UNDERSTANDING HAE

HAEi
HAE International

INDEX

HAEA
US HEREDITARY ANGIOEDEMA ASSOCIATION

HAEi thanks the US HAEA for their significant contribution to the content of this guide.

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 people with HAE

This is the most common form of the condition and is characterized by low quantitative levels of C1-inhibitor.

TYPE II HAE - 15% of people with HAE

Lab tests show normal or elevated levels of C1-inhibitor, but the protein does not function properly.

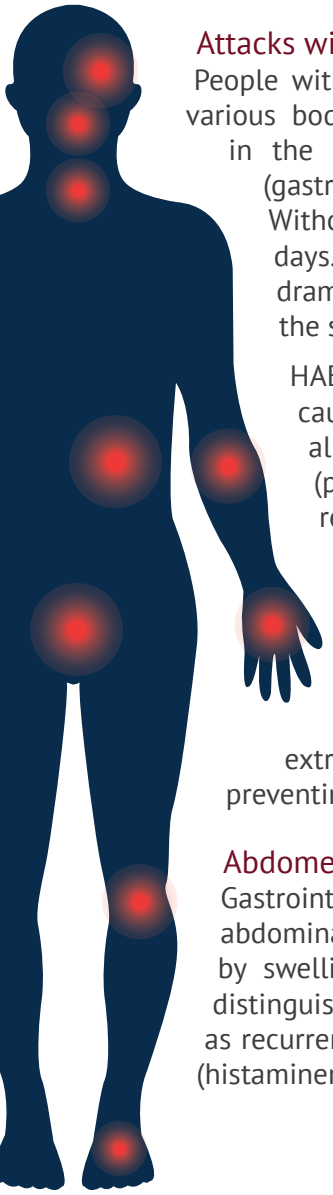
The absence of a family history does not rule out the diagnosis of HAE caused by C1-inhibitor deficiency. Up to 25% of HAE cases result from a spontaneous mutation of the C1-inhibitor gene at conception. Children have a 50% chance of inheriting HAE if one of the parents has the condition.

HAE with normal C1-inhibitor

Symptoms are consistent with HAE, but lab results show normal C1-inhibitor levels and function.

Recent research has confirmed that HAE with normal C1-inhibitor includes a number of inheritable genetic mutations that are linked to swelling. It is expected that more genetic mutations that cause HAE will be identified in the future.

HAE SYMPTOMS



Attacks with swelling and pain

People with HAE experience attacks of swelling that affect various body parts. Swelling attacks occur most commonly in the skin (for example, hands, feet, face), abdomen (gastrointestinal tract), and throat/airway (larynx). Without treatment, attacks can last from two to five days. The frequency and severity of attacks may vary dramatically among people with HAE. It may vary in the same individual during different stages of their life.

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 attacks 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.

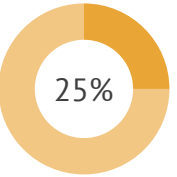
Throat/airway

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

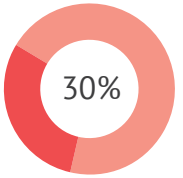
In fact, studies indicate that the death rate for untreated people with HAE with airway angioedema can be around 30%.

Please note that 50% of people with HAE experience one throat/airway swelling in their lifetime.

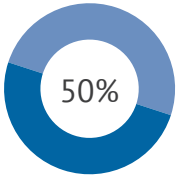
It is important to recognize throat swelling is an emergency that always requires immediate medical attention at the first sign of symptoms, even if effective HAE medication is given at home.



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.



Death from throat/airway swelling among untreated people with HAE can be around 30%.

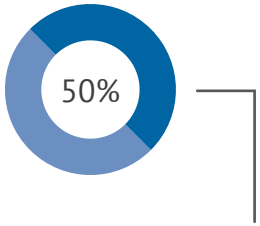


50% of people with HAE experience at least one throat/airway swelling in their lifetime.

