What are the Best Topical Agents for Prophylaxis?

The top antibiotics are those that are most effective against the majority of bacteria, rapidly kill the offending organisms, penetrate the eye well, and are nontoxic.

BY CHRISTOPHER N. TA, MD

Minimizing the risk of postoperative endophthalmitis requires the elimination of or a significant reduction in the bacterial flora that are found on the ocular surface at the time of surgery and during the immediate postoperative period. The major source of bacteria that cause endophthalmitis is a patient's own eyelids and conjunctiva.[1,2] Applying povidone-iodine at the time of surgery can decrease ocular bacteria.[3-14] Topical antibiotics administered for several days and immediately prior to surgery provide an additional killing of bacteria beyond the effects of povidone-iodine,[7,8,13-16] although a prospective randomized study has yet to prove that the use of topical antibiotics reduces the risk of endophthalmitis. Regardless, almost all ophthalmologists prescribe topical antibiotics for patients undergoing intraocular surgery.

Ophthalmologists also use antibiotics postoperatively to minimize the risk of bacteria's entering the eye via the surgical wound. This is of particular concern with clear corneal incisions, because the wound may not be watertight.[17,18] In addition, frequently applying a topical antibiotic may allow the drug to achieve levels in the aqueous that are high enough to kill the bacteria that contaminate the anterior chamber at the time of surgery.[19-29] According to a rabbit study,[30] Vigamox (Alcon Laboratories, Inc., Fort Worth, TX) administered in both the pre- and postoperative period can prevent the development of endophthalmitis following inoculation with *Staphylococcus aureus*.

The ideal topical antibiotics for minimizing the risk of postoperative endophthalmitis must have the following characteristics: broad-spectrum coverage of both gram-positive and gram-negative bacteria; bacteriocidal properties for quick kills of bacteria upon contact; and excellent penetration to achieve intraocular levels that are sufficiently high to kill the offending bacteria. The agent must also be nontoxic to the ocular surface and cost effective.

Several classes of antibiotics are currently available in the US and include the combination therapy of polymixin B and trimethoprim, the aminoglycosides, and the fluoroquinolones. Many ophthalmic ointments are also available, including erythromycin and the combination therapy of bacitracin and polymyxin B. Of all of these antibiotics, fluoroquinolones, in my opinion, may be the most appropriate antibiotics for endophthalmitis prophylaxis. The greatest advantages of these drugs over other classes of antibiotics are that they provide broad-spectrum coverage, are bacteriocidal and nontoxic, and penetrate the anterior chamber well. In contrast, other antibiotics such as polymyxin B and trimethoprim are bacteriostatic, and aminoglycosides carry some risk of toxicity.

Among the commercially available topical ophthalmic fluoroquinolones, ciprofloxacin and ofloxacin have limited gram-positive coverage. The newer fluoroquinolones—specifically Quixin (Santen Inc., Napa, CA), Zymar (Allergan, Inc., Irvine, CA), and Vigamox—have enhanced activity toward gram-positive pathogens while maintaining broad-spectrum coverage against gram-negative organisms.[31-36] They interfere with both topoisomerase II and IV, and bacterial resistance appears to be lower since mutations of both enzymes are necessary.[32]

After reviewing the published literature for the most desirable properties of commercially available antibiotics, I found some minor differences between them. In general, the three most recently FDA-approved antibiotics (Quixin, Zymar, and Vigamox) are excellent antibiotics. Some of their important characteristics include low resistant rates, high efficacy and kill time, reduced surface toxicity, and effective aqueous penetration. This article discusses the off-label use of the approved products Quixin, Zymar, and Vigamox.

ANTIBIOTIC SUSCEPTIBILITY

Several recently published studies have demonstrated excellent efficacy for Quixin, Zymar, and Vigamox against common ocular pathogens.[33,34,36-42] One potential limitation in susceptibility is that the determination is based on the serum level of the drug and not its tear or aqueous level. For that reason, although an antibiotic may be considered resistant, it may still be effective at killing bacteria given the high level of the medication in the tear film compared with the serum. Another limitation is the variations in resistance pattern based on geographic location. Consequently, a comprehensive study involving multiple sites throughout the US will have much more reliable data than one from a single center. For instance, the Tracking Resistance in the United States Today (TRUST) study[43] is a surveillance report of more than 70,000 isolates that were collected from over 200 institutions since 1999. In this comprehensive study, 99% of *Streptococcus pneumoniae* remained susceptible to Quixin despite more than 9 years of extensive systemic use. Currently, ocular isolates are collected and analyzed to determine trends in resistance for the commonly prescribed topical antibiotics in the TRUST study.

