New Directions in Angioedema:

A Focus on Supportive Care and Treatment Options

Volume 1, Issue 3 | September 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 is characterized by intense, localized swelling of the face, abdomen, peripheral extremities, genitalia, larynx, or other parts of the body. This swelling can cause discomfort, particularly when the bowel wall is involved, and even death as a result of airway obstruction.[1] There are a number of therapies available for the prevention and treatment of angioedema; these agents have lead to decreases in the frequency and severity of acute episodes.[1,2] However, mortality rates associated with laryngeal edema are still between 25% and 40%.[1] Consequently, new agents are currently undergoing investigation for the treatment of acute angioedema attacks to further minimize their impact on this patient population.

[1] Temiño VM, Peebles RS Jr. *Am J Med.* 2008;121:282-286.

[2] Grigoriadou S, Longhurst HJ. *Clin Exp Immunol.* 2009;155:367-377.

Educational Objectives

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

- Describe strategies for the prevention of angioedema
- List treatment options for various types of angioedema, including allergic, drug-induced, and hereditary angioedema
- Review side effects of medications used to treat angioedema

Media: Newsletter Series

This is the third 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 September 15, 2009, through September 15, 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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Physician Continuing Education

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Case Study

TJ is a 13-year-old boy with a long history of recurrent swelling and abdominal pain. His symptomatic episodes, which started around the age of 4 years and have increased in severity since that time, occur more frequently (on a weekly basis) between December and March. Each episode lasts about 3 days and is characterized by uncomfortable swelling and severe abdominal pain and vomiting. No bowel movement changes have been noted. These symptoms, particularly the abdominal pain, have limited TJ's ability to participate regularly on his school's wrestling team. In addition, he reports that head locks and other wrestling holds often precipitate swelling in the same location that lasts for hours or days. He has never experienced throat swelling or difficulty breathing, but he admits that he is feeling increasingly depressed because of his limitations. He has no concurrent illnesses or history of food, bee sting, or drug allergies. He takes no medications, and his physical development and school performance have all been within the mean for sex and age. Results of laboratory studies performed during his last episode of abdominal pain showed an elevated leukocyte count with neutrophilia; the remainder of the complete blood count was normal, as were results of a comprehensive metabolic panel and urinalysis.

TJ's father received a diagnosis of hereditary angioedema (HAE) several years ago, and his condition has been well controlled with androgen therapy. Four months ago, TJ's 17-year-old brother experienced an episode of facial swelling; prior to this event, he had occasional episodes of gastroenteritis but no other symptoms of angioedema. The remainder of the family has been in good health.

On physical examination, TJ has no swelling of the face, neck, or extremities. Palpation of the abdomen does not elicit pain. Because of his recurrent symptoms and family history, measurements of C4 and C1-esterase inhibitor antigen levels are performed; results show a C4 concentration of 6 mg/dL (normal,≥12) and a C1-esterase inhibitor antigen concentration on the high end of the normal range. A subsequent assay shows decreased functioning of C1-esterase inhibitor.

Diagnosis: On the basis of the low C1-esterase inhibitor function level, a diagnosis of type 2 HAE is made.

Treatment: At this patient's age (13 years), androgen therapy can decrease growth and affect external genitalia. Because of these contraindications, androgens are not utilized in TJ's case. Instead, C1-esterase inhibitor protein replacement (1000 mg intravenously [IV] weekly) is administered at his home by a visiting nurse. This treatment strategy results in decreased frequency of attacks of HAE, but TJ continues to be symptomatic, and his quality of life is still compromised.

The dose of C1-esterase inhibitor protein is increased to 1000 mg twice weekly with a good response. TJ now experiences minimal symptoms and is able to participate fully on his wrestling team.

