ANNENBERG CENTER FOR HEALTH SCIENCES
AT EISENHOWER
Imparting knowledge. Improving patient care.

EXPERT perspectives

How to Diagnose and Manage a Potentially Fatal Angioedema

Overview

Mark Riedl, MD, MS, discusses how to facilitate earlier identification of patients with hereditary angioedema (HAE) through key characteristics and triggers that differentiate it from other forms of angioedema.

Content Areas:

- Clinical presentation
- Diagnostic strategies
- Underlying causes and triggers for acute attacks
- On-demand, acute therapy
- Short- and long-term prophylactic treatments

Faculty

Marc Riedl, MD, MS
Professor of Medicine
Division of Rheumatology, Allergy & Immunology
Clinical Director
US HAEA Angioedema Center
University of California, San Diego
San Diego, California

Table of Contents

CE Information..... 2

How to Diagnose and Manage a Potentially Fatal Angioedema 3

This educational activity is supported by an independent medical educational grant from Shire.

Participate in interactive questions, download activity slides, and obtain your CE/CME credit online.
http://annenberg.net/medEd/5490/

CE/CME Information

Target Audience
This activity was developed for primary care physicians and other health care professionals who have an interest in angioedema.

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- List symptoms suggestive of hereditary angioedema (HAE)
- Explain steps to differentially diagnose HAE from other forms of angioedema
- Differentiate acute, on-demand therapies, long-term prophylaxis, and short-term prophylaxis for HAE
- Work with patients, caregivers, and/or other clinicians in order to provide optimal, individualized HAE management

Accreditation and Certification
The Annenberg Center for Health Sciences at Eisenhower is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Annenberg Center for Health Sciences at Eisenhower designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Disclosure Statement
It is the policy of the Annenberg Center for Health Sciences to ensure fair balance, independence, objectivity, and scientific rigor in all programming. All faculty and planners participating in sponsored programs are expected to identify and reference off-label product use and disclose any relationship with those supporting the activity or any others with products or services available within the scope of the topic being discussed in the educational presentation.

The Annenberg Center for Health Sciences assesses conflict of interest with its instructors, planners, managers, and other individuals who are in a position to control the content of CE/CME activities. All relevant conflicts of interest that are identified are thoroughly vetted by the Annenberg Center for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. The Annenberg Center is committed to providing its learners with high-quality CE/CME activities and related materials that promote improvements or quality in health care and not a specific proprietary business interest of a commercial interest.

In accordance with the Accreditation Council for Continuing Medical Education Standards, parallel documents from other accrediting bodies, and Annenberg Center for Health Sciences policy, the following disclosures has been made:

Marc Riedl, MD, MS

Research support:	Shire, CSL Behring, Pharming, BioCryst
Consultant:	Adverum, Arrowhead, BioCryst, CSL Behring, Shire, Pharming, KalVista
Speakers Bureau:	CSL Behring, Salix, Shire

The faculty for this activity has disclosed that there will be no discussion about the use of products for non-FDA approved applications.

Additional content planners
The following has no significant relationship to disclose:

Eve J. Wilson, PhD, ELS, CCMEP (medical writer)

Annenberg Center for Health Sciences
John Bayliss, VP, Business Development, spouse is an employee of Amgen, Inc; all other staff at the Annenberg Center for Health Sciences at Eisenhower have no relevant commercial relationships to disclose.

The ideas and opinions presented in this educational activity are those of the faculty and do not necessarily reflect the views of the Annenberg Center and/or its agents. As in all educational activities, we encourage practitioners to use their own judgment in treating and addressing the needs of each individual patient, taking into account that patient's unique clinical situation. The Annenberg Center disclaims all liability and cannot be held responsible for any problems that may arise from participating in this activity or following treatment recommendations presented.

This educational activity is supported by an independent medical educational grant from Shire.

This activity is an online enduring material. Successful completion is achieved by reading and/or viewing the material, reflecting on its implications in your practice, and completing the assessment component.

The estimated time to complete the activity is 1.0 hour.

This activity was originally released on January 31, 2017 and is eligible for credit through January 30, 2018.

Our Policy on Privacy
Annenberg Center for Health Sciences respects your privacy. We don't share information you give us, or have the need to share this information in the normal course of providing the services and information you may request. If there should be a need or request to share this information, we will do so only with your explicit permission. See Privacy Statement and other information at http://www.annenberg.net/privacy-policy/

Contact Information
For help or questions about this activity please contact Continuing Education:

ce@annenberg.net

Annenberg Center for Health Sciences
39000 Bob Hope Drive
Dinah Shore Building
Rancho Mirage, CA 92270
Phone 760-773-4500
Fax 760-773-4513
8 AM – 5 PM, Pacific Time, Monday – Friday

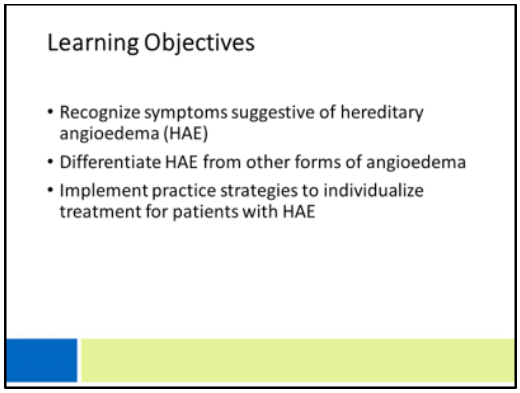
How to Diagnose and Manage a Potentially Fatal Angioedema

I'd like to welcome everyone to this educational webinar entitled "How to Diagnose and Manage a Potentially Fatal Angioedema."

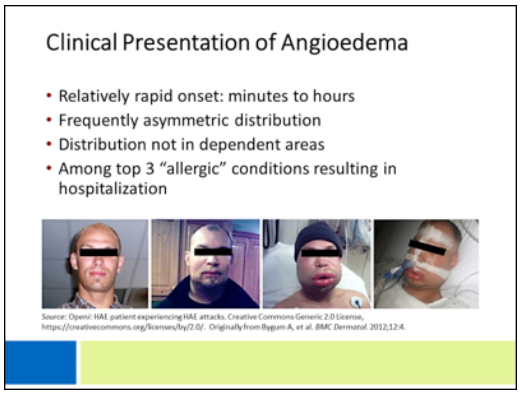
My name is Dr. Marc Riedl. I'm a professor of medicine and clinical director of the US HAEA Angioedema Center in the Division of Rheumatology, Allergy, and Immunology at the University of California at San Diego. I'll be guiding you through this educational program on angioedema today.

Listed here are my disclosures. You can review these for your reference.

The learning objectives of our program today are as follows. We will discuss the symptoms of hereditary angioedema (HAE) as a subtype of angioedema that's important not to miss in clinical practice. Beyond that, we'll also discuss some of the other forms of angioedema that are commonly seen in clinical practice and how to differentiate these other types of angioedema from the hereditary form. Then finally, we'll focus a bit on treatment strategies in clinical practice to improve care in the management of patients that suffer from HAE.

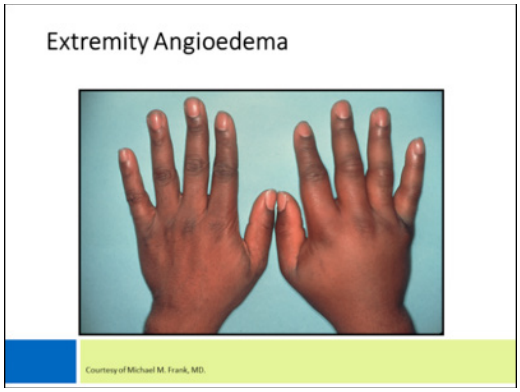


I'd like to begin broadly by discussing in general angioedema as a medical condition. I think this is something most of us in clinical practice recognize when we see the symptoms of swelling that are typical of angioedema. By way of review, recall that angioedema is a condition that has a relatively rapid onset. It begins and develops in patients over minutes to hours and typically has an asymmetrical distribution. Patients that have angioedema typically have swelling that is not in dependent areas. In contrast to edema from heart failure or liver or kidney disease, which tends to localize to the lower extremities, angioedema will often affect the face, the lips, the hands, or other parts of the body not dependent on gravity. In my specialty of allergy and immunology, this is among the top 3 so-called "allergic" conditions that result in emergency room visits and hospitalization—the other 2, of course, being anaphylaxis and severe asthma.



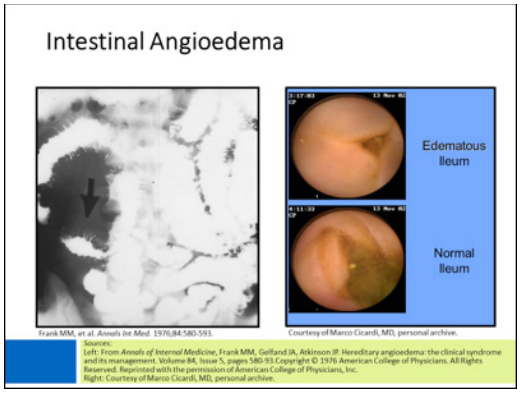
These next slides review the symptoms of angioedema that you may see as patients come through the office or the urgent care center. Of course, angioedema can affect the face and not only be very alarming and disfiguring, but also become quite dangerous if it affects the airway.

We see angioedema of the extremities, including the hands and feet. While this may not be life-threatening, it certainly can be disabling to patients who can't carry out their usual daily work activities or school activities.

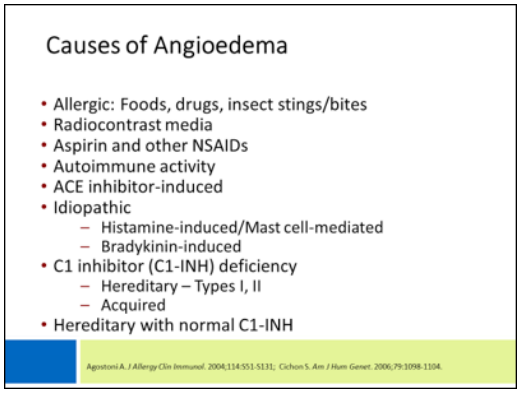


We also occasionally see angioedema of the gastrointestinal (GI) tract. Here we see, on the left, a contrast study with barium, showing spiculations of the small bowel, identified with the arrow. On the right is a capsule endoscopy that captures angioedema of the ileum. You can appreciate how much this obstructs the small bowel. It can function much like a bowel obstruction, with severe abdominal pain, vomiting, nausea, and so forth. While GI angioedema is not the most common manifestation, it's something for us to keep in mind as a possible symptom for these patients. We'll discuss this more as we focus in on the hereditary form of angioedema.

