

# TOPICS IN Ocular Antiinfectives

## Pharmacokinetic and Pharmacodynamic Considerations in the Use of Ocular Antibacterials

Joseph M. Blondeau, PhD

*Pharmacokinetics (PK) describes the fate of a drug as it passes through the body. In this passage, the drug undergoes absorption, distribution to tissues and organs (sites of action), and clearance (biotransformation and elimination). An important consideration, and a fundamental aspect of PK, is the rate at which each of these processes takes place, which in turn determines the drug's concentration in the plasma and at the site(s) where it is needed.*

*Pharmacodynamics (PD) describes the effect of a drug at its site(s) of action in the body. The therapeutic effects described by PD take place inside the time window (described by PK) during which the drug can be found at the action sites. Although they describe different aspects of drug action within the body, PK and PD are inextricably linked, and the clinician must necessarily consider both when making therapeutic decisions.*

PK and PD were developed initially to help us understand and predict the actions of systemic drugs. In ophthalmology, where systemic drugs are the exception not the rule, PK principles, while still very useful, must be applied thoughtfully and in some cases modified to fit the circumstances. For example, while there are some issues related to drug absorption (penetration) in the eye, discussions of enzyme transformation, distribution to distant tissues, and

elimination from the blood, are far more germane to systemic administration than topical.

With respect to PD, questions about a drug's mechanism of action (particularly whether it is bacteriostatic or bactericidal) and its toxicity are highly pertinent, no matter how the drug is delivered.

### Predicting Efficacy

Depending on its mechanism of action, an antibiotic may be described as either time

TABLE 1
Mode of Bacterial Killing
<b>Time Dependent</b>
<ul style="list-style-type: none"><li>• Beta-lactams</li><li>• Clindamycin</li><li>• Erythromycin</li><li>• Clarithromycin</li><li>• Linezolid</li><li>• Vancomycin</li><li>• Macrolides</li></ul>
<b>Concentration dependent</b>
<ul style="list-style-type: none"><li>• Concentration dependent</li><li>• Fluoroquinolones</li><li>• Aminoglycosides</li><li>• Daptomycin</li><li>• Amphotericin</li><li>• Azithromycin</li></ul>

dependent or concentration dependent (Table 1). For concentration-dependent agents like fluoroquinolones and aminoglycosides, systemic studies have found that good bactericidal effect is obtained when the ratio of maximum drug concentration to minimum inhibitory concentration ( $C_{max}/MIC$ ) is at

**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. Describe the basic processes of pharmacokinetics and pharmacodynamics and their relevance in clinical ophthalmology.
2. Utilize pharmacokinetic/pharmacodynamic principles to improve drug selection for empirical therapy of infection and surgical prophylaxis.
3. Apply large-scale strategic thinking on ways to minimize resistance to individual patient encounters.

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least 8 to 10.<sup>1,2</sup> This value has been shown in experimental trials to correlate with a favorable clinical outcome and minimal risk of drug resistance.

For concentration-dependent killing agents, the ratio of the area under the drug concentration curve to MIC totaled over the entire period of drug exposure, also known as area under the inhibitory curve, may also be used to predict bactericidal effect (Figure 1). Although controversial, there is some evidence (in systemic infectious disease) that a ratio greater than 125 correlates with favorable clinical response and minimal drug resistance.<sup>2,3</sup> However, it has been argued that this value is necessary for Gram-negative organisms only; a much lower value of 30-50 would be sufficient for Gram-positive organisms

such as *Streptococcus pneumoniae*.<sup>4</sup>

I believe, however, that even higher ratios are better; because decreasing the area under the inhibitory curve to a point where an organism is exposed to a drug at a range of values approaching the MIC increases the risk of drug resistance.

