Fluoroquinolone Generations: What’s Next?

Parag A. Majmudar, MD

The trend in fluoroquinolone development toward better gram-positive coverage makes later generations particularly valuable for empiric treatment of ocular surface infections. But should the next “generation” be a new mode of delivery rather than a molecular refinement?

A “generation” is a classification marking an advance in pharmaceutical development within a class of agents. With respect to antibiotics, a modification in chemical structure, a twist in the mechanism of action, a shift or expansion of antimicrobial activity, improved efficacy, lower resistance, better tolerability, altered pharmacokinetics, or some combination of the above, may solve a problem presented by a prior generation of the medication.

The class of systemic cephalosporins epitomize the concept of chronologically unfolding generations in antibiotic development, as each new development resulted in a shift in the antimicrobial spectrum toward greater anti-gram-negative and anti-anaerobic activity and improved the range of pharmacokinetic problems associated with the generation before. The result is the diverse catalogue of cephalosporin agents in use today, all using a similar mechanism but with unique antibacterial potencies and properties.

The fluoroquinolone class expanded in the opposite microbiologic direction, starting as mostly gram-negative, but progressing to increasing gram-positive coverage. And while the categories or generations are perhaps less clear compared to cephalosporins (eg, it is unclear whether levofloxacin, the levo-isomer of ofloxacin, is a 2nd or 3rd generation fluoroquinolone), the idea is basically the same.

The systemic fluoroquinolones originated in the 1960s with naladixic acid, an anti-gram-negative agent excreted in high concentrations in urine and used principally for the treatment of urinary tract infection. Ensuing fluoroquinolone generations employed structural modifications to achieve varying affinities for two target enzymes involved in bacterial DNA replication: DNA gyrase (also called topoisomerase II) and topoisomerase IV.

Thus, fluoroquinolone generations evolved from narrow-spectrum anti-gram-negative activity (1st generation, eg, naladixic acid) to expanded anti-gram-negative activity including Pseudomonas (2nd generation, eg, ciprofloxacin) to increasing gram-positive fighting activity (3rd generation, eg, levofloxacin;...
and 4th generation, eg, gatifloxacin, moxifloxacin, and besifloxacin). Specific core and side chain modifications have also been used to improve tolerability, pharmacokinetic properties, and lower resistance risk.2,3

Ocular Fluoroquinolones

The ocular fluoroquinolones are widely prescribed for their broad antibacterial activity, clinical efficacy, good tolerability, and convenient dosing. Earlier-generation topical ocular fluoroquinolones, including ciprofloxacin and levofloxacin, have excellent broad-spectrum coverage and are sometimes preferred to later generation agents for treating ocular infections caused by gram-negative pathogens, including those associated with contact lens wear when *Pseudomonas* is suspected or documented.3,5

The trend in fluoroquinolone development toward better gram-positive coverage makes later generations (eg, moxifloxacin, gatifloxacin, besifloxacin) particularly valuable for empiric treatment of ocular surface infections, a majority of which are due to *Staphylococcus Aureus* and *Corynebacterium*, and other common gram-positive pathogens.6

The first fluoroquinolone to contain a chlorine moiety, ie, the first chloro-fluoroquinolone, besifloxacin binds to both target enzymes in a more balanced fashion than prior fluoroquinolones, which is important for several reasons. First, it broadens the antimicrobial activity spectrum. Besifloxacin has in vitro activity against gram-negative pathogens, including *Pseudomonas*, and gram-positive pathogens, including methicillin-resistant *Staphylococcus Aureus* (MRSA).6,7 This is particularly important, as methicillin resistance has become increasingly prevalent among staphylococcal pathogens in recent decades.8,12

Second, besifloxacin’s dual mode of action reduces risk for the emergence of resistant pathogens since two mutations—one in the gene encoding each enzyme—would be required to incapacitate the drug.2

Besifloxacin is also distinctive for being the only antibiotic that is solely available for human topical ocular use; it has not been developed for systemic use in medicine and is not used in livestock or agriculture.7 Limiting human and veterinary use with appropriate stewardship is important for maintaining sensitive bacterial populations.8

**REFERENCES**


3. Colin J, Hoh HB, Easty DL, et al. *Pseudomonas aeruginosa* infections—given the reality that the most widely used topical antibiotics in ophthalmology have FDA approvals restricted to bacterial conjunctivitis.

