Antibiotic Advances in Ophthalmology

Nicoletta Fynn-Thompson, MD
Roberto Pineda II, MD

History of Fluoroquinolone Use in Ophthalmology

Quinolones rapidly inhibit DNA synthesis by promoting cleavage of bacterial DNA in the DNA-enzyme complexes of both DNA gyrase and type IV topoisomerase, resulting in rapid bacterial death. Gram-negative bacterial activity correlates with inhibition of DNA gyrase, and gram-positive bacterial activity corresponds with inhibition of DNA type IV topoisomerase.[1] The quinolones are categorized into generations based on their antimicrobial activity classification. The first-generation quinolone, nalidixic acid, was introduced in 1962. It is used less often today and has moderate gram-positive coverage and minimal systemic distribution. The second generation has expanded gram-negative coverage, atypical pathogen coverage, but limited gram-positive coverage. The third generation has improved gram-positive coverage and retained gram-negative and atypical activity. The fourth generation has improved gram-positive coverage, gained anaerobic coverage, and maintained gram-negative activity.[2]

At their introduction, topical second-generation fluoroquinolones, ciprofloxacin and ofloxacin, were largely accepted for the treatment of anterior segment-related ocular infections, such as bacterial keratitis and conjunctival infections. Specifically, these fluoroquinolones have good activity against the most frequent gram-positive and gram-negative ocular pathogens.

Ciprofloxacin was approved for use as topical therapy for bacterial corneal ulcers in December 1990. Early studies demonstrated the effectiveness of treating bacterial conjunctivitis with ciprofloxacin 0.3% ophthalmic solution.[3] Ciprofloxacin 0.3% was also compared with fortified tobramycin 1.3%-cefazolin 5.0% in the treatment of bacterial corneal ulcers. Results showed that ciprofloxacin 0.3% monotherapy was equally

effective clinically and statistically to standard dual therapy and was a significantly more comfortable therapy for the patients.[4]

Ofloxacin was approved for treatment of corneal ulcers in May 1996. Several studies have shown ofloxacin provides adequate monotherapy for bacterial keratitis. O'Brien et al published a multicenter study comparing the efficacy and safety of topical ofloxacin 0.3% solution with dual therapy for fortified cefazolin 10% and tobramycin 1.5% for the treatment of acute bacterial keratitis. The end points of the study were a complete re-epithelialization and a nonprogressive stromal infiltrate in 2 consecutive office visits. Results showed that healing time was similar among the groups, and there were fewer side effects, primarily stinging and burning, in the ofloxacin group.[5] The Ofloxacin Study Group, in 1997, compared ofloxacin 0.3% monotherapy to the conventional dual therapy for fortified gentamicin 1.5% and cefuroxime 5.0%. The end point was complete healing of the ulcer without an epithelial defect. The study showed there was no difference in treatment success, with 67.9% of the conventional treatment group and 62.1% of the ofloxacin treatment group being cured within 14 days.[6]

Studies have also demonstrated the corneal stromal penetration and ocular drug penetration in these second-generation fluoroquinolones to reach minimum inhibitory concentration (MIC) of ocular pathogens. McDermott et al studied the human stromal penetration of ciprofloxacin 0.3% in patients undergoing penetrating keratoplasty. Twelve patients scheduled to undergo a penetrating keratoplasty were given a loading dose of 0.3% ciprofloxacin every 15 minutes for the first hour, then hourly for the next 10 hours. The mean corneal stromal ciprofloxacin level was 5.28 ± 3.40 μg/g cornea. There were no toxic effects noted in the eyes and no evidence of precipitation of the antibiotic.[7] Diamond et al tested the corneal stromal penetration of ciprofloxacin, ofloxacin, and norfloxacin (0.3%) by administering 4 drops of each medication in 12 patients 60 minutes prior to penetrating keratoplasty and measured the drug concentration from the host cornea by high performance liquid chromatography (HPLC). The antibiotic concentrations were: ciprofloxacin 0.60 mg/kg, norfloxacin 0.54 mg/kg, and ofloxacin 0.81 mg/kg.[8]

In 2000, levofloxacin ophthalmic solution was approved for use. It was labeled a third-generation fluoroquinolone. The drug is an optical S-isomer of ofloxacin and has improved gram-positive coverage over the second-generation fluoroquinolones.

