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TOPICS IN Ocular Antiinfectives

Pseudomonas aeruginosa Corneal Infection

Linda D. Hazlett, PhD

Frequently isolated in contact lens–associated bacterial infections, the finding of* P. aeruginosa *keratitis is associated with poor visual prognosis and significant ocular morbidity. At this point, our armamentarium of antimicrobial agents effective against this dangerous organism is relatively limited, so it is fortunate that current research is shedding considerable light on the ways in which this formidable pathogen acts.

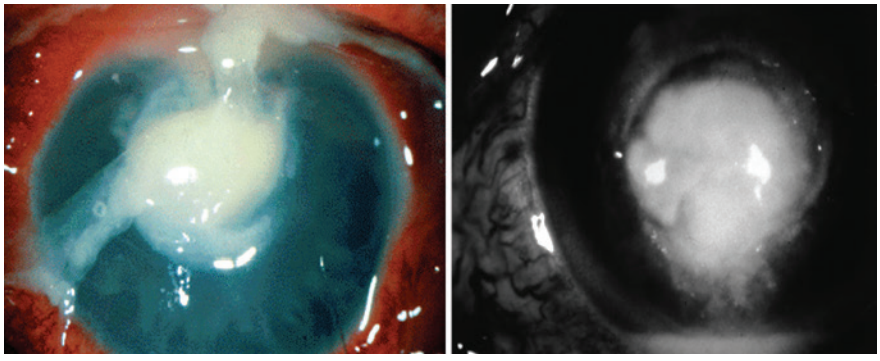

FIGURE 1 *P. aeruginosa* corneal ulcer. *(Image courtesy of Dr. Linda Hazlett.)*

Pseudomonas aeruginosa, a relatively common cause of bacterial keratitis, is the most often isolated pathogen in cases of contact lens-related infections.[1] This gram-negative organism accounts for 6% to 39% of bacterial keratitis cases and 60% to 70% of infections associated with contact lens wear in the US.[1-3]

P. aeruginosa corneal ulcers are particularly concerning because of the treatment challenges they present. *P. aeruginosa* infection has a tendency to progress rapidly, so it is often relatively severe by the time of presentation. The infection can quickly involve the entire cornea and can elicit an acute, destructive inflammatory response that, if not adequately treated, may lead to poor outcomes, with stromal thinning or perforation, and, ultimately, significant scarring.

An Opportunistic Pathogen

P. aeruginosa is commonly found in soil, water, and vegetation. An aerobic bacterium, its relatively complex genetic makeup gives it the ability to survive in a variety of environments. *P. aeruginosa* is a common nosocomial pathogen, causing opportunistic infections in patients with serious underlying medical conditions.

On the ocular surface, *P. aeruginosa* infection typically occurs following a break in the corneal epithelium. The

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 two virulence factors produced by *P. aeruginosa*.
2. Identify corneal ulcer patients at high risk for *P. aeruginosa* keratitis and promptly initiate appropriate antimicrobial treatment.
3. Devise effective strategies for antimicrobial selection in an environment that is becoming increasingly rife with drug-resistant pathogens.

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organism adheres readily to damaged epithelium, giving it a beachhead from which to invade the stroma. In addition to contact lens wear, predisposing factors for *P. aeruginosa* keratitis include ocular trauma, ocular surface disorders (eg, dry eye disease), and ocular surgery (eg, LASIK).[4,5]

Contact lens wearers have a far greater risk of developing ulcerative keratitis compared to non-wearers.[1,6] Although contact lens wear rarely causes a significant break in the corneal surface (such as a corneal epithelial wound or scratch), it can induce hypoxia, increase corneal temperature, and decrease tear flow over the corneal surface. Taken together, these changes can lead to an altered ocular environment that may make the cornea more susceptible to *P. aeruginosa* attachment, growth, and infection. Furthermore, *P. aeruginosa* is a common contaminant of lens care solutions and lens cases, where it forms biofilms that are not removed by simple rinsing of the case.

