Introduction

Hereditary angioedema (HAE) was again a topic of keen interest at the 2012 Annual Meeting of the American College of Allergy, Asthma & Immunology (ACAAI), at which a major new report on angioedema was presented. Titled “International Consensus (ICON) on Hereditary and Acquired Angioedema,” the report was developed under the aegis of the International Collaboration in Asthma, Allergy and Immunology (iCAALL), a joint effort of 4 leading academic societies.

Based on recent advances in the understanding of HAE, the leadership of these societies and the author group determined that the goals of iCAALL would be best served by focusing on angioedema without concomitant hives, concentrating primarily on syndromes characterized by a deficiency of C1-inhibitor (C1-INH). The ICON report was conceived as a resource to support physicians and other health care providers who treat patients with HAE or acquired angioedema (AAE). It achieves this end by examining the pathogenesis, prevalence, clinical manifestations, diagnosis, and management of these disorders.

The ICON report emphasizes that effective medications are available for the treatment of acute attacks of angioedema and that all attacks are eligible for treatment. Patients with frequent or severe attacks—especially laryngeal attacks, which are life threatening —
should be considered for long-term prophylactic therapy. Short-term prophylactic therapy is appropriate for all patients with angioedema before exposure to known attack triggers, such as dental work or surgery with intubation.

The authors of the ICON report also devote attention to angioedema associated with the use of angiotensin-converting enzyme (ACE) inhibitors. These agents block bradykinin degradation and have been known to trigger angioedema, often of the face and lips, in ~0.5% of patients. As ACE inhibitors are widely used, this form of angioedema is far more common than HAE or AAE and represents a significant disease burden.

The ICON report concludes with an important discussion of the unmet needs of angioedema patients in resource-poor countries, where limited access to health care, lack of awareness among patients and physicians as to the nature of the condition, and unavailability of effective treatments may lead to misdiagnosis and unnecessary suffering.

The ACAAI meeting was also notable for the presentation of numerous abstracts and posters investigating the clinical presentation, diagnosis, and management of HAE and AAE. Several of these addressed pressing clinical problems, including the management of pediatric and adolescent patients, misdiagnosis of HAE, and the need to provide patients with ready access to on-demand therapy. This publication reports on the most significant of these presentations and endeavors to establish a contextual background for each, with the aim of making this research more widely known and thereby contributing to effective patient care.

**ICON Report Targets Issues Important to Management of Angioedema**

Four leading allergy/immunology organizations have collaborated to set a new standard for diagnosis and treatment of angioedema, an uncommon condition that often goes unrecognized but may be life threatening. The report was released at the most recent Annual Scientific Meeting of the ACAAI in Anaheim, California.¹ The findings of this report have also been recently published.² It is the latest ICON from iCAALL, a joint project of the ACAAI; the American Academy of Allergy, Asthma & Immunology; the European Academy of Allergy and Clinical Immunology; and the World Allergy Organization.

The report was developed to address consensus-driven information and general recommendations for angioedema, as well as the international lack of understanding about this disorder. The aim of the ICON report is to help ensure the proper diagnosis and management of hereditary and acquired angioedema, while helping patients with these conditions find relief and lead healthy, active lifestyles.³

An international consensus algorithm on HAE, developed by the Canadian Hereditary Angioedema Network and the Canadian Society of Allergy and Clinical Immunology, was published in 2010; it provides specific recommendations for the diagnostic approach to, and reviews treatment options for, HAE.⁴ More recently, the Hereditary Angioedema International Working Group released evidence-based recommendations for treatment of HAE.⁵ Both documents emphasize the need for prompt treatment of HAE attacks, prophylactic therapy for patients who have frequent or serious attacks, and the option of training appropriate patients to self-administer drug treatment to reduce the time to initiation of therapy and limit the severity of attacks.⁴,⁵
**Pathophysiology of Angioedema**

In reviewing the pathophysiology of HAE, the ICON report emphasizes the role of bradykinin as the mediator primarily responsible for the development of HAE symptoms. Activation of the contact system triggers a cascade of events including activation of factor XII, production of kallikrein, and cleaving of bradykinin from high-molecular-weight kininogen. C1-INH regulates several steps of contact system activation; therefore, a reduced level of functional C1-INH leads to excessive bradykinin release and angioedema.