Yamada et al tested the transcorneal penetration of topically applied 0.5% levofloxacin into the aqueous humor in cataract patients. The mean aqueous humor level was 1.00 ± 0.48 μg/mL. Although there was moderate interpatient variability, this mean value was higher than the MIC90 value they chose against most bacteria causing postoperative endophthalmitis.[9]

Vitreous penetration after orally administered levofloxacin (one 500 mg tablet) in uninflamed phakic eyes was measured in patients undergo-

ing macula hole surgery. A peak concentration of 1.6 μg/mL was measured between 2.5 and 4 hours postdosage. These levels, however, did not reach MIC90 they chose for the commonest infecting organisms encountered.[10]

However, when vitreous concentrations of levofloxacin were measured in vitrectomy patients after receiving a double dose of orally administered levofloxacin (two 500 mg tablets), MIC90 levels were achieved against several common ocular pathogens, including *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Bacillus cereus, Haemophilus influenzae,* and *Moraxella catarrhalis*. The mean aqueous and vitreous concentrations were 1.90 ± 0.97 μg/mL and 2.39 ± 0.70 μg/mL, respectively.[11]

Several recent reports have suggested ocular bacterial resistance to these second-generation fluoroquinolones and questioned their efficacy in treatment and prophylaxis of ocular infections. Goldstein et al[12] performed a retrospective review from 1993 to 1997 to examine the percent distribution of gram-positive and gram-negative bacteria causing bacterial keratitis and their susceptibilities to ciprofloxacin and ofloxacin. The most common isolates were *Staphylococcus aureus,* other *Staphylococcus* species, *Streptococcus* species, *Pseudomonas aeruginosa,* and *Serratia marcescens*. Resistance over the 5-year study period of gram-positive bacteria to ciprofloxacin was 21.5% and 2.7% for gram-negative bacteria. The resistance of gram-positive bacteria over the 5-year study period to ofloxacin was 18.1% and 2.7% for gram-negative bacteria. Over the 5-year study period, there was a remarkable annual increase in the resistance of *S. aureus* to ciprofloxacin from 5.8% in 1993 to 35.0% in 1997. Likewise, there was a similar trend with ofloxacin, from 4.7% in 1993 to 35.0% in 1997. *Streptococcus* showed a significant resistance to both ciprofloxacin and ofloxacin (49.6% and 27%, respectively). This level of resistance did not significantly change annually. Additionally, coagulase-negative *Staphylococcus* also showed a trend toward increasing resistance to both ciprofloxacin and ofloxacin. This study demonstrated that there is an overall trend among ocular isolates toward resistance to fluoroquinolones. This pattern is occurring with other systemic infectious processes.[12] Additionally, Chaudry et al reported on the growing concern of emerging ciprofloxacin-resistant *Pseudomonas aeruginosa*.[13] This study reviewed in vitro sensitivities of all ocular isolates of *Pseudomonas aeruginosa* at their eye institute between January 1991 and December 1998. In vitro resistance was defined as MIC of 4 μg/mL or more. The study included 423 ocular isolates, 9 of which were resistant to ciprofloxacin. Of significance, from 1991 to 1994, only 0.44% (1/227) resistance was present. In contrast to that, from 1995 to 1998, emerging resistance increased to 4.1%. This change was calculated to be statistically significant.[13] Kunimoto et al reported in vitro susceptibility of bacterial keratitis pathogens to ciprofloxacin and resistant isolates from an eye hospital in India.[14] Of the 1558 corneal isolates, 478 (30.7%) were not sensitive to ciprofloxacin. These resistant strains in-

cluded both gram-positive and gram-negative organisms, as well as actinomycetes and related organisms. Ninety-five of the corneal isolates were *Pseudomonas aeruginosa*, and 8 (8.4%) were resistant to ciprofloxacin. These data also demonstrate a worldwide trend in the increasing resistance of bacteria to fluoroquinolones.[14] An additional report reviewed 141 culture-proven cases of *Pseudomonas aeruginosa* keratitis from January 1991 to June 1998 and found 22 (15.6%) of these to be ciprofloxacin-resistant.[15]

As a result of these multiple reports of emerging and increasing resistance to fluoroquinolones, newer fourth-generation topical antibiotics, gatifloxacin and moxifloxacin, will soon be introduced to ophthalmology. This report will review the literature on their susceptibility patterns, potencies, and potential uses for treatment and prophylaxis within the ophthalmic community.

