelling.</td>
<td>Normal.</td>
<td>Avoid the substance or behavior that causes the allergic reaction.</td>
</tr>
</tbody>
</table>

*Note: patients with the disease have no significant influence on the treatment. Informed consent is necessary to ensure that senior is not complicated. The risk of hypertension and proteinuria increases without adequate angiotensin converting enzyme inhibition. ACE-I and angiotensin receptor antagonists (ARBs) are not effective in treating angioedema caused by C1-inhibitor deficiency. However, a recent study found success using an anti-ACE receptor to prevent complete acute attacks. The presence of urticaria associated with angioedema strongly suggests a diagnosis other than HAE or C1-inhibitor deficiency.**
What Causes Hereditary Angioedema Attacks?

Most attacks occur spontaneously with no apparent reason, however anxiety, stress, minor trauma, surgery and illnesses such as colds or flu have been cited as triggers. Traumas 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 female patients report a definite increase in the number of attacks during their menstrual periods. During pregnancy, some women 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 required to establish the HAE diagnosis. There are two specific blood tests.

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

Traditionally, HAE has been classified into two types. 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. In Type III HAE, this form of angioedema is yet to be fully described or 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 for swelling in these patients. A minority of cases have been associated with mutations in the coagulation Factor XII gene, however, this mutation has not been shown to be the cause of the condition.

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.

Characteristics of HAE Attacks

Patients often report tingling or tightness at the site where edema will occur minutes to thirty minutes to several hours later. In some cases, this sensation can persist up to twenty-four hours before the onset of swelling. Approximately one fourth of HAE patients experience a flat, non-titching red blotchy rash both before and during an attack. Untreated, an average HAE attack lasts for twenty-four to seventy-two hours, but some residual swelling may persist for up to three or more days. Swelling of the extremities can be painful and debilitating depending on the location of the edema. Attacks that involve the face and throat should be considered a medical emergency and medical treatment should be sought without delay. Severe swelling of the throat can close the airway and cause death by suffocation. The symptoms of an impending airway obstruction include difficulty swallowing and a change in voice pitch. Abdominal attacks cause severe pain, nausea, vomiting, dehydration and watery diarrhea. As noted above, abdominal attacks can mimic a surgical abdomen and many patients have been subjected to unnecessary exploratory surgery.

Newly-Approved Therapies Offer Treatment Options

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

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 concentrate 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 16 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 of age and older. Firazyr® is delivered by subcutaneous injection and is approved for self-administration.

Contact your HAEA regional Patient Services Team Member (see below) for more information about these products.

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)

Region 1 includes: Alaska, California, Colorado, Iowa, Maine, Massachusetts, Michigan, Minnesota, Montana, Nebraska, New York, North Dakota, Ohio, Oklahoma, Oregon, South Dakota, Utah, Vermont, Virginia, Washington, DC, West Virginia

Region - 2 Lois Perry, Director of Patient Services and Clinical Programs

Region 2 includes: Alabama, Arkansas, Kansas, Maryland, Massachusetts, Missouri, Ohio, Tennessee, Washington, Wisconsin

Region - 3 John Williamson, Patient Services Team Member

Region 3 includes: Arizona, Idaho, North Dakota, Nevada, Pennsylvania, Texas, Wyoming

Region - 4 Sally Urbanik, Patient Services Team Member

Region 4 includes: Connecticut, Delaware, Florida, Kentucky, Massachusetts, New Hampshire, New York, Rhode Island

Region - 5 Jenny Barnes, Patient Services Team Member

Region 5 includes: Alabama, Arkansas, Georgia, Illinois, Louisiana, Michigan, Minnesota, Missouri, North Carolina, Oklahoma, South Carolina

Region - 6 Candie Foucaux, Patient Services Team Member

Region 6 includes: Alaska, Arizona, California, Colorado, Connecticut, Delaware, Florida, Georgia, Illinois, Iowa, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Montana, Nebraska, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, West Virginia

Region - 7 Jenny Barnes, Patient Services Team Member

Region 7 includes: Arkansas, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Massachusetts, Michigan, Minnesota, Missouri, Montana, Nebraska, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, West Virginia

Urgent Assistance

For Dental/Surgical Procedures

• captopril (Capoten) + benazepril (Lotensin)
• enalapril (Vasotec) + lisinopril (Prinivil, Zestril)
• fosinopril (Monopril) + ramipril (Altace)
• perindopril (Aceron) + quinapril (Accupril)
• moexipril (Univac) +trandolapril (Mavik)

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.

Before new treatments were FDA-approved, anabolic steroids (also known as androgens) such as danazol, oxandrolone and stanozolol were the most commonly prescribed HAE therapies. While anabolic steroids have been shown to be useful, they are not well-tolerated by 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. The physician treating laryngeal edema may administer an FDA-approved acute HAE therapy if none is available, the physician should focus on maintaining an open airway and providing supportive care.

Even patients who do not require on-going HAE preventive therapy are usually prescribed an FDA-approved prophylactic HAE treatment to prevent swelling that can result from the trauma associated with dental and surgical procedures. Patients should discuss treatment options with their physician.

When an FDA-approved HAE therapy is not available, some physicians may infuse fresh frozen plasma (FFP) or prescribe high-dose anabolic therapy for at least four days prior to surgery and four days afterward.

Treatments on The Horizon

Santarus\Pharmacia continues to seek FDA-approval of 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?

Parents should discuss an individualized HAE treatment plan with their child’s HAE treating physician.

What Medicines Should HAE Patients Avoid?

ACE Inhibitors and estrogen-derived medications (birth control pills and hormone replacement drugs) have been shown 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:

• fosinopril (Monopril) + ramipril (Altace)
• enalapril (Vasotec) + lisinopril (Prinivil, Zestril)
• moexipril (Univac) + trandolapril (Mavik)
• captopril (Capoten) + benazepril (Lotensin)
• perindopril (Aceron) + quinapril (Accupril)
• enalapril (Vasotec) + lisinopril (Prinivil, Zestril)
• fosinopril (Monopril) + ramipril (Altace)
• enalapril (Vasotec) + lisinopril (Prinivil, Zestril)
• lisinopril (Prinivil, Zestril) + enalapril (Vasotec)
• enalapril (Vasotec) + lisinopril (Prinivil, Zestril)