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# TOPICS IN Ocular Antiinfectives

## Lessons from an Atypical Presentation of Herpetic Ocular Disease

**Christopher J. Rapuano, MD**

*Missing a diagnosis of ocular herpes can contribute to treatment delays, inadvertent exposure to medications that can worsen the condition, and miscommunications with the patient and physicians who see the patient in the future. Making the right diagnosis—even when classic signs are lacking—is critical.*

Ocular infection with herpes simplex virus (HSV) is a relatively common problem, with approximately 35,000 new cases occurring annually in the US—in addition to the tens of thousands of individuals who experience recurrences.<sup>1,2</sup> In my corneal subspecialty practice, upwards of 10% of the office visits are due to ocular herpes. Patients are generally relatively young when they first present, and many of them will need ongoing care.

**TARGET AUDIENCE** This educational activity is intended for ophthalmologists and ophthalmologists in residency or fellowship training.

**LEARNING OBJECTIVES** Upon completion of this activity, participants will be able to:

1. Reduce patient morbidity through earlier detection of atypical ocular viral disease.
2. Employ a combination of fortified agents to treat potentially serious corneal ulcers.

Most ocular HSV cases present in a straightforward fashion, and the diagnosis is generally based on the history and physical exam. First-time patients typically complain of unilateral redness, irritation, tearing, discharge, and mild photophobia or foreign body sensation without severe pain.<sup>3</sup> Unless the central cornea is involved, vision may be minimally affected. In most cases, slit lamp examination with fluorescein stain will reveal a classic dendrite in a branching, “tree-like” shape from 1 to 10 mm in length with terminal endbulbs on the surface of the cornea. When it takes this form, HSV epithelial keratitis is readily diagnosed, and topical (and/or oral) antiviral treatment can be instituted.

### Recurrence

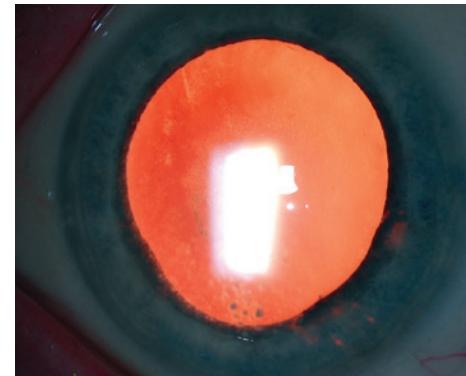
Many patients with a history of ocular HSV have recurrences throughout life, which tend to present in one of

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**FIGURE 1** Iris transillumination defects mostly inferotemporally in this left eye associated with HSV uveitis. Also note the keratic precipitates primarily inferiorly. (Image courtesy of Christopher J. Rapuano, MD.)

two classic ways. Patients may return with a constellation of symptoms and findings quite similar to their initial infectious presentation—ie, characterized by ocular irritation and an observable epithelial dendrite. Alternatively, they may present with stromal keratitis, which is predominantly characterized by

**See INSIDE for:**  
**Topical Ophthalmic Antibiotics: Current Options and Role of Fortified Antibiotics**

by Bennie H. Jeng, MD, MS

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inflammation. These patients typically complain of decreased vision, redness, and/or light sensitivity but have little or no pain. Keratic precipitates (KPs), an anterior chamber reaction, and/or stromal edema are usually present, but there is typically no dendritic ulceration.<sup>3</sup>

Eye care providers must remain vigilant for both classic and variable presentations of ocular HSV. A timely diagnosis allows for quick and appropriate treatment, which can reduce patient symptoms and limit or prevent tissue damage. For example, inflammation that goes unchecked can increase risk for corneal complications including ulceration, perforation, scarring, and visual loss, as well as glaucoma and cataract development.

Secondly, accurate diagnosis em-

powers patients to respond appropriately to recurrences and to speak knowledgeably to other physicians who may take part in their care years from now.

## Case Presentation

A 50-year-old man presented to my clinic complaining of worsening vision for 1 to 2 weeks and mild photophobia in his left eye. His history was unremarkable except for uncomplicated LASIK vision correction 15 years before. He had no history of recent or remote ocular infections, inflammatory events, or trauma.

On examination his visual acuity was diminished to 20/40. External examination of the periocular area was normal. Slit lamp examination of the left eye revealed a fairly clear cornea except

for moderate KPs on the lower half and mild corneal edema with a well healed LASIK flap. A mild anterior chamber reaction was present, and the iris showed numerous transillumination defects. Intraocular pressure (IOP) was elevated at 35 mm Hg (Figure 1).