4. Widespread discussion over the efficacy and safety of novel techniques relatively unfamiliar to comprehensive ophthalmologists.

5. Introduction of new and potentially more efficacious and/or safe topical antibiotics.

6. Introduction of new and potentially more accurate diagnostic techniques for ocular infections.

7. 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 mucoclastics).7,16

8. 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 Antiinfectives 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 antiinfective choices across a range of ophthalmic clinical situations.

**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 prevents and treats 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.1

- The emergence and increasing prevalence of once-atypical infections that may require diagnostic and treatment techniques relatively unfamiliar to comprehensive ophthalmologists.2

- The introduction of new and potentially more efficacious and/or safe topical antiinfectives.3

- The introduction of new and potentially more accurate diagnostic techniques for ocular infections.4

- 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 mucoclastics).7,16

- 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.

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environmental exposure to besifloxacin is a strategy for reducing selective pressure for the development of resistance and prolonging its usefulness as an effective ocular antibiotic, a strategy that may in fact be working. According to recent large microbiologic surveys of topical ocular pathogens, besifloxacin resistance remains low. Ongoing surveillance will shed light on whether this is an enduring phenomenon and, if so, whether besifloxacin’s unique chemical structure and environmental containment are contributing to its longevity.

The Real World

There is some merit to considering antibiotic generation in therapeutic decision-making. Opting for a 3rd generation fluoroquinolone is reasonable when a gram-negative pathogen is suspected, and opting for a 4th generation fluoroquinolone is reasonable when Staphylococcus is more likely. An argument could be made, however, for exclusively using latest-generation agents in clinical practice, as they represent the most advanced iteration of a drug class and are often associated with minimal resistance. Furthermore, later-generation antibiotics are better supported by drug manufacturers, which means that samples are in greater supply.

Still, a “generation” is something of an artificial designation. In real world ophthalmic practice, selecting antibiotics by generation may be beside the point. Other considerations—such as pharmacodynamic or practical ones—may be of greater importance. For example, later-generation antibiotics generally demonstrate greater in vitro potency against resistant pathogens; however, this advantage may be clinically unimportant given the fact that minimal inhibitory concentrations (MICs) reflect organism susceptibility to drug concentrations in the bloodstream, not on the ocular surface. In general, the concern around antibiotic resistance— even resistance that is widespread and increasing, as with MRSA—poses less of a threat to the eye, since antibiotic concentrations achievable on the eye’s surface are orders of magnitude higher than those achievable in the blood or other anatomical sites and likely well above the MIC even for resistant pathogens.

In addition, earlier-generation antibiotics, often dispensed in generic form, may be sufficient for what has become a common, albeit controversial, use for topical ocular antibiotics: prophylaxis around intravitreal injection and intraocular surgery. While the practice of applying topical antibiotics prior to injection or surgery has been shown to reduce bacterial counts on the surface, it has never been shown to reduce the incidence of endophthalmitis over povidone-iodine antisepsis alone. The vast majority—perhaps upwards of 90%—of topical ocular antibiotics prescribed today are dispensed as generic formulations, either because they were prescribed as generic or because a substitution was made by the pharmacist for the purpose of controlling costs. This is a dramatic increase in generic usage compared to 5 to 10 years ago. But widespread use of older and/or generic antibiotics in ophthalmology is not necessarily cause for alarm, as noted above: the ability to achieve high concentrations of antibiotic on the ocular surface enhances efficacy even against pathogens with high MICs; and topically applied antibiotics for prophylactic use may not be necessary in the first place.

