New Directions in Angioedema: A Focus on Etiologies and Clinical Approach

Volume 1, Issue 2 | June 2009

A CME newsletter providing expert perspective on angioedema

Target Audience

This activity has been designed to meet the educational needs of healthcare professionals involved in the care of patients with angioedema.

Purpose

This activity is intended to provide healthcare professionals with clinical information that will contribute to improving competence in the diagnosis and treatment of patients with angioedema.

Statement of Need

Angioedema can be caused by a number of different mechanisms.[1] Although patients with this condition typically present with nearly identical symptoms, optimal treatment of angioedema can vary significantly based on the underlying causative factors. In order to manage angioedema effectively, an understanding of the multiple etiologies of this condition is critical. Thus, it is important that clinicians who treat patients with angioedema fully understand the various signal pathways that, when activated, can trigger angioedema.

[1] Greaves M, Lawlor F. Angioedema: manifestation and management. *J Am Acad Dermatol.* 1991;25:155-165.

Educational Objectives

After completing this activity, the participant should be better able to:

- Define the role of angiotensin-converting enzyme inhibitors in isolated angioedema
- Cite physical examination findings that are consistent with a diagnosis of angioedema
- Identify screening laboratory tests that are useful in patients with a clinical history of angioedema

Media: Newsletter Series

This is the second issue of a three-part newsletter series designed to assist healthcare professionals in understanding how to diagnose and manage angioedema.

Statement of Support

This activity is jointly sponsored by Robert Michael Educational Institute LLC (RMEI) and Postgraduate Institute for Medicine (PIM), and is supported by an educational grant from ViroPharma Incorporated.

Continuing Education

Method of Participation

There are no fees for participating and receiving continuing medical education (CME) credit for this activity. During the period of June 10, 2009, through June 10, 2010, participants must 1) read the learning objectives and faculty disclosures, 2) study the educational activity, 3) complete the Learning Assessment by recording the best answer to each question in the "Learning Assessment Answers" box on the Evaluation form, 4) complete the Evaluation form, and 5) mail or fax the Evaluation form with the Learning Assessment answers to Postgraduate Institute for Medicine. You may also complete the Learning Assessment online at www.cmeuniversity.com.

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Case Study

MB is a 56-year-old man with a history of hypertension that was diagnosed when he was 40 years old. He was initially treated with hydrochlorothiazide, but his treatment was expanded to include lisinopril, an angiotensin-converting enzyme (ACE) inhibitor, approximately 4 years ago. Since the addition of lisinopril, control of his blood pressure has improved significantly. He recently presented to his primary care physician after having three episodes of lip swelling. Each episode of swelling lasted for 1 to 2 days and completely resolved without any further treatment. He did not experience any swelling of his hands or feet or associated shortness of breath, chest tightness, dysphagia, urticaria, or pruritus with these episodes. MB has no recollection of taking acetylsalicylic acid (aspirin) or nonsteroidal anti-inflammatory drugs (NSAIDs) prior to these episodes of swelling, nor does MB have a family history of angioedema. Concerned about the possibility of food allergies, his primary care physician refers MB to an allergist. MB is evaluated by an allergist 4 weeks later; during that time period, he claimed to experience an episode of tongue and upper lip swelling that persisted for 3 days. MB took diphenhydramine in response to these symptoms, but felt that this drug had no impact on his symptoms. The allergist is also concerned about food allergies as well as other causes of angioedema including hereditary or acquired angioedema. Food skin testing is completely negative, and labs are ordered including C4, C1 inhibitor level and function. The allergist also instructs MB to discontinue lisinopril and return for a follow-up appointment in 2 months. When MB returns for his follow-up appointment, he is told that his labs are all normal. MB notes that he did not have any more episodes of angioedema, causing the allergist to conclude that MB's lip and tongue swelling is most likely a drug reaction to lisinopril.

