If you or someone in your family suffers from hereditary angioedema (HAE), you may have questions about your condition and the best way to manage it. At CSL Behring, we are dedicated to helping people affected by rare diseases.

This dedication extends to the entire HAE community, including you and your family, physicians who treat people with HAE, and advocacy groups who provide information and support. This information is brought to you as a service of CSL Behring and is part of our commitment to families affected by HAE.

About HAE

HAE is a rare disease that can cause attacks of swelling in body tissues due to “leaky” blood or lymph vessels in the body.

People with HAE have the disease for life, because it’s part of their genetic makeup. However, depending on the severity of the illness, some people will have many swelling attacks each month, while others can go months — or even years — without an HAE episode. Others may not even be aware they have the condition.

Understanding HAE

Other medical problems, such as swelling due to an allergic reaction, can closely resemble an HAE attack. Because allergic reactions are much more common than HAE attacks, some healthcare professionals, wrongly assume that an HAE attack is due to a common allergic reaction.

Even when HAE is not mistaken for an allergic reaction, it may be attributed to another medical problem. Depending on the site of the swelling, the condition is sometimes misdiagnosed as appendicitis, intestinal blockage, a sprain, or even a psychological problem.

An incorrect diagnosis can lead to ineffective, inappropriate, or inadequate care. At times, the results can prove fatal, which is why CSL Behring is committed to educating families and healthcare professionals about HAE.

Visit allaboutHAE.ca for updated information and helpful tools to manage HAE.
Is It HAE?

Answer the following 8 simple questions that help families and physicians recognize HAE.

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Have you had unexplained attacks of swelling in your hands, feet, arms, legs, face, throat, genitals, or another area of your body?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Have these swelling attacks sometimes occurred on just one side of your body, for example, just your left hand or just your right foot?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Have you had unexplained attacks of abdominal pain?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Have these attacks of swelling or abdominal pain occurred more than once?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Has anyone in your family had similar episodes of swelling or abdominal pain? Or has anyone in your family “choked to death?”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Do you sometimes have sensations (such as fatigue, tingling, nausea, or flu-like symptoms) — minutes, hours, or even days before an attack begins?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Have medications, such as Benadryl, Epi-Pens, or steroid shots, provided little, if any, relief?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. When you’ve had these attacks, have your eyes been watery or itchy?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If you answered “yes” to all or nearly all of the first seven questions and “no” to the last question, your symptoms may be caused by HAE. You should discuss your medical history with a physician who understands and treats HAE.* A blood test can confirm the diagnosis.

The blood tests used to make the diagnosis include testing for levels of blood components known as C4 and C1. Usually, it is best if an HAE expert draws the blood for a C1 level, because not all laboratories are knowledgeable about handling C1 specimens. A physician who specializes in HAE will know which laboratories in your area are best equipped to handle this important blood test.

* See “Finding a Treatment Center” on page 7
What Causes HAE?

HAE is caused by a problem in a person’s genetic code for a single protein, known as C1-esterase (C1-ESS-ter-ace) inhibitor, or C1-INH. An abnormal code can lead to a deficiency in C1-INH (type I HAE) or an inability of C1-INH to function properly (type II HAE).

The Family Tree at allaboutHAE.ca helps you identify HAE in your family.

C1-INH Deficiency

In a healthy person, C1-INH regulates chemical responses in the immune system (the system that deals with foreign invaders, such as bacteria and viruses) and the formation of blood clots. Without adequate, functioning C1-INH, the person with HAE can have a chemical response that is out of proportion with the body’s demand.

A Dominant Gene

As you might recall from health class, people receive half their genetic code from each parent. In some diseases, such as cystic fibrosis or sickle cell anemia, a child must receive one copy of the disease-causing gene from each parent.

This is not the case with HAE. In HAE, having just one problem gene produces the disease. Biologists call this an autosomal (AW-toe-ZOAM-ul) dominant gene. As a result, children born with just one disease-causing gene will have HAE — although, like other people with HAE, they may or may not have attacks due to HAE. The good news is that children born without the abnormal gene will effectively prune the occurrence of HAE from that branch of the family tree. All successive generations (that child’s children and grandchildren) will be free of HAE.

But Nobody in My Family Has HAE

Sometimes people with a new diagnosis of HAE are not aware of the disease in other family members. In hindsight, however, they will discover that a parent, grandparent, or other relative did indeed have symptoms that sound very much like HAE.

Occasionally, HAE occurs in people without a previous family history of the disease. This is due to a spontaneous change in the gene of the sperm or egg that formed the developing person. Not only will these individuals have the disease, but they will also have the potential to pass this changed gene (and HAE) to their children.