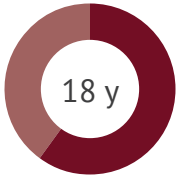
ATTACK TRIGGERS

Studies suggest that 50% of people with HAE report their first symptoms by the age of 10 and most people have experienced symptoms/their first attack before age 18.

Although there are exceptions, HAE symptoms are usually mild in young children, however, attacks have been reported in children as early as 1 year of age. The frequency and severity of HAE attacks may increase during puberty and adolescence.



50% of people with HAE report their first symptoms by the age of 10.



Most people have experienced symptoms/ their first attack before age 18.

Common HAE triggers

Common HAE triggers are:

- Anxiety
- Stress
- Minor trauma
- Surgery
- Ailments such as colds/flu/other viral infections

People with HAE have also reported other triggers such as:

- Exposure to cold
- Activities that cause mechanical trauma such as gardening, hammering or shoveling

Hormones

In women, menstruation and pregnancy can affect HAE symptoms. Some women with HAE report an 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 women with HAE.

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.

People with HAE 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 swelling. Consult with your HAE treating physician before undergoing dental procedures.

DIAGNOSING HAE

How to diagnose HAE

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

HAE with normal C1-inhibitor

For people with HAE with normal C1-inhibitor, the C1-inhibitor levels and function are normal. Researchers have discovered that in some instances, HAE with normal C1-inhibitor is associated with mutations in factor XII (F12), plasminogen (PLG), angiopoietin (ANGPT1), kininogen (KNG1), or myoferlin (MYOF) genes. However, in many cases the genetic cause of HAE with normal C1-inhibitor is unknown. Some commercial laboratories are able to test for Factor XII mutations but there are no routine laboratory tests to confirm a diagnosis of HAE with normal C-1 inhibitor.

ABOUT MEDICINE CLASSES AND NAMES

Medicines with certain similarities can be grouped into *drug classes*. The similarities could be due to the chemical structure of the medicine, their mode of action, or that they are used to treat the same disease.

Every medicine has an approved generic name. This is the name of the active ingredient in that particular medicine. As several companies may make the same generic medicine, each company will give their product a brand or trade name.

An example of this is the painkiller ibuprofen.

- The drug class that ibuprofen belongs to is non-steroidal anti-inflammatory drugs.
- The generic name is ibuprofen, and there are several companies make it with brand names such as Advil®, Neurofen® , Motrin®, Ibumetin®, Dolgit®.

We will refer to drug classes and generic names when discussing specific medicines for HAE.

TREATMENT OPTIONS

There are effective treatments that help reduce the frequency and severity of swellings and relieve symptoms. Sadly, and similar to many other diseases, there is no cure for HAE.

The goals of HAE treatment are to achieve complete control of the disease and to normalize patients' lives. Research is ongoing to develop more and more effective medications for HAE. With the effective modern medication available today for HAE, some people with HAE report that they can live life effectively free from swellings.

Current HAE treatment strategies focus on medications to:

- Provide rapid relief during attacks (on-demand or acute treatment)
- Prevent symptoms in people with HAE who experience a high frequency of attacks (long-term prophylaxis)
- Prevent symptoms in people with HAE who undergo dental or surgical procedures, which may trigger an attack (preprocedural or short-term prophylaxis).

While the symptoms can often be mistaken for an allergic reaction, HAE attacks do not respond to common allergy treatments, including antihistamines, corticosteroids, or epinephrine.

All people with HAE should work with their physician to develop an individualized HAE management plan which includes a treatment action plan.

On-demand or acute treatment

On-demand or acute treatment is used to stop the progression of the swelling and to relieve the symptoms. Rapid use of on-demand or acute treatment is especially important where the swelling in is the throat or airway. If the throat attack is left untreated, it can lead to death by choking (suffocation).

HAE (Type I and II) therapies for on-demand or acute treatment vary from country to country as specific treatments are not licensed in all countries.