Introduction

Drug-induced angioedema—such as the case of angiotensin-converting enzyme (ACE) inhibitor–associated angioedema described above—can manifest with symptoms that are nearly identical to food allergies, hereditary angioedema (HAE), or even acquired angioedema. Hereditary and acquired angioedema are known to be the results of abnormalities in C1 inhibitor protein, while the mechanism of drug-induced and idiopathic angioedema is less clear. There are few laboratory tests available to identify specific underlying mechanisms of angioedema; thus, identification of the root cause of this condition is largely dependent on patient history and symptom presentation. Fortunately, significant advances have been made in recent years with regard to diagnosis and management of patients with angioedema; this progress had led to a significant reduction in morbidity and mortality. However, many questions remain unanswered regarding the pathophysiology and treatment of this complex condition.

The Etiologies of Angioedema

Diagnosing the underlying cause of angioedema can be challenging, as there are multiple etiologies, all of which produce nearly identical symptoms. For this reason, angioedema is often classified into subgroups in accordance with specific causative factors. Subcategories of angioedema include HAE, acquired C1 esterase inhibitor (C1-INH) deficiency angioedema, allergic angioedema, drug-induced angioedema, and idiopathic angioedema.[1] Although the symptoms for each type of angioedema are largely the same, each angioedema subgroup has a different cause that requires a specific treatment approach.

Some types of angioedema are connected to higher levels of a substance known as bradykinin. For example, HAE occurs as a result of either an inherited defect or deficiency of C1-INH. In the human body, C1-INH is responsible for the prevention of C1 complement autoactivation, the inactivation of several coagulation factors, and the direct inhibition of activated kallikrein. Patients with HAE have either low levels of functioning C1-INH or subnormal C1-INH activity and are therefore unable to inhibit kallikrein activity.[2,3] This in turn results in elevated bradykinin levels during acute HAE attacks, which leads to increased vascular permeability, vasodilation, and contraction of nonvascular smooth muscle.[2] Thus the symptoms of HAE typically include swelling and pain.

A second form of bradykinin-associated angioedema is known as acquired C1-INH deficiency. Individuals with this type of angioedema typically exhibit laboratory evidence of C1-INH deficiency but have no family history of HAE.[1] In these cases, the C1-INH deficiency occurs as a result of an underlying immunologic disturbance that is not hereditary in nature. In some patients, the deficiency of C1-INH (and resultant increase in bradykinin production) is related to a lymphoproliferative disorder, such as multiple myeloma or non-Hodgkin lymphoma.[4,5] This type of angioedema is characterized by the consumption of available C1q molecules (which are subunits of the C1 molecule) by various idiotype–anti-idiotype complexes, leading to secondary consumption of large amounts of C1-INH.[5] An additional type of acquired C1-INH deficiency refers to a condition in which immunoglobulin (Ig) G1 autoantibodies are directed specifically at C1-INH molecules.[1,5] These autoantibodies prevent binding of C1-INH to C1. Uncontrolled C1 then degrades C1-INH to an inactive degradation product, resulting in deregulation of the complement system and increased bradykinin production.

Angiotensin-converting enzyme (ACE) inhibitors have been found to cause angioedema in 0.1% to 0.5% of all patients who receive these drugs.

Drug-induced angioedema can be caused by a number of different agents including ACE inhibitors, angiotensin II receptor blockers (ARBs), fibrinolytic agents, and acetylsalicylic acid

(ASA)/nonsteroidal anti-inflammatory drugs (NSAIDs).[6] Like patients with HAE or acquired C1-INH deficiency, patients on ACE inhibitors can develop drug-induced angioedema as a result of increased bradykinin levels. As ACE is known to be a potent deactivator of bradykinin, this correlation is well defined.[7] ACE inhibitors have been found to cause angioedema in 0.1% to 0.5% of all patients who receive these drugs.[6] Among those who develop ACE inhibitor–associated angioedema, 60% are women and 69% are African American.[8] Researchers have failed to explain why, despite the fact that ACE inhibitors block bradykinin universally, only a small percentage of patients receiving these agents present with angioedema. Therefore, it is likely that factors other than impaired bradykinin degradation are involved in the development of angioedema in these patients. ARBs have also been associated with angioedema.[7] Because ARBs do not interfere with the kallikrein-kinin system, the pathogenetic mechanisms of angioedema attributable to this agent remain unexplained. Several incidents of angioedema have also been reported in patients who receive treatment with fibrinolytic agents (streptokinase, alteplase).[7,9,10] These drugs rely on the formation of plasmin in order to dissolve fibrin; plasmin is known to facilitate the generation of bradykinin through several distinct pathways, and it is hypothesized that predisposed patients develop angioedema through this mechanism.[11,12]

