New Directions in Angioedema: A Focus on Pathogenesis and Classification

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A CE newsletter providing expert perspective on angioedema

Target Audience

This activity has been designed to meet the educational needs of physicians, physician assistants, and nurse practitioners 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

Approximately 15% to 24% of people in the United States will experience at least one episode of urticaria (hives), angioedema, or both in their lifetime.[1] Evaluation and management of these patients can be challenging, as both disorders can be caused by a number of immunologic and nonimmunologic mechanisms. Accurate diagnosis of these conditions is further hindered by the seemingly identical presentation of angioedema subtypes. It is important that healthcare professionals who treat angioedema and urticaria understand the pathophysiology of each angioedema subgroup in order to properly identify and treat acute angioedema episodes.

[1] Yates C. *J Am Acad Nurse Pract.* 2002;14:478-483.

Educational Objectives

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

- Describe the pathophysiology of urticaria and angioedema
- Cite the classification of angioedema
- Review common causes of angioedema

Media: Newsletter Series

This is the first issue of a three-part newsletter series designed to assist physicians, physician assistants, and nurse practitioners 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 education (CE) credit for this activity. During the period of March 27, 2009, through March 31, 2011, 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

Mr. TJ is a 67-year-old man who has had episodes of swelling and abdominal pain for as long as he can remember. His father had similar recurrent swelling and abdominal pain, as did other family members from earlier generations. The patient describes his childhood as painful and distressing. He experienced frequent episodes of abdominal pain that he classifies as "the worst pain I had ever experienced or could contemplate experiencing." Mr. TJ received the diagnosis of hereditary angioedema (HAE) at the age of 30, and a family screening at that time revealed that the patient's two brothers and son also had HAE. After initiation of androgen therapy (danazol 200 mg TID), Mr. TJ's symptoms resolved, and he continued to be free of acute attacks for 30 years. Seven years ago, he had a myocardial infarction and was advised to taper the androgen dose because of associated hyperlipidemia, hypertension, and cardiovascular disease. He successfully tapered to once-daily dosing with good control of HAE symptoms. In addition, aggressive therapy was begun to decrease his serum cholesterol and low-density lipoprotein (LDL) levels. Serial blood pressure measurements, biannual lipid panel measurements, and annual liver ultrasound revealed excellent response to his medication regimen; serum LDL levels were consistently below 110 mg/dL, and liver function studies were within normal limits. Two years ago, ultrasound showed a solitary hepatic mass. Computed tomography (CT) scan confirmed the lesion, and biopsy was performed. Histologic findings were consistent with hepatocellular carcinoma, which was thought to be secondary to the use of androgens. Mr. TJ was not a good surgical candidate, therefore the decision was made to begin chemotherapy and gradually discontinue androgen therapy. While his androgen therapy was being tapered, however, he had several recurrences of severe abdominal pain that responded to treatment with fresh frozen plasma. Because of the need to discontinue androgen therapy, the patient was enrolled in a research protocol to receive prophylaxis with nanofiltered C1 esterase inhibitor (nfC1Inh) to control his recurrent severe HAE attacks. After his first infusion of nfC1Inh, the recurrent abdominal attacks ceased. Following the third dose of nfC1Inh, androgen therapy was discontinued but HAE attacks remained under good control. Mr. TJ now receives maintenance therapy with 1000 units of nfC1Inh by intravenous infusion every 3 to 4 days; he has reported no adverse effects, and HAE symptoms are well controlled.

Introduction

Angioedema and associated urticaria (hives) are relatively common conditions. Approximately 15% to 24% of people in the United States will experience at least one episode of urticaria, angioedema, or both in their lifetime, and over a million patients will present to a physician for evaluation and treatment of urticaria or angioedema each year.[1,2] Evaluation and management of these patients can be challenging, as both disorders can be caused by several immunologic and nonimmunologic mechanisms. The resulting list of potential etiologies is extensive, and little information is available regarding propagating factors and underlying conditions. Treatment of these conditions is further hindered by the seemingly identical presentation of angioedema subtypes. However, close evaluation and thorough examination will reveal key insights that can help to identify the causative pathways of angioedema in these patients. Thus, understanding the pathophysiology of each angioedema subgroup is critical for proper diagnosis and treatment of acute angioedema episodes.