The types of specific HAE medication available and recommended for on-demand or acute treatment include:

- Intravenous C1-inhibitor concentrate
  - Products made from blood plasma (pdC1-inhibitor concentrate)
  - Products that are not made from blood plasma (recombinant or rhC1-inhibitor concentrate)
- Plasma kallikrein inhibitor
  - Ecallantide
- Bradykinin-receptor antagonist
  - Icatibant

In countries where HAE-specific on-demand or acute treatments are not available, physicians are limited to non-HAE-specific medications or even just pain killers.

The International WAO/EAACI Guideline for the Management of Hereditary Angioedema makes the following recommendations for acute or on-demand treatment for HAE:

- Early treatment with intravenous C1-inhibitor concentrate, ecallantide or icatibant provides a better response than late treatment; often resulting in a shorter time to complete symptom relief and a shorter duration of overall swelling.
- HAE attacks should be treated as early as possible. Early treatment can be achieved with self-administration. All C1-inhibitor concentrates and icatibant are licensed for self-administration, although approved product uses vary around the world.
- If C1-inhibitor concentrates, ecallantide or icatibant are not available then solvent-detergent treated plasma (SDP) should be used
- If SDP is not available then fresh frozen plasma (FFP) should be used to treat attacks, where a safe supply is available.

The experts who developed the Guideline advise against using antifibrinolytics (e.g., tranexamic acid) or androgens (e.g., danazol) as on-demand treatments for HAE attacks. Studies show no, or very small, effects when used in this way.

Long-term prophylaxis

Long-term prophylaxis (LTP) is where a person with HAE uses regular medication to prevent swelling attacks from occurring. LTP reduces the number of swelling attacks a person with HAE experiences and, some modern LTP medications mean that people with HAE no longer experience swellings.

HAE (Type I and II) therapies for LTP vary from country to country as specific treatments are not licensed in all countries.

This treatment strategy should be tailored to the individual and considered for all people with HAE taking into account the frequency and severity of attacks, the individual's quality of life, the availability of healthcare resources, and failure to achieve adequate control with on- demand or acute treatments.

As swelling attacks can still happen even if LTP is used, all people with HAE using LTP should also have on-demand or acute medication available.

In recent years, additional medications for HAE LTP have been approved by medicine regulators. The types of specific HAE medication available and recommended for LTP include:

- C1-inhibitor concentrate
  - products made from blood plasma (pdC1-inhibitor concentrate)
- Plasma kallikrein inhibitor
  - lanadelumab
  - berotralstat

Where these medications are not available, attenuated androgens can be used for LTP. They have been shown to reduce the number of swelling attacks. However, they have many side effects, contraindications, and drug interactions.

Antifibrinolytics such as tranexamic acid can also be used for LTP when attenuated androgens are contraindicated. Antifibrinolytics are not formally recommended, but the Guideline experts noted that some people with HAE may find them helpful. Their side effects are usually minor.

Short-term prophylaxis

Short-term prophylaxis is usually performed before surgical procedures or dental treatment. Dental procedures or surgery to remove the tonsils are potentially critical triggers as they can cause swelling in the throat/airway (larynx).

Where it is available, the use of intravenous plasma-derived (pd) C1-inhibitor concentrate is considered the short-term prophylaxis treatment of choice. It is administered as close as possible to the start of the procedure.

Recombinant C1-inhibitor concentrate can be considered if intravenous pdC1-inhibitor is not available. Where neither intravenous C1-inhibitor concentrate is available:

- Fresh frozen plasma (FFP) may be used
- Attenuated androgens can also be considered as an alternative. For scheduled pre-procedure prophylaxis, androgens are used for 5 days before and 2-3 days post-event.

There is always the potential that a breakthrough attack can occur, so on-demand treatment needs to be available during the procedure.

HAE treatment in children

Similar to adults, all pediatric HAE patients should develop an HAE management plan including a treatment action plan with their physician.

