Practice parameter

A focused parameter update: Hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor–associated angioedema

***Chief Editors*: Bruce L. Zuraw, MD, Jonathan A. Bernstein, MD, and David M. Lang, MD**

***Workgroup Contributors*: Timothy Craig, DO, David Dreyfus, MD, Fred Hsieh, MD, David Khan, MD, Javed Sheikh, MD, and David Weldon, MD**

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Corresponding author: Joint Council of Allergy, Asthma & Immunology, 50 N Brockway St, #304, Palatine, IL 60067.

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converting enzyme inhibitor–associated angioedema." This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients. Because this document incorporated the efforts of many participants, no single individual, including those who served on the JTFPP, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology. The Joint Task Force on Practice Parameters understands that the cost of diagnostic tests and therapeutic agents is an important concern that might appropriately influence the work-up and treatment chosen for a given patient. The JTFPP recognizes that the emphasis of our primary recommendations regarding a medication might vary, for example, depending on third-party payer issues and product patent expiration dates. However, because the cost of a given test or agent is so widely variable and there is a paucity of pharmacoeconomic data, the JTFPP generally does not consider cost when formulating practice parameter recommendations. In some instances the cost benefit of an intervention is considered relevant, and commentary might be provided. These parameters are not designed for use by pharmaceutical companies in drug promotion. The Joint Task Force is committed to ensuring that the practice parameters are based on the best scientific evidence that is free of commercial bias. To this end, the parameter development process includes multiple layers of rigorous review. These layers include the Workgroup convened to draft the parameter, the Task Force Reviewers, and peer review by members of each sponsoring society. Although the Task Force has the final responsibility for the content of the documents submitted for publication, each reviewer comment will be discussed, and reviewers will receive written responses to comments when appropriate. To preserve the greatest transparency regarding potential conflicts of interest, all members of the Joint Task Force and the Practice Parameters Workgroups will complete a standard potential conflict of interest disclosure form, which will be available for external review by the sponsoring organization and any other interested individual. In addition, before confirming the selection of a Workgroup chairperson, the Joint Task Force will discuss and resolve all relevant potential conflicts of interest associated with this selection. Finally, all members of parameter workgroups will be provided a written statement regarding the importance of ensuring that the parameter development process is free of commercial bias. (J Allergy Clin Immunol 2013;131:1491-3.)

Key words: *Angiotensin-converting enzyme inhibitor, acquired C1 inhibitor deficiency, angioedema, angiotensin receptor blocker, bradykinin, C1 inhibitor deficiency, hereditary angioedema*

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EXECUTIVE SUMMARY

Hereditary angioedema (HAE) usually results from a deficiency of the serine protease inhibitor C1 inhibitor (C1INH). (LB) There are 2 types of HAE; type I is most common. A third form of HAE with normal C1INH has been described; however, there are currently no valid diagnostic tests for this form and the diagnosis is based on exclusion. HAE is caused by mutations in the C1INH gene, resulting in a C1INH functional deficiency. (LB) The primary mediator of swelling in patients with HAE is bradykinin. (LB)

Optimal management of HAE depends on early identification of patients. (D) HAE is characterized by relatively prolonged attacks of angioedema involving the extremities, abdomen, genitourinary tract, face, oropharynx, larynx, or a combination of the above. (C) Onset of swelling in patients with HAE most often begins during childhood and frequently worsens around puberty. (C) HAE is an autosomal dominant disease, and most patients with HAE have a positive family history of angioedema. (A)

Two forms of HAE, which are indistinguishable clinically, can be diagnosed based on laboratory findings: type I HAE presents with low C1INH antigenic and functional levels, whereas type II HAE presents with normal C1INH antigenic levels but decreased C1INH functional levels. (A) Diagnosis of type I or type II HAE requires evidence of a low C1INH antigenic or functional level, as well as decreased C4 levels and generally normal C1q levels. (A)

Disease severity in patients with HAE is highly variable and characterized by episodic rather than continuous swelling. (D) A precipitating cause for most episodes of HAE attacks is unknown; however, stress and trauma have been clearly recognized as precipitants. (D)

Attacks of swelling in patients with HAE generally involve the extremities, abdomen, genitourinary tract, face, oropharynx, or larynx and follow a stereotypical pattern in which the swelling worsens over 24 hours, peaks, and then slowly resolves over the following 48 hours. (A) Attacks of HAE might be preceded by a prodrome. (C) HAE attacks are associated with significant potential morbidity and potential mortality. (A)

Epinephrine, corticosteroids, and antihistamines are not efficacious and are not recommended for the treatment of HAE. (C) Fresh frozen plasma is often effective in abrogating HAE attacks; however, fresh frozen plasma might acutely exacerbate some attacks, and for this reason, caution is required. (D) Management of HAE attacks can involve symptomatic treatment based on the region of body swelling. (C) Neither anabolic androgens nor antifibrinolytic drugs provide reliably effective treatment for acute attacks of angioedema. (D) Consensus US (HAEA) and international (HAWK, iCAALL) guidelines recommend that all patients with HAE should have access to an effective, on-demand HAE-specific agent. Evidence from double-blind, placebo-controlled, randomized clinical trials demonstrates the efficacy and safety for treatment of HAE attacks with C1INH concentrates, a plasma kallikrein inhibitor, or a bradykinin B2 receptor antagonist (A).

Short-term prophylaxis can be achieved by using fresh frozen plasma, C1INH replacement, or short-term, high-dose anabolic androgen therapy. (B) The need for long-term HAE prophylaxis must be individualized based on the patient's situation. (D) Treatment with low-to-moderate doses of anabolic androgens provides effective and relatively safe long-term HAE prophylaxis for many patients. (B) Treatment with antifibrinolytic agents provides somewhat effective and relatively safe long-term HAE prophylaxis but is generally less effective than androgens. (B) Treatment with replacement plasma-derived C1INH provides effective and safe long-term HAE prophylaxis. (A) The novel agents for treatment of patients with C1INH deficiency

syndromes are more costly than alternative treatment with attenuated androgens. Formal studies of cost utility and cost-effectiveness are required to aid providers in the management of patients with C1INH deficiency syndromes. The dose and effectiveness of long-term prophylaxis should be based on clinical criteria and not laboratory parameters. (C) Mechanisms of action of 17α-alkylated androgen and antifibrinolytic drugs for HAE have not been completely elucidated. (D) Adjunctive strategies, such as avoidance of angiotensin-converting enzyme inhibitor (ACE-I) treatment, avoidance of estrogen therapy (as feasible), and stress reduction, are important to decrease the frequency and severity of HAE attacks. (D)

Familial recurrent angioedema characterized by normal C1INH function can be present; however, there are no commonly agreed upon criteria for diagnosing HAE with normal C1INH levels at this time (C). Some kindreds with HAE with normal C1INH levels appear to require high estrogen levels for the angioedema to manifest. (C) HAE with normal C1INH levels can be caused by increased bradykinin signaling. (C) Drugs developed for patients with HAE with reduced C1INH levels have been reported to be effective in some patients with HAE with normal C1INH levels. (C)

Pregnancy can be associated with an increase in the frequency and severity of HAE episodes. For long-term prophylaxis during pregnancy, treatment with androgens is contraindicated, and plasma-derived C1INH is preferred (D).

Clinical characteristics of angioedema episodes in patients with acquired C1INH deficiency are similar to those in patients with HAE attacks. (C) Diagnosis of acquired C1INH deficiency involves demonstration of reduced C1INH function, activation of complement, and reduced antigenic levels of the first component of complement (C1). (C) Acquired C1INH deficiency results from enhanced catabolism of C1INH. (LB) Acquired C1INH deficiency might be associated with C1INH autoantibodies, with or without an underlying condition (eg, lymphoma). (C) The treatment of acquired C1INH deficiency is similar to that for HAE but with some significant differences, such as increased efficacy of antifibrinolytics, decreased efficacy of C1INH replacement, and the need to treat an underlying condition associated with acquired C1INH deficiency. (C) ACE-I treatment is associated with angioedema in approximately 0.1% to 0.7% of patients. (A) Angiotensin receptor blocker (ARB) treatment has been associated with angioedema less commonly. The management of ACE-I (or ARB)–associated angioedema is discontinuation of the ACE-I (or ARB). (A) The angioedema associated with ACE-I is likely due to impaired degradation of bioactive peptides, such as bradykinin. (C) A modest risk of recurrent angioedema exists in patients who experienced angioedema in response to ACE-I therapy and then are switched to ARB therapy; however, most patients who have experienced ACE-I–induced angioedema can safely use ARBs without recurrence of angioedema. (C)

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Published practice parameters of the Joint Task Force on Practice Parameters for Allergy and Immunology include the following:

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl):S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
6. The diagnosis and management of anaphylaxis. J Allergy Clin Immunol 1998;101(suppl):S465-S528.
7. Algorithm for the diagnosis and management of asthma: a practice parameter update. Ann Allergy 1998;81:415-20.
8. Diagnosis and management of rhinitis: parameter documents of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Ann Allergy 1998;81(suppl): S463-S518.
9. Parameters for the diagnosis and management of sinusitis. J Allergy Clin Immunol 1998;102(suppl):S107-S144.
10. Stinging insect hypersensitivity: a practice parameter. J Allergy Clin Immunol 1999;103:963-80.
11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl):S665-S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
13. Allergen immunotherapy: a practice parameter. Ann Allergy 2003;90(suppl):SI-S540.
14. Symptom severity assessment of allergic rhinitis: part I. Ann Allergy 2003;91:105-14.
15. Disease management of atopic dermatitis: an updated practice parameter. Ann Allergy 2004;93(suppl):S1-S21.
16. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 2004;114:869-86.
17. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol 2005;115(suppl):S483-S523.
18. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy 2005;94(suppl): S1-S63.
19. Attaining optimal asthma control: a practice parameter. J Allergy Clin Immunol 2005;116(suppl):S3-S11.
20. The diagnosis and management of sinusitis: a practice parameter update. J Allergy Clin Immunol 2005;116(suppl): S13-S47.
21. Food allergy: a practice parameter. Ann Allergy 200;96(suppl):S1-68.
22. Contact dermatitis: a practice parameter. Ann Allergy 2006;97(suppl):S1-S38.
23. Allergen immunotherapy: a practice parameter second update. J Allergy Clin Immunol 2007;120(suppl):S25-S85.
24. Bernstein IL, Li JT, Bernstein DI, Hamilton R, Spector S, Tan R, et al. Allergy diagnostic testing: an updated practice parameter. Ann Allergy 2008;100(suppl): S1-S147.
25. Wallace D, Dykewicz M, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 2008;121(suppl):S1-S84.
26. Kelso J, Li JT. Adverse reactions to vaccines. Ann Allergy 2009;1003(suppl):S1-S16.
27. Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol 2010;126:477-80, e1-42.
28. Drug allergy: an updated parameter. Ann Allergy 2010;105:259-73.
29. Weiler JM, Anderson SA, Randolph C, Bonini S, Craig TJ, Pearlman DS, et al. Pathogenesis, prevalence, diagnosis and management of exercise-induced bronchoconstriction:

a practice parameter. Ann Allergy 2010;105(suppl):S1-S47.
30. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011;127(suppl):S1-S55.
31. Greenhawt MJ, Li JT. Administering influenza vaccine to egg allergic recipients: a focused practice parameter update. Ann Allergy 2011;106:11-6.
32. Golden DB, Moffitt J, Nicklas RA, Freeman T, Graft DR, Reisman RE, et al. Stinging insect hypersensitivity: a practice parameter update 2011. J Allergy Clin Immunol 2011;127:852-4, e1-23.
33. Portnoy J, Kennedy K, Sublett J, Phipatanakal W, Matsui E, Barnes C, et al. Environmental assessment and exposure control: a practice parameter—furry animals. Ann Allergy 2012;108:223, e1-15.
34. Kelso J, Greenhawt M, Li JT, Nicklas RA, Bernstein DI, Blessing-Moore J, et al. Adverse reactions to vaccines practice parameters 2012 update. J Allergy Clin Immunol 2012;130:25-43.
35. Phipatanakul W, Matsui E, Portnoy J, Williams PB, Barnes C, Kennedy K, et al. Environmental assessment and exposure reduction of rodents: a practice parameter. Ann Allergy Asthma Immunol 2012;109:375-87.

These parameters are also available on the Internet at http://www.jcaai.org.

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CONTRIBUTORS

The Joint Task Force has made a concerted effort to acknowledge all contributors to this parameter. If any contributors have been excluded inadvertently, the Task Force will ensure that appropriate recognition of such contributions is made subsequently.

CHIEF EDITORS

Bruce L. Zuraw, MD
Department of Medicine
Section of Allergy & Immunology
University of California, San Diego
San Diego, California

Jonathan A. Bernstein, MD
Department of Medicine
University of Cincinnati College of Medicine
Department of Internal Medicine
Division of Immunology/Allergy Section
Cincinnati, Ohio

David M. Lang, MD
Allergy/Immunology Section
Asthma Center
Respiratory Institute
Cleveland Clinic Foundation
Cleveland, Ohio

WORKGROUP CONTRIBUTORS

Timothy Craig, DO
Department of Medicine and Pediatrics
Penn State University
Hershey, Pennsylvania

David Dreyfus, MD, PhD
Department of Pediatrics
Yale School of Medicine
New Haven, Connecticut

Fred Hsieh, MD
Allergy/Immunology Section
Respiratory Institute
Department of Pathobiology
Lerner Research Institute
Cleveland Clinic
Cleveland, Ohio

David A. Khan, MD
Department of Medicine
Division of Allergy and Immunology
University of Texas Southwestern Medical Center
Dallas, Texas

Javed Sheikh, MD
Department of Medicine
Harvard Medical School
Boston, Massachusetts

David Weldon, MD
Department of Internal Medicine
Texas A&M University Health Sciences Center
School of Medicine
College Station, Texas

TASK FORCE REVIEWERS

David I. Bernstein, MD
Departments of Medicine and Environmental Health
Division of Immunology, Allergy and Rheumatology
University of Cincinnati College of Medicine
Cincinnati, Ohio

Joann Blessing-Moore, MD
Department of Immunology
Stanford University Medical Center
Palo Alto, California

Linda Cox, MD
Department of Medicine
Nova Southeastern University
Davie, Florida

Richard A. Nicklas, MD
Department of Medicine
George Washington Medical Center
Washington, DC

John Oppenheimer, MD
Department of Internal Medicine
New Jersey Medical School
Morristown, New Jersey

Jay M. Portnoy, MD
Section of Allergy, Asthma & Immunology
The Children's Mercy Hospital
University of Missouri–Kansas City School of Medicine
Kansas City, Missouri

Christopher Randolph, MD
Yale University
Center for Allergy, Asthma and Immunology
Yale Waterbury Regional Program
Waterbury, Connecticut

Diane E. Schuller, MD
Department of Pediatrics
Pennsylvania State University
Milton S. Hershey Medical College
Hershey, Pennsylvania

Sheldon L. Spector, MD
Department of Medicine
UCLA School of Medicine
Los Angeles, California

Stephen A. Tilles, MD
Department of Medicine
University of Washington School of Medicine
Seattle, Washington

Dana Wallace, MD
Department of Medicine
Nova Southeastern University
Davie, Florida

INVITED REVIEWERS

Peter Arkwright, MD, Manchester, United Kingdom
Michael Frank, MD, Durham, North Carolina
Richard Gower, MD, Spokane, Washington
Allen P. Kaplan, MD, Charleston, South Carolina
H. Henry Li, MD, Chevy Chase, Maryland
Marc Riedl, MD, Santa Monica, California

CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE

Category of evidence

Ia Evidence from meta-analysis of randomized controlled trials
Ib Evidence from at least 1 randomized controlled trial
IIa Evidence from at least 1 controlled study without randomization
IIb Evidence from at least 1 other type of quasiexperimental study
III Evidence from nonexperimental descriptive studies, such as comparative studies
IV Evidence from expert committee reports, opinions or clinical experience of respected authorities, or both

Strength of recommendation

A Directly based on category I evidence
B Directly based on category II evidence or extrapolated recommendation from category I evidence
C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
LB Laboratory based
NR Not rated

PRACTICE PARAMETER DEVELOPMENTAL PROCESS

The Joint Task Force on Practice Parameters

The Joint Task Force on Practice Parameters (JTF) is a 13-member task force consisting of 6 representatives assigned by the American Academy of Allergy, Asthma and Immunology (AAAAI); 6 by the American College of Allergy, Asthma and Immunology (ACAAI); and 1 by the Joint Council of Allergy and Immunology. The JTF oversees the development of practice parameters, selects the workgroup chairs, and reviews drafts of the parameters for accuracy, practicality, clarity, and broad utility of the recommendations for clinical practice.