■ Antimicrobial Susceptibility and Potency

As discussed previously, studies have demonstrated gaps in coverage of the second-generation fluoroquinolones to coagulase-negative *Staphylococcus* and *Streptococcus* and a rising resistance of *Staphylococcus aureus*. A recent retrospective in vitro study by Mather et al[16] compared the potencies and antibiotic susceptibilities of ciprofloxacin (CIP), ofloxacin (OFX), levofloxacin (LEV), moxifloxacin (MOX), and gatifloxacin (GAT) against 93 bacterial isolates of endophthalmitis. Eight resistant *S. aureus* isolates to CIP, OFX, and LEV showed 12.5% and 87.5% susceptibility to GAT and MOX, respectively. Ten resistant coagulase-negative *Staphylococcus* species to CIP and OFX showed 10%, 60%, and 50% susceptibility to LEV, GAT, and MOX, respectively. Ten isolates of *Streptococcus pneumoniae* were 60% susceptible to OFX and were 100% susceptible to the remaining 4 fluoroquinolones. Ten isolates of *Streptococcus viridans* that were 60% susceptible to both CIP and OFX, were 100% susceptible to LEV, GAT, and MOX. Additionally, 9 *Enterococci* species that were 77.8% and 67% susceptible to CIP and OFX, respectively, were 89% susceptible to LEV, GAT, and MOX. Finally, as expected, all *S. aureus*, coagulase-negative *Staphylococcus*, *Beta*-hemolytic *Streptococcus*, *Bacillus* species, and gram-negative bacteria that were 100% susceptible to CIP and OFX were also 100% susceptible to LEV, GAT, and MOX. Overall, the most potent fluoroquinolone was MOX, which achieved superior coverage for *S. aureus*, coagulase-negative *Staphylococcus* (second-generation susceptible), *Streptococcus*, and *Enterococcus*. Both MOX and GAT were equally potent for resistant coagulase-negative *Staphylococcus* (second generation) and *Bacillus* species. All had equal potency for treatment of gram-negative bacteria, except OFX, which was less potent.[16]

This study showed that the fourth-generation fluoroquinolones do

show greater potency and susceptibility toward gram-positive bacteria (primarily second- and third-generation resistant *Staphylococci* and second-generation resistant *Streptococci*) that otherwise may be resistant toward CIP and OFX. Overall, fourth-generation fluoroquinolones demonstrated lower MICs than both second- and third-generation fluoroquinolones. They did not, however, show any added benefit in treating gram-negative bacteria when compared with the second- and third-generation fluoroquinolones.

The susceptibility of MOX and GAT was compared with tobramycin and gentamicin for clinical bacterial keratitis isolates. *Streptococcus viridans* and *Streptococcus pneumoniae* demonstrated increased susceptibility to MOX and GAT. Fluoroquinolone-resistant (disk diffusion susceptibility to CIP and OFX) *S. aureus* was most susceptible to gentamicin and MOX. Fluoroquinolone-resistant coagulase-negative *Staphylococcus* was equally susceptible to all 4 antibiotics tested. Lastly, fluoroquinolone-resistant *P. aeruginosa* was most sensitive to tobramycin. Overall, none of the 4 antibiotics tested had complete coverage over the bacterial isolates tested.[17]

Stroman et al tested fourth-generation fluoroquinolone, MOX, against quinolone-resistant isolates of *S. aureus* and *S. epidermidis*. Moxifloxacin was more active in vitro than both CIP and OFX. The highest MIC was 16 g/mL for MOX, a concentration at least 100 times below that typically delivered in topical therapy.[18]

Tissue Penetration

Using confocal microscopy, Reiser and Chuck showed that 4 fluoroquinolones penetrated greater than 80% depth of the corneal epithelium after a total of 6 drops of any 1 of the 4 antibiotics or balanced salt solution control were topically applied to the corneas of enucleated rabbit eyes. Levofloxacin penetrated 95.2% ± 2.4%, followed by GAT 92.4 ± 2.7%, OFX 92.3% ± 3.0%, and CIP 84 ± 6.5%.[19]