Pathophysiology

The term "angioedema" refers to a group of disorders that are multifactorial in etiology but similar in clinical expression. Angioedema is characterized by the sudden onset of swelling of the skin, subcutaneous tissue, or mucous membranes.[3,4] Swelling can involve the arms, legs, hands, feet, bowels, genitalia, trunk, face, tongue, or larynx. It is typically nonpitting and may or may not be erythematous, and it shows a predilection for areas where the skin is lax. This swelling is usually short-lived and dissipates without visible sequelae over a 24- to 72-hour period (with the exception of hereditary angioedema [HAE], which may persist longer). Although swelling is usually self-limiting, involvement of the upper airways and gastrointestinal tract can lead to life-threatening asphyxia and intense abdominal pain, vomiting, and diarrhea, respectively.[5] Angioedema often occurs with urticaria. In the majority of patients, if relapsing urticaria occurs simultaneously or otherwise with angioedema, the two disorders are assumed to be symptoms of the same disease.[6] Approximately 40% of patients experiencing either angioedema or urticaria will present with both conditions occurring simultaneously.[3]

Angioedema occurs as a consequence of local increase in permeability of capillaries and postcapillary venules, causing local plasma extravasation in response to such mediators as histamine (in allergic angioedema) and bradykinin (in nonallergic angioedema).[7] Allergic angioedema is an immunoglobulin (Ig) E–mediated hypersensitivity reaction to food, drugs, environmental contacts, insect stings, or other substances, resulting in systematic release of histamine and other mediators from mast cells; however, most cases are idiopathic.[4,7] Nonallergic angioedema (which can be further classified into hereditary, drug-induced, acquired, and miscellaneous angioedema), occurs primarily as a result of increased bradykinin levels.[4,7]

Bradykinin is part of the kinin family of peptides that are released into body fluids and tissue as a result of the enzymatic action of the kallikrein-kinin system.[7] Bradykinin is thought to be one of the most potent substances in this system because it initiates the release of several important endothelium-derived vasodilatory mediators. The large amount of bradykinin

released during acute attacks of HAE and acquired angioedema (AAE) is believed to be responsible for most symptoms by directly causing increased vascular permeability (edema, swelling, and ascites), vasodilation (congestion, erythema, and hypotension), and contraction of nonvascular smooth muscle (cramps, spasms, and pain).[8] In cases of HAE, the kallikrein-kinin system (and resultant synthesis of bradykinin) fails to be inhibited because of an inherited deficiency or dysfunction of the C1 esterase inhibitor (C1-INH). Similarly, AAE occurs as a result of nongenetic C1-INH deficiency caused by various conditions, including autoimmune disease and lymphoproliferative diseases. Drug-induced angioedema may occur as a result of enzymatic manipulation that results in increases in plasma levels of bradykinin.

Classification of Bradykinin-Induced Angioedema

Bradykinin-induced angioedema can be categorized in different ways. According to Greaves and Lawlor's classification system, based on causative factors, the two primary classifications of angioedema are HAE and AAE.[3] In this system, subsets of HAE include type 1 and type 2 HAE, with potential type 3 HAE currently under investigation. AAE can be subcategorized into acquired C1-INH deficiency angioedema, idiopathic AAE, allergic AAE, drug-induced AAE, and miscellaneous AAE; however, most use the classification of AAE as limited to the bradykinin-induced variety. This type of AAE can be further broken down into two categories. Type 1 AAE is secondary to such diseases as B-cell lymphomas, which produce excessive antibodies that lead to immune complexes and consumption of complement. Type 2 AAE is secondary to autoimmune diseases that generate autoantibodies against C1-esterase inhibitor.

