

Managing hereditary angioedema patients undergoing otolaryngeal procedures

Jonathan A. Bernstein, M.D.

ABSTRACT

Background: Hereditary angioedema (HAE), a rare autosomal dominant disorder, is characterized by repeated attacks of swelling of the skin, gastrointestinal tract, face, larynx, and other organs. In most cases it is caused by low levels of functional C1 esterase inhibitor (C1-INH), a serine protease inhibitor that plays important regulatory roles in the complement, contact, and fibrinolytic pathways.

Methods: Lack of functional C1-INH results in excessive release of bradykinin, which triggers vasodilation, vascular permeability, and edema. Most attacks are mild and self-limiting, but untreated laryngeal attacks may cause rapid asphyxiation and death. Potential triggers of laryngeal attacks include trauma to or manipulation of the face, mouth, or upper airway. Therefore, before performing such a procedure in a patient with HAE, the otolaryngologist should consult with the patient, the physician managing the HAE, and the anesthesiologist and make appropriate preparations for prevention and/or treatment of an attack.

Results: Current World Allergy Organization and European guidelines recommend the use of i.v. plasma-derived C1-INH replacement for short-term prophylaxis of angioedema attacks. Other effective options include danazol given for several days before and after the procedure and fresh-frozen plasma, but these may not be as effective as C1-INH and may be associated with a high rate of adverse events.

Conclusion: Acute attacks, which may occur many hours after a procedure, may be treated with C1-INH; icatibant, a bradykinin B₂-receptor antagonist; or ecallantide, a kallikrein inhibitor, all of which have been shown to reduce the duration and severity of HAE attacks.

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Hereditary angioedema (HAE) is a rare autosomal dominant disorder that causes recurrent attacks of nonpruritic, nonpitting swelling, without urticaria, affecting ~1 in 50,000 persons.^{1,2} It affects ~1/50,000 persons and accounts for ~2% of clinical angioedema.² Most attacks occur in the skin of the extremities or in the gastrointestinal tract and are self-limiting, but attacks may occur in any organ system and those affecting the larynx may cause life-threatening asphyxiation.³ Although attacks of HAE usually occur without recognized triggers, they may be precipitated by minor trauma; dental procedures and manipulation of the face, mouth, or upper airway have been known to trigger laryngeal attacks.⁴ Therefore, despite the rarity of the condition, otolaryngologists should be aware of HAE and familiar with its management, including the use of appropriate prophylactic measures before a procedure and the provision of adequate measures to treat an acute laryngeal attack.⁵ This article provides a brief summary of the pathophysiology and clinical features of HAE and discusses the management of patients undergoing upper airway manipulation or procedures.

PATHOPHYSIOLOGY OF HAE

The most common types of HAE result from lack of functional C1-esterase inhibitor (C1-INH), a serine protease inhibitor that plays important regulatory roles in the contact, complement, and fibrinolytic pathways.¹ Type 1 HAE, which accounts for ~85% of cases, results from genetic mutations that cause both mutated, dysfunctional C1-INH proteins and abnormally low secretion of the defective proteins. In type 2 HAE, genetic aberration results in normal secretory levels of a dysfunctional C1-INH protein (Table 1).¹ The two types are clinically indistinguishable. Reduced C1-INH concentration or function results in the release of vasoactive peptides, including bradykinin.^{4,6–9} Bradykinin release activates endothelial cells, provoking

vasodilation, vascular permeability, and production of inflammatory mediators such as nitric oxide, prostaglandins, and leukotrienes, which together cause edema.¹⁰

A third type of HAE, first identified in 2000, is not associated with deficiency of C1-INH and occurs primarily in women.¹¹ In some patients with this disorder, a mutation has been identified in the gene coding for blood coagulation factor XII, which promotes the generation of kinins.¹² A recent consensus statement recommends that this form of HAE be termed HAE with normal complement with or without a genetic defect.¹³

CLINICAL FEATURES OF HAE

Individuals with HAE experience recurrent episodes of soft tissue swelling affecting various parts of the body.^{2,3} Attacks may be precipitated by events such as dental procedures, infection, daily activities such as household work or typing, emotional stress, or other minor trauma or physical manipulation.^{14,15} Many HAE attacks are mild to moderate in severity and self-limiting; without treatment, symptoms typically escalate during the first 24 hours and then recede over the following 48–72 hours.¹ Laryngeal attacks are less common than peripheral or abdominal attacks, but up to 50% of patients with HAE report having experienced a laryngeal attack during their lifetime and some experience multiple laryngeal attacks.³ Attacks affecting the face and neck may spread to the larynx, and up to one-third of untreated laryngeal attacks may result in death from asphyxiation.^{16,17} Although laryngeal attacks usually progress slowly enough for emergency treatment to be obtained, death from laryngeal edema has been reported to occur in <20 minutes.^{18,19} Diligent prophylaxis and preparation for the possibility of laryngeal edema are thus a priority for the otolaryngologist treating a patient with HAE.