For time-dependent killing agents, such as beta-lactams (including penicillins and cephalosporins), the antibacterial effect occurs when the drug concentration is above the MIC. (This effect is independent of the  $C_{max}/MIC$  ratio.) Estimates in the literature suggest that a favorable response is likely if drug concentration

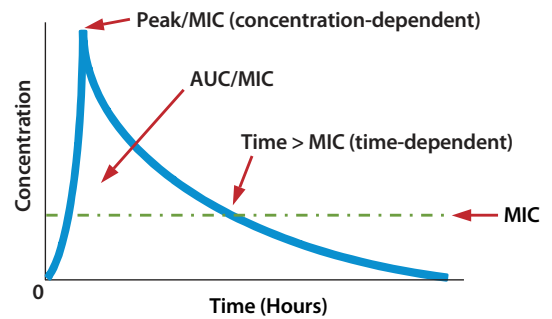


FIGURE 1 PK/PD parameters affecting antibiotic efficacy.

at the binding site exceeds the MIC for 40% to 50% of the dosing interval.<sup>5</sup>

## MIC Values

The susceptibility of an organism to a drug is quantified in the drug's MIC value. Typically, this number is expressed

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### 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 antiinfectives.<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 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.

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## CORE CONCEPTS

- ▶ PK is the effect of the body on a drug; PD is the effect of a drug on the body.
- ▶ PK/PD effects may need to be modified to take into account the largely topical armamentarium of clinical ophthalmology.
- ▶  $C_{max}/MIC$  ratios must be high enough to correlate with a favorable clinical outcome and minimal risk of drug resistance.
- ▶ Concentration-dependent agents confer an advantage because eye surface contact time is relatively short (seconds to minutes).
- ▶ Antibacterial decision trees should include spectrum of activity, safety, previous experience with the agent, and prevalence of resistance.

as the concentration at which a given antimicrobial inhibits either 50% ( $MIC_{50}$ ) or 90% ( $MIC_{90}$ ) of the isolates tested.

Knowing the  $MIC_{50}$  or  $MIC_{90}$  for a particular drug against a particular bacterial species provides an epidemiologic context for comparing potential agents for empiric therapy or prophylaxis. But it does not provide definitive information on how to treat an unknown infection in a given patient. It may still be necessary to know the susceptibility or resistance of the specific organism causing the infection. In patient-specific therapy it is always desirable to test the isolate.

### The Kill Curve

A “kill curve” tells us how quickly and how completely an organism is killed in the presence of a specific drug. To create a kill curve, serial dilutions of a drug are added to a specified concentration of organisms (typically, 100,000 or 1 million organisms per mL), and the killing effect on the population is observed at specified time intervals over a period that may be 3 hours, 24 hours, or some other interval appropriate to the bug/drug pairing.

This assay generates a time-kill curve

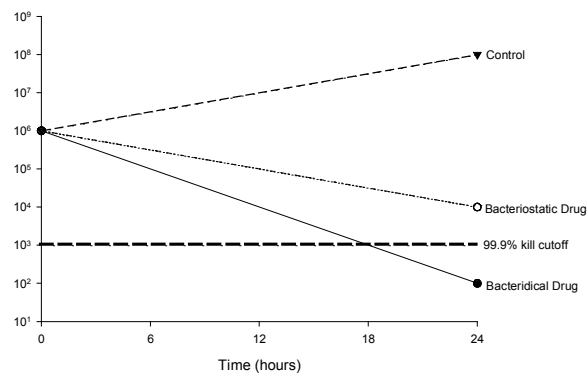
for a drug, which can tell us whether the drug’s mechanism of action is bacteriostatic or bactericidal (Figure 2; Table 2). A drug is generally considered bactericidal if it produces greater than a three- $\log_{10}$  reduction in the number of organisms; bacteriostatic agents produce less than a two- $\log_{10}$  reduction. (Between 2 and 3 logs is a grey area.)

Kill curves also tell us how quickly a drug acts and what fraction of the organisms present it is able to kill.

### PK/PD-Based Therapy Decisions

PK/PD comes into its own when culture and sensitivity testing is not possible (as in prophylaxis) or not practical (eg, when the doctor has no materials available to collect specimen for culture, making empirical treatment necessary). In these common situations, PK/PD provides very useful data for selecting an agent.