Listed here you see a differential diagnosis for underlying causes of angioedema. When we see patients with this type of swelling, we need to consider possible causes. At the top of this list are things that most people in health care are familiar with—certainly allergic causes from a certain food, or medication, or insect sting. We also are aware that there are a number of medications, including radiocontrast agents, nonsteroidal anti-inflammatory drugs (NSAIDs), and angiotensin-converting enzyme (ACE) inhibitors, which can cause angioedema. It's certainly prudent to look at the medication list for any patient that presents with angioedema symptoms.

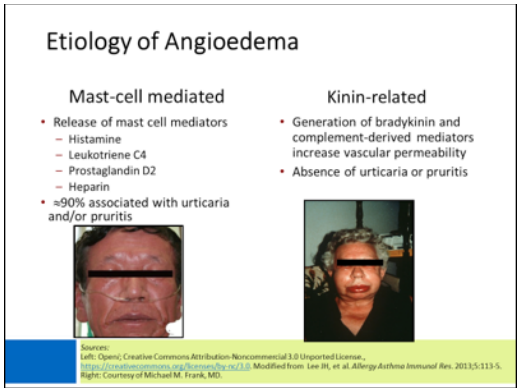


There are some indications that autoimmune conditions can be associated with angioedema. This is particularly relevant for patients that have urticaria as well as angioedema. As we know, there are some autoantibodies that can activate mast cells. Further down the list we see the idiopathic forms of angioedema. I'll be speaking about these in more detail in a moment. They can be broken into either histamine-mediated or bradykinin-mediated forms of swelling. Then we have the hereditary and acquired forms of C1 inhibitor (C1-INH) deficiency, which involves a very distinct pathophysiology that we'll spend some time discussing. Lastly, we have HAE with normal C1-INH, which currently is a poorly defined condition in terms of pathophysiology, but can present with very severe angioedema symptoms.

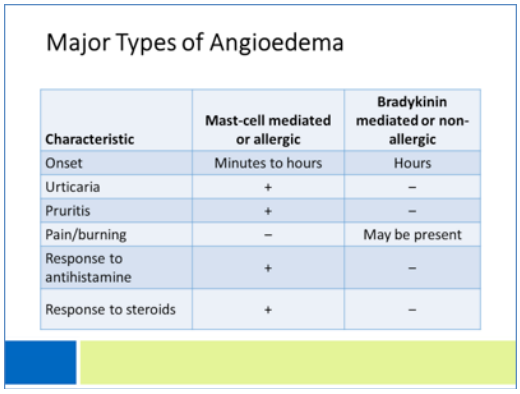


In terms of the underlying cause of the swelling or the angioedema, this is an important slide. This is one of the pearls I'd like for people to remember from this presentation. While the differential diagnosis is extremely important in trying to identify a root cause of angioedema symptoms, for patients who have recurrent angioedema, those conditions on a differential largely break down into one of these 2 buckets—either a mast cell-mediated condition or "allergic" angioedema; or a bradykinin-related swelling disorder. The pointers here, or the hints, are important.

We know that mast cell- or allergic-mediated angioedema is caused by histamine, leukotrienes, prostaglandins—substances that are released from mast cell activation. The majority of these episodes, about 90% or so, are associated with both hives and itching. In contrast, on the right side of this slide, you see the bradykinin-related angioedemas. These are caused by an entirely separate pathophysiology unrelated to allergy or to histamine; rather, they involve generation of bradykinin and possibly other complement-derived mediators. They have a similar effect of causing vascular permeability and therefore swelling, but they occur in the absence of any hives or itching symptoms. Again, in the clinical setting, this can be an important distinguishing factor. Does the patient have hives and itching associated with the angioedema or not? Because ultimately this will guide the list of the differential diagnoses, but, perhaps more importantly, the treatment that will be effective for these particular patients.

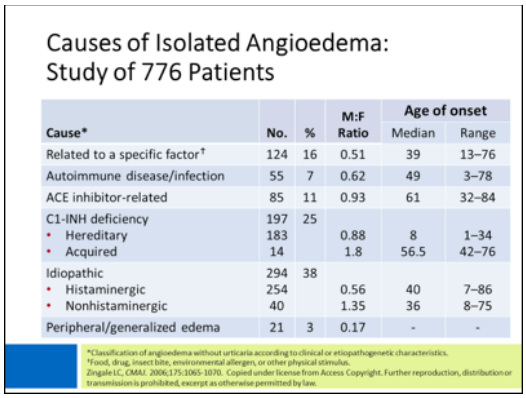


The photographs are just to point out that it's sometimes hard to know the difference just by looking at the patient. On the left is a gentleman with some facial swelling from a drug reaction. On the right is a photo of a woman with swelling associated with the hereditary form of angioedema. The left photo is a histamine-mediated problem; the right is a bradykinin-mediated problem. A physical exam may not always give you the hint. The clinical history becomes very important in distinguishing these 2 separate types of angioedema symptoms.



This table drives home that point. The mast cell or allergic angioedema has a relatively faster onset of minutes to hours, includes the presence of hives and itching, and typically responds readily to antihistamines and corticosteroids. In contrast, the bradykinin-mediated conditions, which have nothing to do with allergy or with mast cells or histamine, are typically slower moving, occurring over hours to sometimes days. Typically there are no hives or pruritus, and sometimes patients will describe their symptoms as painful and burning rather than itching. As we'll talk about, in more detail, the conditions that are bradykinin-mediated, including the hereditary form, are not responsive to antihistamines and corticosteroids. Taking a history of the symptoms, as well as identifying any previous treatments given and the patient's response to those treatments, are sometimes the best clues we have in terms of what tests to order and what management strategies are going to be useful.

Before we focus on the bradykinin-mediated conditions, I want to point out this epidemiological study, which drives home again the reason why it's important to consider hereditary and other kinin-mediated forms of angioedema. These are data from a study of the largest cohort of patients who presented with isolated angioedema; by that, I mean angioedema in the absence of hives or urticaria. If a patient presenting with angioedema has hives or urticaria, we assume they're in the histamine group and go down that path. If they don't have hives or urticaria, then we focus on evaluating for this isolated angioedema.



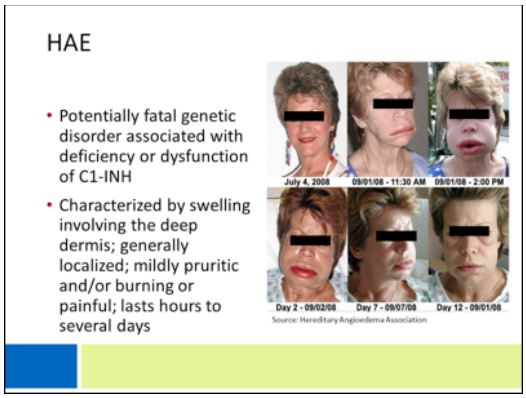
In this case series, which was from a large academic center in Italy, you can see that in a group of over 770 patients, the number one cause of isolated angioedema was unfortunately idiopathic—meaning that after an exhaustive evaluation, no specific underlying cause could be found. I'll point out that within the group, histaminergic angioedema was by far more common than was non-histaminergic angioedema. This is another important clinical pearl: if one cannot find the root of the problem through diagnostic testing, as seen for these idiopathic isolated angioedema patients, about 80% of the time histamine will be the underlying pathophysiology, and treating aggressively with antihistamines and corticosteroids and other histamine-targeted drugs, can be successful in improving the condition.

Beyond that, we see that the second most common cause, observed in about 25% of the cohort, was C1-INH deficiency. There are 2 types: the hereditary form, which we'll talk about in detail; and the acquired form, which is much less common than the hereditary form but is still an important cause of C1-INH deficiency that will show up on diagnostic testing, as we'll discuss further. In fact, behind the unknown cause, the C1-INH deficiency conditions are the second most common cause of isolated angioedema in this large patient population. This highlights the importance of considering a C1-INH deficiency as an important cause of angioedema from a diagnostic standpoint, and then of course for providing effective treatment.

Behind that, you see angioedema related to a specific factor, affecting 16%. These are the patients for whom an allergy to food, medication, an environmental allergen, or some other allergen causes isolated angioedema. Then you see ACE inhibitor-mediated angioedema, autoimmune- or infection-associated issues. Finally, there were people who didn't have angioedema; rather, they had peripheral edema. This included 3% on evaluation, and it is just something to keep in the back of our mind. The number one cause of isolated angioedema was idiopathic; number 2 was C1-INH deficiency; and number 3 was related to a specific allergen exposure.

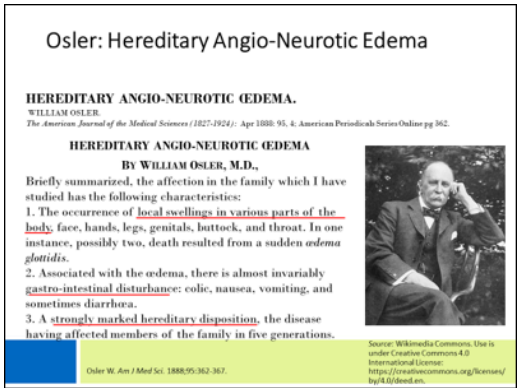
Let's shift gears a bit now and talk more about the hereditary form of angioedema. As we know, this is an important cause of isolated angioedema and has been often overlooked in the past, leading to lots of complications and diagnostic delays for this patient group. The hereditary form of angioedema, as the name suggests, is a genetic disorder. It's caused by a variety of potential mutations in the C1-INH gene, which sits on chromosome 11. We now know from the literature that over 300 different types of mutations that can occur in this gene. There are a variety of things that can go wrong. All of these mutations lead to either a low C1-INH level or a low C1-INH function.