The tear film concentration and ocular tissue penetration after administration of topical GAT 0.3% and CIP 0.3% was compared. The study showed that GAT had significantly greater penetration over CIP into corneal tissue and aqueous humor in rabbits. The concentrations of GAT achieved exceeded the MICs for many species of ocular pathogens.[20]

Preoperative Prophylaxis for Cataract Surgery (Aqueous Humor Penetration)

Multiple studies have investigated the most effective preoperative and intraoperative prophylaxis to prevent postcataract bacterial endophthalmitis. Sterile preparations, preoperative antibiotics, intraoperative antibiotic infusion, postoperative subconjunctival injections, and oral antibiotics have been studied. A recent review of the literature by Ciulla et al

found only preoperative povidone-iodine antisepsis to be of benefit to a limited extent.[21]

Agents that exhibit sufficient penetration into the aqueous humor above MIC90 levels for common ocular pathogens may have the potential to hold a role in preoperative prophylaxis for infection. Studies support that systemic CIP, OFX, and LEV penetrate both the aqueous and vitreous humor in the noninflamed eye better than other antibiotics. However, adequate concentrations may not be achieved with the recommended daily dosage. Garcia-Saenz et al compared the penetration of MOX into the aqueous humor to CIP and LEV. The study included 42 patients undergoing cataract surgery. The patients were divided into 3 groups, receiving an oral dose of CIP (500 mg every 12 hours), LEV (single oral dose of 500 mg), or MOX (single oral dose of 400 mg). The mean aqueous concentrations of CIP, LEV, and MOX were 0.50 ± 0.25 μg/mL, 1.50 ± 0.50 μg/mL, and 2.33 ± 0.85 μg/mL, respectively. This study showed a borderline concentration of CIP in the aqueous humor for *S. epidermidis*, the most common cause of postoperative endophthalmitis. Both LEV and MOX had mean concentration levels that reached the MIC90 of the most frequent gram-positive and gram-negative bacteria present in postoperative endophthalmitis. Additionally, MOX reached inhibitory aqueous concentrations for atypical organisms and anaerobic bacteria. This study demonstrated that it is feasible to treat preoperatively with an oral fluoroquinolone, which has adequate penetration into the aqueous humor to combat bacteria introduced intraoperatively. Moxifloxacin was the most potent and effective. However, the authors caution that such a potent antibiotic should be used only for high-risk cases (diabetes, immune-compromised, or secondary lens implant) or for actual treatment of a postoperative endophthalmitis because it is so superior to the others. Obsessive use may propagate resistance.[22]

Ocular penetration of MOX into the cornea, aqueous humor, iris-ciliary body, tear film, and plasma was compared with OFX. The maximal concentration of MOX remained 2-fold higher than OFX over the course of the study in ocular tissues after a single drop of MOX 0.3% was instilled into rabbit eyes.[23]

The effectiveness of topical antibiotic treatment with bacterial anterior chamber challenge versus a saline control group was recently investigated. One drop every 15 minutes for 1 hour of topical MOX 0.5% or saline was administered to 20 rabbits. The anterior chambers of the twenty rabbits were inoculated with clinical endophthalmitis isolates of *Staphylococcus aureus*. The rabbits were then treated with 5 drops of MOX or control over the next 24 hours. The MOX-treated group had no signs of endophthalmitis, whereas the control group had a significant clinical score of endophthalmitis. The anterior and posterior chambers in the MOX-treated group were negative for *Staphylococcus aureus*. This demonstrated that topical MOX therapy before and after bacterial challenge can prevent bacterial endophthalmitis in a rabbit model.[24]

Postoperative Endophthalmitis (Vitreous Penetration)

The Endophthalmitis Vitrectomy Study (EVS) investigated the use of intravenous amikacin and ceftazidime with intravitreal antibiotics in postoperative endophthalmitis cases. The study showed no improvement in the outcome with the use of intravenous antibiotics.[25] However, later studies show that both amikacin and ceftazidime have poor intravitreal penetration.[26,27] Therefore, one can conclude that intravenous amikacin and ceftazidime should not be used in postoperative endophthalmitis treatment regimens. The most common organisms isolated in cases of acute postoperative endophthalmitis were gram-positive coagulase-negative cocci, *Staphylococcus epidermidis,* and *Staphylococcus aureus.*[28]

