A CONTINUING MEDICAL EDUCATION PUBLICATION

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TOPICS IN Ocular Antiinfectives

Infectious Blepharitis and Ocular Surgery

Thomas John, MD

Recognizing and resolving microbial blepharitis before cataract or refractive surgery can pay double dividends by both reducing the risk of postoperative infection and increasing patient satisfaction with the visual outcome. Too often, however, clinicians pay scant attention to the eyelid margins in the preoperative workup and, as a result, may fail to treat significant blepharitis.

FIGURE 1 Combined anterior and posterior blepharitis: note the occlusion of the meibomian gland orifices with lid margin keratinization and crusting of the eyelashes. (Figure courtesy of Thomas John, MD).

I have long urged a more aggressive approach to the treatment of inflammatory lid disease. This is especially critical prior to ocular surgery, particularly when the etiology of the lid disease is microbial. Avoidance of postoperative infection and reduction of postoperative inflammation are key issues in any ocular surgery. When left untreated, infectious blepharitis can contribute to both of these unwanted and sometimes devastating complications.[1]

Blepharitis and Surgery

My own research and that of others has shown that even uncomplicated intraocular surgery can introduce bacteria into the anterior chamber. In our study of 53 eyes undergoing phacoemulsification surgery, three specimens (6%) aspirated on entry into the anterior chamber cultured positive for live microorganisms, as did four specimens (8%) obtained at the end of surgery.[2] This proved true despite a rigorous preoperative regimen that included both topical antibiotic and povidone-iodine.

Research has also taught us that the bacteria behind most cases of postoperative endophthalmitis can be traced back to a patient's own periocular microflora.[3]

The density of microbes on the ocular surface increases markedly in the presence of infectious blepharitis due to spillover from the infected lid margin into the tear film. We see evidence of this in recent work by Miño de Kaspar and coworkers, who looked at 1,474 patients undergoing intraocular surgery.[4] They associated local risk factors such as blepharitis with an almost five-fold increase in the prevalence of positive conjunctival cultures (from 5% positive in controls with no risk factors to 24% among those with local risk factors).

In another study, these researchers demonstrated that the conjunctival bacteria isolated from patients with blepharitis are significantly more likely to be multidrug resistant than those isolated from patients without such local risk factors.[5] For all these reasons, unresolved blepharitis is likely to be a major risk factor for postoperative infection.[4]

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. State three reasons why it is important to resolve blepharitis prior to ocular surgery and describe a proactive approach to diagnosing and treating blepharitis.
2. Improve their selection of ophthalmic antibiotics based on an improved understanding of multidrug resistance in common ocular pathogens including MRSA.
3. Improve practice-based infection control protocols and antibiotic use patterns based on greater understanding of their role in the emergence of drug-resistant pathogens.

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Blepharitis and Outcomes

Refractive surgeons have always focused on optimizing visual acuity and overall vision quality in the immediate postoperative period. With the introduction of presbyopia correcting intraocular lenses (IOLs), cataract surgeons have likewise become keenly interested in delivering the highest quality postoperative vision. This focus on immediate patient satisfaction provides further reason to fully resolve preoperative blepharitis, as failure to do so is clearly linked to less favorable refractive outcomes.

By what mechanism does blepharitis impact refractive outcomes? First, blepharitis can produce tear-film abnormalities that may make it impossible to obtain an accurate preoperative wavefront scan.[6] So, failure to recognize and resolve blepharitis before surgery can reduce the quality of data used to drive the excimer laser and, therefore, the quality of its results.

Postoperatively, blepharitis-related tear-film abnormalities can degrade image quality and exacerbate postoperative discomfort.[7] My research team recently used anterior segment optical coherence tomography (OCT) to show that the tear meniscus of patients with posterior blepharitis is significantly decreased.[8]

And in a recent retrospective chart review performed at the Wills Eye Institute, blepharitis and/or dry eye disease was the most common diagnosis (27.8%) among patients being seen for complaints related to recent LASIK surgery.[9]

Infectious Blepharitis

Blepharitis has many etiologies and manifestations. Infectious blepharitis most often involves the anterior lid margin, and *Staphylococcus aureus* or *Staphylococcus epidermidis* are the most commonly isolated culprits. Overgrowth of these bacteria can affect the meibomian glands, causing meibomian gland dysfunction (MGD) and associated posterior blepharitis. Conversely, nonmicrobial inspissation of meibomian secretions can foster bacterial overgrowth, which can trigger a vicious cycle of further inspissation and infection (Figure 1).