The Angioedema Practice Parameter Workgroup

The Angioedema workgroup was formed by the JTF to develop a practice parameter that addresses the diagnosis and treatment of angioedema. The Chair, Jonathan Bernstein, MD, invited workgroup members to participate in the parameter development. The charge to the workgroup was to use a systematic literature review in conjunction with consensus expert opinion and workgroup-identified supplementary documents to develop practice parameters that provide a comprehensive approach for the assessment and management of angioedema, with a focus on C1 inhibitor (C1INH) deficiency syndromes and angioedema associated with angiotensin-converting enzyme inhibitors. The diagnosis and management of histamine-mediated angioedema will be addressed in a parameter update on urticaria and angioedema, which is in preparation.

Protocol for selecting, grading, and reviewing evidence

A search of the medical literature was performed for a variety of terms that were considered relevant to this practice parameter. Literature searches were performed on PubMed, Google Scholar, and the Cochrane Database of Systematic Reviews. All reference

types were included in the results. References identified as being relevant were searched for relevant references, and those references also were searched for relevant references. In addition, members of the workgroup were asked for references that were missed by this initial search. Published clinical studies were rated by category of evidence and used to establish the strength of the recommendations.

The parameter was subsequently appraised by reviewers designated by the national organizations of the AAAAI and ACAAI. On the basis of this process, this parameter represents an evidence-based, broadly accepted consensus document.

These parameters are also available on the Internet at http://www.jcaai.org and http://www.allergyparameters.org.

EXECUTIVE SUMMARY

Hereditary angioedema (HAE) usually results from a deficiency of the serine protease inhibitor C1INH. (LB) There are 2 types of HAE; type I is most common. A third form of HAE with normal C1INH has been described; however, there are currently no valid diagnostic tests for this form and the diagnosis is based on exclusion. HAE is caused by mutations in the C1INH gene, resulting in a C1INH functional deficiency. (LB) The primary mediator of swelling in patients with HAE is bradykinin. (LB)

Optimal management of HAE depends on early identification of patients. (D) HAE is characterized by relatively prolonged attacks of angioedema involving the extremities, abdomen, genitourinary tract, face, oropharynx, larynx, or a combination of the above. (C) Onset of swelling in patients with HAE most often begins during childhood and frequently worsens around puberty. (C) HAE is an autosomal dominant disease, and most patients with HAE have a positive family history of angioedema. (A)

Two forms of HAE, which are indistinguishable clinically, can be diagnosed based on laboratory findings: type I HAE presents with low C1INH antigenic and functional levels, whereas type II HAE presents with normal C1INH antigenic levels but decreased C1INH functional levels. (A) Diagnosis of type I or type II HAE requires evidence of a low C1INH antigenic or functional level, as well as decreased C4 levels and generally normal C1q levels. (A)

Disease severity in patients with HAE is highly variable and characterized by episodic rather than continuous swelling. (D) A precipitating cause for most episodes of HAE attacks is unknown; however, stress and trauma have been clearly recognized as precipitants. (D)

Attacks of swelling in patients with HAE generally involve the extremities, abdomen, genitourinary tract, face, oropharynx, or larynx and follow a stereotypical pattern in which the swelling worsens over 24 hours, peaks, and then slowly resolves over the following 48 hours. (A) Attacks of HAE might be preceded by a prodrome. (C) HAE attacks are associated with significant potential morbidity and potential mortality. (A)

Epinephrine, corticosteroids, and antihistamines are not efficacious and are not recommended for the treatment of HAE. (C) Fresh frozen plasma is often effective in abrogating HAE attacks; however, fresh frozen plasma might acutely exacerbate some attacks, and for this reason, caution is required. (D) Management of HAE attacks can involve symptomatic treatment based on the region of body swelling. (C) Neither anabolic androgens nor antifibrinolytic drugs provide reliably effective treatment for acute attacks of angioedema. (D) Consensus US (HAEA) and international (HAWK, iCAALL) guidelines recommend that all patients with HAE should have access to an effective, on-demand HAE-specific agent. Evidence from double-blind, placebo-controlled, randomized clinical trials demonstrates the efficacy and safety for treatment of HAE attacks with C1INH concentrates, a plasma kallikrein inhibitor, or a bradykinin B2 receptor antagonist (A).

Short-term prophylaxis can be achieved by using fresh frozen plasma, C1INH replacement, or short-term, high-dose anabolic androgen therapy. (B) The need for long-term HAE prophylaxis must be individualized based on the patient's situation. (D) Treatment with low-to-moderate doses of anabolic androgens provides effective and relatively safe long-term HAE prophylaxis for many patients. (B) Treatment with antifibrinolytic agents provides somewhat effective and relatively safe long-term HAE prophylaxis but is generally less effective than androgens. (B) Treatment with replacement plasma-derived C1INH provides effective and safe long-term HAE prophylaxis. (A) The novel agents for treatment of patients with C1INH deficiency syndromes are more costly than alternative treatment with attenuated androgens. Formal studies of cost utility and cost-effectiveness are required to aid providers in the management of patients with C1INH deficiency syndromes. The dose and effectiveness of long-term prophylaxis should be based on clinical criteria and not laboratory parameters. (C) Mechanisms of action of 17α-alkylated androgen and antifibrinolytic drugs for HAE have not been completely elucidated. (D) Adjunctive strategies, such as avoidance of angiotensin-converting enzyme inhibitor (ACE-I) treatment, avoidance of estrogen therapy (as feasible), and stress reduction, are important to decrease the frequency and severity of HAE attacks. (D)

Familial recurrent angioedema characterized by normal C1INH function can be present; however, there are no commonly agreed upon criteria for diagnosing HAE with normal C1INH levels at this time (C). Some kindreds with HAE with normal C1INH levels appear to require high estrogen levels for the angioedema to manifest. (C) HAE with normal C1INH levels can be caused by increased bradykinin signaling. (C) Drugs developed for patients with HAE with reduced C1INH levels have been reported to be effective in some patients with HAE with normal C1INH levels. (C)

Pregnancy can be associated with an increase in the frequency and severity of HAE episodes. For long-term prophylaxis during pregnancy, treatment with androgens is contraindicated, and plasma-derived C1INH is preferred (D).

Clinical characteristics of angioedema episodes in patients with acquired C1INH deficiency are similar to those for patients with HAE attacks. (C) Diagnosis of acquired C1INH deficiency involves demonstration of reduced C1INH function, activation of complement, and reduced antigenic levels of the first component of complement (C1). (C) Acquired C1INH deficiency results from enhanced catabolism of C1INH. (LB) Acquired C1INH deficiency might be associated with C1INH autoantibodies, with or without an underlying condition (eg, lymphoma). (C) The treatment of acquired C1INH deficiency is similar to that for HAE but with some significant differences, such as increased efficacy of antifibrinolytics, decreased efficacy of C1INH replacement, and the need to treat an underlying condition associated with acquired C1INH deficiency. (C) ACE-I treatment is associated with angioedema in approximately 0.1% to 0.7% of patients. (A) Angiotensin receptor blocker

(ARB) treatment has been associated with angioedema less commonly. The management of ACE-I (or ARB)–associated angioedema is discontinuation of the ACE-I (or ARB). (A) The angioedema associated with ACE-I is likely due to impaired degradation of bioactive peptides, such as bradykinin. (C) A modest risk of recurrent angioedema exists in patients who experienced angioedema in response to ACE-I therapy and then are switched to ARB therapy; however, most patients who have experienced ACE-I–induced angioedema can safely use ARBs without recurrence of angioedema. (C)

ANGIOEDEMA: DIAGNOSIS AND PATHOPHYSIOLOGY

Annotations for diagnostic algorithm (Fig E1)

Annotation 1: Recurrent angioedema. Angioedema is characterized by an asymmetric nondependent swelling that is generally not pruritic. Like urticaria, angioedema results from increased vascular permeability, with leakage of plasma into the superficial skin in patients with urticaria and into the deeper skin layers in patients with angioedema. The pattern of swelling is an important diagnostic consideration, particularly whether the angioedema occurs with or without urticaria. Urticaria is not a feature of HAE. Patients with recurrent angioedema without coexisting urticaria merit evaluation for C1INH deficiency.

Annotation 2: Recurrent angioedema and urticaria. Most cases of recurrent angioedema occur with concomitant urticaria or pruritis, are responsive to antihistamines, are histamine mediated, and are best considered within the spectrum of chronic urticaria. If chronic urticaria is present and episodes lack a consistent temporal association with angioedema, this might be considered a separate condition.

Annotation 3: Is the patient taking an ACE-I (or ARB)? It is important to inquire whether a patient with recurrent angioedema is being treated with an ACE-I. Treatment with ACE-Is has been associated with recurrent angioedema without urticaria, prominently involving the face and tongue but also involving other areas, including rarely the bowel and extremities. There are published reports of deaths from ACE-I–induced laryngeal edema leading to complete upper airway obstruction.[1-3] Angioedema associated with ACE-I therapy most frequently occurs within the first month of therapy but can occur even after many years of continuous therapy. Patients experiencing angioedema secondary to one ACE-I will typically have angioedema to another ACE-I, which is consistent with this being a class effect and not a hypersensitivity reaction. ACE is a dipeptidyl carboxypeptidase that cleaves certain peptides, including bradykinin and substance P. When ACE is inhibited, bradykinin degradation is expected to be prolonged and thus might contribute to the resultant angioedema. Patients experiencing ACE-I–associated angioedema have been reported to have increased plasma bradykinin levels. It has been speculated that the susceptibility to ACE-I–induced angioedema might be determined by the level or activity of other bradykinin-degrading enzymes. Angioedema caused by ACE-I does not reliably respond to treatment with epinephrine, antihistamines, or corticosteroids; however, medications acting on the contact system might be useful. Open-label reports suggest that ACE-I–induced angioedema might respond to icatibant,[4-6] and clinical trials are in progress in the United States investigating the effectiveness of ecallantide and icatibant for ACE-I–induced angioedema. Much less commonly, angioedema can also occur in patients taking ARBs.

Annotation 4: Does the angioedema resolve when the ACE-I (or ARB) is discontinued? Patients with recurrent angioedema who are also taking an ACE-I should have the ACE-I (or ARB) discontinued with a presumptive diagnosis of ACE-I (or ARB)–induced angioedema. For patients in whom C1INH deficiency is diagnosed, treatment with ACE-I is contraindicated. The diagnosis of ACE-I (or ARB)–associated angioedema is confirmed if the angioedema resolves after the ACE-I (or ARB) is discontinued. However, it is important to note that the proclivity to swell can continue for at least 6 weeks after discontinuation of the ACE-I. African American subjects are at a substantially higher risk of experiencing ACE-I–induced angioedema than white subjects. Other factors that increase the risk of angioedema from ACE-I include a history of smoking, increasing age, and female sex. Diabetic patients have a lower risk than nondiabetic patients.

Annotation 5: Measure C4 and C1INH levels. If the patient is not taking an ACE-I, then C1INH deficiency should be excluded. Measurement of the complement C4 level, C1INH antigenic level, and C1INH functional level provides reliable information regarding the possibility of a C1INH deficiency. The C4 level is an excellent screening tool for C1INH deficiency states. At least 95% of patients with C1INH deficiency will have a reduced C4 level, even between attacks, and this number increases to virtually 100% during angioedema attacks. A normal C4 level during an attack of angioedema strongly suggests an alternative diagnosis rather than C1INH deficiency. In patients in whom there is a high degree of suspicion of a C1INH deficiency, the physician might choose to order C1INH antigenic and functional levels at the same time as a C4 level. However, ordering the C4 level alone is a cost-effective strategy for screening patients with recurrent angioedema. It is important that C4 is sent to the laboratory in a timely fashion because degradation and artificially low C4 levels can be reported if there is a significant delay in transfer. This is also relevant for measurement of C1INH function.

Annotation 6: Recurrent angioedema with normal C4 and C1INH levels. If the complement C4 level is normal in a patient with recurrent angioedema, the possibility of HAE with normal C1INH levels should be considered. At the current time, there is no screening test to rule in a diagnosis of HAE with normal C1INH levels. Therefore the diagnosis is one of exclusion and rests on the history of recurrent angioedema with a strong family history of angioedema.

Annotation 7: HAE with normal C1INH levels. An additional form of inherited angioedema has been described in which multiple generations are involved in a pattern consistent with autosomal dominant inheritance; however, the C1INH gene and protein levels are completely normal. The clinical pattern of angioedema attacks is similar to that seen in patients with HAE with prolonged angioedema episodes and marked differences in severity from patient to patient. At the current time, there is no definitive laboratory or clinical parameter to confirm a diagnosis of HAE with normal C1INH levels, and the diagnosis can only be

considered in patients with a strong family history suggestive of an autosomal dominant pattern. The original descriptions of HAE with normal C1INH levels were of families in which all the affected subjects were women. Furthermore, attacks of angioedema were believed to mirror states of high endogenous estrogen (ie, pregnancy) or administration of exogenous estrogen. Subsequently, a number of families have been described with affected male subjects and with affected female subjects whose angioedema does not depend on high estrogen levels.[7]

Annotation 8: Is the C1INH antigen level low? In patients with recurrent angioedema and a low C4 level, the diagnostic possibilities include type I HAE, type II HAE, and acquired C1INH deficiency. Distinguishing among these can be readily accomplished based on laboratory and clinical criteria. The first question is whether the C1INH antigenic level is low or normal.

Annotation 9: Is the C1INH functional level low? If the C1INH antigenic level is normal, then a C1INH functional level is required. If both the C1INH antigenic and functional levels are normal, then the diagnosis of C1INH deficiency is excluded, and other causes, such as idiopathic angioedema, allergic angioedema in the absence of urticaria, or HAE with normal C1INH levels, should be reconsidered.

Annotation 10: Type II HAE. Although all patients with HAE have decreased C1INH functional levels, patients with type II HAE have normal antigenic C1INH levels. Type II HAE is caused by mutations in the C1INH gene typically involving residues at or near the active site on the reactive mobile loop that result in a mutant C1INH protein that is secreted but dysfunctional. C1INH function should be measured with a chromogenic assay to achieve the greatest sensitivity in detecting C1INH functional deficiency.[8] Clinically, type I and type II HAE cannot be distinguished. Approximately 15% of patients with HAE have type II HAE.

Annotation 11: Measure C1q antigen. If the C1INH antigenic level is low, then the possibilities are either type I HAE or an acquired C1INH deficiency. Typically, it is easy to discriminate between these 2 possibilities in that type I HAE usually presents in the first 2 decades of life; 50% of patients begin swelling by age 10 years, often with a positive family history, whereas acquired C1INH deficiency generally presents in middle-aged or older subjects without a strong family history of angioedema. When the history is unclear, the C1q level can be obtained because this is typically low in patients with acquired C1INH deficiency but normal in patients with type I HAE.

Annotation 12: Type I HAE. The other 85% of patients with HAE have type I HAE.