Introduction

This case study highlights the diagnosis and treatment of hereditary angioedema (HAE). HAE represents one of many different types of angioedema that can occur; other forms of angioedema include acquired C1-inhibitor deficiency angioedema, drug-induced angioedema, allergic angioedema, and idiopathic angioedema. In all cases, angioedema is caused by a complex system of histamine- and bradykinin-mediated physical responses. When these responses are activated, acute attacks of angioedema can occur, consisting of swelling that may involve the face, oropharynx, larynx, gastrointestinal tract, or peripheral extremities. During these attacks, the risk of asphyxiation is present, underscoring the need for effective prevention and emergency treatment strategies. Although several agents exist for the prevention of acute episodes and the treatment of symptoms, angioedema remains uncontrolled in many patients. Fortunately, new therapies being developed that are designed to reduce the severity and frequency of attacks.

Preventing Angioedema: Avoidance of Triggers

Prevention of acute attacks is a key aspect of angioedema management. In many patients, avoidance of known triggers is an effective strategy for prevention of severe episodes of angioedema. Environmental factors, contact stimulation, and certain drugs have been known to cause angioedema, including acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), and angiotensin-converting enzyme (ACE) inhibitors. In the case of drug-induced angioedema, avoidance of certain agents will likely prevent acute episodes of angioedema. Angioedema induced by ASA and NSAIDs is probably the best known form of drug-induced angioedema.[1,2] Reactions to these agents are believed to be provoked through inhibition of prostaglandin biosynthesis and the overproduction of leukotrienes.[2,3] Alternately, ACE inhibitor–induced angioedema is believed to be linked to the decreased degradation of bradykinin, a potent vasodilating peptide.[1,4] Patients who develop angioedema in response to ACE inhibitor angioedema can often be switched to therapy with angiotensin II receptor blockers (ARBs).[1,5] ARBs block the effects of angiotensin II at the receptor level and should have no effect on bradykinin levels.[1] Instances of ARB-associated angioedema have been reported in patients with

Instances of ARB-associated angioedema have been reported in patients with a history of ACE inhibitor–induced angioedema, but at a rate no higher than other medications.

a history of ACE inhibitor–induced angioedema but at a rate no higher than other medications; the use of ARBs is a safe alternative for patients who develop angioedema while using ACE inhibitors.[1,5] Instances of angioedema have also been reported after treatment with fibrinolytic agents (e.g., streptokinase, alteplase); these episodes may be the result of fibrin development, which facilitates generation of bradykinin.[1] Avoidance of triggers is also critical in individuals who experience angioedema reactions to various physical or psychological stimuli, including stress, cold, heat, and vibrations.[6,7]