I'll show you the pathophysiologic pathway in a moment, but the upshot is that missing this protein leads to dysregulation of the kallikrein-bradykinin system. Overproduction of bradykinin causes the symptoms you see here—this fairly severe, localized swelling that happens in a recurrent fashion and can affect the skin at any location on the body, or the airway or GI tract.

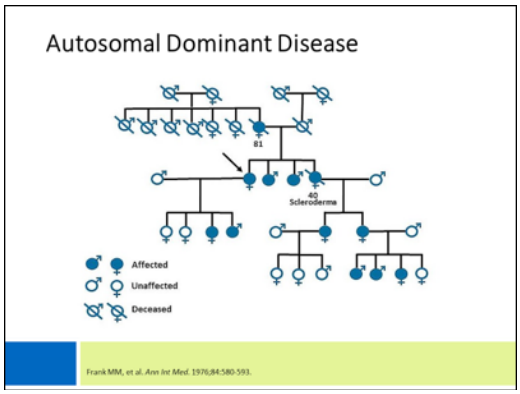


You'll notice if you look at the time stamps on this photo of a woman with HAE that the condition typically evolves over days. This is a fairly protracted course, represented by photos taken over about 12 days. Most patients will have symptoms that run over 3 to 7 days. The point is that this swelling disorder is transient for most. These episodes are protracted compared to the allergic type of angioedema, which typically lasts for a day or 2 at a time. As mentioned, HAE episodes occur in the absence of hives and the absence of itching, and can be quite dangerous if the swelling is severe.

HAE is not a new condition. It was described as early as the 1880s. In fact, in 1888, you see this very detailed description published by Sir William Osler, who we all know as one of the titans of modern medicine. But among his many contributions was his recognition of the hereditary form of angioedema. He termed it "angioneurotic edema." We don't use this term much anymore, because it suggests that there's some neurosis or psychiatric issue at play. Even so, he got the description exactly correct. You see that he described these local swellings of the skin, including the face, hands, legs, genitals, buttocks, and throat. He described the potentially fatal episodes that would cause asphyxiation due to swelling of the throat. He described GI swelling with nausea, vomiting, and diarrhea, and severe abdominal pain.

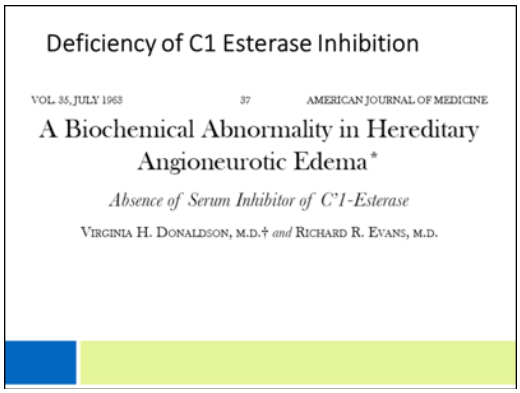


He was probably the first, we think, to describe the hereditary component of this disorder, as he talked with families and patients and drew out pedigrees that demonstrated its genetic basis.

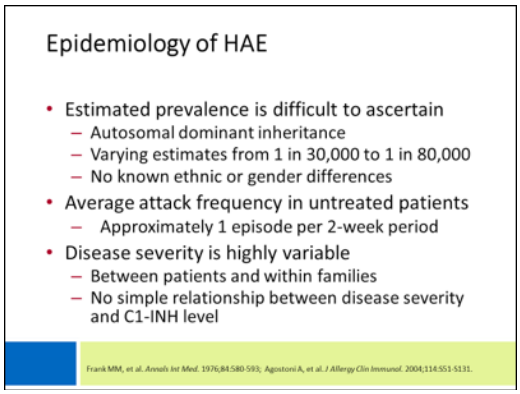


Here's one of the pedigrees that shows HAE is an autosomal dominant condition. That's borne out by the fact that, as you see in this pedigree, HAE does not skip generations. There's a 50/50 chance that each child will have the condition if they have one affected parent. If they don't get the autosomal dominant gene, then of course there's no chance of passing it along to the next generation. But you also see that it affects both males and females equally. This, of course, is one of the hallmarks of an autosomal dominant condition—one that is passed from generation to generation with equal gender distribution.

The underlying pathophysiology of HAE was really not understood until about 80 years later. Osler described the hereditary component and the symptoms, but it wasn't until the 1960s that a couple of groups—including Virginia Donaldson and colleagues at the University of Cincinnati and Nathaniel Landerman's group at [Walter Reed]—discovered almost simultaneously that people with this hereditary swelling disorder were missing a protein, the serum C1 esterase inhibitor. The understanding of C1-INH deficiency and the role it plays in the body has been critical, of course, to both diagnosing and also developing treatments for people affected by HAE.



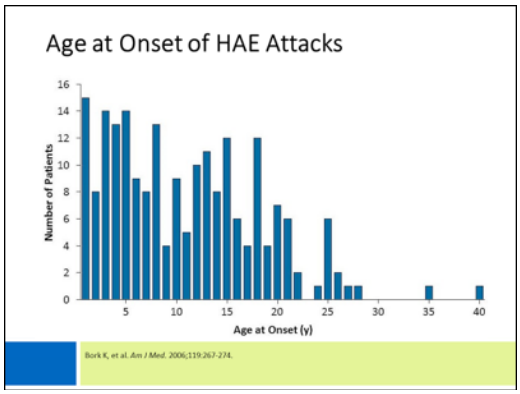
In terms of the epidemiology, we don't know the exact prevalence of HAE, but certainly it's a fairly rare condition. The best data we have suggest that the prevalence is between 1 in 50,000 to 1 in 60,000, but of course, not being certain, you see the numbers here are 1 in 30,000 to 1 in 80,000. That's a very reasonable estimate. As mentioned, there are no gender differences, and to date no ethnic differences have been identified. HAE has been found around the globe in pretty much every country where testing exists for it.



The symptoms themselves are highly variable. We know from large studies that, on average, a patient with C1-INH deficiency suffers an angioedema episode about once every 2 weeks. That said, there's tremendous variability from person to person. In fact, in family studies and even in identical twin studies with HAE, people may have with the exact same genetic mutation, or even the exact same genetic makeup in the case of identical twins, and have widely variable HAE symptoms. You may have a family member that swells once a week and another member of the same family who swells 1 or 2 times per year.

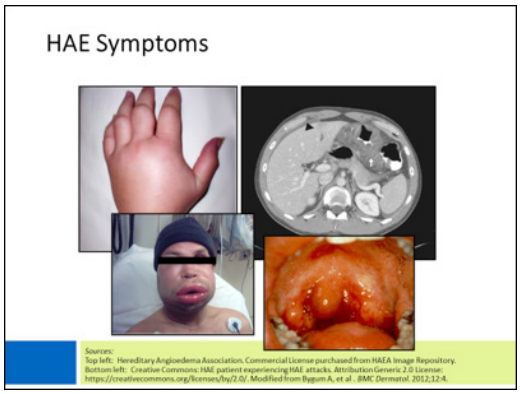
There's a lot we don't understand about the variability of symptoms or the phenotype. Nevertheless, as we talk about treatment, it's important to remember that there's a lot of variability in terms of the types of swelling, the frequency of swelling, and the severity of these attacks, from person to person. In fact, if you follow patients over time, their symptoms may vary from one year to the next. They may have periods of high attack frequency followed by other periods where their condition is relatively quiescent. This is one of the challenges in HAE: tailoring the treatment to match the patient's symptoms and symptom disability, and of course, changing treatment over time as required.

HAE as a genetic condition typically shows up during the pediatric years. As you can see from this chart, most patients will have symptoms during childhood. However, quite often these childhood symptoms are mild, and patients or families will not recognize this as HAE. Symptoms are often attributed to food allergy or traumatic injuries, with swelling of the limbs and the face. But most patients will have symptoms during their childhood or teenage years. It's very common for symptoms to worsen during the adolescent years, which typically has been attributed to hormonal changes that occur during puberty. This is probably most dramatic for women, because estrogens seem to exacerbate HAE symptoms due to their effects on the kallikrein-bradykinin system.



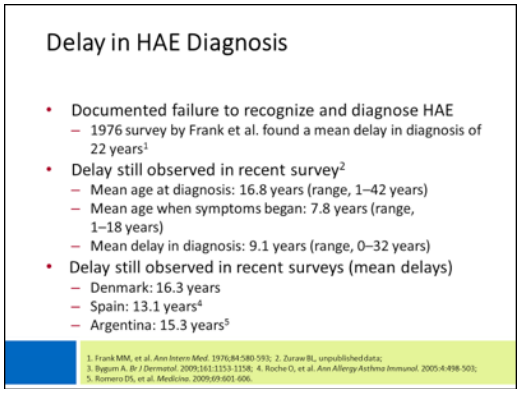
As you get up into the older age groups, it's unusual, but possible, for patients with HAE to have their first symptoms in their 30s or even around age 40 years. After age 40, if people have symptoms suggestive of HAE, we become more concerned about the acquired form of C1-INH deficiency. Often, if testing shows C1-INH deficiency at a later age, with new onset symptoms, we will look for causes of C1- inhibitor consumption, such as lymphoproliferative disease.

We looked at symptoms previously. This is just a reminder that we see various types of angioedema in the hereditary form, including the skin swelling, facial swelling, GI symptoms, as well as airway symptoms. Of course the airway symptoms are most concerning, because they can lead to fatality due to asphyxiation.



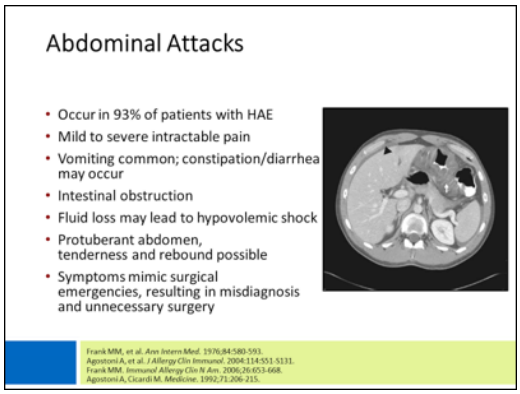
One of the reasons that we do these educational programs is because there's a tremendous delay in the diagnosis of HAE. Years ago, in the 1970s, Michael Frank, at the National Institutes of Health, demonstrated this problem. Then, it took about 22 years on average for a patient to be diagnosed. You could imagine a patient having recurrent swelling, going to numerous specialists and hospitals, and being misdiagnosed or undiagnosed for a long period, and unfortunately having lots of complications, and even dying from this type of swelling, without proper recognition. There have been many educational efforts in recent years, including this one. Some of that has been driven by the fact that we have effective therapies now, which we'll talk about in a moment.

