

Treatment and Prevention of Ocular Bacterial Infections in Asia Part I: The Changing Landscape

Cesar Espiritu^{1,2,3}

¹Department of Ophthalmology, The Manila Doctor's Hospital, ²Cataract Section, Department of Ophthalmology, The Medical City, and ³The American Eye Center, Mandaluyong City, The Philippines

Asia faces unique challenges in the treatment of ocular infections. Aside from regional differences in the epidemiology of disease and bacterial resistance, culture and tradition colour the landscape, playing an important role in approaches to health care delivery. Part I of this 2-part series describes current local and regional trends for ocular infections and microbial resistance in Asia, and how these factors shape the need for modern solutions to improve patient outcomes. Part II will examine the limitations of older antibiotics, the evolution of the newly developing fluoroquinolones, and the role of the fourth-generation fluoroquinolone, moxifloxacin.

Key words: Anti-bacterial agents, Asia, Drug resistance, bacterial, Epidemiology, Eye infections, Fluoroquinolones

Asian J Ophthalmol. 2008;10:380-4

Cultural and Regional Approaches to Treatment

Regional trends in socioeconomic development underlie much of Asia's changing landscape. Many Asian people still reside and work in the relative isolation of rural areas, where delays in reaching needed medical care and supplies have a profound impact on health and the quality of life. Grassroots local health workers are often the only people available to deliver immediate treatment. These individuals have been shown to greatly impact the prevention of post-traumatic corneal ulceration after corneal abrasion, for example, in isolated rural villages of Bhutan, but only if equipped with appropriate antimicrobial agents.¹

A frequent source of ocular infection in these regions is trauma. A 2-year survey in the Kathmandu Valley region of Nepal described the almost epidemic incidence of 4% ocular trauma and 2% corneal abrasion and ulcers in the population. When antibiotic prophylaxis was initiated within 18 hours of injury, no patients progressed to a corneal ulcer. However, 3.9% of patients who presented 18 to 24 hours after injury, and 28.6% who those presented 24 to 48 hours, after injury subsequently progressed to corneal ulceration. This study showed a high prevention rate for post-traumatic corneal

ulceration in this rural setting when antibiotic treatment (in this case, chloramphenicol ointment) was initiated in a timely fashion.² Changing trends in China over a 30-year period showed that, from the 1970s, ordinary trauma outweighed occupational trauma as a cause of corneal blindness, and rural and urban areas were equally represented. Avoiding infection after foreign body injury to the cornea was reportedly a primary concern.³

Predominantly rural areas may also be inclined to use traditional eye medicines (TEM) for the treatment of corneal ulcers, particularly after trauma. In one area of South India, 47.7% of patients presenting with a corneal ulcer had used TEM, with no differentiation for age and sex. These treatments included human breast milk, leafy matter, castor oil, and hen's blood, a circumstance that underscores the need for better education of the population and access to appropriate medical treatments. These local customs persisted despite a population otherwise educated about modern advances, such as cataract surgery and intraocular lens (IOL) implantation.⁴

Regional Epidemiology of Ocular Bacterial Keratitis

The profile of microorganisms causing bacterial keratitis may vary regionally, making data describing local trends in bacterial susceptibility useful for the selection of appropriate topical antibiotics. While the proportion of selected pathogens may vary

Correspondence: Dr Cesar Ramon G Espiritu, American Eye Center, Level 5 Shangri-La Plaza, EDSA Cor, Shaw Blvd, Ortigas Center, Mandaluyong City 1500, The Philippines.
Tel: (63 2) 636 0762;
E-mail: espiritu@eyemd.net

with region, the data indicate that effective antimicrobial agents, along with easier availability and access to medical care are needed.

In The Philippines, a 30-year survey (from 1971 to 2001) by Valenton,^{5,6} studied the various causes of central microbial keratitis in 4170 patients. In this survey, bacteria accounted for 52% of infections (n = 2178), followed by viruses for 22% (n = 915), fungi for 13% (n = 540), and finally amoeba for only 0.2% (n = 8). The remaining infections (n = 529) were of undetermined aetiology. Of the documented bacterial aetiologies, *Moraxella* spp (29%), *Pseudomonas* spp (28%), and *Staphylococcus* spp (25%) comprised the majority of causative organisms. In this population of patients, trauma (76.6%) was the leading predisposing factor.