FACT

Because parents with HAE have one healthy gene that encodes for normal C1-INH and one unhealthy gene that encodes for HAE, each child born to a person with HAE has a 50-50 chance of inheriting the disease.
Where Swelling Episodes Occur?

Attacks of angioedema can occur anywhere in the body. Furthermore, attacks of HAE can occasionally be “migratory.” In other words, they move from one body part to another. Additionally, separate attacks can affect different parts of the body. The most common sites for these swelling episodes include:

- Extremities (hands, feet, arms, legs)
- Intestines (abdomen)
- Face
- Genitals
- Larynx (voice box)

In a recent survey, attacks of the hands, feet, and abdomen were reported most often. These attacks often involve just one side of the body. For example, only the right hand swells, but not the left, or vice versa. In allergic reactions, both sides of the body tend to be equally affected.

HAE episodes can be disabling. For example, swollen fingers may prevent the effective use of one’s hands. Swelling of the intestines can cause severe abdominal pain that interferes with daily activities. Moreover, people with HAE often undergo unnecessary gastrointestinal surgeries as physicians search for an inflamed appendix, an intestinal blockage, or another root source of pain and swelling.

By far, the most serious types of attacks, however, are those that affect the throat and block the airway.

### FACT

HAE attacks can occur anywhere in the body. The most serious attacks affect the voice box.

#### Preventing HAE Attacks

Although attacks of HAE are often unpredictable, some potential triggers have been identified:

- Emotional or psychological stress
- Physical stress (injuries, surgery, or childbirth)
- Physiologic stress (viral or bacterial infections)
- Medications, such as ACE inhibitors (for high blood pressure) or oral contraceptives

If you have HAE, avoid or minimize your exposure to these factors whenever possible. And if you are having frequent attacks or know you’ll be exposed to a potential trigger, talk to an HAE expert. Physicians who are experienced in the treatment of HAE are familiar with prophylactic (PRO•fill•ACK•tick) or preventive therapy.

Preventive therapy can be administered on a...
short-term or long-term basis. Short-term therapy is used to prevent an attack when a person is exposed to known triggers, such as childbirth or surgery. Long-term therapy is used to cut down on the number of attacks in people who are severely affected by HAE.

**Short-term Preventive Therapy**
Short-term prophylaxis before a dental procedure or surgery is often appropriate. Where available, C1-INH infusions are sometimes given 24 hours before a procedure or just prior to another known trigger. C1-INH is available in Canada, for example, and has been available in Europe for more than 25 years.

If C1-INH is not available, physicians usually administer medications known as attenuated androgens (uh-TEN you•ATE•ed AN•droe•jens) or antifibrinolytics (an•TEA•FY•brin•oh•LIT•icks).

**Attenuated Androgens**
Androgens are male hormones. “Attenuated” means that the male hormone is not as potent as the male hormone testosterone. The attenuated androgen that is most commonly prescribed for HAE is danazol. These medications are usually started 5 days before the procedure and continued 2 days afterward.

**Antifibrinolytics**
Antifibrinolytics are medications that are used less often than attenuated androgens in the treatment of HAE. They decrease the breakdown of fibrin, a component of blood clotting. Antifibrinolytics used in the treatment of HAE include tranexamic acid (TA or Cyklokapron), and epsilon-aminocaproic acid (EACA).

Both attenuated androgens and antifibrinolytics are associated with side effects. If you have questions about any medication used to treat HAE, discuss your options with an HAE expert.

**Long-term Preventive Therapy**
As in short-term therapy, attenuated androgens are often used as long-term preventive therapy. Long term side effects of androgens can be serious and for this reason the low doses must be used. However, these drugs are contraindicated in pregnancy and are rarely appropriate for children. As well, androgens can have side effects that are unattractive to women, especially as long-term therapy. Doctors refer to these side effects as virilization (VI•rill•ih•ZA•shun) — the abnormal development of male sexual characteristics in a woman.

In a recent survey of physicians and patients, breakthrough attacks frequently occurred in patients despite the use of androgen therapy. As mentioned previously, antifibrinolytics are used less often than attenuated androgens in the treatment of HAE. Because they can have highly undesirable side effects, their use is generally limited to people who suffer frequent and/or severe attacks and cannot tolerate other medications.

As you would with any medicine, discuss your treatment options with your medical specialist.
Recognizing the Start of an Attack

HAE attacks may occur suddenly and without warning. However, if you’re like many people with HAE, you may notice symptoms that precede an attack. These symptoms are called prodrome (PRO-droam) or prodromal symptoms. As more medications are available for the treatment of HAE, it eventually may be possible to thwart full-blown attacks by taking medication at the first sign of prodrome.