HAE (Type I and II) therapies licensed for children or adolescents vary from country to country as specific treatments are not licensed in all countries.

The types of specific HAE medication available and recommended for **on-demand** or **acute treatment** for children or adolescents include:

- C1-inhibitor concentrate
  - Products made from blood plasma (pdC1-inhibitor concentrate)
  - Products that are not made from blood plasma (recombinant or rhC1-inhibitor concentrate)
- Bradykinin-receptor antagonist
  - icatibant

Where these medications are not available, solvent-detergent treated plasma (SDP) is preferred to fresh frozen plasma (FFP), but both can be considered.

The types of specific HAE medication available and recommended for **long-term prophylaxis** (LTP) in children and adolescents generally mirror those available for adults. Where pdC1-inhibitor concentrate is not available, antifibrinolytics such as tranexamic acid can be used for LTP. Due to their better safety profile, LTP with antifibrinolytics is preferred over androgens in children. However, there is a lack of data to support its use.

Similar to adults, where pdC1-inhibitor concentrate is available it is considered to be the **short-term prophylaxis** of choice. A short course of attenuated androgens can be used as an alternative when C1-inhibitor concentrate is unavailable. There is always the potential that a breakthrough attack can occur, so on-demand treatment should be available during the procedure.

HAE AND CHILDREN

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

Testing is key

Once an individual is diagnosed, experts recommend that all immediate family members (parents, siblings and children) are tested for HAE. Testing for HAE is possible within the first year of life however, some physicians recommend that you wait until a baby is at least one (1) year old before testing. This is due to highly variable C1 antigenic and C4 levels in the first year of life. 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, studies suggest that 50% of people with HAE report their first symptoms by the age of 10 and most people have experienced symptoms/ their first attack before age 18. There also seems to be an increased frequency of attacks during puberty or adolescence.

WOMEN & PREGNANCY

If you want to get pregnant or are pregnant, your doctor will follow you closely to discuss appropriate management of your HAE with you.

HAE treatment

During pregnancy and breastfeeding, treatment with anabolic androgens (or steroids) or tranexamic acid 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 frequent and/or severe HAE attacks, while in other cases, women may find they experience few or no HAE attacks while pregnant.

Delivery

Most women with HAE experience a healthy delivery of their baby, just like those within the general population. HAE attacks are rare at the time of delivery. There is some indication of an increase in attack frequency and severity in the post-partum period.

My baby

As noted earlier, HAE is an inherited condition and each baby born to a parent with HAE has a 50% chance of inheriting the condition. Testing for HAE is possible within the first year of life however, some physicians recommend that you wait until a baby is at least one (1) year old before testing.

TRAVELING

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

Great tips for planning your trip

- Always carry emergency contact information. You can find HAEi's Emergency Cards in many languages in HAEi's Companion App or online on haei.org.
- Get information on medical care options at each destination. You can find a list of HAE knowledgeable physicians and hospitals either in HAEi's Companion App or haei.org.
- Keep HAE medication in a carry-on bag.
- Make sure enough medicine is brought to cover the entire trip.

ABOUT HAEi

HAE International (HAEi) is a global non-profit network of patient associations dedicated to improving the lives of people with HAE.

We are a group of compassionate HAE patients and care givers who make it our life's work to raise awareness of HAE, improve time to diagnosis, and fiercely advocate for approval and reimbursement of lifesaving therapies to everyone living with HAE.

HAEi is company and product neutral and enthusiastically supports drug discovery research aimed at the next generation of HAE therapies. Our great success in supporting clinical trials has resulted in a variety of approved therapeutic options. We work closely with expert physicians to continuously encourage a tailored, patient-focused approach to the use of available therapeutic options.

