

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

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. In the first of a 2-part series, current local and regional trends in ocular infections and microbial resistance in Asia, and how these factors shape the need for modern solutions to improve patient outcomes were described. In this Part II, the limitations of older antibiotics, the evolution of the newly developing fluoroquinolones, and the role of moxifloxacin, a fourth-generation fluoroquinolone, are examined.

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

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Shifting Regional Microbial Resistance

Important changes in antimicrobial resistance to traditionally used antibiotics have emerged over the years, so that interest is increasingly focused on the newly developed antibiotics. Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pneumoniae*, both less susceptible to the β -lactam and macrolide antibiotics, are spreading worldwide. *Enterococcus* spp and many gram-negative species show increased resistance to vital antibiotics such as vancomycin and the β -lactams, and microbes such as *Chlamydia* spp and *Mycoplasma* spp have emerged as important clinical pathogens. A steady increase in β -lactamase production among *Haemophilus influenzae* isolates has been documented since 1973, already estimated at 20% by 1986. Resistance to chloramphenicol and tetracycline was frequently reported throughout Europe and Asia with multiple antimicrobial resistance mechanisms described in those regions as well as in the USA.¹

Increasing resistance among the respiratory pathogens, in particular *S pneumoniae*, *H influenzae*, and *Moraxella catarrhalis*, is occurring at an alarming rate worldwide.² Penicillin resistance of *S pneumoniae* isolates reportedly varies by geographical location, with rates exceeding 20% in the USA, Mexico, Japan, Saudi Arabia,

Israel, Spain, France, Greece, Hungary, and the Slovak Republic, and exceeding 50% in South Africa, Hong Kong, Taiwan, and South Korea. Diminished susceptibility to penicillin is associated with macrolide resistance, which has a prevalence rate of 70% to 80% in some Asian countries. Resistance to trimethoprim-sulfamethoxazole (TMP-SMX) and tetracycline are also associated with this multiple resistance. However, despite the fact that β -lactamase production has increased among some respiratory pathogens, the 'respiratory' fluoroquinolones have remained active against a majority of these pathogens, including atypical mycobacteria.^{3,4} *Mycoplasma* spp and *Chlamydia* spp play an increasingly important role in respiratory tract infections. These microorganisms are not susceptible to β -lactams as *Chlamydia* spp are obligate intracellular pathogens and *Mycoplasma* spp do not exhibit the typical rigid bacterial cell wall. While the early quinolone antibiotics had poor activity against these atypical microbes, the newer classes of fluoroquinolones, including moxifloxacin, exhibit high activity against these species.⁵

These fundamental changes in bacterial susceptibility around the world and in Asia have been linked to factors such as bacterial mutations, resistance in nosocomial infections,⁶ overuse or misuse of antibiotics,⁷ antibiotic use in animals, agriculture, and fisheries, introduction of foreign work forces or expatriate populations, and easy availability of antibiotics without prescription, particularly in developing countries as in the Gulf region,⁸⁻¹⁰ India,¹¹⁻¹³ Korea,¹⁴⁻¹⁶ Thailand and South East Asia,¹⁷ Malaysia,¹⁸ and Japan.¹⁹ The use of antibiotics in animals has also contributed to bacterial resistance,

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: espritu@eyemd.net

although a recent study in Asia showed that resistance by selected pathogens to the fluoroquinolones has not yet been observed.²⁰

Part I of this article presented 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. However, today, modern fluoroquinolones have evolved with targeted modifications that deliver effective antibiotic activity against a host of important pathogens.

History of Fluoroquinolone Development

Modern fluoroquinolone antibiotics originated from work with chloroquine, an antimalarial agent modified to a compound showing antibacterial activity. Nalidixic acid (NegGram) was the first fluoroquinolone antibiotic, patented in 1962. Nalidixic acid had a limited spectrum of action, only against some gram-negative bacteria and, being poorly absorbed orally, was useful primarily for the treatment of urinary tract infections.

