Antibiotic Resistance Among Ocular Pathogens in the United States
Five-Year Results From the Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) Surveillance Study

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**IMPORTANCE** The Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study is the only ongoing nationwide antibiotic resistance surveillance program specific to ocular pathogens.

**OBJECTIVE** To report resistance rates and trends among common ocular isolates collected during the first 5 years of the ARMOR study.

**DESIGN, SETTING, AND PARTICIPANTS** This antibiotic resistance surveillance study was performed at an independent central laboratory. Clinical centers across the United States were invited to submit ocular isolates of *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*. Isolates were collected from January 1, 2009, through December 31, 2013, and analyzed from January 16 to May 15, 2015.

**MAIN OUTCOMES AND MEASURES** Minimum inhibitory concentrations for various antibiotic classes were determined by broth microdilution according to the guidelines of the Clinical and Laboratory Standards Institute. Minimum inhibitory concentrations were interpreted as susceptible, intermediate, or resistant based on established break points.

**RESULTS** A total of 3237 ocular isolates (1169 *S aureus*, 992 CoNS, 330 *S pneumoniae*, 357 *H influenzae*, and 389 *P aeruginosa*) were collected from 72 centers. Methicillin resistance was found among 493 *S aureus* isolates (42.2%; 95% CI, 39.3%-45.1%) and 493 CoNS isolates (49.7%; 95% CI, 46.5%-52.9%), and methicillin-resistant (MR) isolates had a high probability of concurrent resistance to fluoroquinolones, aminoglycosides, or macrolides (*P* < .001). Multidrug resistance to at least 3 additional antibiotic classes was found in 428 MR *S aureus* isolates (86.8%) and 381 MRCoNS isolates (77.3%). All staphylococcal isolates were susceptible to vancomycin. Resistance among *S pneumoniae* isolates was highest for azithromycin (113 isolates [34.2%]) whereas resistance among *P aeruginosa* and *H influenzae* was low against the antibiotics tested. Staphylococcal isolates from elderly patients were more likely to be MR, as were *S aureus* isolates obtained from the southern United States (*P* < .001). Methicillin resistance among staphylococci did not increase during the 5-year study period (*P* = .22), and small decreases in resistance to ciprofloxacin among CoNS and MRCoNS and to tobramycin among CoNS (*P* ≤ .03) were found.

**CONCLUSIONS AND RELEVANCE** Methicillin resistance was prevalent among staphylococcal isolates from ocular infections, with many strains demonstrating multidrug resistance. These findings are consistent with resistance trends reported for nonocular staphylococcal isolates. Overall ocular resistance did not increase during the 5-year study period. Continued surveillance of ocular isolates provides critical information to guide selection of topical antibacterials used for empirical management of ocular infections.
The past 2 decades have seen an increase in antibiotic resistance among bacterial pathogens in general and bacterial pathogens of the eye in particular. For instance, ocular staphylococci have developed resistance to methicillin and other antibiotic classes. Infection by these and other multidrug-resistant pathogens can compromise the choice of antibiotic treatment and threaten vision.

In any bacterial infection, the causative pathogen should be identified and its antibiotic resistance profile should be determined before initiating antibacterial treatment. Current clinical laboratory methods can take several days to grow bacteria in culture and another 1 or 2 days to determine an isolate’s antibiotic resistance profile. In the absence of rapid diagnostic methods, physicians treat ocular infections empirically. Surveillance studies of antibiotic resistance can identify risk groups and susceptibility trends to aid in the choice of empirical treatment.

Although the World Health Organization, the US Food and Drug Administration, the Centers for Disease Control and Prevention, and other agencies monitor antibiotic resistance trends among bacteria that cause systemic diseases, ocular pathogens are rarely a target of these investigations. Resistance trends among ocular pathogens have been reported from single-center studies. However, not until 2008 were results available for the first multicenter, nationwide antibiotic resistance surveillance program specific to ocular pathogens. The Ocular Tracking Resistance in US Today (TRUST) study reported antibiotic resistance among ocular isolates of Staphylococcus aureus, Haemophilus influenzae, and Streptococcus pneumoniae collected from 2005 through 2006 from 35 institutions across the United States. The study found that 16.8% of S. aureus isolates were methicillin resistant (MR), with many isolates concurrently resistant to other antibiotic classes. A significant proportion of pneumococcal isolates had intermediate resistance to penicillin (18.3%), azithromycin (22.4%), and trimethoprim (22.4%) whereas no notable resistance was reported among H. influenzae isolates. Results of the second and third years of the Ocular TRUST study (TRUST2 and TRUST3) showed an increase in methicillin resistance among S. aureus isolates in subsequent years to nearly 50% in 2008, whereas methicillin resistance among coagulase-negative staphylococci (CoNS) was as high as 62.0%. Results for S. pneumoniae and H. influenzae appeared to be unchanged.

The Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study was initiated in 2009 to survey antibiotic resistance among S. aureus, CoNS, S. pneumoniae, H. influenzae, and Pseudomonas aeruginosa isolates from ocular infections. Like the Ocular TRUST study, the ARMOR study is a multicenter, nationwide, prospective surveillance study and provides resistance data to extend the Ocular TRUST data. Herein we present antibiotic resistance profiles and trends for more than 3000 ocular isolates collected during the first 5 years of the ARMOR study.

### Methods

**ARMOR Study Design**

The ARMOR surveillance study has been described before. Herein we report antibiotic resistance among ocular isolates collected from January 1, 2009, through December 31, 2013. Patients tested were enrolled from the United States. The study found that 16.8% of S. aureus isolates were methicillin resistant (MR), with many isolates concurrently resistant to other antibiotic classes. A significant proportion of pneumococcal isolates had intermediate resistance to penicillin (18.3%), azithromycin (22.4%), and trimethoprim (22.4%) whereas no notable resistance was reported among H. influenzae isolates. Results of the second and third years of the Ocular TRUST study (TRUST2 and TRUST3) showed an increase in methicillin resistance among S. aureus isolates in subsequent years to nearly 50% in 2008, whereas methicillin resistance among coagulase-negative staphylococci (CoNS) was as high as 62.0%. Results for S. pneumoniae and H. influenzae appeared to be unchanged.

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### Antibacterial Susceptibility Testing

Bacterial isolates were sent to a central laboratory (Eurofins Medinet) for species confirmation and determination of the antibiotic resistance profile. Minimum inhibitory concentrations (MICs) were determined by broth microdilution according to the Clinical and Laboratory Standards Institute methods using frozen antimicrobial microtiter panels (Thermo Fisher Scientific). Antibiotics from different classes were tested against isolates as appropriate based on species; these included fluoroquinolones (ciprofloxacin, moxifloxacin, gatifloxacin, besifloxacin, levofloxacin, and ofloxacin), macrolides (azithromycin), aminoglycosides (tobramycin), lincosamides (clindamycin), cephalosporins (ceftriaxone and cefazidime), penicillins (oxacillin, penicillin, and piperacillin), carbapenems (imipenem), dihydrofolate reductase inhibitors (trimethoprim), polypeptides (polymyxin B), amphenicols (chloramphenicol), and glycopeptides (vancomycin). Some nonophthalmic antibiotics were included to facilitate comparison of resistance rates of ocular isolates with published rates for nonocular isolates of the same species. Wherever possible, MICs were interpreted as susceptible, intermediate, or resistant according to the Clinical and Laboratory Standards Institute interpretive criteria in use during the collection year for that combination of species and antibiotic. Staphylococci were classified as MR or methicillin susceptible (MS) based on susceptibility to oxacillin. Susceptibility and resistance of S. pneumoniae isolates to penicillin was determined using the

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**At a Glance**

- Data on antibiotic resistance of common ocular bacterial pathogens are needed.
- In all, 3237 ocular isolates (1169 Staphylococcus aureus, 992 coagulase-negative staphylococci [CoNS], 330 Streptococcus pneumoniae, 357 Haemophilus influenzae, and 389 Pseudomonas aeruginosa isolates) were collected from 72 centers in the United States from January 1, 2009, through December 31, 2013, as part of the ongoing Antibiotic Resistance Monitoring in Ocular Microorganisms study.
- Methicillin resistance was found among 493 S aureus isolates (42.2%) and 493 CoNS isolates (49.7%), and methicillin-resistant (MR) isolates had a high probability of concurrent resistance to fluoroquinolones, aminoglycosides, or macrolides ($P < .001$).
- Multidrug resistance to 3 or more additional antibiotic classes continues to be a challenge and was found in 428 MR S aureus isolates (86.8%) and 381 MRCoNS isolates (77.3%).
Table. Minimum Inhibitory Concentrations and Resistance Profiles for Isolates