Pharmacologic Options for Prophylaxis of HAE

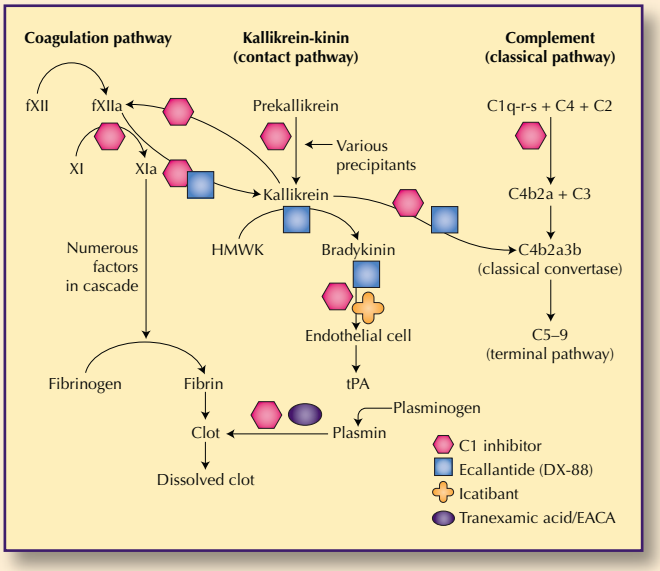
Attenuated Androgens

Many pharmacologic agents have been developed to prevent and treat angioedema.[6] These therapies are designed to halt the internal mechanisms that perpetuate angioedema, either as long- or short-term prophylaxis or as emergency treatment during acute attacks **(Figure 1)**. One widely used class of drugs for both long- and short-term prevention of hereditary angioedema (HAE) in the United States is the attenuated androgens (17α-alkylated androgens). These agents reduce the frequency of acute angioedemic episodes by increasing the biosynthesis of several proteins, including the hepatic production of C1 inhibitor (C1-INH) protein.[5,6] Consequently, attenuated androgens are also effective in some patients with angioedema associated with rheumatologic disorders and B-cell lymphoproliferative diseases. Danazol, stanozolol, and oxandrolone are the most commonly used attenuated androgens in patients with HAE.[6,8] Side effects of attenuated androgens include weight gain, virilization, muscle pain, headaches, hyperlipidemia, depression, fatigue, nausea, constipation, menstrual irregularities, and liver function abnormalities. Rare cases of hepatocellular carcinoma have been attributed to the chronic use of adrogens.[6] Additionally, attenuated androgens can cause decreased growth rate and masculinization; therefore, these agents are contraindicated in children and women who are pregnant.[4,9,10]

Antifibrinolytic Agents

Antifibrinolytic agents, such as tranexamic acid and ϵ-aminocaproic acid, can also be used for long-term prevention of HAE.[6] These agents decrease the frequency and severity of acute attacks by inhibiting plasminogen activation, thus sparing C1-INH consumption. Although these agents do not appear to be as effective as attenuated androgens for patients with HAE, they are highly effective when used for long-term prophylaxis in patients with acquired C1-INH deficiency angioedema.[8] Side effects of antifibrinolytic agents include nausea, vertigo, diarrhea, postural hypotension, fatigue, and muscle cramps. Myalgia is also a potential adverse effect of therapy with this class of drugs; serum creatine phosphokinase and aldolase levels (secondary to rhabdomyolysis) may or may not be increased. Because these agents have been linked to tumors of the retina and liver in animal models, their use has been limited in the United States.[6,12]

Figure 1. Therapeutic effects on various angioedema-promoting signal pathways.[11]



EACA, ϵ-aminocaproic acid; HMWK, high-molecular-weight kininogen; tPA, tissue plasminogen activator.

Adapted from Lock RJ, et al. *Curr Allergy Asthma Rep*. 2007;7:264-269, with permission.