Future Generations

It is unclear exactly what role topical antibiotics will play in ophthalmology in the coming years. Research may help clarify whether or not topical antibiotics are beneficial as infection prophylaxis. Topical ocular antibiotics could lose ground for commercial reasons: for example, the development of new antibiotic molecules is impeded by a lack of financial incentive within the pharmaceutical industry to develop drugs indicated for intermittent, short-term use and whose efficacy is always at least theoretically threatened by the emergence of resistance. Furthermore, there is a growing trend in favor of new modes of delivery, such as intracameral antibiotic injection at intraocular surgery as a means for preventing endophthalmitis. The European Society of Cataract and Refractive Surgery’s landmark study of intracameral prophylaxis in 2007 showed a 5-fold decrease in endophthalmitis after cataract surgery with the use of intracameral cefuroxime. The results were subsequently corroborated in a number of other large, prospective studies by various groups from Europe and Asia.

The first comparative US study on intracameral prophylaxis was published in 2013, showing a 10-fold decline in endophthalmitis rates with the routine use of intracameral injection of cefuroxime, moxifloxacin, or vancomycin. Intraoperative antibiotic prophylaxis is also attractive since it eliminates compliance issues and reduces patients’ post-operative drop burden. With additional prospective studies in the US unlikely to be performed (due to high costs associated with a study of sufficient size to achieve statistical significance of such a rare occurrence), an increasing proportion of surgeons are satisfied with the evidence that exists in support of intracameral prophylaxis and are actively adopting the practice of their European colleagues.

But, in the absence of an antibiotic approved for intracameral use, practical and regulatory issues remain. An ideal “next-generation” ophthalmic antibiotic would not necessarily be a new molecule: it could be a new system that overcomes current practical barriers to more
widespread adoption of intracameral antibiotic prophylaxis. One potential solution might be commercial development of a "cataract kit" containing an approved unit-dose, preservative-free injectable antibiotic, such as moxifloxacin or cefuroxime; and injectable antiinflammatory agents, packaged and marketed specifically for ophthalmic surgery prophylaxis. Such a product would free hospital administrators from tedious and costly workarounds currently required to obtain intracameral antibiotics, would be simpler and more expedient for surgeons, and would quite possibly be safer for surgical patients.

Conclusion

Generations are ways of building on past successes in antibiotic development. When we understand the problem each new generation is trying to surmount, we make more informed clinical decisions.

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REFERENCES
5. Levofoxacin Ophthalmic Solution 0.5% prescribing information. 2007. Apotex, Inc. Toronto, CN.
6. Besivance (besifloxacin ophthalmic suspension) 0.6% prescribing information. 2009. Bausch and Lomb. Tampa, FL.

BLONDEAU REFERENCES continued from page 7

Applying MIC in Antibiotic Drug Selection and Resistance Prevention

Joseph M. Blondeau, PhD

A greater understanding of minimum inhibitory concentration and other microbiological measurements can help ophthalmologists select appropriate antibiotic treatment and prevent antibiotic resistance to ocular pathogens.

Antibiotic resistance to bacterial pathogens is an escalating public health concern across a number of medical specialties, ophthalmology included. The evolution of pathologic organisms from susceptible to increasingly less responsive to antibiotic treatment can complicate ophthalmologists’ management strategies for ocular infections and ultimately threaten patients’ vision.

This phenomenon has resulted from the misuse—and perhaps overuse—of antibiotics to treat staphylococci and streptococci (among other pathogens) responsible for the etiology of ocular infections such as keratitis, conjunctivitis, blepharitis and endophthalmitis. Resistance is likely exacerbated by increased use of the same antibiotics for non-ocular conditions such as respiratory tract infections, which share many of the same pathogens responsible for ocular infection, including Haemophilus influenza, S. pneumoniae, and Pseudomonas aeruginosa.

Resistance Surveillance

To facilitate understanding of ocular antibiotic resistance patterns in the US and generate geographic-specific information on emerging resistance, two surveillance programs have been implemented: Ocular Tracking Resistance in US Today (TRUST), and more recently the Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study. Over a period of 20 years, these studies have been gathering data on resistance of common pathogens to ocular antibiotics based on in vitro susceptibility testing of ocular isolates sent annually from participating clinics throughout all 50 states (Figure 1).