Virulence Factors

P. aeruginosa keratitis is among the most fulminant of ocular bacterial infections thanks to the organism's arsenal of virulence factors, which includes adhesins, destructive enzymes, and exotoxin A. These bacterial products play important roles in the pathogenesis of infection and contribute to the extensive tissue damage and necrotic ulceration characteristic of *P. aeruginosa* infection.

Exotoxin A, a major virulence factor of *P. aeruginosa*, promotes bacterial invasion, local tissue damage, and immunosuppression. This bacterial toxin catalyzes ADP-ribosylation and inactivation of eukaryotic elongation factor 2, resulting in inhibited protein biosynthesis and host cell death. Exoenzyme S (exoS) and other adhesins adhere the organism to epithelial cells. Another bacterial product exoenzyme U (exoU), is a potent, fast-acting cytotoxin associated with cell killing and tissue destruction. *P. aeruginosa* also produces proteases—including LasB elastase, LasA elastase, protease IV, and alkaline

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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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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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protease—which can degrade corneal connective tissue and interfere with the host immunological defense.

P. aeruginosa strains differ in their virulence characteristics and, consequently, affect host cells in distinct and different ways. Strains possessing the exoS gene (which encodes ExoS) are able to invade the host cell, replicate within that cell, and induce cell death by disrupting the cell's actin cytoskeleton. Strains lacking the exoS gene (and instead encoding exoU) are capable of rapid cell killing. These cytotoxic strains replicate extracellularly, causing overwhelming inflammation and tissue damage.

Inflammatory Response: A Two-edged Sword

P. aeruginosa also expresses lipopolysaccharide (LPS) or endotoxin, another important virulence factor that binds to and activates toll-like receptor 4 in host cells. This elicits an acute inflammatory response in the cornea, with a rapid, extensive influx of polymorphonuclear neutrophils (PMNs) and other leukocytes and the production of pro-inflammatory cytokines.

The neutrophilic response in *P. aeruginosa* keratitis is essential to bacterial eradication, but persisting inflammation can have damaging effects that include corneal scarring and perforation. Optimal clinical outcomes, therefore, require that some aspects of the innate immune inflammatory response in the cornea be downregulated and balanced with wound repair and healing, which requires removal of PMNs and upregulation of anti-inflammatory cytokines and other molecules necessary for tissue repair.

Experimental bacterial keratitis models have provided valuable information on the dynamic effects of the immune system in the process of *P. aeruginosa* corneal infection. Work in our laboratory in recent years has shown that the neuropeptide substance P (SP) exacerbates the disease while vasoactive intestinal peptide (VIP) is protective.[7,8]

Treatment Challenges

Given the virulent nature of *P. aeruginosa* infection, early detection and timely treatment are critical to minimize the risk of vision loss. *P. aeruginosa* keratitis should be suspected in contact lens or ocular trauma patients who complain of acute, significant pain, photophobia, and decreased vision. Such patients must be carefully examined using a slit lamp for signs of epithelial defects, edema, corneal thinning, stromal ulceration and perforation. A ring-like stromal infiltrate with epithelial defects, anterior chamber reaction, greenish yellow mucous discharge, and diffuse gray, ground-glass appearance of peripheral areas are all indicative signs of keratitis secondary to *P. aeruginosa* infection (Figure 1).

Scanning laser confocal microscopy can be used to confirm a presumptive diagnosis of bacterial keratitis. However, smears, culture, and corneal biopsy remain the fundamental tools for diagnosis and identification of the causative organism.