A recent study has shown a potential role of the novel fourth-generation fluoroquinolone, GAT, in treatment of bacterial endophthalmitis by demonstrating aqueous and vitreous penetration after preoperative oral administration. Gatifloxacin has 96% oral bioavailability. Serum protein binding is only 20% and is widely distributed in tissues and fluids of the body. Twenty patients undergoing pars plana vitrectomy were instructed to take 2 oral 400 mg GAT tablets 12 hours apart. Samples of aqueous, vitreous, and serum were obtained prior to infusion intravenously and intraocularly by irrigating solution. All samples were collected approximately within 70 minutes of each other; serum first, followed by aqueous, and finally vitreous sample. Gatifloxacin concentration was determined by high-pressure liquid chromatography (HPLC) method. Mean GAT concentrations in serum were 4.98 ± 1.14 μg/mL, vitreous was 1.35 ± 0.36 μg/mL, and aqueous was 1.09 ± 0.57 μg/mL. Vitreous and aqueous concentrations were 27.13% and 21.85%, respectively, of serum GAT levels. Gatifloxacin has proven to have the highest possible intravitreal penetration as well as the lowest MIC90 for the organisms that cause postoperative endophthalmitis. The study demonstrated GAT to be 5.4 times the MIC90 for *S. epidermidis*, 10.4 times the MIC90 for *S. aureus*, 2.7 times the MIC90 for *P. acnes*, 2.7 times the MIC90 for *Streptococcus* species, and 5.4 times the MIC90 for *P. mirabilis*. These are all commonly encountered pathogens in postoperative bacterial endophthalmitis. These studies were tested in an uninflamed and uninfected eyes. Studies have shown intraocular penetration of systemic antibiotics may be higher in inflamed and infected eyes, which gives more importance to the potential use of this antibiotic for treatment of postoperative endophthalmitis.[29]

Treatment of Conjunctivitis

The most common pathogen to cause acute purulent bacterial conjunctivitis is *Streptococcus pneumoniae*. Other common pathogens include *Staphylococcus aureus, Moraxella lacunata, Proteus* species*, Enterobacteriaceae, Pseudomonas aeruginosa, Haemophilus influenzae,* and *Streptococcus pneumoniae*. Virulent species such as *Neisseria gonorrhoeae, Neisseria meningitidis,*

or *Streptococcus pyogenes* cause a hyperacute course within less than 24 hours.

Fluoroquinolones have been studied for the treatment of bacterial conjunctivitis. Leibowitz[3] studied 288 patients diagnosed with bacterial conjunctivitis. The patients were randomized to treatment with CIP 0.3% or placebo. Ciprofloxacin eradicated or reduced the bacteria species in 93.6% compared with 59.5% in the placebo group. Ciprofloxacin was also compared with tobramycin 0.3% and showed no statistical significant difference of either antibiotic to eradicate or reduce the bacterial infection.[3]

Gatifloxacin 0.3% has been compared with OFX 0.3% for the treatment of acute bacterial conjunctivitis in patients 1 to 90 years of age. The study patients instilled 1 to 2 drops every hour (maximum of 8 doses/day) the first 2 days, then 4 times a day for the following 3 days. On day 6, clinical cure rate and the frequency of punctate keratitis and conjunctival disorders were recorded. The study demonstrated that GAT was more effective in curing the conjunctivitis and better tolerated than OFX in the 459 patients studied. There was no comment on the spectrum of pathogens treated.[30]

Recently, a randomized study of neonatal patients with presumed bacterial conjunctivitis compared the safety and efficacy of MOX and CIP. The patients were 2 to 31 days of age with signs of conjunctival injection or discharge. Patients were cultured on day 1 and received 4 days of treatment with either medication. *Staphylococcus epidermidis* was the most frequently cultured organism. Only culture-positive patients were included in the study. The clinical cure rate was equal in both groups; however, MOX had higher percentage of earlier cure. On day 9 after treatment, 92% of MOX and 87% of CIP groups had microbiological eradication. Both drugs were well tolerated.[31]