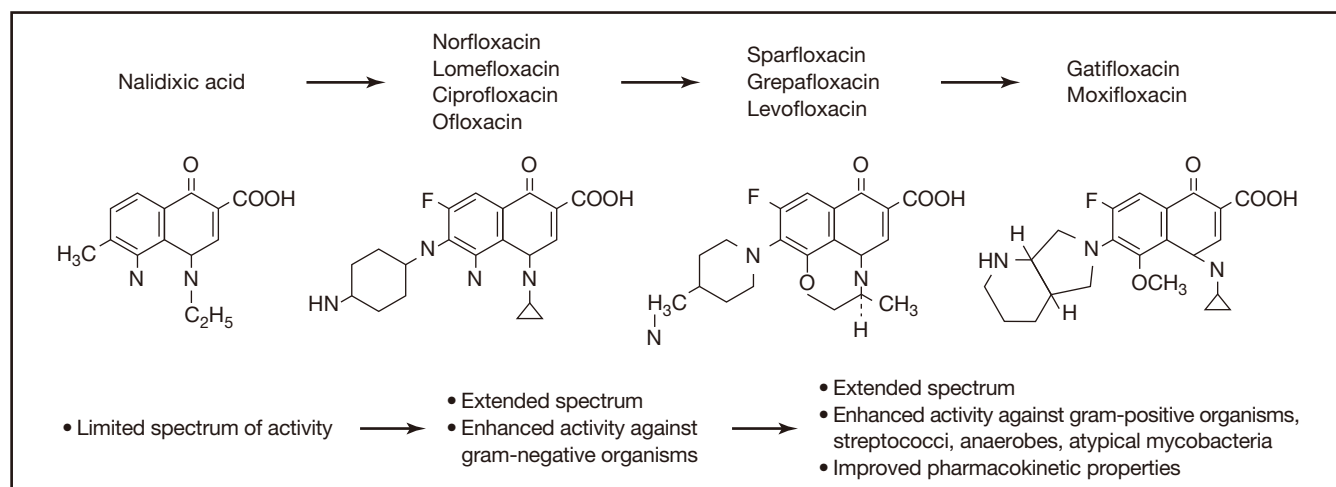
Through extensive research in ensuing years, the nalidixic acid molecule was modified to produce more useful compounds by adding stepwise improvements that expanded the antimicrobial activity and added features (Figure 1). Introduction of a piperazinyl side chain at position 7 improved activity against gram-negative bacteria and the piperazine ring enhanced bacterial cell wall penetration as well. Fluorination at position 6, patented in 1973, created better activity against gram-positive bacteria. The combination of these 2 modifications produced norfloxacin, the first 6-fluorinated compound, patented in 1978. Subsequent research moved rapidly, leading to the development of ciprofloxacin, a compound with an added cyclopropyl side chain at position 1, patented in 1981, and to ofloxacin in 1982. Ofloxacin and its

l-isomer, levofloxacin, added a bridging ring between the N-1 and position 8, extending efficacy against gram-positive microbes, including *S pneumoniae*, while maintaining the characteristically good activity against gram-negative species of the earlier fluoroquinolones. These antibiotics were well absorbed from the gastrointestinal tract, facilitating their use for the treatment of systemic infections.

Modifications that created moxifloxacin incorporated a cyclopropyl group side chain at the position 1 nitrogen, which imparted better activity against gram-negative microbes, and substitutions such as the diazabicyclic ring at position 7 also made it relatively more active against gram-positive bacteria than some other members in its class. A methoxy group at position 8 conferred good anaerobic activity. Better intracellular penetration was created, on a par with the macrolides, but surpassing the β -lactams in usefulness when pathogens are intracellular. Due to their rapid bactericidal, as opposed to bacteriostatic, effect on microbes, the fluoroquinolones became important antibiotics for the treatment of serious infections, especially among elderly people and those with diminished immune capacity, rivalling the β -lactams in clinical importance in only 2 short decades.⁵