The right eye was entirely normal with a well healed LASIK flap, including an iris that did not transilluminate and normal IOP.

## Diagnostic Considerations

This patient has a presentation consistent with anterior uveitis. While HSV was high on my differential diagnosis, I considered a few other conditions.

First, several other viruses—varicella zoster virus (VZV), cytomegalovirus (CMV), and rubella—are known

## Topics in Ocular Antifungals, Issue 47

### STATEMENT OF NEED

Ophthalmologists face numerous challenges in optimizing their competencies and clinical practices in the realm of preventing, diagnosing, and treating ocular infections and their sequelae; these challenges include:

- The widespread “off-label” use of topical ophthalmic antibiotics to prevent and treat serious and sight-threatening infections—given the reality that the most widely used topical antibiotics in ophthalmology have FDA approvals restricted to bacterial conjunctivitis.
- The escalating levels of multi-drug resistance in common ocular pathogens.<sup>1</sup>
- The emergence and increasing prevalence of once-atypical infections that may require diagnostic and treatment techniques relatively unfamiliar to comprehensive ophthalmologists.<sup>2</sup>
- The introduction of new and potentially more efficacious and/or safe ophthalmic antifungals.<sup>3</sup>
- The introduction of new and potentially more accurate diagnostic techniques for ophthalmic infections.<sup>4</sup>
- Widespread discussion over the efficacy and safety of novel or alternative delivery techniques and vehicles for prophylactic ophthalmic antibiotics (including but not limited to intracameral injection and topical mucoadhesives).<sup>5,6</sup>
- Increased understanding of the inflammatory damage caused by ocular infections and the best ways to prevent/ alleviate inflammation without fueling the growth of pathogenic organisms.

Given the continually evolving challenges described above, *Topics in Ocular Antifungals* aims to help ophthalmologists update outdated competencies and narrow gaps between actual and optimal clinical practices. As an ongoing resource, this series will support evidence-based and rational antifungal choices across a range of ophthalmic clinical situations.

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to cause an anterior uveitis that is characterized by elevated IOP, iris atrophy, and/or diffuse KP.<sup>4,5</sup> Uveitis caused by VZV looks strikingly similar to that caused by HSV, and its prevalence is thought to be increasing among middle-aged Americans.<sup>6</sup> However, most (but not all) patients with ocular VZV have a history of periocular shingles.<sup>5</sup>

Noninfectious uveitis may be a manifestation of a systemic inflammatory condition such as rheumatoid arthritis. Typically, however, the uveitis associated with systemic conditions is associated with lower IOP, is often bilateral and patients generally have nonocular signs or symptoms indicative of a systemic process.

Lastly, late occurring adverse effects of LASIK were considered, including diffuse lamellar keratitis (DLK) and pressure-induced interlamellar stromal keratitis (PISK). DLK is characterized by the infiltration of inflammatory cells into the potential space between the LASIK flap and stromal bed. In contrast to the more common form of DLK that occurs shortly (days or weeks) after surgery, late-onset DLK has been reported up to 12 years following uneventful LASIK, usually around some inciting event such as epithelial defect, flap dislocation, subsequent surgery, or trauma.<sup>7</sup> When this occurs, deposits of inflammatory cells in lines or waves may be visible on slit-lamp examination and is sometimes called “sands of the Sahara” since what one sees can resemble shifting desert sands.

PISK is a rare LASIK complication associated with interface haze and elevated IOP. Like DLK, PISK is also more common in the early postoperative period but has been reported up to 9 years after surgery.<sup>8</sup> PISK requires treatment with anti-hypertensive glaucoma medications to lower IOP and is unresponsive or worsened by corticosteroid treatment.<sup>9</sup>

## Diagnosis, Treatment and Followup

The combination of unilateral elevated IOP and iris transillumination defects made me highly suspicious of viral uveitis, most likely HSV. Know-

ing post-LASIK eyes are vulnerable to damage from HSV, it was important to initiate aggressive treatment immediately using both a topical corticosteroid and oral antiviral agent. The expectation was that this dual antiviral/antiinflammatory approach would be sufficient to reduce the patient's IOP, and anti-hypertensive medication was not given. We asked the patient to return to the clinic in 48 hours.

By day 2 of treatment, the patient's IOP had dropped to 23 mmHg, inflammation had somewhat diminished, and his visual acuity had improved to 20/30. By 1 week, the inflammation was markedly improved, and pressure and visual acuity were back to normal. The patient's good response to treatment was essentially what sealed the diagnosis.