Demodex Mites

Infestation with *Demodex* mites is now recognized as a cause of highly symptomatic blepharitis. These patients often complain of ocular itching, irritation, and scaling of lids with possible

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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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OFF-LABEL USE STATEMENT This work discusses off-label uses of antiinfective medications.

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System requirements for this activity are: *For PC users:* Windows® 2000, XP, 2003 Server, or Vista; Internet Explorer® 6.0 or newer, or Mozilla® Firefox® 2.0 or newer (JavaScript™ and Java™ enabled). *For Mac® users:* Mac OS® X 10.4 (Tiger®) or newer; Safari™ 3.0 or newer, Mozilla® Firefox® 2.0 or newer; (JavaScript™ and Java™ enabled).

Internet connection required: Cable modem, DSL, or better.

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DISCLAIMER Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and professional development. The information presented in this activity is not meant to serve as a guideline for patient care. Procedures, medications, and other courses of diagnosis and treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers in use, applicable manufacturer's product information, and comparison with recommendations of other authorities.

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secondary dry eye symptoms, namely: burning, foreign body sensation, and blurred vision. A clinically significant sign in demodicosis is the presence of a collar of tissue surrounding the base of the mite-infested eyelashes.

Demodex folliculorum makes its home in the lash follicles. Its smaller cousin, *Demodex brevis*, burrows into the meibomian and sebaceous glands to block their orifices and produce MGD and evaporative dry eye.[10] The former organism causes anterior blepharitis, while the latter causes posterior blepharitis.

Kim and colleagues recently investigated how it is that *Demodex* can produce such dramatic inflammation and found highly elevated concentrations of the inflammatory cytokine IL-17 in the tears of patients with confirmed *Demodex* infestation (compared to the tears of healthy individuals).[11] This finding helps explain the marked discomfort and telangiectasia frequently found in these patients.

Diagnosis

I believe that blepharitis is one of the most underdiagnosed and undermanaged conditions in ophthalmology. Too often, clinicians give examination of the lid margins short shrift in their haste to address the more prominent signs and symptoms of dry eye. Yet many of the most prominent signs and symptoms of ocular surface disease—dryness, grittiness, burning, redness, and decreased tear lake—can stem from lid inflammation. This is in part because lid inflammation tends to compromise meibomian gland function.[12] And when there is bacterial overgrowth, microbial proteases and lipases can further destabilize the tear film.[13]

For this reason, I recommend making the eyelid margin the initial "landing strip" for the examination. Traversing the entire strip with the slit lamp, I look carefully for the classic blepharitis signs of swelling, thickening, and reddening of the lids—with further attention focused on distinguishing anterior, posterior, or mixed involvement.

I also look at the eyelashes themselves. With the slit lamp light shining directly on the lashes, I note gaps (missing lashes or madarosis), crusting, or lash adherence.

The lid margin is one of the few places in the human body where skin and mucous membrane meet. This demarcation line may be used as a rough guide to differentiating anterior blepharitis from posterior, with the former localized predominantly in the skin part of the eyelid strip and the latter involving the mucosal part of this eyelid strip. I look first for signs of increased keratinization of the skin. If it is present, does it crossover onto the mucosa? In particular, I note whether the lid margin strip shows increased vascularity. Classically, bacterial overgrowth of the anterior lid margin produces crusting and adherence of the lashes (Figure 2). By contrast, scaly dandruff-like debris on the anterior lid margin suggests noninfectious seborrheic blepharitis. (Infectious and seborrheic blepharitis can also coexist.)

Meibomian Glands

In a stepwise manner, the examination should then progress to the meibomian gland orifices. Visual examination and expression can help determine whether these glands are normal or occluded. When there is bacterial overgrowth affecting the meibomian glands, expression of the glands may prove unproductive or produce opaque and thickened secretions, which at the extreme resemble toothpaste (Figure 3).