But even in a very recent survey, we see that in the United States, the mean delay in diagnosis is about 9 years, with some patients taking much longer to get a correct diagnosis. This is not unique to the United States. Around the globe, in various countries, we see similar types of delays. Again, the point is that if we see isolated swelling and the absence of hives, we should be at least considering the possibility of HAE and obtaining a diagnostic test to try to prevent delays and the complications that occur when people with HAE are misdiagnosed or mismanaged.

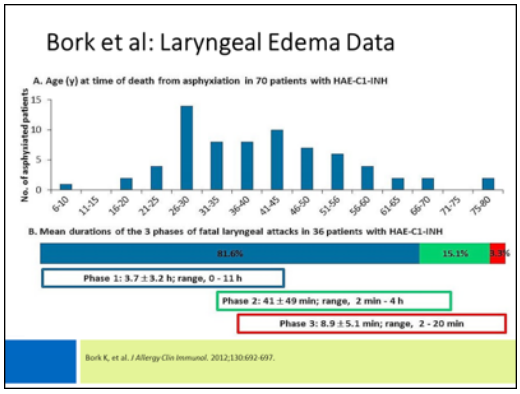


This is just at reminder of how HAE affects patients, to bring us back to the clinical realm. Extremity swelling or skin swelling is the most common manifestation of HAE, as it is with most other angioedema conditions. As mentioned, this is not a life-threatening symptom, but when the hands or feet are affected it's very disabling. Nearly 100% of HAE patients will have some form of skin swelling during the course of their condition. This is the number one symptom that we see—cutaneous swelling that often affects the extremities.

The second most common symptom is swelling in the GI, usually involving the small bowel, although really any part of the GI tract could be affected. More than 90% of patients with HAE have GI attacks. Thus, if you see a patient with cutaneous swelling, an important clinical question to ask is whether he or she has unexplained and recurrent abdominal pain. Linking those 2 symptoms is often a very strong clue that HAE should be high on the list of diagnostic possibilities. Abdominal pain is often very severe; so severe, in fact, that many patients historically have been taken to the operating room for exploratory laparotomies, appendectomies, cholecystectomies, and so forth, with of course the concern that there's a surgical emergency going on due to the severity of the pain. However, upon surgical exploration, often little is found; you'll see some swelling of the bowel that's causing the pain. Symptomatically, these patients frequently have vomiting and occasionally diarrhea. In rare cases, enough fluid can leak into the bowel to cause hypovolemic shock. There are cases of patients ending up in the intensive care unit with hypotension requiring very large amounts of intravenous (IV) fluids to reverse this hypovolemic shock.

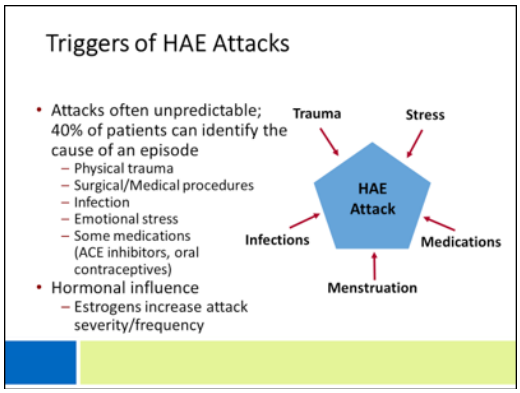


The least common type of swelling is laryngeal or airway angioedema. The data that we have available suggest that about half of HAE patients will experience airway angioedema during their lifetime. In some ways, that's good news. However, the bad news is that it can frequently be fatal if not recognized and treated appropriately.



What you see here is a case series published by Konrad Bork, who runs a very large center in Germany. This series included 70 patients who died from HAE due to C1-INH deficiency. Dr. Bork made an effort to learn from these tragic events. You can see that most of the patients were relatively young, between ages 25–50 years. The course of airway swelling takes several hours to cause major problems. The blue bar at the bottom of the figure represents the first phase of the swelling. The first phase is associated with a feeling of fullness in the throat, sometimes swallowing difficulties and changes in the vocal quality, but no respiratory distress at this point. These are early symptoms of laryngeal swelling, and it's somewhere between 3 and 4 hours before progression beyond this point. We look at this first phase as an opportunity to get patients treated effectively, to get medical attention, and prevent progression of the symptoms. We'll talk about some of those interventions in a moment.

Phase 2 is when patients start to have respiratory distress and difficulty breathing. You can see this is a much shorter phase, lasting about 40 to 45 minutes, before patients progress to phase 3. Phase 3, unfortunately, is loss of consciousness. Not surprisingly, by the time people lose consciousness, only about 8 to 10 minutes remain before the situation becomes fatal. So, most of the time, for laryngeal angioedema is in the early phase and involves symptoms of swallowing difficulty, fullness in the throat, and so forth. We ask patients to pay attention and recognize these symptoms so that effective treatment can be given to prevent the tragic event of death due to HAE. Unfortunately, fatalities still happen; we hear of at least a couple of deaths each year in the United States that should be completely preventable with good diagnostic and therapeutic approaches.

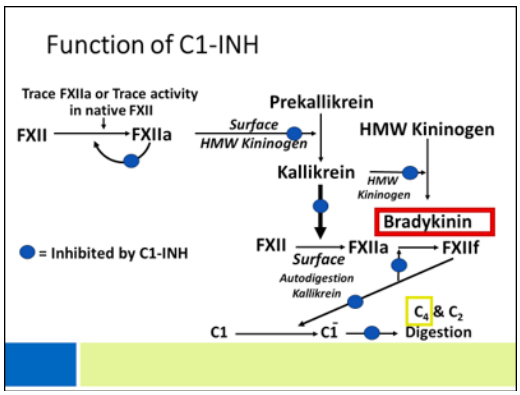


HAE attacks are quite often unpredictable. This presents another real challenge for people living with this condition: they cannot anticipate, generally, when a swelling episode will occur. Here you see some triggers listed. Maybe about 40% of patients, based on studies, will be able to identify a trigger for any given angioedema episode. But that still leaves the majority as unpredictable. So we have to prepare patients to treat these attacks at any place and any time. This is one of the management challenges we'll cover in a moment.

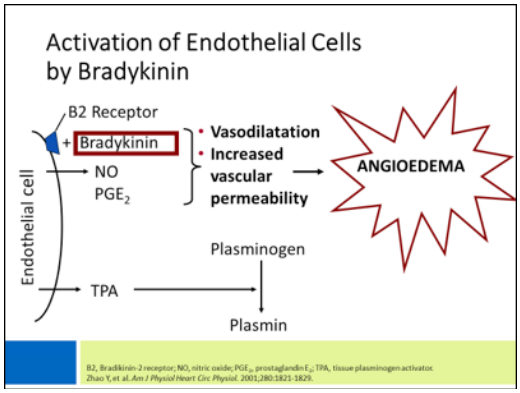
In terms of triggers, though, and counseling patients, we know that physical trauma, including surgical or dental procedures, can instigate these attacks. We have preventive medication that can be used if patients will be undergoing surgical procedures, including anything requiring general anesthesia with intubation, which can trigger airway swelling, but also dental work. Any sort of invasive dental work or oral surgery can cause airway issues, so we pretreat patients with prophylactic medications, generally. Infections are also triggers, and often unpreventable; sometimes respiratory or GI infections will trigger attacks.

Some medications can trigger attacks. I mentioned ACE inhibitors early on as a cause of angioedema, even in patients without C1-INH deficiency. But in the HAE population, ACE inhibitors can cause tremendous exacerbations. We avoid use of ACE inhibitors in patients with HAE, as well as any estrogen-containing medication, which are mostly oral contraceptive drugs. In women, more often than not, exogenous estrogen will exacerbate swelling symptoms, and so, again, these are relatively contraindicated in the HAE population.

I want to go back. I skipped over here emotional stress. I told you earlier that Sir William Osler called this angioneurotic edema. While this is a biochemical disorder, a C1-INH deficiency, it is quite accurate that in some patients psychological or mental stress will cause worsening of their symptoms. We're currently just beginning to figure out the biology, but it does appear that the sympathetic nervous system and the immune system can release heat shock proteins, neuropeptides, and cytokines that activate the contact system. It is likely there is a biochemical reason why psychological stress will exacerbate HAE, but that remains to be defined at this point. I mentioned already the estrogen influence; we have to be careful about using estrogens in women with HAE.



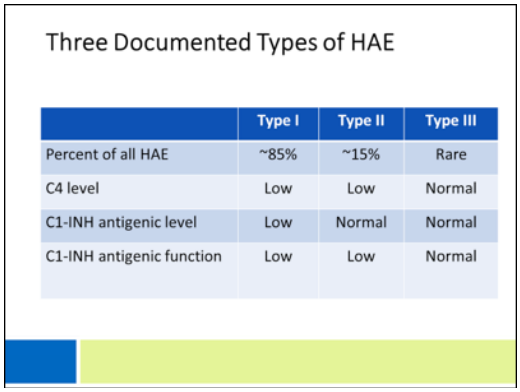
This figure shows the pathophysiology that leads to HAE. The blue dots represent inhibitory activity by the C1-INH protein. Its most important functions, for HAE, are blockade of factor XII, specifically factor XIIa, and also inhibition of kallikrein. Kallikrein is responsible for producing bradykinin from high molecular-weight kininogen. If you're missing this C1-INH protein, which has a number of inhibitory functions, but, most importantly, you lack the brakes on kallikrein and factor XII production. Because of that, you overproduce bradykinin. Bradykinin is ultimately the mediator that causes vascular leakage and the escape of fluid out of the capillaries, the tiny vasculature, into the subcutaneous tissues or the submucosal tissues, leading to swelling and symptoms of angioedema.



