The Art and Science of Infusion Nursing

Ralph S. Shapiro, MD
Lisa Zacek, RN

Training Hereditary Angioedema Patients to Self-administer Intravenous C1 Esterase Inhibitor Concentrate

ABSTRACT

Hereditary angioedema (HAE) is a rare disorder that causes periodic attacks of sometimes painful swelling that may affect any organ system. HAE results in significant morbidity and diminished quality of life and requires patients to seek urgent medical care. HAE can be treated with C1 esterase inhibitor concentrate (C1-INH), icatibant, and ecallantide. Recent consensus guidelines recommend that all HAE patients be considered for training in self-administration of therapy to treat acute attacks or to prevent attacks. Many patients have safely and successfully self-administered intravenous infusions of C1-INH, resulting in rapid treatment, shortened attacks, and improved quality of life. With proper patient selection and adequate guidance and follow-up, self-administered C1-INH therapy is a viable and favorable option to treat HAE, particularly in patients with a moderate to high frequency of attacks.

Key words: hereditary angioedema, C1 esterase inhibitor, self-administration, home therapy

Hereditary angioedema (HAE) is a rare disorder affecting approximately 1 in 50,000 people. It causes frequent attacks of painful nonpitting, nonpruritic edema.[1] Most attacks occur in the skin of the extremities or the gastrointestinal tract, but the face, trunk, genital region, or upper airway also may be affected (Figure 1).[1] Attacks usually develop slowly but may occur rapidly. Most are self-limiting, resolving over 1 to 3 days; however, laryngeal attacks, although uncommon, may be fatal.[2] HAE usually manifests in childhood or adolescence and persists throughout the patient's life.[3] Many attacks of HAE are acutely painful or temporarily disfiguring, and the condition may be associated with lifestyle disruptions and a significant negative impact on quality of life (Figure 1).[4] Attacks may be triggered by trauma or emotional stress, but most have no identifiable trigger.[5] HAE is caused by a wide variety of genetic defects that result in insufficient levels of functional C1 esterase inhibitor (C1-INH), which plays important regulatory roles in the contact, complement, and fibrinolytic systems.[3]

Among the burdens of HAE is the frequent need to seek urgent medical care. Learning to self-administer

Author Affiliation: Midwest Immunology Clinic, Plymouth, Minnesota.

Ralph S. Shapiro, MD, founded the Midwest Immunology Clinic in 1995, where he currently serves as director. His current practice involves the diagnosis and care of primary immune deficiency and autoimmune disorders. Research interests include genetic defects in primary immunodeficiencies, developing novel therapeutic approaches to diseases, and drug development pertaining to IVIG, SCIG, and C1 esterase inhibitors. Dr Shapiro's prior experience includes a fellowship in pediatric hematology and oncology at the University of Minnesota, and attending staff in immunology and bone marrow transplantation at the University of Minnesota.

Lisa Zacek, RN, currently serves as the infusion center manager at the Midwest Immunology Clinic, where she has worked since 2001. Her responsibilities include oversight of the infusion center, study coordinator, and nurse consultant for the CSL SHARE program (SC training).

Ralph S. Shapiro and Lisa Zacek have both served as paid consultants for CSL Behring.

Corresponding Author: Ralph S. Shapiro, MD, Midwest Immunology Clinic, 15700 37th Ave, Suite 110, Plymouth, MN 55446 (rsshapi@hotmail.com).