<table>
<thead>
<tr>
<th>Organisms by Antibiotic</th>
<th>Isolates</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;, μg/mL</th>
<th>No. (%) of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Susceptible</td>
<td>Intermediate</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>MCOsNS</td>
<td>431</td>
<td>8</td>
</tr>
<tr>
<td>MSSA</td>
<td>MRCoNS</td>
<td>417</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>MCOsNS</td>
<td>499</td>
<td>8</td>
</tr>
<tr>
<td>MSSA</td>
<td>MRCoNS</td>
<td>493</td>
<td>64</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>MCOsNS</td>
<td>431</td>
<td>4</td>
</tr>
<tr>
<td>MSSA</td>
<td>MRCoNS</td>
<td>417</td>
<td>128</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>MCOsNS</td>
<td>431</td>
<td>2</td>
</tr>
<tr>
<td>MSSA</td>
<td>MRCoNS</td>
<td>417</td>
<td>32</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>MCOsNS</td>
<td>499</td>
<td>1</td>
</tr>
<tr>
<td>MSSA</td>
<td>MRCoNS</td>
<td>493</td>
<td>32</td>
</tr>
<tr>
<td>Besifloxacin</td>
<td>MCOsNS</td>
<td>499</td>
<td>0.25</td>
</tr>
<tr>
<td>MSSA</td>
<td>MRCoNS</td>
<td>493</td>
<td>4</td>
</tr>
</tbody>
</table>

**Coagulase-Negative Staphylococci**

<table>
<thead>
<tr>
<th>Organisms by Antibiotic</th>
<th>Isolates</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;, μg/mL</th>
<th>No. (%) of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Susceptible</td>
<td>Intermediate</td>
</tr>
<tr>
<td><strong>MRCoNS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus xylosus</td>
<td>499</td>
<td>&gt;512</td>
<td>276 (55.3)</td>
</tr>
<tr>
<td>Staphylococcus caprae</td>
<td>493</td>
<td>&gt;512</td>
<td>107 (21.7)</td>
</tr>
<tr>
<td>Staphylococcus auricularis</td>
<td>499</td>
<td>1</td>
<td>428 (85.8)</td>
</tr>
<tr>
<td>Staphylococcus hominis</td>
<td>493</td>
<td>&gt;2</td>
<td>322 (65.3)</td>
</tr>
<tr>
<td><strong>MRCoNS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus lugdunensis</td>
<td>431</td>
<td>4</td>
<td>428 (99.3)</td>
</tr>
<tr>
<td>Staphylococcus pasteuri</td>
<td>493</td>
<td>16</td>
<td>379 (76.9)</td>
</tr>
<tr>
<td>Staphylococcus schleiferi</td>
<td>499</td>
<td>2</td>
<td>252 (60.4)</td>
</tr>
<tr>
<td><strong>MRCoNS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
<td>493</td>
<td>2</td>
<td>499 (100)</td>
</tr>
</tbody>
</table>

**Streptococcus pneumoniae**

<table>
<thead>
<tr>
<th>Organisms by Antibiotic</th>
<th>Isolates</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;, μg/mL</th>
<th>No. (%) of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Susceptible</td>
<td>Intermediate</td>
</tr>
<tr>
<td><strong>MRCoNS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus condimenti</td>
<td>289</td>
<td>4</td>
<td>257 (88.9)</td>
</tr>
</tbody>
</table>

Abbreviations: CoNS, coagulase-negative staphylococci; MIC<sub>90</sub>, minimum inhibitory concentration that inhibits the growth of 90% of indicated isolates; MRCoNS, methicillin-resistant CoNS; MRSA, methicillin-resistant S aureus; MSCoNS, methicillin-susceptible CoNS; MSSA, methicillin-susceptible S aureus; NA, Clinical and Laboratory Standards Institute interpretive break points currently not available or not applicable.

<sup>a</sup> From the Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) surveillance study, 2009-2013. Percentages may not total 100 owing to rounding.

<sup>b</sup> The 992 CoNS isolates included S aureus (n = 1), Staphylococcus epidermidis (n = 2), Staphylococcus caprae (n = 6), Staphylococcus simulans (n = 1), Staphylococcus hominis (n = 43), Staphylococcus pasteuri (n = 5), Staphylococcus schleiferi (n = 2), Staphylococcus simulans (n = 2), Staphylococcus warneri (n = 34), Staphylococcus xylosus (n = 1), and unspeciated CoNS (n = 55).
break point for oral penicillin. For reporting purposes, resistant isolates were those classified as intermediate or resistant to an antibiotic, and calculations for the percentage of resistance included intermediate isolates unless noted otherwise. **Multidrug resistance** was defined as resistance to at least 3 classes of antibiotics.