Other researchers have classified angioedema into allergic and nonallergic angioedema, which is further broken down into idiopathic, pseudoallergic, renin-angiotensin-aldosterone system blocker–induced, hereditary, and acquired angioedema.[7] Although clinical presentation of these forms of angioedema are similar, the causes of these conditions can vary significantly and should be investigated thoroughly in each patient.

Hereditary Angioedema

Hereditary angioedema (HAE) differs from other types of angioedema in that it occurs as a result of either an inherited defect in C1-INH activity or a deficiency of C1-INH **(Table 1)**. The gene that encodes C1-INH is located on chromosome 11q11-q13.1.[7] It possesses seven exons and approximately seven introns, and it contains multiple Alu repeat sequences. HAE has a primarily autosomal dominant pattern of inheritance; however, 20% to 30% of cases of HAE are estimated

Table 1. Classification and distinguishing features of hereditary and acquired angioedema.[8]

	Hereditary Angioedema			Acquired Angioedema	
	Type 1	**Type 2**	**New Variant "Type 3"**	**Type 1**	**Type 2**
Typical age at presentation	Infancy to second decade of life	Infancy to second decade of life	<1 to 63 y	≥40 y	≥40 y
C1-INH level	↓	Normal or ↑	Normal	↓	Normal or ↓
C1-INH activity	↓	↓	Normal	↓	↓
Serum C4 level	↓	↓	Normal	↓	↓
Serum C1q level	Normal	Normal	Normal	↓	↓
Mode of transmission	AD	AD	Unclear*	NA	NA
Sex predominance	No	No	F>M	No	No
Efficacy of C1-INH concentrate	Yes	Yes	No	Yes	Yes
Efficacy of attenuated androgens	Yes	Yes	Unclear	Yes	No
Efficacy of antifibrinolytic agents	Yes (all)	Yes (all)	No	Yes (ε-aminocaproic acid)	Yes (ε-aminocaproic acid)

all, ε-aminocaproic acid and tranexamic acid; AD, autosomal dominant; C1-INH, C1 esterase inhibitor; ↓, decreased; ↑, increased; NA, not applicable.
*Previously believed to be X-linked, but has since been identified in men as well as women.

Adapted from Nzeako UC, et al. *Arch Intern Med*. 2001;161:2417-2429.

to be the result of spontaneous mutations in individuals with no family history of the disease. In these patients, low levels of C1-INH or subnormal C1-INH activity leads to the loss of direct inhibition of kallikrein activity, resulting in the promotion of bradykinin generation. The nature of the C1-INH defect/deficiency is used to subcategorize HAE into two types.[3,8] Type 1 HAE is caused by the decreased production of C1-INH, resulting in subnormal blood and tissue C1-INH levels.[8] This condition occurs as a result of a variety of mutations with deletions or insertions of single or multiple nucleotides in the C1-INH gene. Phenotypically, type 1 HAE manifests as C1-INH levels as low as 5% to 30% that of normal C1-INH levels, with resultant decreased activity. Type 1 HAE is estimated to occur in 80% to 85% of all HAE patients.

To date, more than 100 different C1-INH gene mutations have been identified in patients with HAE.

Type 2 HAE occurs in the remaining 15% to 20% of patients with HAE.[8] In these patients, normal or elevated quantities of functionally impaired C1-INH are produced as a result of a point mutation in the areas coding for the "reactive center" or "hinge region" of the C1-INH protein.[9] In 70% of those with type 2 HAE, mutations in the C1-INH gene result in substitutions at Arg444 of the C1-INH protein.[9,10] Other mutations result in alternate amino acid changes at position 444 or mutations within the reactive loop.[9] To date, more than 100 different C1-INH gene mutations have been identified in patients with HAE.[8,9] Despite the fact that patients with type 2 HAE possess one normal and one abnormal allele (which theoretically should result in 50% normal and 50% mutant C1-INH protein), research has found that levels of normal C1-INH protein in these patients are typically far below 50%, ranging from 5% to 30%.[11] Such levels are hypothesized to occur because the single normal allele cannot increase synthesis of normal C1-INH at the rate necessary to keep pace with its consumption.[12] As a result of the failure of C1-INH to block the enzymatic activity of C1, levels of the early-acting complement components C4 and C2 are low.[13] In general, a low C4 plasma level is the most important laboratory parameter for correct diagnosis of HAE.[14]