DOI:10.1097/NAN.0000000000000049

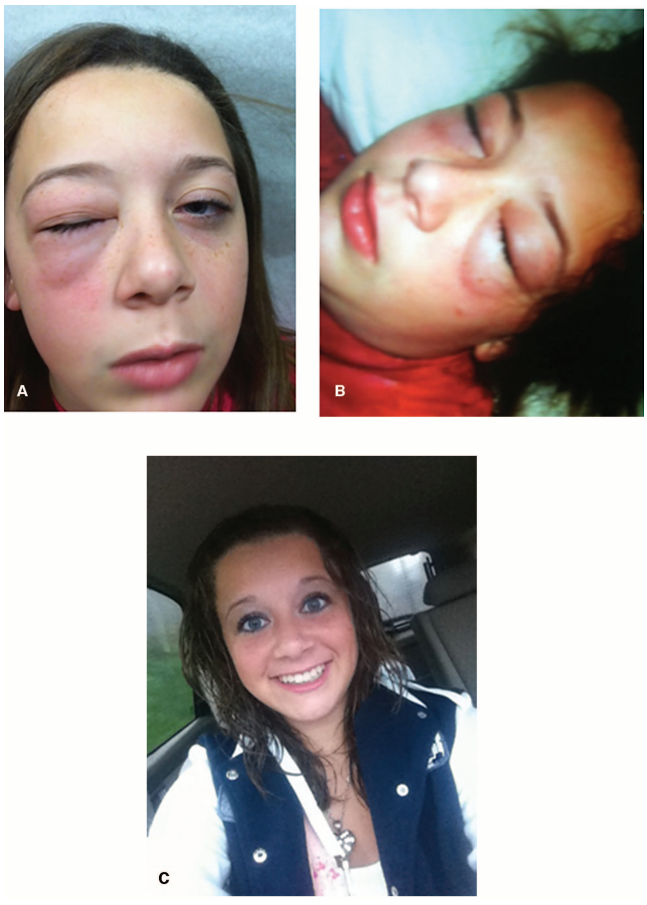

Figure 1 A patient with HAE experiencing a facial attack (A, B) and the same patient, in the absence of swelling (C). (Photographs courtesy of Francine Priestas. Used with permission.)

treatment for HAE, usually with drugs given intravenously or subcutaneously (SC), helps free patients from this demand and provides them with a greater degree of control over their condition and their lives. This article briefly reviews the pathophysiology and clinical presentation of HAE and available treatment options for the disorder, with an emphasis on their safety and efficacy when self-administered. It also provides guidance to infusion nurses for training patients with HAE to administer their own medication, with the goal of improving outcomes and reducing the burden of illness.

PATHOPHYSIOLOGY OF HAE

Most cases of HAE result from a lack of functional C1-INH.[5] Type 1 HAE, which accounts for approximately 85% of cases, is caused by genetic mutations that result in production of truncated or misfolded proteins that are not normally secreted. It is associated with abnormally low concentrations of C1-INH.[5] Type 2 HAE, accounting for approximately 15% of cases, is caused by mutations that result in production of dysfunctional C1-INH protein that is secreted normally; for this reason, this type of HAE is associated with normal concentrations of C1-INH but in a dysfunctional form.[5] The 2 types cannot be distinguished clinically. Lacking the regulatory effects of C1-INH, the immune system releases excessive vasoactive peptides, including bradykinin, in response to trauma or another stimulus.[1] Bradykinin activates endothelial cells, provoking vasodilation, vascular permeability, and production of inflammatory mediators, which together cause edema.[6]

A third type of HAE, which occurs primarily in women, is associated with normal concentrations and function of C1-INH.[7] In some patients, this disorder is associated with a mutation in the gene coding for blood coagulation factor XII, which promotes the generation of kinins.[8]

CLINICAL FEATURES

People with HAE experience recurrent episodes of swelling. Attacks occur most frequently in the skin or gastrointestinal tract, but the upper respiratory tract, oropharynx, genitalia, or any other region may be affected.[1,9] Attacks that begin in one organ system may migrate to another.[5] Some attacks have an identifiable trigger, such as trauma, dental procedures, infection, daily activities such as housework or typing, or emotional stress, but usually the trigger is unknown.[10] Mild to moderate HAE attacks, such as most of those affecting the skin of the extremities, usually resolve in a few days without treatment.[1,11] Abdominal attacks may be accompanied by severe pain and nausea or diarrhea and may require prolonged bed rest or hospitalization.[9] Laryngeal attacks are rare, but as many as 50% of patients with HAE experience 1 or more laryngeal attacks during their lifetime.[12] As many as one-third of untreated laryngeal attacks have been reported to cause death from asphyxiation.[11,13]