THERAPEUTIC OPTIONS FOR HAE

Several new treatments for HAE have been introduced in the United States in recent years (Table 2). These agents have various sites of action in the complement, contact, and fibrinolytic systems, but all ultimately prevent edema by reducing the production of or blocking the effects of bradykinin, the final mediator (Fig. 1).

Human plasma-derived C1-INH concentrate (pdC1-INH) has been available in Europe and Canada for several decades, and two i.v. preparations are now available in the United States (Berinert; CSL Behring, Kankakee, IL; Cinryze; ViroPharma, Inc., Exton,

From the Division of Immunology/Allergy Section, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio

JA Bernstein is a Principal Investigator, Consultant and Speaker for CSL Behring, ViroPharma, Dyax, and Shire and he is a Principal Investigator for Pharming and a co-editor of the AAAAI/ACAAI Joint Task Force Practice Parameter for Angioedema. Address correspondence to Jonathan A. Bernstein, M.D., 3255 Eden Avenue ML Number 563, Suite 350, Cincinnati, OH 45267-0563

E-mail address: Jonathan.Bernstein@uc.edu

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Table 1 Characteristics of type 1 and type 2 HAE and HAE with normal C1-INH

Type	Proportion of Cases	C4	Antigenic C1-INH	Functional C1-INH	C1q
Type 1	85%	Decreased	Decreased	Decreased	Normal
Type 2	15%	Decreased	Normal or elevated	Decreased	Normal
HAE with normal C1-INH	Rare; occurs primarily in women	Normal	Normal	Normal	Normal

Source: Ref. 1.

HAE = hereditary angioedema; C1-INH = C1 esterase inhibitor.

Table 2 Therapeutic options for management of HAE

	pdC1-INH	Recombinant Human C1-INH	Ecallantide	Icatibant
Route	Intravenous	Intravenous	Subcutaneous	Subcutaneous
Primary safety issue	Infectious (?)	Allergic (?)	Allergic	Local pain
Acute use	++++	++++	++++	++++
Short-term prophylaxis	++++	?	?	?
Long-term prophylaxis	++++	—	—	—
Home use	++	++	—	++++

Source: Ref. 17.

pdC1-INH = plasma-derived C1 esterase inhibitor; HAE = hereditary angioedema.

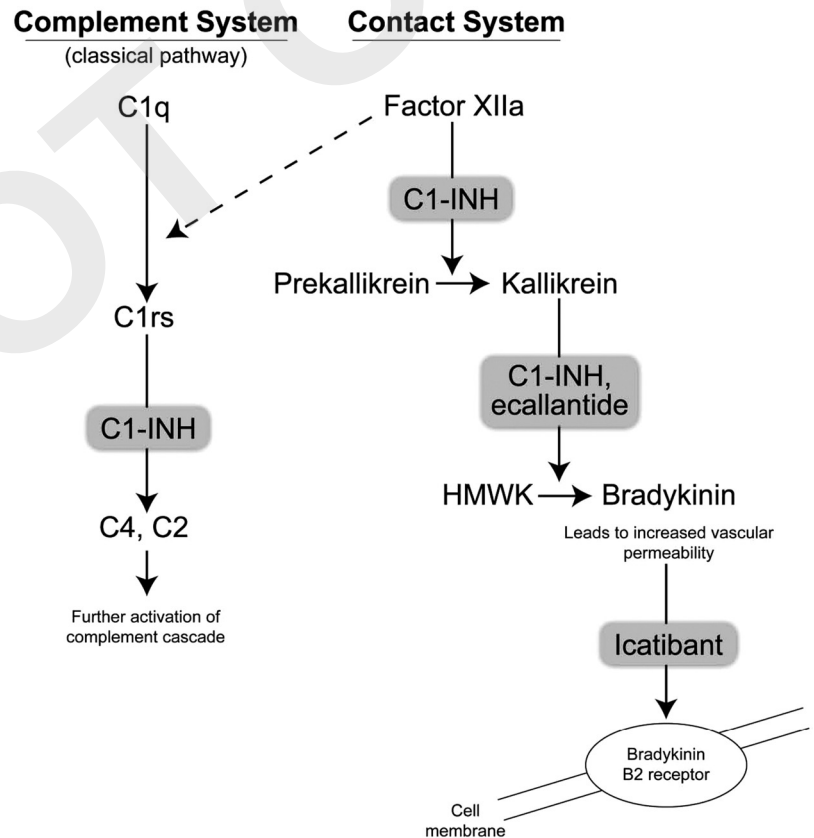


Figure 1. Physiological pathways involved in hereditary angioedema (C1 esterase inhibitor [C1-INH] deficiency) pathology and sites of action for available treatments (C1-INH, ecallantide, and icatibant). (Source: Adapted from Banerji A, and Sheffer AL. Allergy Asthma Proc 30:11–16, 2009.)⁶²

Adapted from Banerji A, Sheffer AL, Allergy Asthma Proc 2009;30:11-16.