In Taiwan, a 12-year study (from 1994 to 2005) examined in vitro antibiotic susceptibility trends from bacterial keratitis isolates.⁷ Of the 272 identified pathogens, *Pseudomonas* spp were identified most often (46.7%), followed by *Staphylococcus* spp (11%), *Propionibacterium* spp (8.1%), *Streptococcus* spp (7.6%), and non-tuberculous *Mycobacteria* (6.6%). During this period, no significant changes occurred in microbial sensitivities for *Staphylococcus* spp, *Streptococcus* spp, *Pseudomonas* spp, or non-tuberculous *Mycobacteria* spp, with 95.8% of gram-negative organisms remaining susceptible to the fluoroquinolone, ciprofloxacin.⁷ A study from Singapore (from 1992 to 1993) also found that bacterial keratitis was most commonly due to gram-negative bacteria (80.4%) with *Pseudomonas aeruginosa* the most frequent organism overall, and the most frequent in contact lens ulcers (78.6%).⁸

However, in Japan, during the 5-year period from 1999 to 2003, among 99 different organisms isolated from bacterial keratitis samples, the majority (77.8%) were gram-positive bacteria, with only 18.2% being gram-negative bacteria (and 1 case of *Acanthamoeba* spp).⁹ The primary risk factor for microbial keratitis in this study was contact lens wear, present in 54.5% of cases. In contrast, a study from South India showed that when microbial keratitis was associated with contact lens wear, *Pseudomonas* spp were the most commonly isolated organisms (52%).¹⁰

In rural Bangladesh, *Streptococcus pneumoniae* and *Pseudomonas* spp were described as the most common causes of microbial keratitis, overall,¹¹ but tropical developing countries, such as India and Ghana, report that fungi cause most cases. *Pseudomonas* spp were the most frequently isolated bacteria from suppurative corneal ulcers in Ghana, but streptococci were the most common in India, emphasising that knowledge of local aetiological factors is essential for the management of infectious keratitis.¹² Interestingly, a fundamentally different profile was found in a worldwide survey of infectious keratitis after LASIK, where atypical mycobacteria and staphylococci were most frequently implicated.¹³

Acanthamoeba Keratitis

Keratitis due to *Acanthamoeba* spp occurs infrequently, but may have a shifting prevalence in rural areas. In Valenton's 30-year survey of *Cornea and External Eye Disease Problems in The Philippines*, *Acanthamoeba* spp was identified in only 8 of 4170 eyes (0.2%) with central keratitis.⁵ In South India, *Acanthamoeba* keratitis accounted for 1.04% of corneal ulcers from rural areas during a 3-year period, with most (72.7%) occurring in patients younger than 51 years. Agricultural workers accounted for 78.79% of patients, and all patients had a history of corneal injury, 84.85% due to mud. TEMs had been used by approximately one-third of these patients. Delayed diagnosis and inappropriate antimicrobial therapy were identified as primary risk factors for a poor visual outcome.¹⁴

Conjunctivitis

The micro-organisms commonly causing acute bacterial conjunctivitis in adults in the USA include *Staphylococcus aureus*, *S pneumoniae*, gram-positive anaerobes (*Peptostreptococcus* spp) *Haemophilus* spp (*H influenzae* and *H influenzae* biogroup *aegyptius*), and *Streptococcus pyogenes*, with *H influenzae*, *S pneumoniae* and *Moraxella catarrhalis* being most common in children. Chronic conjunctivitis may be caused by *Moraxella lacunata*, *Klebsiella pneumoniae*, *Serratia marcescens*, and *Escherichia coli*.¹⁵ In The Philippines, Valenton's study also showed that among bacterial conjunctivitis, *Staphylococcus* spp was the primary cause, with an incidence of 44.2%.^{5,6} This was followed by *Moraxella* spp (22.6%), *Neisseria gonorrhoeae* (18.5%), and *Haemophilus* spp (12.2%). *S pneumoniae*, on the other hand, accounted for only 1.3% of cases.