Angioedema-associated allergic reactions are not limited to drugs, but can also occur as a result of exposure to a wide range of substances including food, insect stings, and contact with certain materials or chemicals.

Other types of drug-induced angioedema (with or without urticaria) are associated with pseudoallergic reactions. Inhibition of cyclooxygenase (COX)-1 and COX-2 has been proposed to be a major underlying mechanism of angioedema in patients receiving ASAs and NSAIDs via the inhibition of prostaglandin biosynthesis, which perpetuates reactions that are pseudoallergic in nature (as opposed to bradykinin-induced reactions).[13,14] Rarely, patients who take NSAIDs can also develop angioedema as a result of an acute immunologic hypersensitivity involving specific IgE antibodies.[15] In this situation, histamine is the primary mediator of this reaction, and treatment with histamine H1 antagonists (antihistamines) usually resolves the symptoms. Angioedema-associated allergic reactions are not limited to drugs, but can also occur as a result of exposure to a wide range of substances including food, insect stings, and contact with certain materials or chemicals.[1,16] In most instances of allergic angioedema, release of histamine is responsible for symptomatic reactions. Rarely, hypersensitivity reactions to physical stimuli (including cold, vibration, pressure, etc.) and idiopathic angioedema will occur.[1] These types of reactions are poorly understood, and may involve a number of immunologic and nonimmunologic mechanisms.

Angioedema: Clinical Evaluation and Diagnosis

Symptom recognition is the first step toward accurately diagnosing angioedema. Patients with angioedema will typically present with nonpitting, occasionally erythematous swelling of the skin, subcutaneous tissue, or mucus membranes. This swelling can involve the face, tongue, larynx, bowels, genitalia, and extremities and can persist for a 24- to 72-hour period. Angioedema is usually self-limiting; however, edema of the upper airways and gastrointestinal tract can lead to life-threatening asphyxia, intense abdominal pain, vomiting, and diarrhea, respectively. In approximately 40% to 48% of cases of angioedema, swelling is accompanied by urticaria (hives).[1,16] Urticaria in this setting is characterized by pruritic, erythematous, circumscribed, or coalescent wheals that wax and wane over a 24-hour period.[17] These lesions routinely blanch with pressure, indicating the presence of dilated blood vessels and edema. They may appear anywhere, but commonly involve the trunk and extremities. The presence of urticaria typically indicates a histamine-mediated reaction (as opposed to a bradykinin-mediated reaction) and can help to diagnose the origin of angioedema.

Evaluation of acute angioedema should begin with an assessment of hemodynamic stability, as laryngeal edema/spasm and cardiovascular collapse pose a risk to patients experiencing acute angioedema.[17] It is recommended by the American Academy of Emergency Medicine that patients who present to the emergency department with acute angioedema undergo fiberoptic nasopharyngolaryngoscopy (NPL) to determine the severity of laryngeal compromise.[18] This is particularly critical in patients who complain of dyspnea, hoarseness, voice change, odynophagia, or have stridor on examination, as recent studies suggest that these patients are likely to have edema of the larynx.[18,19] Those individuals who demonstrate evidence of laryngeal edema should be admitted to the intensive care unit, as upper airway involvement can be life-threatening.[18] A number of alternate patient factors have been correlated with increased risk of serious complications during attacks of acute IgE-mediated or histamine-mediated angioedema, including a history of anaphylactic reaction, presence of bronchial asthma, and a lack of emergency plan or EpiPen™ (**Table 1**). Healthcare professionals should consider hospitalization for close monitoring in patients who present with angioedema and any of these risk factors.