The early TRUST data demonstrated that, after more than a decade of systemic use, fluoroquinolones remained active in vitro in approximately 80% of ocular methicillin-sensitive S. aureus (MSSA) isolates, 90% to 100% of S. pneumoniae isolates (100% susceptibility with gatifloxacin, levofloxacin, and moxifloxacin, and approximately 90% susceptibility with ciprofloxacin), and 100% of H. influenza isolates. In contrast, fluoroquinolones were active in only about 15% of methicillin-resistant S. aureus (MRSA) isolates, suggesting the need to consider alternative antibiotics for this pathogen (Figure 2). The much later ARMOR data showed in vitro methicillin resistance in 42% of S. aureus isolates and about 50% of coagulase-negative staphylococci (CNS) isolates—and that these also had a high probability of concurrent resistance to the fluoroquinolones, aminoglycosides, or macrolides (87% in MRSA isolates and 77% in methicillin-resistant CNS isolates). While all staphylococcal isolates remained susceptible to vancomycin, resistance among S. pneumoniae isolates was highest for azithromycin (34%), and resistance among P. aeruginosa and H. influenzae was low against the various antibiotics tested.

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With respect to geographic trends, ARMOR revealed small differences across the US in susceptibility among *S. aureus*, *S. pneumoniae*, and *P. aeruginosa* isolates, with gram-positive isolates from the West having the lowest rates of resistance, and *S. aureus* isolates in the South having the highest resistance.²

These data demonstrate that antibiotic resistance is becoming prevalent among common bacterial causes of ocular infections such as CNS and *S. aureus*. The 3rd-generation fluoroquinolone antibiotics (ciprofloxacin, ofloxacin, and levofloxacin), which have long been the mainstay for treating ocular infections due to their broad-spectrum antibiotic effect and high in vitro potency, are becoming increasingly less active against gram-positive and gram-negative organisms.¹,³ This is particularly true in MRSA infections which, while a less prevalent cause of ocular infection, are showing an increasingly more severe clinical course than the MSSA strains. The newer 4th-generation fluoroquinolones (moxifloxacin and gatifloxacin) demonstrate broad-spectrum antibiotic effect against both gram-positive and gram-negative organisms; however, ongoing surveillance is also showing some MRSA resistance to these agents, and preservation of their efficacy in targeting ocular pathogens is of paramount importance.

**Measuring Antibiotic Potential**

The internationally accepted measurement of the potential efficacy of an antibiotic is minimum inhibitory concentration (MIC). Defined as the lowest concentration of an antimicrobial drug that is required to inhibit visible growth of 10⁵ colony-forming units (CFU) following in vitro incubation for 18 to 24 hours, MIC is used to confirm antibiotic resistance of existing antimicrobial drugs and establish effective concentrations of new drugs.⁴ By using either the broth microdilution test, agar dilution test, or Epsilometer test, laboratories compare the new MIC values with previously established drug breakpoint concentrations, known achievable and sustained drug concentrations within the host, pharmacokinetic and pharmacodynamic data, and drug toxicity data to determine pathogenic bacteria susceptibility or resistance to the antibiotic under investigation and thus potential for clinical success or failure (Figure 3).⁵

In vitro testing does not always translate absolutely to clinical outcomes, as several other factors influence a patient’s response to infection—especially his or her natural capacity for defense. In addition, MIC evaluations may be more valuable for patients with self-limiting, mild to moderate infection. The most significant limitation of in vitro MIC testing on its predictive value may be that it uses a static density of 10⁵ CFU per ml; this can result in overestimation in instances where organism density of an infection is lower than 10⁵ and underestimation of the drug concentration required where organism density is higher than 10⁵.⁶ Nevertheless, MIC remains the gold standard for in vitro susceptibility testing of pathogens to antibiotics and provides a valuable guide for physicians in managing the majority of patients.