With respect to prophylaxis, despite some impressive data from the ESCRS trial, routine use of intracameral prophylaxis remains controversial in North America.<sup>6</sup> There are many reasons why North American surgeons haven’t rushed to embrace intracameral prophylaxis, including the lack of FDA approval in the US, the need to obtain drug from a compounding pharmacy or prepare it on site in the OR, the hazards of on-site preparation (eg, contamina-



**Figure 2** Time kill curve of bacteria after exposure to a bactericidal drug, a bacteriostatic drug, or no antimicrobial (control). For both classifications, bacteria are typically killed over the 18-24 hour interval, unless in vitro resistance is present or an insufficient drug concentration is tested. Bactericidal drugs kill  $\geq 99.9\%$  of target organisms over this interval, while bacteriostatic drugs kill less than 99.9%.

tion, concentration errors), the absence of data on long-term risk, and the fact that there is no evidence based standard for intracameral dosing. So although for some surgeons intracameral prophylaxis may be appropriate, there are good reasons for others to remain with topical prophylaxis.

If one is selecting an intracameral prophylactic agent, PK/PD issues are dwarfed by more basic issues such as availability of a nonpreserved drug, safety, and spectrum of activity. PK/PD data for intracameral drug use is largely unknown; PK/PD can, however, be very helpful in choosing an agent for topical prophylaxis.

For topical prophylaxis, use of a time-dependent drug has one very practical difficulty to overcome: sufficient contact time at adequate concentration is critical

**TABLE 2**

Bacteriostatic and Bactericidal Antibiotics

#### Bacteriostatic Antimicrobials

Chloramphenicol<sup>a</sup>  
 Macrolide/azalides (erythromycin, clarithromycin, azithromycin)  
 Clindamycin  
 Linezolid  
 Sulfonamides (trimethoprim-sulfamethoxazole)<sup>a</sup>

#### Bactericidal Antimicrobials

Aminoglycosides (amikacin, gentamicin, tobramycin)  
 Beta-lactams (penicillins, cephalosporins, carbapenems)  
 Fluoroquinolones  
 Glycopeptides (vancomycin)<sup>b</sup> Daptomycin<sup>c</sup>  
 Metronidazole  
 Polypeptides (polymyxin, colistin)

<sup>a</sup> May be bacteriostatic or bactericidal depending on organism.

<sup>b</sup> Generally considered “slowly cidal” as typically takes the full 18-24 hours to achieve  $\geq 99.9\%$  kill

<sup>c</sup> Only antimicrobial currently available that is bactericidal against *Enterococcus* species

to these agents' function, yet any soluble drug on the ocular surface is subject to rapid washout and tear dilution.

Time on the ocular surface is a smaller issue for concentration-dependent agents because when the concentration is adequate, the killing effect can be rapid—if the concentration is high enough, the time element becomes relatively insignificant. But these drugs are challenged to maintain high drug concentration-to-MIC ratios in the presence of normal tear dilution and drainage. Still, concentration-dependent agents can kill quickly when the concentration is adequate; and it is possible that that lethal effect may continue even when the concentration drops.

A recent report from our laboratory, using a novel in vitro microtiter assay, showed rapid killing of *Staphylococcus epidermidis* and methicillin resistant *Staphylococcus aureus* by fluoroquinolones when 1–8 drops of ocular antimicrobial drug formulations were added to kill assays. This assay (we believe) more closely mimics how the drugs are used clinically, as it assesses the antimicrobial impact for the drops straight out of the bottle against ocular pathogens.

