

Update on angioedema: Evaluation, diagnosis, and treatment

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ABSTRACT

Hereditary Angioedema (HAE) is a multisystem, autosomal dominant disease that affects ~1:10,000 to 1:50,000 individuals in the United States. The disease has several clinical characteristics that distinguish it from other forms of angioedema. Recurrent swelling attacks involve the abdomen, face, extremities, genitalia, oropharynx, or larynx without urticaria. The swelling attacks are typically unilateral, nonpitting, nonpruritic, and, although uncomfortable, are often painless. Other forms of isolated angioedema such as acquired angioedema and angiotensin-converting enzyme-induced angioedema have similar characteristics of HAE. Therefore, evaluation of patients with recurrent angioedema should be directed at excluding these different forms of angioedema before a diagnosis of idiopathic angioedema is made. The objective of this article is to provide an overview of the differential diagnosis of angioedema that reflects the angioedema guidelines that are currently in development.

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Hereditary angioedema (HAE) is a multisystem, autosomal dominant disease that affects ~1:10,000 to 1:50,000 individuals in the United States.¹ It affects all ethnic groups equally and there is no gender predilection.¹ Although typically there is a strong family history because of the autosomal dominant inheritance in 75% of cases, in 25% of cases there may be spontaneous mutations and therefore a family history is not always evident.¹ The disease has several clinical characteristics that distinguish it from other forms of angioedema. Recurrent swelling attacks involve the abdomen, face, extremities, genitalia, oropharynx, or larynx without urticaria. The swelling attacks are typically unilateral, nonpitting, nonpruritic, and although uncomfortable are often painless.¹

Other forms of isolated angioedema such as acquired angioedema and angiotensin-converting enzyme (ACE)–induced angioedema have similar characteristics of HAE. Therefore, evaluation of patients with recurrent angioedema should be directed at excluding these different forms of angioedema before a diagnosis of idiopathic angioedema is made. The objective of this article is to provide an overview of the differential diagnosis of angioedema that reflects the angioedema guidelines that are currently in development.

DIFFERENTIAL DIAGNOSIS OF ANGIOEDEMA

The differential diagnosis of angioedema includes idiopathic angioedema (with or without urticaria); C1 inhibitor deficiency; acquired C1 inhibitor deficiency; type III angioedema (genetic or drug induced factor XII activation); ACE inhibitor–associated angioedema (ACE and angiotensin receptor blocker); acute allergic angioedema; delayed pressure angioedema; nonsteroidal anti-inflammatory drug–associated angioedema; hydrostatic edema; oncotic edema (protein deficiency); Muckle-Wells syndrome; cytokine-induced angioedema (rIL-2, interferon α); episodic angioedema associated with eosinophilia (Gleich's syndrome; IL-5); non-episodic angioedema; nodules, eosinophilia, rheumatism, dermatitis, and swelling; and Clarkson's syndrome (capillary leak syndrome).^{1–11} It is beyond the scope of this review to discuss all of these disorders and therefore the focus will be on HAE types I through III, acquired angioedema, and ACE-induced angioedema.

HEREDITARY ANGIOEDEMA

Pathogenesis of HAE

The pathogenesis of HAE relates to a quantitative or functional deficiency of C1 esterase inhibitor (C1INH), which is a member of a group of related proteins referred to as serpins (*serine protease inhibitors*).¹² Serpins inactivate proteases by forming stable one-to-one complexes with proteases and are characteristically referred to as suicide inhibitors.¹² Serine proteases work by cleaving the reactive center loop of C1INH leading to formation of a covalent bond between the protease active site (a serine) and the reactive center (an amino acid) of the serpin. Rearrangement of the serpin occurs as a result of insertion of the reactive center loop into the β -sheet resulting in movement of the protease from one pole to the other thus resulting in its structural distortion.¹²