The mutant prevention concentration (MPC) test addresses some of the limitations associated with MIC testing.⁶ This novel technique not only measures a much higher density of organisms than MIC and determines the drug concentration required to inhibit the least susceptible cell present within the population, but it also measures the frequency with which a microbe mutates and develops resistance.⁷ The drug concentration required to block the mutant cells (ie, the MPC) is typically higher than the MIC drug concentration with the mutant selection window, a so-called “danger zone” for the selective amplification of resistant subpopulations falling between these.⁶ Although more demanding and less adaptable to routine clinical settings, MPC is a valuable tool when used in conjunction with MIC.⁸

**PK and PD Data**

The application of pharmacokinetics (PK) and pharmacodynamics (PD) to MIC and MPC outcomes is important in characterizing the antibacterial activity of compounds. PK data define the fate of a drug in the body (eg, its absorption, transformation, distribution, and elimination), while PD data define the effect of a drug on the body and infecting organism (eg, its mechanism of action and efficacy).

Drug curves, for example, provide PK and PD data on the peak or maximum drug concentration (C_max), the trough concentration, area under the curve (AUC), and the drug’s half-life (which determines dosing frequency).⁶ Antimicrobial compounds may be classified as concentration-dependent agents, for which C_max/MIC and AUC:MIC ratios are important predictors of outcome with antimicrobial treatment; or time-dependent agents, for which the time that the drug concentration remains in excess of the MIC is important to determining its
Choosing an Antibiotic

MIC, MPC, and PK/PD results from in vitro testing of antimicrobial agents are fundamental in supporting ophthalmologists to design appropriate treatment strategies for patients to treat ocular infections. Ophthalmologists should consider whether the chosen antibiotic demonstrates sufficient spectrum of activity to cover all potential infection-causing pathogens and whether the administered ocular dose is of adequate concentration to exceed the anticipated MIC/MPC of the drug for those specific organisms. Keep in mind that the MIC and MPC used to measure antibiotic susceptibility to resistance apply to systemic use of antibiotics, which may not always be appropriate for topical (eg, ocular) antibiotic use, where higher concentrations are more typically administered.

Resistance to an antibiotic is based on a drug concentration breakpoint, whereby an organism with an MIC at or above that breakpoint is considered resistant. Breakpoints are based on several parameters, including the systemic drug concentration achievable with approved dosing. Drug concentration breakpoints are not calculated for topical antimicrobials, but bacterial strains can still be classified as low-level or high-level in terms of their resistance for the purposes of choosing topical antimicrobials. Low-level resistance means the MIC is close to the (systemic) drug concentration breakpoint, whereas high-level resistance means the MIC is many times higher than the (systemic) drug concentration breakpoint. Organisms of high-level resistance are unlikely to respond to topical antimicrobials if the MIC is very high. In vitro susceptibility testing provides clinical useful information on susceptibility/resistance and drug use, including for topically applied drugs.

It is also valuable for ophthalmologists to become familiar with antibiotic resistance trends in their geographical region (such as those becoming increasingly available through the TRUST and ARMOR surveillance studies) to help tailor management strategies, be aware of specific drug toxicity data that may influence choice of drug for patients with particular medical histories, and, finally, have an understanding of drug constituents beyond the active ingredient. For example, the preservative benzalkonium chloride (BAK) may confer intrinsic bacteriocidal activity against predominantly gram-positive species, including MRSA. In vitro studies have shown that, when added to gatifloxacin and moxifloxacin, BAK substantially lowers their MICs and MPCs against MRSA.

Preventing Antibiotic Resistance

The emergence of antimicrobial resistance of ocular pathogens suggest that new strategies must be employed to inappropriate use of antibiotics. One strategy is for ophthalmologists to utilize their local microbiology lab for testing organism susceptibility and resistance in patient isolates to therapeutic agents. Currently, this is not an uncommon practice for refractory cases; however, it may be valuable to expand this to manage routine cases.