Initiating aggressive antibiotic treatment with broad-spectrum antimicrobial activity such as cefazolin/tobramycin combination therapy or fluoroquinolone monotherapy is the standard of care for empirical treatment of bacterial keratitis. *P. aeruginosa* is intrinsically resistant to many antimicrobial agents, including most beta-lactams, older fluoroquinolones, and macrolides.[9] Agents recommended specifically for *P. aeruginosa* infection include ceftazidime, tobramycin, and the newer fluoroquinolones.[1] Systemic and ocular surveillance data, though, has suggested that multidrug resistance, including resistance to agents such as ceftazidime, tobramycin, and fluoroquinolones, is becoming increasingly common among *P. aeruginosa* isolates.[9,10]

Role of Topical Corticosteroids

Given the damaging effects of the host inflammatory response in bacterial corneal ulcers, adjunctive corticosteroid therapy is presumably beneficial in reducing inflammation and its sequelae such as corneal scarring and vision loss. Topical corticosteroids, however, may also elevate intraocular pressure, prolong infection, and inhibit collagen synthesis, predisposing to corneal melting. These adverse effects are particularly concerning in *P. aeruginosa* infections, which are more invasive and destructive than many other infections.

Until recently, the use of corticosteroids in the treatment of bacterial corneal ulcers has remained a matter of debate; and the debate has been particularly contentious with respect to severe infections such as those caused by *P. aeruginosa*. The Steroids for Corneal Ulcers Trial (SCUT), a randomized controlled clinical trial initiated in 2007, reported on 500 cases of bacterial ulcers and was the first and only large scale study of the impact of adjunctive topical corticosteroid treatment on the visual outcomes of bacterial corneal ulcers.[11]

In SCUT, topical corticosteroids used as adjunctive therapy for bacterial corneal ulcers demonstrated neither overall benefit nor overall harm; subgroup analyses of the 110 patients

CORE CONCEPTS

- *P. aeruginosa* remains the most dangerous common pathogen for contact lens wearers and ocular trauma patients.
- *P. aeruginosa* can produce a range of virulence factors that contribute to rapid development of infection.
- Resolution or exacerbation of the host inflammatory response induced by *P. aeruginosa* has a direct impact on the clinical outcome. Persistence of an intense inflammatory reaction in the cornea can cause sight-threatening complications such as scarring.
- There is an increasing trend toward multidrug resistance among *P. aeruginosa* isolates.
- With appropriate antibiotic coverage, topical corticosteroids are generally safe for the treatment of *P. aeruginosa* and other bacterial corneal ulcers, but the adjunctive therapy also provides little, if any, benefit.

with confirmed *P. aeruginosa* infection yielded similar results.[11,12] However, another more recent study of the *P. aeruginosa* subgroup found that adjunctive corticosteroid improved visual outcome in invasive-strain ulcers but not in cytotoxic ulcers.[13]

Ongoing Research

Current research on *P. aeruginosa* keratitis is heavily focused on disease mechanisms and the role of the host immune response. The ultimate goal is to develop novel treatment approaches to improve patient outcomes.

In this regard, studies have recently identified endogenous keratin-derived antimicrobial peptides (KDAMPs) on the healthy human cornea.[14] Synthetic analogs of these naturally occurring KDAMPs have shown rapid bactericidal activity against multiple bacterial pathogens and the ability to protect epithelial cells from the virulence mechanisms of *P. aeruginosa*.

Most recently, our own research work has identified high mobility group box 1—a ubiquitous DNA-binding protein that mediates inflammatory tissue injury—as a potential therapeutic target in the treatment of *P. aeruginosa* infection.[15] Researchers are also examining the healing effects of neuropeptides such as vasoactive intestinal polypeptide in the treatment of bacterial keratitis, and they are developing new antibiotics to fight against evolving bacteria.

Linda D. Hazlett, PhD, is distinguished professor and chair, department of anatomy and cell biology Wayne State University School of Medicine in Detroit, MI. She reports that in the past 12 months, she 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. Medical writer Ying Guo, MBBS, PhD, assisted in the preparation of this article.

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Mechanisms and Clinical Implications of Antibiotic Resistance

Joseph M. Blondeau, PhD

Antibiotic-resistant pathogens threaten the health of patients and complicate treatment. Slowing antibiotic resistance starts with physicians.