TREATMENT OF HAE

Several expert panels composed of clinicians, researchers, pharmacologists, and public health workers have conducted extensive literature reviews and met to develop consensus guidelines on the diagnosis and treatment of HAE.[14-17] These guidelines agree that treatment should be individualized to the patient's needs to provide optimal care and restore the patient's quality of life.[14-17] Management of HAE may rely on "on-demand" treatment of acute attacks as they occur or ongoing, regular prophylactic therapy to prevent attacks.[14-16]

On-Demand Treatment

Options for on-demand therapy include C1-INH concentrate, icatibant, and ecallantide. Plasma-derived C1-INH concentrate is a pasteurized, nanofiltered product with a rapid onset of action and a long half-life.[18,19] Two C1-INH concentrate products, both given intravenously, are available in the United States (Cinryze, ViroPharma; Berinert, CSL Behring).

Randomized, controlled trials of C1-INH concentrate administered in a clinic have shown it to be safe and effective for the treatment of acute attacks of HAE, reducing the duration and severity of symptoms with a low incidence of adverse events.[20-22] A study of 31 patients trained to self-administer C1-INH concentrate found that time to initiation of therapy, time to initial symptom relief, and time to complete resolution of symptoms declined significantly with home therapy compared with previous treatment in a clinic, without the occurrence of serious adverse events.[23] Studies comparing patients who self-administered C1-INH concentrate with patients treated in a clinic found that those who self-infused reported less severe attacks, briefer attacks, fewer emergency room visits, less use of narcotic pain medications, fewer days of work missed, and fewer nights of disrupted sleep compared with patients treated in a clinic.[24,25] Self-treating patients also report improved quality of life, including better family life and social life.[25,26] With the help of a parent or guardian, pediatric patients have successfully administered C1-INH concentrate, with faster initiation of treatment, less time to symptom relief, and fewer days of hospitalization and days lost from school.[27]

Icatibant (Firazyr, Shire) is a selective antagonist of the bradykinin B2 receptor given SC.[28] It has been shown to be superior to placebo in reduction of symptom severity, time to initial relief of symptoms, and time to almost-complete symptom relief.[28] Icatibant is well tolerated, with a low incidence of adverse events, although injection site reactions occur in a majority of patients, and the administration of a second dose is sometimes necessary.[28,29] An observational study of patients with HAE treated with icatibant found that among patients who self-administered the drug, 44% of attacks were treated within 1 hour compared with 22% in patients who received treatment in a clinic, and the duration of attacks was significantly briefer in patients who self-administered icatibant.[30]

Ecallantide (Kalbitor, Dyax) is a potent, specific inhibitor of plasma kallikrein, which is given SC. It has been shown to reduce significantly the duration and severity of acute attacks of HAE.[31] However, hypersensitivity reactions to ecallantide, including anaphylaxis, have been reported, making it unsuitable for self-administration.[32] Ecallantide has been administered in home settings by trained health care professionals.

Long-Term Prophylactic Therapy

Attenuated androgens—danazol, stanozolol, oxymetholone, and methyltestosterone—have been widely used for prophylactic therapy of HAE and have been shown to reduce the frequency of attacks by 84%.[33] However, as many as 25% of patients discontinue attenuated androgens because of intolerable adverse events.[33] Attenuated androgen therapy may be associated with serious adverse effects including virilization of women, hypertension, liver neoplasms, and erythrocytosis; these agents are contraindicated in childhood and pregnancy.[1]

C1-INH concentrate is recommended in clinical guidelines for long-term prophylaxis of HAE attacks.[14-17] The rapid onset of action, long half-life, and low incidence of adverse effects of C1-INH concentrate make it suitable for prophylactic use.[18,19,34] In a prospective study, 10 patients with HAE who had frequent attacks despite danazol prophylaxis or who were intolerant of danazol were trained in prophylactic self-administration of C1-INH concentrate.[23] There was a significant decline in frequency of attacks, and most patients were attack-free during follow-up of 3.5 years. A study of 22 patients with HAE refractory to danazol found that prophylactic self-administration of C1-INH concentrate resulted in a significant decrease in attack frequency (mean decrease of 43 attacks per year).[35]

