

TOPICS IN Ocular Antiinfectives

Ocular Microbiology: Studies Every Ophthalmologist Should Know

Sonia H. Yoo, MD

Epidemiological and clinical studies provide critical guidance for optimizing the use of ophthalmic antiinfective agents. This paper reviews some of the most clinically relevant studies of the last decade.

The ocular pathogens that threaten eyesight are continually evolving. Indeed, in no other area of eyecare do we expect our medications to become less effective as time goes on. To keep up with the ever-changing threat of drug resistance, we need ongoing epidemiological and clinical trials to measure the efficacy of new and old antibiotics against historical and emerging pathogens.

Clinical studies also provide insights into the relative advantages of popular vs proposed antiinfective regimens, be that topical vs intracameral prophylaxis in cataract surgery or the use of antiviral medications to prevent or treat sight-threatening recurrences of ocular herpes.

PROTEKT and SENTRY

By the end of the 20th century, bacterial resistance to antibiotics had increased markedly in the United States and around the world. In 2000, PROTEKT US (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin in the United States) began monitoring the emergence of drug resistance in common respiratory pathogens, some of which are of clinical relevance to ophthalmologists.¹

Over its first four years, PROTEKT revealed the emergence of multidrug resistance to a variety of important antimicrobials, including penicillin, azithromycin, second-generation cephalosporins, and trimethoprim-sulfamethoxazole. Importantly, PROTEKT looked at the genetic mechanisms of resistance and identified a high prevalence of mobile resistance elements able to spread between pathogens. Over the study's 4-year span, the percentage of bacterial isolates carrying both the erm(B) and the mef(A) resistance elements increased from 9.7% to 18.4%, with their

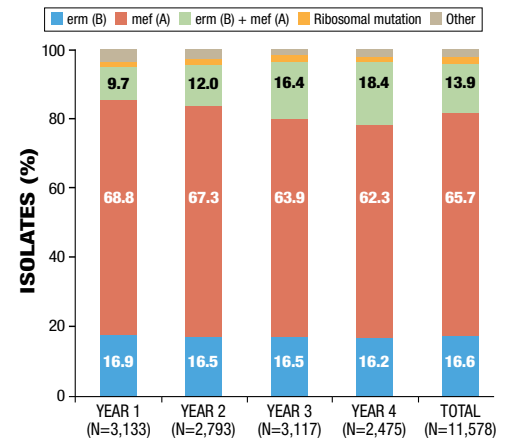


FIGURE 1 PROTEKT revealed the growing prevalence—and genetic mechanisms—of multidrug resistance in clinical isolates of *S. pneumoniae* across the United States. (Source: Reference 1)

combined presence conferring high levels of multidrug resistance (Figure 1).

With the 2006 and 2007 results of the SENTRY Antimicrobial Surveillance Program, we witnessed the international emergence of multidrug-resistant *Streptococcus pneumoniae* and vancomycin-

TARGET AUDIENCE This educational activity is intended for ophthalmologists and ophthalmologists in residency or fellowship training.

LEARNING OBJECTIVES

Upon completion of this activity participants will be able to:

1. Apply the results of major epidemiological studies to the selection of topical antibiotics for the prevention and treatment of ocular infections.
2. Apply the results of the HEDS study to create a prophylactic regimen against ocular herpetic disease.
3. Make evidence-based clinical judgments about the possible benefit of antibiotic prophylaxis in ophthalmic surgery.
4. Evaluate and implement variations in povidone-iodine disinfection techniques.

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resistant enterococcus.^{2,3}

Although enterococcus is an extremely rare cause of ocular infection, the prognosis for enterococcal endophthalmitis is grim. So it was particularly worrisome to see this pathogen develop resistance to vancomycin, our so-called drug of last resort. Moreover, the emergence of vancomycin resistance in any bacterium is worrisome, given the ability of resistance-producing genetic elements to spread between strains and species.

Tracking Resistance in Ocular Pathogens

Since the introduction of levofloxacin in 1996, the US FDA has required antimicrobial susceptibility surveillance for new systemic antibiotics. Initiated the same year, Tracking Resistance in

the US Today (TRUST) involved in vitro susceptibility testing of isolates submitted to an independent laboratory by more than 200 clinical labs across the nation. TRUST testing included a smattering of ocular isolates, but there was no systematic tracking of ocular pathogens and their susceptibilities until the initiation of Ocular TRUST in October 2005.