Annotation 13: Acquired C1INH deficiency. Acquired C1INH deficiency presents clinically in a manner very similar to HAE, except that HAE tends to manifest during childhood, whereas acquired C1INH deficiency tends to manifest in middle-aged or older patients. Acquired C1INH deficiency is not associated with a positive family history of angioedema. All middle-aged or older patients presenting with isolated recurrent angioedema should have the possibility of an acquired C1INH deficiency considered. The syndrome of acquired C1INH deficiency is not associated with a mutation of the C1INH gene or impaired synthesis of functional C1INH. Rather, it occurs because of increased catabolism of C1INH that outstrips the capacity of the host to synthesize new C1INH, as can occur in a patient with an underlying lymphoreticular malignancy or an autoantibody directed against C1INH. In some cases successful treatment of the underlying disease has been associated with improvement in the acquired C1INH deficiency. Most patients with acquired C1INH deficiency have autoantibodies that specifically recognize normal C1INH. A monoclonal gammopathy without evident lymphoma can present as acquired C1INH deficiency because of monoclonal anti-C1INH. Rarely, connective tissue diseases, such as systemic lupus erythematosus, can present in this fashion.

Annotation 14: Not C1INH deficiency. Consider idiopathic angioedema. Patients with idiopathic angioedema are encountered much more frequently than patients with C1INH deficiency syndromes. The diagnosis and management of idiopathic angioedema is reviewed in detail in a parameter on urticaria and angioedema, which is in preparation.

HEREDITARY ANGIOEDEMA

Diagnosis and pathophysiology

Summary Statement 1: Most cases of HAE result from a deficiency of the serine protease inhibitor C1INH. (LB) There are 3 types of HAE; type I is most common.

HAE has classically been recognized as resulting from a deficiency of the broad-spectrum serine protease inhibitor C1INH[9] and is further subdivided into type I or type II HAE, depending on whether the plasma C1INH antigenic levels are low or normal, respectively. Another hereditary form of angioedema that does not involve C1INH, HAE with normal C1INH levels, has recently been described.[10,11] This additional form of HAE has also been called new HAE, type III HAE, or estrogen-dependent/associated angioedema.

The prevalence of HAE is estimated to be between 1:30,000 and 1:80,000 in the general population, and there is no evidence of any sex, ethnic, or racial differences in the prevalence of HAE. Type I HAE is the most common form of HAE, accounting for approximately 85% of cases, with type II HAE accounting for the other 15% of cases.[12] Relatively few cases of HAE with normal C1INH levels have been reported; however, as discussed below, this might be due to the absence of a valid diagnostic test for HAE with normal C1INH levels. Because HAE with normal C1INH levels is so distinct from the C1INH deficiency–associated forms of HAE, it will be discussed separately.

Summary Statement 2: HAE is caused by mutations in the C1INH gene, resulting in a C1INH functional deficiency. (LB)

C1INH is a member of the serpin (serine protease inhibitor) superfamily with significant homology to α_1-antitrypsin. Like other serpins, C1INH functions as a "molecular mousetrap," undergoing large-scale rearrangement and trapping the target protease when it is cleaved.[13] C1INH is a suicide inhibitor, forming a 1:1 stoichiometric complex with the target protease, followed by clearance of the entire complex. In cases of overwhelming proteolytic activation, C1INH can be cleaved into a modified inactive form without forming a complex with or inhibiting the protease.[14]

The 2.1-kb C1INH cDNA was initially cloned and sequenced in 1986.[15-17] C1INH is a 110-kDa single-chain glycoprotein

consisting of 478 amino acids plus a 22-residue signal peptide.[16] The protein is organized into 2 domains: the N-terminal 100 amino acids contain most of the N- and O-linked carbohydrates, whereas the carboxy 378 amino acids contain the active site in a stressed loop conformation typical of the serpins.[16] The 17,159-bp genomic sequence of the gene was published in 1991.[18] The gene, now named *SERPING1*, is located on chromosome 11 (p11.2-q13), contains 8 exons and 7 introns, does not contain a 5′ TATA box, and is distinguished by 17 Alu repeats in introns 3 to 7. More recently, the crystal structure has been solved.[19]

HAE is an autosomal dominant disease caused by mutations in the *SERPING1* gene. A large number of mutations have been identified,[20-25] with additional mutations still being reported. A database tabulating known *SERPING1* gene mutations (http://hae.enzim.hu) currently lists more than 250 different mutations identified in patients with HAE.

Summary Statement 3: The primary mediator of swelling in patients with HAE is bradykinin. (A)

C1INH is a major inhibitor of the complement C1 proteases C1r and C1s, the proteases of the mannose-binding lectin pathway of complement, and the contact system proteases plasma kallikrein and activated Hageman factor (coagulation factor XIIa).[21,26] C1INH is also an inhibitor of coagulation factor XIa and plasmin. Evidence initially suggested that a vascular permeability–enhancing factor was generated in patients with HAE either through activation of the classical complement pathway with generation of C2 kinin[27] or through activation of the contact system with generation of bradykinin.[28] However, later studies identified bradykinin as the vascular permeability enhancing factor in HAE plasma, and showed that there is no kinin derived from C2, and that plasma from patients with HAE is unstable and generates bradykinin readily.[29,30] Compelling laboratory and clinical data have now demonstrated that bradykinin is the primary mediator that enhances vascular permeability in patients with HAE.[14,31-36]

Summary Statement 4: Optimal management of HAE depends on early identification of patients. (D)

A key step in proper management of HAE is making the correct diagnosis, which in turn depends on understanding when to suspect the possibility of underlying HAE. Unfortunately, there is often a long interval between the onset of HAE symptoms and establishing a diagnosis,[12,37-39] implying that a significant proportion of patients with HAE might remain improperly diagnosed. Considering the unique treatment strategies required and the potential morbidity and mortality associated with HAE attacks, it is critical to establish the correct diagnosis of HAE as early as possible. In practice, this involves excluding the diagnosis in all patients with a compatible history.

Summary Statement 5: HAE is characterized by relatively prolonged attacks of angioedema involving the extremities, genitourinary tract, abdomen, face, oropharynx or larynx. (C)

Patients with HAE typically present with a history of discrete episodes of nonpruritic, nonpitting angioedema involving the extremities, abdomen, genitourinary tract, face, oropharynx, larynx, or a combination of the above.[12,40] HAE attacks are usually distinguished from allergic or idiopathic angioedema by their longer duration and lack of response to antihistamines, corticosteroids, or epinephrine. The typical HAE attack tends to progressively worsen for 24 hours and then slowly remit over the following 48 to 72 hours; however, attacks can occasionally last longer, particularly if the swelling moves from site to site.

Summary Statement 6: Onset of swelling in patients with HAE most often begins during childhood and frequently worsens around puberty. (C)

Most often, patients with HAE begin swelling and experiencing abdominal pain during childhood. Fifty percent of patients with HAE begin swelling at less than 10 years of age, with some patients manifesting angioedema by age 1 year.[41-43] Most patients then experience a worsening of symptoms around puberty.[12] Occasionally, patients with HAE do not begin to show evidence of angioedema until their late teens or early adulthood. Rare patients with HAE have been reported who never experience angioedema.[42,44] Although some patients appear to experience a decrease in symptoms as they age, other patients continue to experience HAE attacks throughout their lives.

Summary Statement 7: HAE is an autosomal dominant disease, and most patients with HAE have a positive family history of angioedema. (A)

The autosomal dominant pattern of HAE has been long recognized. Each child of an affected patient has a 50% chance of having HAE. Importantly, HAE does not skip generations. However, lack of a positive family history of angioedema cannot be used to exclude the diagnosis. Although approximately 75% of patients provide a compatible history of having an affected parent, the remaining 25% of patients presumably have a *de novo* mutation of the C1INH gene that results in HAE.[45]

Summary Statement 8: Two forms of HAE, which are indistinguishable clinically, can be diagnosed by laboratory findings: type I HAE presents with low C1INH antigenic and functional levels, whereas type II HAE presents with normal C1INH antigenic levels but decreased C1INH functional levels. (A)

Although all patients with HAE have decreased C1INH functional levels, patients with type II HAE have normal antigenic C1INH levels.[46,47] In general, type I HAE is caused by mutations in the C1INH gene that result in either truncated proteins or misfolded proteins that cannot be secreted.[48] In contrast, type II HAE is identical in its clinical presentation, course, and management and is caused by mutations in the C1INH gene, typically involving residues at or near the active site on the reactive mobile loop that result in a mutant C1INH protein that is secreted but dysfunctional.[49-54] Therefore C1INH antigenic levels cannot be used as the only diagnostic test for HAE. C1INH function should be measured with a chromogenic assay to achieve the greatest sensitivity in detecting C1INH functional deficiency.[8]

Summary Statement 9: Diagnosis of type I or type II HAE requires evidence of low C1INH antigenic or functional levels, as well as decreased C4 levels and generally normal C1q levels. (A)

When a diagnosis of HAE is suspected, confirmation requires laboratory testing.[40,55] The typical patterns of complement levels for type I HAE, type II HAE, HAE with normal C1INH levels, acquired C1INH deficiency, ACE-I–associated angioedema, and allergic or idiopathic angioedema are shown in Table E1.[7,12]

In addition, an algorithm for the diagnosis of HAE is shown in Fig E1. Measuring complement C4 levels is recommended as the best initial screening test to exclude a diagnosis of HAE.[56,57] In a study in which the diagnostic utility of screening tests for HAE was assessed, all 20 patients with untreated C1INH deficiency had a low level of C4,[57] implying that a low C4 level is generally present in patients with C1INH deficiency. However, C4 levels can be normal, particularly if the patient is already being treated

for a presumed diagnosis of HAE.[56] However, when repeated during an HAE attack, the C4 level should be low. A normal C4 level during an attack of HAE strongly suggests that a diagnosis of HAE is unlikely.

In a patient suspected of having HAE after confirmation of a low C4 level, the next step should be to measure C1INH antigen (and function if the antigenic level is normal).[12] The functional level should be less than 50% to 60% of the lower limit of normal to be compatible with HAE. In a patient with a compatible history and clinical course, the combination of low C4 and low C1INH antigen levels can confirm a diagnosis of type I HAE; the combination of low C4 levels, normal C1INH antigen levels, and low C1INH function can confirm a diagnosis of type II HAE.[12,40,55,57] A chromogenic functional C1INH assay widely used in Europe appears to be superior to the ELISA-based C1INH functional assay used most frequently in the United States.[8] Measurement of C1INH function with a hemolytic complement assay is the most accurate test but is technically difficult to perform and not readily available. Positive screening test results for a diagnosis of HAE should be repeated once to exclude *ex vivo* degradation of the sample or laboratory error. In many situations it might be more practical to order quantitative and functional C1INH assays at the same time.

Acquired C1INH deficiency (see Summary Statements 32-36) typically presents with decreased C1INH antigen and C4 levels. To differentiate acquired C1INH deficiency from type I HAE, the complement C1 (or complement C1q) level should be measured. This order should specifically stipulate C1q level and not C1q binding, which is an assay for immune complexes. C1q levels should be normal in patients with HAE but decreased in most cases of acquired C1INH deficiency.[12,58]

Attacks of angioedema in type I or type II HAE

Summary Statement 10: Disease severity in patients with HAE is highly variable, as characterized by episodic rather than continuous swelling. (D)

Disease severity in patients with HAE is highly variable. Patients not taking prophylactic medications often have swelling every 10 to 20 days, with each attack lasting 2 to 5 days.[12] A relatively small number of patients with HAE swell very frequently, up to twice per week. Some patients with HAE never swell. The swelling in patients with HAE is always episodic and not continuous daily swelling.

Summary Statement 11: A precipitating cause for most episodes of HAE attacks is unknown; however, stress and trauma have been clearly recognized as precipitants. (D)

Several stressors have been associated with precipitating HAE attacks, especially trauma (even relatively minor trauma, such as sitting on a hard surface for a prolonged time) and emotional stress.[12] Of particular concern are athletic activities and iatrogenic trauma, such as dental work, medical procedures, and surgery. Because ACE-Is decrease the catabolism of bradykinin,[59] ACE-Is can precipitate attacks of angioedema and should be avoided in patients with HAE.[60] Infections have also been recognized as a potential precipitant for HAE attacks. A potential role for *Helicobacter pylori* infection in triggering abdominal attacks has been reported,[61] although most investigators have not observed this relationship. Although active *H pylori* infections should be treated in patients with HAE, the same as in other patients, it is not recommended to test for *H pylori* in patients with HAE without clinical evidence suggestive of active infection. No clear precipitating cause can be determined for many, if not most, HAE attacks.

Hormonal changes can affect disease severity.[12,62,63] The effect of pregnancy on HAE disease severity is variable, with some women worsening and other women having less swelling during their pregnancy. Universally, women appear to be relatively protected against swelling at the time of parturition; however, their risk of swelling increases dramatically during the postpartum period.[64] Birth control pills containing estrogen and estrogen replacement therapy both appear to increase the frequency of swelling and should be avoided in all women with HAE. Advice regarding alternative forms of contraception is an important part of any management plan.[65,66]

Summary Statement 12: Attacks of swelling in patients with HAE generally involve the extremities, abdomen, genitourinary tract, face, oropharynx, or larynx and follow a stereotypical pattern in which the swelling worsens over 24 hours, peaks, and then slowly resolves over the following 48 to 72 hours. (A)

The predictable course of an HAE attack has already been described. Typically, the angioedema worsens over 24 hours, peaks, and then gradually resolves over the ensuing 48 to 72 hours.[12,42,43] Generally, the angioedema worsens slowly but relentlessly; however, the patient cannot rely on the slow pace of the angioedema, and it can build quickly on occasion. Attacks involving the extremities and abdomen are the most common, each representing almost 50% of all attacks. Over a lifetime, almost 100% of patients with HAE experience both extremity and abdominal attacks.[43] The most dangerous attacks occur in the oropharynx and might threaten laryngeal patency (see Summary Statement 14). Although these types of attacks occur much less frequently than extremity or abdominal attacks, more than 50% of patients with HAE experience at least 1 laryngeal attack during their lifetime.[43] Some patients with HAE experience multiple oropharyngeal attacks. An important consideration is that all patients with HAE must be considered at risk for a potential oropharyngeal attack, irrespective of their disease severity or whether they have ever had a facial or oropharyngeal attack in the past. Angioedema involving other locations (including the kidney, brain, heart, and joints) has been reported in patients with HAE; however, the evidence supporting attacks in these locations is not strong.

Summary Statement 13: Attacks of HAE can be preceded by a prodrome. (C)

Patients with HAE can experience prodromal manifestations several hours or up to a day before the onset of an attack. The most common prodromal symptoms are an erythematous nonurticarial rash (erythema marginatum), localized tingling, or a sense of skin tightness.[12] Other prodromal symptoms include fatigue, malaise, flu-like symptoms, irritability, mood changes, hyperactivity, thirst, or nausea.[67] Up to 50% of patients report prodromes before their attacks; these symptoms can be reliable harbingers of attacks in some patients but less commonly in children.

Summary Statement 14: HAE attacks are associated with significant potential morbidity and potential mortality. (A)

Like the overall disease severity, individual HAE attack severity displays considerable variability.[68] It is impossible to predict the ultimate severity of an attack at the onset of that attack. Swelling of the extremities can result in temporary inability to walk because of swelling of the feet or to use the swollen hand for writing or typing. In rare instances compartment syndromes have been observed in the extremities because of severe

angioedema. Genitourinary attacks can cause significant discomfort and lead to a temporary inability to urinate.

