

ANTIBIOTIC RESISTANCE: UPDATE FROM THE ARMOR SURVEILLANCE STUDY AND TREATMENT IMPLICATIONS

BILL G. BELL, MD AND DEREK N. CUNNINGHAM, OD

BACTERIAL RESISTANCE TO antibiotics is a global public health concern and presents a challenge for the effective management of infectious diseases, including ocular infections. Factors identified as contributing to bacterial antibiotic resistance include antibiotic overuse, inappropriate prescribing, including use of antibiotics that provide subinhibitory concentrations, and extensive agricultural use.¹

Due to the lag time required for determining the causative pathogen and its antibiotic susceptibility, antibiotics for the treatment of suspected bacterial ocular infections are typically initiated empirically based on knowledge of the most common pathogens and the spectrum of activity of topical antibiotics. In this way, surveillance studies that track pathogen susceptibility and resistance patterns enables us to understand local bacterial resistance, which helps guide empirical prescribing.

Currently, the Antibiotic Resistance Monitoring in Ocular microoRganisms (ARMOR) study is the only ongoing nationwide surveillance project specific to ocular pathogens. The most recent data from ARMOR highlight the presence of antibiotic resistance among common ocular pathogens and of significant differences in the potency of commonly used topical antibiotics.^{2,3}

ARMOR UPDATE

Initiated in 2009, ARMOR tracks minimum inhibitory concentrations (MICs) for 19 antibiotics across 11 classes. The various antibiotic classes represent ophthalmic and nonophthalmic agents and include: fluoroquinolones (besifloxacin, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, and

ofloxacin); macrolides (azithromycin); aminoglycosides (tobramycin); lincosamides (clindamycin); cephalosporins (ceftriaxone and ceftazidime), penicillins (oxacillin, penicillin, and piperacillin); carapenems (imipenem); dihydrofolate reductase inhibitors (trimethoprim); polypeptides (polymixin B); amphenicols (chloramphenicol); and glycopeptides (vancomycin).

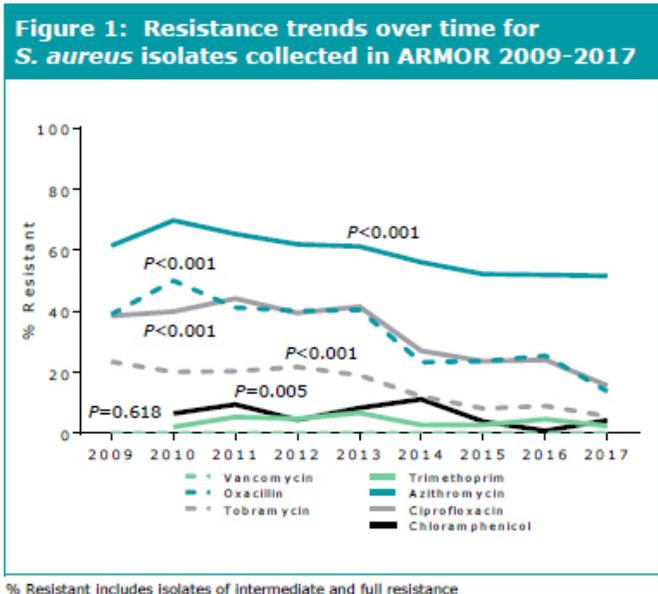
Participating sites in the United States are invited to submit isolates of *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*. ARMOR sites are comprised of ocular centers, community hospitals, and university hospitals. All microbiological testing for ARMOR is done at an independent central laboratory using broth microdilution techniques. The MIC results are interpreted as susceptible, intermediate, or resistant based on established systemic breakpoints. Staphylococci are classified as methicillin resistant (MR) or methicillin susceptible (MS) based on susceptibility to oxacillin.