**Statistical Analysis**

Data were analyzed from January 16 to May 15, 2015. Confidence intervals for cumulative antibiotic resistance rates were computed using the Wilson score\(^3\) with a correction for continuity. Logistic regression models for concurrent resistance to each antibiotic were used to obtain odds ratios based on methicillin resistance. We used 1-way analyses of variance (ANOVA) to evaluate antibiotic resistance by patient age or geographic region. Because not all antibiotic classes were tested in each of the 5 years of the study period, the ANOVA used the means of the percentage of drug classes to which each isolate of a species or a species group was resistant. The ANOVA that showed statistical significance underwent the Tukey honestly significant difference test for pairwise differences. For the analysis by geography, isolates were categorized into 4 regions based on state of origin, including the western (Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming), the midwestern (Iowa, Illinois, Indiana, Kansas, Kentucky, Michigan, Minnesota, Missouri, North Dakota, Nebraska, Ohio, South Dakota, and Wisconsin), southern (Alabama, Arkansas, Florida, Georgia, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia), and northeastern (Connecticut, Delaware, Massachusetts, Maine, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont) states. Differences among staphylococcal isolates by methicillin resistance status were determined via a \(\chi^2\) test where indicated. Changes in resistance rates over time were evaluated using a Cochran-Armitage test\(^4\) for linear trends in a proportion. Statistical testing was performed using Statistix 10 (Analytical Software) or Prism (version 5.01; GraphPad Software).

**Results**

**Source of Isolates**

A total of 3237 isolates (1169 *S aureus*, 992 CoNS, 330 *S pneumoniae*, 357 *H influenzae*, and 389 *P aeruginosa* isolates) were collected from 72 eye care centers, community hospitals, and academic or university hospitals across 36 states in the West (632 isolates), Midwest (1147 isolates), South (612 isolates), and Northeast (846 isolates). Of patients contributing samples, 1407 (43.5%) were male, 1555 (48.0%) were female, and sex was not reported for 275 (8.5%). A total of 2657 isolates were obtained from patients with specified ages (463 isolates, \(<10\) years; 133 isolates, 10-19 years; 193 isolates, 20-29 years; 171 isolates, 30-39 years; 220 isolates, 40-49 years; 319 isolates, 50-59 years; 292 isolates, 60-69 years; 323 isolates, 70-79 years; 367 isolates, 80-89 years; and 176 isolates, \(\geq 90\) years). *Haemophilus influenzae* and *S pneumoniae* isolates were more likely to be obtained from patients younger than 10 years, whereas *S aureus* isolates were commonly obtained from adults. *Pseudomonas aeruginosa* isolates were obtained most often from patients aged 10 to 29 years. The anatomical source was known for 1280 isolates (39.5%) and included the conjunctiva (n = 546), cornea (n = 593), aqueous humor (n = 48), and vitreous humor (n = 93). Among the 216 *P aeruginosa* isolates with a known anatomical source, 176 (81.5%) were obtained from corneal scrapings; among the 90 *H influenzae* isolates with a known anatomical source, 72 (80.0%) were collected from the conjunctiva.

**Cumulative Antibiotic Resistance Rates**

Of the 1169 *S aureus* isolates, 493 (42.2%), 465 (39.8%), and 743 (63.6%) were resistant to oxacillin (MR *S aureus* [MRSA]), ciprofloxacin, and azithromycin, respectively. Resistance to clindamycin was found in 196 isolates (16.8%); to tobramycin, in 227 isolates (19.4%). All *S aureus* isolates were susceptible to vancomycin, and only a small proportion were resistant to trimethoprim (46 of 969 [4.7%]) and chloramphenicol (4 of 969 [0.4%]). As shown in the **Table**, resistance among MRSA was high for all fluoroquinolones, azithromycin, and tobramycin; among MS *S aureus* (MSSA) isolates, resistance was high only for azithromycin. Within the fluoroquinolone class, MIC\(_{90}\) values for MSSA and MRSA, referring to the lowest drug concentration at which 90% of isolates were inhibited, were lower for the newer fluoroquinolones (besifloxacin, moxifloxacin, and gatifloxacin) compared with the older fluoroquinolones (ofloxacin, ciprofloxacin, and levofloxacin), with besifloxacin demonstrating the lowest MIC\(_{90}\).