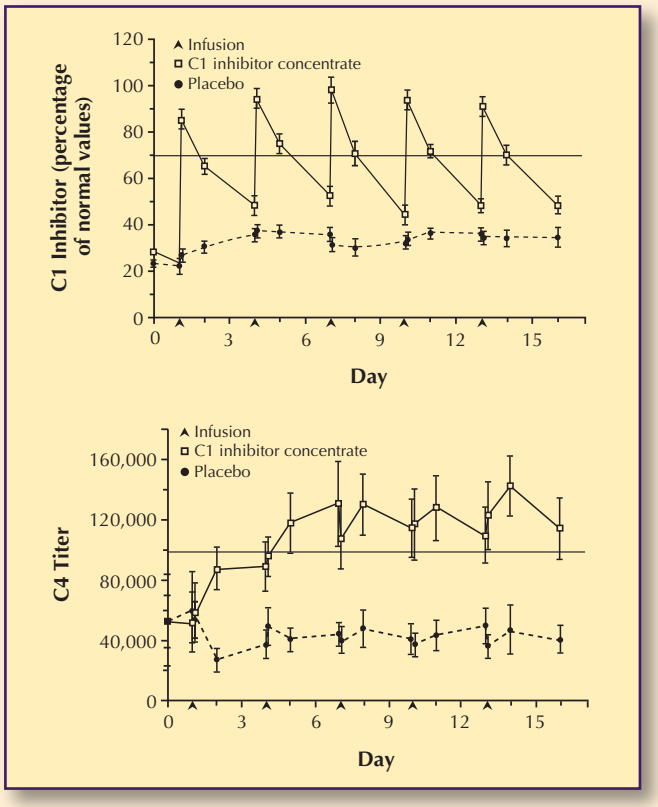
C1-INH Replacement Therapy

Although several C1-INH replacement therapies are currently undergoing investigation for the prevention of angioedema, only one agent has been approved for the prophylactic treatment of HAE in the United States.[13] This plasma-derived human C1-INH replacement product (Cinryze®) was approved by the US Food and Drug Administration (FDA) in October 2008 on the basis of results from the CHANGE (C1 inhibitor in Hereditary Angioedema Nanofiltration Generation evaluating Efficacy) trials. Patients who received C1-INH replacement therapy during this investigation experienced a 51% reduction in the mean number of attacks over a 12-week period.[13,14] In randomized, open-label phase II studies of this agent, the most common adverse events were upper respiratory infections and sinusitis. Full results are anticipated to be publicized later this year.[13]

Purified C1-INH Concentrate (Europe)

Intravenous purified, vapor-heated C1-INH concentrate has been shown to increase serum levels of C1-INH and C4 in patients with HAE and acquired C1-INH deficiency.[8,15] In a 1996 study, prophylactic infusions of C1-INH concentrate resulted in a significant increase in plasma levels of C1-INH and C4, whereas placebo had no effect on either C1-INH or C4 **(Figure 2)**.[15] C1-INH was also evaluated for use during acute attacks of HAE: 69% of attacks treated with C1-INH responded within 30 minutes, and 95% of attacks treated with this agent responded within 4 hours. Response rates associated with placebo infusion were 2% and 12%, respectively. This study prompted the use of C1-INH concentrate in Europe. However, this treatment is currently not approved for use in the United States.

Figure 2. Mean functional C1-INH levels and C4 levels in patients with HAE after infusions of C1-INH concentrate or placebo.[15]



Waytes TA, et al. *N Engl J Med*. 1996;334:1630-1634, with permission.

Pharmacologic Options for Treatment of Acute Attacks

Antihistamines, Corticosteroids, and Epinephrine

Antihistamines, corticosteroids, and epinephrine may be effective for emergency care of some forms of angioedema. In patients presenting with angioedema that is not HAE, a first- or second-generation H1-blocking antihistamine can be used to relieve symptoms; however, sedation is a significant side-effect of these first-generation agents.[16,17] Corticosteroids are not necessary for all cases of angioedema. The American Academy of Emergency Medicine recommends the use of corticosteroids in patients with anaphylaxis, laryngeal edema, and severe symptoms unresponsive to antihistamines.[16] Practice guidelines developed by the Joint Task Force on Practice Parameters (representing the American Academy of Allergy, Asthma, and Immunology, the American College of Allergy, Asthma, and Immunology, and the Joint Council of Allergy, Asthma, and Immunology) discourage the use of corticosteroids in cases that are not severe.[18] Corticosteroids are ineffective for treatment of acute HAE and should be avoided in these patients.[7,8] Epinephrine can be used to treat some types of angioedema, such as hypersensitivity or allergic angioedema, particularly in cases of anaphylaxis.[6,18] However, like corticosteroids, epinephrine does not appear to be effective in patients with HAE.[8]

Fresh Frozen Plasma

Intravenous administration of fresh frozen plasma (FFP) can be used to abort acute attacks of C1-INH deficiency or HAE-associated angioedema by increasing serum levels of C1-INH, but this therapy is associated with two disadvantages.[6,8,11] First, FFP corrects deficiencies in C1-INH but also contributes to increased levels of C1 esterase substrates, which can result in symptom exacerbation and further tissue damage.[7,8] Second, FFP carries the risk of transmission of viral infections and such variants as Creutzfeldt-Jakob disease.[6,7] Yet, despite these disadvantages, recent literature supports the emergent use of FFP in the United States for acute attacks because of its efficacy and the lack of evidence that symptoms worsen with its use.[19]