A recent study by Bork and colleagues describes a novel type of HAE that appears to occur in the setting of normal C1-INH level and function.[6] Initially labeled *type 3* HAE, this condition was described in 10 women and was later identified in 26 additional female family members. These patients all manifested symptoms indistinguishable from types 1 and 2 HAE, including recurring skin lesions, abdominal cramping, and laryngeal edema. This variant may represent a congenital deficiency or phenotypic decrease in function of numerous enzymes including angiotensin-converting enzyme (ACE), carboxypeptidase N, and α2-macroglobulin.[6,8] It has also been hypothesized that these individuals produce an unknown substance, unregulated by C1-INH, that is capable of cleaving large quantities of high molecular weight kininogen to produce bradykinin.[6,8] This type of HAE was initially found to occur only in women, suggesting an X-linked–dominant pattern of inheritance.[6,8] More recently, however, it has also been described in men.[15] Even though this type 3 HAE is secondary to bradykinin, the mechanism of activation of bradykinin is different than in other types of HAE, and most experts would like to classify this new type of angioedema with such terminology as *familial angioedema*.

Acquired C1-INH Deficiency

Patients who experience recurrent severe attacks of angioedema and exhibit laboratory evidence of C1-INH deficiency but have no family history of HAE are likely to have acquired C1-INH deficiency, especially if the onset of angioedema is after 40 years of age.[3] Although these patients have a clinical picture that is identical to that of HAE, patients with acquired C1-INH deficiency have an underlying immunologic disturbance that is not hereditary in nature. Acquired C1-INH deficiencies can be separated into two distinct categories.[3,16] One type of acquired C1-INH deficiency is associated with lymphoproliferative disorders.[17] These disorders range from multiple myeloma to non-Hodgkin lymphoma.[17,18] In this setting, various idiotype–anti-idiotype immune complexes appear to consume available C1q molecules (subunits of the C1 molecule), which results in secondary consumption of large amounts of C1-INH. This results in quantitative and functional deficiency of C1-INH, leading to symptomatic angioedema.[18] A second subtype of acquired C1-INH deficiency is related to a condition in which autoantibodies are directed specifically at C1-INH molecules.[3,18] This type of angioedema is believed to occur when IgG1 autoantibodies prevent binding of C1-INH to C1. Uncontrolled C1 then degrades C1-INH to an inactive degradation product. The resulting dysregulation of the complement system then leads to angioedema. Both types of acquired C1-INH deficiency are distinguished by low plasma levels of C1-INH and can also be identified by unusually low levels of C1.[3] This marker helps to separate C1-INH deficiency from HAE because patients with HAE typically exhibit normal levels of C1.[7,19] In general, assessment of C1q plasma levels is the optimal way to discern between acquired C1-INH deficiency and HAE.

AAE: Allergic/Drug-Induced Angioedema

Angioedema has long been associated with allergic reactions.[3] Hypersensitive patients will frequently develop angioedema following exposure to such triggers as foods, insect stings, and medications.[3,4] Angioedemic reactions to these stimuli are frequently accompanied by urticaria, which is antigen specific and represents a form of immediate (type 1) hypersensitivity involving IgE antibodies. Histamine is typically the mediator of allergic angioedema and urticaria; this acute condition typically responds to therapy with histamine H1 antagonists (antihistamines).

Angioedema is a well-recognized manifestation of drug intolerance.[20] Many occurrences of drug-related angioedema are associated with allergic or para-allergic reactions. For example, acute immunologic hypersensitivity involving specific IgE antibodies is a condition typically seen in those who are allergic to penicillin.[3] In these patients, histamine is again the primary mediator of the reaction, and treatment with antihistamines will often resolve the condition.[20] However, drug-induced angioedema can also occur as a result of non-immunologic mechanisms. Examples of agents that have been associated with angioedema include ACE inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs) **(Table 2)**.