Abdominal attacks are a frequent cause of morbidity. The angioedema can result in severe abdominal pain with intractable nausea and vomiting and third-space sequestration of fluid that can induce significant hypotension. Because of the severe presentation of some abdominal attacks, many patients with HAE undergo unnecessary and inappropriate surgical interventions. Angioedema of the oropharynx in patients with HAE is capable of closing the airway and resulting in death caused by asphyxiation. Historical surveys suggest a mortality rate in patients with HAE caused by laryngeal angioedema of approximately 30% or higher.[12] Even today, although less commonly, patients with HAE continue to die of laryngeal angioedema, and this possibility needs to be firmly understood by patients and their health care providers (Fig E2).

Treatment of HAE: Annotations for therapeutic algorithm (Fig E2)

Annotation 1: Treatment of HAE. The treatment of HAE can be classified into 2 approaches: treatment of acute attacks and prophylactic treatment (short-term and long-term). All patients with HAE, irrespective of their past history, are at risk for severe angioedema attacks. Patients with HAE should have an established plan in place regarding how to respond to a severe attack of angioedema.

Annotation 2: Acute attacks of angioedema. Patients with HAE typically present with a history of discrete episodes of nonpruritic, nonpitting angioedema involving the extremities, abdomen, genitourinary tract, face, oropharynx, larynx, or a combination of the above. Patients with HAE can experience prodromal manifestations several hours or up to a day before the onset of an attack. The most common prodromal symptoms are an erythematous nonurticarial rash (erythema marginatum), localized tingling, or a sense of skin tightness. The swelling in patients with HAE is always episodic and not continuous daily swelling. The typical HAE attack tends to progressively worsen for 24 hours and then slowly remit over the following 48 to 72 hours; however, attacks can occasionally last longer, particularly if the swelling moves from site to site. Disease severity in patients with HAE is highly variable, both between patients and even within a single patient over time. Attacks involving the extremities and abdomen are the most common, each representing almost 50% of all attacks. Abdominal attacks are a frequent cause of morbidity. The angioedema can result in severe abdominal pain with intractable nausea and vomiting and third-space sequestration of fluid that can induce significant hypotension. Because of the severe presentation of some abdominal attacks, many patients with HAE undergo unnecessary and inappropriate surgical interventions. Over a lifetime, almost 100% of patients with HAE experience both extremity and abdominal attacks. The most dangerous attacks occur in the oropharynx and threaten laryngeal patency, potentially leading to asphyxiation. Although these types of attacks occur much less frequently than the extremity or abdominal attacks, more than 50% of patients with HAE experience at least 1 laryngeal attack during their lifetimes.

Annotation 3: On-demand treatment of acute attacks of angioedema. The treatment of acute attacks of HAE has changed dramatically in the last several years. There are currently 3 medications approved in the United States for the treatment of acute attacks of angioedema: plasma-derived C1INH, the B2 bradykinin receptor antagonist icatibant, and the plasma kallikrein inhibitor ecallantide. All have been shown to be safe and efficacious for the treatment of acute HAE attacks. On-demand treatment is most effective when administered as early as possible in an attack.

Standard angioedema treatment modalities, such as epinephrine, corticosteroids, or antihistamines, do not have a significant effect on the swelling in patients with HAE. Fresh frozen plasma has been used to treat acute angioedema attacks, and although it is usually successful, it can sometimes cause a sudden worsening of symptoms and carries the inherent risk of viral transmission. Attenuated androgens and antifibrinolytic agents are not effective for acute angioedema attacks. For the above reasons, the use of one of the newer specific medicines is preferred for treatment of angioedema attacks.

If one of the specific effective on-demand medications is not available, management of individual attacks can also involve symptomatic treatment. Patients often require narcotic medications for control of the pain during abdominal attacks, as well as antiemetics for nausea and vomiting. Because third-space sequestration of fluid is typically a problem during abdominal attacks, aggressive hydration is usually helpful. Narcotic addiction is a risk for patients with HAE who experience frequent attacks. In particular, out-of-hospital use of potent narcotics, such as fentanyl patches or oxycodone, is a serious concern in these patients and should be avoided. The management of oropharyngeal and laryngeal attacks is primarily focused on maintaining airway patency. All patients experiencing oropharyngeal or laryngeal attacks should be observed in a medical facility that can perform intubation or tracheostomy should it become necessary. Patients should be closely monitored for signs and symptoms of impending airway closure, including change in voice, loss of ability to swallow, and difficulty breathing.

Annotation 4: Predictable upcoming stressor. Short-term prophylactic therapy is meant to protect patients against the likelihood of experiencing acute attacks during a defined temporal window after a stimulus known to precipitate HAE attacks (eg, extensive dental work or invasive medical or surgical procedures). All patients with HAE are candidates for short-term prophylaxis for times when they are exposed to situations that are likely to trigger angioedema attacks.

Annotation 5: Short-term prophylaxis. Effective short-term prophylactic therapy can be achieved in several ways. C1INH replacement is efficacious, well tolerated, and approved in the United States for prophylactic use. Administration of 1000 to 2000 U or 20 U/kg for children of plasma-derived C1INH provides effective short-term prophylaxis. Traditionally, short-term prophylaxis has entailed the infusion of 2 U (10 mL/kg for children) of solvent/detergent-treated plasma or fresh frozen plasma several hours up to 12 hours before the expected procedure. Compared with solvent/detergent-treated plasma or fresh frozen plasma, plasma-derived C1INH provides a more standardized dose of C1INH protein and has undergone more rigorous viral inactivation steps. An alternative strategy for short-term prophylaxis consists of having the patient take high-dose 17α-alkylated androgens (6-10 mg/kg/d in divided doses to a

maximum of 200 mg of danazol 3 times daily or equivalent) for 5 to 10 days before the insult and 2 days after the procedure. There are no comparative studies that have directly assessed the efficacy of plasma-derived C1INH and 17α-alkylated androgens for short-term prophylaxis. The decision as to which agent to prescribe should be based on an individualized assessment of harm/burden compared with benefit, cost considerations, and patients' values and preferences. For emergency procedures and in pregnant patients, administration of plasma-derived C1INH is preferred.

A dose of on-demand acute treatment drug (plasma-derived C1INH, ecallantide, or icatibant) should be readily available in case it is needed, particularly for dental procedures or surgical procedures requiring intubation. In some cases, when the trauma is expected to be minimal and on-demand therapy is readily available, deferring preprocedural treatment in favor of observation for the first signs of an attack with rapid treatment can be an alternative management strategy.

Annotation 6: Is the angioedema well controlled? If patients have frequent attacks of angioedema, the role of several potential exacerbating factors should be considered and reduced or eliminated, if possible. Disease severity in patients with HAE is highly variable. Patients not taking prophylactic medications often have swelling every 10 to 20 days. A relatively small number of patients with HAE swell very frequently, up to twice per week, and some patients with HAE never experience swelling. A change in the frequency of attacks in a given patient should trigger a search for an exacerbating factor.

Annotation 7: Minimize exacerbating factors. Several stressors have been associated with precipitating HAE attacks, especially trauma (even relatively minor trauma, such as sitting on a hard surface for a prolonged time) and emotional stress. Because ACE-Is decrease the catabolism of bradykinin, these drugs can precipitate attacks of angioedema and should be avoided in patients with HAE. A potential role for *H pylori* infection in triggering abdominal attacks has been reported; however, critical appraisal of these data leads to the interpretation that *H pylori* infection is not a significant factor in precipitating HAE attacks in most patients. Hormonal changes can affect disease severity. The effect of pregnancy on HAE disease severity is variable, with some women worsening and other women having less swelling during their pregnancy. Universally, women appear to be relatively protected against swelling at the time of parturition; however, their risk of swelling increases dramatically during the postpartum period. Birth control pills containing estrogen and estrogen replacement therapy both appear to increase the frequency of swelling and should be avoided in all women with HAE. Advice regarding alternative forms of contraception is an important part of any management plan.

Annotation 8. Long-term prophylaxis. In patients whose symptoms are not managed successfully with on-demand therapy, consideration for long-term prophylaxis therapy should be given. Factors, such as attack frequency, attack severity, location of attacks, access to acute care, comorbid conditions, and individual preference, can all influence the decision on whom to treat with long-term prophylaxis. On the basis of its relatively long plasma half-life (>30 hours), plasma-derived C1INH has been approved for long-term prophylaxis of HAE. A starting dose of 1000 U every 3 to 4 days is suggested with the possibility of adjusting the dose based on patient responses. Treatment with orally administered 17α-alkylated androgens also confers benefit in terms of decreasing the frequency and severity of HAE attacks; however, they can be associated with significant side effects. Both the efficacy and side effects of the 17α-alkylated androgens are dose related, and these must be balanced against each other. If used, it is critical that the dosage be adjusted to the lowest dose that provides effective control of the HAE. The effectiveness of the antifibrinolytic drug ε aminocaproic acid (EACA; tranexamic acid [Lysteda] Amicar; Xanodyne Pharmaceuticals, Newport, Ky) for long-term prophylaxis of HAE has also been demonstrated in a randomized placebo-controlled study but appears to be the least effective of the prophylactic modalities.

Treatment of HAE: Attacks

Summary Statement 15: Epinephrine, corticosteroids, and antihistamines are not efficacious and not recommended for the treatment of HAE. (C)

One of the most important considerations in dealing with patients with HAE is the recognition that standard angioedema treatment modalities, such as epinephrine, corticosteroids, or antihistamines, do not have a significant effect on the swelling seen in patients with HAE. Unlike allergic or most cases of idiopathic angioedema, the mechanism of swelling in patients with HAE involves generation of bradykinin. Not only do these treatment modalities not antagonize the effect of bradykinin, they also do not affect the generation of bradykinin from continuing contact system activation. There is no evidence that corticosteroids or antihistamines have any beneficial effect on HAE attacks. Epinephrine likely has a temporary effect through vasoconstriction and might provide transient benefit; however, there is no evidence that epinephrine changes the overall course of an attack.

Summary Statement 16: Fresh frozen plasma is often effective in abrogating HAE attacks; however, fresh frozen plasma might acutely exacerbate some attacks, and for this reason, caution is required. (D)

The use of fresh frozen plasma to treat attacks of HAE is controversial. Fresh frozen plasma has been used for this purpose for many years because normal plasma contains high circulating levels of C1INH protein. There is abundant evidence that fresh frozen plasma is generally effective in treating acute attacks of angioedema.[69] The controversy surrounding its use is related to the additional protein components of the contact system contained in plasma: plasma prekallikrein, coagulation factor XII, and high-molecular-weight kininogen. During severe attacks of angioedema, contact system proteins can be depleted; however, administration of fresh frozen plasma provides both C1INH and fresh contact system substrates. There are anecdotal reports of worsening of angioedema immediately after administration of fresh frozen plasma, an outcome compatible with a burst of additional contact system activation.[12,70,71] The viral safety of fresh frozen plasma is another potential harm associated with its administration. The determination to use fresh frozen plasma for a patient with HAE should be approached from the standpoint of balancing the potential for benefit with the potential for harm, include a consideration of patient circumstances, and include patients' values and preferences in the decision-making process. The decision process to use fresh frozen plasma should also take into account the availability of alternative safer medications.

If the treating physician elects to use fresh frozen plasma to treat acute attacks of angioedema, it is recommended that he or she be prepared to deal with a paradoxical exacerbation of symptoms. Because newer effective therapies have become available (see Summary Statement 19), the only indication for the use of fresh frozen plasma for acute HAE attacks will be if the more effective specific therapy is not readily available.

Summary Statement 17: Management of HAE attacks can involve symptomatic treatment based on the region of body swelling. (C)

Because not all angioedema attacks in all patients with HAE are likely to be treated with one of the newer specific drugs, the management of individual attacks can also involve symptomatic treatment.[68] Extremity attacks can be disabling; however, there is no specific symptomatic therapy to relieve the symptoms. Genitourinary attacks can require pain medication if the discomfort is severe and could require catheterization if the patient cannot urinate.

Moderate and severe abdominal attacks frequently require symptomatic treatment. Patients often require narcotic medications for control of pain and antiemetics for control of nausea and vomiting. Because third-space sequestration of fluid is typically a problem during abdominal attacks, aggressive hydration is usually required. Narcotic addiction is a risk for patients with HAE who experience frequent attacks. In particular, out-of-hospital use of potent narcotics, such as fentanyl patches or oxycodone, is a serious concern in these patients and should be avoided.

The management of oropharyngeal and laryngeal attacks is primarily focused on maintaining the patency of the airway. All patients experiencing oropharyngeal or laryngeal attacks should be observed in a medical facility that can perform intubation or tracheostomy should it become necessary. Patients should be closely monitored for signs and symptoms of impending airway closure, including change in voice, loss of the ability to swallow, and difficulty breathing. Because there is no clear evidence to determine the duration of observation required for oropharyngeal or laryngeal episodes, the observation period should be individualized. It is generally advisable not to directly visualize the airway because the trauma of the procedure can worsen the angioedema. If the patient exhibits signs and symptoms of impending airway closure, elective intubation should be considered. The anatomy of the airway can be highly distorted by the angioedema; for this reason, physicians who are highly skilled in airway management might be required for performing intubation. Immediate availability of backup tracheostomy is necessary in case the intubation is not successful.

Summary Statement 18: Neither anabolic androgens nor antifibrinolytic drugs provide reliably effective treatment for acute attacks of angioedema. (D)

Although both 17α-alkylated androgens and antifibrinolytic drugs have been shown to be efficacious in preventing HAE attacks, their use during acute HAE attacks is unlikely to be reliably effective. Both classes of medication require several days before they become optimally effective and thus might not have any therapeutic effect during the worsening phase of the attack. In addition, the necessity for delivering 17α-alkylated androgens orally largely precludes their use during acute abdominal attacks. There is anecdotal evidence that both of these medications can shorten the duration of attacks if begun early in an episode.[55,72]

Summary Statement 19: All patients with HAE should have access to an effective, on-demand HAE-specific agent. Evidence from double-blind, placebo-controlled randomized clinical trials demonstrates the efficacy and safety of treatment of HAE attacks with C1INH concentrates, a plasma kallikrein inhibitor, or a bradykinin B2 receptor antagonist (A).

Five novel drugs have been shown to be efficacious and safe for the treatment of HAE attacks in double-blind, placebo-controlled trials in the United States.[73-77] Three of the drugs involve replacement therapy with C1INH (Cinryze [ViroPharma, Exton, Pa], Berinert [CSL Behring, King of Prussia, Pa], and Rhucin [Pharming, Leiden, The Netherlands]). Cinryze and Berinert are both pasteurized, plasma-derived C1INH concentrates, and both are nanofiltered. Rhucin is a recombinant human C1INH concentrate purified from rabbit breast milk. Both of the plasma-derived C1INH concentrates have been approved for use in adolescent and adult patients with HAE (Cinryze in Europe and Berinert in Europe and the United States) to treat acute attacks. Rhucin is awaiting US Food and Drug Administration review in the United States and has been granted market authorization in Europe. The other 2 drugs antagonize bradykinin generation or action by inhibiting plasma kallikrein (ecallantide) or antagonizing bradykinin effects at the bradykinin B2 receptor (icatibant). Ecallantide (Kalbitor; Dyax, Burlington, Mass) and icatibant (Firazyr; Shire, Dublin, Ireland) have been approved for use in the United States for treatment of acute attacks in patients with HAE who are 16 years and older and 18 years and older, respectively. Table E2 summarizes the known clinical pharmacology, efficacy, and safety data for these 5 drugs.[68,78]

Berinert, ecallantide, and icatibant have all been approved in the United States for the treatment of acute attacks of angioedema in patients with HAE. Berinert (20 U/kg) was shown to be safe and effective for the treatment of acute moderate-to-severe abdominal and facial attacks.[73] However, the dose of 10 U/kg did not provide significant relief in this study. Both doses of Berinert were safe and well tolerated. Plasma-derived C1INH replacement therapy has been associated with no remarkable untoward effects.[79] Home treatment with plasma-derived C1INH has also been shown to be efficacious and safe.[80-82]

Ecallantide (30 mg administered subcutaneously as 2-3 separate injections) was also shown to be effective in the treatment of moderate-to-severe acute attacks.[83,84] Some patients who received multiple doses of ecallantide had nonneutralizing antibodies to the drug. Two to three percent of patients have experienced anaphylactoid-type reactions. A relationship between antibodies to the drug and these anaphylactoid type reactions has not been established. Because of these adverse events, the US Food and Drug Administration requires that ecallantide be administered by a health care professional in a medically supervised setting.