Prophylactic Agents for Emergency Care

Antifibrinolytic agents and attenuated androgens are occasionally used for the treatment of acute attacks of HAE.[20] Although little clinical trial data exist to support this practice, ϵ-aminocaproic acid is routinely administered intravenously for acute angioedema attacks; the efficacy of this treatment in the emergency setting is largely unknown. High doses of attenuated androgens can also be administered to help modify the course of an acute attack. However, the effects of these agents are delayed for 1 to 2 days after initial administration.[11,20]

Recent literature supports the emergent use of FFP in the United States for acute attacks because of its efficacy and the lack of evidence that symptoms worsen with its use.

Investigational Agents for Angioedema

Several emerging therapies are currently being evaluated for use in patients with angioedema associated with deficient or dysfunctional C1-INH **(Table 1)**. Ecallantide (DX-88) is a plasma kallikrein inhibitor that appears to have an excellent efficacy and safety profile.[11,13] In a phase III trial, symptom relief was significantly greater in patients who received ecallantide than in those receiving placebo.[13,14] Another agent, icatibant, is a synthetic decapeptide that functions as a highly specific and potent antagonist of the bradykinin type 2 receptor (BK2R).[13] In two phase III trials of icatibant, time to first symptom improvement was shorter in the icatibant group than in those receiving placebo or tranexamic acid.[13,14] Other C1-INH replacement therapies are also being investigated for use in angioedema, including a purified human C1-INH product (Berinert® P) that is used commercially in Europe and Canada, and a recombinant human C1-INH developed from the milk of transgenic rabbits (Rhucin®).[13] All of these investigational agents appear promising for symptom control, and some will likely be used for treatment of angioedema in the United States.

Table 1. Emergency Therapy for the Treatment of Angioedema Associated With Deficient or Dysfunctional C1-INH[13]

Company	Agent	Action	Route	Half-life (hr)	Safety	Study phase	US FDA Status
CSL Behring	Berinert P	Plasma-derived C1-INH	IV	36–48	No serious adverse effects	Completed phase III	NDA submission pending for acute HAE
Pharming Group NV	Rhucin	Recombinant C1-INH	IV	36–48	No serious adverse effects	Completed phase III	Open-label trial
Dyax Corp.	Ecallantide	Kallikrien inhibitor	SC	2–4	Very safe; no evidence of anaphylaxis in phase III trials	Completed phase III	Awaiting final FDA decision after risk mitigation strategy submission
Jerini AG	Icatibant	BK2R antagonist	SC	2–4	Local injection site reactions; no serious adverse effects	Completed phase III	FDA Nonapprovable Letter issued; awaiting new study results
ViroPharma Incorporated	Cinryze	Plasma-derived C1-INH	IV	36–48	No serious adverse effects	Completed phase III	FDA has requested an additional clinical study for acute treatment

IV, intravenous; NDA, new drug application; SC, subcutaneous.

Emergency Care and Patient Management

Airway obstruction is of primary concern when treating acute attacks of angioedema.[21] Patients with evidence of laryngeal edema should be admitted to the intensive care unit (ICU) for airway monitoring.[16] ICU admission is also recommended for patients with edema of the tongue or floor of the mouth, and in those who present with severe symptoms or observable disease progression while in the emergency department. Medical management of airway obstruction with epinephrine, diphenhydramine, and intravenous methylprednisolone has been proposed, but empiric evidence falls short of demonstrating a benefit of these agents for the management of HAE in the emergency setting.[1] In cases of acute airway obstruction, an emergency cricothyroidotomy is recommended because oral intubation of the trachea is associated with considerable risk.[1,22] FFP can be administered for acute HAE attacks, but with close observation. Results of early research suggest that other aforementioned therapies may be very beneficial in this setting.