Whether anterior or posterior, staphylococcal blepharitis commonly produces discharge and is associated with a bubbly, or foamy, tear meniscus. It can also produce ulceration and other alterations of the lid margin, as well as sterile infiltrates of the peripheral cornea.

D. folliculorum infestation, in turn, often produces the telltale sign of circular scales, sometimes called "sleeves" or "collarettes," around the base of eyelashes; and longstanding infestation can produce significant lash loss.[14] Oftentimes, the clinician can isolate and view mites simply by plucking one or two lashes and examining them under a low power microscope. The smaller *D. brevis* is more difficult to extract and view, and its infestation of the meibomian glands can be difficult to distinguish from other forms of MGD.

CORE CONCEPTS

- **Blepharitis may be among ophthalmology's most underdiagnosed yet clinically significant conditions.**
- **Failure to resolve infectious blepharitis prior to surgery increases the risk of postoperative infection and disappointing visual outcomes.**
- **Staphylococci are the most common microbial causes of anterior blepharitis, while *Demodex* mites are an increasingly recognized cause of highly symptomatic infections.**
- **Blepharitis treatment should be tailored according to etiology and severity.**
- **Elective ocular surgery should be put off until infection is resolved and inflammation minimized.**

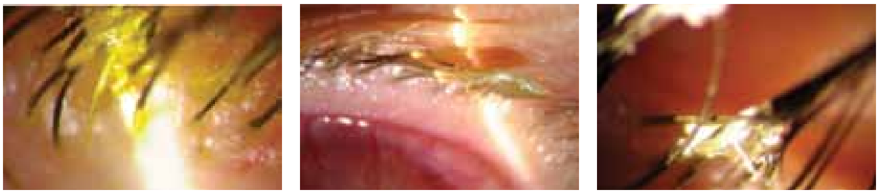

FIGURE 2 Anterior blepharitis with matting of the eyelashes. (Figure courtesy of Thomas John, MD).

FIGURE 3 Posterior blepharitis with toothpaste-like meibomian gland secretion. (Figure courtesy of Kenneth R. Kenyon, MD)

In this stepwise manner, the clinician can identify the inflammatory and infectious components of anterior, posterior, or mixed blepharitis. Even before the slit lamp examination, the clinician can pick up clues to infectious blepharitis by simply observing patients and listening to their ocular complaints. Facial rosacea, for example, is commonly associated with blepharitis and/or may be secondary to *Demodex* infestation. Patient complaints of sticky eyelashes on waking suggests anterior blepharitis, while "sandpaper eye" on waking suggests posterior blepharitis, or MGD. Infectious blepharitis can also produce patient complaints of ocular burning, foreign body sensation, frequent blinking, and photosensitivity.

Treatment

Whatever its form or etiology, blepharitis warrants postponement of elective ocular surgery until the inflammation and/or infection are resolved.

Treatment begins with faithful adherence to a regimen of eyelid hygiene with either baby shampoo diluted with sterile saline solution or a commercially available lid scrub. The patient should use their chosen lid scrub at least twice daily, followed by warm compresses.

Beyond lid hygiene, treatment should proceed according to classification of the etiology and degree of signs and symptoms (Tables 1 and 2). Nighttime application of erythromycin, bacitracin ointment, or azithromycin solution 1% can help control staphylococcal infection and related inflammation. I instruct patients to apply the antibiotic solution directly to the eye lashes and lid margin, gently rubbing it into the lashes, or to apply the antibiotic ointment in the lower conjunctival sac while pulling lid away from the eye with the other hand.

A number of antibiotics demonstrate antiinflammatory powers that can help resolve posterior blepharitis. These include oral tetracycline or doxycycline. While it was once common to dose oral doxycycline at 100 mg, we now know that 20 mg twice a day is quite effective and has far fewer systemic side effects. After 1 week, the frequency of dosing can be decreased to once a day and then maintained for an additional 3 weeks.