Icatibant (30 mg administered as a single injection) was also shown to be effective in the treatment of moderate-to-severe acute attacks.[77] Icatibant was approved for self-administration and has a good safety profile, except for pain at the injection site.

Recognition and management of anaphylaxis potentially related to administration of a number of these agents can be complicated by the possible similarity of symptoms manifesting in patients with HAE and anaphylaxis.

Treatment with HAE-specific agents is preferred for all acute laryngeal/oropharygeal attacks and for moderate-to-severe attacks at other anatomic locations causing patient disability. A recent international consensus paper recommended consideration of on-demand treatment for all attacks in all locations to reduce the morbidity and mortality of HAE.[85] Patients with HAE should have a contingency plan for management of acute attacks.

This should include the option for on-demand treatment with an HAE-specific agent prescribed to the patient. In some areas medical personnel might not be permitted to administer agents brought by a patient; for this reason, advance arrangements would need to be implemented.

Prophylactic treatment of HAE

Summary Statement 20: Short-term prophylaxis can be achieved by using fresh frozen plasma, C1INH replacement, or short-term, high-dose anabolic androgen therapy. (B)

The goal of short-term prophylactic treatment is to protect patients against the likelihood of experiencing acute attacks during a defined temporal window after a stimulus known to precipitate HAE attacks. All patients with HAE are candidates for short-term prophylaxis for times when they are exposed to situations likely to trigger attacks of angioedema. It is thus critical that patients be educated concerning when to seek short-term prophylaxis. Examples of the type of situations that might call for short-term prophylaxis include significant dental work (more than routine teeth cleaning), surgical procedures, and invasive medical procedures, such as endoscopy.

Effective short-term prophylactic therapy can be achieved in several ways.[40,55,86] C1INH replacement therapy provides safe and effective short-term prophylaxis.[87] Traditionally, this has been administered by infusing patients with 2 U, or 10 mL/kg for children, of solvent/detergent-treated plasma or fresh frozen plasma several hours up to 12 hours before the expected procedure. Unlike the situation encountered during treatment of acute HAE attacks, in which the contact system is already highly activated, there is no evidence of prophylactic fresh frozen plasma either causing or worsening HAE attacks. Because plasma-derived C1INH has now been approved in the United States for prophylactic use, administration of 1000 to 2000 U of plasma-derived C1INH might be a better short-term prophylactic therapy than fresh frozen plasma based on the more standardized dose of C1INH protein and the more rigorous viral inactivation steps used to produce C1INH concentrates.[68,78]

In adults a second strategy for short-term prophylaxis consists of having the patient take high-dose 17α-alkylated androgens (6-10 mg/kg/d in divided doses to a maximum of 200 mg of danazol 3 times daily or equivalent) for 5 to 10 days before the procedure[40,55] and 2 days after.

In properly selected cases, when the trauma is expected to be minimal and on-demand therapy is readily available, deferring preprocedural treatment in favor of observation for first signs of an attack with rapid treatment can be an alternative management strategy.

Because no strategy is infallible, a dose of on-demand acute treatment drug should be readily available in case it is needed.

Summary Statement 21: The need for long-term HAE prophylaxis must be individualized based on the patient's situation. (D)

The goal of long-term prophylaxis is to decrease the frequency and severity of HAE attacks. Not all patients with HAE require long-term prophylaxis, and the decision regarding who should receive it must be individualized. Factors, such as attack frequency, attack severity, location of attacks, access to acute care, comorbid condition, and patient preference can all influence the decision of whom to treat. In addition, the need for long-term prophylactic treatment can change in a given patient over time. As an alternative (or in addition) to prophylactic management, on-demand treatment with an HAE-specific agent (Table E2) for attacks should be considered for management of patients with HAE.

Summary Statement 22: Treatment with low-to-moderate doses of anabolic androgens provides effective and relatively safe long-term HAE prophylaxis for many patients. (B)

Treatment with orally administered 17α-alkylated androgens has been shown in controlled double-blind studies to confer benefit in terms of decreasing the frequency and severity of HAE attacks.[88] Parenterally administered androgens that are not 17 α-alkylated are not effective for the treatment of HAE.

The 17α-alkylated androgens used most commonly to treat HAE include danazol (Danocrine; Sanofi-Synthelabo, Paris, France), stanozolol (Winstrol; Bayer, Leverkusen, Germany), oxandralone (Oxandrin; Savient Pharmaceuticals, Brunswick, NJ) and methyltestosterone.[40,55,89] The range of doses used for each is summarized in Table E3. Both the efficacy and side effects of the 17α-alkylated androgens are dose related and thus must be balanced against each other.[90] Therapy with a 17α-alkylated androgen can be initiated with either a high or low dose and then slowly titrated to achieve the desired effect. The choice of whether to begin treatment with a high or low dose is best determined by the needs and desires of the patient. High-dose initial therapy will result in the fastest control of disease severity, whereas low-dose initial therapy results in the least side effects. However, it is critical that the dosage be adjusted to the lowest dose that provides effective control of HAE. Because the beneficial effects of 17α-alkylated androgens accrue slowly, it is generally not advisable to change the dosage faster than 1 time per week. Almost all patients with HAE will exhibit an improvement in their HAE symptoms when taking 17α-alkylated androgens; however, the paucity of prospective studies examining efficacy and risks makes it difficult to select an optimal drug and dosage.

There is a relative contraindication for use of these drugs in children and adolescents.

The most common side effects from the 17α-alkylated androgens include masculinization in women along with menstrual irregularities, acne, changes in libido, changes in mood, increased aggression, abnormalities in the lipid profile, weight gain, and increased blood pressure.[91-93] Because these drugs can also cause hepatotoxicity, including development of hepatic adenomas and hepatic carcinoma,[94,95] periodic liver enzyme monitoring and performance of ultrasound are recommended. Side effects from the 17α-alkylated androgens are dose related, with a greater risk of significant side effects as the dosage is increased. In general, patients with HAE have been able to use relatively low doses of 17α-alkylated androgens (ie, ≤200 mg/d danazol) for decades with good safety; nevertheless, many of these patients do experience non–life-threatening side effects. Performing liver function tests every 6 months, as well as annual liver ultrasound examinations, is advisable in patients receiving regular 17α-alkylated androgen therapy.[68] Use of the 17α-alkylated androgens is relatively contraindicated in children, patients with breast or prostate cancer or pre-existing hepatic dysfunction, and women who are pregnant.[41,55]

Summary Statement 23: Treatment with antifibrinolytic agents provides somewhat effective and relatively safe long-term HAE prophylaxis but is generally less effective than androgens. (B)

The effectiveness of the antifibrinolytic drug EACA for long-term prophylaxis of HAE has also been demonstrated in a randomized placebo-controlled study.[96] Another antifibrinolytic

drug, tranexamic acid (Cyklokapron; Pfizer, New York, NY), has also been widely used in Europe for long-term prophylaxis of HAE.[97] The usual doses of EACA and tranexamic acid for HAE are shown in Table E3. Most, but not all, patients with HAE appear to derive benefit from treatment with the antifibrinolytic drugs.[40,55]

Common side effects of the antifibrinolytic drugs include nausea and diarrhea, vertigo, postural hypotension, fatigue, and muscle cramps/weakness with an increase in muscle enzyme concentrations. In addition, there is concern for enhanced thrombosis from these drugs.

Summary Statement 24: Treatment with replacement plasma-derived C1INH provides effective and safe long-term HAE prophylaxis. (A)

On the basis of its relatively long plasma half-life (>30 hours), plasma-derived C1INH has been assessed for long-term prophylaxis of HAE, as well as acute treatment. Double-blind, randomized, placebo-controlled studies have demonstrated that it is effective for long-term prophylaxis.[74,98,99] In a double-blind, placebo-controlled crossover trial to assess the utility of Cinryze as prophylaxis, the frequency of attacks was significantly reduced: 6.26 per 12 weeks on Cinryze compared with 12.73 per 12 weeks on placebo.[74] Furthermore, attacks were generally milder and of shorter duration. On the basis of these studies, plasma-derived C1INH (Cinryze) was approved for prophylactic therapy of HAE in the United States. A starting dose of 1000 U every 3 to 4 days is suggested, with the possibility of adjusting the dose based on patients' responses. Open-label experience with prophylactic plasma-derived C1INH in 146 patients for up to 3 years showed that the median attack rate on treatment decreased to less than 1 attack per 5 months from a median historical rate of 3 attacks per month.[100] C1INH replacement therapy has not been associated with remarkable untoward effects in more than 20 years of use in Europe[79]; however, chronic use of plasma-derived C1INH is associated with the burden of administration of an intravenous drug, as well as a potential risk for complications (eg, thrombosis and infection) associated with parenteral therapy. A recent survey of 66 physicians managing 856 patients with a C1INH product found that 5 (0.6%) had a clotting episode.[101] Patients managed with an indwelling catheter would be at increased risk for such untoward events, implying that placement of a central venous catheter in this setting should be considered carefully from an individualized risk/benefit standpoint.

It is not yet entirely clear which patients are appropriate candidates for long-term prophylactic treatment with plasma-derived C1INH. Patients who have severe disease with frequent attacks despite androgen or antifibrinolytic drugs, who do not tolerate these drugs, or for whom use of these drugs might be contraindicated (eg, pregnancy or children) are appropriate candidates. There are no studies in which the effectiveness and safety of C1INH and an attenuated androgen have been compared. The decision as to whether to prescribe C1INH replacement or an attenuated androgen for long-term prophylaxis should be based on an individualized assessment of harm/burden compared with benefit, cost considerations, and patients' values and preferences.

Patients receiving prophylactic plasma-derived C1INH experience reduced frequency of attacks; however, the risk for attacks is not eliminated for some patients. For this reason, the physician and patient need to be prepared to deal with any breakthrough attack. Whether these attacks while receiving regular prophylactic C1INH therapy are due to an inadequate dose of C1INH, too long an interval between injections, or other reasons remains to be established. Even though prophylactic treatment with C1INH has not been approved for patients with HAE who are children or adolescents, administration of this drug in properly selected patients might be warranted.[102]

Summary Statement 25: The novel agents for treatment of patients with C1INH deficiency syndromes are more costly than alternative treatment with attenuated androgens. Formal studies of cost utility and cost-effectiveness are required to aid providers in the management of patients with C1INH deficiency syndromes. (D)

The direct cost of the novel agents for treatment of C1INH deficiency syndromes is substantially more than the cost of attenuated androgens.[103] There is an honest difference of opinion as to whether the greater direct cost of the novel agents should influence the decision to prescribe these agents for long-term/short-term prophylaxis or for on-demand treatment of less severe attacks. Some view costs as an important outcome of care; health care costs are shared by society as a whole, including employers and patients.[104] The greater cost of these agents might be counterbalanced by lower rates of health service use and indirect medical expenditures caused by fewer exacerbations over time, less risk for harm, and improved quality of life. Formal economic models using cost-utility (cost per quality year of life gained) and cost-effectiveness (cost per attack prevented) analyses will be helpful to aid allergy/immunology providers in clarifying this issue.

Summary Statement 26: The dose and effectiveness of long-term prophylaxis should be based on clinical criteria and not laboratory parameters. (C)

The optimal dose for each of these medications (17α-alkylated androgens, antifibrinolytic agents, or plasma-derived C1INH) should be based on the clinical response rather than the C1INH plasma level or the C4 level.[12] There is little relationship between HAE severity and C1INH levels; a correlation of severity with C1INH functional assay results, as determined by using C1s-C1INH ELISA, might exist.[105] In general, there is no need to measure C1INH or C4 levels in a patient with HAE once the diagnosis has been made.

Summary Statement 27: Mechanisms of action of 17α-alkylated androgen and antifibrinolytic drugs for HAE have not been completely elucidated. (D)

The mechanism underlying the effectiveness of C1INH is replacement of the protein that is deficient in patients with HAE. In contrast, the mechanisms underlying the efficacy of 17α-alkylated androgen and antifibrinolytic drugs are uncertain. Treatment with high-dose 17α-alkylated androgens will result in increased C1INH levels; however, this does not correlate well with clinical responses.[88] Although androgens have been reported to result in a small increase in C1INH mRNA levels in blood monocytes,[106] no evidence of androgen-stimulated C1INH protein synthesis has been reported. Androgens have also been shown to increase levels of kininases (proteases that degrade bradykinin), an effect that might contribute to their effectiveness.[107] The mechanism underlying antifibrinolytic agents in the treatment of HAE is unknown.

Summary Statement 28: Adjunctive strategies, such as avoidance of ACE-Is, avoidance of estrogen therapy as feasible, and stress reduction, are important to decrease the frequency and severity of HAE attacks. (D)

ACE-Is can substantially enhance the frequency or severity of attacks[60]; for this reason, ACE-Is should be avoided. Many women experience considerable worsening of their HAE when

given exogenous estrogens.[62] Estrogen-containing birth control pills or hormonal replacement therapy should be approached cautiously or avoided, if possible. Stress reduction might have a noticeable effect on decreasing HAE attacks.[108]

Summary Statement 29: Pregnancy might be associated with an increase in the frequency and severity of HAE episodes. For long-term prophylaxis during pregnancy, treatment with androgens is contraindicated, and plasma-derived C1INH is preferred (D).

Changes in estrogen levels in association with puberty, menopause, oral contraceptive use, or pregnancy can provoke or exacerbate a tendency toward more frequent attacks, severe attacks, or both in some women with C1INH deficiency.[63] Ideally, all medications should be avoided in pregnancy; however, for patients with a propensity for more serious flares of HAE, long-term prophylaxis is appropriate because the potential for harm and burden associated with treatment is exceeded by the potential for benefit.[109] The decision to prescribe long-term prophylaxis during pregnancy should be made from an individualized risk/benefit standpoint and involve the patient in the decision-making process. Treatment of HAE with androgens is contraindicated during pregnancy[110]; for this reason, plasma-derived C1INH administration is preferred for long-term prophylaxis during pregnancy and might be considered for women who wish to become pregnant.[111] Angioedema attacks during delivery are relatively rare.[109] This low-risk situation can be managed expectantly by having an agent, such as plasma-derived C1INH, available in the delivery suite should an episode of angioedema occur.

HAE with normal C1INH levels

Summary Statement 30: Familial recurrent angioedema characterized by normal C1INH function might represent HAE with normal C1INH levels; however, there are no agreed upon criteria for diagnosing HAE with normal C1INH levels at this time (C).

An additional form of inherited angioedema has been described in which multiple generations are involved in a pattern consistent with an autosomal dominant inheritance; however, levels of the C1INH gene and protein are completely normal.[10,11] The clinical pattern of angioedema attacks is similar to that seen in patients with HAE with prolonged angioedema episodes and marked differences in severity from patient to patient.[112] At the current time, there is no definitive laboratory or clinical parameter to confirm a diagnosis of HAE with normal C1INH levels, and the diagnosis can only be considered in patients with a strong family history suggestive of an autosomal dominant pattern.