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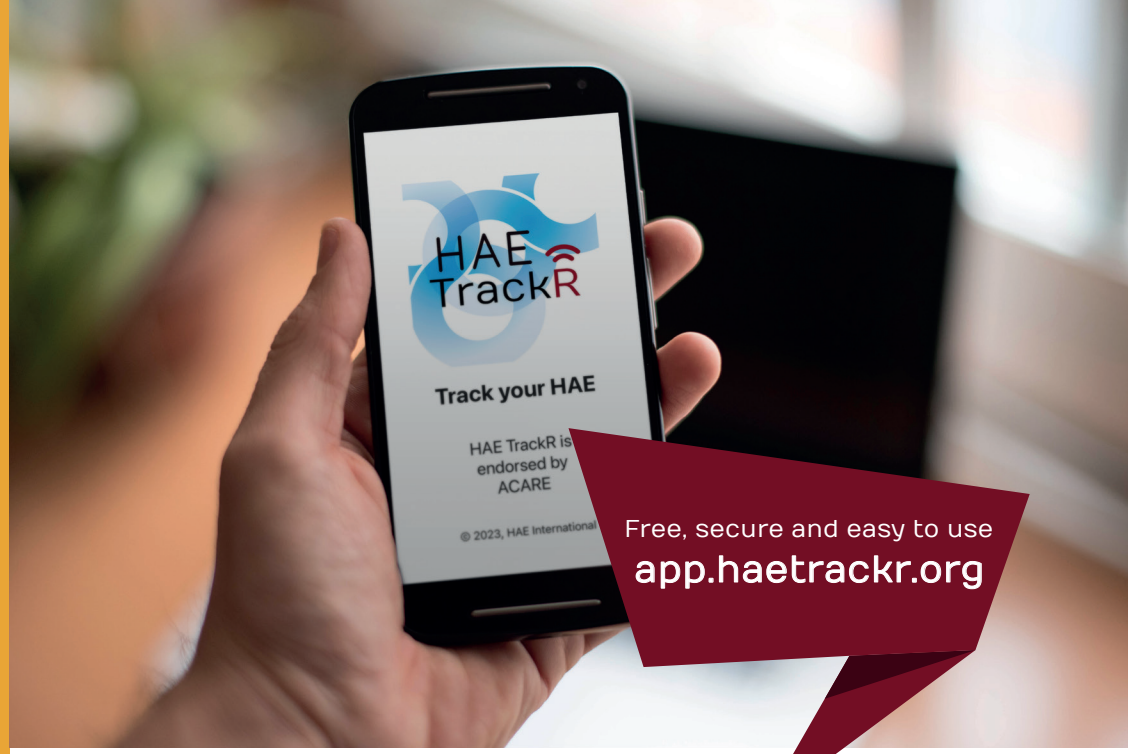
HAEI'S RESOURCES

We provide our member organizations with specially designed tools and technical assistance that promote disease education and support activities addressing the unique needs of HAE patients and their families.

In this leaflet you will find brief information about some of them – find much more information on our website haei.org.



HAE TrackR app

Developed by fellow HAE patients at HAEi, **HAE TrackR** is an easy-to-use electronic diary designed to record your HAE attacks, treatments, and the impact HAE has on your life and the life of your loved ones.

HAE TrackR is a secure, product and company neutral app, where all data gathered is the sole property of the user. It strictly protects your data and privacy and is fully EU-GDPR compliant.

HAE TrackR is a tool both patients and physicians can use to make important decisions on how best to manage your HAE. For example you can share a report of your attacks and treatments with your physician if you choose to.

HAE TrackR can be accessed from any device (smartphone, tablet, or computer) anywhere in the world – visit haetrackr.org to know more and start using the app.

Emergency Cards

HAEi has developed emergency cards containing clear and straightforward information about HAE, and treatment required during an attack. Emergency cards in many languages are available both through our HAE Companion app and on the HAEi website.

HAE Companion app

The HAE Companion app provides an easy way to access and store the popular HAEi emergency card electronically.

The app is available on both Apple's App Store and Google Play for the Android platform.