TABLE 1

Graded treatment of anterior blepharitis (skin)
1 (Trace) and 2 (Mild) • Lid hygiene with diluted baby shampoo • Ophthalmic antibiotic ointment or drops QHS to lashes and lid margins
3 (Moderate) • Lid hygiene with commercial cleanser • Ophthalmic antibiotic QHS to lashes and lid margins • Topical calcineurin inhibitors* (TCI) – Tacrolimus or Pimecrolimus ointment
4 (Severe) • Lid hygiene with commercial cleanser • Ophthalmic antibiotic QHS to lashes and lid margins • Topical steroid cream – short course • Stop steroid and start TCI • Shampoo and lotions containing • Selinium sulfide • Zinc pyrithone
* Decreases inflammation; useful in seborrheic and atopic dermatitis

TABLE 2

Graded treatment of posterior blepharitis (mucosa)
1 (Trace) and 2 (Mild) • Warm compress • Ophthalmic antibiotic ointment or drops QHS
3 (Moderate) • Warm compress • Ophthalmic antibiotic ointment or drops QHS • Mechanical expression • Cyclosprine BID • Omega-3 nutritional supplement
4 (Severe) • Warm compress • Ophthalmic antibiotic ointment or drops QHS • Mechanical expression • Cyclosprine BID • Omega-3 nutritional supplement • Systemic treatment: – Adults (any of the following): Tetracycline** Doxycycline Minocycline – Children: Erythromycin
** If allergic to tetracycline, consider clarithromycin

Corticosteroids should be reserved for severe inflammatory responses, as when staphylococcal blepharitis produces marginal keratitis or phlyctenular keratoconjunctivitis. These conditions can be treated with a mild topical corticosteroid for a relatively short period of time to minimize associated risks.

Demodex Treatment

In recent years, a number of studies have demonstrated the efficacy of tea tree oil in either controlling *Demodex* infestation or significantly lowering the density of the mites and the associated inflammation. Highly astringent, tea tree oil should never be used undiluted, but should be mixed in equal parts with mineral oil. The result is a lid scrub with demonstrated antibacterial, antifungal, and antiinflammatory effects.[15]

A more recent and promising *Demodex* treatment comes in the form of the broad-spectrum antiparasitic agent ivermectin, approved by the US FDA for the treatment of intestinal thread worms and onchocerciasis ("river blindness"). Treatment typically consists of a single oral dose based on body weight (200 mg per kg). This systemic dose is generally well tolerated, with the most commonly reported side effects including pruritus, mild nausea, diarrhea, and dizziness.[16]

In a recent uncontrolled case series of 12 patients with refractory posterior blepharitis, patients were given two doses of oral ivermectin spaced 1 week apart. They showed an overall decrease in the number of *D. folliculorum* isolated on lash sampling, as well as an overall improvement in Schirmer test values and tear film breakup time.[17]

Proceeding to Surgery

When I initiate preoperative treatment of blepharitis, I generally instruct the patient to return in 3 to 4 weeks for reevaluation. Knowing that it may not be possible to totally eradicate blepharitis, I nonetheless look for a significant degree of clinical resolution. Only when I feel that infection is resolved and inflammation minimized and well controlled do I schedule the patient for surgery. It is not usually possible to completely eradicate blepharitis with treatment.

Thomas John, MD, is a clinical associate professor at Loyola University, Chicago, visiting professor, Department of Defense, Military Medical Academy, Belgrade, Serbia; and in private practice in Oak Brook, Tinley Park, and Oak Lawn, IL. He states that in the previous twelve 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.

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Beyond MRSA: Emerging Resistance in Common Ocular Pathogens

Gail L. Torkildsen, MD

While the increasing prevalence of MRSA demands clinical attention, ophthalmologists should also be guided by what surveillance studies tell us about the emergence of other drug-resistant pathogens.

Over the last 20 years, several large surveillance studies have revealed disturbing patterns of drug-resistance in a number of ocular pathogens. The dramatic spread of methicillin-resistant *Staphylococcus aureus* (MRSA) has garnered the most attention, and deservedly so. Yet it behooves us as clinicians and surgeons to look beyond MRSA to gauge the challenges we face from the emergence of multidrug resistance.