Introduced nearly 80 years ago, antibiotics launched a revolution in medicine, dramatically reducing the morbidity and mortality associated with infectious disease. Over the decades, however, widespread antibiotic use (and misuse) has selected for increasingly resistant strains of pathogenic and commensal organisms and kicked off an intense and seemingly endless contest between humans, pathogenic and commensal (opportunistic) microbes. With the number of antibiotics (specifically broad spectrum) in development dropping and the prevalence of resistance increasing, it looks as if the bugs are getting the upper hand: How has this occurred?[1]

Antibiotic Use

To some extent, even the most appropriate antibiotic prescribing will produce some resistant organisms. Antibiotic treatment kills susceptible organisms—hopefully the disease-causing ones—but in so doing it provides a low-competition environment for the survivors, some of which survived because they carry genes that render the antibiotic less effective. These genes can be passed to daughter cells and

transferred laterally to other organisms.

Additionally, inappropriate prescribing—such as underdosing, incomplete regimens, or ineffective empiric treatments—may cause prolonged exposure to subinhibitory concentrations of drug and thereby provide a supportive environment for selecting resistant pathogens.[1] Massive antibiotic use in the livestock industry to prevent and treat veterinary infection, and, more commonly, to boost growth in the healthy animals, has contributed substantially to our antibiotic resistance crisis.[2] Many countries have now banned antimicrobials for growth promotion.

Of all the antibiotic produced today more than half passes through the bodies of livestock and is excreted into soil, waste systems, waterways, and the animal and vegetable food we eat—albeit at extremely low levels. In addition, improper disposal of an incalculable tonnage of antibiotics and other biocidal agents, such as hand sanitizers, perpetuates the accumulation of resistance genes. Indeed, the natural world is now replete with resistance genes that are potentially transferable to infecting bacteria, a vast reservoir of genes that scientists call the environmental antibiotic resistome.[1]

The paradoxical result of our many advances against deadly infectious diseases is a serious dilemma faced by all clinicians today: the need to deal effectively with infection or infection risk in the individual patient without contributing to the collapse of antibiotic potency for all.[3] With that challenge in mind, it is useful to review how bugs dodge our therapies and what that means for clinical practice.

Resistance Mechanisms

Basic science researchers are continually uncovering new ways that microorganisms have devised to evade antimicrobial action; these mechanisms fall into roughly four broad categories: guarding against drug entry; pumping drug out after it has entered the bacterial cell but before it does harm; degrading the drug with extracellular enzymes; and modifying the drug's binding sites on bacterial molecules as a result of genetic mutations. Many resistant organisms utilize multiple resistance pathways, and some resistance traits provide resistance to multiple antibiotics. We can look at each of these resistance mechanisms individually.

Diffusion inhibition: Some organisms guard against drug entry or diffusion into the cell, thus limiting intracellular drug accumulation and efficacy. The outer membrane of *Pseudomonas aeruginosa* is intrinsically resistant to penetration by many antibiotics.[2] In addition, *Escherichia coli*, *P. aeruginosa* and other gram-negative organisms may carry mutations in the genes for outer membrane proteins (OMPs) or porin channels. Unmodified porin channels permit entry of beta-lactam and quinolone antibiotics into the cell; mutated OMP varieties do not.[2,4]

Efflux pump: Efflux pumps are ubiquitous among bacterial species and are thought to perform a variety of detoxification and housekeeping functions. Beyond their basic physiologic functions, some efflux pumps are capable of returning antibiotic agents back to the extracellular environment.[5] *E. coli*, *Pseudomonas spp.*, *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]), and *Streptococcus pneumoniae* are among the many organisms that employ this defense tactic against macrolides, tetracycline, trimethoprim-sulfamethoxazole, chloramphenicol, beta-lactams, aminoglycosides and older quinolones.[1,2]

Bacterial efflux pumps vary in their specificity for drugs. Some are highly specific and may, for example, export one quinolone but not another. Others are capable of removing a range of chemically dissimilar drugs from the cell, conferring multidrug resistance on a bacterium.[2,5]

Enzymatic degradation: Sometimes bacteria go on the offensive, engineering enzymes that destroy specific chemical structures in drugs. Beta-lactamases, for example, hydrolyze the beta-lactam ring of penicillin and other beta-lactam antibiotics; other enzymes acetylate the amino group or adenylate or phosphorylate the hydroxyl groups of aminglycosides.[4]

