GUIDE TO HAE

Hereditary Angioedema (HAE) is a very rare and potentially life-threatening genetic condition that occurs in about 1 in 10,000 to 1 in 50,000 people. HAE causes symptoms of angioedema (swelling) in various parts of the body, including: hands, feet, face and throat/airway. People with HAE often suffer excruciating abdominal pain, nausea, and vomiting caused by swelling in the intestinal wall. Swelling of the airway or throat is particularly dangerous, because it can cause death by choking.

Most people with HAE have a defect in the gene that controls an important protein called C1-Inhibitor that is found in plasma - the fluid part of blood. 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 plasma. Left uncontrolled, these interactions produce a substance called Bradykinin that causes swelling by allowing plasma fluids to leak into the soft tissue of various body parts. As described on the next page, HAE with C1-Inhibitor deficiency is classified into Type I and Type II.

There are also people who experience symptoms that are similar to Type I and II but blood tests reveal normal levels and function of C1-Inhibitor.
HAE TYPES

**TYPE I HAE - 85%** of patients
This is the most common form of the disease and is characterized by low quantitative levels of C1-Inhibitor.

**TYPE II HAE - 15%** of patients
Patients who have normal or elevated levels of C1-Inhibitor, but the protein does not function properly.

The absence of a family history does not rule out the diagnosis of HAE caused by C1-Inhibitor deficiency. Scientific reports indicate that up to 25% of HAE cases result from a spontaneous mutation of the C1-Inhibitor gene at conception. Children have a 50% chance of inheriting HAE if one of the parents has the disease.

**HAE WITH NORMAL C1-INHIBITOR**
Patients who have symptoms consistent with HAE but normal C1-Inhibitor lab results.

Recent research has confirmed that HAE with Normal C1-Inhibitor includes a number of inheritable genetic mutations that are linked to swelling, but currently, genetic tests are generally available only for Factor XII. It is expected that more genetic mutations that cause HAE will be identified in the future.
The HAEA is actively funding research to find additional causes and, more importantly, identify the most effective treatment strategies for patients suffering from HAE with Normal C1-Inhibitor.

**HAE SYMPTOMS**

**ATTACKS WITH SWELLING AND PAIN**
People with HAE experience recurrent episodes of swelling in the hands, feet, gastrointestinal tract, genitals and throat/airway that can last from two to five days. The frequency and severity of attacks may vary dramatically among patients, even those in the same family.

HAE-related swelling is **NOT** the same as swelling caused by allergies and cannot be treated as an allergic reaction. Antihistamines, corticosteroids (prednisone) and epinephrine are ineffective in relieving angioedema.
symptoms of HAE. About 25% of people with HAE experience a non-itchy, blotchy red rash (also can appear as red circles), that often occurs before or during an HAE attack.

Swelling involving body parts such as the hands, feet, face and genitals are disfiguring and can be extremely painful and disabling to the point of preventing participation in normal daily activities.

ABDOMEN
Gastrointestinal attacks usually involve excruciating abdominal pain, nausea, vomiting, and diarrhea caused by swelling in the intestinal wall. These symptoms are distinguishing features of HAE with C1-Inhibitor deficiency as recurrent severe abdominal pain is rarely seen in allergic (histaminergic) angioedema.

THROAT/AIRWAY
Episodes of throat/airway swelling are the most dangerous HAE symptoms
because the airway can close and cause death by choking.

In fact, studies indicate that the death rate for untreated HAE patients with airway angioedema can be as high as 30%. Please note that 50% of HAE patients experience one throat/airway swelling in their lifetime.

It is important to recognize throat swelling is a medical emergency that always requires immediate medical attention at the first sign of symptoms even if effective HAE medication is given at home.

ATTACK TRIGGERS

Studies suggest that 50% of HAE patients report their first symptoms by the age of 7 and over 60% report they became symptomatic by the age of 13. Although there are exceptions, HAE symptoms are usually mild in
young children, however, attacks have been reported in those under the age of 2. The frequency and severity of HAE attacks may increase during puberty and adolescence.