Angioedema may be classified according to its underlying pathophysiology. Type I HAE is characterized by low levels of C1-INH, whereas type II HAE is associated with normal levels of a nonfunctional form of C1-INH. Another form of HAE is observed in patients who have normal C1-INH and results from a mutation in the gene for factor XII or from other, unknown causes. Acquired C1-INH deficiency may be associated with lymphoproliferative diseases, the presence of autoantibodies against C1-INH, or autoimmune disorders such as lupus erythematosus. Finally, angioedema may occur as an adverse reaction to ACE inhibitors, which inhibit bradykinin degradation.

**Treatment of Angioedema**

The strategies for the management of HAE are treatment of acute attacks (on-demand treatment) and, for some patients, long-term or short-term prophylaxis.

Patients with C1-INH deficiency should have an established plan to respond to acute attacks and have effective drugs readily available. Treatment for an acute attack should be started as soon as possible after onset to reduce its severity and duration.

Long-term prophylaxis should be considered for patients with frequent or severe attacks, comorbid conditions, limited access to acute care, or a strong preference for a preventive approach. Plasma-derived C1-INH is effective for prophylaxis. Regular use of oral 17α-alkylated androgens reduces the frequency and severity of attacks but may be associated with numerous adverse effects.

Short-term prophylaxis is recommended for patients with HAE prior to known attack triggers, such as dental procedures or surgery requiring intubation. C1-INH is preferred for short-term prophylaxis given before the procedure, but if it is not available, solvent/detergent-treated plasma or fresh frozen plasma several hours prior to the procedure or high-dose 17α-alkylated androgens for 5 days before and 2 days after the procedure may be substituted. On-demand acute treatment should be available during and after the procedure.

**ACE Inhibitor–Associated Angioedema**

Approximately 0.5% of patients treated with ACE inhibitors experience angioedema, usually of the face or tongue, making it more common than HAE. Bradykinin levels are elevated during ACE inhibitor–associated angioedema, suggesting that bradykinin mediates symptoms much as it does in patients with HAE. Management requires discontinuation of the ACE inhibitor and avoiding use of all drugs in the class as well as aliskiren, a renin inhibitor. Most patients may tolerate treatment with angiotensin receptor blocking agents.

**Unmet Needs**

The ICON report concludes by pointing out that the diagnostic and therapeutic needs of patients with angioedema are often not met in resource-limited environments. Among the reasons for this are a lack of awareness by patients of the nature of their condition,
particularly in those whose symptoms have been infrequent or mild; misdiagnosis by health care providers who are unfamiliar with these rare conditions; and unavailability of the laboratory tests that can provide a definitive diagnosis. Moreover, in many countries, newer drugs for the treatment of HAE are not available. The difficulty of managing HAE is compounded by poor patient adherence, a particular problem in countries where large segments of the population have limited access to health care.

References

Studies Explore Dosing of C1-INH Concentrate for Prophylaxis, Treatment of Acute HAE Attacks

Two recent trials have demonstrated the benefits of expanded dosing options for C1-INH concentrate in the prophylaxis and acute treatment of HAE.

Prophylactic Dosing
Bernstein et al conducted an open-label study of nanofiltered C1-INH (Cinryze®, ViroPharma Incorporated, Exton, Pennsylvania) in patients with HAE who continued to have ≥1 attack per month despite routine prophylactic treatment with the approved dose of 1000-U every 3 to 4 days. Dosing was escalated to 1500-U every 3 or 4 days and patients were reevaluated after 12 weeks. Those who continued to have ≥1 attack/month could be escalated to 2000-U every 3 or 4 days for a further 12 weeks, and then to 2500-U every 3 or 4 days if necessary.1

All 20 patients enrolled in the study started at 1500-U. A total of 13 patients were escalated to 2000-U and 12 patients were escalated to 2500-U. Three patients discontinued the study for reasons not related to safety. Eleven patients (5 in the 1500-U group and 6 in the 2500-U group) were treated successfully or continued on their final dose at follow-up. A total of 91 adverse events were reported by 18 patients: 85% were mild or moderate in severity and 95% were unrelated to C1-INH therapy. The most common adverse events were upper respiratory tract infection and nasopharyngitis. Two patients reported 4 serious adverse events (cerebral hygroma, laryngeal HAE attack, worsening of anemia, and choledocholithiasis), none of which were judged to be related to the study treatment. No systemic thrombotic events, discontinuations due to adverse events, or deaths occurred.1
Dose escalation of nanofiltered C1-INH is not approved in the United States for patients with breakthrough attacks on standard dosing. More studies investigating the use of dose escalation in these patients are needed.