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The C1 IHH gene is located on chromosome 11 and consists of eight exons and seven introns. It is $\sim 1.7 \times 10^4$ base pairs in length. Notably, there are several polymorphic sites on this gene making spontaneous mutations feasible.¹³ Its relationship with regulating the classic complement system led many to originally speculate that HAE was caused by defective complement regulation.^{14,15} However, it has since been recognized that C1INH also regulates the contact and fibrinolytic pathways.¹⁴ In fact, its ability to block kallikrein's breakdown of factor XII to XIIa, conversion of prekallikrein to kallikrein and from high molecular weight kininogen to kallikrein are the most important sites for regulating the overproduction of bradykinin, which is now known to be the central bioactive mediator leading to vasodilation, smooth muscle contraction, and subsequent edema.¹⁵ The role of bradykinin has been well established in C1INH knockout mice.^{16,17} Mice homogeneously knocked out for C1INH (C1INH^{-/-}) have been shown to uniformly have intestinal wall edema as shown by extravasation of Evans blue dye compared with mice with a heterogeneous genotype (C1INH^{+/-}) where only $\sim 50\%$ of mice show marked intestinal wall edema.^{16,17} Treatment of the homogeneous C1INH knockout mice with C1INH replacement therapy prevented the intestinal wall edema manifested as a decreased extravasation of dye.^{16,17} To show that bradykinin was involved, C1INH^{-/-} mice were crossbred with bradykinin type 2 receptor double knockout mice (Bk2R^{-/-}) because bradykinin is known to induce increased vascular permeability through the Bk2R. Not surprisingly, the mice with C1INH (-/-)/Bk2R^{-/-} and mice with C1INH^{+/-}/Bk2R^{+/-} had no evidence of blue dye extravasation (*i.e.*, intestinal wall edema) because there was either no expression of Bk2R for bradykinin to bind or C1INH was able to regulate the production of bradykinin, respectively.^{16,17} In contrast, the mice with C1INH^{-/-}/Bk2R^{+/-} had significant blue dye extravasation (*i.e.*, intestinal wall edema) because there was no C1INH to regulate the production of endogenous bradykinin, which could thus bind freely to Bk2R.^{16,17} To further verify the role of bradykinin, therapeutic agents such as ecallantide, a kallikrein inhibitor, and icatibant, a Bk2R antagonist, were able to block the unchecked effect of bradykinin in this model.^{16,17} Thus, using this knockout mouse model, it was possible to definitively establish the role of bradykinin in causing edema in HAE patients.

Clinical Presentation

The age of onset of swelling in HAE patients often begins during childhood (average age, 11 years old) and typically worsens around puberty.¹⁸ The most frequent sites of swelling in HAE patients are the skin (100%) followed by the abdomen (98%) and then larynx (54%), although a number of other sites can be involved including the uvula, tongue,

chest, brain, esophagus, genitourinary tract, muscles, and joints.¹⁸ It is estimated that 50% of HAE patients will have swelling of their throat at some point in their life that may not manifest for many years after the initial diagnosis.¹⁸ The disease severity in HAE is very variable, characterized by episodic rather than continuous swelling.¹⁹ Most patients with HAE swell every 10–20 days if not treated. Swelling attacks typically worsen over 24 hours, peak, and then slowly resolve over 48 hours; however, morbidity associated with these attacks can be protracted lasting 3–5 days.¹⁹ Patients may have an aura or prodromal symptoms (*i.e.*, tingling, a sense of uneasiness, *etc.*) before the onset of an attack.^{20,21} The frequency of patients presenting with these early warning signs vary among different reporting investigators ranging from 30% to $>95\%$ of patients.^{20,21} Many HAE patients may manifest a characteristic rash called erythema marginatum before or in between attacks.^{20,21} This rash is has serpiginous borders, which are slightly raised, that typically involves the trunk and inner surfaces of arms and legs, sparing the face. Although erythema marginatum can be confused with hives because of its erythematous irregular borders with pale centers that blanch with pressure or worsen with heat and evanescent nature, it typically does not itch in stark contrast to classic urticaria.^{20,21} Patients with HAE may note specific triggers such as trauma, surgery, menstruation, infection, or stress that stimulate an attack.¹⁹ However, many patients have spontaneous attacks without recollection of inciting events.

Diagnosis

HAE manifests as a quantitative C1INH deficiency in 85% of patients referred to as type I HAE and as a functionally abnormal C1INH in 15% of cases referred to as type II HAE.²² Table 1 summarizes the complement profiles that help differentiate the different HAE types from other forms of angioedema.²² Patients with type I and II HAE and acquired angioedema typically have a decreased C4 level during and between attacks and a decreased C2 level during acute attacks. C1INH levels are decreased and are functionally abnormal in type I HAE whereas C1INH levels are normal or increased but functionally abnormal in type II HAE.²² Acquired angioedema has a similar profile to type I HAE but the C1q complement component level is decreased in acquired angioedema but normal in type I HAE.²² Type III HAE and ACE-induced and idiopathic angioedema have normal complement profiles.²² Their diagnoses are typically made by history and excluding other potential causes of angioedema.