Recent consensus guidelines include the following key recommendations for treatment of HAE[14]:

- Any HAE attack can become disabling or life-threatening; therefore, all patients with C1-INH deficiency, even if asymptomatic, should have access to therapy.
- Whenever possible, patients should have access to on-demand treatment for acute attacks at home and should be trained to self-administer their treatment.
- All attacks, irrespective of location, are eligible for treatment as soon as they are clearly recognized by the patient, ideally before visible or disabling symptoms develop.
- On-demand treatment for acute attacks should be the initial goal for all patients because it may reduce morbidity and prevent mortality.
- Long-term prophylactic treatment should be provided to patients with frequent or severe attacks or for whom on-demand treatment is inadequate to minimize the burden of illness due to HAE.

Home-Based Treatment of HAE

Although the concept of IV therapy self-administered at home may appear daunting for both patients and health care providers, it has been successfully used for many years for patients with hemophilia, cystic fibrosis, and immunodeficiency.[3]

The experience of patients with hemophilia illustrates many of the needs and challenges that patients with HAE face when providing self-administered therapy. With effective teaching, patients have demonstrated that they can be fully informed about their illness, aware of disease pathology and presentation, able to recognize when treatment is necessary, knowledgeable about how and when to get support, and able to manage unfamiliar situations, such as travel.[36] Research with hemophilia patients has demonstrated that they learn to self-administer blood products primarily through individualized instruction and their own experience rather than through formal educational programs.[37] Successful home treatment of hemophilia is associated with establishing a supportive learning environment, managing anxiety, fostering a belief in the benefits of home treatment, and establishing a good relationship with health care providers.[38,39] Working with HAE patients has demonstrated that their educational needs are similar to those of hemophilia patients and that many are capable of successfully treating their symptoms at home.

Although not every patient is an appropriate candidate for IV self-administration, the practice offers clinical and personal benefits compared with routinely seeking treatment from a hospital or outpatient facility:

- Because HAE is a rare disorder, hospitals may not stock C1-INH or other HAE treatments, and staff may be unfamiliar with HAE.[3,15]
- Travel time to a hospital and waiting time in the emergency department can lead to a delay in treatment.[15]
- Some patients will opt not to treat an HAE attack if obtaining treatment at a hospital is too cumbersome, thus prolonging symptoms and contributing to greater absenteeism from work or school and loss of productivity.[15]
- Data from clinical trials demonstrate that early treatment may reduce the duration of an HAE attack and reduce the severity of symptoms.[23,25,27]

NURSING NEEDS OF PATIENTS SELF-ADMINISTERING HAE MEDICATIONS

Nurses play a key role in facilitating home treatment of HAE. The nurse is responsible for ensuring that the patient has adequate knowledge of the cause, symptoms, clinical course, and treatment of the disease. Most patients with the rare, lifelong condition have become familiar with these topics out of necessity. The nurse should conduct an evaluation to confirm that the patient is physically and mentally capable of learning to self-administer an IV medication and should make a home visit to determine whether the environment is a safe place to store and administer the agent. Finally, the nurse teaches the patient when and how to administer the agent and follows the patient's progress to ensure quality of care. Table 1 shows specific teaching objectives for patients who will self-treat HAE.

Patient Selection

All patients with HAE should be considered for training in self-administration and managing an ongoing treatment program at home.[2,15] Factors to evaluate regarding the individual patient include:

- Is the patient mentally and physically capable of self-administering an IV drug?
- Is the patient reliable (eg, does the patient keep scheduled appointments or call to reschedule when necessary)?
- Is the patient motivated to learn self-administration and willing to invest the time required for training?
- Does the patient have adequate veins?