**Dosing for Acute Attacks**

The efficacy and safety of purified C1-INH (Berinert®, CSL Behring LLC, Kankakee, Illinois) given at a dose of 20 U/kg of body weight were established for individual attacks in the IMPACT 1 (International Multicenter Prospective Angioedema C1-INH Trial 1) study and for successive attacks in the IMPACT 2 study. However, the efficacy of C1-INH in obese versus nonobese patients was not addressed in those trials.

To investigate this, Bernstein et al conducted a retrospective analysis of data from >1000 HAE attacks recorded in IMPACT 2. The attacks were grouped by body mass index (BMI) of patients at the time of study entry: normal weight (18.4 to <25 kg/m²), overweight (25 to <30 kg/m²), and obese (30 to <40 kg/m²). Of the 57 patients included in this analysis, 24 patients treated for 530 attacks were normal weight, 20 patients treated for 451 attacks were overweight, and 13 patients treated for 104 attacks were obese.

The median time to onset of symptom relief was 0.37 hours in normal-weight patients, 0.48 hours in overweight patients, and 0.58 hours in obese patients. The median time to complete resolution of HAE attacks was 15.2 hours in normal-weight patients, 22.6 hours in overweight patients, and 11.0 hours in obese patients. Adverse events were reported in 54% of normal-weight patients, 30% of overweight patients, and 54% of obese patients. Thus, the efficacy and safety of weight-based dosing of C1-INH for treatment of acute attacks of HAE did not appear to be affected by BMI.

**References**

4. Bernstein JA, Craig TJ, Keinecke H, Machnig T. Efficacy and safety of C1 esterase inhibitor concentrate (Berinert®) for the treatment of acute hereditary angioedema in obese vs. non-obese patients. Poster presented at: Annual Scientific Meeting of the American College of Allergy, Asthma & Immunology; November 8-13, 2012; Anaheim, CA.

**HAE With Normal C1-INH Poses Clinical Challenge**

A recent article by Zuraw et al provides diagnostic criteria for patients suspected of having HAE with normal C1-INH. The proposed criteria include a history of recurrent angioedema (without concomitant hives or use of medications known to cause angioedema); documented normal (or near normal) C4, C1-INH antigen, and C1-INH function; and either the presence of an F12 mutation or positive family history of angioedema with failure of high-dose antihistamine therapy for ≥1 month’s duration and a time interval expected to be associated with ≥3 angioedema attacks.

Recent case reports illustrate the challenges in managing patients with HAE with normal C1-INH, previously referred to as type III HAE. Zhu and Bewtra reported a case of a 65-year-old
woman with a 5-year history of recurrent abdominal pain and occasional swelling of the face and lips. An abdominal computed tomography (CT) scan taken during an episode demonstrated thickening of the intestinal wall. Laboratory testing showed that C1-INH level and function, C4, C3, and C1q were normal, and she received a diagnosis of HAE with normal C1-INH. Although she responded well at first to C1-INH concentrate (Berinert®), within 2 months her symptoms were not adequately controlled and she was switched to ecallantide, a plasma kallikrein inhibitor.2

The second case was a 13-year-old girl who first experienced painful swelling of the lips, tongue, and mouth at age 3 years. Her symptoms had worsened over the previous year and episodes became more frequent, occurring once per month. During hospitalization, she underwent testing for HAE types I and II but the results were negative. Genetic testing and family history were unavailable. Empiric treatment with fresh frozen plasma and, later, C1-INH concentrate (Berinert®) relieved her symptoms and she is currently being treated on-demand with adequate symptom control.2