In noncritical patients with acute angioedema with or without urticaria, determining the underlying cause of the condition should be a priority (**Figure 1**). Because there is usually no exogenous cause of symptoms, confirmation of clinical features over time is critical for accurate diagnosis.[20] A careful patient history should be documented with an emphasis on clinical features such as speed of onset, presence or absence of urticaria, site of symptom development (facial/peripheral/abdominal), natural history of attack, age of first onset, drug history, family history, and presence of features suggestive of rare causes of angioedema (such as connective tissue diseases). A rapid onset of symptoms and/or systemic anaphylaxis is

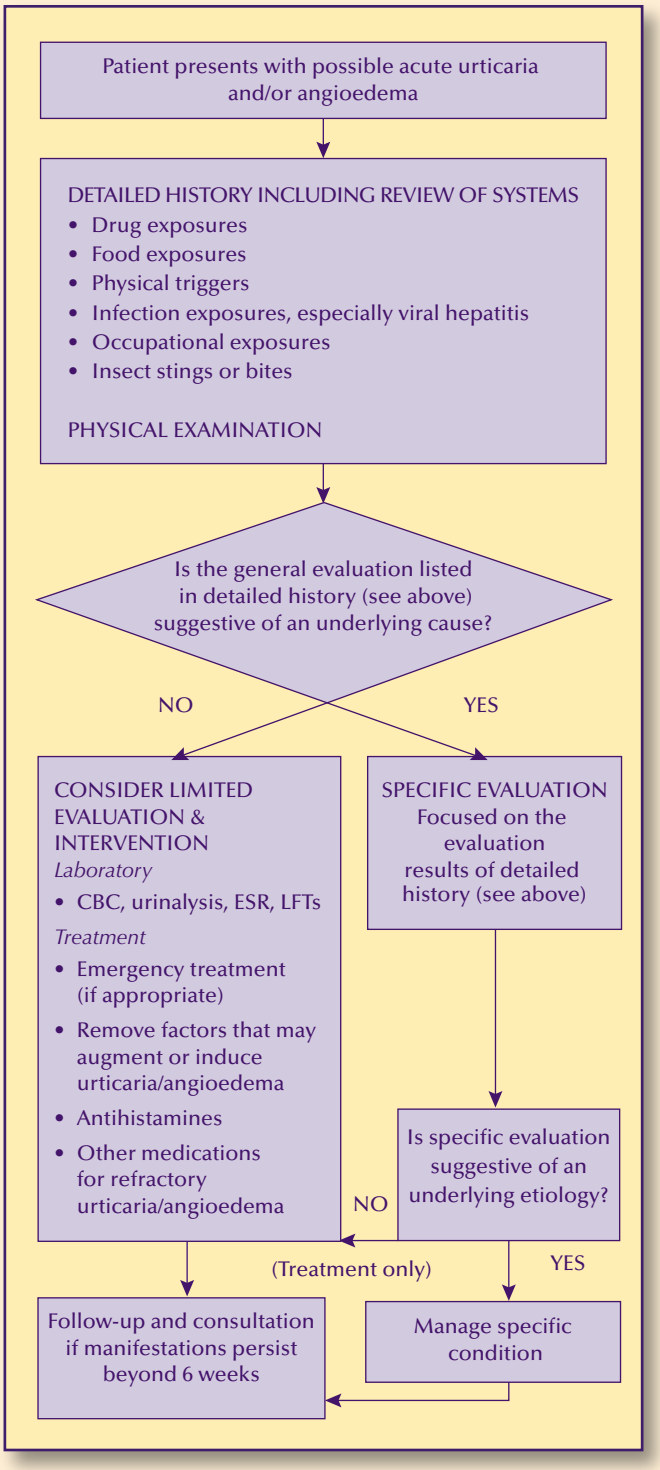
Table 1. Factors associated with serious complications during acute IgE-mediated or histamine-mediated angioedema[18]