**COMMON HAE TRIGGERS ARE:**
- Anxiety
- Stress
- Minor trauma
- Surgery
- Ailments such as colds or flu

Patients have also reported swelling in extremities following:
- Typing
- Prolonged writing
- Pushing a lawn mower
- Hammering
- Shoveling
- Other physical activities

**HORMONES**
In women, menstruation and pregnancy are reported to have a major effect on disease activity. Some female patients report a definite increase in the number of attacks during their menstrual periods. The scientific literature reveals that there is considerable variation in the frequency of attacks experienced by pregnant HAE patients.
Use of estrogen-derived medicines, such as oral contraceptives and hormone replacement therapy, are also associated with an increase in frequency and severity of HAE attacks.

Patients should consult with their HAE treating physician regarding alternative, non-estrogen, birth control options.

**ACE INHIBITORS**

Often used to treat high blood pressure, Ace Inhibitors are known to increase the frequency and severity of HAE attacks, and, therefore, should be avoided.

**DENTAL PROCEDURES**

Trauma to the mouth caused by dental procedures can trigger oral swelling and increase the risk of throat/airway angioedema. Consult with your HAE treating physician before undergoing dental procedures.
DIAGNOSING HAE

HOW TO DIAGNOSE HAE

It is important to note that MOST cases of angioedema or swelling are NOT HAE or C1-Inhibitor deficiency. Laboratory analysis of blood samples, or genetic samples, are required to establish the HAE diagnosis.

There are three specific blood tests used to confirm Hereditary Angioedema Type I or II.

C1 - Inhibitor quantitative (antigenic)
C1 - Inhibitor functional
C4

Genetic testing to confirm Factor XII as a cause of HAE with Normal C1-Inhibitor is now available in the United States. Various centers around the world are currently working to establish the capability to test for other mutations that cause HAE-type swelling.
TREATMENT OPTIONS

HAE symptoms are not the same for every person, even within the same family. Therefore, people with HAE must partner with an HAE treating specialist to create an individualized treatment plan that matches their needs and provides the best opportunity to lead a normal life.

Prior to early 2009, treatment options in the United States were limited to anabolic steroids. Now, HAE patients and their physicians can choose from seven FDA-approved medications including those for prevention and on demand treatment when an attack occurs. Below is a list (in alphabetical order) and brief synopsis of each modern HAE treatment.

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BERINERT® - is a plasma derived C1-Inhibitor concentrate for treating HAE attacks in adults and pediatric patients. Berinert is delivered intravenously and is approved for self-administration. For more information visit: www.berinert.com.

CINRYZE® - is a plasma derived C1-esterase inhibitor indicated for routine prevention of HAE attacks in adults, adolescents and youngsters (6 years and older). Cinryze is delivered intravenously and is approved for self-administration. For more information visit: www.cinryze.com.

FIRAZYR® - is a B2 bradykinin receptor antagonist for treating HAE attacks for people who are 18 years and older. Firazyr is delivered by subcutaneous injection and is approved for self-administration. For more information visit: www.firazyr.com.

HAEGARDA® - is a plasma-derived C1-esterase inhibitor concentrate for preventing HAE attacks in adolescents and adults. It is delivered by subcutaneous injection and is approved for self-administration. For more information visit: www.haegarda.com.
KALBITOR® - is a kallikrein inhibitor for treating HAE attacks in people 12 years and over. Kalbitor is delivered by subcutaneous injection and must be administered by a healthcare professional.
For more information visit: www.kalbitor.com.

RUCONEST® - is a plasma free recombinant C1-Inhibitor concentrate for treating HAE attacks in adults and adolescents. Ruconest is delivered intravenously and is approved for self-administration.
For more information visit: www.ruconest.com.