The app features the full range of emergency cards developed by HAEi and allows smartphone users to download them to their device. HAE Companion also links to contact information on ACARE centers (Angioedema Centers of Reference and Excellence) as well as HAE knowledgeable hospitals and physicians worldwide. Using Google Maps or Apple Map, the app indicates directions and distance to the nearest place.

Global Access Program

The HAEi Global Access Program (GAP) is available to offer access to HAE medications in countries where modern therapies are otherwise unavailable. This is the first program of its kind in HAE, and, we believe, the first time this type of program has been initiated by a patient organization.

HAEi is committed to securing access to HAE medications for patients across the globe. We are extremely proud to have established HAEi GAP with our current partners and will continue to work with other manufacturers with the hope of expanding the program in the future.

Website and social media

On our website – haei.org – you will find lots of useful information related to HAE, e.g., information about the disease and treatments, patient stories, a comprehensive resource center with links to magazines, clinical trial information, news and events etc.

Our website also contains information about our almost 100 member organizations around the world.

On social media you can stay up to date on HAE related news and join a closed Facebook group for people with HAE and their caregivers to network in a safe and closed environments:

- Facebook group: facebook.com/groups/HAEinternational
- Facebook page: facebook.com/haeinternational
- Instagram: instagram.com/hae_international
- Twitter: twitter.com/HAEDAY
- LinkedIn: linkedin.com/company/3363107

hae day :-) raising global awareness

Since 2012 we have celebrated **hae day :-)** every year on 16 May.

hae day :-) is a grassroots movement with our member organizations championing and using their creativity to raise HAE awareness.

hae day :-) unites the HAE community with 16 May as a focus for activities to raise awareness of HAE amongst the general public, healthcare professionals, healthcare decision-makers and industry representatives.

In past years our Global Walks have united people around the world to create awareness for HAE by walking and generating steps for HAE awareness.

In 2021 we celebrated the 10th **hae day :-)** with an extended activity campaign that included not only walking, but all kinds of physical or wellbeing activities. These were converted into steps that took us through each of our regions to visit all our member organizations.

You will find more information and inspiration on haeday.org.

Global Perspectives magazine

Published quarterly, HAEi's Global Perspectives magazine offers a comprehensive overview of just about everything that is going on in the world of HAE including inspirational articles featuring HAE patients, detailed information from our member organizations, ongoing clinical trials, and the latest news from industry.

You can find all issues of the Global Perspectives magazines on our website, haei.org.

HAE conferences and workshops

Through HAEi's conferences and workshops we bring people with HAE, caregivers, healthcare professionals and industry representatives together. These events provide participants with an HAE focused environment that facilitates sharing of knowledge, experiences and strategies for broadening access to and reimbursement of modern HAE treatments.

Due to the COVID-19 coronavirus pandemic the 2020 conference was successfully conducted virtually, and all presentations can be found on haei.org.

Also due to the COVID-19 pandemic our in-person regional workshops were transformed into virtual presentation events that you can also find on our website. All presentations are recorded in the native languages of the speakers and subtitled into the languages of the regions.

Youngsters' Community

The HAEi Youngsters' Community is for people with HAE and their caregivers, siblings and partners between the ages of 12 and 25.

The community is for all youngsters, whether they are newly diagnosed with HAE looking for more information and support, starting at a new school and would like to know of other people's experiences or moving to a new country and looking for new connections.

On the youngsters website parents can find a collection of activity books, coloring pages and resources for kids, developed by HAEi's member organizations around the world, to help introduce HAE in a fun and empowering way.

The HAEi Youngsters' Advisory Group comprises six (6) community members, all volunteering to oversee the direction and long-term objectives of the HAEi Youngsters' Community, promote the work of the community, carry out different projects and social media campaigns, and last but not least, act as the contact point between the HAEi Youngsters' Community and HAEi.

If you are interested in knowing more about the HAEi Youngsters' Community, you can visit their webpage at youngsters.haei.org.

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Read more on haei.org · March 2022