In Ocular TRUST's first year, participating centers submitted specimens from nearly 300 ocular infections, including 197 *Staphylococcus aureus*, 49 *S. pneumoniae*, and 32 *Haemophilus influenzae* isolates.⁴ Among the *S. aureus* isolates, 83% (164) were methicillin susceptible (MSSA) and 17% (33) were methicillin resistant (MRSA). The latter also demonstrated high levels of resistance to both moxifloxacin and gatifloxacin.

In fact, with the exception of trimethoprim and tobramycin, no ophthalmic antimicrobial demonstrated efficacy against more than a third of the study's MRSA isolates (Figure 2). Not included in Ocular TRUST was the newest fluoroquinolone, besifloxacin, which has demonstrated greater efficacy against MRSA in some animal and in vitro studies.⁵⁻⁷

Beyond the staphylococci, Ocular TRUST showed current-generation fluoroquinolones to be consistently active against *S. pneumoniae* and *H. influenzae*, and *H. influenzae* isolates remained fully susceptible to all tested antibiotics except trimethoprim and tobramycin.

Like PROTEKT and SENTRY before it, Ocular TRUST employed susceptibility testing standards based on the achievable blood plasma levels

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STATEMENT OF NEED

Ophthalmologists face numerous challenges in optimizing their competencies and clinical practices in the realm of preventing, diagnosing, and treating ocular infections and their sequelae; these challenges include:

- The widespread "off-label" use of topical ophthalmic antibiotics to prevent and treat serious and sight-threatening infections—given the reality that the most widely used topical antibiotics in ophthalmology have FDA approvals restricted to bacterial conjunctivitis.
- The escalating levels of multi-drug resistance in common ocular pathogens.¹
- The emergence and increasing prevalence of once-atypical infections that may require diagnostic and treatment techniques relatively unfamiliar to comprehensive ophthalmologists.²
- The introduction of new and potentially more efficacious and/or safe ophthalmic antiinfectives.³
- The introduction of new and potentially more accurate diagnostic techniques for ophthalmic infections.⁴
- Widespread discussion over the efficacy and safety of novel or alternative delivery techniques and vehicles for prophylactic ophthalmic antibiotics (including but not limited to intracameral injection and topical mucoadhesives).^{5,6}
- Increased understanding of the inflammatory damage caused by ocular infections and the best ways to prevent/alleviate inflammation without fueling the growth of pathogenic organisms.

Given the continually evolving challenges described above, *Topics in Ocular Antiinfectives* aims to help ophthalmologists update outdated competencies and narrow gaps between actual and optimal clinical practices. As an ongoing resource, this series will support evidence-based and rational antiinfective choices across a range of ophthalmic clinical situations.

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CORE CONCEPTS

- ▶ PROTEKT revealed the emergence of multidrug resistance conveyed by mobile genetic elements spread between bacteria.
- ▶ SENTRY revealed the global emergence of vancomycin-resistance among enterococci.
- ▶ HEDS demonstrated that oral acyclovir halves the recurrence rate of Herpes simplex keratitis and allows the safe use of ocular steroids in the actively infected.
- ▶ ARMOR surveillance shows continued increase in the prevalence of MRSA and MRSE—with considerable cross resistance to ophthalmic fluoroquinolones.

associated with systemic antibiotic use, rather than the ocular levels achievable with topical ophthalmic formulations. Because topical drops allow us to place high concentrations of antibiotic directly on a corneal infection, we have reason to believe that greater clinical efficacy can be achieved in eyecare—at least in treating external infections. In addition, *in vitro* testing fails to consider factors that may enhance a topical ophthalmic antibiotic's clinical efficacy—factors such as a drug's dwell time on the ocular surface or its penetration into the aqueous humor.

Surgical Prophylaxis

In a recent (2008) survey of the American Society of Cataract and Refractive Surgeons, the majority of respondents indicated that they opted for topical current generation fluoroquinolones for perioperative prophylaxis, with most initiating prophylaxis 1 to 3 days prior to surgery and continuing postoperatively for 2 weeks.⁸

Such practices are consistent with the findings of the Ocular TRUST—specifically that current generation fluoroquinolones demonstrate the widest spectrum of activity against common ocular pathogens. However, our heavy dependence on fluoroquinolones gives us pause when we consider a recent study by Hori and col-

leagues at Japan's Osaka University Hospital.⁹ The authors took conjunctival swabs from 200 eyes of patients who were about to undergo cataract surgery. As one would expect, approximately 82% of these eyes cultured positive for bacteria, and most of the cultured bacteria were Gram-positive—the kind of organisms that typically cause endophthalmitis. What was striking about Hori's finding was that 40% of the staphylococci cultured from patients' eyes were methicillin resistant, and 82% of these MRSA and MRSE isolates were cross-resistant to fluoroquinolones.