Insights from the Alexander Project

Initiated in 1992, the Alexander Project was an international, multicenter, longitudinal surveillance study of antimicrobial susceptibility among common pathogens. Specifically it looked for emerging patterns of resistance in *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* at national, regional, and global levels.[1]

This 10-year survey was historic in that, at the time, there was little data that had been collected in a way that allowed meaningful comparisons between studies, locations, or over time. The project employed central laboratories and standardized methods for the collection of isolates and determination of susceptibility. Determination and publication of quantitative minimum inhibitory concentrations (MICs) enabled assessment of changes in susceptibility distribution and potential clinical efficacy.

Of particular importance, the juxtaposition of antimicrobial usage patterns and resistance prevalences enabled making hypotheses about the role of antimicrobial use in the selection and spread of resistance. The collection of isolates that resulted from the project has continued to provide a valuable resource for studies into the evolution of resistance over time.

Of immediate importance, the Alexander Project revealed the global emergence of multidrug resistance in all three strains of bacteria being tracked. On an international level, this was and continues to be disturbing. It clearly demonstrates the rapidity of the evolution of bacterial resistance and provides insights into geographic and national variations in the development of antibiotic resistance, with implications that local patterns of antibiotic use may be a driving factor (Figure 1).

CORE CONCEPTS

- By 2002, global surveillance showed emerging multidrug resistance in *S. pneumoniae, H. influenzae* and *M. catarrhalis.*
- Antibiotic prescribing patterns may drive local differences in the prevalence of drug resistance.
- Research reveals highly mobile genetic elements behind the spread of multidrug resistance.
- With the exception of MRSA, common ocular pathogens remain susceptible to current generation fluoroquinolones.
- Rigorous infection control can help slow the rise and spread of drug resistance.

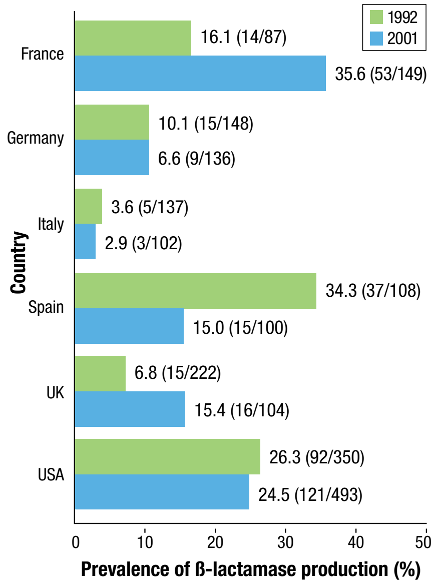

FIGURE 1 The Alexander Project was the first large surveillance study to suggest that national and regional variations in antibiotic use may be responsible for differing rates of emerging drug resistance—illustrated here by increased production of beta-lactamase (which neutralized beta-lactam antibiotics) among isolates *H. influenzae*. (Data source: Reference 1.)

Insights from PROTEKT

By the end of the 20th century, antimicrobial resistance had increased markedly in the United States as well as globally. In 2000, PROTEKT US (Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin in the US) was initiated to monitor resistance trends in *S. pneumoniae* and other common respiratory pathogens.[2]

Over its first 4 years, this US survey confirmed relatively high levels of resistance to many antimicrobial agents, including penicillin, azithromycin, second-generation cephalosporins, macrolides, tetracyclines, and/or trimethoprim-sulfamethoxazole. For example, among the 39,495 *S. pneumoniae* isolates tested, the percentages resistant to erythromycin and penicillin were 29.3% and 21.2%, respectively—though with marked regional variability in these rates.

Importantly, PROTEKT looked at the genetic mechanisms of resistance and identified a high prevalence of mobile resistance elements capable of spreading to other bacterial pathogens. Over the 4-year course of the study, the percentage of isolates carrying both erm(B) and mef(A) resistance elements increased from 9.7% to 18.4%. And over 99% of all the erm(B)+mef(A)-positive isolates collected exhibited multidrug resistance (Figure 2).

In a glimmer of relative good news, the proportion of isolates exhibiting multidrug resistance remained stable, at approximately 30%, over the study period. Unfortunately multidrug resistance among pneumococcal isolates continues to increase today and poses a growing worldwide health threat.