TAKHZYRO™ - is a monoclonal antibody for preventing HAE attacks in people 12 years of age and older. TAKHZYRO is administered by subcutaneous injection and is approved for self-administration.
For more information visit: www.takhzyro.com.
**HAE AND CHILDREN**

The gene defect that causes HAE is hereditary. Children of a parent with HAE have a 50/50 chance of inheriting the disease.

**EARLY TESTING IS KEY**

HAE physician experts recommend testing a child’s C1-Inhibitor levels as early as at one year old. Early testing allows parents or legal guardians to work in advance with their child’s physician to create an individualized treatment plan.

**ONSET OF HAE SYMPTOMS IN CHILDREN VARY**

The age of HAE onset varies considerably, however, in one study, half of the patients reported onset of their symptoms by the age of 7, and over two thirds became symptomatic by the age of 13. There also seems to be an increased frequency of attacks during puberty or adolescence.
HAE TREATMENTS ARE AVAILABLE FOR PEDIATRIC CARE
One of the available HAE therapies may be an appropriate choice for use with children. Parents should work with their child's HAE treating physician to create an individualized treatment plan for each child.

WOMEN & PREGNANCY
Just like the symptoms of HAE, each pregnancy experience is variable. Talk to your HAE treating physician as well as your obstetrician in advance about your HAE treatment plan while pregnant.

DURING PREGNANCY
During pregnancy, treatment with anabolic steroids (also known as androgens) such as Danazol, Oxandrolone, and Stanozolol is not recommended. Your HAE treating physician
can help you develop a treatment plan specific to your individual needs before, during, and after giving birth, and while breastfeeding.

**HAE ATTACKS**
Women with HAE report that each pregnancy can be different. In some instances, women may experience more severe and more frequent HAE attacks while in other instances, women may find they experience no HAE attacks while pregnant.

**DELIVERY**
Current scientific literature indicates that well over 90 percent of women experience normal healthy deliveries just like those within the general population. While HAE attacks are rare at the time of delivery, treatment should be available in case an attack occurs. There is some indication of an increase in attack frequency and severity post-partum.

**MY BABY**
HAE is an inherited condition and each baby born to a parent with HAE has a 50/50 chance of inheriting the disease. Most clinicians recommend that you wait until your baby is at least one year old before being tested.
TRAVELING

Whether you are going away for business or pleasure, here are a few things to consider as you prepare for your trip.

The more prepared you are, the more enjoyable your travel will be.

FIVE GREAT TIPS FOR PLANNING YOUR TRIP

• Carry your emergency contact information with you.
• Get information on medical care options at your destination. Feel free to contact a HAEA Patient Advocate for assistance.
• Keep your HAE medication with you in your carry-on bag.
• Make sure you have enough medicine available for your trip AND after you are back home.
• Request a doctor's note or prescription to take on your trip.
HOW HAS THE TREATMENT OF HAE CHANGED DURING THE LAST FEW YEARS?
Prior to 2008, limited treatment options were available to HAE patients in the United States. Now, HAE patients can choose from seven FDA-approved medications for managing their condition.
HOW HAVE THESE CHANGES AFFECTED THE LIVES OF PATIENTS?
Therapies introduced in the past few years have dramatically improved HAE patients’ quality of life. Most patients receive their HAE treatment at home, and the number of hospitalizations and visits to the emergency room has decreased dramatically.

WHY IS ON-DEMAND TREATMENT IMPORTANT?
Acute HAE attacks can occur even in patients who are on a prophylaxis regimen. Quickly and effectively treating these attacks prevents complications and minimizes interference with everyday activities.