Treatment

Important considerations in differentiating HAE types I, II, and III and acquired angioedema from other forms of angioedema are that they are often aggravated by estrogen and are unresponsive to conventional therapies

Table 1 Complement profiles in angioedema

	C1INH Antigen	C1INH Function	C4	C2	C1q	Autoantibody
HAE type 1	↓	↓	↓	↓	NI	Absent
HAE type 2	NI or ↑	↓	↓	↓	NI	Absent
HAE type 3	NI	NI	NI	NI	NI	Absent
Acquired angioedema	NI or ↓	↓	↓	↓	↓	Present
Idiopathic	NI	NI	NI	NI	NI	Absent

HAE = hereditary angioedema; C1INH = C1 esterase inhibitor.

such as corticosteroids, antihistamines, and epinephrine.¹ Patients with HAE should avoid taking oral contraception and estrogen replacement therapy, ACE inhibitors, and other stressors.⁵ Before the introduction of newer therapies, conventional treatment of acute angioedema attacks has been limited. For extremity attacks, treatment has been symptomatic supportive care whereas treatment of gastrointestinal attacks focused on relief of pain and nausea and treatment of oropharyngeal attacks involved hospitalization with careful observation and intubation if necessary. Fresh frozen plasma has been used to treat moderate-to-severe attacks successfully but carries the risk of viral transmission.^{1,5}

For those patients who have frequent swelling episodes, androgens and antifibrinolytic agents have been found to be effective in ameliorating attacks.^{23,24} However, androgens have many side effects that may limit their long-term use in some individuals, especially at daily doses above 200 mg.²⁵ Side effects include virilization (alopecia, hirsutism, deepened voice, etc.), hepatotoxicity (mild transaminase elevation), weight gain, menstrual abnormalities, acne, altered libido, mood alteration, and anxiety.²⁵ Side effects of antifibrinolytics include nausea and diarrhea, vertigo and postural hypotension, fatigue and muscle cramps/weakness with an increase in muscle enzymes concentrations, enhanced thrombosis, enhanced tumor growth (tranexamic acid), and teratogenicity.^{26,27}

Recently, several new therapies have been introduced in the United States and Europe that provide patients with HAE more options for acute and prophylactic therapy than ever before.¹ Although C1 esterase replacement therapy has been available in Europe and Canada for many years, it has only become available in the United States in the past 2 years. There are two plasma-derived C1INH replacement therapy products available: one for prophylactic treatment (Cinryz; Viropharma, Exton, PA) and one for acute on-demand therapy (Berinert P; CSL Behring, King of Prussia, PA).^{28–31} Both have been shown in clinical trials to be very effective for their stated purpose, having the ability to inhibit plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin.^{29–31} Both of these agents are administered i.v.^{30,31} Cinryze can be administered by home visiting nurses but many patients who are receiving either agent have re-

quested being taught how to self-administer to reduce costs and improve timely access of treatment.³² Both agents have undergone extensive purification processes to eliminate the risk of pathogen transmission.^{30,31} The other agent available in the United States for acute on-demand therapy is ecallantide (Dyax Corp.), which is a selective recombinant kallikrein inhibitor.^{33,34} Ecallantide, unlike the C1INH replacement therapies, is administered subcutaneously.^{33,34} Clinical trials have indicated that it was very effective in resolving acute angioedema attacks but it was observed that 3.9% of patients experienced an allergic/anaphylactic reaction.^{33,34} For this reason, it is recommended that this agent be administered in a medical facility by personnel experienced in the treatment of anaphylaxis and that patients be prescribed epinephrine to have available should such a reaction occur.³⁵ (Pharming Group NV, AL Leiden, The Netherlands). Icatibant, approved in Europe and recently approved without restrictions in the United States, like ecallantide, is administered subcutaneously.³⁶ Unlike ecallantide, icatibant is not associated with allergic reactions.³⁶ However, icatibant is associated with localized pain and swelling at the injection site.³⁶ Rhucin (Pharming Group NV, AL Leiden, The Netherlands), approved in Europe but still undergoing clinical trials in the United States, has a similar mechanism of action as C1INH but differs by having a relatively short half-life (2–4 hours) compared with the plasma-derived C1INH agents (24–48 hours).^{1,37} It is also administered i.v. and is contraindicated in individuals with a history of rabbit hypersensitivity.^{1,37} Figure 1 illustrates the mechanism of action of these newer agents.

