Crisis Management: Antibiotic Resistance in Ocular Infections

A review of surveillance studies and their clinical implications.

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Emerging resistance to antimicrobial drugs has been reported among most of the ocular pathogens. The factors contributing to development of drug resistance among ocular isolates include the overuse of antibiotics for systemic infection, antibiotic use in farm animals, as well as overuse of topical antibiotics in the eye.[1] Other contributory factors may be improper dosing regimens, the misuse of antibiotics for viral and other nonbacterial infections, extended duration of therapy, undertreatment of infection, patients' noncompliance, environmental changes, globalization, and migration. The most disturbing trend has been the emergence of fluoroquinolone resistance by gram-positive organisms, pseudomonas, and atypical mycobacteria. In addition to increased resistance, an important concern is the fact that the prevalence of gram-positive organisms, specifically *Staphylococci*, has been increasing dramatically during the past decade.

RISING PREVALENCE OF DRUG-RESISTANT *STAPHYLOCOCCI* IN OCULAR INFECTIONS

Methicillin-resistant *Staphylococcus aureus* (MRSA) isolates are resistant to all available penicillins and other β-lactam antimicrobial drugs. Recently, there has been a drastic rise in the proportion of MRSA isolates from ocular infections. A study on *S aureus* isolates from eye infections submitted to The Surveillance Network (TSN) by more than 200 laboratories in the United States from January 2000 to December 2005 showed that the proportion of MRSA in serious ocular *S aureus* infections increased from 29.5% in 2000 to 41.6% in 2005.[2] The changing epidemiology of MRSA infections is also evident in cases with microbial keratitis after keratorefractive surgery. In surveys conducted by the American Society of Cataract and Refractive Surgery, although the number of postrefractive surgery keratitis cases decreased from 116 cases in 2001 to 48 cases in 2004 and to 19 cases in 2008, the incidence of MRSA increased from none in 2001 and 2004 to 28% in 2008, with MRSA being the most common organism cultured.[3-5]

Although predominantly considered to be a nosocomial infection, the incidence of community-acquired MRSA is rising. Community-acquired MRSA represents a hybrid between MRSA that spread from the hospital environment and strains that were once easily treatable in the community. Most of the hybrid strains also acquired a factor that increases their virulence. Although easier to treat compared with hospital-acquired strains, community-acquired MRSA is more virulent, and is now becoming increasingly more drug resistant even in the ocular setting.[6]

HOW IS THE ANTIBIOTIC RESISTANCE/SUSCEPTIBILITY MEASURED?

Tissue concentration and potency are important factors that determine the efficacy of new antimicrobial agents. Higher tissue concentrations will produce a better kill rate and will also reduce the minimum inhibitory concentration (MIC) required to kill a given pathogen. Comparative MIC data are expressed in terms of the MIC_{50} (the concentration necessary to

fully inhibit growth of ≥ 50% of at least six independent isolates) and the MIC_{90} (the concentration necessary to fully inhibit growth of ≥ 90% of at least 10 independent isolates). A better measure of efficacy is the inhibitory quotient. Its value is calculated by dividing the concentration of drug achieved in tissue by the MIC_{90}. An optimal antibiotic should have high potency (as reflected by a low MIC_{90}) and also achieve high concentrations at the site of infection.

The susceptibility of bacterial isolates from the eye is evaluated using Clinical and Laboratory Standards Institute procedures based on breakpoints derived from serum/plasma/cerebrospinal fluid levels of antibiotics. Using systemic breakpoints to evaluate topical drugs may affect the predictive value of susceptibility testing of ocular isolates. Although topical antibiotics may be rapidly washed out from tears as compared to other body fluids, the concentration of antibiotic reached in external ocular tissue on topical application may exceed the concentration reached in body fluids on systemic intake and in fact, may exceed the minimum inhibitory concentration for common ocular isolates.[7,8] Future studies are needed to resolve this issue; nonetheless, many researchers agree that the use of systemic breakpoints remains useful to track trends of susceptibility and compare data on ocular isolates.[9]