It has become a commonplace that most endophthalmitis originates from organisms on the ocular surface.<sup>7</sup> That has several corollaries: a concentration-dependent agent should, for the reasons mentioned, maximize killing on the surface and therefore be preferred. In addition, formulations that retain drug on the ocular surface (eg, besifloxacin and a new formulation of moxifloxacin) should also foster surface killing and, hopefully, prophylactic efficacy. For example, in rabbits, besifloxacin was shown to have an ocular PK profile characterized by high and sustained concentrations in tear fluid, resulting in AUC<sub>0-24</sub>/MIC<sub>90</sub> ratios of ~800 for staphylococci that were both methicillin resistant ciprofloxacin resistant.<sup>8</sup>

### The Therapeutic Decision Tree

In the most desirable scenario, the organism responsible for an infection has been isolated and found susceptible to a drug approved for that indication, with the particular circumstances and physiologic (immune) status of the

patient also taken into account. But in ophthalmology most antibiotics are approved for very limited indications, so finding an approved agent may not be possible. Nor is laboratory testing likely to be pursued, given ophthalmology's near wholesale adoption of empirical therapy with fluoroquinolones.

Instead, an empiric approach is typically adopted in cases of acute eye infection. Here, the decision process for drug selection should include the following queries:

- Does a candidate drug have the right spectrum of activity for the likely pathogens involved?
- Are there safety factors to be considered with the drug?
- How much clinical experience (especially the clinician's own) has there been with the drug?
- How prevalent is resistance to the drug (is local epidemiologic data available for it)?

The answers to these questions, in conjunction with relevant PK/PD data, should help direct a decision as to which class of drug to choose from, and which formulary product in the class best fits the patient's needs.

Of interest is the fact that some formulations are preserved with benzalkonium chloride, which may confer an advantage over formulations without it because this compound has intrinsic antimicrobial activity, including against multidrug-resistant Gram-positive organisms.<sup>9,10</sup>

### Drug Resistance Changes Things

Some 10 years ago, a frequently recommended approach to the treatment of systemic infectious disease was to sidestep laboratory identification of pathogens in favor of empirical protocols. If one drug didn't work, another was used. Laboratory susceptibility testing was reserved for the 10% or so of cases that did not respond at all.

In ophthalmology, thanks to great success with topical fluoroquinolone monotherapy, this attitude is perhaps even more prevalent. Ophthalmologists are helped, of course, by the much higher drug concentrations made possible on the ocular surface by topical drug delivery; such

concentrations, it may be argued, are likely to overcome even resistant organisms.

However, the likelihood of an infection being the result of a drug-resistant strain is much higher now than it was a few years ago, and this should have an impact on choice of drugs and the decision whether or not to treat empirically. Certainly, having the patient endure one and possibly more drug failures before resorting to the laboratory is not in the best interest of either patient or clinician. With resistance now highly prevalent and becoming more so, it is time to take greater advantage of laboratory identification and susceptibility testing.

In reviewing basics of PK/PD for clinical ophthalmologists, it is important to emphasize that the pharmacology of antibacterial action in eye infection cannot be discussed in isolation. Inevitably, microbiology, pathology, immunology, and clinical outcomes must also be considered to create an integrated medical solution. This approach is all the more exigent in the current environment of multidrug resistance.

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# Fluoroquinolones in Ophthalmology: Past, Present, and Future

David G. Hwang, MD, FACS

*The susceptibility pattern of ocular isolates has undergone a substantial shift, with antimicrobial resistance rising rapidly. This argues for the development not only of alternative antibacterial agents but, more importantly, a new antibiotic strategy.*

With their excellent tissue penetration, broad spectrum activity, and low toxicity, fluoroquinolones have for almost two decades been the mainstay of ophthalmic antimicrobials. Recent studies, however, document rising rates of fluoroquinolone resistance among ocular pathogens.<sup>1</sup>

Before considering how best to address the future of ophthalmic fluoroquinolones, especially in view of rising resistance, let us first review their history and how they became the predominant agents for preventing and treating ocular infections.

## The Rise of Ophthalmic Fluoroquinolones

Fluoroquinolones are derived from the urinary antiseptic nalidixic acid through side chain modifications to a common fluorinated chemical backbone. Compared to nalidixic acid, which is active only against a limited number of Gram-negative bacteria, fluoroquinolones have both greater potency and a broader spectrum, particularly against Gram-positive bacteria and also Gram-negatives like *Pseudomonas aeruginosa*. Since the mid-1980s, when the first systemic fluoroquinolones—ciprofloxacin, norfloxacin, and ofloxacin—were introduced, the fluoroquinolone family has evolved rapidly.