Today, fluoroquinolones have earned an indisputable place in the treatment of a wide variety of systemic infections and are recommended as alternate drugs of choice for infections caused by *S aureus* and *S epidermidis*, both methicillin-susceptible and methicillin-resistant strains. In vitro activity against most *S pneumoniae* is excellent, including penicillin- and cephalosporin-resistant strains. Moxifloxacin is also recommended for the treatment of infections caused by *S pneumoniae* that is penicillin-susceptible or has intermediate resistance, and may be included as a drug of choice for infections caused by these organisms with high-level penicillin resistance. The fluoroquinolones are

Figure 1. The evolution of the fluoroquinolones.



recommended as treatment against several enteric gram-negative bacilli including *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Serratia* spp, and against *H influenzae*, as well as *Enterococcus* spp causing uncomplicated urinary tract infections. The fluoroquinolones are also effective against, and are alternate drugs of choice for, the atypical pathogens, *Mycobacterium tuberculosis* and *Chlamydomphila* infections.²¹

Selection of Antibiotics for Ophthalmic Infections

The indicators of clinical success, as described above, against microorganisms causing systemic infections may offer useful guidelines to ophthalmologists for the management of ocular infections when data relating to ocular isolates is less readily available. Moreover, bacteria colonising the face, nasal passages, and adjacent tissues may also affect the bacterial flora surrounding the eye.

In Part I of this article, the changing trends in the microbial flora causing ocular infections throughout Asia and other parts of the world, as well as cultural factors unique to the region that may influence patient outcome were described. One must bear in mind that the majority of Asia's socio-economic distribution is in rural areas, where modest medical health care delivery systems often do not have facilities for specific identification of causative infectious organisms. Eye care practitioners usually rely on typical or pathognomonic clinical presentations for making educated guesses as to aetiology. This, in addition to the possibility of multi-organism infection, underscores the need for antimicrobial agents that will be effective against most, if not all, of the potential pathogens. Many of the antibiotics once relied on for ophthalmic care in the Asian region are now becoming outdated for a variety of reasons.

Disadvantages of Older Antibiotics in Ophthalmology

The clinical usefulness of the older ophthalmic antibiotics is fading because of limitations in the spectrum of activity, bacterial resistance, and unwanted adverse effects. Bacterial susceptibility to sulfacetamide has decreased during recent years and it may be sensitising in some individuals, on rare occasions causing Stevens-Johnson syndrome. Neomycin has a limited spectrum of activity and causes local sensitivity reactions in approximately 5% to 10% of patients. Chloramphenicol has been associated with rare cases of aplastic anaemia, even from topical administration, and its mechanism of action is bacteriostatic rather than bactericidal. However, outside of the USA, chloramphenicol is still commonly used, primarily because of its economical cost. The aminoglycosides

gentamycin and tobramycin have poor in vitro efficacy against most streptococci. Bacitracin and erythromycin are not active against the gram-negative microorganisms causing ophthalmic infections and polymyxin B has activity only against gram-negative organisms, but is poorly effective.²²⁻²⁵

In the past, truly broad-spectrum topical antibiotics for ocular infections were unavailable, and sufficiently potent formulations often required 2 different antibiotics and extemporaneous formulation to fulfil clinical needs.²⁵ The newer fluoroquinolones have evolved through methodical, stepwise research to produce compounds that are broad spectrum, clinically useful, and effective.

Moxifloxacin 0.5% Ophthalmic Eye Drops

The great contribution of the fourth-generation fluoroquinolones, which includes moxifloxacin, was the dramatic improvement in activity against most gram-positive bacteria, while retaining much of the activity against gram-negative bacteria seen with the older fluoroquinolone, ciprofloxacin. In addition, many strains that had become resistant to earlier fluoroquinolones now showed good susceptibility to moxifloxacin, with anaerobes also being more susceptible.^{5,26,27} In 2006, an ophthalmic eye drop preparation of moxifloxacin was commercially launched in Japan, the first to be available in the Asian region. As a fourth-generation fluoroquinolone antibiotic, moxifloxacin 0.5% ophthalmic solution is evolving as a standard of care for many treatment and prophylactic regimens, and may play an important role against the broad range of ocular infections described in Asian populations.

