ARE GENERIC MEDICATIONS CONTRIBUTING TO THE RISE OF SUPERBUGS?

Looser regulation leads to variability in nonbranded formulations.

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National and international concerns continue to mount over the rise of so-called "superbugs," or antimicrobial-resistant bacteria. Concerns regarding increasing levels of microbial resistance in bacteria are not new, and in eye care this debate dates as far back as when the Ocular Tracking Resistance in US Today (TRUST) studies were conceived.[1,2]

The reality is that few if any new antimicrobial drugs are being licensed or developed, and managing superbug infections remains a growing challenge as existing molecules are proving to be less effective at managing these bacteria. It is time to look beyond monitoring the mechanisms of bacterial adaptation and start a conversation regarding factors such as physicians' clinical behavior and the variability of available drugs, both of which contribute to this emerging and accelerating problem.

The variability found in generic antibiotics is not often discussed, but it may be a potential contributor to the phenomenon of bacterial resistance. The possible contributory role of generics in the development of bacterial resistance has been previously voiced.[3]

We cannot determine the relationship between the rise of generic antibiotics and the potential contribution of these less-regulated entities to the issue of antimicrobial resistance because we do not have scientific data that suggest a link. However, we also cannot discount this possibility. Perhaps, in a small but significant manner, these compounds are partially contributing to the rise of the superbugs.

Generic drug use accounts for about 80% of prescriptions, and generics are an integral part of eye care. These compounds are easily accessible, at times much less expensive than their branded counterparts, and often a requested alternative by patients under the assumption that they are equal in efficacy and safety to the branded drugs.[4,5]

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Might it just be a coincidence that, because of the accessibility, frequency of use, and cost of these generic agents, we are seeing more resistance to the medications that are available as generics? The most recent Antibiotic Resistance Monitoring in Ocular Microrganisms (ARMOR) report noted increases in antimicrobial resistance in many of the isolates tested. Notably, *Pseudomonas aeruginosa* isolates more than doubled their ability to fend off ciprofloxacin, a staple antibiotic that has been used in topical ocular and systemic formulations for many years.[6]

Should we be suspicious of the use of generics? It is worth noting that generic manufacturers are not required to be as stringent in their formulations, as variations are allowed in inactive ingredients and larger variations in the analytical formulation.[6] Generic formulations do not have to adhere to strict guidelines for effectiveness as branded drugs do, and, unlike branded products, clinical trials are not required for their approval.

A study comparing various generic formulations of ciprofloxacin showed variation by as much as 20% in potency.[7] There is no current requirement for generic manufacturers to demonstrate antimicrobial efficacy; they merely have to show the equivalency of the ingredients in their products to their branded counterparts.[8,9]

With the continued rise of bacterial resistance, should these variations be a professional concern? It is questionable whether the antimicrobial efficacy of a generic agent, such

FROM TRUST TO ARMOR: WHERE WE STAND

Tracking studies document changes in antibiotic resistance over time.

The Centers for Disease Control and Prevention (CDC) reports that approximately 2 million Americans experience an infection with an antibiotic-resistant microorganism each year.[1] Antibiotic-resistant infection can occur in any part of the body, and the eyes are no exception. Drug-resistant ocular infections, once a rarity, have become much more common.

The CDC has developed a program to try to gain an upper hand in the battle against these growing enemies in our midst, the multidrug-resistant microorganisms called superbugs. The CDC identified four core actions to serve as a long-term solution to this preeminent problem.[1] These core actions are described as follows:

- detecting and tracking patterns of antibiotic resistance
- responding to outbreaks involving antibiotic-resistant bacteria;
- preventing infection from occurring and bacterial resistance from spreading
- discovering new antibiotics and new diagnostic tests for resistant bacteria.

Tracking antibiotic resistance—one of the four core actions of the CDC—is not a new endeavor. One of the most effective surveillance strategies for antibiotic-resistant ocular infection is the ARMOR study. This ongoing effort strives to be more than just intellectual armor against the epidemic of antibiotic resistance; it also actively tries to combat the spread of these agents.

A predecessor of ARMOR was the Ocular TRUST study. This surveillance study looked closely at the prevalence of ocular antibiotic resistance and monitored the susceptibility patterns of ocular isolates between the years 2000 and 2005, and again from 2005 to 2006.[2] The ARMOR surveillance program was designed and implemented in 2009 in the United States to continue the efforts of the Ocular TRUST program.