The treatment of conjunctivitis in developing regions worldwide may be complicated by profound differences in the availability of medical care, socioeconomic factors, and culture. An epidemic outbreak of acute haemorrhagic conjunctivitis in rural communities is likely to have profound economic consequences.¹⁶ In one study, positive cultures for superinfection were found in 86% of patients with corneal ulceration, with *P aeruginosa* found in 25% and *S aureus* in 16% (with *Fusarium* spp and *Aspergillus* spp in 25% and 16%, respectively).¹⁷ Conjunctivitis was the most common ocular infection among primary school children and was similar in type and prevalence in both rural and urban slum areas of Delhi. There was a rise in incidence with increasing age and a significant association between ocular infections and religion, but not per capita income.¹⁸

Other Ocular Infections

In developing countries, penetrating injuries pose a particular hazard, because immediate medical treatment is often inaccessible.

In a study of microbial cultures in open globe injuries in southern India, corneoscleral laceration and delay in surgical intervention were among the factors contributing to a positive microbial culture.¹⁹

Other ocular infections also show regional differences. In one region, the causative organisms of chronic dacryocystitis and dacryoabcess showed a shift to a higher incidence of gram-negative organisms (61%) versus gram-positive organisms (39%), with *Pseudomonas* spp being the most common organism (22%) followed by *S aureus* (13%), *Enterobacter* (10%), *Citrobacter* (10%), *S pneumoniae*, *E coli*, and *Enterococcus* spp (7%). Some uncommon gram-negative organisms were also isolated, including *Alcaligenes* spp (5%) and *Stenotrophomonas maltophilia* (2.5%). Less than 30% of gram-negative isolates were sensitive to cefalexin and ampicillin.²⁰ In an Indian hospital, some cases of ophthalmia neonatorum were found to be culture-positive for bacterial species, *P aeruginosa* being the most common, with the highest sensitivity to the fluoroquinolone antibiotics.²¹

Endophthalmitis

Even in the best of circumstances, treatment of infectious endophthalmitis is considered a medical emergency, with early intervention key to an optimal visual outcome. In remote regions of the world, this may not be possible, and prevention becomes more important. In a study of post-traumatic endophthalmitis in South Vietnam, the mean time interval from trauma to diagnosis was 16.8 days (SD, 5.6 days) and visual acuity at the time of diagnosis was finger counting only or light perception in 96% of patients.²² Positive cultures showed 51% gram-positive bacteria, and 33% gram-negative bacteria (and 16% fungi). Noted among significant risk factors for a poor prognosis were a purely corneal wound, surgical intervention more than 24 hours after the trauma, a rural setting, and inadequate antibiotic treatment. The authors stressed the importance of comprehensive antibiotic treatment at the time of injury to the eye.²²

Prevention of postoperative endophthalmitis after cataract surgery relies heavily on pre- and perioperative administration of local antibiotics and cleansing of the surface of the eye. Here again, availability of broad-spectrum effective antibiotics is a critical part of modern prophylactic regimens. The importance of topical antibiotic delivery is also underscored by reports that describe a higher incidence of postoperative endophthalmitis in patients not receiving a subconjunctival injection of antibiotic.^{23,24} Although this route of prophylaxis has lost favour in recent years, such reports support the usefulness of local antibiotic delivery during surgery to help reduce the ocular surface flora and incidence of endophthalmitis.^{23,24} In recent years, the intracameral route of injection has also been used by some clinicians for prophylaxis of post-cataract surgical infection.²⁵⁻²⁹

Data from the USA³⁰ and Asia³¹ identify gram-positive organisms as the primary causes of culture-proven postoperative endophthalmitis, led by *Staphylococcus epidermidis* (coagulase-negative staphylococci) and *S aureus*. However, as endophthalmitis may also be caused by gram-negative species and virulent strains that result in poor visual outcomes, broad-spectrum treatment, and prophylaxis, are appropriate. Some data suggest that the rates of postoperative endophthalmitis in Asia are similar to rates reported worldwide.³¹ However, regional differences play a role if one considers that contamination during surgery often occurs from the patient's own flora. Differences between ethnic groups in Asia, such as pre-existing diseases, anterior chamber contamination, and anterior blepharitis, have been cited as regional risk factors.³¹

Regional Shifts in Susceptibility of Ocular Isolates

Data describing a gradual increase in bacterial resistance of ocular isolates have been accumulating over the years, but are more difficult to obtain than data describing more generalised infections. These changing bacterial resistance patterns, documented by local bacterial susceptibility and epidemiological data, where available, help to guide the selection of appropriate topical antibiotic therapy. Table 1 presents local bacterial susceptibility data from The Manila Doctors Hospital and The Medical City Hospital, both premier tertiary care facilities in Manila, The Philippines, that support these worldwide trends, showing substantially diminished susceptibility of important bacteria to commonly used antibiotics.