Rapid mutation and transfer of beta-lactamase production—particularly those known as "extended spectrum beta-lactamases" (ESBLs), which confer resistance to most beta-lactam antibiotics—has hindered the efficacy of penicillins, cephalosporins, monobactams and in some instances carbapenems against gram-negative infections worldwide.[1,6,7] More than 1000 unique beta-lactamases (including extended spectrum beta-lactamases) have been identified to date (Figure 1).[1] Unfortunately, some ESBLs are also co-resistant to non-beta lactam agents thereby putting greater need on the clinical microbiology laboratory to accurately and quickly identify these organisms and susceptibility/resistance profiles.

Binding site modification: Many

CORE CONCEPTS

- Resistance emerges from antibiotic use in human and veterinary medicine (mainly subinhibitory exposures), antibiotic and biocide presence in consumer products (eg, hand sanitizer), and often inappropriate antibiotic use in livestock.
- Microbes resist being killed by drugs through diffusion inhibition, efflux pumps, enzymatic degradation, and binding site modification.
- Fluoroquinolone- and multidrug resistance are becoming common in ocular and nonocular infections.
- Topical prophylaxis contributes to resistance-induction in ocular flora.
- Pathogen identification and susceptibility testing can improve cure rates and reduce potentially resistance-inciting overexposures.
- Familiarity with local MIC trends can improve empirical prescribing.

bacteria have cultivated the ability to modify or camouflage cell structures that antibiotics use as binding sites or targets. Quinolones, which are designed to inhibit bacterial topoisomerases III and IV, are increasingly rebuffed by gram-negative and gram-positive bacteria that have mutated to modify the structure of these enzymes to evade antibiotic binding without damaging their function in DNA replication.[2]

Research in *S. aureus* has shown that the number of topoisomerase mutations present in a bacterial species' genome is correlated with the species' level of quinolone resistance. The more mutations that accumulate, the higher the minimum inhibitory concentration (MIC) to relevant drugs.[8,9] This may explain why drugs that are used sparingly and those that are newer to market tend to be more active than older or more widely used agents.

Microbiologic Trends

Resistant microbes pose a significant threat in all areas of medicine. Extended spectrum beta-lactamase-containing *Pseudomonas*, *E. coli*, and *Klebsiella* species are causing increasing numbers of nonhospital-associated antibiotic-resistant systemic infections.[6,7,10] MRSA is now widespread in community settings as well. Recent reports reveal that resistance rates among ocular pathogens are similarly high. Methicillin resistance rates among *S. aureus* and *S. epidermidis* are roughly 40% and 50%, respectively; and a significant proportion of these are multidrug resistant.[11] Compared with methicillin-susceptible strains, methicillin-resistant staphylococci were more commonly resistant to other agents—ciprofloxacin, clindamycin, azithromycin and tobramycin—and more likely to be resistant to more than one class of drug.[11]

In recent years, the incidence of fluoroquinolone resistance has increased in microorganisms of concern to ophthalmologists. A recent report on 38 endophthalmitis isolates of methicillin-susceptible *S. epidermidis* (MSSE) collected between 2005 and 2010 at Bascom Palmer found high levels of resistance to moxifloxacin and gatifloxacin (40%, although the rate was higher in the later years of the study and lower at the start).[9]

Notably, 87% (13 of 15) of patients with MSSE resistant to moxifloxacin or gatifloxacin had recent or current exposure to the same antibiotic for prophylaxis related to either phacoemulsification surgery or intravitreal injection. (Antibiotic status of the remaining two patients was not available.[9]) This is consistent with reports of rapid development of resistance and co-resistance among ocular flora exposed to topical fluoroquinolones—moxifloxacin, gatifloxacin, and ofloxacin—as prophylaxis in association with intravitreal injections.[12,13]