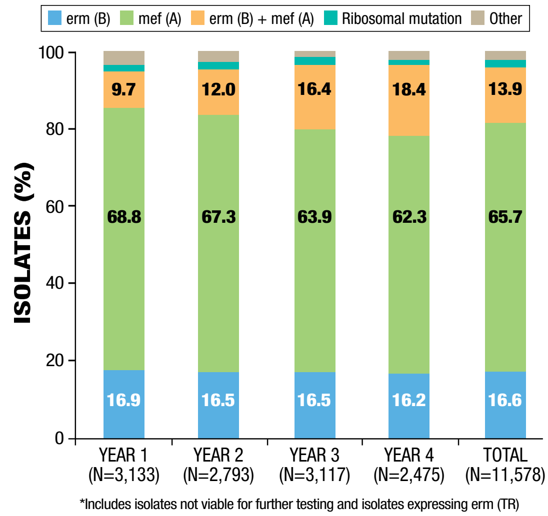

FIGURE 2 PROTEKT revealed the growing prevalence—and genetic mechanisms--of multidrug resistance in clinical isolates of *S. pneumoniae* across the United States. (Data source: Reference 2)

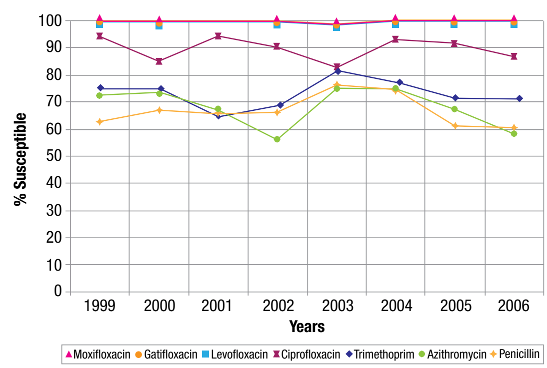

FIGURE 3 According to Ocular TRUST testing, *Streptococcus pneumonia* isolates remained highly susceptible to current-generation fluoroquinolones up through 2006. (Data source: Reference 3.)

Ocular TRUST

With the introduction of levofloxacin in 1996, the Food and Drug Administration (FDA) began requiring antimicrobial susceptibility surveillance for all new systemically administered antibiotics. Initiated that same year, the TRUST program (Tracking Resistance in the US Today) has drawn on this database to put local findings of antibiotic resistance into perspective with national trends. In the TRUST study, isolates are submitted to a central laboratory by over 200 clinical laboratories across all 50 states.

Although ocular isolates have been among the TRUST isolates since the program's inception, there was no systematic tracking of the in vitro susceptibility of ocular pathogens until TRUST was expanded to include an eye-specific substudy—Ocular TRUST—in 2005/2006.

In 2008, the Ocular TRUST reported on its first year results, with particular focus on the fluoroquinolones so widely used in ophthalmology.[3] The data confirmed that fluoroquinolones remained the most consistently active antibiotics across the range of all common ocular pathogens (Figure 3).

However, Ocular TRUST, like PROTEKT and the Alexander Project before it, employed susceptibility testing standards based on reasonably achievable blood plasma levels rather than on the reasonably achievable ocular levels more clinically relevant to ophthalmology. So these results may not be a particularly accurate reflection of the clinical efficacy of the antibiotics we commonly use to treat ocular infections.

In vitro testing, such as that performed in the Ocular TRUST, also fails to take into consideration factors that can influence an antibiotic's clinical action—including dwell time on the ocular surface and penetration into the aqueous humor.

While Ocular TRUST data has shown high levels of antimicrobial efficacy against methicillin-sensitive *S. aureus* (MSSA), the picture was less rosy for methicillin-resistant *S. aureus* (MRSA). With the exception of trimethoprim and tobramycin, ophthalmic antimicrobials demonstrated efficacy against less than a third of the MRSA strains tested.