In Beijing, China, 347 ocular isolates were tested during the 2-year period from 1999 to 2000.³² Gram-positive cocci accounted for 55.3% of isolates, gram-negative cocci for 4.6%, gram-positive bacilli for 12.7%, gram-negative bacilli for 25.7%, and *Nocardia* spp for 1.7%. Overall resistance rates of 26% to 35% to the earlier fluoroquinolones, ofloxacin, ciprofloxacin, and norfloxacin, were detected. *Streptococcus* spp showed 52.9% and 70.6% resistance to gentamycin and tobramycin, respectively, and 23.5% to norfloxacin, but resistance was lower to ofloxacin (5.9%) and ciprofloxacin (11.8%). *Pseudomonas* spp were significantly more resistant (42%) to gentamycin than to the fluoroquinolones (6% to 14%). *Staphylococcus* spp were equally susceptible to gentamycin/tobramycin and ofloxacin/ciprofloxacin. The fluoroquinolones, ofloxacin and ciprofloxacin, had better overall in vitro activity during those years.

In India, significant resistance of *S aureus* isolates from patients with keratitis was already noted in one study performed from 1993 to 2000, in which 20.6% of isolates showed resistance to ciprofloxacin.³³ In a later 6-year period, from 1991 to 1997, 30.7% of 1558 corneal isolates from culture-proven bacterial keratitis had become resistant to ciprofloxacin.³⁴ This included 32.5% of the

Table 1. Surveillance of antibiotic resistance patterns of bacterial isolates from January to December 2007 at The Manila Doctors Hospital and The Medical City Hospital, Manila, The Philippines.

Antibiotic	Bacterial isolates (% sensitive)		
	<i>Staphylococcus aureus</i> *	<i>Streptococcus epidermidis</i>	<i>Pseudomonas aeruginosa</i>
Amikacin			/92.0
Ceftazidime			/97.3
Cefuroxime sodium			0/
Chloramphenicol	52.4/—†	69.7/—	
Ciprofloxacin	50.8/89.0	38.1/82.0	75.7/96.0
Erythromycin	44.1/66.5	22.8/62.3	
Gatifloxacin		56.2/—	
Gentamycin	66.9/—	53.1/—	71.4/81
Levofloxacin	85.5/66.5	57.8/85.7	45.5/—
Linezolid	—/100.0	—/100.0	
Moxifloxacin		50.0/—	
Norfloxacin	67.4/—	50.0/—	
Ofloxacin	28.6/—	43.4/—	—/71.5
Oxacillin	—/89.5	—/69.7	
Tetracycline	56.7/—	40.8/—	
Tobramycin		40.0/—	78.1/—
Vancomycin	93.0/100.0	95.4/100.0	

* Of 113 specimens of methicillin-resistant *Staphylococcus aureus* identified, only 1 isolate was ocular.

† Data from The Manila Doctors Hospital/data from The Medical City Hospital.

gram-positive cocci, 10.0% of the gram-positive bacilli, 13.3% of the gram-negative organisms, and 35.1% of the *Actinomycetes* and related organisms.

In South Australia, resistance to cephazolin, the current first-line antibiotic for gram-positive cocci during the study period 1998 to 2003, was noted in 35% of cases due to coagulase negative *Staphylococcus*.³⁵ However, all *Pseudomonas* isolates remained susceptible to ciprofloxacin. In the USA, resistance to the early fluoroquinolones was detected somewhat later than in Asia.³⁶ Resistance to ciprofloxacin in corneal and conjunctival isolates of *S aureus* rose from a mean 8.0% during 1990 to 1995 to 20.7% during 1996 to 2001. In South Florida, in vitro resistance of *S aureus* isolates to ofloxacin and ciprofloxacin increased from 11% in 1990 to 28% in 1998, showing a 3-fold increase.³⁷ In a slightly different region, *S aureus* resistance to ciprofloxacin and ofloxacin increased yearly from approximately 5% to 35% between 1993 and 1997, and significant resistance of *Streptococcus* spp and coagulase-negative *Staphylococcus* spp was noted, remaining unchanged during this period.³⁸ However, gram-negative organisms remained susceptible to fluoroquinolones throughout.