### Clinical Pearls

- **Unusual Presentations** Patients with ocular HSV conjunctivitis can present with conjunctival “dendrites.” Like corneal dendrites, bulbar conjunctival lesions take up fluorescein stain but are more amorphous and do not demonstrate a classic branching pattern typical of lesions of the corneal epithelium. Another nonclassic presentation of ocular HSV is lid margin ulcerations with no involvement of the eyeball except for some redness or inflammation (Figure 2).

- **Treatment** Topical corticosteroid treatment of ocular HSV inflammation must be tapered very slowly. A taper that is too quick increases the risk of rebound inflammation. Once signs of inflammation have resolved, I recommend tapering to a low dose corticosteroid and, rather than stopping altogether, continue at very low dose for several months. I might start treatment with a strong steroid such as prednisolone acetate 1%, taper slowly to a daily dose, and then change to an ester-based agent, such as loteprednol etabonate, since the later is associ-

## CORE CONCEPTS

- Timely diagnosis of HSV ocular disease may improve outcomes and reduce patient discomfort and anxiety.
- A subset of patients experiencing an initial episode of HSV ocular infection will have unusual findings and may lack the pathognomonic corneal dendrite.
- Viral anterior uveitis is often characterized by keratic precipitates, iris changes, and elevated IOP. HSV and VZV are the most well described causes, but CMV and other viruses can produce this condition.
- Patients with suspected HSV anterior uveitis should be treated with a topical corticosteroid and a systemic antiviral agent and monitored closely. Slower corticosteroid tapers reduce risk of rebound inflammation.

ated with fewer side effects over the long term.<sup>10</sup> Once on loteprednol etabonate, I might stretch out the dosing interval from once daily to every second or every third day.

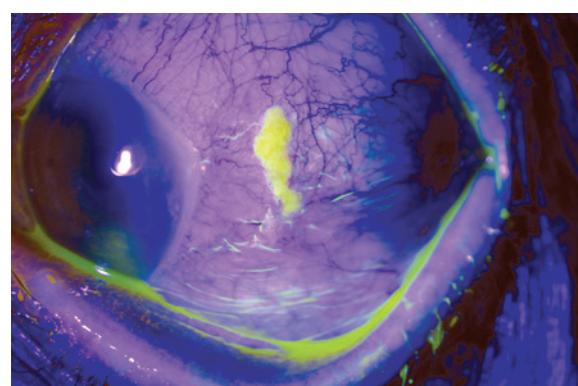


FIGURE 2 Conjunctival HSV lesion temporally. (Image courtesy of Christopher J. Rapuano, MD.)

Bear in mind that many patients with ocular HSV disease need to be on corticosteroids for a substantial stretch of time. Regardless of management, some patients will not be able to come off of corticosteroid

treatment and will have an ongoing requirement for low dose treatment.

- **Oral Antiviral** Oral antiviral treatment should be continued for weeks to months; it may or may not be discontinued depending on the particular situation. My practice is to try to discontinue oral antiviral therapy once patients are doing well on once-a-day corticosteroid. However, in keeping with findings from the Herpetic Eye Disease Study (HEDS), patients who experience ocular HSV recurrences—particularly recurrences that are inflammatory in nature—warrant long-term prophylactic antiviral therapy.<sup>11,12</sup>

If there are uncharacteristic or concerning findings, or if there is any question about the certainty of the diagnosis, ask patients to return for follow-up earlier than you otherwise would, for example, at 48 hours rather than 1 week. In the case of our patient, high IOP and history of LASIK made me want to see him back promptly.

## Conclusion

Not all patients with first-time ocular HSV will present with a corneal dendrite. Consider the diagnosis of HSV uveitis among patients presenting with KP, raised IOP, and iris transillumination defects.

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# Topical Ophthalmic Antibiotics: Current Options and Role of Fortified Antibiotics

Bennie H. Jeng, MD, MS

*Empirical fluoroquinolone therapy is a staple treatment for many ocular infections. But in an era of increasing antibiotic resistance, initiating therapy with a combination of fortified broad-spectrum antibiotics may make good sense when confronted by serious bacterial corneal ulcers.*

Today, the management of both bacterial conjunctivitis and bacterial keratitis typically involves the empirical use of a topical, broad-spectrum antibiotic, in most cases a fluoroquinolone. Antibiotic treatment is useful in bacterial conjunctivitis to reduce disease severity and risk of transmission, but treatment is critical in bacterial keratitis, where an optimal outcome may not be possible without an antibiotic. Bacterial keratitis is a serious condition that can cause rapidly progressive destruction of ocular tissues, leading to vision-threatening complications. Prompt treatment is critical, and the choice of the initial antibiotic treatment can be of paramount importance.