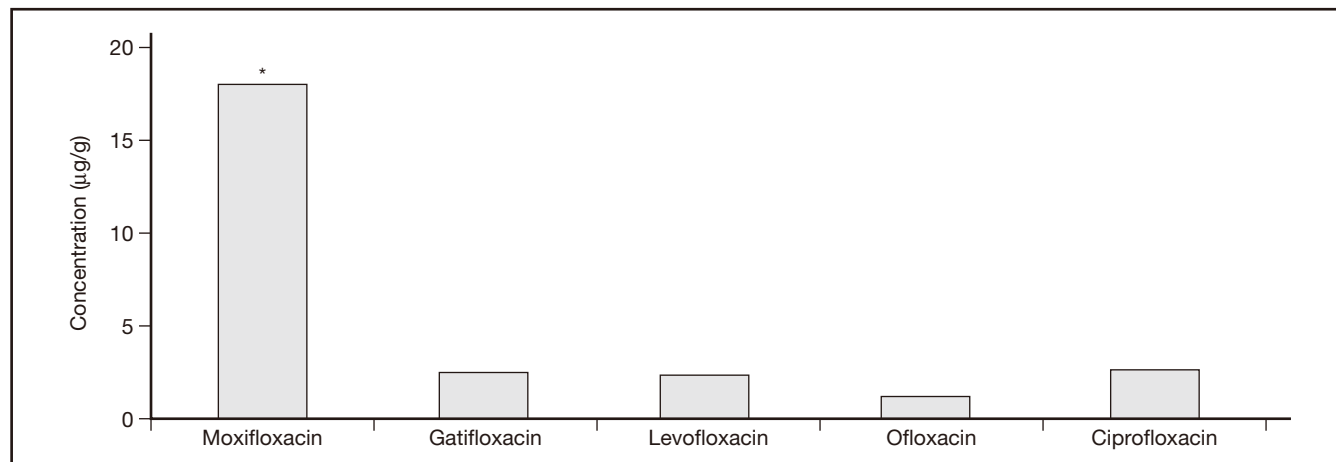
Moxifloxacin 0.5% is a new fourth-generation fluoroquinolone antibiotic, available in ophthalmic drop form (Vigamox®), that exhibits a broad spectrum of antimicrobial action against the majority of important ocular pathogens, including gram-positive and gram-negative bacteria, anaerobes, and atypical mycobacteria. Drug penetration to ocular tissues after topical administration (from eye drops) produces effective antimicrobial levels with a high degree of safety to the eye. Moxifloxacin has a bactericidal mechanism of action, as opposed to a bacteriostatic mechanism. In bacterial keratitis²⁶ and/or endophthalmitis isolates,^{27,28} moxifloxacin has demonstrated increased efficacy against gram-positive microbes and especially against *S aureus* isolates resistant to older fluoroquinolones such as ciprofloxacin, levofloxacin, and ofloxacin, while still maintaining good efficacy against gram-negative bacteria.

Ocular Safety

The safety of moxifloxacin to ocular tissues is well documented.²⁹⁻³² Vigamox eye drops are compatible with ocular tissues, being isotonic, with osmolality of 290 mOsm/kg and a pH near 6.8.³³ Vigamox

Figure 2. Conjunctiva concentrations of the fluoroquinolones.

* $p < 0.001$.



is sterile and self-preserved, eliminating the need for added preservatives that are known to have toxic effects on the corneal epithelium.^{34,35}

A study of endothelial and epithelial cell counts and tear break-up time after 1 drop of moxifloxacin administered 4 times daily for 3 days in volunteers resulted in no significant differences between treated eyes and fellow control eyes.²⁹ No effects on visual acuity or ocular surface integrity were noted. Furthermore, in eyes with an epithelial defect, healing rates were significantly better in eyes treated with moxifloxacin after photorefractive keratectomy than in eyes treated with topical gatifloxacin drops.³²

Ocular Penetration and Efficacy

Effective antimicrobial action is closely tied to the peak concentrations achievable, as high levels are associated with higher degrees of bacterial kill. When compared with other available topical fluoroquinolones, moxifloxacin shows favourable penetration characteristics.