Global Phenomenon

We at the Bascom Palmer Eye Institute in Miami have also seen similar increases in methicillin resistance among incoming cases of staphylococcal endophthalmitis. This prompted a retrospective case review and the revelation that, between 1995 and 2008, 41% of the *S. aureus* endophthalmitis cases seen at Bascom Palmer involved MRSA.¹⁰ By contrast, not a single case of MRSA appeared in the records of our high-volume eye clinic between 1984 and 1992.

This pair of studies reminds us that when the fluoroquinolones were first introduced, they demonstrated excellent activity against the range of Gram-positive organisms including *Staphylococcus epidermidis* and *S. aureus*. Today, we face a very different reality—there now exists a high level of resistance to fluoroquinolones among methicillin/oxacillin-resistant organisms. Fortunately, these multidrug resistant strains are still susceptible to vancomycin, which has become the gold standard for the treatment of MRSA and MRSE ocular infections.

The ARMOR Study

Picking up where the Ocular TRUST left off, the 2009 ARMOR (Antibiotic Resistance Monitoring in Ocular Microorganisms) surveillance study determined the antibacterial susceptibility of eye infection isolates sent to a central laboratory from 34 institutions across the United

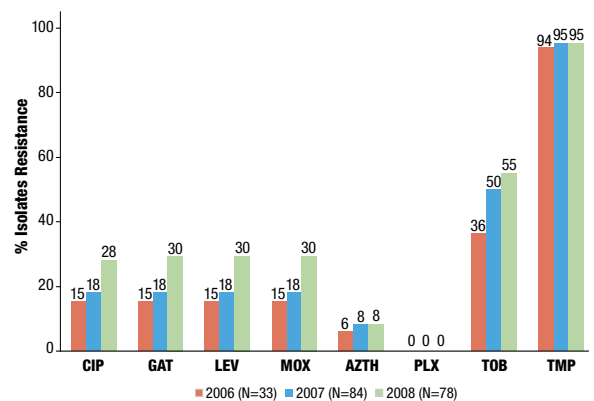


FIGURE 2 With the exception of trimethoprim and tobramycin, no ophthalmic antimicrobial demonstrated efficacy against more than a third of MRSA isolates tested in the Ocular TRUST study. (Data source: Reference 4)

States. These isolates included *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *H. influenzae*, and *P. aeruginosa*; and they were tested against all relevant antibiotics including the newest ophthalmic fluoroquinolone, besifloxacin.¹¹

The inclusion of besifloxacin is of particular interest because this antimicrobial is only now becoming widely used in ophthalmology and has never been used systemically (as both gatifloxacin and moxifloxacin have been) or in an agricultural or veterinary setting. In theory, this reduces selection pressure for the development of resistance, although cross-resistance among current generation fluoroquinolones is extensive. In addition, *in vitro* studies indicate that besifloxacin has overall lower minimum inhibitory concentration (MIC₉₀) values against ocular pathogens including MRSA.¹²

ARMOR 2009 revealed a high proportion of staphylococcal infections resistant to oxacillin/methicillin and azithromycin, as well as to the fluoroquinolones. It documented multidrug resistance in 46.5% of *S. aureus*, 58% of *S. epidermidis*, 9.0% of *P. aeruginosa* and 9.3% of pneumococcal isolates.¹¹ By contrast, 97% of the *H. influenzae* isolates tested remained fully susceptible to fluoroquinolones, aminoglycosides, and macrolides.

Preliminary results from ARMOR's second surveillance year (2010) were reported at this spring's meeting of the Association for Research in Vision and Ophthalmology (ARVO).¹³ These results showed a general increase in drug

resistance over 2009 levels, particularly among the already problematic staphylococci (Figure 3). Based on MIC₉₀ values, besifloxacin, vancomycin, and imipenem were the most potent against *S. aureus* isolates, while ciprofloxacin, tobramycin, and azithromycin were the least potent.

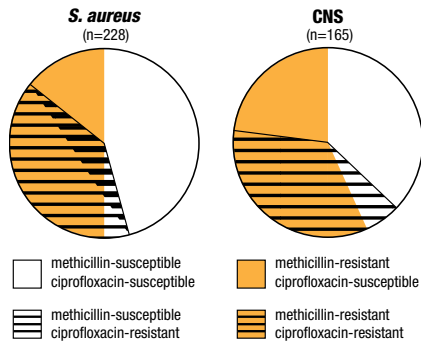


FIGURE 3 The second year of ARMOR surveillance (2010) demonstrated increased multidrug resistance among staphylococcal isolates (including *S. aureus* and coagulase-negative staphylococci, with significant but not complete overlap between methicillin/oxacillin resistance and resistance to fluoroquinolones. (Source: Reference 13) Figure courtesy of Bausch + Lomb, Inc.