Summary Statement 31: Some kindreds with HAE with normal C1INH levels appear to require high estrogen levels for the angioedema to manifest. (C)

The original descriptions of HAE with normal C1INH levels described families in which all the affected subjects were women. Furthermore, attacks of angioedema were believed to mirror states of high endogenous estrogen (ie, pregnancy) or administration of exogenous estrogen. Subsequently, a number of families have been described with affected male subjects and with affected female subjects whose angioedema does not depend on high estrogen levels.[7]

Summary Statement 32: HAE with normal C1INH levels can be caused by increased bradykinin signaling. (C)

Recently, several of the kindreds with HAE with normal C1INH levels have been reported to have a gain-of-function mutation in coagulation factor XII that might result in enhanced generation of bradykinin.[113-115] However, other families with HAE with normal C1INH levels were screened for this mutation and found not to have it, with the incidence of factor XII mutations in this population being approximately 30%. The prevalence of this factor XII mutation in HAE with normal C1INH patients in the United States appears to be much lower. A more recent study did not confirm that this factor XII mutation caused a gain of function.[116] It is possible that HAE with normal C1INH levels is a heterogeneous disease with multiple underlying causes, possibly involving kinin-forming enzymes, kininases, or bradykinin receptors. Appropriate laboratory tests to assess this pathway are not generally available at this time.

Summary Statement 33: Drugs developed for patients with HAE with reduced C1INH function have been reported to be effective in some patients with HAE with normal C1INH levels. (C)

A number of open-label reports have been published showing that patients with HAE with normal C1INH levels might respond to many of the same drugs as do patients with type I and type II HAE. As with type I and type II HAE, corticosteroids and antihistamines are ineffective for HAE with normal C1INH levels. There are reports of successful on-demand treatment with the C1INH concentrates, ecallantide and icatibant.[117-119] In addition, some patients with HAE with normal C1INH levels have been reported to show improvement with long-term prophylactic therapy with danazol, progesterone, or tranexamic acid.[118-121]

ACQUIRED C1INH DEFICIENCY

Summary Statement 34: Clinical characteristics of angioedema episodes in patients with acquired C1INH deficiency are similar to those for HAE attacks. (C)

Acquired C1INH deficiency presents clinically in a manner that is indistinguishable from HAE, except that HAE tends to manifest during childhood, whereas acquired C1INH deficiency tends to manifest in middle-aged or older patients.[38] Acquired C1INH deficiency is not associated with a positive family history of angioedema, and all middle-aged or older patients presenting with isolated recurrent angioedema should have the possibility of an acquired C1INH deficiency considered.

Summary Statement 35: Diagnosis of acquired C1INH deficiency involves demonstration of reduced C1INH function, activation of complement, and reduced antigenic levels of the first component of complement (C1). (C)

As shown in Table E1, patients with acquired C1INH deficiency are distinguished from patients with HAE primarily by their low complement C1 levels. In addition, many patients with acquired C1INH deficiency have high-titer anti-C1INH antibodies. It can otherwise be difficult to distinguish patients with acquired C1INH deficiency from patients with type I HAE caused by a *de novo* C1INH mutation (thus without a family history of HAE).

Summary Statement 36: Acquired C1INH deficiency results from enhanced catabolism of C1INH. (LB)

The syndrome of acquired C1INH deficiency is not associated with a mutation of the C1INH gene or impaired synthesis of functional C1INH. It occurs because of increased catabolism of C1INH that outstrips the capacity of the host to synthesize new C1INH.[38]

C1INH acts as a suicide inactivator in which one molecule of C1INH inactivates a single molecule of its substrate by forming a nonreversible complex with the protease, followed by removal and destruction of the complex. This suggests a stoichiometric mechanism whereby C1INH is depleted when its synthesis cannot keep pace with the activation of its target proteases. Consistent with this mechanism, the original reports of acquired C1INH deficiency implied that the affected patients had an underlying disease that led to continuous activation of the classical complement pathway with consequent depletion of C1INH.[122] A number of associated underlying diseases have been described, including systemic lupus erythematosus and various malignancies, especially lymphoproliferative malignancies.[123,124] Successful treatment of the underlying disease has been associated with improvement in the acquired C1INH deficiency.

Summary Statement 37: Acquired C1INH deficiency might be associated with C1INH autoantibodies, with or without an underlying condition (eg, lymphoma). (C)

Some patients with acquired C1INH deficiency were found to have autoantibodies that specifically recognized normal C1INH levels.[125,126] Additional studies showed that these antibodies promoted an ineffective interaction between C1INH and its target proteases wherein the C1INH is cleaved into an inactive form by the protease without inactivating the protease.[127] Thus autoantibodies leading to protease activation could in theory result in inactivation of large amounts of C1INH. Patients with acquired C1INH deficiency with autoantibodies have been referred to as having type II acquired C1INH deficiency, whereas patients with acquired C1INH deficiency without autoantibodies are referred to as having type I acquired C1INH deficiency. However, the basis for this distinction has been questioned by the observation that many patients with acquired C1INH deficiency and antibodies against C1INH also have an underlying lymphoma or monoclonal gammopathy; the common feature appears to be B-cell proliferation, whether malignant (lymphoma) or benign (monoclonal gammopathy).[128]

Summary Statement 38: The treatment of acquired C1INH deficiency is similar to that for HAE, although with some significant differences, such as increased efficacy of antifibrinolytic agents, decreased efficacy of C1INH replacement, and the need to treat an underlying condition associated with acquired C1INH deficiency. (C)

Patients with acquired C1INH deficiency require attention to both prophylactic and acute treatment.[129] As is the case for HAE, acute attacks of angioedema in patients with acquired C1INH deficiency do not respond to antihistamines or corticosteroids and have only a transient and nonreliable response to epinephrine. Reports from Europe suggest that acute attacks of angioedema in patients with acquired C1INH deficiency might respond to C1INH replacement therapy; however, patients with high levels of C1INH autoantibodies might be resistant to C1INH replacement therapy.[130] The efficacy of ecallantide and icatibant for the treatment of acquired C1INH deficiency has been reported.[58,131]

Androgens and antifibrinolytic drugs have been successfully used for long-term prophylaxis in patients with acquired C1INH deficiency. Unlike patients with HAE, patients with acquired C1INH deficiency often respond better to antifibrinolytic drugs than to 17α-alkylated androgens.[132] As mentioned above, treatment of the underlying disease in patients who have the deficiency because of an underlying disease has been shown to be beneficial and might lead to remission. Several different strategies to decrease the anti-C1INH antibody levels in autoantibody-positive patients have been reported, including plasmapheresis, cyclophosphamide, and high-dose intravenous immunoglobulin.[133] More recently, 3 autoantibody-positive patients with acquired C1INH deficiency were treated with rituximab and experienced sustained remission.[134]

ACE-I–ASSOCIATED ANGIOEDEMA

Summary Statement 39: ACE-Is are associated with angioedema in approximately 0.1% to 0.7% of patients. (A) ARBs have been associated with angioedema less commonly. (A)

Treatment with ACE-Is has been associated with recurrent angioedema without urticaria in 0.1% to 0.7% of patients exposed to these drugs, prominently involving the face and tongue but also involving other areas, including the bowel and extremities.[59] Angioedema associated with ACE-I therapy frequently occurs within the first few months of therapy but can occur even after years of continuous therapy. Patients experiencing angioedema secondary to one ACE-I will typically have angioedema to another ACE-I, which is consistent with this as a class effect and not a hypersensitivity reaction.

African American subjects are at a substantially higher risk of experiencing ACE-I–induced angioedema than white subjects.[135] Other factors that increase the risk of angioedema from ACE-Is include a history of smoking, increasing age, and female sex. In contrast, diabetic patients have a lower risk than nondiabetic patients.[59]

Summary Statement 40: The management of ACE-I (or ARB)–associated angioedema is discontinuation of the ACE-I (or ARB). (A)

Discontinuation of the ACE-I (or ARB) is the cornerstone of therapy for these patients, although there might be a significant time lag between discontinuation of the drug and the propensity for angioedema.[59] During acute attacks, patients need to be observed in a controlled environment in case they require intubation. Treatment with antihistamines, corticosteroids, or epinephrine has not been shown to be efficacious. Efficacy of icatibant and fresh frozen plasma[4,6] have been described for ACE-I–associated angioedema; however, no controlled studies have been reported.

Summary Statement 41: The angioedema associated with ACE-Is is likely due to impaired degradation of bioactive peptides, such as bradykinin. (C)

ACE is a dipeptidyl carboxypeptidase that cleaves certain peptides, including bradykinin and substance P. When ACE is inhibited, bradykinin degradation is expected to be prolonged and thus might contribute to the resultant angioedema. Patients experiencing ACE-I–associated angioedema have been reported to have increased plasma bradykinin levels.[35] It has been speculated that the susceptibility to ACE-I–induced angioedema might be determined by the level or activity of other bradykinin-degrading enzymes.[136,137] Indeed, clinical studies with a combined ACE and neutral endopeptidase inhibitor resulted in a higher incidence of angioedema than seen from an ACE-I alone.[138] Dipeptidyl peptidase IV is another kininase. Introduction of dipeptidyl peptidase IV inhibitors for the treatment of diabetes can also increase the risk of angioedema, especially because many diabetic patients are already taking an ACE-I. The mechanism for ARB-associated angioedema has not been clearly determined; data suggest that ARBs might also influence bradykinin levels, but further studies are required to substantiate this.[139]

Summary Statement 42: A modest risk of recurrent angioedema exists in patients who experienced angioedema in response to ACE-I therapy and then are switched to ARB therapy; however, most patients who have experienced ACE-I–induced angioedema can safely use ARBs without recurrence of angioedema. (C)

A modest risk of recurrent angioedema exists in patients who experienced angioedema in response to ACE-I therapy and then are switched to ARB therapy[140]; however, most can safely be treated by ARBs without recurrence of angioedema.[141] In one study rates of subsequent angioedema were compared in patients who had had angioedema while receiving ACE-Is who were switched to an ARB versus a calcium-channel blocker; no statistically significant difference was observed.[142] A recent meta-analysis[143] found a risk for recurrence of angioedema in patients who had ACE-I–induced angioedema and were switched to an ARB of 2% to 17%. Additional studies are required to define this risk more precisely.

Angioedema has recently been reported in association with aliskiren, a renin inhibitor and treatment for essential hypertension. A pooled analysis[144] of 31 studies with more than 12,000 patients found a 0.4% rate of angioedema (relative risk of 0.31 [95% CI, 0.07-1.47] for 150 mg; relative risk of 0.57 [95% CI, 0.17-1.89] for 300 mg). Patients with a history of angioedema during treatment with an ACE-I might be at increased risk if switched to aliskiren as an alternative antihypertensive agent. The mechanism for angioedema from aliskiren has not been determined.

The decision to switch to an ARB or to aliskiren when suspending an ACE-I because of angioedema should be considered in the context of a careful assessment of potential harm (recurrent angioedema) compared with benefit (therapeutic need for angiotensin/renin inhibition) and involve the patient in the decision-making process.

REFERENCES

1. Cupido C, Rayner B. Life-threatening angio-oedema and death associated with the ACE inhibitor enalapril. S Afr Med J 2007;97:244-5, III.
2. Jason DR. Fatal angioedema associated with captopril. J Forensic Sci 1992;37: 1418-21, III.
3. Ulmer JL, Garvey MJ. Fatal angioedema associated with lisinopril. Ann Pharmacother 1992;26:1245-6, III.
4. Bas M, Greve J, Stelter K, Bier H, Stark T, Hoffmann TK, et al. Therapeutic efficacy of icatibant in angioedema induced by angiotensin-converting enzyme inhibitors: a case series. Ann Emerg Med 2010;56:278-82, IIb.
5. Gallitelli M, Alzetta M. Icatibant: a novel approach to the treatment of angioedema related to the use of angiotensin-converting enzyme inhibitors. Am J Emerg Med 2012;30(1664):e1-2, IV.
6. Schmidt PW, Hirschl MM, Trautinger F. Treatment of angiotensin-converting enzyme inhibitor-related angioedema with the bradykinin B2 receptor antagonist icatibant. J Am Acad Dermatol 2010;63:913-4, III.
7. Bork K, Gul D, Dewald G. Hereditary angio-oedema with normal C1 inhibitor in a family with affected women and men. Br J Dermatol 2006;154:542-5, III.
8. Wagenaar-Bos IG, Drouet C, Aygoren-Pursun E, Bork K, Bucher C, Bygum A, et al. Functional C1-inhibitor diagnostics in hereditary angioedema: assay evaluation and recommendations. J Immunol Methods 2008;338:14-20, IV.
9. Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C' 1-esterase. Am J Med 1963;35: 37-44, III.
10. Binkley KE, Davis A 3rd. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. J Allergy Clin Immunol 2000;106:546-50, III.
11. Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. Lancet 2000;356:213-7, III.
12. Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. Ann Intern Med 1976;84:580-93, IV.
13. Lomas DA, Belorgey D, Mallya M, Miranda E, Kinghorn KJ, Sharp LK, et al. Molecular mousetraps and the serpinopathies. Biochem Soc Trans 2005;33: 321-30, IV.
14. Zuraw BL, Curd JG. Demonstration of modified inactive first component of complement (C1) inhibitor in the plasmas of C1 inhibitor-deficient patients. J Clin Invest 1986;78:567-75, III.
15. Davis AE 3rd, Whitehead AS, Harrison RA, Dauphinais A, Bruns GA, Cicardi M, et al. Human inhibitor of the first component of complement, C1: characterization of cDNA clones and localization of the gene to chromosome 11. Proc Natl Acad Sci U S A 1986;83:3161-5, IIb.
16. Bock SC, Skriver K, Nielsen E, Thogersen HC, Wiman B, Donaldson VH, et al. Human C1 inhibitor: primary structure, cDNA cloning, and chromosomal localization. Biochemistry 1986;25:4292-301, III.
17. Tosi M, Duponchel C, Bourgarel P, Colomb M, Meo T. Molecular cloning of human C1 inhibitor: sequence homologies with alpha 1-antitrypsin and other members of the serpins superfamily. Gene 1986;42:265-72, LB.
18. Carter PE, Duponchel C, Tosi M, Fothergill JE. Complete nucleotide sequence of the gene for human C1 inhibitor with an unusually high density of Alu elements. Eur J Biochem 1991;197:301-8, LB.
19. Beinrohr L, Harmat V, Dobo J, Lorincz Z, Gal P, Zavodszky P. C1 inhibitor serpin domain structure reveals the likely mechanism of heparin potentiation and conformational disease. J Biol Chem 2007;282:21100-9, LB.
20. Bissler JJ, Aulak KS, Donaldson VH, Rosen FS, Cicardi M, Harrison RA, et al. Molecular defects in hereditary angioneurotic edema. Proc Assoc Am Physicians 1997;109:164-73, III.
21. Davis AE 3rd. C1 inhibitor and hereditary angioneurotic edema. Annu Rev Immunol 1988;6:595-628, III.
22. Verpy E, Biasotto M, Brai M, Misiano G, Meo T, Tosi M. Exhaustive mutation scanning by fluorescence-assisted mismatch analysis discloses new genotype-phenotype correlations in angiodema. Am J Hum Genet 1996;59:308-19, III.
23. Zuraw BL, Herschbach J. Detection of C1 inhibitor mutations in patients with hereditary angioedema. J Allergy Clin Immunol 2000;105:541-6, III.
24. Pappalardo E, Caccia S, Suffritti C, Tordai A, Zingale LC, Cicardi M. Mutation screening of C1 inhibitor gene in 108 unrelated families with hereditary angioedema: functional and structural correlates. Mol Immunol 2008;45: 3536-44, IIb.
25. Gosswein T, Kocot A, Emmert G, Kreuz W, Martinez-Saguer I, Aygoren-Pursun E, et al. Mutational spectrum of the C1INH (SERPING1) gene in patients with hereditary angioedema. Cytogenet Genome Res 2008;121:181-8, III.
26. Davis AE 3rd. Mechanism of angioedema in first complement component inhibitor deficiency. Immunol Allergy Clin North Am 2006;26:633-51, IV.
27. Donaldson VH, Rosen FS, Bing DH. Role of the second component of complement (C2) and plasmin in kinin release in hereditary angioneurotic edema (H.A.N.E.) plasma. Trans Assoc Am Physicians 1977;90:174-83, III.
28. Curd JG, Prograis LJ Jr, Cochrane CG. Detection of active kallikrein in induced blister fluids of hereditary angioedema patients. J Exp Med 1980;152:742-7, IIb.
29. Curd JG, Yelvington M, Burridge N, Stimler NP, Gerard C, Prograis L Jr, et al. Generation of bradykinin during incubation of hereditary angioedema plasma [abstract]. Mol Immunol 1982;19:1365, IIb.
30. Fields T, Ghebrehiwet B, Kaplan AP. Kinin formation in hereditary angioedema plasma: evidence against kinin derivation from C2 and in support of "spontaneous" formation of bradykinin. J Allergy Clin Immunol 1983;72:54-60, LB.
31. Schapira M, Silver LD, Scott CF, Schmaier AH, Prograis LJ Jr, Curd JG, et al. Prekallikrein activation and high-molecular-weight kininogen consumption in hereditary angioedema. N Engl J Med 1983;308:1050-3, III.
32. Lammle B, Zuraw BL, Heeb MJ, Schwarz HP, Berrettini M, Curd JG, et al. Detection and quantitation of cleaved and uncleaved high molecular weight kininogen in plasma by ligand blotting with radiolabeled plasma prekallikrein or factor XI. Thromb Haemost 1988;59:151-61, LB.
33. Shoemaker LR, Schurman SJ, Donaldson VH, Davis AE 3rd. Hereditary angioneurotic oedema: characterization of plasma kinin and vascular permeability-enhancing activities. Clin Exp Immunol 1994;95:22-8, IV.
34. Han ED, MacFarlane RC, Mulligan AN, Scafidi J, Davis AE 3rd. Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. J Clin Invest 2002;109:1057-63, LB.
35. Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angio-oedema. Lancet 1998;351:1693-7, IIa.
36. Bork K, Frank J, Grundt B, Schlattmann P, Nussberger J, Kreuz W. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). J Allergy Clin Immunol 2007;119:1497-503, IIb.
37. Roche O, Blanch A, Caballero T, Sastre N, Callejo D, Lopez-Trascasa M. Hereditary angioedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. Ann Allergy Asthma Immunol 2005;94: 498-503, III.