Comparisons of conjunctival concentrations of 5 ophthalmic fluoroquinolones after instillation of a single eye drop showed that moxifloxacin attained concentrations 6 to 15 times higher, than the other 4 agents tested ($p < 0.001$; Figure 2).³⁶ This indicates that moxifloxacin has excellent tissue penetration characteristics, with both hydrophilic and lipophilic, or biphasic, characteristics. High concentrations in the conjunctiva support the efficacy of moxifloxacin for the treatment of infectious conjunctivitis.

Corneal penetration of moxifloxacin was measured after instillation of 2 preoperative drops given 5 minutes apart. Moxifloxacin reached mean peak levels of 48.5 µg/g in corneal stroma, approximately 3 times higher than levels after gatifloxacin drops administered the same way. These peak levels of moxifloxacin were approximately 12 to 800 times higher than the minimum

bactericidal concentration₅₀ (MBC₅₀) for *S aureus*, *S epidermidis*, *P aeruginosa*, and *S marcescens*.³⁷

Penetration into aqueous humour after topical eye drop administration has relevance for preoperative prophylaxis of endophthalmitis. While levels achieved in aqueous humour are generally lower than those in corneal stroma, after multiple eye drop administration effective levels may penetrate to the aqueous humour. A number of eye drop regimens have been evaluated clinically. Moxifloxacin was instilled in 1 of 2 regimens for patients with cataract, as follows:³⁸

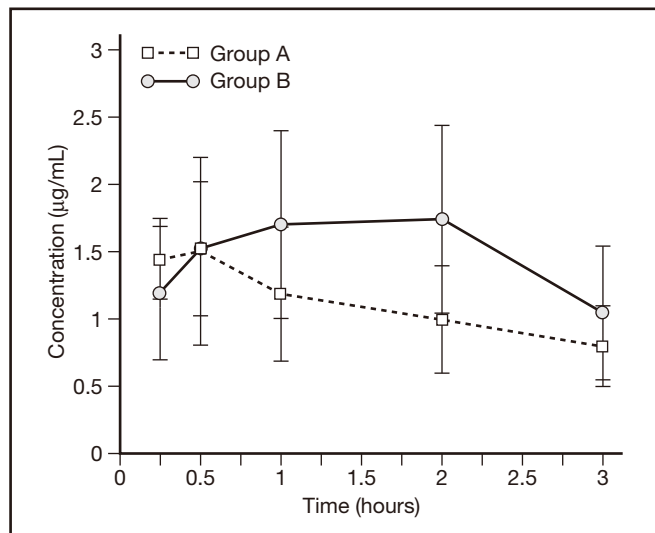
- group A — 1 drop every 15 minutes for 4 doses before surgery
- group B — 1 drop 4 times daily on the day before surgery plus the regimen of group A.

Patients were randomised so that the last dose was administered 0.25, 0.50, 1, 2, or 3 hours before aqueous humour sampling. The results showed that moxifloxacin was well absorbed into the aqueous humour, reaching levels >1 µg/mL within 15 minutes (Figure 3). While there was no statistically significant difference in mean peak levels between the 2 treatment groups, there was a higher overall drug concentration over time (area under the curve_{0-3h}) in the group receiving the combination treatment regimens. A different eye drop regimen of 1 drop every 10 minutes for 4 doses beginning 1 hour prior to surgery compared the aqueous humour levels after preoperative administration of moxifloxacin 0.5% or gatifloxacin 0.3%.³⁹ Mean aqueous humour peak levels for moxifloxacin reached 1.8 µg/mL (SD, 1.21 µg/mL), levels that were 3.8 times higher than those for gatifloxacin. In a report from Hong Kong, application of 1 drop of moxifloxacin 0.5% every 10 minutes for 1 hour before cataract surgery produced aqueous humour levels of 1.576 µg/mL (SD, 0.745 µg/mL).⁴⁰ Comparable levels (1.86 µg/mL [SD, 1.06 µg/mL]) were also found in a USA study after 1 drop was given 4 times daily on the day before surgery with an additional drop 1 hour before surgery.⁴¹

Figure 3. Mean aqueous humour concentrations of moxifloxacin as a function of time.