EFFICACY IN KILLING BACTERIA

Fluoroquinolones as a class effectively kill bacteria, unlike bacteriostatic antibiotics, which inhibit bacterial growth. A fluoroquinolone's efficacy is dependent upon its concentration; the higher the concentration, the greater the kill rate.[44] Frequent dosing of the medication during a short period of time may therefore be more appropriate than infrequent long-term use.

As with any topical antibiotic, the goal is to eradicate the bacteria as quickly as possible. There is some recent evidence suggesting that the preservative benzalkonium chloride (BAK) may have a synergistic effect in improving an agent's kill time.[45-48] A recent in vitro study[45] demonstrated that 0.005% BAK alone or 0.3% gatifloxacin with 0.005% BAK (Zymar) kills *Staphylococcus epidermidis* and *S. aureus* within 1 hour, compared with 4 hours for 0.5% moxifloxacin alone (Vigamox)[45] (Figure 1). Another study demonstrated similar results, with Zymar eliminating all *Staphylococcus* within 60 minutes,
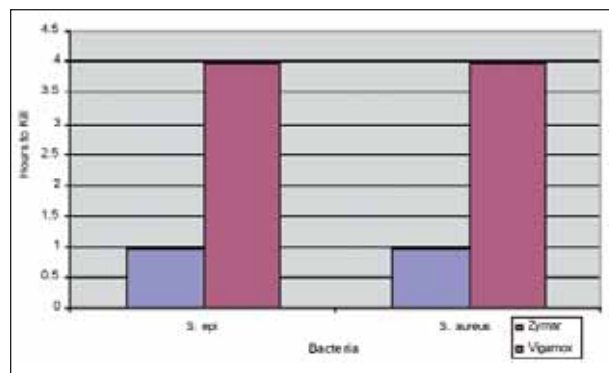

Figure 1. An in vitro laboratory study demonstrating time-kill for *S. epidermidis* and *S. aureus*. Both bacteria are killed 1 hour following exposure to Zymar, compared to 4 hours for Vigamox.
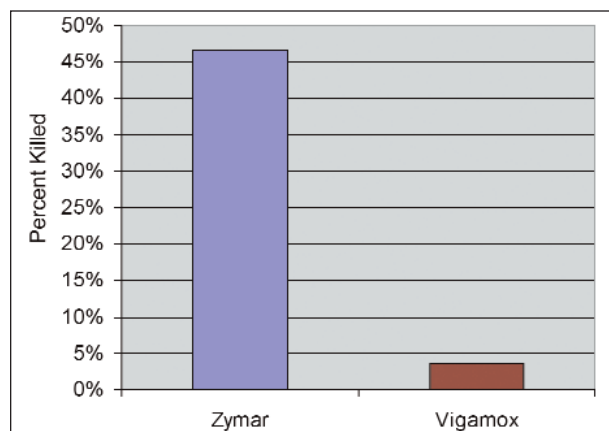

Figure 2. The percentage of bacteria eliminated from the ocular surface following a 1-hour application of antibiotics is shown.

whereas 50% of the bacteria treated with Vigamox remained.[46]