Cytotoxic Effects on Corneal Epithelial, Stromal, and Endothelial Cells

Topical fluoroquinolones were tested to compare their effect on corneal epithelial and stromal cells. Using in vivo confocal microscopy to measure corneal epithelial thickness and stromal thickness, both eyes of 7 rabbits were treated for 7 days with any 1 of 5 different fluoroquinolones or artificial tears (Tears Natural Free) control. Epithelial thickness was significantly decreased (indicating superficial cell loss) after exposure to LEV, CIP, and GAT. Exposure to OFX also caused a decrease from baseline; however, it was not significant. Interestingly, these antibiotics all contained benzalkonium chloride (BAC). Moxifloxacin did not have a significant change in epithelial thickness. It does not contain BAC. None of the groups treated with fluoroquinolones had significant change in stromal thickness.[32]

By exposing human corneal stromal keratocytes (HCK) and endothe-

lial cells (HCE) monolayers to fluoroquinolones, the cytotoxic effects of these antibiotics were evaluated. The number of live cells remaining measured toxicity, which was quantitated using a calcein amalgam (AM) fluorescent bioassay. Varying concentrations of LEV, OFX, CIP, MOX, and GAT were tested. Levofloxacin was the least cytotoxic to both keratocytes and endothelial cells, followed by OFX, GAT, and MOX. The most toxic fluoroquinolone was CIP.[33]

■ Discussion

Fluoroquinolones have been attractive antibiotics for ophthalmic use because of their broad spectrum of bacterial coverage, their bactericidal effect, their ability to penetrate the cornea with topical administration, and their minimal side effects.

Since their introduction, several reviews have reported increased resistance to these antibiotics, creating gaps in their spectrum of coverage. As each newer generation of fluoroquinolone emerges, each has a broader range of gram-positive bacterial coverage (particularly to CIP- and OFX-resistant bacteria), and increased potency. This allows for not only the possibility of more concentrated levels of antibiotic to kill bacteria, thus faster healing times, but a broader spectrum of use for this new generation of fluoroquinolones.

Moxifloxacin and GAT have shown greater bacterial susceptibility and potency toward fluoroquinolone-resistant (resistant to CIP and OFX) *Staphylococcus aureus*. Of the 2 newer fourth-generation fluoroquinolones, MOX appears to have a higher percentage of susceptibility and potency. When compared to dual therapy tobramycin and gentamicin, both MOX and GAT showed increased coverage against *Streptococcus pneumoniae* and *Streptococcus viridans*. This may be due to their ability to block both DNA gyrase and DNA type IV topoisomerase.

Corneal penetration of topical GAT is equal, if not better, than other fluoroquinolones (MOX not tested). Moxifloxacin concentration has been shown to reach the MIC90 for most frequent gram-positive, gram-negative, atypical, and anaerobic bacteria in the aqueous humor by oral administration in uninflamed eyes. Because its intraocular concentration is higher than other fluoroquinolones tested (CIP and LEV, in particular), it is reasonable to assume MOX's action against bacterial pathogens will be stronger and quicker. The ocular penetration of topical MOX was even higher than OFX.

For the treatment of endophthalmitis, it is conceivable that oral GAT may act as adjunctive therapy to the commonly used intravitreal antibiotics. It was shown to have the highest penetration into the vitreous humor and lowest MIC for all common postoperative bacterial pathogens.

These newer-generation fluoroquinolones have shown to be equally

or less cytotoxic to corneal cells. Moxifloxacin may be less cytotoxic to corneal epithelial cells because it does not contain BAC. However, when tested on stromal keratocytes and endothelial cells, MOX, GAT, and OFX were equally toxic. Levofloxacin was the least toxic, and CIP was the most cytotoxic.

■ Conclusion

Gatifloxacin and MOX, the new fourth-generation fluoroquinolones, show promise in treating gram-positive bacteria that are currently resistant to existing fluoroquinolones. It is important to acknowledge they do not necessarily increase the gram-negative bacterial coverage. Given their increased penetration into the aqueous by topical administration and increased penetration into the vitreous by oral administration, they should be considered key antibiotics in the prophylaxis and treatment of bacterial infections in the anterior and posterior segments of the eye. However, one must be cautious and not be indiscriminate with their use, because the risk of building resistance always exists.