CHANGING PATTERNS OF ANTIBIOTIC SENSITIVITY AND RESISTANCE

The first Ocular Tracking Resistance in US Today (TRUST)[10] prospective surveillance study of more than 250 ocular isolates from 35 centers all over the United States showed that methicillin-sensitive *S aureus* (MSSA) or MRSA susceptibility patterns were virtually identical for the fluoroquinolones, that is, MSSA susceptibility was 79.9% to 81.1%, and MRSA susceptibility was 15.2%. Trimethoprim was the only agent tested with high activity against MRSA.

Another national antibiotic resistance surveillance of ocular isolates was initiated in 2009 with the Antibiotic Resistance Monitoring of Ocular Microorganisms (ARMOR).[11] In this study, 200 *S aureus* and 144 coagulase-negative *Staphylococci* (CNS) ocular isolates were collected from 34 centers across the United States. Of the *S aureus* isolates, 39% were fluoroquinolone-resistant, 39% were methicillin resistant, and 31% were resistant to both. Of the CNS isolates, 43% were fluoroquinolone resistant, 53% were methicillin resistant, and 36% were resistant to both. All *S aureus* and CNS isolates were susceptible to vancomycin. Notably, 11.5% of *S aureus* and 6.3% of CNS isolates were multidrug resistant (ie, resistant to five of the six classes of antibacterial drugs tested in this study, including the widely used β-lactams, fluoroquinolones, aminoglycosides, and macrolides). Results for *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* were less alarming, although 4% to 6% of isolates from those two species were resistant to three or more classes of antibacterials.

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The newest member of the fluoroquinolone family, besifloxacin (Besivance; Bausch + Lomb), has shown high in vitro potency against fluoroquinolone-resistant gram-positive and gram-negative organisms.[12] In particular, common ocular pathogens like *S aureus* (including MRSA), *Staphylococcus epidermidis* (including methicillin-resistant), *S pneumoniae* and *Haemophilus influenzae*, including isolates that were resistant to other fluoroquinolones, aminoglycosides, β-lactams, and aminoglycosides were susceptible to besifloxacin.[13] As besifloxacin is developed exclusively for ocular use, there is no systemic breakpoint for it. Hence, its potency is measured by MIC and inhibitory quotient. In the ARMOR study, vancomycin and besifloxacin had the lowest MIC_{50} and MIC_{90} for *S aureus* as compared to all other fluoroquinolones and azithromycin (AzaSite; Merck & Co.). In addition, besifloxacin had an inhibitory quotient (IQ) of 2.3 compared to moxifloxacin with an IQ of 1.3. Thus, although besifloxacin achieves lower tissue concentrations, it also has a lower MIC_{90}, resulting in a higher IQ.

IMPLICATIONS IN CLINICAL PRACTICE

Like their systemic counterparts, ocular pathogens are constantly evolving and becoming increasingly resistant to the current generation of antimicrobials. Although newer drugs like besifloxacin hold promise, the threat of resistance still exists due to cross-resistance seen between different fluoroquinolones. It is prudent to be aware of these changing dynamics while treating ocular infections. Knowing the pathogen at hand, selecting the right antibiotic based on the current susceptibility and resistance patterns, avoiding under- or overtreatment, and limiting the use of newer antibiotics for only the resistant bugs may help curb the growing trend of resistance.

THE FUTURE OF ANTI-INFECTIVE TREATMENT

Given the growing evidence of resistance worldwide to currently available antibiotics, it will be important to follow surveillance data to enable clinicians to best select initial treatment for patient care, and it is essential that future research look at new antibiotics as well as novel ways to treat infections. Some of the novel approaches under consideration are antimicrobial peptides,[14,15] aganocides (NovaBay Pharmaceuticals),[16,17] and the use of riboflavin ultraviolet cross-linking as adjunctive therapy.[18,19] ■

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