Other clinical studies have confirmed the slow kill rate of Vigamox (Figure 2). In a study[47] of 60 patients undergoing intraocular surgery, after a 1-hour application of Vigamox preoperatively, there was no effect on killing bacterial flora on the ocular surface. At baseline, 55% of eyes had positive cultures compared with 53% of the eyes after treatment with Vigamox for 1 hour. In contrast, my colleagues and I will report a study at this year's ARVO Annual Meeting in which a 1-hour preoperative application of Zymar significantly decreased the rate of bacterial contamination of the conjunctiva in patients undergoing intraocular surgery from a baseline of 75% to 40%. These studies suggest that antibiotics preserved with BAK may be much more efficacious in the rapid killing of bacteria compared with antibiotics without BAK. Quixin, which is 0.5% levofloxacin and 0.005% BAK, and Zymar therefore may kill bacteria much quicker than Vigamox.
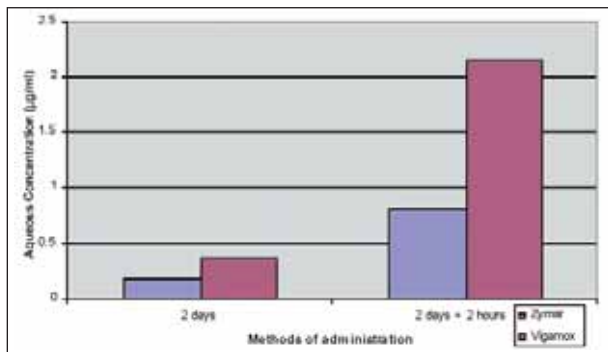
Figure 3. The comparison of the aqueous penetration of Zymar to Vigamox is shown. The study's investigators administered antibiotics q.i.d. for 2 days prior to surgery in one group. In another group, both drugs were given to patients q.i.d. for 2 days, with three additional applications 2 hours immediately before surgery. According to the study, Zymar and Vigamox achieved levels above the minimal inhibitory concentration (MIC) (range, 0.09 to 0.38 μg/mL for most pathogens for the 2-days-plus-2-hours group). (Data adapted from Ong-Tone).[64]

TOXICITY

In general, fluoroquinolones have an excellent safety profile, which is important given the millions of prescriptions written for this class of drugs every year. A concern with any topical ophthalmic medication is the preservative BAK. A study by Cha et al demonstrated in tissue culture that BAK can cause epithelial cell death that is dependent on concentration and duration of exposure.[47] Although Vigamox does not have BAK, recently published research[49-51] suggests that Vigamox may be toxic to the ocular surface. In a double-masked, prospective study,[48] 28 eyes of 14 patients were randomized to receive either Zymar or Vigamox. The investigators reported that the eyes that received Vigamox had a significantly higher degree of conjunctival injection, discomfort, and corneal epithelial cell loss compared to eyes treated with Zymar. This finding was confirmed by an in vitro study[49] in which the exposure of corneal and conjunctival epithelial cells to different concentrations of Vigamox resulted in poor cellular migration and adhesion. Furthermore, eyes exposed to Vigamox achieved a significant reduction in the production of collagen type IV and fibronectin than eyes exposed to Zymar. Effects on cellular migration, proliferation, and production of collagen and fibronectin are important for wound healing and the health of the ocular surface. These in vitro findings were confirmed by animal studies[50] in which incisions were created in rabbit corneas and exposed to either Zymar or Vigamox. Eyes exposed to Vigamox demonstrated a decrease in collagen IV production, disorganized and slower wound healing, inhibition of cellular proliferation, and a loss of the normal structure of the basal lamina.

In contrast to the aforementioned studies, Burka et al[51] conducted a prospective, masked, randomized study comparing Zymar and Vigamox in patients undergoing PRK. The investigators found that eyes treated with Vigamox healed faster and had smaller epithelial defects compared with those treated with Zymar. Of course, no corneal incision is created during the refractive procedure. In another PRK study,[52] no difference was found with respect to haze, visual acuity, or epithelial healing between eyes treated with Zymar and Vigmox. Finally, Walter and Tyler[53] reported two patients with worsening and persistent corneal ulcers as well as endothelial cell dysfunction while on Vigamox. The patients' conditions resolved after the discontinuation of Vigamox and the initiation of Zymar and corticosteroid treatment.

Adverse side effects are rare with the topical fluoroquinolones. For most patients, Quixin, Zymar, and Vigamox are safe medications. In patients with compromised wound healing ability—such as those with ocular surface disease, dry eyes, and neurotrophic corneas, among other conditions—the surgeon needs to consider the potentially toxic effects of Vigamox.