These basic trends underlie the need to examine more closely newer antibiotics such as the fluoroquinolones. In Part II of this series, the characteristics and applicability of these agents, and moxifloxacin in particular, for the prevention and treatment of ocular infections will be examined.

Conclusions

Changes in worldwide bacterial resistance patterns and the epidemiology of ocular infections throughout Asia pose unique

challenges for the management of ocular infections in these regions, both rural and urban. Access to effective and safe broad-spectrum topical antibiotics are paramount to addressing these needs. Better access by local health workers to effective and safe topical antibiotics is cited as a primary factor for improving patient outcomes and quality of life.

Acknowledgements

The author would like to acknowledge Susanne Gardner for medical writing contributions.

References

1. Getshen K, Srinivasan M, Upadhyay MP, Priyadarsini B, Mahalaksmi R, Whitcher JP. Corneal ulceration in South East Asia. I: a model for the prevention of bacterial ulcers at the village level in rural Bhutan. *Br J Ophthalmol*. 2006;90:276-8.
2. Upadhyay MP, Karmacharya PC, Koirala S, et al. The Bhaktapur eye study: ocular trauma and antibiotic prophylaxis for the prevention of corneal ulceration in Nepal. *Br J Ophthalmol*. 2001;85:388-92.
3. Zhang M, He Y, Wei H, Mai C. An analysis of 1,001 blinding patients with corneal disease in 1960-1989. *Yan Ke Xue Bao*. 1998;14:48-51.
4. Praina NV, Pillai MR, Manimegalai TK, Srinivasan M. Use of traditional eye medicines by corneal ulcer patients presenting to a hospital in South India. *Indian J Ophthalmol*. 1999;47:15-8.
5. Valenton MJ. Cornea and external disease eye disease problems in the Philippines: a twenty year survey (1971-1991), summary and highlights. *Phil J Ophthalmol*. 1993;22:52-5.
6. Valenton M. Central microbial keratitis. *Phil J Ophthalmol*. 2000;25:10-21.
7. Fong CF, Hu FR, Tseng CH, Wang IJ, Chen WL, Hou YC. Antibiotic susceptibility of bacterial isolates from bacterial keratitis cases in a university hospital in Taiwan. *Am J Ophthalmol*. 2007;144:682-9.
8. Tan DT, Lee CP, Lim AS. Corneal ulcers in two institutions in Singapore: analysis of causative factors, organisms and antibiotic resistance. *Ann Acad Med Singapore*. 1995;24:823-9.