Table 2. Drugs associated with angioedema.

- ACE inhibitors
- Nonsteroidal anti-inflammatory drugs
- Other drugs
  - Fibrinolytic agents
  - Estrogen
  - Radiocontrast
  - Narcotics
  - Some antibiotics

Angioedema is known to occur in 0.1% to 0.5% of patients who receive ACE inhibitors.[21] Considering that 35 to 40 million patients worldwide are treated with ACE inhibitors, this drug class is responsible for the development of drug-induced angioedema in many people and perpetuates hundreds of incidences of laryngeal edema.[20,22] ACE inhibitor–associated angioedema is more frequently localized to the head and neck, although it occasionally involves the intestine.[20] The pathogenetic mechanism associated with this condition appears to be linked to the decreased degradation of bradykinin. ACE is a potent deactivator of bradykinin; pharmacologic inhibition of ACE leads to increased plasma levels of bradykinin and associated angioedema.[20,23] However, despite the fact that bradykinin is blocked universally in all patients treated with ACE inhibitors, only a small percentage of these patients develop angioedema.[20] Researchers have hypothesized that abnormalities in enzymes involved in bradykinin catabolism may predispose patients to this condition.

NSAIDs and aspirin have also been linked with angioedema and urticaria.[24] NSAIDs selectively or preferentially inhibit two cyclooxygenase (COX) isoenzymes, COX-1 and COX-2. Inhibition of these enzymes has been proposed as a major mechanism producing urticaria and angioedema via two distinct pathogenetic pathways. A pseudoallergic reaction to NSAIDs may be the result of inhibition of prostaglandin biosynthesis. In this regard, it has been shown that the prostaglandin E_2 prevents mast cells and basophils from releasing histamine.[24,25] NSAID-associated urticaria and angioedema reactions have also been attributed to IgE-mediated immunologic (allergic) reactions, particularly in the case of pyrazolones.[26] Furthermore, some patients will experience NSAID-mediated reactions only while experiencing acute viral infections accompanied by fever, although the mechanisms perpetrating this reaction have yet to be identified.[24]

Scattered reports also describe incidences of angioedema associated with numerous other drugs. Several incidents of angioedema have been reported in patients who received treatment with such fibrinolytic agents as streptokinase and alteplase for acute myocardial infarction, acute ischemic stroke, and deep vein thrombosis.[20,27,28] These agents require the formation of plasmin in order to dissolve fibrin. Plasmin facilitates generation of bradykinin by way of two pathways: 1) activation of the contact system by converting factor XII into its active form, and 2) increasing susceptibility of un-cleaved high molecular weight kininogen to the cleavage by kallikrein.[29,30] One hypothesis is that predisposed patients develop angioedema through this pathway. Other drugs have been reported to cause angioedema in very isolated incidences, including estrogen, radiocontrast, narcotics, and certain antibiotics (such as vancomycin and quinolone antibiotics).[31,32]

AAE: Idiopathic/Miscellaneous Angioedema and Urticaria

There are additional reports of angioedema and urticaria that fall outside the aforementioned categories, including case reports of angioedema-associated eosinophilia.[3,33,34] This condition was first described by Gleich and colleagues in 1984, who observed four patients with recurrent angioedema, urticaria, and fever; leukocyte counts in these patients increased to as high as 108,000/mL with 88% eosinophils.[33] A more recent report from Japan describes four cases and reviews 33 cases of nonepisodic angioedema associated with eosinophilia and increased body weight.[34] Angioedema has also been associated with physical urticarias in patients who are highly sensitive to various physical stimuli.[3] Examples of such stimuli include exercise, sunlight, vibrations, pressure, heat, cold, or water.