AQUEOUS PENETRATION

Occasionally, bacteria can gain access to the anterior chamber during the perioperative period. If this happens, it is important to choose an antibiotic that can penetrate the cornea and achieve levels in the aqueous high enough to eliminate the bacteria. All three of the most recent fluoroquinolones have excellent tissue penetration. Quixin achieves a high drug level in the tear film after a single dose. The peak level was 221.0 μg/mL 15 minutes following the drug's administration, and the level remained above the (MIC) of 2.0 μg/mL for more than 6 hours (6.6 μg/mL).[54] Furthermore, Quixin can achieve levels in the aqueous above the MIC following three to four applications prior to surgery.[55-61] Similar studies[62-65] of Zymar and Vigamox demonstrated their excellent penetration into the aqueous humor. In directly comparative studies,[62-65] Vigamox has been shown to have better penetration than Zymar and to achieve higher drug levels in the aqueous humor. Quixin, Zymar, and Vigamox all achieved aqueous levels above the MIC following typical preoperative application.

Figure 3 summarizes the results of a study by Ong-Tone.[64]

IN SUMMARY

Quixin, Zymar, and Vigamox all provide broad-spectrum coverage against both gram-positive and gram-negative bacteria. Thus far, bacterial resistance against these fluoroquinolones is uncommon. As a class, these

fluoroquinolones are well tolerated with minimal toxicity, and they penetrate the aqueous humor well.

The choice of antibiotic depends on the clinical situation. To quickly kill bacteria, those drugs preserved with BAK, such as Zymar and Quixin, may be indicated. Vigamox has better penetration into the aqueous humor, however, and may be more appropriate in eyes for which bacterial contamination of the anterior chamber is likely, although some evidence suggests that the drug may impair wound healing.

Based upon the literature mentioned herein, the later generations of topical fluoroquinolones represent the best of the available antibiotics. ■

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1. Bannerman TL, Rhoden DL, McAllister SK, et al. The source of coagulase-negative staphylococci in the Endophthalmitis Vitrectomy Study. A comparison of eyelid and intraocular isolates using pulsed-field gel electrophoresis. *Arch Ophthalmol*. 1997;115:357-361.

2. Speaker MG, Milch FA, Shah MK, et al. Role of external bacterial flora in the pathogenesis of acute postoperative endophthalmitis. *Ophthalmology*. 1991;98:639-649; discussion 650.

3. Apt L, Isenberg S, Yoshimori R, Paez J. Chemical preparation of the eye in ophthalmic surgery III: effect of povidone-iodine on the conjunctiva. *Arch Ophthalmol*. 1984;102:728-729.

4. Hale M. Povidone-iodine in ophthalmic surgery. *Ophthalmic Surgery*. 1970;1:9-13.

5. Caldwell D, Kastl P, Cook J, Simon J. Povidone-iodine: its efficacy as a preoperative conjunctival and periocular preparation. *Ann Ophthalmol*. 1984;16:577-580.

6. Alp B, Elibol O, Sargon M, et al. The effect of povidone iodine on the corneal endothelium. *Cornea*. 2000;19:546-550.

7. Grimes S, Mein C, Trevino S. Preoperative antibiotic and povidone-iodine preparation of the eye. *Ann Ophthalmol*. 1991;23:263-266.

8. Schmitz S, Dick H, Krummenauer F, Pfeiffer N. Endophthalmitis in cataract surgery: results of a German survey. *Ophthalmology*. 1999;106:1869-1877.

9. Dereklis DL, Bufidis TA, Tsiakiri EP, Palassopoulos SI. Preoperative ocular disinfection by the use of povidone-iodine 5%. *Acta Ophthalmol (Copenh)*. 1994;72:627-630.

10. Speaker MG, Menikoff JA. Prophylaxis of endophthalmitis with topical povidone-iodine. *Ophthalmology*. 1991;98:1769-1775.

11. Miño de Kaspar H, Singh G, Egbert PR, et al. Ten-fold reduction of conjunctival bacterial contamination rate using a combined 3-day application of topical ofloxacin and iodine irrigation in patients undergoing anterior segment intraocular surgery. Paper presented at: The ARVO Annual Meeting; May 5, 2003; Fort Lauderdale, FL.