The criteria for appropriate use of these novel agents in the management of HAE are still evolving. It is clear that for acute moderate-to-severe abdominal and facial attacks, the benefits of using Berinert P or Kalbitor outweigh the risks and most likely the costs given the significant direct and indirect costs associated with an attack.³⁸ Today, the use of these agents before a traumatic procedure (i.e., extensive dental work or surgery) is not an approved indication in the United States. However, evidence suggests there is an inherent advantage in pretreating patients whose attacks are triggered by trauma.³⁹ With respect to long-term prophylactic use of C1INH replacement therapy, several factors such as frequency and severity of attacks, associated mor-

C1-INH:
Berinert P
Cinryze
Rhucin

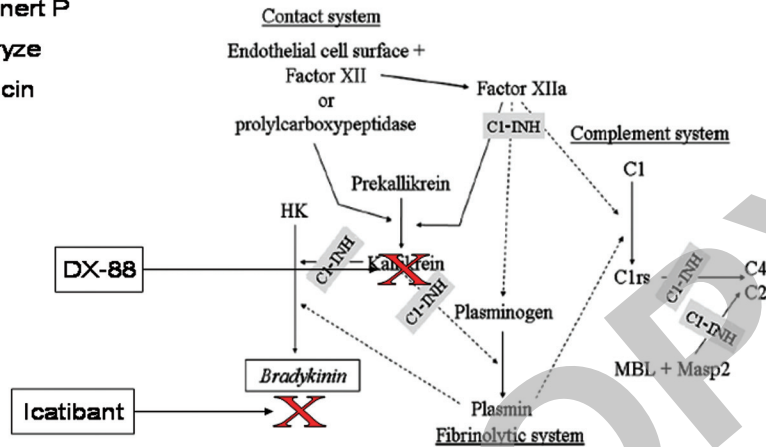


Figure 1. Mechanism of action for newly developed HAE drugs.

bility, and previous response and/or tolerance to low-to-moderate doses of androgens (≤ 200 mg/day) should be carefully considered given the significant costs associated with this therapy.³⁸

TYPE III HAE

Type III HAE was originally described in women with a strong family history of recurrent swelling attacks and normal biochemical C1 inhibitor function.⁴⁰ Further investigation revealed that this unique form of angioedema was significantly aggravated during conditions where estrogen levels were high such as pregnancy or with the use of oral contraceptives. Initial genotyping of these women revealed two missense mutations (c.1032C $\rightarrow$ A and c.1032C $\rightarrow$ G) in F12, the gene encoding human coagulation factor XII (FXII or Hageman factor), which were suggested to be a possible cause of HAE type III.¹⁸ Subsequently, this form of angioedema has been reported in men as well and not all patients manifest the originally reported genotype. Therefore, a better term for type III HAE may be familial recurrent angioedema because there is no commonly agreed on criteria for diagnosis. Similar to HAE types I and II, type III individuals require high estrogen levels to elicit an angioedema attack and the primary mediator appears to be bradykinin.¹⁵ Treatment of type III HAE is still unclear but anabolic androgens have been shown to be effective in some patients.

ACQUIRED C1 INHIBITOR DEFICIENCY

Acquired angioedema begins later in life and is associated with lymphoproliferative diseases or other autoimmune and neoplastic disorders in ~ 10 – 15% of cases.⁴¹ Many of these individuals may also have with C1 inhibitor autoantibodies. The clinical characteristics of angioedema episodes in patients with acquired C1INH deficiency are similar to HAE attacks.⁴¹ As mentioned earlier,

patients with acquired C1INH deficiency have reduced C1INH function, complement activation, and reduced antigenic levels of the first complement component, C1q.⁴¹ Acquired C1INH deficiency is the result of enhanced catabolism of C1INH.⁴¹ Treatment of acquired C1INH deficiency is similar to HAE but may be more responsive to antifibrinolytics while having a decreased response to C1INH replacement therapy.⁴¹