Among the many topical antibiotic eye drops in current use, fourth generation fluoroquinolones are the most popular choice amongst many providers as first-line antibiotic therapy. For bacterial keratitis, however, especially the severe cases of keratitis, fortified-antibiotic combination therapy is still counted on by many as the standard of care. A number of clinical studies have suggested a rough equivalence in efficacy between topical fluoroquinolones and combined fortified antibiotics in the treatment of bacterial keratitis.<sup>1-4</sup> However, the two approaches may not be interchangeable, especially in severe cases.

## Common Pathogens

Gram-positive pathogens—including *Staphylococcus epidermidis*, *Staphylococcus aureus*, and streptococci species—are the most common causes of both bacterial conjunctivitis and keratitis.<sup>5,6</sup> Gram-negative organisms play a smaller but still significant role, with *Haemophilus influenzae* the most frequently isolated gram-negative organism in bacterial conjunctivitis.<sup>6</sup> Among contact lens wearers, the gram-negative *Pseudomonas aeruginosa* is a particularly virulent and relatively common cause of keratitis.<sup>7,8</sup>

## The Broad-spectrum Approach

Because of the potential for rapid progression, immediate and effective antibiotic treatment of bacterial ulcers is necessary to prevent ocular morbidity and visual impairment. Since there is no time to wait for culture results, clinicians typically initiate empirical therapy with a broad-spectrum topical antibiotic.

If there is a microbiology laboratory close by or if the clinician is able to perform microscopic examination in the clinic, a gram stain can be helpful for antibiotic selection, but the usefulness of this technique may vary depending on the clinician's experience and the materials acquired from scraping for testing.

For the most part, clinicians still need to rely on a shotgun approach to antibiotic therapy, using broad a spectrum antibiotic to increase the chance of eradicating the pathogen. In those cases where the causative organism is clearly identified and its susceptibility profile known, more specific management tools can be applied, but this does not usually occur until after culture results have come back.

## CORE CONCEPTS

- ▶ Gram-positive bacterial pathogens, in particular staphylococci and streptococci, are the most common causes of ocular infections; gram-negative organisms are less common but a frequent causative pathogen in predisposed populations such as contact lens wearers.
- ▶ There has been a notable increase in the prevalence of highly resistant strains such as MRSA and MRSE in hospital and community acquired ocular infections, and in parallel, a trend of increasing resistance to fluoroquinolones and other common topical antibiotics among ocular isolates.
- ▶ The initial treatment for bacterial keratitis is empiric and usually involves intensive use of a topical broad-spectrum antibiotic.
- ▶ Fluoroquinolones are generally equivalent to fortified antibiotics in terms of efficacy, but their use in severe infections may be limited by increasing antibiotic resistance among ocular pathogens, particularly MRSA.
- ▶ Dual-therapy of fortified antibiotics provides the highest local antibiotic concentration and the most complete spectrum of coverage. They can be advantageous in the treatment for vision-threatening corneal ulcers.

## Current Options

Nearly all currently used commercially-available topical ophthalmic antibiotics are “broad-spectrum.” Among these, aminoglycosides (eg, gentamicin and tobramycin) are bactericidal against many gram-negative and some gram-positive bacteria. Aminoglycosides act by binding irreversibly to the 30S bacterial ribosome, which disrupts translation and protein synthesis.

Polymixin B and trimethoprim are also a commonly used combination eye drop. Polymixin B is bactericidal—it destroys bacterial cell membranes by interacting with their phospholipid components. Able to provide good gram-negative coverage, polymixin B is often used in combination with other agents like trimethoprim, a bacteriostatic antibiotic that binds to dihydrofolate reductase to block bacterial synthesis of tetrahydrofolic acid. Trimethoprim is effective against fewer gram-negatives than polymixin B but has better gram-positive coverage. Combined, the two agents can provide reasonably broad coverage against both gram-positive and gram-negative pathogens.

Of course, neither the aminoglycosides nor the polymixin B/trimethoprim combination is nearly as widely used by ophthalmologists as the fluoroquinolones, including both the older generations (ciprofloxacin, ofloxacin, levofloxacin) and the newer fluoroquinolones (gatifloxacin, moxifloxacin, and besifloxacin). Broad-spectrum and bactericidal, the fluoroquinolones act on bacterial topoisomerase enzymes to prevent replication of bacterial DNA, leading to cell death.