12. Miño de Kaspar H, Chang R, Egbert P, et al. Greater elimination of conjunctival bacteria after preoperative irrigation with 10cc of 5% povidone-iodine. Paper presented at: The AAO Annual Meeting; October 22, 2002; Orlando, FL.

13. Isenberg SJ, Apt L, Yoshimori R, Khwarg S. Chemical preparation of the eye in ophthalmic surgery. IV. Comparison of povidone-iodine on the conjunctiva with a prophylactic antibiotic. *Arch Ophthalmol*. 1985;103:1340-1342.

14. Grimes SR, Mein CE, Trevino S. Preoperative antibiotic and povidone-iodine preparation of the eye. *Ann Ophthalmol*. 1991;23:263-266.

15. De Kaspar HM, Chang RT, Shriver EM, et al. Three-day application of topical ofloxacin reduces the contamination rate of microsurgical knives in cataract surgery: a prospective randomized study. *Ophthalmology*. 2004;111:1352-1355.

16. Ta CN, Egbert PR, Singh K, et al. Prospective randomized comparison of 3-day versus 1-hour preoperative ofloxacin prophylaxis for cataract surgery. *Ophthalmology*. 2002;109:2036-2041.

17. Herretes S, Stark WJ, Pirouzmanesh A, et al. Inflow of ocular surface fluid into the anterior chamber after phacoemulsification through sutureless corneal cataract wounds. *Am J Ophthalmol*. 2005;14:737-740.

18. Taban M, Sarayba MA, Ignacio TS, et al. Ingress of India ink into the anterior chamber through sutureless clear corneal cataract wounds. *Arch Ophthalmol*. 2005;123:643-648.

19. Mistlberger A, Ruckhofer J, Raithel E, et al. Anterior chamber contamination during cataract surgery with intraocular lens implantation. *J Cataract Refract Surg*. 1997;23:1064-1069.

20. Dickey J, Thompson K, Jay W. Anterior chamber aspirate cultures after uncomplicated cataract surgery. *Am J Ophthalmol*. 1991;112:278-282.

21. Soto A, Mendivil M. The effect of topical povidone-iodine, intraocular vancomycin, or both on aqueous humor cultures at the time of cataract surgery. *Am J Ophthalmol*. 2001;131:293-300.

22. Samad A, Solomon L, Miller M, Mendelson J. Anterior chamber contamination after uncomplicated phacoemulsification and intraocular lens implantation. *Am J Ophthalmol*. 1995;120:143-150.

23. Tervo T, Ljungberg P, Kautiaimen T, et al. Prospective evaluation of external ocular microbioal growth and aqueous humor contamination during cataract surgery. *J Cataract Refract Surg*. 1999;25:65-71.

24. Duch-Samper AM, Menezo JL, Hurtado-Sarrio M, et al. Anterior chamber contamination following uncomplicated cataract surgery: comparative results using intravenous imipenem. *Ophthalmic Surg Lasers*. 1996;27:1005-1011.

25. Leong JK, Shah R, McCluskey PJ, et al. Bacterial contamination of the anterior chamber during phacoemulsification cataract surgery. *J Cataract Refract Surg*. 2002;28:826-833.

26. Ariyasu RG, Nakamura T, Trousdale MD, Smith RE. Intraoperative bacterial contamination of the aqueous humor. *Ophthalmic Surg*. 1993;24:367-373; discussion: 373-374.

27. Assalian A, Thompson P, St-Antoine P, et al. Anterior chamber fluid contamination after uncomplicated phacoemulsification. *J Cataract Refract Surg*. 1995;21:539-542.

28. Beigi B, Westlake W, Mangelschots E, et al. Perioperative microbial contamination of anterior chamber aspirates during extracapsular cataract extraction and phacoemulsification. *Br J Ophthalmol*. 1997;81:953-955.

29. Ta CN, Egbert PR, Singh K, et al. The challenge of determining aqueous contamination rate in anterior segment intraocular surgery. *Am J Ophthalmol*. 2004;137:662-667.

30. Kowalski RP, Romanowski EG, Mah FS, et al. Topical prophylaxis with moxifloxacin prevents endophthalmitis in a rabbit model. *Am J Ophthalmol*. 2004;138:33-37.