PA).^{20,21} To reduce viral transmission risk, both pdC1-INH products undergo pasteurization and nanofiltration.^{20,21} In the International multicenter prospective angioedema C1-INH trial-1 (I.M.P.A.C.T.1) and I.M.P.A.C.T.2, trials, pdC1-INH given to treat HAE attacks was found to significantly reduce the duration and severity of attacks with few adverse events.^{22,23} Prophylactic use of pdC1-INH was found in two randomized trials to reduce the frequency of HAE attacks and was

well tolerated.^{24,25} Recombinant human C1-INH, derived from the milk of transgenic rabbits, has been studied in randomized, double-blind trials for treatment of acute attacks of HAE and found to be safe and effective, but although approved in Europe is not currently approved in the United States.²⁶ Patients can be trained to self-administer C1-INH concentrate at home, thereby reducing the time from symptom onset to start of therapy.^{27,28}

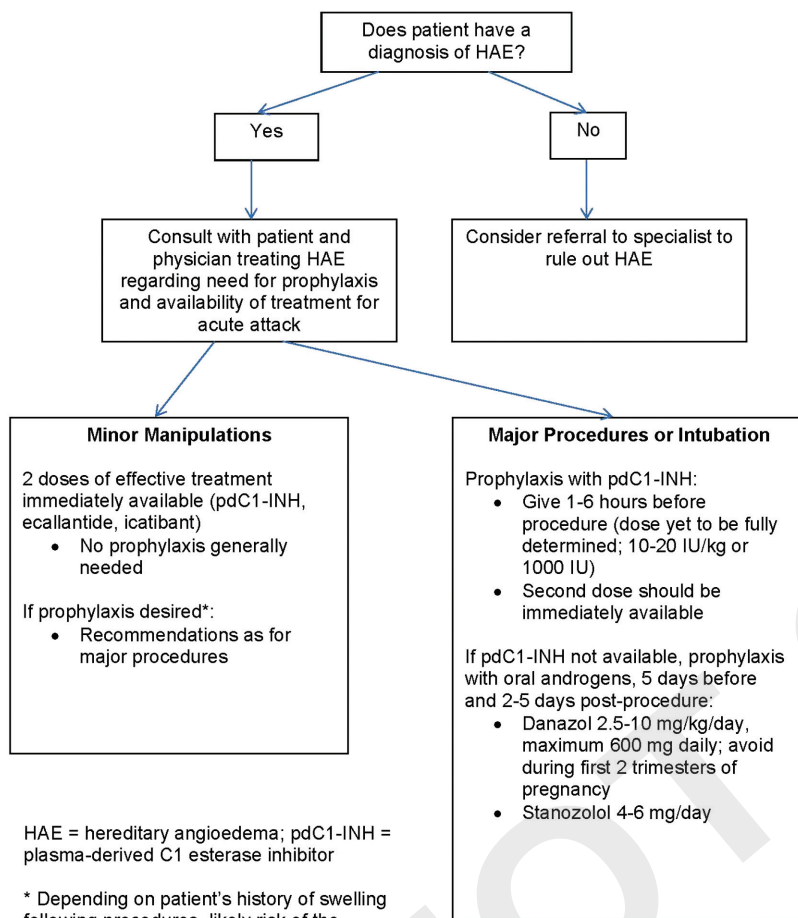


Figure 2. Considerations before an ear, nose, and throat (ENT) procedure in a patient with a history of angioedema (Source: Bowen 2010, WHO guidelines).³⁷

Ecallantide (Kalbitor; Dyax, Burlington, MA), a recombinant protein, is a potent, specific inhibitor of plasma kallikrein administered *via* subcutaneous injection.²⁹ In the randomized, controlled Evaluation of DX-88's Effects in Mitigating Angioedema 3 (EDEMA3) trial, ecallantide was shown to be significantly superior to placebo for relief of acute attacks of HAE.²⁹ Hypersensitivity reactions to ecallantide, including anaphylaxis, have been reported; therefore, ecallantide is not recommended for self-administration but can be safely administered in the patient's home under the supervision of a trained health care professional.^{30,31}