Conclusion

Despite the fact that the first case of angioedema was described more than 100 years ago, the etiology and pathophysiology of hereditary forms of angioedema are not yet fully understood.[3] Insights into such signal pathways as the kallikrein-kinin and complement systems have illuminated potential mediating factors, but many incidences of angioedema have been encountered that defy current knowledge of the pathogenetic mechanisms involved in angioedema. Identification of the various subgroups of angioedema is an important first step in recognizing the multiple etiologies of this condition, but much research is needed to illuminate the complete patho-physiology of each form of angioedema so that specific therapy can be used appropriately.

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New Directions in Angioedema: A Focus on Pathogenesis and Classification

Project ID: 6288 ES 29

Learning Assessment and Evaluation Form

In order to receive continuing education credit for completing this activity, mail or fax both completed sides of the Evaluation form to: Postgraduate Institute for Medicine (PIM), Attn: Record Keeping Department, 367 Inverness Parkway, Suite 215, Englewood, CO 80112, Fax: 303-790-4876. You may also take the post-test online at www.cmeuniversity.com. Click on "Find Post-Test/Evaluation by Course" on the navigation menu, and search by project ID 6288. Upon successfully completing the Learning Assessment and Evaluation online, your certificate will be made available immediately.

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. **Approximately ___ of patients experiencing either angioedema or urticaria will present with both conditions occurring simultaneously.**
   a. 20%
   b. 40%
   c. 60%
   d. 80%

2. **Which of the following statements is correct?**
   a. Bradykinin is released as a result of the enzymatic action of the kallikrein-kinin system.
   b. Bradykinin is believed to be a mediator of allergic angioedema.
   c. Bradykinin is believed to cause decreased vascular permeability, vasospasm, and contraction of nonvascular smooth muscle.
   d. Bradykinin when released is degraded by kallikrein.

3. **Patients with type 1 hereditary angioedema (HAE) will exhibit:**
   a. High plasma levels of C1-esterase inhibitor (C1-INH)
   b. Low plasma levels of C1-INH
   c. No C1-INH in plasma
   d. Normal plasma levels of functionally impaired C1-INH

4. **Patients with angioedema and normal or elevated quantities of functionally impaired C1-INH are most likely to have:**
   a. Type 1 HAE
   b. Type 2 HAE
   c. Type 1 acquired angioedema
   d. Type 2 acquired angioedema

5. **A low plasma ___ level is the most important laboratory parameter for correct diagnosis of HAE.**
   a. C3
   b. C5
   c. C1
   d. C4

6. **The best method to distinguish between acquired C1-INH deficiency and HAE is:**
   a. Assessment of C1q plasma level
   b. Assessment of C2a plasma level
   c. Assessment of C4b plasma level
   d. Assessment of C5a plasma level

7. **Allergic angioedema can be triggered by which of the following stimuli:**
   a. Medications
   b. Foods
   c. Insect stings
   d. All of the above

8. **Angiotensin-converting enzyme (ACE) inhibitor–associated angioedema appears to be caused by:**
   a. Decreased degradation of bradykinin
   b. Release of histamine
   c. Release of functionally impaired C1-INH
   d. Release of C1-INH–specific antibodies

9. **Nonsteroidal anti-inflammatory drug (NSAID)-associated angioedema appears to be caused by:**
   a. Decreased degradation of bradykinin
   b. Release of functionally impaired C1-INH
   c. Inhibition of cyclo-oxygenase (COX)-1 and COX-2
   d. Release of C1-INH–specific antibodies

10. **Exercise, exposure to sunlight, and exposure to vibration have all been found to induce angioedema and urticaria in hypersensitive patients.**
    a. True
    b. False

Learning Assessment Answers

(Continued on page 8)

1	2	3	4	5	6	7	8	9	10

New Directions in Angioedema: A Focus on Pathogenesis and Classification

Project ID: 6288 ES 29

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:

Describe the pathophysiology of urticaria and angioedema	1	2	3	4	5
Cite the classification of angioedema	1	2	3	4	5
Review common causes 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.

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For Physicians Only

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

- ❍ I participated in the entire activity and claim 1.0 credit.
- ❍ I participated in only part of the activity and claim _____ credit.