The results also demonstrated that, overall, staphylococcal isolates tend to be more susceptible to the fluoroquinolones than to azithromycin. Gatifloxacin and moxifloxacin demonstrated equivalent efficacy, indicating that resistance to one implies resistance to the other. Not included in the first year of the Ocular TRUST was the newest fluoroquinolone: besifloxacin, which has demonstrated somewhat greater efficacy against MRSA in both animal and in vitro studies.[4-6]

Beyond the staphylococci, Ocular TRUST showed current generation fluoroquinolones to be consistently active against *S. pneumoniae*, and *H. influenzae*—a tremendous reassurance after more than a decade of intensive systemic use of older fluoroquinolones such as ciprofloxacin. Even resistance to ciprofloxacin remained under 15%, and *H. influenzae* isolates remained fully susceptible to all tested antibiotics *except* trimethoprim and tobramycin.

Maximizing the Efficacy of Ophthalmic Formulations

Of all the types of medications used in ophthalmology, antibiotics are the only class that we expect to decline in efficacy in the years ahead. For ophthalmic antibiotics to maintain their efficacy against a highly adaptive bacterial kingdom, they too must continue to evolve.

We know, for example, that bacteria can become resistant to fluoroquinolones through genetic mutations that alter the antibiotic's target within the bacterial cell. Bacteria can also upregulate their efflux pump mechanisms—giving them the ability to expel antibiotics nearly as fast as the drug molecules enter the bacterial cell. The end result is that the drug binds less strongly (or not at all) to its molecular target and/or is unable to achieve effective concentrations within the microbial cell.

With *topical* ophthalmic antibiotics, we have the opportunity to try to tip the balance by increasing concentrations in target ocular tissue to overcome moderate levels of drug resistance. To do so, drug developers are continually experimenting with new topical formulations to improve such factors such as an antibiotic's dwell time on the ocular surface or its penetration rate in to the aqueous humor.

Besifloxacin, for example, is formulated with a mucoadhesive delivery vehicle that helps sustain significant drug levels in the tear film and on the ocular surface.[7] Moxifloxacin, in turn, has better penetration into the aqueous humor, as demonstrated by a recent study by Balzli and associates.[8]

Our own group recently demonstrated that besifloxacin, gatifloxacin, and moxifloxacin all reach peak mean concentrations in conjunctival tissue 15 minutes after dosing, with concentrations of 2.30 +/- 1.42 mg/g for besifloxacin, 4.03 +/- 3.84 mg/g for gatifloxacin, and 10.7 +/- 5.89 mg/g for moxifloxacin.[7]

Besifloxacin, in turn, had the greatest mean residence time (4.7 hours) in conjunctival tissue. With regard to methicillin-resistant strains of *S. aureus* and *Staphylococcus epidermidis*, besifloxacin had the greatest area-under-the-curve (AUC) to MIC_{90} ratio. All three topical fluoroquinolones were well tolerated.

The Clinician's Role

In an age when antimicrobial resistance poses an increasing threat to health, it is important to remember the importance of basic sanitation in slowing the cycle of person-to-person spread of infection. Thorough hand washing and alcohol-based hand sanitizers are proven tools in this fight, and clinicians should take full advantage of these measures and insist on their consistent use by staff members. Also important is a consistent protocol for appropriate cleaning of equipment and other relevant exam room and operating suite surfaces between patients. Remember that bacteria can remain viable in linens, clothing, and dust for hours, sometimes more than a day.

Physicians can also advocate and implement improved drug recycling programs to decrease the level of antibiotic exposure via the environment. We can likewise support professional and public campaigns that seek to rein in the alarming amount of inappropriate antibiotic use we see in our communities. This overuse is particularly great in countries that allow the sale of antibiotics without prescription, but it is a problem in our own nation as well.

On a positive note, US physicians have been doing a much better job of educating patients that antibiotics are not warranted with viral infections unless there is a clear threat of secondary bacterial involvement. I also see tangible benefits from public awareness campaigns about the appropriate use of antibiotics, such as the "Get Smart" campaign of the Centers for Disease Control and Prevention (http://www.cdc.gov/getsmart/).

Emerging Pathogens of Tomorrow

Vaccines are a boon in that they lower antibiotic use by harnessing the immune system to eradicate pathogens before clinical infection can develop. However, they can induce a kind of replacement phenomenon when their elimination of targeted strains allows other, less common strains to increase in prevalence. We may be seeing this, for example, with pneumococcal vaccines. It is a trend to watch, as it can be difficult to predict the antibiotic susceptibility of rapidly emerging strains.