Findings from the ARMOR study were first published in 2011, documenting the results of cultures of ocular isolates obtained in 2009.[3] This study has continued every year, and the most recent ARMOR study contained data from isolates collected in 2012 and 2013.[4] In 2012, the ARMOR surveillance study includeds sites in Canada as well.

IMPLEMENTING CORE ACTIONS

Ocular antibiotic resistance was once a rare condition. Over years of repeated use of ophthalmic antibiotics, bacteria have become more resilient and harder to kill. The CDC's core actions were designed to provide effective means to fight the epidemic of antibiotic resistance.

Tracking the changes in microbial culture results and the susceptibility profile patterns of ocular antibiotics over time can help to determine which types of ophthalmic antibiotics are most effective against specific types of bacteria or other pathogenic microorganisms. Surveillance studies such as ARMOR can also help guide eye care professionals to prevent the abuse and misuse of ocular antibiotics and keep them from being rendered ineffective by resistant microorganisms.

This monitoring strategy can also lead to effective implementation of other CDC core actions, such as preventing the spread of antibiotic resistance. Tracking changes over time can also help to determine whether certain antibiotics need to be "rested," which antibiotics should continue to be actively used, and the rate at which any one species of bacteria may be on the run towards antibiotic resistance.

In 2012, the ARMOR study included 798 ocular infection isolates from 32 sites in the United States. This study included 289 isolates of *Staphylococcus aureus*, 268 isolates of coagulase-negative staphylococci, 82 isolates of *Streptococcus pneumoniae*, 73 isolates of *Haemophilus influenzae*, and 86 isolates of *Pseudomonas aeruginosa*; to date in 2013, 239 isolates from 27 sites were collected.[4]

It is important to note that results have changed substantially over time, and the ARMOR study has documented this. In the initial study from 2009, large percentages of *S aureus* and coagulase-negative staphylococci were found to be resistant to oxacillin, methicillin, azithromycin, or fluoroquinolones. Furthermore, 46.5% of isolates with *S aureus*, 58.3% of isolates with coagulase negative staphylococci, 9.0% of isolates with *P aeruginosa*, and 9.3% of pneumococcal isolates were nonsusceptible or resistant to two or more antibiotic drug

classes. Only 2.7% of *H influenzae* isolates were resistant to one of the antimicrobial agents tested.

In the most recent studies of 2012 and 2013, the ARMOR data showed that *S aureus* and coagulase-negative staphylococci species continued to demonstrate high rates of resistance to a number of antibiotics. Specifically, both microorganisms had resistance rates exceeding 25% for eight of the 15 representative antibiotics tested. Preliminary ARMOR 2013 results indicate that *S aureus* and coagulase-negative staphylococci were non-susceptible to oxacillin (43%-59%), ciprofloxacin (33%-43%), clindamycin (21%), and azithromycin (60%-63%), showing slight increases over the previous year. Very important and worth noting is that multidrug resistance to three or more classes of antibiotics also remained prevalent in *S aureus* and coagulase-negative staphylococci isolates (38%-39%), especially among methicillin-resistant staphylococci (60%-81%).

CONCLUSIONS

To summarize the data collected over the years of the ARMOR surveillance study, it has been noted that the antibiotic resistance of pathogenic bacteria identified in these studies has gradually increased over the course of time. In addition, these same ocular bacteria have developed resistance to more classes of antibiotics each year, and the rates of resistance to these specific drug classes have also increased as well.

The rise of bacterial resistance is quickly becoming a major concern in ophthalmology clinics. With increases in the frequency of ophthalmic surgical procedures due to the aging of the population, the fight against these pathogens in the prevention of infections and complications will be a continued challenge. With few products in the pipeline to take over for older antimicrobials, the processes of monitoring antimicrobial resistance and carefully husbanding the use of existing molecules will be important in our clinical decision-making processes in the management of ocular infections.

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as a topical ophthalmic solution, is equivalent to that of its more controlled and reproducible branded counterpart.

The therapeutic healing process depends on sound scientific knowledge and a trust that the offending agent will be best managed by effective antimicrobial medications. Most prescribing physicians rely on empirical prescribing, as cultures are not routinely performed, and prophylactic treatment relies on the assumption that a given medication is effective in actively managing potential pathogens. With uneven regulatory oversight, lack of evidence-based microbial efficacy metrics, and low costs to consumers for generic drugs, and with market forces making the development of new drugs a financial challenge, medical professionals should be concerned. We must be conscious of our role in managing antimicrobial usage, our use of generic medications, and the ever-increasing threat of antimicrobial-resistant superbugs. ■

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