Group A regimen — 1 drop every 15 minutes for 4 doses before surgery.

Group B regimen — 1 drop 4 times on the day before surgery plus the regimen for group A.



Most recently, use of the moxifloxacin ophthalmic solution by direct intracameral injection has also been explored for prophylaxis for endophthalmitis, without apparent adverse effects.⁴²⁻⁴⁴ As microorganisms may linger in the surgical field or enter the eye near the close of cataract surgery through wound imperfections, effective antibiotic coverage throughout the perioperative period is beneficial. Anterior chamber contamination rates of 5% to 43% have been reported after routine cataract surgery.⁴⁵⁻⁴⁷ One recent study in Japan also examined the stepwise changes in ocular surface contamination from 1 week preoperatively to intra-operatively.⁵ Despite preoperative eye drops and use of surgical scrubs, microbes were still isolated from the conjunctiva and ocular fluids, showing a relative rise in the proportion of *Propionibacterium acnes* during this period. This study pointed out that complete sterilisation of the ocular surgical field may not be possible and that *P acnes*, commonly implicated in late onset endophthalmitis, was still present on the ocular surface in the midst of the operation itself. These findings emphasise the need for delivery and maintenance of effective antibiotic levels throughout the surgical period.

Antibacterial Efficacy and Bacterial Resistance in Ocular Isolates

The delivery of effective antibiotic levels to targeted ocular tissues is fundamental to a therapeutic outcome. Antimicrobial efficacy is measured by parameters such as the minimum inhibitory concentration (MIC) and the MBC. The mutant prevention concentration describes a level sufficiently high to retard the development of intrinsic resistance in microbial organisms. Although the MIC is

the common standard for infections outside the eye, where host immune responses play a major role, ocular infections are unique in that targeted areas are often poorly vascularised and separated by tissue barriers from the systemic circulation. Therefore, the MBC has greater relevance when discussing antimicrobial effectiveness in ocular infections.⁴⁸⁻⁵² The MBC₅₀ of moxifloxacin against important ocular pathogens in corneal stroma and aqueous humour is shown in Figures 4 and 5.⁵³

Figure 4. Minimum bactericidal concentration₅₀ of moxifloxacin in corneal stroma.

* Fluoroquinolone-sensitive pathogens.

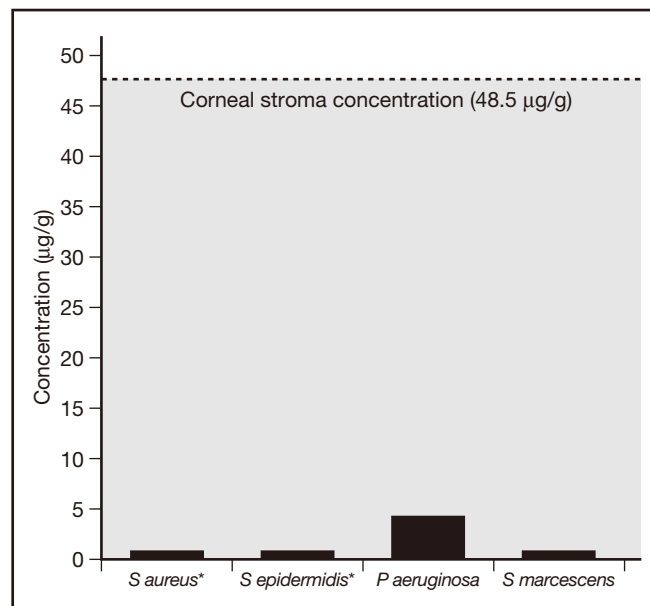
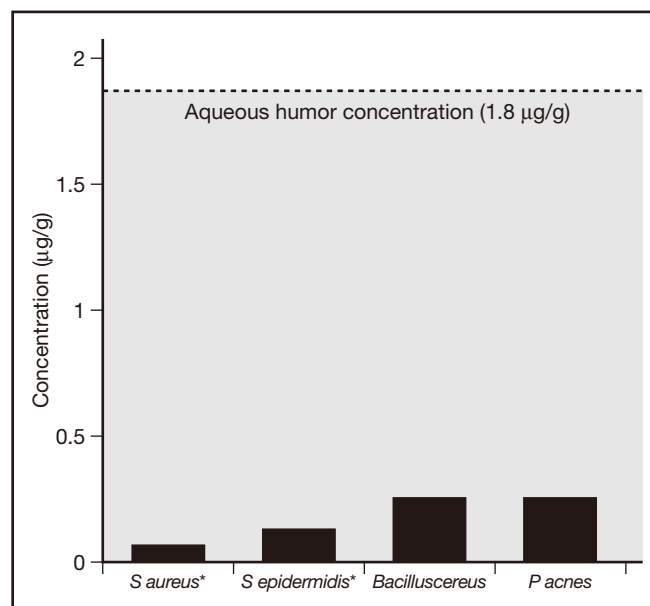