The popularity of the fluoroquinolones is largely attributable to the agents’ efficacy against nearly all common bacterial ocular pathogens, as well as their ready availability from pharmacies. They are also well-tolerated and offer excellent ocular penetration, an advantage in treating corneal ulcers.

## Antibiotic Resistance

As with systemic pathogens, growing antibiotic resistance has become a

serious concern with respect to ocular pathogens. In particular, methicillin-resistant *S. aureus* (MRSA) and methicillin-resistant *S. epidermidis* (MRSE) are being reported more often in serious ocular infections.<sup>9,10</sup> Furthermore, MRSA is becoming increasingly common not only in healthcare facilities but in the community setting as well, with community-acquired MRSA being as resistant as hospital-acquired strains.<sup>11</sup>

The increasing bacterial resistance poses a great challenge to the management of ocular infection and use of fluoroquinolones. MRSA organisms are generally resistant to multiple antibiotics including fluoroquinolones, and the rise of MRSA corresponds to a trend of increasing fluoroquinolone resistance among ocular pathogens.<sup>9,10</sup>

## Fortified Antibiotics

The traditional treatment mainstay for severe cases of bacterial keratitis has been a combination of fortified antibiotics. These antibiotics in concentrated preparations achieve higher concentrations than commercially available topical antibiotics. Breadth of coverage can be obtained by using one agent for gram-positive coverage and second agent for gram-negative coverage, making the combination suitable for initial empiric treatment.

While fortified antibiotics are advantageous in terms of strength and coverage, their use is associated with some significant challenges. Fortified antibiotics must be prepared by a compounding pharmacy, which can increase cost and certainly limits availability. Although fortified antibiotics are made under sterile conditions, there is always a risk of contamination. In addition, these highly concentrated antibiotic preparations often cause ocular irritation and may suffer from drug instability, variability in concentration and/or pH, and have a short shelf-life.

## Choice of Treatment

Earlier research by the Bacterial Keratitis Study Group found that ofloxacin and ciprofloxacin were as

effective as fortified cefazolin and tobramycin in the treatment of bacterial keratitis.<sup>1,2</sup> More recent studies have made similar findings with fourth generation fluoroquinolones (moxifloxacin or gatifloxacin).<sup>3,4</sup> Indeed, fluoroquinolone monotherapy provides additional benefits, including widespread availability without compounding, ease of use, reduced epithelial toxicity, and better ocular tolerance.

However, given the worrisome trend of increasing antibiotic resistance and the rise of highly resistant bacterial strains such as MRSA, fortified antibiotics still have an important role as the standard treatment for sight-threatening bacterial corneal ulcers or ulcers that respond poorly to the initial treatment. I personally use fortified antibiotic for any corneal ulcer located within the central 3 mm of the cornea or for any peripheral ulcer larger than 2 mm. I also use fortified antibiotics if the patient has had a corneal transplant.

Although there are many available antibiotics to choose from in making a fortified drop, the choice is limited by antibiotic resistance. Because of the high prevalence of methicillin resistance among ocular pathogens, I no longer use the conventional cefazolin as a first line agent for gram-positive coverage. Instead, I use vancomycin, a glycopeptide antibiotic that inhibits cell wall synthesis in gram-positive bacteria and one of the few antibiotics that is still highly active against resistant strains such as MRSA.<sup>10</sup> For gram-negative coverage I typically choose ceftazidime. Compared with other popular choices for gram-negative coverage (such as gentamicin and tobramycin), ceftazidime may cause less ocular discomfort.

## Conclusion

There is no standard protocol for the selection of antibiotics and treatment of corneal ulcers: providers all have their own regimens in mind, and every infection is different. As such, each patient needs to be considered on a case-by-case basis. However, an understanding of the currently available treatment options, as

well as an awareness of current microbial resistance patterns, will allow the provider to make the best choice possible for treatment of each patient to ensure an optimal outcome.

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## EXAMINATION QUESTIONS TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 47

This CME program is sponsored by the University of Florida College of Medicine and supported by an unrestricted educational grant from Bausch + Lomb, Inc. **DIRECTIONS:** Select the one best answer to each question in the Exam (Questions 1–10) and in the Evaluation (Questions 11–16) below by circling one letter for each answer. Participants must score at least 80% on the questions and complete the entire Evaluation section on the form below. The University of Florida College of Medicine designates this activity for a maximum of 1.0 AMA PRA Category 1 Credit™. There is no fee to participate in this activity. You can take the test online at <http://cme.ufl.edu/ocular>.