You'll note also in this figure that C1-INH, not surprisingly, also inhibits complement component C1. That's how it got its name; it was the original function of the protein. C1 inhibition, it turns out, is probably not important for the swelling that we see in patients with HAE. But it is still useful, because if you lack inhibition of C1 you digest C4 at a very rapid rate. As I'll show in a moment, C4 levels are low in patients that are missing C1-INH. We can use that to our advantage as a useful screening test to diagnose these patients, because the vast majority of them will have continuously low C4 levels, regardless of whether they have angioedema symptoms.

Bradykinin, as I mentioned, is overproduced in patients with C1-INH deficiency. The problem is that bradykinin binds to the B2 receptor. This leads to endothelial cell dysfunction and the vasodilation and vascular permeability that cause angioedema. Again, at the end of the day, it's bradykinin that leads to the swelling. Just to reiterate, antihistamines and corticosteroids have no influence on the bradykinin pathway. You can give patients having an angioedema episode lots of allergy drugs, including epinephrine, and have little-to-no effect on their symptoms. Very specific agents, directed at this kallikrein-bradykinin pathway, are needed to have any clinical benefit. We'll review those momentarily.

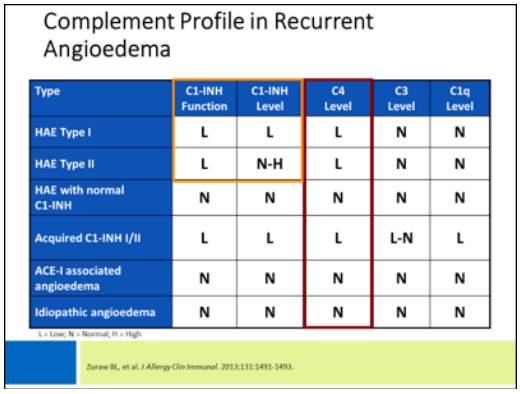
We've talked about the symptoms and the pathophysiology. Just a reminder, there are 3 subtypes of HAE. They all look very similar in the clinical setting, especially types I and II, meaning that in most cases you can't tell the difference by looking at the patient or getting a history. But both of type I and type II HAE are caused by a deficiency in C1-INH protein. Most patients don't make enough C1-INH protein, meaning that both the levels and the function of that protein are low when measured in blood work. Also, as I mentioned, C4 levels are very useful, because in about 85 to 90% of patients you will see a low C4 level regardless of whether they're having angioedema symptoms.



A small group of patients with type I or type II HAE have normal C4 levels when they're asymptomatic, probably about 10 to 15%. But invariably, C4 levels will drop when they have angioedema symptoms. When in doubt, we measure either C4 level when patient is symptomatic or we proceed to measuring C1-INH level and function, which will always be low, as shown in this table, regardless of any angioedema symptoms.

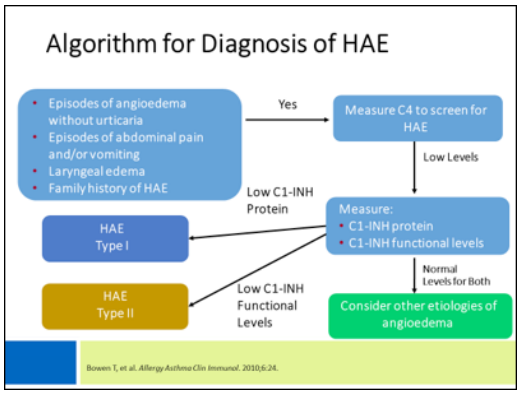
Type III HAE is also known as HAE with normal C1-INH. This is a very rare condition. It appears to be much rarer than type I or type II. These are patients, largely women, who have clinical symptoms that are very similar to those I've described for HAE, but have entirely normal lab testing when we look at their C4 and their C1-INH results. We don't have a good diagnostic test for these patients; in fact, we have a poor understanding of why they swell. But we believe type III HAE is a bradykinin-mediated angioedema, based on its response to some of the bradykinin-targeted medications.

This table may be helpful in clinical practice. It's a bit busy, but the point is that C4 level is a useful screening test. It will distinguish type I from type II HAE, as well as acquired C1-INH deficiency from some of the other subtypes we've talked about, including the idiopathic or ACE inhibitor-associated angioedema. Then the confirmatory testing is the C1-INH level and function, which, again, based on the pattern you see, will diagnose either a type I or type II HAE. C1-INH levels and function will also be low in the rare, acquired form that shows up usually in older adults and most often with lymphoproliferative diseases.



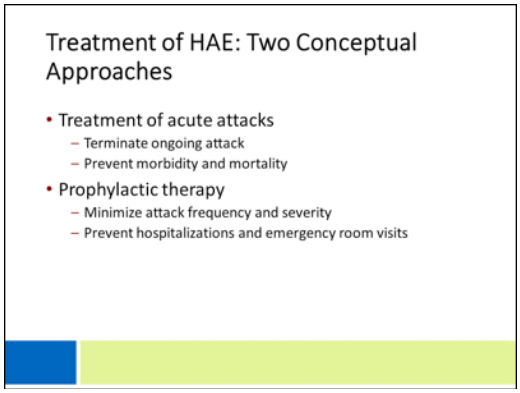
C3 levels are generally normal in angioedema conditions. C1q levels will be normal in patients with the hereditary form, but often low in those with the acquired form of C1-INH deficiency. Assessment of C1q is another useful tool if it's not clear whether you're dealing with hereditary or acquired C1-INH deficiency; it can often differentiate between the 2 conditions. Genetic testing is another way to differentiate. The C1-INH gene can be sequenced, and patients with the hereditary form of angioedema will have a mutation, but those with acquired C1-INH deficiency will not.

To recap the diagnostic workup, again, the most important thing is to consider HAE as a cause of recurrent angioedema. We've been over this. Usually it presents as angioedema without urticaria, often with some episodes of abdominal pain mixed in. Laryngeal edema is often the most dramatic presentation. I wasn't explicit about this, but most patients have a family history of HAE. However, family history is not required for a diagnosis. In fact, about 25% of patients with HAE will be the first in their family to have the condition due to a de novo mutation. Usually, taking the family history is very helpful if you get a story of angioedema. You need to consider the hereditary form. But occasionally there are patients who have C1-INH deficiency and no family history due to a spontaneous mutation that occurs and can then be passed on in an autosomal dominant fashion.

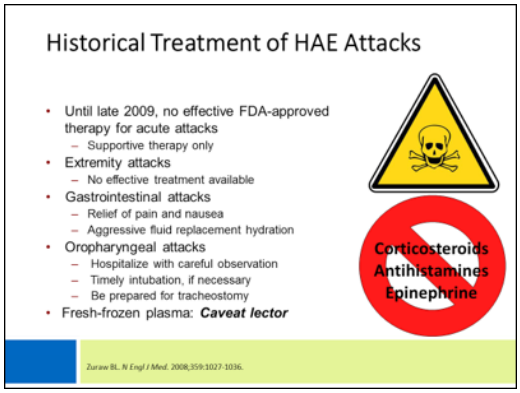


If you have a clinical suspicion based on these factors, assessing C4 level is not perfect, but it is an excellent screening test. A low C4 level would give impetus to move on to C1-INH testing, for both level and function. That will confirm type I or type II HAE. If C4 level and C1-INH level and function tests are normal, then one has to move on and consider other causes of angioedema.

For the last portion of this program, let's shift gears and talk a bit about treatment of HAE. To frame the discussion, I'll mention that 2 strategies are used to manage HAE. There's acute treatment, which involves giving a medication at the time of the swelling attack. Of course, this aims to stop the attack as quickly as possible and prevent complications. Then there's a prophylactic approach, which means giving a medication on a regular basis, even in an asymptomatic patient, to try to prevent attacks from occurring, or at least reduce the frequency and severity of the episodes. We'll talk a little bit about the options out there in regard to these 2 treatment approaches.



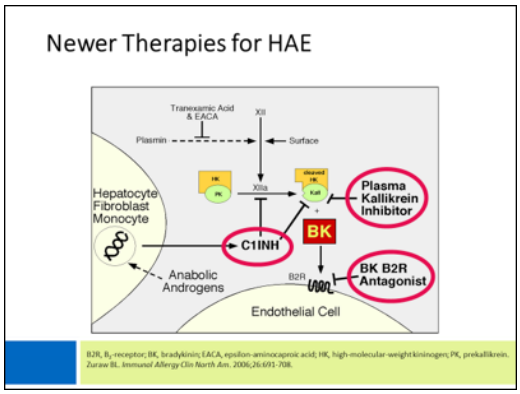
For context, I should mention that we've had effective HAE treatments for only a few years. In fact, going back 2009 or earlier, we had no US Food and Drug Administration (FDA)-approved HAE-specific medications to treat acute attacks of HAE. We were stuck with just supporting patients as best we could. We would give pain medications for severe abdominal pain and IV fluids for fluid replacement. For airway attacks, we would hospitalize patients and perform intubation or even tracheostomy if the attacks were severe enough to cause asphyxiation. Now, we're in a new era of treating HAE, with a number of effective medications, and we have moved on from this history of having few effective treatments.

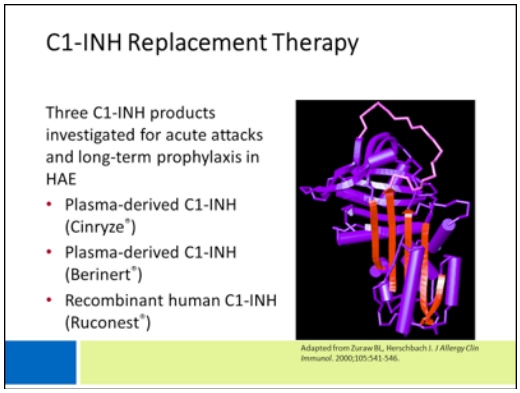


Historically, we treated HAE attacks with fresh frozen plasma (FFP). The efficacy of this approach has never been proven in controlled studies, but there are case series showing that it appears to be beneficial in many patients if they lack access to specific, proven HAE medications. The warning with FFP is that in some cases it can cause worsening of HAE symptoms. This is because the plasma products contain substrates that can create more bradykinin, rather than shutting off the bradykinin system, as we do with the more specific HAE drugs.