Figure 5. Minimum bactericidal concentration₅₀ of moxifloxacin in aqueous humour.

* Fluoroquinolone-sensitive pathogens.



One aspect of antibiotic treatment unique to ocular infections involves the principle that high concentrations of antibiotic, relative to the MIC or MBC, are delivered via topical drops and alternative dosing regimens. These regimens deliver antibiotic levels to ocular tissues that are often several multiples above the MIC or MBC determined by laboratory measurements. As a result, a better than expected clinical response is often seen.^{24,54} However, one study showed that when staphylococcal isolates from bacterial keratitis were resistant in vitro to ciprofloxacin, the clinical response was also weaker than when isolates were susceptible.⁵⁵

Nevertheless, high concentrations of antibiotic may be more effective clinically than anticipated from laboratory sensitivity data, and are also thought to retard development of bacterial resistance. As mentioned above, one should keep in mind that local antibiotic administration to the eye, whether via topical, subconjunctival or intracameral routes, delivers extremely high concentrations of antibiotic that far exceed reference levels used in sensitivity testing that refers to levels achieved in serum. The newer fluoroquinolones seem to have a lower rate of development of mutant strains of bacteria. Their enhanced antimicrobial action is due to the targeting of both the microbial DNA gyrase and topoisomerase IV, whereas older compounds targeted only a single step mutation.⁵

In one European report, the newer quinolones showed better activity against gram-positive organisms and anaerobes, with similar activity against gram-positives organisms.⁵⁶ Activity against *S pneumoniae* and *Enterobacteriaceae* was less reliable, although moxifloxacin was more active against *S pneumoniae* and *S aureus* than levofloxacin, gatifloxacin, and gemifloxacin. Resistant subpopulations emerged after exposure to levofloxacin and gatifloxacin, but not to moxifloxacin. Emergence of resistance was noted to be tied to both achievable drug concentrations in vivo and microbial resistance patterns. The authors suggested that the use of more potent fluoroquinolones, in effective concentrations, should be used as first-line agents to preserve the potential of this class of compounds and to provide the best treatment regimens.

Conclusions

In Part I, and this Part II of this series, the changes in bacterial resistance patterns throughout Asia, the shifting trends in the epidemiology of ocular infections, and the cultural factors that pose unique challenges for health care workers have been reviewed. Better access to effective and safe topical antibiotics has been cited as a primary factor for improving patient outcomes and quality of life. These challenges point to the need for a broad-spectrum antibiotic, with greater antibacterial efficacy than older, traditionally used agents, one that can be applied safely in a variety of dosage regimens to deliver effective antibiotic levels to

the eye. In many regions, moxifloxacin 0.5% ophthalmic solution is evolving as a standard of care for treatment and prophylactic regimens. This series has described the targeted evolution of the new fourth-generation fluoroquinolone antibiotic, moxifloxacin, and has examined its unique characteristics and applicability for the management of ocular infections throughout the changing landscape of Asia.

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