Age need not prevent training for home IV therapy, although young patients and those of advanced age will likely require assistance with infusions.[15]

The patient's living and social situation can influence the decision to institute home therapy. Patients who are unable to reach a hospital emergency department or clinic within approximately 1 hour because of geographic or transportation issues, those who are temporarily away from home (eg, at college), or those who are

TABLE 1

Teaching Objectives for Patients Who Will Treat HAE at Home

Patients with HAE should be able to demonstrate knowledge of:	
1.	Basic information regarding the cause, pathophysiology, symptoms, and clinical course of HAE
2.	Which HAE attacks require treatment
3.	When to initiate treatment
4.	How to administer the intravenous agent (see Table 2)
5.	An appropriate backup plan if the first treatment is not successful
6.	Management of treatment-associated adverse events
7.	When and how to seek help from a health care professional
8.	Appropriate documentation of the time, location, severity, and outcome of each attack

Abbreviation: HAE, hereditary angioedema.

frequent travelers may derive particular benefit from home therapy. Although some patients may be able to manage on their own, in most cases, patients should have a family member or caregiver who is willing to participate in the training and will be available to help administer the drug and monitor the patient's condition.[15] All patients should be able to reach their health care team by telephone and obtain transportation to a hospital or clinic, if problems arise during self-administration.

It's also important to consider the nature and frequency of the patient's HAE attacks when considering home therapy. Some experts suggest that home therapy is appropriate for patients who routinely experience more than 1 HAE attack a month; others suggest that an attack frequency of once every 3 months is sufficient.[2,27] Whatever minimum frequency is used, patients should treat attacks often enough so that they retain self-administration skills. For this reason, patients who self-administer prophylactic therapy or frequent on-demand therapy may do better than those who use the drug infrequently. Patients with a moderate to high frequency of attacks, in particular, become quite proficient in the IV administration technique and are particularly good candidates for self-infusion training. Nevertheless, patients with infrequent attacks may be appropriate candidates for home therapy, if they are highly motivated and well trained; some patients may be interested in implementing C1-INH as backup therapy if other primary intervention fails. For these patients, regular review of self-administration technique is advisable. Attack location may also influence the decision to institute home therapy. For a patient with frequent laryngeal attacks, home therapy may be lifesaving, but a patient whose attacks frequently affect extremities (eg, hands) may find it difficult or impossible to self-administer medication.

Training Process

Training patients to self-administer medication to treat or prevent attacks of HAE can usually be accomplished in 1 to 3 sessions, depending on the patient's level of ability. The assistance of a nurse who frequently treats patients with hemophilia or cystic fibrosis may be helpful. It's recommended that a family member or caregiver, if available, attend the training sessions so that the patient has backup support when necessary. The first session should begin with a demonstration of the proper infusion technique to the patient and caregiver, and continue with practice by the patient, including actual insertion of the winged infusion set and administration of normal saline or the first dose of drug. In subsequent sessions, the technique should be reviewed. The patient should demonstrate the technique in front of the instructor and be given an opportunity to ask questions. Topics covered during training are listed in Table 2.

Backup Plan

It's prudent for HAE patients to have a backup plan in the event that their initial intervention is not successful. This may include administering a second dose of C1-INH after a sufficient time has elapsed, using an alternate product, or seeking medical care.

Patient Follow-up

It's crucial that the patient have 24-hour access to a member of the health care team in the event of a problem with self-administration of C1-INH. Each attack treated at home should be reported to the health care team or recorded for later review so that the clinic can track the patient's attack frequency and the efficacy of the treatment. Patients should have regularly scheduled checkups at the clinic. These are scheduled every

TABLE 2

Topics to Cover When Training Patients to Self-administer C1-INH Concentrate

1.	Sterile technique, including hand washing or use of sterile gloves and cleaning work surface
2.	Confirming that the product is at the correct temperature and has not reached its expiration date
3.	Mixing the product
4.	Inspecting the product for cloudy or discolored appearance or particles
5.	Drawing the solution into the syringe
6.	Priming the infusion set
7.	Preparing the infusion site by applying a tourniquet and cleaning area with alcohol wipe
8.	Inserting and securing the winged infusion set
9.	Confirming that the needle is in a vein
10.	Attaching the syringe to the tubing and starting the infusion
11.	Removing the butterfly needle and covering the infusion site
12.	Properly disposing of the empty vials, used needles, and syringe
13.	Recording the infusion details
14.	Care of veins

Abbreviation: C1-INH, C1 esterase inhibitor concentrate.