Ophthalmic fluoroquinolones were introduced in the early 1990s.<sup>2</sup> Compared to other ophthalmic antibiotic classes available at the time, fluoroquinolones offered better penetration into the cornea and aqueous humor, better antimicrobial activity across the Gram-positive and Gram-negative spectrum, and were as well or better tolerated by patients. Although norfloxacin was not widely adopted due to its poor activity, the excellent activity and patient acceptance of ciprofloxacin (0.3%) and ofloxacin (0.3%) resulted in their rapid adoption in the United States as the ophthalmic antimicrobial of choice for both infection treatment and surgical prophylaxis.

Ciprofloxacin, the first ophthalmic fluoroquinolone introduced to the US market, had superior activity against *Pseudomonas aeruginosa*.<sup>3</sup> Unfortunately, it is only weakly soluble, which limits its formulation concentration to 0.3%, increases its potential for precipitation, and encumbers tissue penetration. Additionally, ciprofloxacin shows relatively poor activity against Gram-positive cocci (especially streptococci). Although ciprofloxacin is still commonly used systemically, its ophthalmic usage dropped off with the advent of newer fluoroquinolones. Ofloxacin 0.3% has better solubility and tissue penetration.

## Ofloxacin Evolves

In the 1990s, cataract surgeons began to change their incision technique from scleral tunnels to clear corneal incisions. Coincident with this change was a change in prophylaxis from subconjunctival injection to topical drops. Then, in the late 1990s, reported rates of postoperative endophthalmitis appeared

### CORE CONCEPTS

- Fluoroquinolones should be used with a "get in, hit hard, and get out" strategy. Sublethal fluoroquinolone dosing fosters resistance.
- MRSA has become an increasingly important ocular pathogen. Approximately 80% of MRSA strains show in vitro resistance to currently available fluoroquinolones.
- While systemic anti-MRSA drugs have been available and more are under development, no agents are yet emerging from the pipeline for ophthalmic applications.
- To prevent further development of resistance, antibiotic strategies should involve selective and appropriate use of agents. Further studies are needed to determine optimal usage patterns to forestall the development of resistance.

to increase, in some cases quite dramatically. Some eye centers that had adopted both clear corneal incisions and topical fluoroquinolone prophylaxis reported endophthalmitis rates of 1 in 350 cases, a startlingly higher level than the baseline level of 1 in 1,000.<sup>4,5</sup>

Potential explanations included changes in wound construction and location, as well as changes in perioperative antibiotic selection and delivery. The unsutured clear corneal incision, if not constructed scrupulously to ensure a watertight seal, could

serve as a conduit for entry of bacteria.<sup>6</sup> Even though ofloxacin offered better penetration than ciprofloxacin, neither achieved levels greater than 1 to 2 µg/mL and so failed to exceed the MIC<sub>90</sub> of many of the pathogens responsible for endophthalmitis.<sup>7</sup> Nonetheless, the transition to clear corneal surgery and topical prophylaxis went forward, albeit with greater attention to the details of wound construction and increased interest in alternative antibiotic prophylaxis approaches.

It was thought that if fluoroquinolones could be delivered in fortified concentrations, more effective intraocular concentrations might be achieved. For ciprofloxacin and to a lesser extent ofloxacin, however, limitations in aqueous solubility restricted commercial formulations to a concentration of 0.3%. This triggered a search for agents that could be formulated at higher concentrations and/or penetrate into the corneal and aqueous compartments more effectively.

A number of drugs exist as racemic mixtures—ie, two mirror isomers only one of which may be biologically active. One such drug, ofloxacin, was processed to remove the inactive isomer. This yielded the pure, biologically active isomer, levofloxacin, which also had excellent solubility. Levofloxacin 0.5% had 3.3 times the activity of ofloxacin 0.3%, and levofloxacin 1.5% had 10 times the activity of ofloxacin 0.3%.