- History of an anaphylactic reaction
- Highly atopic individuals
- Comorbidity of bronchial asthma
- Food allergies (peanuts, tree nuts, shellfish, and other fish)
- Unidentified allergens/aggravating agents
- Lack of an emergency plan or EpiPen™

often indicative of exposure to allergens, particularly when urticaria is present as well.[17,20] Allergic angioedema can be triggered by food exposures, occupational exposures (e.g., latex), or insect stings or bites. In this setting, administration of an antihistamine, corticosteroids, and epinephrine will likely resolve symptoms. In cases of drug-associated angioedema, identifying the perpetrating drug can be difficult in these patients, particularly in the case of ACE inhibitor–induced angioedema, which can manifest anywhere from a few hours to 8 years after an ACE inhibitor was first taken.[7] Additionally, *in vitro* tests for confirmation of NSAID sensitivity have been developed based on the release of sulfidoleukotrienes from C5a-stimulated leukocytes, but these tests are not readily available.[13] Challenges to confirm drug sensitivity are generally not recommended in order to avoid provoking unnecessary discomfort or risk. Taking careful patient history of drug use is recommended in order to identify the causal agent.

Recurrent peripheral swelling and abdominal pain without pruritus and urticaria is suggestive of HAE or acquired C1-INH deficiency (**Figure 2**).[20,21] A family history of angioedema and onset of symptoms in the first or second decade of life should alert clinicians to the possibility of HAE; however, this factor is not a prerequisite for an HAE diagnosis, as up to 25% of patients with HAE report no family history of the condition.[3,20] In patients with suspected HAE who are currently asymptomatic, serum C1-INH and C1q should be measured.[3] A diagnosis of HAE can be validated in those individuals who have normal C1q levels and markedly decreased C1-INH activity, although the actual level of C1-INH may be decreased, normal, or elevated depending on the subtype of HAE diagnosed. During acute presentation of symptoms consistent with a diagnosis of HAE, C4 and C2 levels will be markedly decreased as well, occasionally to undetectable levels.[21] Similarly, patients with acquired C1-INH deficiency will also demonstrate decreased C1-INH activity. These individuals can be distinguished from HAE patients by demonstrating decreased levels of C1q. Some types of C1-INH deficiency occur as a result of a malignant condition, so patients with confirmed acquired C1-INH deficiency should be screened for lymphoproliferative

Figure 1. Algorithm for evaluation and diagnosis of acute urticaria/angioedema.[17]



CBC, complete blood count; ESR, erythrocyte sedimentation rate; LFTs, liver function tests.

Adapted from Yates C. *J Am Acad Nurse Pract.* 2002;14:478-483.