Just one more reminder—HAE is not an allergic condition. It's not caused by histamine or mast cell activity, and so there's really no role for corticosteroids or antihistamines in managing HAE. They're simply ineffective, and steroids will cause side effects without rendering any benefit. Epinephrine also is generally ineffective for HAE. Certainly one would never be faulted for trying epinephrine in a patient who has airway swelling and is at risk for asphyxiation. But generally speaking, epinephrine will not provide any dramatic effects and should not be relied upon to treat airway swelling caused by HAE.

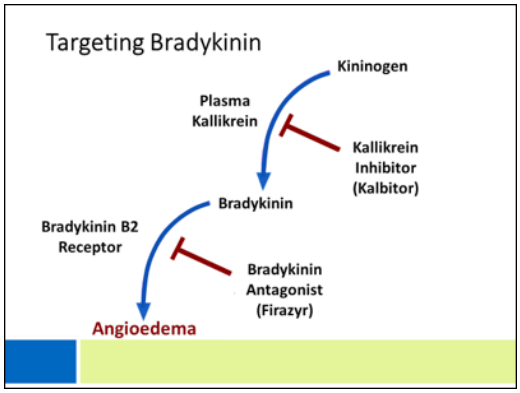
The medications that we now have, that have been proven effective to treat HAE, are based on the pathophysiology we've reviewed. There are 3 basic strategies for shutting off the dysregulation of bradykinin. We can replace the missing C1-INH protein or use a very specific plasma kallikrein inhibitor, which blocks the activity of kallikrein and thereby shuts off bradykinin production. Or we can block the effects of bradykinin on the vasculature and endothelial cells using a very specific bradykinin receptor antagonist. I'll briefly review these medications so you're familiar with them and can envision how we incorporate them into practice.



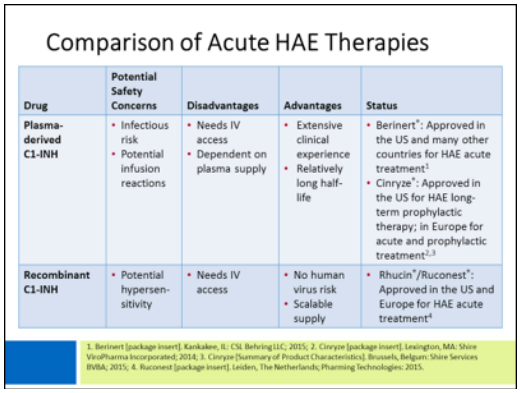


C1-INH replacement therapy is currently available in 3 varieties. There are 2 plasma-derived C1-INH concentrates. Their trade names are Cinryze, which was been studied and FDA-approved for prophylactic treatment, and Berinert, which has been studied and FDA-approved for acute treatment of HAE attacks. Then there's a recombinant C1-INH concentrate—so, not plasma-derived—which has the same inhibitory properties as the plasma-derived C1-INHs, and its trade name is Ruconest. This medication has also been studied and FDA-approved for the treatment of acute attacks of HAE.

There are other synthetic drugs, as listed here. We have a kallikrein inhibitor, ecallantide (trade name Kalbitor) which is a targeted drug that shuts off plasma kallikrein activity and thereby stops bradykinin production. We have a bradykinin receptor antagonist, icatibant (trade name Firazyr), which blocks the effects of bradykinin on that B2 receptor and prevents the vascular leakage that occurs with B2 activation. Both of these are FDA-approved for the acute treatment of HAE angioedema attacks.

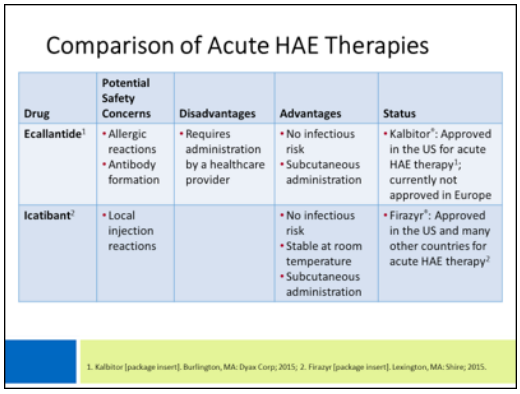


We have a couple of tables here to compare and contrast some of the features of these medications. Of course, all drugs have potential side effects and safety concerns that must be taken into consideration when discussing options with patients. For the plasma-derived C1-INH products, there's always a theoretical risk of infection. These products have been quite safe in recent years. But because they are blood products, we always have to be aware of possible infectious risks and also infusion reactions. The recombinant C1-INH product is free of these concerns, but there have been rare allergic reactions, and so we certainly counsel patients about this possibility.



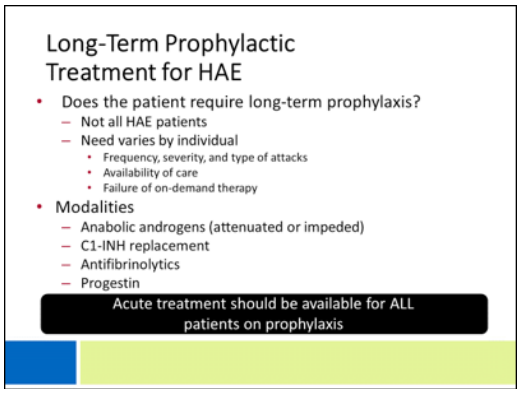
The C1-INH products are all currently given IV, so that's a potential disadvantage—you must have IV access. But we have extensive experience with the plasma products. Many practitioners and patients are comfortable with the safety data we have available. Recombinant C1-INH is a relatively newer product, but also so far it has an excellent safety record.

The synthetic products, ecallantide and icatibant, are given subcutaneously. This is a potential advantage, in that they don't require IV access. Use of ecallantide has been complicated by a low but real risk of anaphylaxis, which occurs about 3 to 4% of patients. Because of that, it must be administered by a health care provider. Icatibant can be self-administered, but may cause painful local injection-site reactions, including swelling, burning, and discomfort. We have to counsel patients to be aware of this possible adverse effect. Again, both of these agents are synthetic, so there is no theoretical infectious risk, as seen with the plasma-derived products.



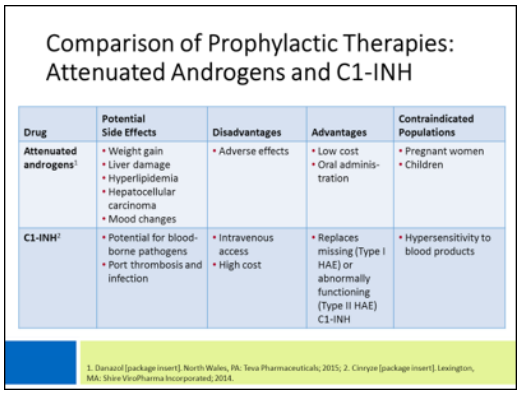
In terms of long-term prophylaxis, most of the drugs I just mentioned—4 of the 5 drugs—are used for acute treatment. One of the cornerstones of HAE management, which I want to be sure is clear, is that all patients need access to an acute treatment. Much like a patient with a food allergy, for whom we're uncertain when the next attack may occur, HAE attacks are unpredictable. Every patient diagnosed with HAE needs access to one of the acute treatments. Again, we have 4 of those to choose from. Each patient should have acute access to a drug that can terminate an attack of angioedema.

The other approach we often use is long-term prophylaxis. We use this selectively in patients. Not every patient with HAE will require a long-term prophylactic medication, but certainly many patients will benefit from it. We have to discuss with each patient their particular needs regarding the frequency of attacks, the types and severity of attacks, the complications they've experienced, and their comfort level with using an on-demand therapy alone. For prophylactic treatment, we have a few choices, but most patients currently will choose either attenuated androgens or C1-INH replacement infusions. Antifibrinolytics represent another, less effective option. These include as tranexamic acid or aminocaproic acid. In a subset of women with HAE, oral progestin may be helpful in preventing attacks. But efficacy data suggest that androgens and C1-INH replacement are the most effective options for long-term prophylaxis.



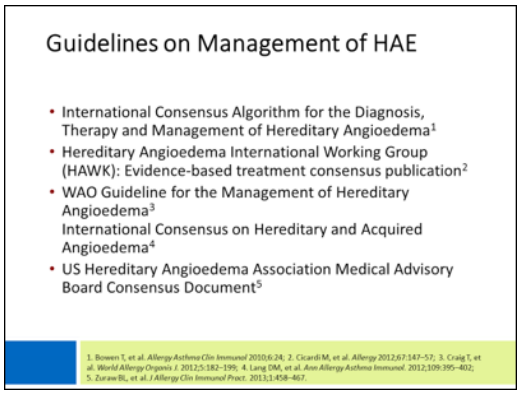
To reiterate the importance of acute treatment, even patients who are on long-term prophylaxis should have an acute treatment available, because none of the long-term prophylactic options have been proven to be 100% effective. There's always a risk for a serious, breakthrough angioedema attack.

As I mentioned, most patients will choose between attenuated androgens and C1-INH replacement for long-term prophylaxis. The androgen therapies, such as danazol, have been around for many years. In fact, for years they were the only treatment available in the United States for treating or preventing HAE attacks. Historically, many patients have used these agents, but unfortunately we've seen a high rate of side effects. You see some of these listed in the table. They include serious complications, such as hepatotoxicity, hyperlipidemia, and even, in some cases, hepatocellular carcinoma. Many patients report weight gain, hypertension, and psychiatric effects as side effects of attenuated androgen therapy. As you can imagine, attenuated androgens are incredibly difficult for female patients to take, given that they have virilizing effects. While they are oral drugs, and are relatively simple to take from a logistical standpoint, they can have many serious long-term side effects. There has been a shift away from androgens in recent years, given the morbidity associated with side effects.