Levofloxacin showed good activity against both Gram-negative bacteria and atypical mycobacteria. But significant questions remained about its ability to reduce the risk of postoperative endophthalmitis, prompting an ESCRS-sponsored head-to-head comparison of topical levofloxacin 0.5% vs intracameral cefuroxime vs both for preventing postoperative endophthalmitis.<sup>8</sup>

### New Structural Modification

The ESCRS study found a clear benefit of intracameral cefuroxime but only a small, statistically insignificant effect of topical levofloxacin 0.5%.<sup>8</sup> The results cast doubt on the ability not just of levofloxacin but the entire fluoroquinolone class to reach adequate aqueous levels. While surgeons in Europe and elsewhere embraced the ESCRS results and shifted from topical fluoroquinolones to intracameral cefuroxime, US and Canadian surgeons by and large continued to prefer topical fluoroquinolones, citing the lack of a commercially available preparation of cefuroxime for intracameral use.<sup>9</sup> At the same time, they embraced the introduction of two new fluoroquinolones, which promised even better Gram-positive activity with comparable or better aqueous penetration.

These two fluoroquinolones, gatifloxacin (0.3%; later available in a 0.5% concentration) and moxifloxacin (0.5%), incorporated a new side chain modification, the addition of a methoxy (-OCH<sub>3</sub>) group to the fluoroquinolone backbone at position 8. These drugs' enhanced Gram-positive activity was especially beneficial, since approximately 90% of serious ocular infections, including postoperative endophthalmitis, are caused by Gram-positive pathogens.<sup>10</sup> The 8-methoxy fluoroquinolones are also less likely to select for spontaneous resistance, because they simultaneously disrupt two different enzymes necessary for faithful DNA replication: topoisomerase II and IV.<sup>2</sup>

As fluoroquinolones gained in Gram-positive activity, a new problem began to emerge: the progressive rise in the proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) causing serious ocular infections, including keratitis and endophthalmitis. In a survey of ASCRS members conducted in 2001, for example, Gram-positive cocci and atypical mycobacteria were reported as equally frequent causes of post-LASIK infection.<sup>11</sup> When the survey was repeated in 2004, post-LASIK infection caused by atypical mycobacteria had diminished considerably, possibly due to the newly introduced 8-methoxy fluoroquinolones.<sup>12,13</sup> In the latest ASCRS report, released this year, atypical mycobacteria had disappeared and there was a resurgence of Gram-positive cocci—a high proportion of it MRSA—among post-LASIK infections.<sup>12</sup>

### MRSA: The Achilles Heel

Staphylococci are among the bacterial species most frequently responsible for ocular infections, but until the past decade MRSA infections were relatively uncommon—under 10% of cases—and usually associated with nosocomial

acquisition. Within the past decade, however, there has been a steady rise of methicillin resistance in ocular staphylococci isolates, exactly paralleling the rise in systemic MRSA.<sup>14,15</sup> In the recent ARMOR surveillance study, 40% of all ocular *S. aureus* isolates were MRSA.<sup>16</sup> Moreover, an increasing proportion of systemic MRSA appear to be community-acquired strains rather than healthcare-associated isolates.<sup>17,18</sup>

The growing prevalence of MRSA exposed a known weakness of fluoroquinolones: most MRSA strains are fluoroquinolone-resistant. This attracted little attention when the fluoroquinolones were first introduced for ophthalmic use because, at that time, MRSA ocular infections were quite uncommon. But as the number of MRSA infections has risen to clinically meaningful levels, this shortcoming has become an issue of concern. While it is important to note that in vitro resistance does not necessarily correlate with clinical failure, it is also likely true that declining in vitro susceptibility will at some point indicate a higher probability of in vivo failure.