Treatment for angioedema without respiratory compromise and abdominal pain are basically supportive. Pain relief with narcotics is often indicated, as is hydration. Prophylaxis use has been evolving, and US guidelines for instituting prophylaxis have just recently been published.[23] Because therapy with such agents as attenuated androgens and antifibrinolytic agents are associated with side effects, patients receiving these agents should be monitored closely. Complete blood count, liver function tests, fasting lipid panel, and abdominal ultrasound screening for hepatocellular adenoma and pelosis hepatis should be performed in all patients receiving long-term prophylaxis. Attenuated androgens are contraindicated during pregnancy; if prophylaxis is necessary, tranexamic may be used with caution. Attenuated androgens should also be avoided in children because of adverse effects on growth and development. Children who require long-term prophylaxis should receive tranexamic acid (50 mg/kg daily). Purified C1-INH concentrate has also been successfully used in children.[13,15]

Conclusion

Much progress has been made in the treatment of angioedema. Through increased understanding of the underlying mechanisms that contribute to symptom presentation, many patients are now able to avoid environmental, physiologic, and pharmacologic triggers. Moreover, therapeutic strategies have been developed that target and interrupt these signal pathways, leading to significant decreases in the rate of recurrence and severity of attacks. While many of these therapies are currently in use, several investigational agents are likely to be added to the current treatment armamentarium over the next several years. As the fundamental epidemiology of angioedema becomes further elucidated, the symptomatic presentation of angioedema will hopefully one day be eliminated.

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New Directions in Angioedema: A Focus on Supportive Care and Treatment Options

Project ID: 6290 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. **Acute attacks of angioedema can include swelling of:**
   a. The face
   b. The larynx
   c. The gastrointestinal tract
   d. All of the above

2. **Prevention of acute attacks is a key aspect of angioedema management.**
   a. True
   b. False

3. **Danazol, stanozolol, and oxandrolone are all examples of which class of drugs?**
   a. Attenuated androgens
   b. Antifibrinolytic agents
   c. Fresh frozen plasma
   d. C1-esterase inhibitor (C1-INH) replacement therapy

4. **Which class of drugs reduces the frequency and severity of acute attacks of angioedema by inhibiting plasminogen activation?**
   a. Attenuated androgens
   b. Antifibrinolytic agents
   c. Fresh frozen plasma
   d. C1-INH therapy

5. **Purified, vapor-heated C1-INH concentrate has been shown to increase serum levels of which substance?**
   a. C1
   b. C3
   c. C4
   d. C5

6. **Which of the following treatments have been shown to be effective for acute attacks of HAE?**
   a. Antihistamines
   b. Epinephrine
   c. Corticosteroids
   d. None of the above

7. **Which of the following agents works by inhibiting plasma kallikrein?**
   a. Ecallantide (DX-88)
   b. Icatibant
   c. Recombinant human C1-INH
   d. Plasma-derived C1-INH

8. **Which of the following agents is synthetic decapeptide that functions as a potent antagonist of the bradykinin type 2 receptor?**
   a. Ecallantide (DX-88)
   b. Icatibant
   c. Recombinant human C1-INH
   d. Plasma-derived C1-INH

9. **All of the following symptoms are ground for admission to the intensive care unit (ICU) *except*:**
   a. Evidence of laryngeal edema
   b. Edema of the tongue or floor of the mouth
   c. Evidence of gastrointestinal edema
   d. Observable disease progression during emergency department visit

10. **Attenuated androgens should be avoided in which of the following patient populations?**
    a. Pregnant women
    b. Children over the age of 16 years
    c. The elderly
    d. Patients with depression

Learning Assessment Answers

(Continued on page 8)

1	2	3	4	5	6	7	8	9	10

New Directions in Angioedema:

A Focus on Supportive Care and Treatment Options

Project ID: 6290 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 strategies for the prevention of angioedema	1	2	3	4	5
List treatment options for various types of angioedema, including allergic, drug-induced, and hereditary angioedema	1	2	3	4	5
Review side effects of medications used to treat 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 1.0 credit.
- ❍ I participated in only part of the activity and claim _____ credit.