Icatibant (Firazyr; Shire, Lexington, MA) is a selective antagonist of the bradykinin B₂-receptor given by subcutaneous injection for the treatment of acute HAE attacks.³² In a series of controlled trials it was shown to be superior to placebo or tranexamic acid in reduction of symptom severity, time to initial relief of symptoms, and time to almost complete symptom relief.^{32,33} Localized, painful injection site reactions occur in a majority of patients treated with icatibant.^{32,33} Icatibant has been used successfully for at-home treatment of acute HAE attacks.³⁴

PATIENT MANAGEMENT

Identifying Patients at Risk

Surgical and manipulative procedures on the airways pose a significant risk to patients with HAE.⁴ Laryngeal attacks, some of which were fatal, have been reported after tooth extraction.^{35,36} In one case series, the mean time between tooth extraction and onset of facial and/or laryngeal swelling was 14.3 hours, with a range of 1-72 hours reported.³⁶

Before a procedure or surgery, patients should be asked about a history of skin swelling and, if it is present, whether they have ever been diagnosed with HAE. Patients who have received a diagnosis generally become quite knowledgeable about their disease, and many have affected family members as well. Patients and their family members or caregivers should be viewed as credible sources of information and treated as partners in deciding on a management strategy. If patients report a personal or family history of skin swelling but have not received a diagnosis, an allergist or other specialist with expertise in the evaluation, diagnosis, and management of HAE should be consulted for further evaluation before the procedure is performed.

Developing an HAE-Specific Strategy before Ear, Nose, and Throat Procedures

When a diagnosis of HAE has been confirmed, a periprocedural management plan should be designed using a multidisciplinary approach that includes the patient or caregiver, the otolaryngologist, the patient's primary HAE physician, and the anesthesiologist (Fig. 2). Patients known to have HAE should be informed that the procedure might trigger an episode of edema, possibly a laryngeal episode. Short-term preoperative prophylaxis reduces the risk of HAE attacks associated with surgery, dental work, and other procedures and should be offered to patients undergoing ear, nose, and throat (ENT) procedures.^{1,37} However, no double-blind, placebo-controlled study has been conducted to determine if empiric short-term prophylaxis is more clinically effective or cost-effective than having "on-demand" therapy readily available during a procedure. This would be espe-

cially important to know in a patient without a history of angioedema during or after invasive procedures. Furthermore, taking long-term prophylaxis (*i.e.*, pdC1-INH replacement therapy or androgens) does not completely eliminate the risk of HAE attacks secondary to surgical procedures; therefore, two doses of an agent indicated for acute treatment of attacks should be immediately available during the procedure because it is potentially life-saving and the ENT staff should be familiar with its use.^{14,36,38,39}

The patient and family members should be counseled regarding the possibility of laryngeal edema during or after the procedure. Although causation is not always definitive, HAE attacks after dental procedures have been reported to occur as much as a day or two after the procedure, and presumably the same would hold true for ENT procedures.³⁶ A plan should be developed for the patient to treat a laryngeal attack that occurs after discharge from the care of the ENT. This will in all likelihood be the same treatment strategy that the patient has been using routinely. Patients who are not already using on-demand therapy at home might be encouraged to obtain training for self-administration of an agent for the treatment of HAE; this strategy can greatly shorten the time from attack onset to treatment, a factor that has been shown to significantly reduce the duration and severity of attacks.^{28,40} Many patients are already trained to treat acute HAE attacks by self-administration of pdC1-INH or icatibant; with input and assistance from the HAE physician and nursing staff, patients not already trained might be given the option.

CLINICAL OPTIONS

Acute angioedema in patients with HAE differs in pathophysiology from more typical IgE-mediated allergic angioedema and does not respond to interventions such as antihistamines, corticosteroids, or adrenaline.⁴¹ Over the past several years, new treatments have become available in the United States that specifically target the physiological pathways involved in HAE attacks (Table 2; Fig. 1).

Prophylactic Therapy

Periprocedural prophylaxis regimens can help prevent acute HAE attacks by temporarily increasing plasma C1-INH levels. Before the availability of pdC1-INH concentrate, danazol, antifibrinolytic agents, and fresh frozen plasma were relied on for prophylaxis against HAE attacks.