The newest ophthalmic fluoroquinolone, besifloxacin 0.6%, demonstrates even better Gram-positive activity than moxifloxacin or gatifloxacin. Unlike other fluoroquinolones, besifloxacin was not previously developed as a systemic agent; however, this fact does not necessarily imply that besifloxacin is unaffected by fluoroquinolone cross resistance. In fact, most strains that develop resistance to one particular fluoroquinolone will also show significantly decreased susceptibility to the other fluoroquinolones. Thus the enhanced Gram-positive activity of besifloxacin, while a positive attribute, does not guarantee clinical efficacy against MRSA or other fluoroquinolone-resistant strains of bacteria. Besifloxacin appears to have greater in vitro activity against MRSA and methicillin-resistant *Staphylococcus epidermidis* (MRSE) than moxifloxacin and gatifloxacin, but the clinical relevance of this finding is not yet fully defined.

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### Weakness Despite Strength

By the time gatifloxacin 0.3% and moxifloxacin 0.5% were introduced, ris-

ing in vitro resistance to ciprofloxacin and ofloxacin had been well documented.<sup>19-21</sup> This increasing resistance was found not only in Gram-positive bacteria but also Gram-negative pathogens such as *P. aeruginosa*.<sup>22</sup> In addition, resistance to newer topical fluoroquinolones has been increasing.<sup>23,24</sup> As for MRSA, greater than 80% of the strains are resistant in vitro to all currently available ophthalmic fluoroquinolones.<sup>16</sup> Many practitioners assume incorrectly that newer fluoroquinolones will be clinically effective against MRSA or other Gram-positive strains that are resistant to older fluoroquinolones.

Fluoroquinolones kill susceptible bacteria by disrupting the fidelity of DNA synthesis and thus replication of DNA. This unique mechanism of action, however, is also responsible for the intrinsic ability of fluoroquinolones to actually accelerate the production of random mutants, some of which will confer resistance.

Sublethal exposure to fluoroquinolones can generate large numbers of mutants with random errors in DNA replication.<sup>2</sup> Those resistant mutations will be rapidly selected, and with repeated fluoroquinolone exposure, the population may soon acquire a series of mutations, each conferring an additional degree of fluoroquinolone resistance.

Fortunately, recent research has given hope that appropriate dosing strategies may be able to counter this tendency. In animal models and in vitro, maintenance of a fluoroquinolone concentration at levels at least 3 to 4 times higher than the MIC of the causative bacteria can minimize resistance development.<sup>25,26</sup>

## Rethinking Antibiotic Strategy

Recently an investigational fluoroquinolone with potent in vitro activity against Gram-positive and Gram-negative pathogens, including MRSA, has entered late-stage clinical testing for systemic use.<sup>27,28</sup> The prospects for ophthalmic application of such a fluoroquinolone remain uncertain, but an exciting possibility nonetheless.

That said, efforts to develop systemic anti-MRSA agents have largely focused on antibiotic classes other than fluoroquinolones. A number of drugs have emerged from the pipeline and more

candidate molecules are in late-stage testing. But for multiple reasons, none of these drugs has yet entered late-stage development for ophthalmic use. Vancomycin remains the most commonly used agent for systemic MRSA infections, but its ophthalmic use is limited by its potential for ocular surface toxicity, relatively slow speed of bacterial killing, and lack of commercially available preparation.

For some indications, a readily available alternative to vancomycin should be considered. Trimethoprim has retained good activity against MRSA and MRSE. In a recent nationwide surveillance study, about 95% of tested ocular MRSA isolates were susceptible to trimethoprim.<sup>14</sup> Commercially available trimethoprim preparations possess neither the potency nor the penetration to treat established MRSA keratitis or for prophylaxis of postoperative endophthalmitis. Its good tolerability and excellent anti-MRSA activity, however, could qualify it as a choice for surface prophylaxis and treatment of superficial MRSA infections such as conjunctivitis or blepharitis.