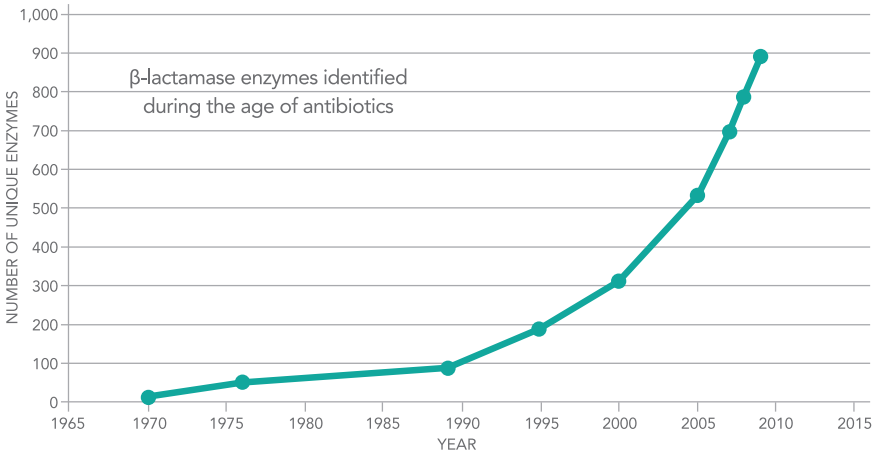

FIGURE 1 Rapid rise in the number of distinct beta-lactamase enzymes. *(Adapted from Reference 1.)*

This propensity of topical prophylaxis to induce resistance reopens the subject of topical antibiotic prophylaxis to debate.[13] Some caution is required in interpreting susceptibility/resistance data (particularly resistance data) where an ocular pathogen is encountered and a topical antimicrobial agent is to be used. The determination of susceptibility/resistance is based on systemic drug concentration levels and separate breakpoints for topically applied antibiotics do not exist. As such, there may not be a direct correlation between the in vitro result and clinical outcome. What is important is the recognition that ocular pathogens (like pathogens associated with systemic infections) are less susceptible to drugs than they were just a few years ago.

Clinical Implications

There are numerous ways in which clinicians can optimize management of antibiotic resistant infections and reduce the likelihood of contributing to the emergence of additional resistant strains. First, rapid identification of causative pathogen, including species and antibiotic minimum inhibitory concentration (MIC), is an important goal. In my view, specimens for identification should be taken from all patients with infections serious enough to warrant treatment prior to the initiation of antibiotic therapy. As the number of effective therapeutic options diminish due to growing resistance, it will become increasingly important to take samples for identification before instituting empirical therapy. Failure to do so may increase the difficulty of determining the causative organism should empirical therapy fail.

At our center here in Canada (and in many European centers) nearly all of our pathogen identification has been converted from standard biochemical methods (including semi-automated technologies) to matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS), a semi-automated system that considerably diminishes the time required to get actionable results (ie, organism identification).[14] These systems differentiate bacterial (and some fungal) species by detecting distinctions in ribosomal pro-

tein spectra.[15] Tools for detecting MRSA and ESBL using MALDI-TOF technology are in development. (MALDI-TOF microbiologic diagnostic systems are not yet available in the US.)

Antibiotic Selection

Antibiotic patterns vary widely from region to region and even from center to center within a region. Communicating regularly with specialists in clinical microbiology and infectious disease can help clinicians stay atop shifting resistance trends and make the most effective empiric treatment choices. When reading antibiograms, it is important to recognize that broad categories of "susceptible," "intermediate," and "resistant," tell, at best, only part of the story; the MIC value provides more information and more accurately differentiates high and low levels of resistance. This is particularly important when choosing a topical antibiotic, as low level resistance may be overcome with the high concentrations achievable by topical administration.

When treating infection, multiple pharmacodynamic variables become important for antibiotic selection: drug concentration, MIC, and the presence and potency of any preservative in the formulation. Since susceptibility designations reflect systemic not topical administration, they provide at best a rough guideline for choosing topical ocular antibiotics. To overcome that disadvantage, it is useful to know the microgram amount of drug being administered in a drop or ointment and compare that to MIC. For the treatment of serious infections, help in calculating the dosage of topical antibiotics is available from clinical pharmacologists and microbiologists.