Since ARMOR was started in 2009, there have been several reports from analyses of the collected data. The latest report described trends in antibiotic resistance among Staphylococcal isolates submitted from January 2009, when ARMOR was launched, through October 2017.²

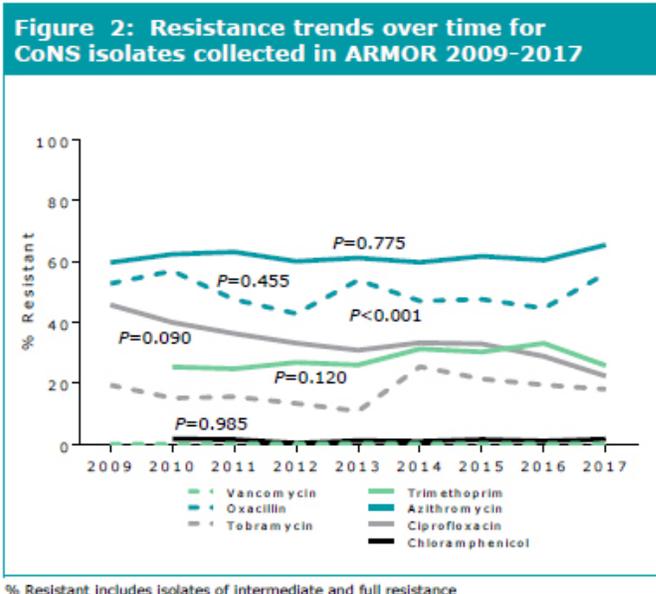
The analysis was based on MIC testing of 1,854 *Staphylococcus aureus* isolates and 1,591 CoNS isolates. One of the key findings was that the rate of methicillin-resistance among *S. aureus* isolates decreased from 39% in 2009 to 14% in 2017. *S. aureus* resistance to azithromycin, ciprofloxacin, tobramycin, and chloramphenicol also decreased over the 8-year study period (FIGURE 1). Nevertheless, in 2017, 16% of 159 *S. aureus*

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% Resistant includes isolates of intermediate and full resistance



% Resistant includes isolates of intermediate and full resistance

isolates were still resistant to ciprofloxacin and 52% were resistant to azithromycin.

The analysis also found that the rate of methicillin-resistance among CoNS remained high and was relatively unchanged during the study period (FIGURE 2). In 2017, approximately 50% of CoNS isolates were resistant to methicillin. Fluoroquinolone resistance among CoNS isolates decreased over time, and the change in resistance to ciprofloxacin was statistically significant. Among 116 CoNS isolates submitted in 2017 isolates, however, 22% were still resistant to ciprofloxacin (FIGURE 2).

Multidrug resistance, defined as resistance to ≥3 antibiotic classes, was demonstrated by 11% of *S. aureus* isolates and 41% of CoNS isolates from 2017. None of the staphylococcal isolates demonstrated resistance to vancomycin.

The MIC values for besifloxacin remained stable over the 9-year study period. In 2017, besifloxacin and vancomycin had the lowest MIC₉₀ values against MRSA *S. aureus* (MRSA) and MRCoNS isolates (Table 1). Compared with other fluoroquinolones, the MIC₉₀ values of besifloxacin (and vancomycin) for MRSA and MRCoNS isolates were 8- to 64-fold lower than all other fluoroquinolones. Another recent ARMOR analysis that included data from non-staphylococcal isolates showed that besifloxacin had an MIC₉₀ of 4 µg/mL against *Pseudomonas aeruginosa*, 0.03 µg/mL against *Haemophilus influenzae*, and 0.06 µg/mL against *Streptococcus pneumoniae*, which was the lowest MIC₉₀ of all tested antibiotics.³

The data from ARMOR need to be considered with the study's limitations in mind. They include the potential for sampling bias due to the infrequent practice of culturing bacterial pathogens. In addition, the application of systemic break-

Table 1: Minimum inhibitory concentrations for ARMOR 2017 staphylococcal isolates

Agent	MIC ₅₀ /MIC ₉₀ (µg/mL)			
	<i>Staphylococcus aureus</i>		Coagulase-negative staphylococci	
	All (n=159)	MRSA (n=22)	All (n=116)	MRCoNS (n=65)
BESIFLOXACIN	0.03/0.25	0.12/1	0.03/0.5	0.03/2
CIPROFLOXACIN	0.25/8	2/64	0.12/32	0.25/64
MOXIFLOXACIN	0.06/2	0.12/16	0.06/4	0.12/16
GATIFLOXACIN	0.06/2	0.12/16	0.12/2	0.12/16
LEVOFLOXACIN	0.25/4	0.5/64	0.25/16	0.25/128
OFLOXACIN	0.5/8	1/16	0.25/16	0.5/32
TOBRAMYCIN	0.25/1	0.5/256	≤0.06/16	0.12/64
AZITHROMYCIN	32/>512	>512/>512	256/>512	>512/>512
CHLORAMPHENICOL	4/8	4/8	4/4	4/8
CLINDAMYCIN	0.12/0.25	0.12/>2	0.12/>64	0.12/>64
OXACILLIN	0.5/>2	>2/>2	2/>2	>2/>2
TETRACYCLINE	0.25/0.5	0.25/0.25	0.25/>16	0.5/>16
TRIMETHOPRIM	2/4	1/4	1/>256	1/>256
VANCOMYCIN	1/1	1/1	1/2	1/2