These cases highlight the heterogeneous nature of HAE with normal C1-INH as well as the lack of a consistent approach to diagnosis. HAE with normal C1-INH was first described in 2000 and was thought to occur only in women.3,4 Its clinical presentation is similar to that of types I and II HAE but with a later age of onset, a lower frequency of attacks, a predilection to affect the face and tongue, and an association with pregnancy or oral contraceptive use.5 More recently, HAE with normal C1-INH has been identified in men, although they comprise only a minority of patients. Some affected families carry a mutation in the coagulation factor XII gene; however, in most patients, the underlying genetic cause cannot be determined.6

Berinert® was used successfully as preprocedural prophylaxis in a 59-year-old woman with an 8-year history of abdominal angioedema, a previous episode of laryngeal edema during laparoscopy, and a family history of similar symptoms. Serologic workup revealed normal C1-INH level and function as well as normal C4, C2, and C1q. After an infusion of C1-INH 20 mg/kg 18 hours prior to her procedure, she underwent colonoscopy with polypectomy and hemorrhoidal banding without complications and no signs of angioedema. This is the first report of successful preprocedural prophylaxis using C1-INH in a patient with HAE and normal C1-INH.7

References
2. Zhu N, Bewtra A. Type 3 hereditary angioedema: a case report. Poster presented at: Annual Scientific Meeting of the American College of Allergy, Asthma & Immunology; November 8-13, 2012; Anaheim, CA.
7. Scott DR, Woessner KM. Successful use of C1INH-RP as procedural prophylaxis in a patient with isolated abdominal attacks of hereditary angioedema and normal C1INH. Poster presented at: Annual Scientific Meeting of the American College of Allergy, Asthma & Immunology; November 8-13, 2012; Anaheim, CA.
Home Therapy of Acute HAE Attacks Improves Response Time, Lowers Cost

Home therapy has emerged as an important management strategy for patients with HAE because it holds the potential to reduce the overall disease burden, including time lost from work or school, medical expenses, lost income, urgent trips to an emergency department, and frequent hospitalization.\(^1\) Prospective trials have shown that successful home therapy can decrease the time to initiation of treatment, reduce attack duration and severity, reduce interference with family and social life, and improve patient satisfaction.\(^2,3\)

For an acute HAE attack, the plasma kallikrein inhibitor ecallantide can be given subcutaneously and has been shown in controlled trials to be effective for relief of HAE symptoms.\(^4,5\) Its use has been associated with rare occurrences of anaphylaxis; therefore, it is not suitable for self-administration and must be given with appropriate observation by a health care professional.\(^6\)

A recent observational trial demonstrated that nurse-administered home therapy with ecallantide for HAE is an option that has the potential to improve management of HAE symptoms while reducing costs.\(^7\) The investigators evaluated the experience of 6 patients who received ~100 doses of nurse-administered ecallantide at home for acute HAE attacks. Following patient phone calls, nurse response times ranged from 4 to 165 minutes. The time from administration of ecallantide to initial symptom response ranged from 10 to 360 minutes. In most cases, patients required only 1 dose of ecallantide. The cost of the nurse visit was $125 for the first 2 hours plus $50 for supplies. By contrast, the cost of emergency department visits for HAE in the same community ranged from $2285 to $10,550, and the costs of 2 separate hospitalizations were $23,768 and $39,711. Thus, significant cost savings were realized for each episode in which a nurse visit rendered an emergency department visit or hospitalization unnecessary.

References

7. Boyden N, Vegh AB. Patient experience with ecallantide nurse home administration. Poster presented at: Annual Scientific Meeting of the American College of Allergy, Asthma & Immunology; November 8-13, 2012; Anaheim, CA.
Self-administration of C1-INH Effective in Controlling Attacks

A retrospective analysis of patients trained to self-administer C1-INH for prophylaxis or on-demand therapy of HAE found that self-administration was both safe and effective, with patients being able to manage HAE attacks in a wide variety of settings. A total of 13 patients were trained by a nurse to self-administer C1-INH intravenously and included in the study. Six patients were trained to self-administer prophylactic therapy with nanofiltered C1-INH (Cinryze®) at a dose of 1000-U once weekly, twice weekly, every 3 days, or every 4 days. Seven patients were trained to self-administer on-demand therapy with purified C1-INH (Berinert®) at a dose of 1000 to 1500-U at the first sign of an acute attack. After completing the training, 3 patients in the on-demand group chose not to self-administer the drug. 1