Given several days before and after a procedure, danazol is effective for prevention of HAE attacks.^{35,37,42,43} However, in one published case series, almost one-half of HAE patients receiving long-term prophylactic therapy with danazol and tranexamic acid continued to experience frequent attacks of angioedema.²⁸ Another case series reported six patients who developed laryngeal edema (not associated with a medical or surgical procedure) despite being on long-term prophylaxis with danazol.⁴

Use of danazol, antifibrinolytics, and fresh frozen plasma may be complicated by their pharmacologic properties and propensity to cause adverse events. Several days of danazol treatment are required before it becomes effective, which may cause the procedure to be delayed, and unlike C1-INH, danazol is contraindicated during pregnancy and lactation.^{1,44} No studies support the use of antifibrinolytic agents for periprocedural prophylaxis of HAE attacks; moreover, they may cause muscle cramps and increases in creatine kinase and aldolase.⁴⁵ Fresh frozen plasma may be required for short-term prophylaxis if other options are unavailable, but its use carries a risk of transmitting infection.¹

The long half-life (31–48 hours) of pdC1-INH concentrate makes it suitable for prophylaxis against HAE attacks.⁴⁶ pdC1-INH has a long and established record of successfully preventing HAE attacks during surgeries and procedures including oral and dental surgery, tonsillectomy, endotracheal intubation, gastroscopy, induced abortion, and cardiac surgery.^{36,47–51} pdC1-INH also has been shown to reduce the frequency and severity of attacks when given as long-term prophylaxis.^{25,52,53}

Current international and European guidelines for the management of HAE recommend the use of pdC1-INH for short-term prophylaxis during high-risk events such as medical and dental procedures as well as for long-term prophylaxis in patients with frequent or severe attacks.^{27,37,38,42,54} It is important that an adequate dose of pdC1-INH is used. A retrospective analysis of patients who underwent tooth extractions found that HAE attacks occurred in 21.5% of cases in which no prophylaxis was provided, 16% of cases in which patients were given 500 U of pdC1-INH, and 7.5% of cases in which patients were given 1000 U of pdC1-INH.³⁶ Weight-based dosing may be a preferable approach for short-term prophylaxis.

Icatibant, ecallantide, and recombinant human C1-INH have short half-lives and are therefore not recommended for short- or long-term prophylactic management of HAE.^{27,55}

Treatment of an Acute Laryngeal Attack

Acute HAE attacks have been treated with pdC1-INH concentrate for >30 years, and a number of studies have documented rapid and effective relief of HAE symptoms with its use, as well as improved quality of life.^{22,23,28,56} In the prospective, open-label I.M.P.A.C.T.2 trial, pdC1-INH was used for the treatment of 1085 HAE attacks, primarily abdominal or peripheral, in 57 patients.²³ The median time to the onset of symptom relief was 0.46 hours and the individual average time to symptom relief was <1 hour in 90% of patients. The median time to complete resolution of HAE symptoms was 15.5 hours. An analysis of 39 laryngeal attacks that occurred among 16 patients enrolled in I.M.P.A.C.T.2. found that the median time from the beginning of the attack to the start of treatment was 2.8 hours.⁵⁷ The median time to the onset of symptom relief was 0.25 hours and was <1 hour in 95% of attacks. The median time to complete resolution of symptoms was 8.25 hours and was <16 hours in 75% of patients. All laryngeal attacks were treated successfully and no serious drug-related adverse events occurred.

In a survey of 123 patients with HAE who were followed for a mean of 7.1 years, 61 reported having experienced at least 1 laryngeal attack and, overall, 596 laryngeal attacks occurred.⁴ A total of 208 laryngeal episodes in 25 patients were treated with C1-INH.⁴ In 207 of these episodes, resolution of symptoms began within 30–60 minutes after the injection. The mean duration of laryngeal edema attacks was 15.0 hours in patients treated with pdC1-INH and 103 hours in patients not treated with pdC1-INH. No deaths occurred and neither intubation nor tracheostomy was required for any patient whose laryngeal attack was treated with pdC1-INH.

Retrospective analysis of data from 95 patients with HAE found that over a 30-year period, 42 had at least one laryngeal episode.⁵⁸ Of the 517 laryngeal episodes that occurred, 193 were treated with pdC1-INH. Treatment was successful in all cases and no emergency procedures were required. Onset of symptom relief began within 30–60 minutes of injection of pdC1-INH in most cases and within 4 hours of injection in all cases. Prophylactic pdC1-INH was administered to two patients before dental surgery and to one patient on three occasions before abdominal surgeries. No attacks of angioedema occurred during any of these procedures, and no adverse drug reactions were reported among any of the patients who were administered pdC1-INH.