Common Prodromal Symptoms

- Fatigue
- Tingling
- Nausea
- Bowel movement changes
- Non-itchy rash with pale colored centers
- Flu-like feelings
- Hives
- Rumbling

In a recent survey of people with HAE, some people noticed these symptoms minutes or hours before an attack, while others said they could feel them a day or two before the full attack began. In the survey, people with HAE most often reported tingling, fatigue, flu-like symptoms, and nausea. Some of these symptoms, such as nausea or changes in bowel movement, only occurred before abdominal attacks.

The advantage of warning symptoms is the ability to predict an attack, and therefore initiate treatment sooner.

Managing Attacks

As a person with HAE, it is important for you to become your own advocate. Recognize the symptoms of HAE attacks and learn as much as you can about treatment. Monitor symptoms and work with your doctor to choose the best treatment plan for you.

Both Canada and Europe have developed guidelines for the treatment of HAE. In both regions, the treatment of choice in acute attacks is replacement with C1-INH concentrate.

Although not considered an ideal treatment, Solvent detergent plasma (SDP) and fresh-frozen plasma (FFP) are often used to treat HAE attacks in Canada, because not all Hospitals have C1-INH available.

Because fluids are redistributed outside the vascular system in HAE attacks, intravenous fluids are often helpful to rehydrate a person who is having an attack. Moreover, where few treatment options are available, pain medications may be necessary, particularly during abdominal attacks.

Continued on next page ➔
Preventive treatments — danazol, tranexamic acid (TA), and epsilon-aminocaproic acid (EACA) — may also be administered during an HAE episode, especially in countries where C1-INH concentrate is not available.

**WARNING!**
Call your local emergency number, if you notice:
- Hoarse voice or laryngitis
- Whistling or wheezing when breathing
- Shortness of breath
- Swollen tongue
- Lip or facial swelling
- Throat swelling

These can be the first indications of potentially life-threatening attacks.

**What’s Most Important to Know**
One of the most serious types of attacks is an attack of the voice box or larynx (lair•ingks). These laryngeal (luh•RIN•jee•ul) attacks are most serious, because they can cut off the air supply to the lungs and therefore are life-threatening attacks. This is a medical emergency. Sometimes a tracheotomy (TRA•kee•OTT•uh•mee) must be performed to allow oxygen to flow into the lungs. A tracheotomy is an incision through the neck into the windpipe, which is made when the upper airway is blocked.

A hoarse or absent voice, whistling or wheezing, coughing, swollen tongue, or shortness of breath may be the first signs of a life-threatening attack. Lip and facial swelling can also progress to laryngeal edema. People who experience any of these symptoms should seek medical help immediately.

**Finding a Treatment Center**
Because HAE is a rare disease, few community physicians ever have the opportunity to see patients with HAE.

Throughout North America, Europe, and the rest of the world, a select group of hospitals and physicians have distinguished themselves in the diagnosis and management of HAE. These centers not only treat a relatively large community of families with HAE, they also have participated in research studies (clinical trials), and have established themselves as thought leaders on the forefront of HAE management.

To learn more, visit [www.allabouthae.ca](http://www.allabouthae.ca)
How Patients made an IMPACT

In order for C1-INH concentrate to be available in Canada, CSL Behring has sponsored two studies. Both used human C1-INH concentrate to treat acute attacks of HAE:

- **I.M.P.A.C.T. 1**: Used human C1-INH in acute attacks of the abdomen or face
- **I.M.P.A.C.T. 2**: Uses human C1-INH in acute attacks

Both studies have treated only people with type I HAE. The vast majority of HAE patients (about 85%) have this type of HAE.

In a double-blind study, some subjects receive placebo and some receive medication, but neither the subjects nor the investigators know which patients receive which medications. I.M.P.A.C.T. 1 was a “double-blind” study. However, this does NOT mean that those in the placebo group never received C1-INH. Instead, the I.M.P.A.C.T. 1 protocol called for the use of concentrate within 4 hours in any person who did not respond to the placebo.

I.M.P.A.C.T. 2 was an extension of I.M.P.A.C.T. 1, but it was not a blinded study. This type of study is called an “open-label” study. In I.M.P.A.C.T. 2, all subjects received the human C1-INH. Moreover, unlike the I.M.P.A.C.T. 1 study, the medication could be used for different types of attacks. Patients must have first participated in I.M.P.A.C.T. 1 before they could be part of I.M.P.A.C.T. 2, because the latter is an extension of the first study.

To learn more, visit [www.allabouthae.ca](http://www.allabouthae.ca)
Living Better With HAE

Knowledge is power. And understanding how HAE can impact your life at various stages can help empower you to confidently lead a successful and happy life.