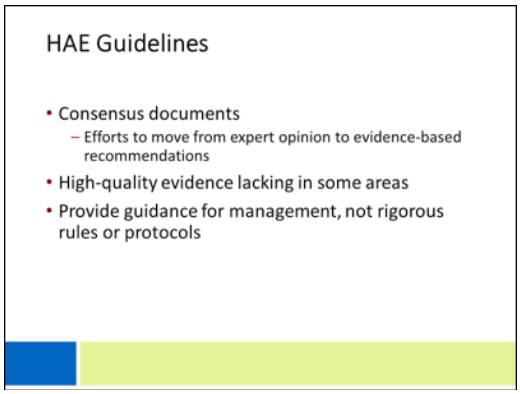


C1-INH replacement therapy is a newer option. C1-INH concentrate is a plasma-derived product given as an infusion. Cinryze is FDA-approved for this indication. It can be very effective, but it requires twice-weekly infusions, and the need for IV access can lead to difficulties over time. Some patients develop access issues. Port placement is sometimes complicated by thrombotic or infectious complications. Generally we try to avoid placing ports in patients just for prophylactic C1-INH therapy. Nevertheless, this treatment strategy has been a very successful and useful for patients who are more severely affected by HAE and require long-term prophylaxis.

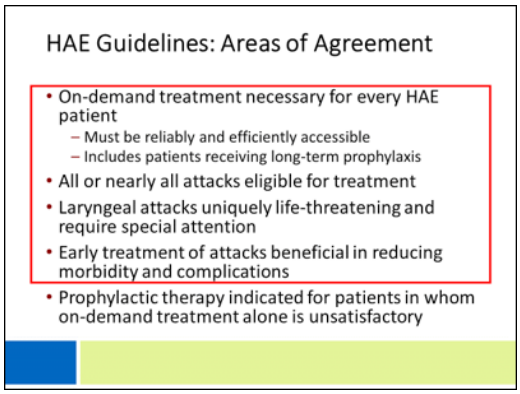
We have these approaches: acute treatment and long-term prophylactic treatment. How do we put these together to create a meaningful and beneficial plan for individual patients? Several evidence-based guidelines have been published. These are listed here, and they're used as references nationally and globally. Guideline developers reviewed the literature and the evidence, and put together some guiding principles for HAE management.



There are several documents that we can look to for guidance. However, they mostly say the same thing. Of course, they are an effort to move HAE treatment toward evidence-based management. We do have high quality data in some areas, which I'll mention to you. But we also recognize that these are guidance documents. They're not intended to dictate rigorous rules or protocols, because we know that each patient has individual symptoms and needs, and we have to tailor guideline recommendations to meet each patient's requirements.

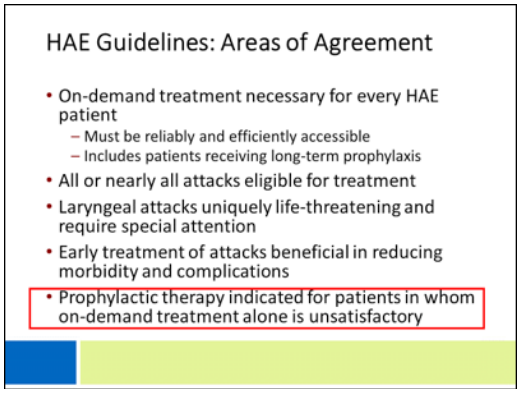


The high points of these documents, the guiding principles, are as follows. The guidelines all agree that on-demand treatment is necessary for every patient with HAE. As I mentioned, each patient affected by this condition must have on-demand access to treatment available. Treatment should be reliably and efficiently available. As I mentioned before, the need for on-demand access includes patients who elect to go on long-term prophylaxis. With regard to use of on-demand medication, the guidelines say that all—or nearly all—attacks are eligible for treatment, including not only airway attacks and GI attacks, but also those cutaneous attacks that we've discussed, based on high-quality evidence showing the disability associated with skin swelling, even if it is not life-threatening. Patients should consider treatment for any attacks that have the potential for disability.

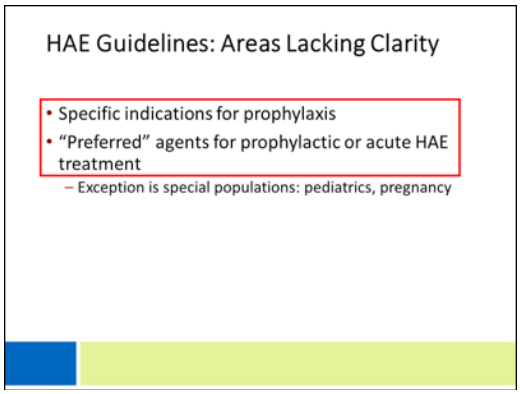


Laryngeal attacks are uniquely life-threatening; I think we all recognize that. Thus, the guidelines state that patients with airway attacks should be seen in the health care setting, preferably in the emergency department, so that effective treatment can be given, but also so that the airway can be maintained quickly if decompensation occurs. Early treatment of attacks is beneficial in reducing morbidity and complications. Again, a number of studies in the literature now show that treating these swelling attacks soon after onset reduces complications, reduces duration of disability, and in some instances reduces the amount of medicine needed to relieve the symptoms. So we encourage treatment early on, once the attack is recognized, rather than waiting until the attack has become severe.

Finally, the guidelines agree that prophylactic therapy is indicated when on-demand treatment alone is unsatisfactory. This recommendation is purposefully vague; we don't have rigid criteria for use of long-term prophylaxis, but we should use it selectively in patients that continue to struggle despite having access to on-demand treatment. We have recommendations from the guidelines in these areas, both with acute treatment and for prophylactic therapy.

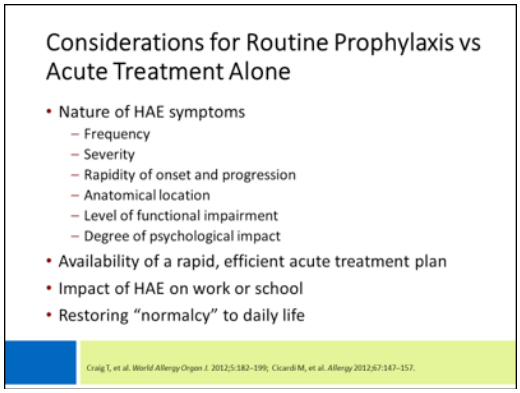


The guidelines don't give us specific answers on a few topics. For example, they don't describe specifically which patients should get prophylactic therapy. As I mentioned, there's no set formula for using long-term prophylaxis. That's primarily because we have no studies showing who most benefits from long-term prophylaxis; really, it's more art than science in terms of deciding who will benefit from long-term prophylactic therapy. The guidelines also do not give us a preferred agent for either acute or prophylactic treatment.

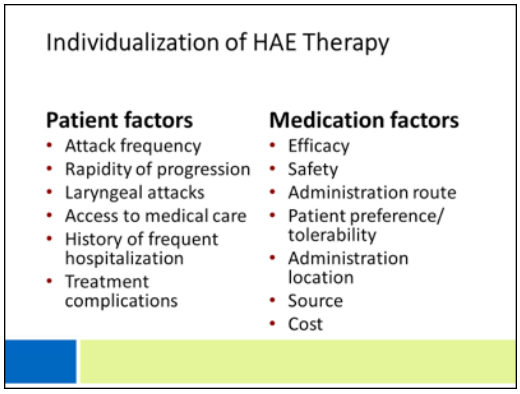


If you think back to those tables I showed earlier, we choose from available treatments based on our discussions with patients. We have no indication that one drug is better or more effective or safer than the other, because drug studies have all been different in their design and their primary outcomes. Choosing from these options, knowing the pros and cons, discussing the risks and benefits with the patient—these are considerations that lead to a specific prescription for each patient. There's no guidance from the guidelines on which specific drugs to use, with the exception of children and pregnant women. In those cases, the plasma-derived C1-INH products are recommended by the guidelines as preferred medication. That's due to the longer track record of safety with those products compared to the newly developed products, for which the data for use in children or pregnant women are very sparse. In kids and pregnant women, plasma-derived C1-INH products are preferred.

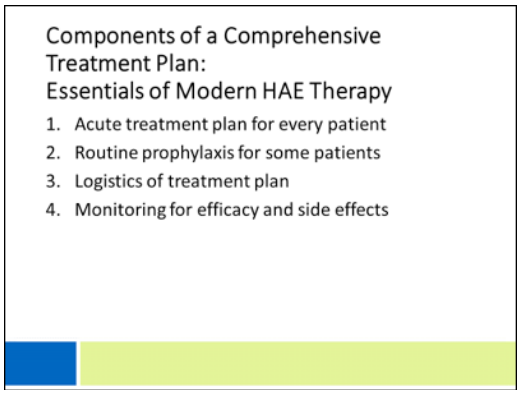
As we move toward the end of this program, I'll just mention a few considerations in managing HAE patients. As I mentioned, every patient needs acute treatment. Prophylactic therapy is in some ways a judgment call based on your discussions with the patient. We do take into account, again, the nature of their symptoms. That could mean frequency or severity of attacks, how rapidly attacks progress, where the routine attacks are occurring physically—with those affecting the airway being more life- threatening and potentially more serious than other types. We should consider patients' level of functional impairment and the impact HAE symptoms have in daily life. Ultimately, the goal is to develop a plan that will get patients back to their normal life, whatever that may mean to them, but certainly it includes pursuing professional and educational goals without limitation from HAE.



In terms of developing a comprehensive modern treatment plan for HAE, these are the important bullet points. Acute treatment is a must for every patient. We use long-term prophylaxis in some patients. Then, when setting up the nuts and bolts of the treatment plan, logistics can be incredibly important. Certainly monitoring for efficacy and side effects over time is critical.



The acute treatment plan, is, again, essential for every patient. It needs to be tailored to patients' individual circumstances. I'll go back to the fact that we have choices here. Walking through those choices with each patient is important, so that they're comfortable with the treatment plan. Developing a backup plan is also critically important. Even with the best-laid plans, sometimes things will still go wrong and a patient will have a severe swelling attack that needs medical attention. That may be a call to the physician and perhaps a trip to the hospital. But certainly having a "plan B" is very important, due to the life-threatening nature of this condition.