■ References

1. Hooper D. Quinolones. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases.* 5th ed. Philadelphia, PA: Churchill Livingstone; 2000:404–423.
2. Ambrose PG, Owens RC, Quintiliani R, et al. New generations of quinolones: with particular attention to levofloxacin. *Conn Med.* 1997;61:269–272.
3. Leibowitz HM. Antibacterial effectiveness of ciprofloxacin 0.3% ophthalmic solution in the treatment of bacterial conjunctivitis. *Am J Ophthalmol.* 1991;112:29S–33S.
4. Hyndiuk RA, Eiferman RA, Caldwell DR, et al. Comparison of ciprofloxacin ophthalmic solution 0.3% to fortified tobramycin-cefazolin in treating bacterial corneal ulcers. *Ophthalmology.* 1996;103:1854–1863.
5. O'Brien TP, Maguire MG, Fink NE, et al. Efficacy of ofloxacin vs. cefazolin and tobramycin in the therapy for bacterial keratitis. *Arch Ophthalmol.* 1995;113:1257–1265.
6. Ofloxacin monotherapy for the primary treatment of microbial keratitis: a double-masked, randomized, controlled trial with conventional dual therapy. The Ofloxacin Study Group. *Ophthalmology.* 1997;104:1902–1909.
7. McDermott ML, Tran TD, Cowden JW, et al. Corneal stromal penetration of topical ciprofloxacin in humans. *Ophthalmology.* 1993;100:197–200.
8. Diamond JP, White L, Leeming JP, et al. Topical 0.3% ciprofloxacin, norfloxacin, and ofloxacin in treatment of bacterial keratitis: a new method for comparative evaluation of ocular drug penetration. *Br J Ophthalmol.* 1995;79:606–609.
9. Yamada M, Mochizuki H, Yamada K, et al. Aqueous humor levels of topically applied levofloxacin in human eyes. *Curr Eye Res.* 2002;24:403–406.
10. Herbert EN, Pearce IA, McGalliard J, et al. Vitreous penetration of levofloxacin in the uninflamed phakic human eye. *Br J Ophthalmol.* 2002;86:387–389.
11. Fiscella RG, Nguyen TK, Cwik MJ, et al. Aqueous and vitreous penetration of levofloxacin after oral administration. *Ophthalmology.* 1999;106:2286–2290.