38. Zingale LC, Castelli R, Zanichelli A, Cicardi M. Acquired deficiency of the inhibitor of the first complement component: presentation, diagnosis, course, and conventional management. Immunol Allergy Clin North Am 2006;26: 669-90, IV.
39. Lunn ML, Santos CB, Craig TJ. Is there a need for clinical guidelines in the United States for the diagnosis of hereditary angioedema and the screening of family members of affected patients? Ann Allergy Asthma Immunol 2010;104: 211-4, III.
40. Bowen T, Cicardi M, Bork K, Zuraw B, Frank M, Ritchie B, et al. Hereditary angiodema: 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): S30-40, IV.
41. Farkas H, Varga L, Szeplaki G, Visy B, Harmat G, Bowen T. Management of hereditary angioedema in pediatric patients. Pediatrics 2007;120:e713-22, IV.
42. Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. Medicine (Baltimore) 1992;71: 206-15, III.
43. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. Am J Med 2006;119:267-74, III.
44. Molina C, Brun J, Coulet M, Betail G, Wahl D, Hartmann L. Diagnostic and therapeutic problems associated with hereditary deficiency of the C1 esterase inhibitor. Clin Allergy 1977;7:127-35, III.
45. Pappalardo E, Cicardi M, Duponchel C, Carugati A, Choquet S, Agostoni A, et al. Frequent de novo mutations and exon deletions in the C1inhibitor gene of patients with angioedema. J Allergy Clin Immunol 2000;106:1147-54, III.
46. Rosen FS, Alper CA, Pensky J, Klemperer MR, Donaldson VH. Genetically determined heterogeneity of the C1 esterase inhibitor in patients with hereditary angioneurotic edema. J Clin Invest 1971;50:2143-9, IIb.
47. Rosen FS, Pensky J, Donaldson V, Charache P. Hereditary angioneurotic edema: two genetic variants. Science 1965;148:957-8, IIb.
48. Verpy E, Couture-Tosi E, Eldering E, Lopez-Trascasa M, Spath P, Meo T, et al. Crucial residues in the carboxy-terminal end of C1 inhibitor revealed by pathogenic mutants impaired in secretion or function. J Clin Invest 1995; 95:350-9, LB.
49. Aulak KS, Pemberton PA, Rosen FS, Carrell RW, Lachmann PJ, Harrison RA. Dysfunctional C1-inhibitor(At), isolated from a type II hereditary-angioedema plasma, contains a P1 'reactive centre' (Arg444—His) mutation. Biochem J 1988;253:615-8, III.
50. Donaldson VH, Harrison RA, Rosen FS, Bing DH, Kindness G, Canar J, et al. Variability in purified dysfunctional C1(-)-inhibitor proteins from patients with hereditary angioneurotic edema. Functional and analytical gel studies. J Clin Invest 1985;75:124-32, IIa.
51. Donaldson VH, Bissler JJ. C1- inhibitors and their genes: an update. J Lab Clin Med 1992;119(4):330-3, III.
52. Frangi D, Aulak KS, Cicardi M, Harrison RA, Davis AE III. A dysfunctional C1 inhibitor protein with a new reactive center mutation (Arg-444 → Leu). FEBS Lett 1992;301:34-6, III.
53. Skriver K, Radziejewska E, Silbermann JA, Donaldson VH, Bock SC. CpG mutations in the reactive site of human C1 inhibitor. J Biol Chem 1989;264:3066-71, LB.
54. Parad RB, Kramer J, Strunk RC, Rosen FS, Davis AE 3rd. Dysfunctional C1 inhibitor Ta: deletion of Lys-251 results in acquisition of an N-glycosylation site. Proc Natl Acad Sci U S A 1990;87:6786-90, LB.
55. Gompels MM, Lock RJ, Abinun M, Bethune CA, Davies G, Grattan C, et al. C1 inhibitor deficiency: consensus document. Clin Exp Immunol 2005;139: 379-94, IV.
56. Zuraw BL, Sugimoto S, Curd JG. The value of rocket immunoelectrophoresis for C4 activation in the evaluation of patients with angioedema or C1-inhibitor deficiency. J Allergy Clin Immunol 1986;78:1115-20, IIa.
57. Gompels MM, Lock RJ, Morgan JE, Osborne J, Brown A, Virgo PF. A multicentre evaluation of the diagnostic efficiency of serological investigations for C1 inhibitor deficiency. J Clin Pathol 2002;55:145-7, Ib.
58. Cicardi M, Zanichelli A. Acquired angioedema. Allergy Asthma Clin Immunol 2010;6:14, IV.
59. Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. Immunol Allergy Clin North Am 2006;26:725-37, IV.
60. Shepherd GM. Possible contraindication of angiotensin converting enzyme inhibitors in patients with hereditary angioedema. Am J Med 1990;88:446, III.
61. Visy B, Fust G, Bygum A, Bork K, Longhurst H, Bucher C, et al. *Helicobacter pylori* infection as a triggering factor of attacks in patients with hereditary angioedema. Helicobacter 2007;12:251-7, Ib.
62. Frank MM. Effect of sex hormones on the complement-related clinical disorder of hereditary angioedema. Arthritis Rheum 1979;22:1295-9, IV.
63. Bouillet L, Longhurst H, Boccon-Gibod I, Bork K, Bucher C, Bygum A, et al. Disease expression in women with hereditary angioedema. Am J Obstet Gynecol 2008;199(484):e1-4, III.
64. Chappatte O, de Swiet M. Hereditary angioneurotic oedema and pregnancy. Case reports and review of the literature. Br J Obstet Gynaecol 1988;95: 938-42, III.
65. Caballero T, Farkas H, Bouillet L, Bowen T, Gompel A, Fagerberg C, 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 2012;129:308-20, IV.
66. Bouillet L. Hereditary angioedema in women. Allergy Asthma Clin Immunol 2010;6:17, IV.
67. Prematta MJ, Kemp JG, Gibbs JG, Mende C, Rhoads C, Craig TJ. Frequency, timing, and type of prodromal symptoms associated with hereditary angioedema attacks. Allergy Asthma Proc 2009;30:506-11, III.
68. Zuraw BL. Clinical practice. Hereditary angioedema. N Engl J Med 2008;359: 1027-36, IV.
69. Prematta M, Gibbs JG, Pratt EL, Stoughton TR, Craig TJ. Fresh frozen plasma for the treatment of hereditary angioedema. Ann Allergy Asthma Immunol 2007;98: 383-8, IV.
70. Rosen FS, Austen KF. The "neurotic edema" (hereditary angioedema). N Engl J Med 1969;280:1356-7, IV.
71. Donaldson VH. Therapy of "the neurotic edema." N Engl J Med 1972;286:835-6, IV.
72. Carugati A, Pappalardo E, Zingale LC, Cicardi M. C1-inhibitor deficiency and angioedema. Mol Immunol 2001;38:161-73, IV.
73. Craig TJ, Levy RJ, Wasserman RL, Bewtra AK, Hurewitz D, Obtulowicz K, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. J Allergy Clin Immunol 2009; 124:801-8, Ib.
74. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med 2010;363:513-22, Ib.
75. Zuraw B, Cicardi M, Levy RJ, Nuijens JH, Relan A, Visscher S, et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. J Allergy Clin Immunol 2010;126:821-7, e14. (Ib).
76. Cicardi M, Banerji A, Bracho F, Malbran A, Rosenkranz B, Riedl M, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N Engl J Med 2010;363:532-41, Ib.
77. Lumry WR, Li HH, Levy RJ, Potter PC, Farkas H, Moldovan D, et al. Randomized placebo-controlled trial of the bradykinin B receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. Ann Allergy Asthma Immunol 2011;107:529-37, Ib.
78. Zuraw BL, Christiansen SC. New promise and hope for treating hereditary angioedema. Expert Opin Investig Drugs 2008;17:697-706, IV.
79. De Serres J, Groner A, Lindner J. Safety and efficacy of pasteurized C1 inhibitor concentrate (Berinert P) in hereditary angioedema: a review. jean.de.serres@aventis.com. Transfus Apher Sci 2003;29:247-54, IV.
80. 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;117:904-8, IIb.
81. Kreuz W, Martinez-Saguer I, Aygoren-Pursun 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; 49:1987-95, IIb.
82. 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 2011;157:417-24, IIa.
83. Bernstein JA, Qazi M. Ecallantide: its pharmacology, pharmacokinetics, clinical efficacy and tolerability. Expert Rev Clin Immunol 2010;6:29-39, IV.
84. Zuraw B, Yasothan U, Kirkpatrick P. Ecallantide. Nat Rev Drug Discov 2010;9: 189-90, IV.
85. Cicardi M, Bork K, Caballero T, Craig T, Li HH, Longhurst H, 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 2012;67:147-57, Ia.
86. Jaffe CJ, Atkinson JP, Gelfand JA, Frank MM. Hereditary angioedema: the use of fresh frozen plasma for prophylaxis in patients undergoing oral surgery. J Allergy Clin Immunol 1975;55:386-93, IIb.
87. Bork K, Hardt J, Staubach-Renz P, 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 2011; 112:58-64, IIb.

88. Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol. Reversal of clinical and biochemical abnormalities. N Engl J Med 1976;295:1444-8, Ib.
89. Craig TJ. Appraisal of danazol prophylaxis for hereditary angioedema. Allergy Asthma Proc 2008;29:225-31, IV.
90. 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; 100:153-61, IIb.
91. Cicardi M, Castelli R, Zingale LC, Agostoni A. Side effects of long-term prophylaxis with attenuated androgens in hereditary angioedema: comparison of treated and untreated patients. J Allergy Clin Immunol 1997;99:194-6, IIa.
92. Szeplaki G, Varga L, Valentin S, Kleiber M, Karadi I, Romics L, et al. Adverse effects of danazol prophylaxis on the lipid profiles of patients with hereditary angioedema. J Allergy Clin Immunol 2005;115:864-9, IIa.
93. Sloane DE, Lee CW, Sheffer AL. Hereditary angioedema: safety of long-term stanozolol therapy. J Allergy Clin Immunol 2007;120:654-8, III.
94. Bork K, Pitton M, Harten P, Koch P. Hepatocellular adenomas in patients taking danazol for hereditary angio-oedema. Lancet 1999;353:1066-7, III.
95. Monnier N, Ponard D, Duponchel C, Csopaki F, Bouillet L, Tosi M, et al. Characterisation of a new C1 inhibitor mutant in a patient with hepatocellular carcinoma. Mol Immunol 2006;43:2161-8, III.
96. Frank MM, Sergent JS, Kane MA, Alling DW. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema. A double-blind study. N Engl J Med 1972; 286:808-12, Ib.
97. Agostoni A, Aygoren-Pursun E, Binkley KE, Blanch A, Bork K, Bouillet L, 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):S51-131, IV.
98. Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. N Engl J Med 1996;334:1630-4, Ib.
99. Kunschak M, Engl W, Maritsch F, Rosen FS, Eder G, Zerlauth G, et al. A randomized, controlled trial to study the efficacy and safety of C1 inhibitor concentrate in treating hereditary angioedema. Transfusion 1998;38:540-9, Ib.
100. Zuraw B, Kalfus I. Safety and efficacy of prophylactic nanofiltered C1 inhibitor in hereditary angioedema. Am J Med 2012;125(938):e1-7.
101. Kalaria S, Crait T. Hereditary angioedema treatments and their risk of thrombotic events [abstract]. Ann Allergy Asthma Immunol 2011;107:A107.
102. Kreuz W, Rusicke E, Martinez-Saguer I, Aygoren-Pursun E, Heller C, Klingebiel T. Home therapy with intravenous human C1-inhibitor in children and adolescents with hereditary angioedema. Transfusion 2012;52:100-7, III.
103. Tilles SA, Borish L. A new generation of hereditary angioedema treatments: remarkable advances clash with disturbing economic reality. Ann Allergy Asthma Immunol 2011;106:264-6, IV.
104. Guyatt GH, Oxman AD, Kunz R, Jaeschke R, Helfand M, Liberati A, et al. Incorporating considerations of resources use into grading recommendations. BMJ 2008;336:1170-3, IV.
105. Kelemen Z, Moldovan D, Mihaly E, Visy B, Szeplaki G, Csuka D, et al. Baseline level of functional C1-inhibitor correlates with disease severity scores in hereditary angioedema. Clin Immunol 2010;134:354-8, III.
106. Pappalardo E, Zingale LC, Cicardi M. Increased expression of C1-inhibitor mRNA in patients with hereditary angioedema treated with Danazol. Immunol Lett 2003;86:271-6, IIa.
107. Drouet C, Desormeaux A, Robillard J, Ponard D, Bouillet L, Martin L, et al. Metallopeptidase activities in hereditary angioedema: effect of androgen prophylaxis on plasma aminopeptidase P. J Allergy Clin Immunol 2008;121: 429-33, IIa.
108. Nielsen EW, Gran JT, Straume B, Mellbye OJ, Johansen HT, Mollnes TE. Hereditary angio-oedema: new clinical observations and autoimmune screening, complement and kallikrein-kinin analyses. J Intern Med 1996;239: 119-30, III.
109. Czaller I, Visy B, Csuka D, Fust G, Toth F, Farkas H. The natural history of hereditary angioedema and the impact of treatment with human C1-inhibitor concentrate during pregnancy: a long-term survey. Eur J Obstet Gynecol Reprod Biol 2010;152:44-9, III.
110. Sheffer AL, Fearon DT, Austen KF. Hereditary angioedema: a decade of management with stanozolol. J Allergy Clin Immunol 1987;80:855-60, IIb.
111. Farkas H, Jakab L, Temesszentandrasi G, Visy B, Harmat G, Fust G, et al. Hereditary angioedema: a decade of human C1-inhibitor concentrate therapy. J Allergy Clin Immunol 2007;120:941-7, III.
112. Bork K, Gul D, Hardt J, Dewald G. Hereditary angioedema with normal C1 inhibitor: clinical symptoms and course. Am J Med 2007;120:987-92, III.
113. Cichon S, Martin L, Hennies HC, Muller F, Van Driessche K, Karpushova A, et al. Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. Am J Hum Genet 2006;79:1098-104, IIa.
114. Dewald G, Bork K. Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. Biochem Biophys Res Commun 2006;343:1286-9, III.
115. Duan QL, Binkley K, Rouleau GA. Genetic analysis of Factor XII and bradykinin catabolic enzymes in a family with estrogen-dependent inherited angioedema. J Allergy Clin Immunol 2009;123:906-10, III.
116. Bork K, Kleist R, Hardt J, Witzke G. Kallikrein-kinin system and fibrinolysis in hereditary angioedema due to factor XII gene mutation Thr309Lys. Blood Coagul Fibrinolysis 2009;20:325-32, III.
117. Bouillet L, Ponard D, Rousset H, Cichon S, Drouet C. A case of hereditary angioedema type III presenting with C1-inhibitor cleavage and a missense mutation in the F12 gene. Br J Dermatol 2007;156:1063-5, III.
118. Vitrat-Hincky V, Gompel A, Dumestre-Perard C, Boccon-Gibod I, Drouet C, Cesbron JY, et al. Type III hereditary angio-oedema: clinical and biological features in a French cohort. Allergy 2010;65:1331-6, IIb.
119. Bouillet L, Boccon-Gibod I, Ponard D, Drouet C, Cesbron JY, Dumestre-Perard C, et al. Bradykinin receptor 2 antagonist (icatibant) for hereditary angioedema type III attacks. Ann Allergy Asthma Immunol 2009;103:448, IV.
120. Bork K. Hereditary angioedema with normal C1 inhibitor activity including hereditary angioedema with coagulation factor XII gene mutations. Immunol Allergy Clin North Am 2006;26:709-24, III.
121. Cronin JA, Maples KM. Treatment of an acute attack of type III hereditary angioedema with ecallantide. Ann Allergy Asthma Immunol 2012;108: 61-2, III.
122. Geha RS, Quinti I, Austen KF, Cicardi M, Sheffer A, Rosen FS. Acquired C1-inhibitor deficiency associated with antiidiotypic antibody to monoclonal immunoglobulins. N Engl J Med 1985;312:534-40, III.
123. Caldwell JR, Ruddy S, Schur PH, Austen KF. Acquired C1 inhibitor deficiency in lymphosarcoma. Clin Immunol Immunopathol 1972;1:39-52, III.
124. Schreiber AD, Zweiman B, Atkins P, Goldwein F, Pietra G, Atkinson B, et al. Acquired angioedema with lymphoproliferative disorder: association of C1 inhibitor deficiency with cellular abnormality. Blood 1976;48:567-80, III.
125. Jackson J, Sim RB, Whelan A, Feighery C. An IgG autoantibody which inactivates C1-inhibitor. Nature 1986;323:722-4, III.
126. Alsenz J, Bork K, Loos M. Autoantibody-mediated acquired deficiency of C1 inhibitor. N Engl J Med 1987;316:1360-6, III.
127. Jackson J, Sim RB, Whaley K, Feighery C. Autoantibody facilitated cleavage of C1-inhibitor in autoimmune angioedema. J Clin Invest 1989;83: 698-707, III.
128. Cicardi M, Beretta A, Colombo M, Gioffre D, Cugno M, Agostoni A. Relevance of lymphoproliferative disorders and of anti-C1 inhibitor autoantibodies in acquired angio-oedema. Clin Exp Immunol 1996;106:475-80, IIb.
129. Zingale LC, Beltrami L, Zanichelli A, Maggioni L, Pappalardo E, Cicardi B, et al. Angioedema without urticaria: a large clinical survey. CMAJ 2006;175: 1065-70, III.
130. Alsenz J, Lambris JD, Bork K, Loos M. Acquired C1 inhibitor (C1-INH) deficiency type II. Replacement therapy with C1-INH and analysis of patients' C1-INH and anti-C1-INH autoantibodies. J Clin Invest 1989;83:1794-9, IIb.
131. Zanichelli A, Badini M, Nataloni I, Montano N, Cicardi M. Treatment of acquired angioedema with icatibant: a case report. Intern Emerg Med 2011;6: 279-80, III.
132. Cicardi M, Zingale LC, Pappalardo E, Folcioni A, Agostoni A. Autoantibodies and lymphoproliferative diseases in acquired C1-inhibitor deficiencies. Medicine (Baltimore) 2003;82:274-81, IV.
133. Donaldson VH, Bernstein DI, Wagner CJ, Mitchell BH, Scinto J, Bernstein IL. Angioneurotic edema with acquired C1- inhibitor deficiency and autoantibody to C1- inhibitor: response to plasmapheresis and cytotoxic therapy. J Lab Clin Med 1992;119:397-406, III.
134. Levi M, Hack CE, van Oers MH. Rituximab-induced elimination of acquired angioedema due to C1-inhibitor deficiency. Am J Med 2006;119:e3-5, III.
135. Brown NJ, Ray WA, Snowden M, Griffin MR. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. Clin Pharmacol Ther 1996;60:8-13, III.
136. Blais C Jr, Rouleau JL, Brown NJ, Lepage Y, Spence D, Munoz C, et al. Serum metabolism of bradykinin and des-Arg9-bradykinin in patients with angiotensin-converting enzyme inhibitor-associated angioedema. Immunopharmacology 1999;43:293-302, IIb.
137. Adam A, Cugno M, Molinaro G, Perez M, Lepage Y, Agostoni A. Aminopeptidase P in individuals with a history of angio-oedema on ACE inhibitors. Lancet 2002;359:2088-9, IIa.
138. Campbell DJ. Vasopeptidase inhibition: a double-edged sword? Hypertension 2003;41:383-9, IV.
139. Campbell DJ, Krum H, Esler MD. Losartan increases bradykinin levels in hypertensive humans. Circulation 2005;111:315-20, Ib.

140. Boxer M. Accupril- and Cozaar-induced angioedema in the same patient. J Allergy Clin Immunol 1996;98:471, III.
141. Beavers CJ, Dunn SP, Macaulay TE. The role of angiotensin receptor blockers in patients with angiotensin-converting enzyme inhibitor-induced angioedema. Ann Pharmacother 2011;45:520-4, Ia.
142. Cicardi M, Zingale LC, Bergamaschini L, Agostoni A. Angioedema associated with angiotensin-converting enzyme inhibitor use: outcome after switching to a different treatment. Arch Intern Med 2004;164:910-3, IIb.
143. Haymore BR, Yoon J, Mikita CP, Klote MM, DeZee KJ. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis. Ann Allergy Asthma Immunol 2008;101:495-9, Ia.
144. White WB, Bresalier R, Kaplan AP, Palmer BF, Riddell RH, Lesogor A, et al. Safety and tolerability of the direct renin inhibitor aliskiren: a pooled analysis of clinical experience in more than 12,000 patients with hypertension. J Clin Hypertens 2010;12:765-75, Ia.

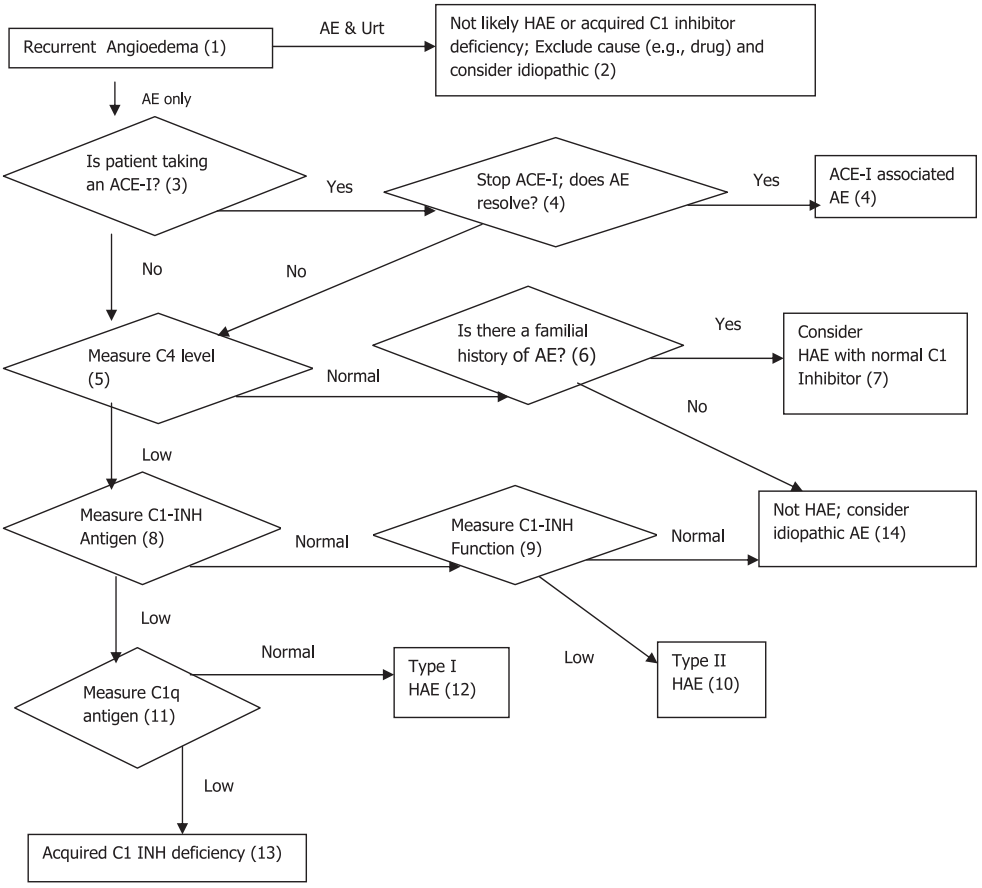

FIG E1. Recurrent angioedema diagnostic algorithm. *AE*, Angioedema; *URT*, urticaria.

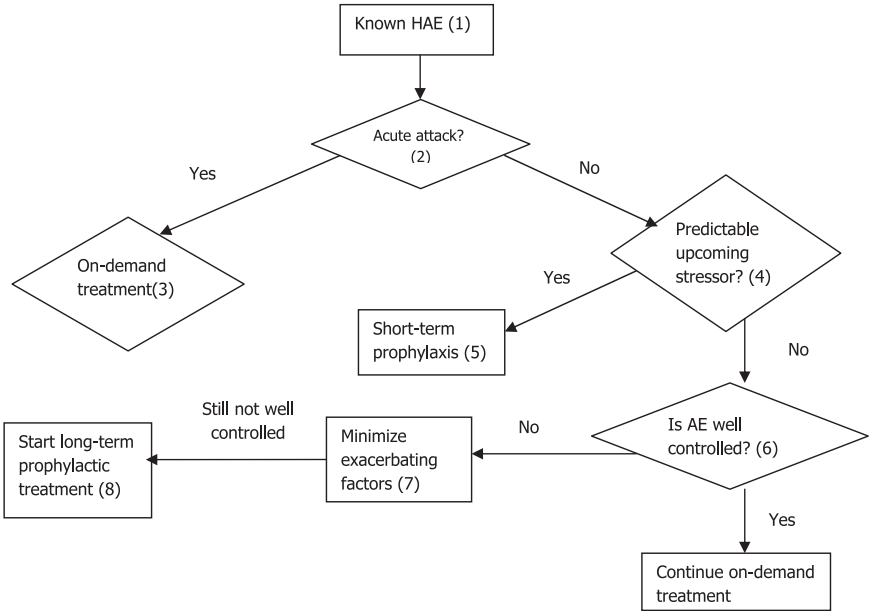

FIG E2. HAE treatment algorithm. *AE*, Angioedema.

TABLE E1. Complement profiles for diagnosis of different types of angioedema

	C1INH level	C1INH function	C4 level	C3 level	C1Q level
HAE type I	Low	Low	Low	Normal	Normal
HAE type II	Normal-High	Low	Low	Normal	Normal
HAE with normal C1INH levels	Normal	Normal	Normal	Normal	Normal
Acquired C1INH deficiency	Low	Low	Low	Low-Normal	Low
ACE-I	Normal	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal	Normal

TABLE E2. HAE-specific agents

Generic name (trade name, manufacturer)	FDA indications	Dosage	Mechanism	Anticipated potential side effects
Plasma-derived nanofiltered C1INH (Cinryze, ViroPharma)	Long-term prophylaxis	1000 U administered intravenously every 3-4 d	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis Theoretical: transmission of infectious agent
Plasma-derived nanofiltered C1INH (Berinert-P, CSL Behring)	Acute attacks	20 U/kg administered intravenously	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis Theoretical: transmission of infectious agent
Ecallantide (Kalbitor, Dyax)	Acute attacks	30 mg administered subcutaneously (administered as 3 injections of 1 mL each)	Inhibits plasma kallikrein	Uncommon: anti-drug antibodies, risk of anaphylaxis
Icatibant (Firazyr, Shire)	Acute attacks	30 mg administered subcutaneously	Bradykinin B2 receptor antagonist	Common: injection-site reactions
Recombinant human C1INH (Rhucin, Pharming)	Acute attacks (pending)	50-100 U/kg administered intravenously	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Uncommon: risk of anaphylaxis in rabbit-sensitized subjects

Adapted from Zuraw.[68]

FDA, US Food and Drug Administration; *MASP*, mannan-binding lectin serine protease.

TABLE E3. Drugs commonly used for long-term HAE prophylaxis

Class	Drug name (generic, trade)	Adult dosage (usual, range)	Pediatric dosage* (usual, range)	FDA approved/HAE indication	Side effects
17α-Alkylated androgens					
	Danazol (Danocrine)	200 mg/d (100 mg every 3 d-600 mg/d)	50 mg/d (50 mg/wk-200 mg/d)	Yes/Yes	Common: weight gain, virilization, acne, altered libido, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual abnormalities and increase in liver enzymes, hypertension, alterations in lipid profile; Unusual: Decreased growth rate in children, masculinization of the female fetus, cholestatic jaundice, peliosis hepatis and hepatocellular adenoma
	Stanozolol (Winstrol)	2 mg/d (1 mg every 3 d-6 mg/d)	0.5 mg/d (0.5 mg/wk-2 mg/d)	Yes/yes	
	Oxandralone (Oxandrin)	10 mg/d (2.5 mg every 3 d-20 mg/d)	0.1 mg/kg/d (2.5 mg/wk-7.5 mg/d)	Yes/no	
	Methyltestosterone (Android)	Men only: 10 mg/d (5 mg every 3 d-30 mg/d)	Not recommended for children	Yes/no	
Antifibrinolytics					
	ε Aminocaproic acid (Amicar)	2 g TID (1 g BID-4 g TID)	0.05 g/kg BID (0.025 gm/kg BID-0.1 g/kg BID)	Yes/no	Potential side effects: nausea, vertigo, diarrhea, postural hypotension, fatigue, muscle cramps with increased muscle enzymes Unusual: enhanced thrombosis
	Tranexamic acid (available in US for oral and intravenous administration [Lysteda, Cyklocapron])	1 g BID (0.25 g BID-1.5 g BID)	20 mg/kg BID (10 mg/kg BID-25 mg/kg TID)	Yes/no	

Adapted from Zuraw.[68]

BID, Twice daily; *FDA*, US Food and Drug Administration; *TID*, 3 times daily.