Against MRSA, besifloxacin maintained potency with an MIC₅₀/MIC₉₀ of 0.5/1 µg/mL—compared with 2/8 µg/mL for moxifloxacin and 8/256 µg/mL for ciprofloxacin. *H. influenzae* remained generally susceptible to all agents; and *S. pneumoniae* resistance to penicillin remained steady at 5% but rose to 29% against azithromycin.

Topical vs Intracameral Prophylaxis

Clearly the efficacy of perioperative prophylaxis involves more than the relative potency of the various antibiotics at our disposal. *How* we deploy these antibiotics is also of prime concern, and only large clinical studies can reveal differences in the efficacy of various regimens.

In 2006, the European Society of Cataract and Refractive Surgery (ESCRS) reported the results of a multicenter clinical trial involving 16,603 cataract patients randomized to receive either intracameral injection of cefuroxime at the end of surgery or topical levofloxacin administered at 60 minutes and 30 minutes prior to surgery.^{14,15} The dramatic results showed that patients receiving intracameral

cefuroxime had a fivefold lower risk for culture-positive endophthalmitis compared to those who received the topical levofloxacin. However, even this sizeable study lacked the statistical power to show whether or not topical antibiotic prophylaxis provided a modest risk reduction over use of povidone-iodine disinfection alone. Another criticism is that the ESCRS study did not use a current generation fluoroquinolone.

HEDS

The herpes simplex virus causes approximately 50,000 cases of keratitis each year in the United States, and corneal scarring from chronic herpetic keratitis remains a significant cause of corneal blindness.^{16,17} Moreover, the trauma of ocular surgery and the intense light exposure of laser procedures can trigger the reactivation of latent Herpes simplex virus, which is near ubiquitous in the general population.^{18,19} Ocular steroids, in turn, can exacerbate the course of ocular herpes.²⁰

Fortunately, we have clear guidance on the prevention of these infections from the Herpetic Eye Disease Study (HEDS). HEDS demonstrated that long-term use of oral acyclovir (400 mg BID) can halve the annual recurrence rate of vision-threatening herpetic keratitis (14% with acyclovir vs 28% with placebo) among those who have had prior ocular outbreaks.²¹ HEDS also demonstrated that the concurrent use of an antiherpetic allows the safe employment of ocular steroids in the presence of active or latent infection.²⁰

Since HEDS, we have seen the introduction of the more potent oral antiviral valacyclovir as well as a topical ophthalmic formulation of ganciclovir, the latter being the European standard of care for the treatment of herpes keratitis for over a decade.²² Both these options—oral valacyclovir and topical ganciclovir gel—improve our options for preventing and treating herpes infections.

Povidone-iodine Disinfection

Given the persistent uncertainties regarding topical antibiotic prophylaxis, it is all the more important to remember the results Mark Speaker's research on the source of intraocular contamination

during surgery and the related efficacy of preoperative povidone-iodine disinfection. This research demonstrated that a patient's own periocular microflora is almost always the source of infection and that appropriate use of povidone-iodine disinfection can reduce the incidence of postoperative endophthalmitis.^{23,24}

Conclusion

As surgeons and general ophthalmologists, we must recognize that the ocular pathogens we see today are, in some cases, starkly different from those encountered a decade ago, with the most notable change being marked increases in the prevalence of multidrug resistance. Given local variations in bacterial strain prevalence, it behooves us to stay abreast of the most recent drug-susceptibility reports from our institutions and our communities, in addition to the larger perspective provided by national and international studies.

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When Clinical Studies Are Lacking: The Evidence and Logic behind Antiinfective Practices in Ophthalmology

Khayyam Durrani, MD, and C. Stephen Foster, MD, FACS

We in ophthalmology lack scientific proof of efficacy for many of our most common antiinfective practices. While the majority of these practices are logical extensions of indirect evidence of benefit, at least one may be both illogical and unwise.

As eye surgeons, we face an uncomfortable fact on a daily basis: We use prophylactic antibiotics based on slim evidence of tangible benefit. This doesn't mean that what we do is random or irrational; it does, however, mean that we use antibiotics for prophylaxis in ocular surgery without the benefit of large, well designed clinical trials to demonstrate the efficacy of that practice.