Until a commercial anti-MRSA drug is developed, our only option is to use our existing drugs in a rational manner that minimizes further development of community resistance. In a retrospective study from our institution, patients with MRSA had twice the likelihood of having used a topical fluoroquinolone in the prior 3 months than patients who hadn't.<sup>29</sup>

Inappropriate or prolonged topical fluoroquinolone use can encourage the development of local fluoroquinolone resistance. Likewise, any sublethal dosing regimen—including insufficient dosing, intermittent dosing, and tapered dosing—can promote the rapid development of resistance.

Rather than relying on one agent for all prophylaxis or treatment indications, a tiered approach should be considered, depending on the pathogen and on the severity and location of the infection. Whenever possible, narrow-spectrum and older agents should be employed.

## New Thinking

As practitioners, our thinking has to go beyond the welfare of the single patient we are treating at a given mo-

ment. We will need to think strategically about how to extend the useful lifespan of antimicrobials. We should use fluoroquinolones in a more effective and rational way, choosing the newer fluoroquinolones over the older ones to enhance not only clinical effectiveness but also to reduce the likelihood of propagating resistance, and we should use them at relatively high doses for short durations—a “get in, hit hard, and get out” strategy to avoid at all costs sub-lethal exposures that can rapidly promote resistance.<sup>2</sup>

To establish guidance for the proper use of antimicrobials, we need more evidence-based pharmacodynamic studies in clinically relevant ocular models to determine the optimal antimicrobial selection, dosing, and duration for a given infection. In countering the rising tide of antimicrobial resistance, such efforts may ultimately prove more efficient and cost-effective than the equally important—but more daunting—task of searching for the next blockbuster candidate to replace the ophthalmic fluoroquinolones.

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## EXAMINATION QUESTIONS TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 25

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>.

- Which of the following is *not* a pharmacokinetic response?
  - Drug absorption
  - Drug distribution
  - Drug mechanism of killing
  - Drug clearance
- For concentration-dependent antibacterial agents to reliably achieve a systemic bactericidal effect, the  $C_{max}/MIC$  ratio should exceed
  - 125
  - 30 to 50
  - 8 to 10
  - 1
- A time-kill curve of a drug in vitro can determine
  - Rate of killing
  - Total killing capacity
  - Bactericidal or bacteriostatic response
  - All of the above
- Fluoroquinolones act by:
  - Inhibiting cell wall synthesis
  - Disrupting protein synthesis
  - Disrupting DNA synthesis
  - Inhibiting mitochondria
- According to Dr. Blondeau, which of the following is *underutilized*?
  - Fluoroquinolone monotherapy
  - Laboratory susceptibility testing
  - Povidone-iodine prophylaxis
  - Topical antibiotic prophylaxis
- The typical duration of contact time after application of antibacterial drops to the ocular surface may be reckoned in
  - Seconds to minutes
  - Hours to days
  - Days to weeks
  - It depends on the drug
- The majority of serious ocular infections are caused by
  - Gram-positive bacteria
  - Gram-negative bacteria
  - Atypical mycobacteria
  - Viruses
- In vitro studies have found approximately which level of fluoroquinolone reduces the likelihood of developing resistance?
  - Double the MIC
  - 3 to 4 times the MIC
  - 10 times the MIC
  - Half the MIC
- In the most recent tracking study from the ASCRS, which pathogen had become a common cause of post-LASIK infection?
  - Pseudomonas aeruginosa*
  - Atypical mycobacteria
  - MRSA
  - Haemophilus influenzae*
- When using fluoroquinolones, which of the following can help reduce the risk of promoting resistance?
  - Higher dose
  - Greater antimicrobial activity (ie, lower MIC)
  - Shorter duration of dosing
  - All of the above

## EXAMINATION ANSWER SHEET TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 25

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 September 30, 2012.

### 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

- Extent to which the activity met the identified
  - Objective 1: 1 2 3 4 5
  - Objective 2: 1 2 3 4 5
  - Objective 3: 1 2 3 4 5
- 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
- Will the information presented cause you to make any changes in your practice? Yes No
- If yes, please describe: \_\_\_\_\_
- How committed are you to making these changes?
  - 1 2 3 4 5
- 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 —

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