The dose of Berinert, a pdC1-INH approved in the United States for acute “on-demand” treatment of HAE attacks, is individualized according to weight, with a recommended dosage of 20 IU/kg. An analysis of patient data from the I.M.P.A.C.T.2 study that categorized patients by body mass index found no significant differences among normal weight, overweight, and obese patients in time to onset of symptom relief or complete resolution of symptoms or in the frequency of adverse events.⁵⁹ Weight-based dosing may be expected to reduce the need for redosing compared with products given at a fixed dose.

In the For Angioedema Subcutaneous Treatment - 3 (FAST-3) trial of icatibant for the treatment of acute HAE attacks, five patients had

mild-to-moderate laryngeal attacks, three treated with icatibant and two treated with placebo, and five patients had severe laryngeal attacks, all treated with icatibant.³³ The median times to onset of symptom relief were 2.5 hours in mild-to-moderate attacks and 2.3 hours in severe attacks.³³ Both subjects randomized to placebo treatment eventually required icatibant for relief of laryngeal symptoms.³³ One icatibant-treated patient was treated with C1-INH as rescue medication for recurrence/worsening of symptoms. No serious drug-related adverse events occurred in icatibant-treated subjects. In the earlier FAST-1 and FAST-2 trials, 11 patients with laryngeal attacks were treated with icatibant; the median time to first improvement was 0.6 hours in FAST-1 and 1.0 hours in FAST-2, and 9 of the 11 patients had complete relief of symptoms by 4 hours.³² Three of the 8 patients with laryngeal symptoms treated with icatibant in FAST-1 required rescue medication within 24 hours for new or recurrent symptoms. Icatibant is administered subcutaneously and can be self-administered for acute attacks.³⁴

There are limited data regarding the efficacy of ecallantide for the treatment of laryngeal HAE attacks. In the randomized, double-blind, placebo-controlled EDEMA4 trial, ecallantide was found to relieve symptoms more rapidly than placebo in both laryngeal and nonlaryngeal attacks; three placebo-treated and no ecallantide-treated patients experienced emerging laryngeal symptoms.⁶⁰ One of eight ecallantide-treated patients experiencing a laryngeal attack required a second dose to control symptoms. A pooled analysis of the EDEMA4 and EDEMA3 trials found that, in patients with laryngeal attacks, symptom relief at 4 hours was significantly greater in ecallantide-treated patients than in placebo-treated patients.⁶¹ Ecallantide use has rarely been associated with the occurrence of anaphylaxis; therefore, it is inappropriate for self-administration.³¹ It can, however, be given at home under medical supervision.

CONCLUSIONS

Otolaryngologists should be aware of HAE and its potential to cause life-threatening laryngeal angioedema attacks during or after ENT procedures. Questioning patients with a history of angioedema may reveal a diagnosis of HAE. Before the procedure, the otolaryngologist should consult with the patient and his/her primary HAE physician to develop a plan for short-term prophylaxis of HAE attacks and, should this occur, treatment of an acute attack. During the procedure, it is essential that "on-demand" treatment be immediately available. Current international and European guidelines recommend the use of pdC1-INH for short-term prophylaxis of HAE attacks. Acute attacks may be treated with pdC1-INH, ecallantide, or icatibant. Patients should be made aware that an HAE attack may occur 24 hours or more after a procedure, and that they should be alert for symptoms of an attack and have access to effective treatment.