12. Goldstein MH, Kowalski RP, Gordon J. Emerging fluoroquinolone resistance in bacterial keratitis: a 5-year review. *Ophthalmology.* 1999;106:1313–1318.
13. Chaudry NA, Flynn HW, Murray TG, et al. Emerging ciprofloxacin-resistant Pseudomonas aeruginosa. *Am J Ophthalmol.* 1999;128:509–510.
14. Kunimoto DY, Sharma S, Garg P, et al. In vitro susceptibility of bacterial keratitis pathogens to ciprofloxacin: emerging resistance. *Ophthalmology.* 1999;106:80–85.
15. Garg P, Sharma S, Rao GN. Ciprofloxacin-resistant pseudomonas keratitis. *Ophthalmol.* 1999;106:1319–1323.
16. Mather R, Karenchak LM, Romanowski EG, et al. Fourth generation fluoroquinolones: new weapons in the arsenal ophthalmic antibiotics. *Am J Ophthalmol.* 2002;133:463–466.
17. Harvey TM, Kowalski RP, Karenchak LM, et al. An in vitro comparison of tobramycin and gentamicin to moxifloxacin and gatifloxacin using bacterial keratitis isolates [abstract]. Presented at: 2003 Annual Meeting of the Association for Research in Vision and Ophthalmology; May 4–9, 2003; Fort Lauderdale, Florida. Program Planner accessed at www.arvo.org.
18. Stroman DW, Clark L, Macke L, et al. Moxifloxacin activity against quinolone resistant staphylococcal ocular isolates. *IOVS.* 2001;42:S255.
19. Reiser BJ, Chuck RS. Penetration of fluoroquinolone antibiotics in the rabbit cornea as detected by confocal microscopy [abstract]. Presented at: 2003 Annual Meeting of the Association for Research in Vision and Ophthalmology; May 4–9, 2003; Fort Lauderdale, Florida. Program Planner accessed at www.arvo.org.
20. Batoosingh AL, Lee E, Welty DF, et al. Gatifloxacin 0.3% vs. ciprofloxacin 0.3%: ocular pharmacokinetic profile following topical application in rabbits [abstract]. Presented at: 2003 Annual Meeting of the Association for Research in Vision and Ophthalmology; May 4–9, 2003; Fort Lauderdale, Florida. Program Planner accessed at www.arvo.org.
21. Ciulla TA, Starr MB, Masket S. Bacterial endophthalmitis prophylaxis for cataract surgery: an evidence-based update. *Ophthalmology.* 2002;109:13–26.
22. Garcia-Saenz MC, Arias-Puente A, Fresnadillo MJ, et al. Human aqueous humor levels of oral ciprofloxacin, levofloxacin, and moxifloxacin. *J Cataract Refract Surg.* 2001;27:1969–1974.
23. Robertson SM, Sanders M, Jasheway D, et al. Penetration and distribution of moxifloxacin and ofloxacin into ocular tissues and plasma following topical ocular administration to pigmented rabbits [abstract]. Presented at: 2003 Annual Meeting of the Association for Research in Vision and Ophthalmology; May 4–9, 2003; Fort Lauderdale, Florida. Program Planner accessed at www.arvo.org.
24. Kowalski RP, Romanowski EG, Mah FS, et al. The prevention of bacterial endophthalmitis by topical moxifloxacin in a rabbit prophylaxis model [abstract]. Presented at: 2003 Annual Meeting of the Association for Research in Vision and Ophthalmology; May 4–9, 2003; Fort Lauderdale, Florida. Program Planner accessed at www.arvo.org.
25. Endophthalmitis Vitrectomy Study Group. Results of the Endophthalmitis Vitrectomy Study: a randomized trial of immediate vitrectomy and of intravenous antibiotics for the treatment of postoperative bacterial endophthalmitis. *Arch Ophthalmol.* 1995;113:1479–1496.
26. el-Massry A, Meredith TA, Aguilar HE, et al. Aminoglycoside levels in the rabbit vitreous cavity after intravenous administration. *Am J Ophthalmol.* 1999;122:684–689.
27. Aguilar HE, Meredith TA, Shaarawy A, et al. Vitreous cavity penetration of ceftazidime after intravenous administration. *Retina.* 1995;15:154–159.
28. Speaker MG, Milch FA, Shah MK, et al. Role of external bacterial flora in the pathogenesis of acute postoperative bacterial endophthalmitis. *Ophthalmology.* 1991;98:639–649.
29. Hariprasad SM, Mieler WF, Holz ER. Vitreous penetration of orally administered gatifloxacin in humans. *Trans Am Ophthalmol Soc.* 2002;100:153–160.
30. Tepidino ME, Jensen HG. Efficacy and safety of gatifloxacin 0.3% ophthalmic solution

compared to ofloxacin 0.3% for treatment of acute bacterial conjunctivitis [abstract]. Presented at 2002 Joint Meeting of the American Academy of Ophthalmology and Pan-American Association of Ophthalmology; October 20–23, 2002; Orlando, Florida. Scientific Poster 165.

31. Gross RD, Silas P, Oshman S, et al. A comparison of the safety and efficacy of moxifloxacin and ciprofloxacin in the treatment of presumed bacterial conjunctivitis in neonatal patients [abstract]. 2003 Annual Meeting and Program Planner accessed at www.arvo.org. Association for Research in Vision and Ophthalmology.
32. Kim AS, McCulley JP, Cavanaugh HD, et al. Evaluation of the effects of topical ophthalmic fluoroquinolones (FQ) on the cornea using in vivo confocal microscopy [abstract]. Presented at: 2003 Annual Meeting of the Association for Research in Vision and Ophthalmology; May 4–9, 2003; Fort Lauderdale, Florida. Program Planner accessed at www.arvo.org.
33. Skelnik DL, Clark LA, Bezwada P. Effect of drug concentration and exposure time to levofloxacin, ofloxacin, ciprofloxacin, gatifloxacin, and moxifloxacin on human corneal endothelial cells and keratocytes [abstract]. Presented at: 2003 Annual Meeting of the Association for Research in Vision and Ophthalmology; May 4–9, 2003; Fort Lauderdale, Florida. Program Planner accessed at www.arvo.org.