A more dramatic threat lies in the simple reality of our growing global population, with crowding and increased travel fostering the rapid spread of pathogens. At the same time, many pharmaceutical companies have indicated that they are curtailing antiinfective research programs.[9] Here, too, I see a role for advocacy on the part of physician groups—in this case for a renewed focus on federal incentive programs such as tax credits or increased grant funding for antibiotic research.

Meanwhile, drug-resistant strains of *S. pneumoniae* and *S. epidermidis* are becoming increasingly prevalent and we are seeing a rise in mortality rates among patients with bacteremia caused by multidrug-resistant *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, and coagulase-negative staphylococci. How are these organisms able to neutralize the efficacy of antibiotics? How do patients commonly come into contact with these organisms? For the pathogens that cause ocular infection, what can studies tell us about how resistance prevalence is affecting our ability to prevent and treat ophthalmic infections? We need answers to these questions in our continuing struggle with the age-old challenge of infectious disease.

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UPCOMING TOPICS

- **Evidence and Logic behind Antiinfective Practices in Ophthalmology**
- **Ocular Microbiology: Studies Every Ophthalmologist Should Know**

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EXAMINATION QUESTIONS TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 23

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**.

1. Which of the following has shown efficacy in reducing *Demodex* mite infestation?
   A. 50% mineral oil
   B. Lid massage
   C. Tea tree oil
   D. Doxycycline

2. In a study discussed by Dr. John, which of the following was the most common diagnosis among patients seen for complaints related to recent LASIK surgery?
   A. Microbial keratitis
   B. Dry eye and/or blepharitis
   C. Hyperopic astigmatism
   D. *Demodex* infestation

3. In a study of patients undergoing intraocular surgery (Miño de Kaspar, et al), the prevalence of viable conjunctival bacteria (positive culture) was how much higher in patients with local risk factors (eg, blepharitis), compared to patients with no such risk factors?
   A. No higher
   B. Slightly more than twice as high
   C. Almost five times as high
   D. 50 times as high

4. Which of the following qualities are more prevalent in conjunctival bacteria isolated from patients with local risk factors than in bacteria isolated from patients without local risk factors?
   A. Invasiveness
   B. Susceptibility to fluoroquinolones
   C. High expression of lipases
   D. Multidrug resistance

5. Which of the following is a sanitation measure that can slow person-to-person spread of infection?
   A. Hand washing
   B. Alcohol-based hand sanitizers
   C. Appropriate cleaning of instruments and examination and treatment room surfaces
   D. All of the above

6. As one of the first large surveillance studies of microbial resistance, the Alexander Project produced insights into which of the following phenomena?
   A. The rise of multiple variants of the resistance element mecA
   B. Variations in national, regional, and global resistance rates
   C. Unexpected decreases in overall drug resistance
   D. Unexpected decreases in drug resistance in specific countries

7. Which systemic drug has been shown effective against *Demodex* blepharitis?
   A. Ivermectin
   B. Imidazole
   C. Triazole
   D. Tinidazole

8. According to the results of PROTEKT, what percentage of erm(B)+mef(A)-positive isolates exhibited multidrug resistance?
   A. Less than 5%
   B. 15%
   C. 50%
   D. More than 99%

9. According to the first-year results of Ocular TRUST, *H. influenzae* isolates were fully susceptible to all tested antibiotics *except*
   A. Trimethoprim and tobramycin
   B. Penicillin and polymyxin
   C. Azithromycin and polymyxin
   D. Azithromycin and penicillin

10. Vaccines may:
   A. Increase the need for and utilization of antibiotics
   B. Decrease the need for and utilization of antibiotics
   C. Increase the efficacy of antibiotics
   D. Decrease the efficacy of antibiotics

EXAMINATION ANSWER SHEET TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 23

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 August 31, 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

11. 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

12. 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

13. Will the information presented cause you to make any changes in your practice? Yes No

14. If yes, please describe: ____________________

____

15. How committed are you to making these changes? 1 2 3 4 5

16. 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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