REFERENCES

- Zuraw BL. Hereditary angioedema. *N Engl J Med* 359:1027–1036, 2008.
- 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* 100(suppl 2):S30–S40, 2008.
- Bork K, Meng G, Staubach P, and Hardt J. Hereditary angioedema: New findings concerning symptoms, affected organs, and course. *Am J Med* 119:267–274, 2006.
- Bork K, Hardt J, Schicketanz K-H, and Ressel N. Clinical studies of sudden upper airway obstruction in patients with hereditary angioedema due to C1 esterase inhibitor deficiency. *Arch Intern Med* 163:1229–1235, 2003.
- Jensen NF, and Weiler JM. C1 esterase inhibitor deficiency, airway compromise, and anesthesia. *Anesth Analg* 87:480–488, 1998.
- Shoemaker LR, Schurman SJ, Donaldson VH, and Davis AE III. Hereditary angioneurotic oedema: Characterization of plasma kinin and vascular permeability-enhancing activities. *Clin Exp Immunol* 95:22–28, 1994.
- Bernstein IL. Hereditary angioedema: A current state-of-the-art review, II: Historical perspective of non-histamine-induced angioedema. *Ann Allergy Asthma Immunol* 100(suppl 2):S2–S6, 2008.
- Weis M. Clinical review of hereditary angioedema: Diagnosis and management. *Postgrad Med* 121:113–120, 2009.
- Nussberger J, Cugno M, and Cicardi M. Bradykinin-mediated angioedema. *N Engl J Med* 347:621–622, 2002.
- Dobó J, Major B, Kékesi KA, et al. Cleavage of kininogen and subsequent bradykinin release by the complement component: Mannose-binding lectin-associated serine protease (MASP)-1. *PLoS One* 6:e20036, 2011.
- Bork K, Barnstedt SE, Koch P, and Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 356:213–217, 2000.
- 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* 79:1098–1104, 2006.
- Zuraw BL, Bork K, Binkley KE, et al. Hereditary angioedema with normal C1 inhibitor function: Consensus of an international expert panel. *Allergy Asthma Proc* 33:S145–S156, 2012.
- Levy JH, Freiburger DJ, and Roback J. Hereditary angioedema: Current and emerging treatment options. *Anesth Analg* 110:1271–1280, 2010.
- Frank MM, Gelfand JA, and Atkinson JP. Hereditary angioedema: The clinical syndrome and its management. *Ann Intern Med* 84:580–593, 1976.
- Bernstein JA, and Moellman JJ. Progress in the emergency management of hereditary angioedema: Focus on new treatment options in the United States. *Postgrad Med* 124:91–100, 2012.
- Christiansen SC, and Zuraw BL. Hereditary angioedema: management of laryngeal attacks. *Am J Rhinol Allergy* 25:379–382, 2011.
- Moellman JJ, and Bernstein JA. Diagnosis and management of hereditary angioedema: An emergency medicine perspective. *J Emerg Med* 43:391–400, 2012.
- Bork K, Siedlecki K, Bosch S, et al. Asphyxiation by laryngeal edema in patients with hereditary angioedema. *Mayo Clin Proc* 75:349–354, 2000.
- CSL Bering, LLC. Berinert package insert. Kankakee, IL; 2012. (Last revision, December 2011).
- ViroPharma Biologics, Inc. Cinryze package insert. Exton, PA; 2012. (Last revision, November 2012).
- 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* 124:801–808, 2009.
- Craig TJ, Bewtra AK, Bahna DL, et al. C1 esterase inhibitor concentrate in 1085 hereditary angioedema attacks—Final results of the I.M.P.A.C.T. 2 study. *Allergy* 66:1604–1611, 2011.
- Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 363:513–522, 2010.
- Zuraw BL, and Kalfus I. Safety and efficacy of prophylactic nanofiltered C1-inhibitor in hereditary angioedema. *Am J Med* 125:938.e1–938.7, 2012.
- Zuraw B, Cicardi M, Levy RJ, et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. *J Allergy Clin Immunol* 126:821–827, 2010.
- Longhurst HJ, Farkas H, Craig T, et al. HAE international home therapy consensus document. *Allergy Asthma Clin Immunol* 6:22, 2010.
- Levi M, Choi G, Picavet C, and Hack CE. Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency. *J Allergy Clin Immunol* 117:904–908, 2006.
- Cicardi M, Levy RJ, McNeil DL, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med* 363:523–531, 2010.
- Lunn M, and Banta E. Ecallantide for the treatment of hereditary angioedema in adults. *Clin Med Insights Cardiol* 5:49–54, 2011.
- Caballero T, and López-Serrano C. Anaphylactic reaction and antibodies to DX-88 (kallikrein inhibitor) in a patient with hereditary angioedema. *J Allergy Clin Immunol* 117:476–477, 2006.

32. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 363: 532–541, 2010.
33. 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* 107:529–537, 2011.
34. Farkas H, Csuka D, Zotter L, et al. At-home treatment of patients with acute attacks of hereditary angioedema with the bradykinin B₂ receptor antagonist icatibant. *J Allergy Clin Immunol* 127:AB233, 2011 (Abs).
35. Bork K, and Barnstedt SE. Laryngeal edema and death from asphyxiation after tooth extraction in four patients with hereditary angioedema. *J Am Dent Assoc* 134:1088–1094, 2003.
36. Bork K, Hardt J, Staubach-Renz P, and Witzke G. Risk of laryngeal edema and facial swellings after tooth extraction in patients with hereditary angioedema with and without prophylaxis with C1 inhibitor concentrate: a retrospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 112:58–64, 2011.
37. 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* 6:24, 2010.
38. Craig T, Pürsün EA, Bork K, et al. WAO guideline for the management of hereditary angioedema. *World Allergy Organ J* 5:182–199, 2012.
39. Wall RT, Frank M, and Hahn M. A review of 25 patients with hereditary angioedema requiring surgery. *Anesthesiology* 71:309–311, 1989.
40. Tourangeau LM, Castaldo AJ, Davis DK, et al. Safety and efficacy of physician-supervised self-managed C1 inhibitor replacement therapy. *Int Arch Allergy Immunol* 157:417–424, 2012.
41. Roche O, Blanch A, Caballero T, et al. Hereditary angioedema due to C1 inhibitor deficiency: Patient registry and approach to the prevalence in Spain. *Ann Allergy Asthma Immunol* 94:498–503, 2005.
42. Farkas H, Gyeney L, Gidófalvy E, et al. The efficacy of short-term danazol prophylaxis in hereditary angioedema patients undergoing maxillofacial and dental procedures. *J Oral Maxillofac Surg* 57:404–408, 1999.
43. Gompels MM, Lock RJ, Abinun M, et al. C1 inhibitor deficiency: Consensus document. *Clin Exp Immunol* 139:379–394, 2005.
44. Caballero T, Farkas H, Bouillet L, et al. International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. *J Allergy Clin Immunol* 129:308–320, 2012.
45. Van Sickels NJ, Hunsaker RB, and Van Sickels JE. Hereditary angioedema: Treatment, management, and precautions in patients presenting for dental care. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 109:168–172, 2010.
46. Keating GM. Human C1-esterase inhibitor concentrate (Berinert). *Biodrugs* 23:399–406, 2009.
47. Farkas H, Varga L, Szeplaki G, et al. Management of hereditary angioedema in pediatric patients. *Pediatrics* 120:e713–e722, 2007.
48. Farkas H, Jakab L, Temesszentandrás G, et al. Hereditary angioedema: A decade of human C1-inhibitor concentrate therapy. *J Allergy Clin Immunol* 120:941–947, 2007.
49. Bernstein JA, Coleman S, and Bonnin AJ. Successful C1 inhibitor short-term prophylaxis during redo mitral valve replacement in a patient with hereditary angioedema. *J Cardiothor Surg* 5:86, 2010.
50. Hermans C, VanDer Vorst S, and Lambert C. Successful management of hereditary angioedema during tonsillectomy: A case report. *Blood Coagul Fibrinolysis* 23:155–157, 2012.
51. Grant JA, White MV, Li HH, et al. Preprocedural administration of nanofiltered C1 esterase inhibitor to prevent hereditary angioedema attacks. *Allergy Asthma Proc* 33:348–353, 2012.
52. Bork K, and Hardt J. Hereditary angioedema: Long-term treatment with one or more injections of C1 inhibitor concentrate per week. *Int Arch Allergy Immunol* 154:81–88, 2011.
53. Lumry WR. Hereditary angioedema: A case of near fatal laryngeal swelling in a 41-year-old woman. *Allergy Asthma Proc* 32:S13–S15, 2011.
54. Caballero T, Baeza ML, Cabanas R, et al. Consensus statement on the diagnosis, management, and treatment of angioedema mediated by bradykinin. Part II. Treatment, follow-up, and special situations. *J Investig Allergol Clin Immunol* 21:422–441, 2011.
55. Craig T, Riedl M, Dykewicz MS, et al. When is prophylaxis for hereditary angioedema necessary? *Ann Allergy Asthma Immunol* 102:366–372, 2009.
56. Bewtra AK, Levy RJ, Jacobson KW, et al. C1-inhibitor therapy for hereditary angioedema attacks: Prospective patient assessments of health-related quality of life. *Allergy Asthma Proc* 33:427–431, 2012.
57. Craig TJ, Wasserman RL, Levy RJ, et al. Prospective study of rapid relief provided by C1 esterase inhibitor in emergency treatment of acute laryngeal attacks in hereditary angioedema. *J Clin Immunol* 30:823–829, 2010.
58. Bork K, and Barnstedt S-E. Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema. *Arch Intern Med* 161:714–718, 2001.
59. Bernstein JA, Craig TJ, Keinecke HO, and 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 American College of Allergy, Asthma, and Immunology 2012 Annual Scientific Meeting, Anaheim, CA, November 8–13, 2012.
60. Levy RJ, Lumry WR, McNeil DL, et al. EDEMA4: A phase 3, double-blind study of subcutaneous ecallantide treatment for acute attacks of hereditary angioedema. *Ann Allergy Asthma Immunol* 104:523–529, 2010.
61. Sheffer AL, Campion M, Levy RJ, et al. Ecallantide (DX-88) for acute hereditary angioedema attacks: Integrated analysis of 2 double-blind, phase 3 studies. *J Allergy Clin Immunol* 128:153–159, 2011.
62. Banerji A and Sheffer AL. The spectrum of chronic angioedema. *Allergy Asthma Proc* 30:11–16, 2009. □

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