Evidence vs Logic

In the contemporary practice of evidence-based medicine, the gold standard is the randomized, placebo-controlled clinical

trial with sufficiently large numbers of subjects to yield a statistically valid result. In theory, there should be no problem designing such a trial to determine whether antibiotic prophylaxis reduces the risk of postoperative infection in any given ophthalmic surgery.

In reality the huge number of subjects needed to get statistically significant results in such a trial would make it prohibitively expensive. Given our extremely low rates of postoperative endophthalmitis, we would need thousands of cataract patients to determine whether prophylaxis provides a real reduction in postoperative endophthalmitis rates.

As a result, if our infection control protocols were strictly evidence-based, we would not go beyond the implementation of sterile field technique and preoperative disinfection with povidone-iodine.

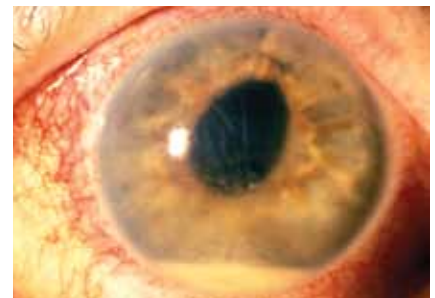


FIGURE 1 Bacterial endophthalmitis is most often caused by intraocular contamination by the patient's own microflora.

Avoiding Liability

Having said this, we concur with the near universal use of prophylactic antibiotics by North American cataract surgeons. In part, this stems from the legal liability to which surgeons would be exposed if they *didn't* use antibiotic prophylaxis. Today, antibiotic prophylaxis is the standard of care in ophthalmic surgery—any surgeon who omits it from his or her protocol would face significant legal exposure if endophthalmitis were to occur.

Beyond legal concerns, do we have scientific evidence to support a claim of medical benefit? Lacking sufficiently large and convincing clinical trials, we must rely on logic and inference. It is logical, for example, to infer that if postoperative endophthalmitis results

CORE CONCEPTS

- ▶ The efficacy of topical antibiotic prophylaxis has not been conclusively demonstrated due to the size and cost of the clinical trials that would be required.
- ▶ Logic and indirect evidence support the belief that topical antibiotic prophylaxis reduces the risk of ocular infection.
- ▶ The ESCRS study of intracameral vs topical prophylaxis does not speak directly to the efficacy of topical prophylaxis as practiced in the US.
- ▶ Preoperative povidone-iodine disinfection reduces the incidence of endophthalmitis.
- ▶ The routine use of antibiotics to treat viral conjunctivitis is unwarranted and unwise.

from bacterial contamination of the aqueous humor, then we should be able to reduce that risk with measures known to reduce the opportunities for aqueous humor contamination.

Preoperative Prophylaxis

The logic behind preoperative prophylaxis stems from the accepted paradigm of how endophthalmitis occurs. This understanding begins with the work of Mark Speaker, who determined that the pathogens that cause postoperative endophthalmitis almost always trace to a patient's own periocular flora (Figure 1).¹

We know too that, even with rigorous povidone-iodine disinfection and sterile draping techniques, bacteria commonly enter the eye during otherwise uncomplicated ocular surgery. For example, Thomas John and associates aspirated anterior chamber specimens from 53 eyes at the beginning and end of sutureless, small incision, single-port phacoemulsification cataract surgery.² At the start of surgery, 6% (3) specimens cultured positive for bacteria. At the end of surgery, 8% (4) specimens did so. Similar studies show a range of intraoperative aqueous humor contamination rates, from a low of 2% to more than 40%.³⁻⁶

Clearly these contamination rates are many times higher than the incidence of endophthalmitis, which implies that the eye's own immunologic defenses are remarkably adept at clearing small amounts of bacteria and other microorganisms. Still, it is logical to conclude that the greater the load of organisms, the greater the risk of postoperative endophthalmitis.

Following this logic, one should be able to reduce the incidence of postoperative infection by reducing the amount of viable bacteria on the ocular surface. Our most compelling evidence for this comes from clinical studies demonstrating the benefit of thorough preoperative povidone-iodine disinfection.^{7,8}

Should We Add Antibiotic?

The logic behind using topical antibiotics in addition to povidone-iodine is based, in large part, on the belief that by doing so we are further reducing bacterial

levels on the ocular surface (and thereby reducing the incidence of endophthalmitis).