31. Alfonso E, Crider J. Ophthalmic infections and their anti-infective challenges. *Surv Ophthalmol*. 2005;50(suppl 1):S1-S6.

32. Ruiz J. Mechanisms of resistance to quinolones: target alterations, decreased accumulation and DNA gyrase protection. *J Antimicrob Chemother*. 2003;51:1109-1117.

33. Epstein SP, Bottone EJ, Asbell PA. Susceptibility testing of clinical isolates of *Pseudomonas aeruginosa* to levofloxacin, moxifloxacin, and gatifloxacin as a guide to treating *Pseudomonas* ocular infections. *Eye Contact Lens*. 2006;32:240-244.

34. Kotlus BS, Wymbs RA, Vellozzi EM, Udell IJ. In vitro activity of fluoroquinolones, vancomycin, and gentamicin against methicillin-resistant *Staphylococcus aureus* ocular isolates. *Am J Ophthalmol*. 2006;142:726-729.

35. Oliveira AD, D'Azevedo PA, Francisco W, Hofling-Lima ALCAHP. In vitro activity of fluoroquinolones against ocular bacterial isolates in São Paulo, Brazil. *Cornea*. 2007;26:194-198.

36. Miño de Kaspar H, Koss MJ, He L, et al. Antibiotic susceptibility of preoperative normal conjunctival bacteria. *Am J Ophthalmol*. 2005;139:730-733.

37. Begum NN, Al-Khattaf AS, Al-Mansouri SM, et al. A study of bacterial isolates from corneal specimens and their antibiotic resistance profile. *Saudi Med J*. 2006;27:41-45.

38. Marangon FB, Miller D, Muallem MS, et al. Ciprofloxacin and levofloxacin resistance among methicillin-sensitive *Staphylococcus aureus* isolates from keratitis and conjunctivitis. *Am J Ophthalmol*. 2004;137:453-458.

39. Miller D, Alfonso EC. Comparative in vitro activity of levofloxacin, ofloxacin, and ciprofloxacin against ocular streptococcal isolates. *Cornea*. 2004;23:289-293.

40. Morrissey I, Burnett R, Viljoen L, Robbins M. Surveillance of the susceptibility of ocular bacterial pathogens to the fluoroquinolone gatifloxacin and other antimicrobials in Europe during 2001/2002. *J Infect*. 2004;49:109-114.

41. Smitha S, Lalitha P, Prajna VN, Srinivasan M. Susceptibility trends of *Pseudomonas* species from corneal ulcers. *Indian J Med Microbiol*. 2005;23:168-171.

42. Ta CN, Chang RT, Singh K, et al. Antibiotic resistance patterns of ocular bacterial flora: a prospective study of patients undergoing anterior segment surgery. *Ophthalmology*. 2003;110:1946-1951.

43. Ta CN, Sahm DF, Ingerman A. Levofloxacin susceptibility in multi-drug-resistant *S. pneumoniae* isolates from the nationwide TRUST surveillance study, 2000-2004. Paper presented at: The ARVO Annual Meeting; May 3, 2006; Fort Lauderdale, FL.

44. Wispelwey B. Clinical implications of pharmacokinetics and pharmacodynamics of fluoroquinolones. *Clin Infect Dis*. 2005;41(suppl 2):S127-S135.

45. Kowalski RP, Kowalski BR, Romanowski EG, et al. The in vitro impact of moxifloxacin and gatifloxacin concentration (0.5% vs 0.3%) and the addition of benzalkonium chloride on antibacterial efficacy. *Am J Ophthalmol*. 2006;142:730-735.

46. Eser I, Hyon J, Hose S, O'Brien TP. Comparative antimicrobial efficacy of preserved and preservative-free topical fourth generation fluoroquinolones against various strains of

Staphylococcus. Paper presented at: The ARVO Annual Meeting; April 29, 2004; Fort Lauderdale, FL.

47. Cha SH, Lee JS, Oum BS, Kim CD. Corneal epithelial cellular dysfunction from benzalkonium chloride (BAC) in vitro. *Clin Experiment Ophthalmol*. 2004;32:180-184.