As an inherited disorder, HAE is a lifelong disease. However, the severity and frequency of your attacks may vary during one life stage compared to another.

**Childhood**

In families affected by HAE, all children should be tested for C4 and C1 levels after the age of 1. (Before this age, tests aren’t very accurate.) Even if a child has no symptoms, an advance diagnosis may help you be prepared for the possibility of a future attack. Alternatively, your worries may be set to rest, if your child’s test results are normal. Physicians report that their youngest patients who have HAE attacks tend to be preschoolers rather than infants or toddlers. However, many people do not experience attacks until their teen years or later.

If your young child does have attacks, keep in mind that children usually have more difficulty than adults in conveying feelings of discomfort, pain, and other medical symptoms. Be alert to your child’s changes in mood or behavior that may herald the onset of an attack. As your child grows, help him or her identify and name warning (prodromal) symptoms and personal triggers.

If your child has HAE, inform healthcare professionals and first responders at day-care centers, schools, summer camps, and after-school programs. It’s a good idea to create a “Patient Information Card” that includes key family and medical contact numbers and instructions describing steps to be taken in the event of an HAE emergency. In addition, a letter from your child’s physician to other healthcare professionals should be available wherever your child plays or “works.”

**Teenage Years**

Hormonal and emotional changes increase during the teen years. Consequently, many people report the onset of their first HAE attacks during puberty.

As independence grows, it becomes increasingly important that children carry personal medical information with them. A medical alert ID bracelet or chain, a card in a wallet or purse, and an understanding of the condition among your teen’s inner circle of friends can discreetly help keep your teen safe at a time when a desire to fit in with peers becomes important.

During the teen years, the ultimate responsibility for your child’s health must gradually shift from parent to child. Your teen’s firm grasp of personal triggers, warning symptoms, and treatment options will help with the transition to college and/or the working world.

**Pregnancy**

Hormonal changes can change patterns of HAE attacks. Some women notice an increase in frequency of attacks during pregnancy. For others, the number and severity of attacks fall during pregnancy. For many, the frequency of attacks returns to normal after giving birth, while others experience a permanent change in the pattern of attacks after childbirth.

**The Perimenopausal Years**

The perimenopausal years are a time of physiological changes and alterations in hormonal levels. If you are considering estrogen replacement therapy during this change of life, discuss your treatment options with your HAE physician specialist.
3 Steps For Managing HAE In Your Daily Life

1. RECOGNIZE YOUR TRIGGERS
   Be aware of events, changes in medications, or situations that may precede or trigger an HAE attack.

   For many people, emotional or physical stress can prompt swelling episodes. For others, attacks may occur at random without any noticeable triggers.
   - Keep a journal of the location, duration, and frequency of attacks.
   - Be aware of patterns that may occur (such as emotional triggers, medication changes, and, in women, the timing in relation to your menstrual cycle).
   - Record any warning signs or symptoms, which can precede some attacks. Early recognition can lead to early treatment and may help thwart full-blown attacks.

2. AVOID THE TRIGGERS
   Avoid situations that may spark an attack. And talk to your doctor before exposure to any known triggers, such as dental work, surgery, or childbirth.
   - For women, do not use contraceptives that contain estrogen.
   - If emotional stress is a trigger, avoid highly charged situations. Enlist the help and support of others, and use coping strategies.
   - Discuss with your physician the possibility of short- or long-term preventive therapy, if a trigger is unavoidable.
   - Plan for circumstances that may prompt an HAE event, and structure your daily life to avoid as many potential triggers as you can.

3. BE PREPARED FOR AN ATTACK
   For many people with HAE, an attack is not preventable. In that case, the best policy is to be prepared.
   - Educate family, loved ones, and coworkers about your condition.
   - Before you travel, locate a nearby treatment center.
   - Discuss your medical condition and dental work options with both your HAE specialist and your dentist.
   - Talk to your doctor if you are a candidate for a surgical procedure.
   - Keep an HAE letter from your doctor with you at all times.
   - Carry an emergency patient information card that:
     - Identifies your condition.
     - Provides family emergency names and numbers.
     - Supplies your doctor’s emergency contact information.

Connecting With the HAE Community
Without support, families affected by a rare hereditary illness can often feel isolated and alone. For families affected by HAE, however, many helpful resources are available:

Web Sites
All About HAE: www.allaboutHAE.ca
Canadian Hereditary Angioedema Patient Association: www.hae.ca
International Patient Organization for C1-Inhibitor Deficiencies: www.haei.org

The Patient Journal at allaboutHAE.ca can help you track HAE symptoms, doctor’s appointments, and medication use.

The Family Tree at allaboutHAE.ca helps you identify HAE in your family.