To show the potential for this small but real benefit, we look to measures of how well topical antibiotics reduce bacterial levels on the eye. In one series of relevant studies, Stanford University researchers looked at differences in conjunctival bacteria levels following various prophylactic regimens. In one study, they found that antibiotic prophylaxis initiated 1 day prior to surgery resulted in significantly lower levels of conjunctival bacteria than did 1-hour preoperative prophylaxis alone.⁹ In other studies, they found that 1-day and 3-day preoperative regimens did not differ in reducing ocular surface bacterial levels, though the former increased the prevalence of drug-resistant organisms.^{10,11}

In theory, the ability of topical prophylaxis to clear the ocular surface of potential pathogens is increased by prolonging the drug's dwell time on the ocular surface. The newest fluoroquinolone, besifloxacin, has the greatest mean residence time in the conjunctiva (4.7 hours) of the current generation fluoroquinolones.¹² Beyond surface killing, the theoretical benefit of topical antibiotics is furthered by their penetration into the aqueous humor at levels sufficient to eliminate introduced bacteria. As a group, current generation fluoroquinolones achieve greater penetration into the aqueous humor than do older fluoroquinolones, and moxifloxacin demonstrates the highest penetration in the group.^{13,14}

Indeed, we have solid scientific evidence that we can achieve clinically useful intraocular levels with topical application of current generation fluoroquinolones.¹⁵⁻²¹ These studies demonstrate attainment of peak antibiotic levels that are near the minimum inhibitory concentrations (MICs) of common ocular pathogens. However, these drug levels drop significantly with aqueous humor turnover (approximately 2 hours). In addition, data shows that the peak aqueous humor levels achieved with topical fluoroquinolones vary substantially between patients and studies.^{15,21-24}

Postoperative Prophylaxis

In addition to entering the anterior

chamber during cataract surgery, we have evidence that bacteria can enter the eye postoperatively via healing wounds and/or sutures. In particular, "self-sealing," clear corneal incisions have the potential to draw surface bacteria into the eye for up to a day after surgery.²⁵

Logically, lowering bacterial levels on the ocular surface would reduce the risk of potential pathogens entering the eye postoperatively, while inhibitory levels of antibiotic inside the eye would help eliminate any bacteria that managed to enter the eye.

This logic supports the current standard practice of 1-week, postoperative use of a current generation fluoroquinolone—besifloxacin having the edge in ocular surface dwell time and moxifloxacin and gatifloxacin demonstrating relatively higher levels of penetration.

Topical vs Intracameral

Most ophthalmic surgeons are familiar with the results of the large, multicenter endophthalmitis study conducted by the European Society of Cataract and Refractive Surgery (ESCRS). This study compared the efficacy of a prophylactic regimen of topical levofloxacin 0.5%

(one drop at 60 and 30 minutes before surgery followed by three pulsed drops 5 minutes apart at the close of surgery) with the intracameral injection of cefuroxime (1 mg at the close of surgery).²⁶ In this study, intracameral injection reduced endophthalmitis rates by approximately fivefold over controls, while the topical levofloxacin drop regimen did not achieve a statistically significant effect.

While clearly demonstrating a benefit to intracameral antibiotics, this study failed to address American clinicians' need for a definitive judgment on topical prophylaxis. Why? The ESCRS used the wrong drop. For a comparison to be useful to US surgeons, it would need to have employed one of the later generation fluoroquinolones currently used in the US—and one with better corneal penetration than levofloxacin 0.5%.

From an American perspective, the ESCRS study had other problematic aspects as well. We do not, for example, have access to a cefuroxime formulation suitable for intracameral injection. Self-mixing, in turn, introduces room for error and potential toxicity. Finally, we must weigh the potential benefit of intracameral injection against the costs associated with its implementation.

Could Povidone-iodine Be Enough?

As mentioned, only povidone-iodine disinfection of the eyelids and conjunctiva meets the gold standard of proven efficacy in reducing the incidence of postoperative endophthalmitis. In 1991, Speaker and Menikoff established a clear disinfection protocol for ophthalmic surgeons and inspired further research into maximizing this protection.⁷ In 2006, Wu and coworkers analyzed the records of 10,614 cataract surgeries that included 12 cases of postoperative endophthalmitis and then compared these 12 cases against 120 control eyes matched for age and gender.⁸ They found that preoperative application of 5% povidone-iodine to the conjunctiva combined with application of 10% povidone-iodine to the periocular area significantly decreased the postoperative infection rate compared to no conjunctival povidone-iodine and 5% povidone-iodine skin disinfection.