The 992 CoNS isolates had similar resistance profiles to *S aureus* isolates, with 493 (49.7%), 341 (34.4%), and 608 (61.3%) showing resistance to oxacillin, ciprofloxacin, and azithromycin, respectively. Resistance to clindamycin, chloramphenicol, and tobramycin was seen in 191 of 992 isolates (19.3%), 7 of 848 isolates (0.8%), and 81 of 992 isolates (8.2%), respectively; however, 219 of 848 isolates (25.8%) were resistant to trimethoprim.

All CoNS isolates were susceptible to vancomycin. Similar to MRSA isolates, MRCoNS isolates had higher resistance rates to ciprofloxacin, azithromycin, and other drugs, including trimethoprim, compared with MSCoNS isolates (Table). As with *S aureus* isolates, the newer fluoroquinolones had generally lower MIC\(_{90}\) values against MSCoNS and MRCoNS.

Most of the 330 *S pneumoniae* isolates were susceptible to the antibiotics tested, with the exception of azithromycin and penicillin (Table). Almost all *S pneumoniae* isolates were susceptible to chloramphenicol and the fluoroquinolones, and besifloxacin had the lowest MIC\(_{90}\) among the fluoroquinolones tested.

Among *P aeruginosa* isolates, resistance rates were low to those antibiotics tested, with good susceptibility to fluoroquinolones and tobramycin (Table). However, ciprofloxacin had the lowest MIC\(_{90}\) of the fluoroquinolones.

With the exception of 1 isolate resistant to azithromycin and 1 resistant to chloramphenicol, all *H influenzae* isolates were susceptible to all antibiotics tested. The MIC\(_{90}\) values for the antibiotics tested were no greater than 0.06 \(\mu\)g/mL for the fluoroquinolones, 2 \(\mu\)g/mL for azithromycin, 0.5 \(\mu\)g/mL for chloramphenicol, no greater than 0.03 \(\mu\)g/mL for ceftriaxone, and 1 \(\mu\)g/mL for imipenem.
Multidrug Resistance
Methicillin-resistant staphylococcal isolates were more likely to be concurrently resistant to another drug class when compared with MS staphylococcal isolates, with \( P < .001 \) for resistance to macrolides, fluoroquinolones (using break points for ciprofloxacin), lincosamides, and aminoglycosides (Figure 1). Based on the high probability of concurrent resistance to an additional antibiotic class, we summarized the percentage of multidrug resistance among staphylococcal isolates. Overall, among all \( S \) aureus and all CoNS isolates, rates of multidrug resistance (resistance to \( \geq 3 \) classes of antibiotics) included 472 (40.4%) and 424 isolates (42.7%), respectively, whereas among MRSA and MRCoNS, they included 428 (86.8%) and 381 (77.3%), respectively (Figure 2).

Antibiotic Resistance Rates by Age of the Patient or Geography
Analysis of the mean percentage of resistance by patient age (categorized by decade of life) showed differences among staphylococci isolates (\( P < .001 \); Figure 3), with higher rates in elderly patients. Pairwise differences were found between \( S. \) aureus isolates from patients 80 years or older compared with patients younger than 80 years, between CoNS isolates from patients 70 years or older compared with those younger than 30 years, and between CoNS isolates from patients 30 years or older compared with patients aged 10 to 29 years. Methicillin resistance, specifically, also differed by age group for \( S. \) aureus and CoNS isolates (\( P < .001 \)), again with the highest resistance observed in elderly patients. Resistance rates among \( S. \) pneumoniae, \( P. \) aeruginosa, and \( H. \) influenzae isolates did not differ by age group (\( P \geq .24 \)).

Differences were found in the mean percentage of resistance by geographic region of origin for \( S. \) aureus (\( P < .001 \)), \( S. \) pneumoniae (\( P = .05 \)), and \( P. \) aeruginosa (\( P = .01 \)) isolates. Mean (SE) percentages of resistance among \( S. \) aureus isolates were 26.0% (1.6%), 25.1% (1.1%), 24.0% (1.3%), and 17.9% (1.6%) in the South, Midwest, Northeast, and West, respectively, with a pairwise difference between the West and the other regions. Methicillin resistance paralleled that for the mean percentage of resistance, with rates of 50.0%, 45.7%, 41.0%, and 28.9% in the respective geographic regions (\( P < .001 \)). For \( S. \) pneumoniae, the mean (SE) percentage of resistance was...
21.3% (2.0%), 16.5% (2.8%), 15.3% (2.4%), and 13.0% (2.3%) in the Midwest, South, Northeast, and West, respectively, with a pairwise difference between the Midwest and West. Among *P aeruginosa* isolates, the mean (SE) percentage of resistance was 17.4% (1.8%), 13.1% (2.4%), 12.2% (2.0%), and 8.1% (2.1%) in the Midwest, West, Northeast, and South, respectively, with a pairwise difference between the Midwest and South.