6 months in the authors' practice. A system should be in place to ensure that patients have access to a sufficient quantity of the medication they will use. In the authors' practice, the clinic provides all supplies for home treatment of HAE, which serves as an indirect means of tracking product use and attack frequency. If this isn't practical, patients may obtain the drug and supplies through a specialty pharmacy.

Patient Resources

The US Hereditary Angioedema Association (www.haea.org), a patient advocacy and educational organization, provides extensive information for patients online and in print. The manufacturers of C1-INH products (CSL Behring [Berinert] and ViroPharma [Cinryze]) have multiple resources in a variety of media to help patients learn to self-administer IV medications. Such resources may be useful for training purposes as well as ongoing support for patients who are self-administering at home.

Comprehensive Care Clinics

Training patients for home therapy for HAE may be facilitated by the establishment of an HAE comprehensive care clinic modeled on hemophilia clinics that supervise all aspects of patient care. For HAE patients, a single center that provides services, such as treatment for acute attacks, prophylactic therapy, education about the disease, dental consultation, access to resources, and training in self-administration, may improve quality of care. Key to the successful implementation of a comprehensive care clinic are the services of a dedicated nurse who can coordinate patient care and adapt the model to each individual's needs.

CONCLUSIONS

HAE is a lifelong disease with significant morbidity that may have a marked impact on a patient's quality of life. HAE attacks may be frequent, and the need to seek treatment in a hospital or clinic poses substantial burdens on patients in terms of economics and convenience; as a result, some patients may choose to forgo treatment rather than travel to a facility to avoid missing work or school while seeking treatment. With motivation and proper training, most patients are able to learn to self-administer C1-INH concentrate at home, which may reduce the time from the onset of symptoms to the beginning of treatment, provide faster onset of relief, reduce the overall cost of care and severity and duration of attacks, and improve the patient's quality of life. Patients who use C1-INH prophylactically may significantly reduce the frequency of attacks. By learning to treat attacks at home without the need to travel to a medical facility, patients can gain a degree of independence and control over their condition and enjoy improved quality of life.

ACKNOWLEDGMENTS

The authors thank Churchill Communications (Maplewood, New Jersey) for assistance in preparing this manuscript. This assistance was funded by CSL Behring.

REFERENCES

1. Bowen T, Cicardi M, Bork K, et al. Hereditary angioedema: a current state-of-the-art review, VII: Canadian Hungarian 2007 international consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2008;100(suppl 2):30S-40S.
2. Gompels MM, Lock RJ, Abinun M, et al. C1 inhibitor deficiency: consensus document. *Clin Exp Immunol*. 2005;139:379-394.
3. Agostoni A, Aygören-Pürsün E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004;114(suppl 3):51S-131S.
4. Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, Horn PT. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc*. 2010;31:407-414.
5. Zuraw BL. Clinical practice: hereditary angioedema. *N Engl J Med*. 2008;359:1027-1036.
6. Dobó J, Major B, Kékesi KA, et al. Cleavage of kininogen and subsequent bradykinin release by the kinin component: mannose-binding lectin-associated serine protease (MASP)-1. PLoS One. 2011;6(5):e20036. Available at: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0020036. Accessed June 18, 2014.
7. Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet*. 2000;356:213-217.
8. Cichon S, Martin L, Hennies HC, et al. Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. *Am J Hum Genet*. 2006;79:1098-1104.
9. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med*. 2006;119(3):267-274.
10. Levy JH, Freiberger DJ, Roback J. Hereditary angioedema. *Anesth Analg*. 2010;110(5):1271-1280.
11. Bernstein JA, Moellman JJ. Progress in the emergency management of hereditary angioedema: focus on new treatment options in the United States. *Postgrad Med*. 2012;124(3):91-100.
12. Bork K, Staubach P, Eckardt AJ, Hardt J. Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. *Am J Gastroenterol*. 2006;101(3):619-627.
13. Christiansen SC, Zuraw BL. Hereditary angioedema: management of laryngeal attacks. *Am J Rhinol Allergy*. 2011;25:379-382.
14. Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy*. 2011;67:147-157.