Even though comparative clinical trials are typically designed to show only antibiotic equivalence or "non-inferiority" in clinical outcomes, they often uncover important differences in microbiologic effects. Careful attention to data beyond the primary endpoint can assist in clinical decision-making and make a real difference for patients.

Finally, to reduce the potential for inducing resistance, clinicians should prescribe with the individual patient in mind and aim to ensure proper dosing thereby optimizing therapy.

Trends

There is a grave need for the development of new antibiotic compounds with novel modes and targets of action. Fortunately, approaches such as inhibiting cell–cell communication, targeting virulence (rather than cell viability), and improving immune capacity, as well as alternative modes of antibiotic delivery, are under investigation.[1]

In the meantime, adhering to the tenets of antibiotic stewardship and environmental protection is critical if we are to stem the rise of resistance. The Infectious Diseases Society of America and other organizations are leading efforts to improve public health by urging reductions in unnecessary antibiotic use in farming and agriculture.[16] Similar efforts have been shown to be effective in Scandinavia and other parts of the world.[1]

Treating infection in the era of resistance is an uphill climb. Understanding resistance patterns and drug pharmacodynamics should influence prescribing habits to ensure optimal treatment and, to the degree possible, prevent resistance.

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EXAMINATION QUESTIONS TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 51

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. With respect to the effect of adjunctive topical corticosteroid in the treatment of *P. aeruginosa* corneal ulcers, SCUT data suggest that:
   A. Corticosteroids significantly improve visual outcomes
   B. Corticosteroids are unsafe for use with severe corneal ulcers
   C. Corticosteroids may benefit ulcers caused by certain strains of *P. aeruginosa*
   D. None of the above is correct

2. Which of the following best describes the environmental antibiotic resistome?
   A. Resistance genes among nonhospital-acquired ocular infections
   B. Pool of resistance genes present in organisms cultured from the environment
   C. Mass spectrometry device used in Europe and Canada for detection of resistance traits
   D. Medical organization charged with reducing antibiotic exposures in animals

3. KDAMPs are:
   A. The class name for the current generation of fluoroquinolones
   B. Endogenous antimicrobial peptides
   C. Sloughed off epithelial cells that harbor bacteria
   D. A form of adenosine monophosphate found on the ocular surface

4. Which one of the following is a virulence factors that differentiates the cytotoxic *P. aeruginosa* strains from the others?
   A. ExoU
   B. Vasoactive intestinal polypeptide
   C. Substance P
   D. Lipopolysaccharide

5. Which of the following is NOT a novel approach to combatting infection?
   A. Inhibiting cell–cell communication
   B. Targeting virulence factors (rather than cell viability)
   C. Creation of mutated porin channels
   D. Improving host immune capacity

6. A patient presents with an obvious corneal infection; which of the following patient characteristics should trigger suspicion of *P. aeruginosa*?
   A. Blue irides
   B. History of smoking
   C. Contact lens wear
   D. All of the above

7. Modification of outer membrane proteins is an example of:
   A. Extended spectrum beta-lactamase production
   B. Enzymatic degradation
   C. Drug efflux pumping
   D. Diffusion inhibition

8. Which of the following has NOT contributed to the selection of antibiotic-resistant pathogens?
   A. Novel compounds directed against virulence factors
   B. Antibiotic use in livestock
   C. Subtherapeutic dosing in humans
   D. Inappropriate disposal of antimicrobials

9. Which of the following molecules is NOT a virulence factor of *P. aeruginosa*?
   A. Exotoxin A
   B. Alkaline protease
   C. LasB elastase
   D. Vasoactive intestinal polypeptide

10. Quinolone resistance can be accomplished by which of the following bacterial mechanisms?
    A. Target modification
    B. Diffusion inhibition
    C. Efflux pump
    D. All of the above

EXAMINATION ANSWER SHEET TOPICS IN OCULAR ANTIINFECTIVES, ISSUE 51

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, 2015.

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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