During a mean follow-up of 18.1 months, the 6 patients on prophylactic therapy self-administered ~945 doses of C1-INH and experienced an average of 0.34 attacks per month. The patients trained in on-demand therapy successfully treated attacks at home, school, and camp. Only 1 attack could not be treated by the patient, because of swelling in a location that interfered with intravenous (IV) placement. The majority of acute attacks were successfully treated with a single dose of medication, with only 3 attacks requiring a second dose of C1-INH. A single, severe laryngeal attack required a 24-hour hospital stay for observation. Adverse events were infrequent and mild, and no complications from IV self-administration occurred. 1

Self-administration of C1-INH, either as on-demand therapy or individual replacement therapy, has been successfully used for many years for control of HAE symptoms. 2

A majority of adult patients are able to learn to self-administer an IV drug safely, and a substantial proportion of adolescent patients can be treated at home with the help of family members. 3 Given the clinical benefits of self-administered therapy, current consensus statements and treatment guidelines recommend that all patients with HAE be considered for home therapy. 4, 5

References
1. Shapiro R. Self intravenous (IV) administration of C1-INH concentrate for hereditary angioedema: a retrospective analysis of patient outcomes. Poster presented at: Annual Scientific Meeting of the American College of Allergy, Asthma & Immunology; November 8-13, 2012; Anaheim, CA.
a 9-year-old girl with diagnosed HAE and a history of attacks who presented to an emergency department with a 10-hour history of emesis, anorexia, and periumbilical pain. She had an elevated white blood cell (WBC) count with magnetic resonance imaging showing edema of the proximal small bowel, an enlarged appendix, and fluid in the peritoneal cavity. She was administered 1000-U of C1-INH and 1 hour later an appendectomy was performed; her appendix was found to be normal. The second case was an 11-year-old girl with a diagnosis of HAE but no history of attacks. She presented to an emergency department with a 2-day history of biliary emesis, right lower quadrant abdominal pain, and diarrhea. Abdominal examination showed diffuse tenderness with mild rebound tenderness. Her WBC was elevated at 12.2 K/μL. CT scan revealed mesenteric edema and free peritoneal fluid. She was observed for 24 hours, then received 1000-U of C1-INH and underwent diagnostic laparotomy with appendectomy; her appendix was found to be normal.1

As a rare illness, HAE is often unrecognized, misdiagnosed, and inappropriately treated. Many physicians are unfamiliar with the condition, and many patients are unaware that they have it. A survey of 313 patients with HAE found that the average time to diagnosis after the first episode was 8.3 years, and that patients visited an average of 4.4 physicians before being correctly diagnosed.2 Almost two-thirds of patients had received a misdiagnosis of their condition, most commonly allergy or appendicitis. Alarmingly, about one-fourth of patients had undergone an unnecessary surgical procedure, such as appendectomy. Case reports in the literature describe HAE being mistaken for allergy, gastroenteritis, or anaphylaxis and being treated with antihistamines, corticosteroids, IV fluids and promethazine, and epinephrine, none of which are effective for this bradykinin-mediated disorder.3-5

Zingale et al reported a series of 929 consecutive patients who presented with angioedema without concomitant urticaria over a 10-year period. Extensive diagnostic workup revealed that 25% had either type I or type II HAE. Thus, although the condition is quite rare, HAE should be considered in any patient who presents with edema without concomitant urticaria.6

The case reports presented by Dispenza et al demonstrate that having a diagnosis of HAE may not be enough to avoid inappropriate treatment. The authors urge that all patients with HAE have a plan in place to treat acute attacks, preferably at home, so that symptoms can be promptly controlled, unnecessary emergency department visits can be prevented, and an HAE attack can be distinguished from a true surgical emergency.1

References
1. Dispenza M, Gutierrez M, Bajaj P, Craig T. The need for individualized hereditary angioedema acute action plans: two case studies of misdiagnosed attacks and unnecessary surgeries. Poster presented at: Annual Scientific Meeting of the American College of Allergy, Asthma & Immunology; November 8-13, 2012; Anaheim, CA.
Acquired Angioedema: Treat Underlying Disorder, Control Acute Attacks