In addition, it is important for ophthalmologists to let the testing laboratory know of the types of microbes that are common in ocular samples, as some ocular pathogens, such as *S. epidermidis* or CNS, are commonly considered contaminants in other systemic samples and thus often ignored. To this end, establishing dialogue to modify existing culturing procedures at the laboratory so they are relevant to the identification of ocular pathogens is an important aspect in utilizing in vitro testing laboratories.

Of course, it is also important that treating ophthalmologists prescribe the antibiotic of choice in accordance with the manufacturer’s instructions—ie, at the correct dose and for the correct length of time—and that patients are informed of the consequences of non-compliance with these instructions (as is often the case when the condition starts to resolve). An increasing number of clinical studies are addressing the question of whether shorter dosing periods may be as effective as the currently longer courses of therapy in systemic infectious disease areas, such as for urinary tract infections, and such information would be valuable in the field of ophthalmology.

Conclusion

The rise of antibiotic resistance to common ocular infections threatens to diminish the clinical utility of important classes of drugs and ultimately impact patient vision. By increasing awareness of evolving resistance patterns and implementing in-clinic strategies to better target pathogens, ophthalmologists may help preserve drug utility for the benefit of present and future patients.

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REFERENCES


BLONDEAU REFERENCES continue on page 4
3. Which statement regarding MIC is FALSE?
   A. MIC is defined as the lowest concentration of an antimicrobial drug that is required to inhibit visible growth of 105 CFU following incubation for 18 to 24 hours.
   B. MIC is a valuable tool for determining effective concentrations of drugs for systemic infections.
   C. MIC measures the frequency of a microbe to mutate and develop resistance.
   D. The ratio of drug area under the curve (AUC) to MIC provides important information to predict outcomes with antimicrobial treatment.

4. Which of the following advancements are present in later-generation ophthalmic fluoroquinolones?
   A. Greater anti-gram-negative activity
   B. Higher risk for resistance selection
   C. More balanced MOA
   D. None of the above

5. Which of the following has NOT been proven to reduce the incidence of postoperative endophthalmitis following intraocular surgery?
   A. Povidone-iodine prep
   B. Topical ocular moxifloxacin prophylaxis
   C. Intracameral cefuroxime prophylaxis
   D. All of the above are proven to prevent endophthalmitis

6. Which statement is TRUE regarding the addition of excipients to antibiotic formulations?
   A. Higher MIC and MPC values are observed when benzalkonium chloride is added to gatifloxacin and moxifloxacin.
   B. Lower MIC and MPC values against MRSA are observed when BAK is added to gatifloxacin and moxifloxacin.
   C. Higher MIC and MPC values are observed when polyethylene glycol is added to moxifloxacin.
   D. Mannitol increases the in vitro activity of gatifloxacin.

7. Which statement is TRUE regarding the key findings of the surveillance studies TRUST and ARMOR?
   A. Fluoroquinolones remain active in the majority of MRSA isolates.
   B. In vitro S. aureus and CNS isolates have a high probability of resistance to the fluoroquinolones aminoglycosides and or macrolides.
   C. TRUST data show that fluoroquinolone activity has been significantly diminished in the majority of MSSA, S. pneumoniae, and H. influenzae isolates.
   D. Vancomycin remains active in staphylococcal isolates, but the fourth-generation fluoroquinolones (moxifloxacin and gatifloxacin) demonstrate decreased spectrum antibiotic effect against both the gram-positive and gram-negative organisms.

8. Which of the following may be modified in a new generation of antibiotic?
   A. Chemical structure
   B. Antimicrobial activity
   C. Resistance profile
   D. Any of the above may be modified

9. Fluoroquinolones target which of the following bacterial enzymes?
   A. DNA gyrase
   B. Topoisomerase IV
   C. Beta-lactamase
   D. A and B

10. Recommended strategies for minimizing antibiotic resistance:
    A. Include in vitro testing of refractory and routine cases
    B. Strict adherence to drug manufacturers' prescribing information, and patient education on the importance of treatment compliance
    C. Increasing the awareness of evolving resistance patterns
    D. All of the above

EXAMINATION ANSWER SHEET

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 October 31, 2017.

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
5. A  B  C  D  10. A  B  C  D