ACE ANGIOEDEMA

Patients treated with ACE-I are associated with a significantly increased rate of angioedema.⁷ Treatment of ACE-I-associated angioedema requires discontinuation of the ACE-I medication. ACE-induced angioedema is thought to be caused by impaired degradation of bioactive peptides, such as bradykinin.⁷ A deficiency in serum dipeptidyl peptidase activity, an enzyme important for degrading neuropeptides such as substance P, may predispose individuals taking an ACE inhibitor to develop angioedema.^{42,43} Most patients with a history of ACE-I-induced angioedema have been found to be at no increased risk of recurrence angioedema when using ARBs.^{7,42}

CONCLUSIONS

For patients presenting with an acute HAE attack, traditional therapy has, until now, included fresh frozen plasma and ϵ -aminocaproic acid (Amicar). The three currently approved agents for the treatment of acute HAE in the United States, Berinert P, ecallantide and icatibant, have a quick onset of action and provide appropriate options for HAE patients experiencing moderate-to-severe attacks. Patients with more frequent and severe attacks should be treated with prophylactic androgens and/or C1INH replacement therapy. In managing this condition, it is important to consider the severity and frequency of HAE attacks in conjunction with the safety and cost/benefit of the medication(s) being prescribed.

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REFERENCES

1. Epstein TG, and Bernstein JA. Current and emerging management options for hereditary angioedema in the US. *Drugs* 68: 2561–2573, 2008.
2. Abraham D, and McGrath KG. Hypersensitivity to aldesleukin (interleukin-2 and proleukin) presenting as facial angioedema and erythema. *Allergy Asthma Proc* 24:291–294, 2003.
3. Banerji A, Oren E, et al. Ten-year study of causes of moderate to severe angioedema seen by an inpatient allergy/immunology consult service. *Allergy Asthma Proc* 29:88–92, 2008.
4. Banerji A, Weller PF, and Sheikh J. Cytokine-associated angioedema syndromes including episodic angioedema with eosinophilia (Gleich's Syndrome). *Immunol Allergy Clin North Am* 26:769–781, 2006.
5. Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 6:24, 2010.
6. Dover JS, Black AK, Ward AM, Greaves MW. Delayed pressure urticaria. Clinical features, laboratory investigations, and response to therapy of 44 patients. *J Am Acad Dermatol* 18:1289–1298, 1988.
7. Hoover T, Lippmann M, Grouzmann E, et al. Angiotensin converting enzyme inhibitor induced angio-oedema: A review of the pathophysiology and risk factors. *Clin Exp Allergy* 40:50–61, 2009.
8. Jesus AA, Oliveira JB, Hilario MO, et al. Pediatric hereditary autoinflammatory syndromes. *J Pediatr (Rio J)* 86:353–366, 2010.
9. Kapoor P, Greipp PT, Schaefer EW, et al. Idiopathic systemic capillary leak syndrome (Clarkson's disease): The Mayo clinic experience. *Mayo Clin Proc* 85:905–912, 2010.
10. Kimura G. Pathogenesis of edema and its classification. *Nippon Rinsho* 63:11–6, 2005.
11. Ohmoto K, and Yamamoto S. Angioedema after interferon therapy for chronic hepatitis C. *Am J Gastroenterol* 96:1311–1312, 2001.
12. Huntington JA. Shape-shifting serpins—advantages of a mobile mechanism. *Trends Biochem Sci* 31:427–435, 2006.
13. Zuraw BL, and Herschbach J. Detection of C1 inhibitor mutations in patients with hereditary angioedema. *J Allergy Clin Immunol* 105:541–546, 2000.
14. Nzeako UC, Frigas E, and Tremaine WJ. Hereditary angioedema: A broad review for clinicians. *Arch Intern Med* 161: 2417–2429, 2001.
15. Kaplan AP. Enzymatic pathways in the pathogenesis of hereditary angioedema: The role of C1 inhibitor therapy. *J Allergy Clin Immunol* 126:918–925, 2010.
16. Davis AE III. The pathogenesis of hereditary angioedema. *Transfus Apher Sci* 29:195–203, 2003.
17. Han ED, MacFarlane RC, Mulligan AN, et al. Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. *J Clin Invest* 109:1057–1063, 2002.
18. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: New findings concerning symptoms, affected organs, and course. *Am J Med* 119:267–274, 2006.
19. Khan DA. Hereditary angioedema: Historical aspects, classification, pathophysiology, clinical presentation, and laboratory diagnosis. *Allergy Asthma Proc* 32:1–10, 2011.
20. Kemp JG, and Craig TJ. Variability of prodromal signs and symptoms associated with hereditary angioedema attacks: A literature review. *Allergy Asthma Proc* 30:493–499, 2009.
21. Prematta MJ, Kemp JG, Gibbs JG, et al. Frequency, timing, and type of prodromal symptoms associated with hereditary angioedema attacks. *Allergy Asthma Proc* 30:506–511, 2009.
22. Zuraw BL, and Christiansen SC. Pathogenesis and laboratory diagnosis of hereditary angioedema. *Allergy Asthma Proc* 30:487–492, 2009.
23. Frank MM, Sargent JS, Kane MA, Alling DW. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema. A double-blind study. *N Engl J Med* 286:808–812, 1972.
24. Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol. Reversal of clinical and biochemical abnormalities. *N Engl J Med* 295:1444–1448, 1976.
25. Banerji A, Sloane DE, and Sheffer AL. Hereditary angioedema: a current state-of-the-art review, V: Attenuated androgens for the treatment of hereditary angioedema. *Ann Allergy Asthma Immunol* 100(suppl 2):S19–22, 2008.
26. Zuraw BL. Clinical practice. Hereditary angioedema. *N Engl J Med* 359:1027–1036, 2008.
27. Zuraw BL. Hereditary angioedema: A current state-of-the-art review, IV: Short- and long-term treatment of hereditary angioedema: Out with the old and in with the new? *Ann Allergy Asthma Immunol* 100(suppl 2):S13–S18, 2008.
28. Riedl MA. Update on the acute treatment of hereditary angioedema. *Allergy Asthma Proc* 32:11–16, 2010.
29. Zuraw BL. HAE therapies: Past present and future. *Allergy Asthma Clin Immunol* 6:23, 2010.
30. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 363:513–522, 2010.
31. Craig TJ, Wasserman RL, Levy RJ, et al. Prospective study of rapid relief provided by C1 esterase inhibitor in emergency treatment of acute laryngeal attacks in hereditary angioedema. *J Clin Immunol* 30:823–829, 2010.
32. Longhurst HJ, Farkas H, Craig T, et al. HAE international home therapy consensus document. *Allergy Asthma Clin Immunol* 6:22, 2010.
33. Bernstein JA, and Qazi M. Ecallantide: Its pharmacology, pharmacokinetics, clinical efficacy, and tolerability. *Expert Rev Clin Immunol* 6:29–39, 2010.
34. Cicardi M, Levy RJ, McNeil DL, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med* 363:523–531, 2010.
35. Stolz LE, and Horn PT. Ecallantide: A plasma kallikrein inhibitor for the treatment of acute attacks of hereditary angioedema. *Drugs Today (Barc)* 46:547–555, 2010.
36. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 363:532–541, 2010.
37. Longhurst H. Rhucin, a recombinant C1 inhibitor for the treatment of hereditary angioedema and cerebral ischemia. *Curr Opin Investig Drugs* 9:310–323, 2008.
38. Lumry WR, Castaldo AJ, Vernon MK, et al. The humanistic burden of hereditary angioedema: Impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc* 31:407–414, 2010.
39. Bernstein JA, Coleman S, and Bonnin AJ. Successful C1 inhibitor short-term prophylaxis during redo mitral valve replacement in a patient with hereditary angioedema. *J Cardiothorac Surg* 5:86, 2010.
40. Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 356:213–217, 2000.
41. Cicardi M, and Zanichelli A. Acquired angioedema. *Allergy Asthma Clin Immunol* 6:14, 2010.
42. Byrd JB, Adam A, and Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. *Immunol Allergy Clin North Am* 26:725–737, 2006.
43. Byrd JB, Shreevatsa A, Putlur P, et al. Dipeptidyl peptidase IV deficiency increases susceptibility to angiotensin-converting enzyme inhibitor-induced peritracheal edema. *J Allergy Clin Immunol* 120:403–408, 2007. □

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