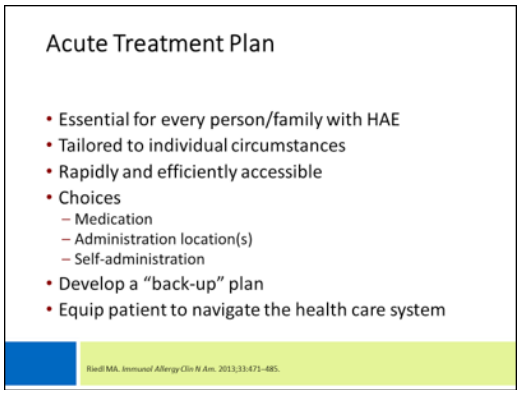


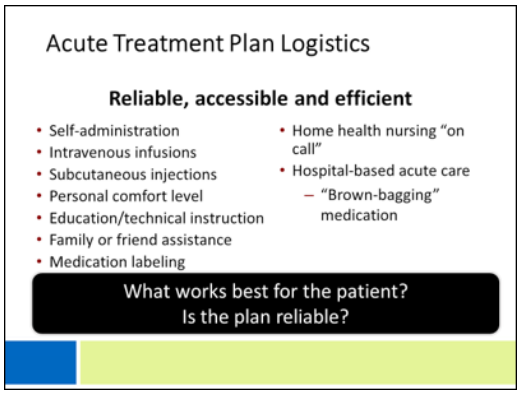
The action plan is something we discuss often in HAE. This involves equipping patients to navigate the health care system. Because HAE is a rare condition, patients often find it frustrating to deal with the health care system. Putting together a plan that describes the condition and their treatment plan and provides their medical record can be very, very useful.

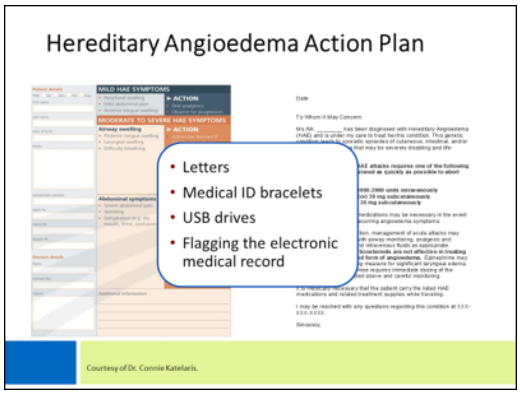
There are a variety of ways to communicate the plan. It can be done on paper; a letter that explains the condition can be drafted, and can identify the medication the patient needs to receive. Some people wear medical alert bracelets. Flagging the electronic medical record has now been proven to be very useful to helping patients navigate the system and not get misdiagnosed or mismanaged once they have a confirmed diagnosis of HAE.

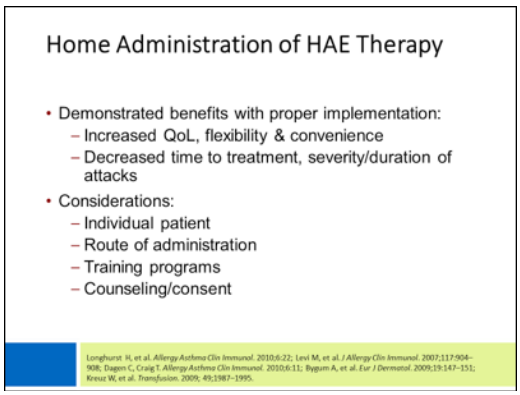
Beyond that, I'll finish with a few words about self-administration. Data that has emerged over the last few years have shown that self-administration or home administration of HAE medications is beneficial in improving patients' quality of life and reducing the amount of time they are affected by angioedema attacks. Most of the medications that I discussed are indicated for self-administration. Once patients learn how to do this—they're taught by a health care provider how to self-administer either the subcutaneous medications or the IV medications—they are very successful. This, in turn, allows them a better quality of life and decreases the time to getting the treatment that they need. The result is a reduction in both the severity and the duration of their angioedema attacks. Most patients can self-administer HAE treatments. Not every patient is comfortable with self-administering treatment, but most are, and will recognize its benefits once they've had proper instruction.

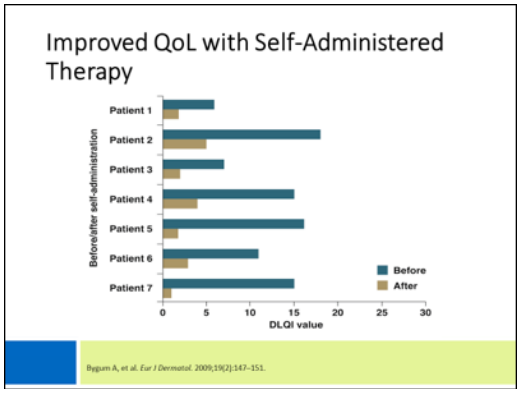
This slide shows just one small study demonstrating that quality of life improved with self-administration. Once patients learned to self-administer their medications their quality of life is greatly improved. Other studies have shown a reduction in the duration of angioedema swelling with self-administration programs.









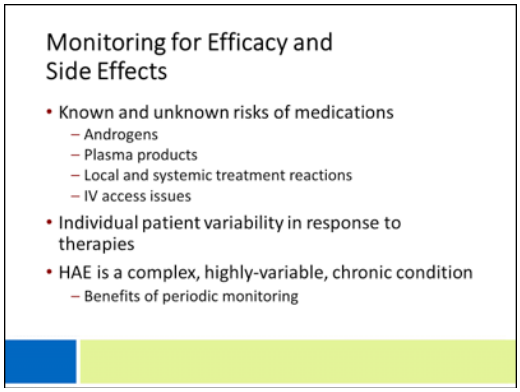


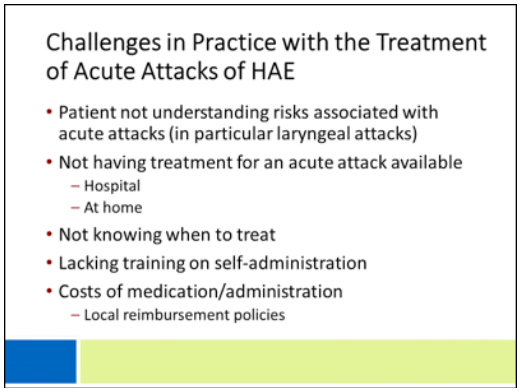
Monitoring treatment, whether self-administered or given by a health care provider, is important. I've mentioned side effects, seen particularly with androgens and plasma products, but also with the synthetic medications. We have to be vigilant for potential side effects. Also, given the complexity and the variability of HAE, we should see these patients regularly, because we may need to make adjustments to their treatment plans, as symptomology may change over time.

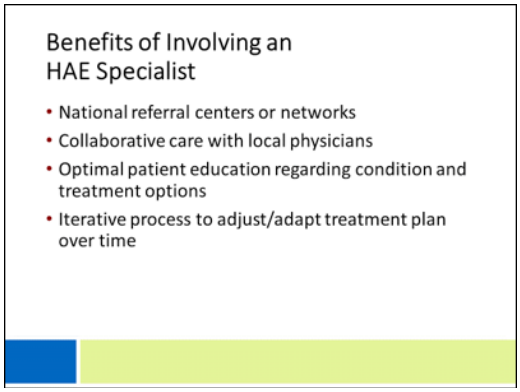
Finally, one of the challenges of treating HAE is that often patients don't fully understand the risks, particularly those associated with airway attacks. It's vital that they understand the seriousness of airway issues and the need to seek medical advice, even if they've used their acute treatment to try to stop the attack. Not having an acute treatment—lack of access to effective HAE medications—is a big problem in HAE. In addition, we often need to discuss with patients when to treat. Again, earlier is better. Then we need to provide training on self-administration, and we need to work with payers to get the medications covered and reimbursed.

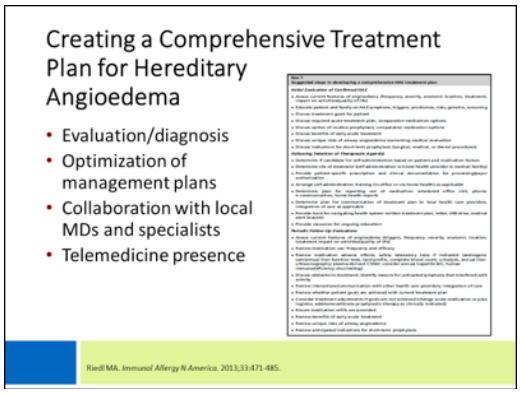
In that vein, angioedema specialty and referral centers have been established; I'm a part of one, and there are others across the country. These centers can be very helpful for collaborating, to help manage patients with angioedema—whether there are diagnostic questions or management questions—toward optimizing both patient education and the treatment plan.

This slide shows an article that we published a few years back that explains how time-consuming and complex it can be to review all of the issues, complications, side effects, and benefits of the different management options. Having knowledge of this, but also collaborating with a specialist, can sometimes be very useful. We're actively engaged in efforts to make telemedicine an option, so that we can reach more people more efficiently.

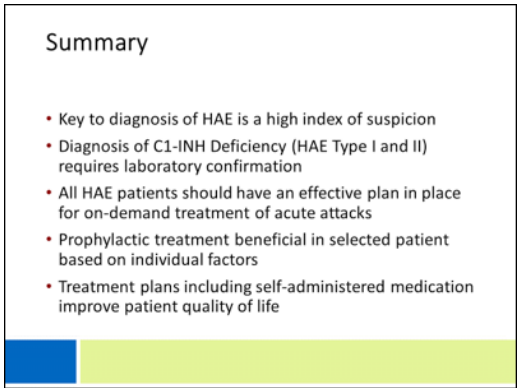








I'll finish this webinar with a quick summary. Please keep HAE in mind if you're seeing patients with angioedema symptoms. HAE is often not considered, and as a result, patients are often misdiagnosed or undiagnosed, which leads to long delays in treatment and many complications. We talked about laboratory tests, including C4 level as a screening test, and C1-INH level and function as the confirmatory tests for type I and type II HAE. Please remember that if you see patients with HAE, they need to have an effective acute treatment plan, without exception. Prophylactic treatment can also be very beneficial for certain patients, particularly those who have a higher degree of severity or disability from HAE.



Lastly, we have moved increasingly to self-administered medication in HAE to try to empower patients, improve their quality of life, and give them the independence that they desire so that HAE isn't controlling their professional, educational, and family endeavors.

With that, I'll close. Thanks very much for your attention. I hope you found this information useful and will be able to apply it in your clinical practice. Thanks very much.

Participate in interactive questions, download activity slides, and obtain your CE/CME credit online.
http://annenberg.net/medEd/5490/