9. Toshida H, Kogure N, Inoue N, Murakami A. Trends in microbial keratitis in Japan. *Eye Contact Lens*. 2007;33:70-3.
10. Sharma S, Gopalakrishnan S, Aasuri MK, Garg P, Rao GN. Trends in contact lens-associated microbial keratitis in Southern India. *Ophthalmology*. 2003;110:138-43.
11. Williams, McClellan K, Billson F. Suppurative keratitis in rural Bangladesh: the value of gram stain in planning management. *Int Ophthalmol*. 1991;15:131-5.
12. Leck AK, Thomas PA, Hagan M, et al. Aetiology of suppurative corneal ulcers in Ghana and south India, and epidemiology of fungal keratitis. *Br J Ophthalmol*. 2002;86:1211-5.
13. Solomon R, Donnenfeld ED, Azar DT, et al. Infectious keratitis after laser in situ keratomileusis: results of an ASCRS survey. *J Cataract Refract Surg*. 2003;29:2001-6.
14. Bharathi JM, Srinivasan M, Ramakrishnan R, Meenakshi R, Padmavathy S, Lalitha PN. A study of the spectrum of *Acanthamoeba* keratitis: a three-year study at a tertiary eye care referral center in South India. *Indian J Ophthalmol*. 2007;55:37-42.
15. Ophthalmic moxifloxacin (Vigamox) and gatifloxacin (Zymar). *Med Lett Drugs Ther*. 2004;46:25-7.
16. Srinivasa DK, D'Souza V. Economic aspects of an epidemic of haemorrhagic conjunctivitis in a rural community. *J Epidemiol Community Health*. 1987;41:79-81.
17. Vajpayee RB, Sharma N, Chand M, Tabin GC, Vajpayee M, Anand JR. Corneal superinfection in acute hemorrhagic conjunctivitis. *Cornea*. 1998;17:614-7.
18. Kumar R, Mehra M, Dabas P, Kamlesh, Raha R. A study of ocular infections amongst primary school children in Delhi. *J Commun Dis*. 2004;36:121-6.
19. Gupta A, Srinivasan R, Kaliaperumal S, Setia S. Microbial cultures in open globe injuries in southern India. *Clin Exp Ophthalmol*. 2007;35:432-8.
20. Briscoe D, Rubowitz A, Assia EI. Changing bacterial isolates and antibiotic sensitivities of purulent dacryocystitis. *Orbit*. 2005;24:95-8.
21. Mani VR, Vidya KC. A microbiological study of ophthalmia neonatorum in hospital-born babies. *J Indian Med Assoc*. 1997;95:416-7, 421.
22. Tran TP, Le TM, Bui HT, Nguyen TM, Kuchle M, Nguyen NX. Post-traumatic endophthalmitis after penetrating injury in Vietnam: risk factors, microbiological aspect and visual outcome. *Klin Monatsbl Augenheilkd*. 2003;220:481-5.
23. Ahmed S, Bhan K, McKibbin M. Endophthalmitis in an Asian population. *Ophthalmology*. 2005;112:944.
24. Lehmann OJ, Roberts CJ, Ikram K, Campbell MJ, McGill JI. Association between nonadministration of subconjunctival cefuroxime and postoperative endophthalmitis. *J Cataract Refract Surg*. 1997;23:889-93.
25. ESCRS Study Group. Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. *J Cataract Refract Surg*. 2007;33:978-88.
26. Espiritu CR, Caparas VL, Bolinao JG. Safety of prophylactic intracameral moxifloxacin 0.5% ophthalmic solution in cataract surgery patients. *J Cataract Refract Surg*. 2007;33:63-8.
27. Arbisser LB. Safety of intracameral moxifloxacin for prophylaxis of endophthalmitis after cataract surgery. *J Cataract Refract Surg*. 2008;34:1114-20.
28. Lane SS, Osher RH, Masket S, Belani S. Evaluation of the safety of prophylactic intracameral moxifloxacin in cataract surgery. *J Cataract Refract Surg*. 2008;34:1451-9.
29. O'Brien TP, Arshinoff SA, Mah FS. Perspectives on antibiotics for postoperative endophthalmitis prophylaxis: potential role of moxifloxacin. *J Cataract Refract Surg*. 2007;33:1790-800.
30. The 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;113:1479-96.
31. Wong TY, Chee SP. The epidemiology of acute endophthalmitis after cataract surgery in an Asian population. *Ophthalmology*. 2004;111:699-705.
32. Sun XG, Wang ZO, Li R, et al. In vitro fluoroquinolone resistance in ocular bacterial isolates. *Zhonghua Yan Ke Za Zhi*. 2003;39:163-6.
33. Sharma V, Sharma S, Garg P, Rao GN. Clinical resistance of *Staphylococcus* keratitis to ciprofloxacin monotherapy. *Indian J Ophthalmol*. 2004;52:287-92.
34. Kunimoto DY, Sharma S, Garq P, Rao GN. In vitro susceptibility of bacterial keratitis pathogens to ciprofloxacin. *Emerging resistance*. *Ophthalmology*. 1999;106:80-5.
35. Leibovitch I, Lai TF, Senarath L, Hsuan J, Selva D. Infectious keratitis in South Australia: emerging resistance to cephazolin. *Eur J Ophthalmol*. 2005;15:23-6.
36. Marangon FB, Miller D, Muallem MS, Romano AC, Alfonso EC. Ciprofloxacin and levofloxacin resistance among methicillin-sensitive *Staphylococcus aureus* isolates from keratitis and conjunctivitis. *Am J Ophthalmol*. 2004;137:453-8.
37. Alexandrakis G, Alfonso EC, Miller D. Shifting trends in bacterial keratitis in south Florida and emerging resistance to fluoroquinolones. *Ophthalmology*. 2000;107:1497-502.
38. Goldstein MH, Kowalski RP, Gordon YJ. Emerging fluoroquinolone resistance in bacterial keratitis: a 5-year review. *Ophthalmology*. 1999;106:1313-8.