AAE is an extremely rare condition characterized by noninherited C1-INH deficiency with hyperactivation of the classical complement system and dysregulation of the contact-kinin system, which lead to recurrent episodes of swelling.\(^1\)

The symptoms of both AAE and HAE are triggered by bradykinin release, and the 2 conditions cannot be distinguished clinically. Only in the age of onset—before age 20 years for most patients with HAE, after age 40 years for most with AAE—do the presentations differ notably. The earliest described cases occurred in the presence of lymphoma. Later, discovery of anti–C1-INH autoantibodies coexisting with lymphoma led to the understanding that AAE is a condition associated with various forms of B-cell lymphoproliferative disease. Angioedema occurs when lymphoma cells activate the complement system consuming C1 or due to the presence of autoantibodies that deplete C1-INH. The optimal approach to therapy of AAE is to treat the underlying condition; in addition, treatment is required for acute attacks of angioedema.\(^1\)

Another study reported the use of ecallantide to treat attacks of angioedema in 4 patients with AAE. All 4 had recurrent episodes of angioedema and low levels of C4, C1q, and C1-INH. Three patients had monoclonal gammopathy of undetermined significance, and the fourth had monoclonal immunoglobulin G in the urine but not in the blood along with a history of psoriasis. Three patients were found to have anti–C1-INH autoantibodies. Thirteen episodes of swelling—10 abdominal, 2 in the lips, and 1 of the uvula and posterior pharyngeal wall—were treated with ecallantide in doses ranging from 30 to 80 mg. Symptoms resolved within 1 to 8 hours in all cases and no adverse events occurred.\(^2\)

Garg et al reported the case of a 25-year-old woman with a history of nodular sclerosing Hodgkin’s lymphoma and Crohn’s disease who presented with multiple episodes of swelling of the hand, foot, and face with subsequent diagnosis of AAE. She also experienced urticaria and anaphylaxis during IV infusion of iron. At the time of diagnosis, the patient’s C1-INH level and function were low and C4 was normal. Over a period of several months, she was repeatedly hospitalized with severe nausea, vomiting, constipation, and abdominal pain, which was treated with purified C1-INH (Berinert\(^\text{®}\)). She was also treated with corticosteroids for flares of Crohn’s disease and eventually underwent right hemicolecotony. It is believed that this patient had developed an anti-idiotype antibody due to previous exposure to IV iron preparations that may have chronically activated the complement system leading to AAE.\(^3\)

References
2. Vernon N, Ghaffari G. Acute attacks of acquired angioedema responding to kallikrein inhibitor (ecallantide). Poster presented at: Annual Scientific Meeting of the American College of Allergy, Asthma & Immunology; November 8-13, 2012; Anaheim, CA.
Conclusions and a Look to the Future

These presentations at the 2012 Annual Meeting of the ACAAI were consistent with the meeting’s theme of “Over the Horizon: Expanding Expertise.” The allergy and immunology community continues to look beyond the horizon for a better understanding of our patients with angioedema while expanding our expertise in the appropriate use of currently available treatments for this underserved population.

The collaboration between the major international allergy societies to produce the ICON report was a landmark achievement. This document addresses current challenges and future needs to best treat patients with hereditary and acquired angioedema. This consensus provides practical information about the diagnosis and treatment of these rare disorders that will be useful to clinicians, academicians, and researchers throughout the world.

The clinical presentations cited above outline how much has been learned about angioedema without urticaria, but much remains to be understood. Decreasing the time to diagnosis, eliminating unnecessary medical procedures, and selection of the best option to treat and prevent swelling attacks in patients with HAE and AAE with C1-INH deficiency remain a challenge. The causes and appropriate treatment of HAE with normal C1-INH are for the most part unknown. With emphasis on home care and appropriate monitoring as well as self-management utilization, resources used to treat HAE and AAE will be a challenge patients, providers and payors, must address.

Although we looked to the future and expanded our expertise, there is still much work to be done to understand these rare, often disabling and potentially fatal diseases. I look forward to this challenge.