WHAT ARE THE BENEFITS OF NEW PROPHYLACTIC TREATMENT?
New subcutaneous prophylactic HAE treatments are highly effective and data from clinical trials reveals that the vast majority of people taking these medications will be free of HAE attacks. For patients who choose to treat their attacks on-demand, short-term prophylaxis should be given prior to a surgical or dental procedure. Patients receiving prophylactic treatment should still have on-demand treatment available in the event of a break-through attack.
HAE Symptoms

Hereditary Angioedema (HAE) is a very rare and potentially life-threatening condition characterized by attacks of swelling, particularly in the gastrointestinal tract, the respiratory tract, and the skin. Symptoms can include:

- Swelling in the hands, feet, abdomen, face, throat, or eyelids
- Swelling of the airway or throat, which can be particularly dangerous
- Excruciating abdominal pain
- Vomiting and diarrhea caused by swelling
- A non-itchy, disfiguring rash
- Blotchy red rash (can appear as red circles)

HAE Symptoms Are Usually Mild in Young Children

Studies suggest that 50% of HAE patients become symptomatic by the age of 7 and over 60% report they became symptomatic by the age of puberty or adolescence. Children of a parent with HAE have a 50/50 chance of inheriting hereditary HAE. Patients who have symptoms consistent with HAE but normal C1-Inhibitor levels have HAE with normal C1-Inhibitor.

Most people with HAE have a defect in the gene that controls an important protein, C1-Inhibitor, which helps control swelling. The gene defect that causes HAE is inherited in an autosomal dominant manner. Therefore, one affected parent usually has a 50% chance of passing the gene defect to their child. Children of an affected parent with a normal family history for HAE may still develop HAE because the gene defect that causes HAE can be caused by the combination of two gene defects, one from each parent.

Types of HAE

HAE is classified into two types:

- Type I HAE
- Type II HAE

Type I HAE is less common and affects only a small number of patients. Type II HAE affects 1 in 50,000 people. HAE is classified as Type II if patients have symptoms consistent with HAE but normal C1-Inhibitor levels. A genetic test can help confirm whether a patient has Type I or Type II HAE. Patients with Type II HAE have a genetic defect in the gene that controls C1-Inhibitor levels, which are normal in the blood. Type II HAE is usually diagnosed in the first half of life. Patients with Type II HAE are typically asymptomatic at birth and usually develop symptoms in early puberty or adolescence.

Type II HAE cannot be treated as an allergic (histaminergic) angioedema. Attacks can be life-threatening and cause symptoms that are similar to those of allergic (histaminergic) angioedema, such as abdominal pain, vomiting, and diarrhea. Type II HAE attacks, and, therefore, should be treated with medications designed for the treatment of HAE, not medications designed for treatment of allergic (histaminergic) angioedema.

A genetic test can help confirm whether a patient has Type I or Type II HAE. Type I HAE is often diagnosed in early infancy. Type I HAE is less common and affects only a small number of patients. Type I HAE is usually diagnosed in the first half of life. Patients with Type I HAE are typically asymptomatic at birth and usually develop symptoms in early puberty or adolescence.

About the US HAEA

The US Hereditary Angioedema Association (HAEA) is a non-profit patient advocacy organization with a long history of providing our patient community with a wide range of programs and activities that support people with HAE, their caregivers, and family members through every step of their HAE journey.

Our team of highly experienced and well-trained Patient Health Advocates (many of who also have HAE and/or serve as caregivers) offer kind and compassionate support that includes referrals to specialists for diagnosis and treatment recommendations.
ADVANCE HAE SCIENTIFIC REGISTRY

Advance HAE Scientific Registry is a confidential database created by the US HAEA to obtain HAE disease information, and help scientists advance HAE research.

As a member, you will enjoy special benefits:

- Access to customized health statistics generated by your report submissions.
- Personalized health records with graphics to illustrate your own HAE attack history.
- Easy access to enter your attack reports through the new advanced HAE mobile app.
- Fast and convenient reporting via your own electronic device.
- Exclusive invitations to educational webinars with HAE expert physicians from the US HAEA Angioedema Center at the University of California San Diego.

To become a member of the Advance HAE Scientific Registry visit www.haea.org