1. Which of the following is gram-negative pathogen commonly associated with contact lens-related keratitis?
  - A. *Staphylococcus aureus*
  - B. *Haemophilus influenzae*
  - C. *Streptococcus pneumoniae*
  - D. *Pseudomonas aeruginosa*
2. According to Dr. Jeng, which of the following conditions calls for fortified antibiotic therapy?
  - A. Central corneal ulcer
  - B. Large peripheral ulcer
  - C. Corneal ulcer in a post-transplant patient
  - D. All of the above
3. Which of the following is NOT true of the “dendritic” lesion seen in HSV conjunctivitis?
  - A. It stains with fluorescein
  - B. It tends to be amorphous in shape
  - C. It tends to be clearly defined and branching
  - D. None of the above
4. Which of the following is true regarding DLK?
  - A. It is characterized by inflammatory cell infiltrates between the LASIK flap and corneal stroma
  - B. It can be incited by ocular infection or trauma
  - C. It occurs most often between 10 and 20 years post-LASIK
  - D. Both A and B are correct
5. Which of the following viruses have been implicated as a cause of anterior uveitis?
  - A. CMV
  - B. HSV
  - C. Rubella
  - D. All of the above
6. Which of the following is NOT characteristic of ocular HSV infection?
  - A. Diffuse lamellar keratitis
  - B. Corneal dendrite
  - C. Redness and tearing
  - D. Mild or moderate photophobia
7. Which of the following antibiotics has best activity against MRSA?
  - A. Moxifloxacin
  - B. Vancomycin
  - C. Tobramycin
  - D. Cefuroxime
8. Fluoroquinolones kill bacteria by:
  - A. Preventing DNA replication
  - B. Inhibiting protein synthesis
  - C. Damaging cell membranes
  - D. Blocking tetrahydrofolic acid synthesis
9. In the management of HSV uveitis, corticosteroids should be:
  - A. Tapered quickly to avoid IOP elevation
  - B. Tapered slowly over several months as able
  - C. Tapered within 1 week following resolution of inflammation
  - D. Maintained indefinitely without attempting to discontinue
10. Which of the following statements about fortified antibiotics is NOT true?
  - A. They provide increased antibiotic concentrations
  - B. Used in combination, they can provide a complete spectrum of coverage
  - C. They are well tolerated on the ocular surface
  - D. They have a short shelf life compared to commercial fluoroquinolones

## EXAMINATION ANSWER SHEET

### TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 47

This CME activity is jointly sponsored by the University of Florida and Candeo Clinical/Science Communications, LLC, and supported by an unrestricted educational grant from Bausch + Lomb, Inc. Mail to: University of Florida CME Office, PO Box 100233, Gainesville, FL 32610-0233. **DIRECTIONS:** Select the one best answer for each question in the exam above (Questions 1–10). Participants must score at least 80% on the questions and complete the entire Evaluation (Questions 11–16) to receive CME credit. CME exam expires January 31, 2015.

#### ANSWERS:

- |            |             |
|------------|-------------|
| 1. A B C D | 6. A B C D  |
| 2. A B C D | 7. A B C D  |
| 3. A B C D | 8. A B C D  |
| 4. A B C D | 9. A B C D  |
| 5. A B C D | 10. A B C D |

#### EVALUATION:

1=Poor 2=Fair 3=Satisfactory 4=Good 5=Outstanding

11. Extent to which the activity met the identified  
Objective 1: 1 2 3 4 5  
Objective 2: 1 2 3 4 5
  12. Rate the overall effectiveness of how the activity:  
Related to my practice: 1 2 3 4 5  
Will influence how I practice: 1 2 3 4 5  
Will help me improve patient care: 1 2 3 4 5  
Stimulated my intellectual curiosity: 1 2 3 4 5  
Overall quality of material: 1 2 3 4 5  
Overall met my expectations: 1 2 3 4 5  
Avoided commercial bias/influence: 1 2 3 4 5
  13. Will the information presented cause you to make any changes in your practice? Yes No
  14. If yes, please describe: \_\_\_\_\_
  15. How committed are you to making these changes? 1 2 3 4 5
  16. Are future activities on this topic important to you? Yes No
- If you wish to receive credit for this activity, please fill in the following information. Retain a copy for your records.
- PLEASE PRINT CLEARLY**
- |                        |           |        |
|------------------------|-----------|--------|
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| PHONE FAX              |           |        |
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