15. Longhurst HJ, Farkas H, Craig T, et al. HAE international home therapy consensus document. *Allergy Asthma Clin Immunol*. 2010;6(1):22.
16. Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol*. 2010;6:24.
17. Craig TJ, Aygören-Pürsün E, Bork K, et al. WAO guideline for the management of hereditary angioedema. *World Allergy Organ J*. 2012;5:182-199.
18. Berinert [package insert]. Kankakee, IL: CSL Behring LLC; 2012.
19. Cinryze [package insert]. Exton, PA: ViroPharma Biologics Inc; 2012.
20. Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol*. 2009;124:801-808.
21. Craig TJ, Bewtra AK, Bahna SL, et al. C1 esterase inhibitor concentrate in 1085 hereditary angioedema attacks: final results of the I.M.P.A.C.T.2 study. *Allergy*. 2011;66:1604-1611.
22. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med*. 2010;363(6):513-522.
23. Levi M, Choi G, Picavet C, Hack CE. Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency. *J Allergy Clin Immunol*. 2006;117:904-908.
24. Longhurst HJ, Carr S, Khair K. C1-inhibitor concentrate home therapy for hereditary angioedema: a viable, effective treatment option. *Clin Exp Immunol*. 2006;147(1):11-17.
25. Tourangeau LM, Castaldo AJ, Davis DK, Koziol J, Christiansen SC, Zuraw BL. Safety and efficacy of physician-supervised self-managed C1 inhibitor replacement therapy. *Int Arch Allergy Immunol*. 2012;157:417-424.
26. Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. *Eur J Dermatol*. 2009;19:147-151.
27. Kreuz W, Rusicke E, Martinez-Saguer I, Aygören-Pürsün E, Heller C, Klingebiel T. Home therapy with intravenous human C1-inhibitor in children and adolescents with hereditary angioedema. *Transfusion*. 2012;52:100-107.
28. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med*. 2010;363(6):532-541.
29. Lumry WR, Li HH, Levy RJ, et al. Randomized placebo-controlled trial of the bradykinin B2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. *Ann Allergy Asthma Immunol*. 2011;107:529-537
30. Maurer M, Aberer W, Bouillet L, et al. Hereditary angioedema attacks resolve faster and are shorter after early icatibant treatment. *PloS ONE*. 2013;8(2):e53773. Available at: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0053773. Accessed June 18, 2014.
31. Cicardi M, Levy RJ, McNeil DL, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med*. 2010;363(6):523-531.
32. Caballero T, López-Serrano C. Anaphylactic reaction and antibodies to DX-88 (kallikrein inhibitor) in a patient with hereditary angioedema. *J Allergy Clin Immunol*. 2006;117(2):476-477.
33. Bork K, Bygum A, Hardt J. Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. *Ann Allergy Asthma Immunol*. 2008;100:153-161.
34. Bork K, Hardt J. Hereditary angioedema: long-term treatment with one or more injections of C1 inhibitor concentrate per week. *Int Arch Allergy Immunol*. 2011;154(1):81-88.
35. Kreuz W, Martinez-Saguer I, Aygören-Pürsün E, Rusicke E, Heller C, Klingebiel T. C1-Inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. *Transfusion*. 2009;49(9):1987-1995.
36. Lane S, Arnold E, Webert KE, Chan A, Walker I, Heddle NM. What should men living with severe haemophilia need to know? The perspectives of Canadian haemophilia health care providers. *Haemophilia*. 2013;19(4):503-510.
37. Khair K, Meerabeau L, Gibson F. Self-management and skills acquisition in boys with haemophilia [published online May 27, 2013]. *Health Expect*. doi: 10.1111/hex.12083.
38. Furmedge J, Lima S, Monagle P, Barnes C, Newall F. 'I don't want to hurt him': parents' experiences of learning to administer clotting factor to their child. *Haemophilia*. 2013;19(2):206-211.
39. Schrijvers LH, Uitslager N, Schuurmans MJ, Fischer K. Barriers and motivators of adherence to prophylactic treatment in haemophilia: a systematic review. *Haemophilia*. 2013;19(3):355-361.