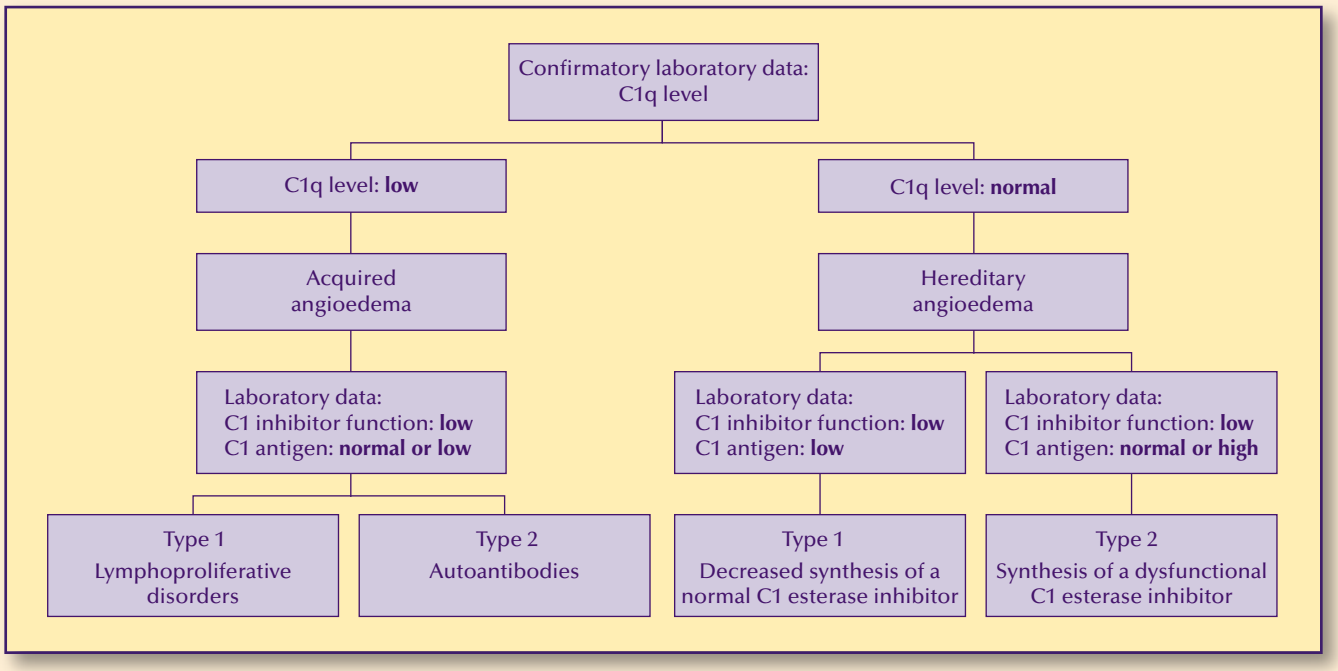
diseases by way of a full blood count and film, erythrocyte sedimentation rate or plasma viscosity, immunoglobulin, and protein electrophoresis.[20,21] In cases where suspicion is high, screening should also include urinary electrophoresis, peripheral blood lymphocyte immunophenotyping, bone marrow examination, and computed tomography of the chest, abdomen, and pelvis to reveal evidence of lymphoproliferative or other solid tumors.[20,21] Patients with negative initial test results should continue to undergo additional testing every 3 to 6 months, as angioedema has been documented to occur as early as 7 years prior to diagnosis of underlying malignant disease.[21]

If initial evaluation of angioedema is not suggestive of a specific etiology, obtaining an erythrocyte sedimentation rate, urinalysis, thyroid-stimulating hormone test, and liver function test can yield information regarding infections, inflammatory disorders, and malignancies.[17] Antithyroid antibody testing may also be beneficial if the patient history is consistent with thyroid disease, the patient is female, or the symptoms are unresponsive to therapy. Other rare causes of angioedema that should be considered include connective tissue diseases (such as systemic lupus erythematosus or urticaria/vasculitis), Gleich's syndrome, Clarkson syndrome, or NERDS (nodules, eosinophilia, rheumatism, dermatitis, and swelling).[20] It is also important for healthcare professionals to recognize that there are a number of cutaneous reactions that can mimic angioedema, especially when symptoms are atypical. Facial cellulitis, superior vena cava syndrome, systemic amyloidosis, hypoproteinemia-related edema, Crohn's disease, and blepharochalasis are all conditions that may present with symptoms that are nearly identical to angioedema and may be misdiagnosed accordingly.

Conclusion

Given the long list of potential etiologies associated with angioedema, it is not surprising that this condition bears significant diagnostic challenges. In some instances, laboratory testing for factors such as C4 levels, C1-INH activity and C1q levels can assist with correct diagnosis. In others, a detailed history of familial symptoms or drug use (e.g., ACE inhibitors, NSAIDs) can reveal the underlying cause of angioedema. However, despite these potential clues, a large proportion of patients have an idiopathic form of angioedema, and no cause is ever ascertained.[20] Additional research into the signal pathways that trigger angioedemic responses will likely streamline the diagnostic process and perhaps even clarify the mechanisms behind idiopathic disease. In this manner, understanding of this complex pathophysiology is clearly a critical first step in improving treatments for individuals with angioedema.

Figure 2. Laboratory data for patients with a clinical history of angioedema.[21]



Adapted from Markovic SN, et al. *Ann Intern Med*. 2000;132:144-150.