Most recently, we have the results of a prospective case series from Japan that involved 404 consecutive eyes undergoing cataract surgery. Half the eyes received near-continuous irrigation with 0.25% povidone-iodine via the infusion fluid delivered through the phaco hand-piece. The eyes in the control group were irrigated with standard infusion fluid. Cultures of the ocular surface at the start of surgery showed

no significant differences in bacterial levels between the two groups of patients. By contrast, culture of anterior chamber fluid taken at the end of surgery revealed no viable bacteria (0%) in the eyes that received the povidone-iodine irrigation compared to the presence of viable bacteria in 10 eyes (5%) from the control group.²⁷

When Antibiotic Use Defies Logic

While indirect evidence supports the use of antibiotics in surgical prophylaxis, the routine use of topical antibiotics for the treatment of viral conjunctivitis defies all logic. Research demonstrates that eye physicians do not do very well at distinguishing bacterial from viral conjunctivitis during the first week of infection (a 42% misdiagnosis rate).²⁸ Many practitioners reach for a prescription rather than look for clinical signs that might point them to a clear diagnosis of bacterial vs viral infection (Figure 2).

This is inappropriate on many levels, beginning with the hard reality that the indiscriminate use of antibiotics encourages the emergence of drug-resistant ocular pathogens. In addition, antibiotics represent a significant cost to our patients and the healthcare system. Thus, prescribing antibiotics to treat viral conjunctivitis has significant downsides and provides no benefit whatsoever—other than speeding the patient's exit from the office.

Of course, we have all seen cases where viral conjunctivitis leads to secondary bacterial infection. At the Massachusetts Eye Research and Surgery Institution, we



FIGURE 2 Simply examining the eye typically does not provide enough information to distinguish between adenoviral conjunctivitis (photo on left) and bacterial conjunctivitis (photo on right). A careful history and the presence or absence of a palpable preauricular node can be helpful in determining the cause. Using antibiotics to treat viral disease is ineffective but not innocuous—inappropriate use of antibiotics is expensive and can foster the development of resistant bacteria. (Photo courtesy of Shachar Tauber, MD)

take this possibility seriously and, so, culture and/or closely monitor patients with probable viral conjunctivitis to ensure that their condition does not worsen.

The safety and efficacy of this “watch and wait” approach has the support of a randomized controlled trial involving 307 patients with acute infective conjunctivitis at 30 general practices in the south of England.²⁹ The patients were randomized to receive an immediate antibiotic, no antibiotic, or delayed antibiotic (3 days after presentation). These prescribing strategies made *no* significant difference in severity of symptoms or resolution of infection. The researchers concluded—and we agree—that logic favors a delayed prescription for antibiotic (to be used only if needed) as the most appropriate course for managing acute conjunctivitis.

Khayyam Durrani, MD, is a fellow in the Ocular Immunology and Uveitis training program at the Massachusetts Eye Research and Surgery Institution, Cambridge, MA. He states that in the past 12 months, he has not had a financial relationship with any commercial organization that produces, markets, re-sells, or distributes healthcare goods or services consumed by or used on patients. C. Stephen Foster, MD, FACS, is a clinical professor of ophthalmology at Harvard Medical School, a consulting staff member of the Massachusetts Eye and Ear Infirmary, and the founder and president of the Ocular Immunology and Uveitis Foundation and of the Massachusetts Eye Research and Surgery Institution. He states that in the past 12 months he has been a consultant to Abbott Medical Optics, Lux Biosciences, and Novartis Pharmaceuticals; and he has received grant support from Alcon, AMO, Allergan, Lux Biosciences, and Novartis. He is also an equity owner of Eyegate Pharma.

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UPCOMING TOPICS

- **Pharmacokinetics and Pharmacodynamics: A Review for Clinical Ophthalmologists**
- **Fluoroquinolones in Ophthalmology: Past, Present, and Future**

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EXAMINATION QUESTIONS TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 24

This CME program is sponsored by the University of Florida College of Medicine and supported by an unrestricted educational grant from Bausch + Lomb, Inc. **DIRECTIONS:** Select the one best answer to each question in the Exam (Questions 1-10) and in the Evaluation (Questions 11-16) below by circling one letter for each answer. Participants must score at least 80% on the questions and complete the entire Evaluation section on the form below. The University of Florida College of Medicine designates this activity for a maximum of 1.0 AMA PRA Category 1 Credit™. There is no fee to participate in this activity. You can take the test online at <http://cme.ufl.edu/ocular>.