MIC₅₀: Minimum inhibitory concentration that inhibits 50% of isolates
 MIC₉₀: Minimum inhibitory concentration that inhibits 90% of isolates

points to define susceptibility to ocular treatments and thus the applicability to topically applied antibiotics may not be relevant. Although it is assumed that the topically applied antibiotics achieve concentrations at the target site that match or exceed those achieved with systemic administration, because blinking and tear turnover cause topically applied antibiotics to be removed rapidly from the ocular surface, the antibiotic concentration in ocular tissue may not be indicative of the actual concentration effect. Despite these issues, the findings from ARMOR offer a useful reference for informing decisions when clinicians are empirically prescribing an antibiotic to treat ocular infections.

MANAGEMENT OF ACUTE BACTERIAL CONJUNCTIVITIS

Treatment of acute bacterial conjunctivitis is the only FDA-approved indication that is common to all commercially available ophthalmic antibiotics and the only FDA-approved indication for some.

The etiology of acute bacterial conjunctivitis varies across different age groups, and often the infection may develop as a result of abnormal proliferation of commensal flora of the skin and nasopharynx or from spread of organisms causing otitis or an upper respiratory infection. Staphylococci, including *S. aureus* and coagulase-negative staphylococci, are the most common pathogens in adults.⁴ Studies show that methicillin-resistance is common among staphylococcal conjunctival isolates.^{5,6} *H. influenzae*, *S. pneumoniae*, and *Moraxella catarrhalis* are most commonly isolated in children.⁴ *P. aeruginosa* may be found particularly in cases of acute bacterial conjunctivitis occurring in contact lens wearers.⁴

Based on history and clinical features, an eye care provider can often differentiate acute bacterial conjunctivitis from common non-infectious causes of red eye or viral conjunctivitis. Acute bacterial conjunctivitis typically presents with moderate-to-severe erythema along with a mucopurulent discharge, and usually it involves either one eye only or began as a unilateral condition.^{7,8}

Acute bacterial conjunctivitis is usually a self-limiting infection, but it is highly contagious and has the potential to progress to keratitis.⁸ Treatment with a topical antibiotic has benefits for hastening resolution of the infection along with its signs and symptoms.⁹ Proof of treatment initiation may also be required before a child with acute bacterial conjunctivitis is allowed to return to school or daycare.¹⁰

Based on knowledge of the most common causes of acute bacterial conjunctivitis, a broad-spectrum antibiotic that provides coverage against both gram-positive and gram-negative bacteria is preferred for empiric therapy. Activity against methicillin-resistant staphylococci is important considering data showing its prevalence as an isolate in ocular infections.^{2,3} Recent MIC data from the ARMOR study showing that besifloxacin has the greatest *in vitro* activity against common causes of acute bacterial conjunctivitis, including staphylococci and *S. pneumoniae*, supports its consideration as first-line therapy for acute bacterial conjunctivitis.

Patients age 1 and older who are being treated for acute bacterial conjunctivitis may be scheduled for a follow-up visit after 1 week to check for clinical resolution. Signs and symptoms of acute bacterial conjunctivitis should improve quickly once the patient starts on effective therapy. Patients

BESIFLOXACIN

Besifloxacin's potent and stable broad-spectrum antimicrobial activity may be explained by several features that distinguish it from other topical ophthalmic antibiotics. Besifloxacin is a bactericidal agent that acts by potent balanced inhibition of bacterial topoisomerase II (also called DNA gyrase) and topoisomerase IV.¹¹ Dual inhibition of topoisomerase II and IV distinguishes besifloxacin from older fluoroquinolones (ciprofloxacin, ofloxacin, and levofloxacin) that primarily inhibit topoisomerase II and confers increased activity against gram-positive pathogens.¹¹ In addition, dual inhibition of both topoisomerase enzymes is thought to reduce spontaneous emergence of bacterial resistance because two point mutations would be needed for resistance to occur.