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Project ID: 6289 ES 29

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Learning Assessment

Select the best answer for each Learning Assessment question and write the letter (a, b, c, or d) in the corresponding box below.

1. **Subcategories of angioedema include all of the following except:**
   a. Hereditary angioedema (HAE)
   b. Cell-mediated angioedema
   c. Allergic angioedema
   d. Drug-induced angioedema

2. **Unregulated production of bradykinin is associated with which type(s) of angioedema?**
   a. HAE
   b. Acquired C1 esterase inhibitor (C1-INH) deficiency angioedema
   c. Allergic angioedema
   d. Both A and B

3. **Which of the following agents has/have been known to cause drug-induced angioedema?**
   a. Angiotensin-converting enzyme (ACE) inhibitors
   b. Nonsteroidal anti-inflammatory drugs (NSAIDs)
   c. Fibrinolytic agents
   d. All of the above

4. **In approximately _____ of patients with angioedema, swelling is accompanied by urticaria (hives).**
   a. 10% to 18% b. 23% to 30%
   c. 40% to 48% d. 52% to 60%

5. **It is recommended by the American Academy of Emergency Medicine that patients who present to the emergency department with acute angioedema undergo fiberoptic nasopharyngolaryngoscopy (NPL) to determine the severity of laryngeal compromise.**
   a. True b. False

6. **Which of the following clinical features should be documented when initially evaluating a patient with angioedema?**
   a. Speed of symptom onset
   b. Presence or absence of urticaria
   c. Age of first onset
   d. All of the above

7. **All individuals with HAE report a family history of the condition.**
   a. True b. False

8. **Patients with HAE have ____ C1q levels, whereas patients with acquired C1-INH deficiency angioedema have ____ C1q levels.**
   a. Elevated; decreased
   b. Decreased; normal
   c. Normal; decreased
   d. Decreased; elevated

9. **Patients with ____ should be screened for lymphoproliferative diseases.**
   a. Acquired C1-INH deficiency angioedema
   b. Drug-induced angioedema
   c. HAE
   d. Allergic angioedema

10. **Which of the following conditions has/have been known to cause angioedema?**
    a. Systemic lupus erythematosus
    b. Gleich's syndrome
    c. Clarkson syndrome
    d. All of the above

(Continued on page 8)

Learning Assessment Answers

1	2	3	4	5	6	7	8	9	10

New Directions in Angioedema: A Focus on Etiologies and Clinical Approach

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Evaluation *(Continued)*

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a moment to complete this Evaluation form.

Please answer the following questions by circling the appropriate rating:

1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Extent to which program activity met the identified objectives

After completing this activity, I am now better able to:

Define the role of angiotensin-converting enzyme inhibitors in isolated angioedema	1	2	3	4	5
Cite physical examination findings that are consistent with a diagnosis of angioedema	1	2	3	4	5
Identify screening laboratory tests that are useful in patients with a clinical history of angioedema	1	2	3	4	5

Overall effectiveness of the activity

The content presented:

Was timely and will influence how I practice	1	2	3	4	5
Enhanced my current knowledge base	1	2	3	4	5
Addressed my most pressing questions	1	2	3	4	5
Provided new ideas or information I expect to use	1	2	3	4	5
Addressed competencies identified by my specialty	1	2	3	4	5
Avoided commercial bias or influence	1	2	3	4	5

Impact of the activity

Name one thing you intend to change in your practice as a result of completing this activity: _____

_____

_____

_____

Please list any topics you would like to see addressed in future educational activities: _____

_____

_____

_____

Additional comments about this activity: _____

_____

_____

Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

- ❍ Yes, I would be interested in participating in a follow-up survey.
- ❍ No, I am not interested in participating in a follow-up survey.

Request for Credit

Name _____

Degree _____

Organization _____

Specialty _____

Address _____

_____

City _____

State _____ Zip _____

Telephone _____

Fax _____

E-mail _____

Signature _____

Date _____

I certify my actual time spent to complete this educational activity to be:

- ❍ I participated in the entire activity and claim 0.5 credit.
- ❍ I participated in only part of the activity and claim _____ credit.