- Over the 4-year span of the PROTEKT study, the percentage of isolates carrying both the erm(B) and the mef(A) resistance elements increased between which of the following levels?
 - 0% to 9.7%
 - 9.7% to 18.4%
 - 18.4% to 36.8%
 - 36.8% to 44.4%
- According to Ocular TRUST data, *H. influenzae* isolates were fully susceptible to all tested antibiotics except:
 - Trimethoprim and tobramycin
 - Moxifloxacin and gatifloxacin
 - Ciprofloxacin and levofloxacin
 - Amikacin and gentamicin
- In HEDS the annual recurrence rate of herpetic stromal keratitis was reduced to:
 - 6% with acyclovir vs 45% with placebo
 - 12% with acyclovir vs 80% with placebo
 - 14% with acyclovir vs 28% with placebo
 - 60% with acyclovir vs 8% with placebo
- Which of the following has been conclusively shown to reduce endophthalmitis rates following cataract surgery?
 - Intracameral cefuroxime
 - Povidone-iodine disinfection
 - Neither A nor B is correct
 - Both A and B are correct
- Resistance to vancomycin in enterococci is worrisome to ophthalmology because:
 - Enterococci make up a large part of the normal ocular flora
 - Enterococci cause more than half of all endophthalmitis
 - Resistance elements are readily shared, and vancomycin is often the drug of last resort in ocular infection
 - All of the above are true
- The efficacy of topical antibiotic prophylaxis in ocular surgery is based on which of the following?
 - Clinically significant reductions in endophthalmitis as demonstrated in large randomized clinical trials
 - Logical inference from indirect evidence of benefit
 - Clinical studies involving the use of systemic antibiotics
 - Clinical studies on the treatment of infectious conjunctivitis
- Which of the following best describes Durrani and Foster's objection to the ESCRS endophthalmitis study's conclusion of no benefit to topical prophylaxis in cataract surgery?
 - The study was not properly randomized
 - The study population did not include North American patients
 - The study employed an older generation fluoroquinolone
 - The study was not masked
- In studies of intraoperative bacterial contamination of the aqueous humor, positive culture rates have ranged between which of the following low-to-high values?
 - 1% to 5%
 - 1% to 10%
 - 2% to 12%
 - 2% to 40%
- Which of the following factors support the use of postoperative antibiotic prophylaxis?
 - Bacteria can enter the eye through healing incisions
 - Topical antibiotics reduce levels of ocular surface bacteria
 - Topical fluoroquinolones can achieve greater-than-MIC levels in the aqueous humor
 - All of the above
- In a randomized controlled trial described by Durrani and Foster, a 3-day delay in the antibiotic treatment of acute infectious conjunctivitis resulted in which of the following?
 - No significant difference in symptom severity or infection duration compared to immediate antibiotic treatment
 - A worsening of symptoms compared to immediate antibiotic treatment
 - A significant prolongation of infection compared to immediate treatment
 - A shortening of symptoms compared to immediate antibiotic treatment

EXAMINATION ANSWER SHEET TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 24

This CME activity is jointly sponsored by the University of Florida and Candeo Clinical/Science Communications, LLC, and supported by an unrestricted educational grant from Bausch + Lomb, Inc. Mail to: University of Florida CME Office, PO Box 100233, Gainesville, FL 32610-0233. **DIRECTIONS:** Select the one best answer for each question in the exam above (Questions 1–10). Participants must score at least 80% on the questions and complete the entire Evaluation (Questions 11-16) to receive CME credit. CME exam expires September 30, 2012.

ANSWERS:

- | | |
|------------|-------------|
| 1. A B C D | 6. A B C D |
| 2. A B C D | 7. A B C D |
| 3. A B C D | 8. A B C D |
| 4. A B C D | 9. A B C D |
| 5. A B C D | 10. A B C D |

EVALUATION:

1=Poor 2=Fair 3=Satisfactory 4=Good 5=Outstanding

- Extent to which the activity met the identified
 - Objective 1: 1 2 3 4 5
 - Objective 2: 1 2 3 4 5
 - Objective 3: 1 2 3 4 5
 - Objective 4: 1 2 3 4 5
- Rate the overall effectiveness of how the activity:
 - Related to my practice: 1 2 3 4 5
 - Will influence how I practice: 1 2 3 4 5
 - Will help me improve patient care: 1 2 3 4 5
 - Stimulated my intellectual curiosity: 1 2 3 4 5
 - Overall quality of material: 1 2 3 4 5
 - Overall met my expectations: 1 2 3 4 5
 - Avoided commercial bias/influence: 1 2 3 4 5
- Will the information presented cause you to make any changes in your practice? Yes No
- If yes, please describe: _____
- How committed are you to making these changes? 1 2 3 4 5
- Are future activities on this topic important to you? Yes No

If you wish to receive credit for this activity, please fill in the following information. Retain a copy for your records —

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