48. Kaufman SC, Rusinek C, Salahuddin A, et al. Comparison of the biocompatibility of gatifloxacin 0.3% and moxifloxacin 0.5%. *Cornea*. 2006;25(suppl 2):S31-S44.

49. McDermott M, Wheater M. In vitro comparison of the effects of clinically available ophthalmic solutions of gatifloxacin 0.3% and moxifloxacin 0.5% on human corneal and conjunctival epithelial cell adhesion and migration and on collagen type IV protein expression. *Cornea*. 2006;25(suppl 2):S25-S30.

50. Stern ME, Gao J, Beuerman RW, et al. Effects of fourth-generation fluoroquinolones on the ocular surface, epithelium, and wound healing. *Cornea*. 2006;25(suppl 2):S12-S24.

51. Burka JM, Bower KS, Vanroekel RC, et al. The effect of fourth-generation fluoroquinolones gatifloxacin and moxifloxacin on epithelial healing following photorefractive keratectomy. *Am J Ophthalmol*. 2005;140:83-87.

52. Yee RW, Setabutr P, Foltermann MO, et al. The effects of topical moxifloxacin 0.5% ophthalmic solution and gatifloxacin 0.3% solution on corneal healing after bilateral photorefractive keratectomy. *Cornea*. 2006;25(9 Suppl 2):S8-S11.

53. Walter K, Tyler ME. Severe corneal toxicity after topical fluoroquinolone therapy: report of two cases. *Cornea* 2006;25:855-857.

54. Raizman MB, Rubin JM, Graves AL, Rinehart M. Tear concentrations of levofloxacin following topical administration of a single dose of 0.5% levofloxacin ophthalmic solution in healthy volunteers. *Clin Ther*. 2002;24:1439-1450.

55. Healy DP, Holland EJ, Nordlund ML, et al. Concentrations of levofloxacin, ofloxacin, and ciprofloxacin in human corneal stromal tissue and aqueous humor after topical administration. *Cornea*. 2004;23:255-263.

56. Kobayakawa S, Tochikubo T, Tsuji A. Penetration of levofloxacin into human aqueous humor. *Ophthalmic Res*. 2003;35:97-101.

57. Koch HR, Kulus SC, Roessler M, et al. Corneal penetration of fluoroquinolones: aqueous humor concentrations after topical application of levofloxacin 0.5% and ofloxacin 0.3% eyedrops. *J Cataract Refract Surg*. 2005;31:1377-1385.

58. Levine JM, Noecker RJ, Lane LC, et al. Aqueous penetration of gatifloxacin and levofloxacin into the rabbit aqueous humor following topical dosing. *J Ocul Pharmacol Ther*. 2004;20:210-216.

59. Mizuki N, Watanabe Y, Miyamoto M, et al. Flomoxef sodium and levofloxacin concentrations in aqueous humor. *Ocul Immunol Inflamm*. 2005;13:229-234.

60. 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.

61. Yamada M, Mochizuki H, Yamada K, et al. Aqueous humor levels of topically applied levofloxacin, norfloxacin, and lomefloxacin in the same human eyes. *J Cataract Refract Surg*. 2003;29:1771-1775.

62. Kim DH, Stark WJ, O'Brien TP. Ocular penetration of moxifloxacin 0.5% and gatifloxacin 0.3% ophthalmic solutions into the aqueous humor following topical administration prior to routine cataract surgery. *Curr Med Res Opin*. 2005;21:93-94.

63. Levine JM, Noecker RJ, Lane LC, et al. Comparative penetration of moxifloxacin and gatifloxacin in rabbit aqueous humor after topical dosing. *J Cataract Refract Surg*. 2004;30:2177-2182.

64. Ong-Tone L. Aqueous humor penetration of gatifloxacin and moxifloxacin eyedrops given by different methods before cataract surgery. *J Cataract Refract Surg*. 2007;33:59-62.

65. Solomon R, Donnenfeld ED, Perry HD, et al. Penetration of topically applied gatifloxacin 0.3%, moxifloxacin 0.5%, and ciprofloxacin 0.3% into the aqueous humor. *Ophthalmology*. 2005;112:466-469.