Moxifloxacin and gatifloxacin also inhibit topoisomerase II and IV, but there is evidence that besifloxacin may have more potent activity against both enzymes compared with moxifloxacin.¹¹ The difference may be explained by a molecular structure difference.¹² Besifloxacin is a chloro-fluoroquinolone and is distinguished from moxifloxacin and gatifloxacin by the presence of a chlorine atom and a zepiny group in its molecular structure.¹³

Besifloxacin is also the only topical ophthalmic anti-

biotic that was developed specifically for ophthalmic use and used exclusively in the eye. The more restricted use of besifloxacin relative to other ophthalmic antibiotics that are also prescribed for the treatment of cutaneous and systemic infections and used in agriculture may be important for limiting selective pressure that can promote emergence of bacterial resistance.

In addition, besifloxacin is the only topical ophthalmic fluoroquinolone that is formulated in a mucoadhesive polymer vehicle (DuraSite®). This proprietary drug delivery system enhances drop residence time on the ocular surface and prolongs exposure of microorganisms to a therapeutically effective concentration. Studies show that besifloxacin formulated in the polymer vehicle can provide antibiotic coverage lasting up to 12 hours.¹⁴

Clinical trial results show that topical besifloxacin 0.6% ophthalmic suspension (Besivance®, Bausch + Lomb) is well-tolerated. Although the mucoadhesive polymer creates blurring and a physical sensation in the eye, these effects can provide confirmation that the drops were correctly instilled. Patients can experience difficulty with self-administering eye drops, and those who are uncertain whether placement was successful may waste medication by re-instillation. Side effects may include eye redness, blurred vision, eye pain, eye irritation, eye pruritus and headache.

should be counseled to call their eye care professional if their condition does not significantly improve after 2 to 3 days or worsens after treatment.

When a patient diagnosed clinically with acute bacterial conjunctivitis has not responded to empiric antibiotic treatment, clinicians should explore treatment adherence and if necessary, reconsider the diagnosis. If acute bacterial conjunctivitis is still strongly suspected, a specimen should be obtained for culture and sensitivity testing to guide effective therapy.

When prescribing any medication, patient allergies should always be taken into account and consideration should be given to cost. However, the potential for savings with manufacturer’s rebates or coupons and from avoiding costs incurred when primary treatment fails need to be factored into the economic equation. Prescribing an antibiotic for acute

bacterial conjunctivitis that provides potent activity against common pathogens both serves patients and may lessen the risk for the development of bacterial resistance.



Dr Bell is in private practice as a general ophthalmologist with an emphasis on anterior segment surgery and ocular surface disease.

Dr Bell is medical director of Bell Eye Care Institute.

Dr Bell has no financial interest in Bausch + Lomb except he is a member of their Speakers Bureau.



Derek N. Cunningham, OD, is Director, Dell Eye Institute for Dry Eye Research, Dell Laser Consultants, Austin, TX.

Dr. Bell and Dr. Cunningham are paid consultants of Bausch + Lomb.

INDICATION

BESIVANCE® (besifloxacin ophthalmic suspension) 0.6% is a quinolone antimicrobial indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria: *Aerococcus viridans**, CDC coryneform group G, *Corynebacterium pseudodiphtheriticum**, *Corynebacterium striatum**, *Haemophilus influenzae*, *Moraxella catarrhalis**, *Moraxella lacunata**, *Pseudomonas aeruginosa**, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus hominis**, *Staphylococcus lugdunensis**, *Staphylococcus warneri**, *Streptococcus mitis* group, *Streptococcus oralis*, *Streptococcus pneumoniae*, *Streptococcus salivarius**

*Efficacy for this organism was studied in fewer than 10 infections.

IMPORTANT SAFETY INFORMATION

- BESIVANCE is not for injection into the eye.
- As with other anti-infectives, prolonged use of BESIVANCE may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy.
- Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with BESIVANCE.
- The most common adverse event reported in approximately 2% of patients treated with BESIVANCE was conjunctival redness. Other adverse events reported in patients receiving BESIVANCE occurring in approximately 1–2% of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.
- Safety and effectiveness in infants below one year of age have not been established.

Click [here](#) for full Prescribing Information for BESIVANCE.

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