### Resistance Rates Over Time

We found few changes in resistance rates during the 5-year study period (Figure 4). Methicillin resistance did not increase among *S aureus* (*P* = .22) or CoNS (*P* = .11) isolates, and we found a small decrease in resistance to ciprofloxacin among CoNS (*P* = .002) and MRCoNS (*P* = .02) isolates. Additional exploratory analysis showed a small decrease in resistance to tobramycin among CoNS isolates (*P* = .03). No other changes in resistance rates were noted.

### Discussion

The ARMOR surveillance study provides nationwide antibiotic resistance rates among ocular isolates of *S aureus*, CoNS, *S pneumoniae*, *H influenzae*, and *P aeruginosa*, the most frequently occurring ocular pathogens. The first ARMOR analysis, based solely on isolates collected in 2009, showed that antibiotic resistance among ocular pathogens was a concern, especially among *S aureus* and CoNS isolates. The present report expands on the 2009 data by including more than 2500 additional isolates collected during the ensuing 4 years and by testing additional antibiotics used within and outside ophthalmology. Altogether, the resistance profiles of the 3237 isolates from ocular infections collected across 36 US states were determined, making this the most robust evaluation of nationwide antibacterial susceptibility of common ocular pathogens to date.

Results show that antibiotic resistance continues to be high among staphylococci, with nearly half of these isolates resistant to methicillin and a high probability of concurrent resistance among MR staphylococci to other commonly used antibiotic classes. The MRSA isolates were 16 to 18 times and the MRCoNS isolates were 4 to 8 times more likely to be resistant to ciprofloxacin, azithromycin, or tobramycin compared with the MS strains, and most of the MR staphylococci isolates were multidrug resistant. However, vancomycin remained active against these isolates. In contrast, resistance among *P aeruginosa* and *H influenzae* isolates was low against the antibiotics tested while resistance among *S pneumoniae* isolates was notable only for azithromycin and penicillin (based on oral break points). These findings agree with data from the latest report of the Ocular TRUST study with a single exception: cumulative rates of methicillin resistance among *S aureus* and CoNS isolates in our study (42.2% and 49.7%, respectively) were slightly lower than the corresponding rates from the Ocular TRUST3 study for isolates collected from 2007 to 2008 (48.1% and 62.0%). Although *P aeruginosa* and *H influenzae* isolates were not evaluated in the Ocular TRUST3 study, the low resistance rates we found among *H influenzae* isolates are in agreement with data from the Ocular TRUST1 study.

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**Figure 2. Multidrug Resistance**

![Graph A: Staphylococcus aureus](image1)

![Graph B: Methicillin-resistant *S aureus*](image2)

![Graph C: Coagulase-negative staphylococci](image3)

![Graph D: Methicillin-resistant CoNS](image4)
With respect to MIC90, we found large differences consistent with other studies among fluoroquinolone class of antibiotics, in particular against staphylococci, with newer fluoroquinolones having a lower MIC90 compared with older fluoroquinolones. Besifloxacin, a chlorofluoroquinolone developed for ophthalmic use only, had the lowest MIC90 for gram-positive isolates; however, because no interpretive breakpoint is available for besifloxacin, the clinical relevance of this finding is unknown. Besifloxacin was as effective as moxifloxacin in the treatment of bacterial conjunctivitis but more effective at eliminating bacteria from the ocular surface before cataract surgery.

The large sample of isolates in this study allowed for analysis of resistance trends. Consistent with previous reports, antibiotic resistance among staphylococci isolates was highest among elderly patients. This finding was not unexpected given that elderly patients may spend more time in nursing homes and hospitals, which are known risk factors for carrying antibiotic-resistant bacteria. Based on the reported increase in antibiotic resistance among ocular staphylococci in the years before 2009, we hypothesized that staphylococcal resistance to methicillin and ciprofloxacin would continue to increase during the 5-year study period. However, no increase in methicillin resistance was observed among staphylococci isolates in our study, and, contrary to expectations, a small decrease occurred in resistance to ciprofloxacin among CoNS and MRCoNS isolates. These findings are promising and may reflect improved antibiotic stewardship. Indeed, programs advocating judicious antibiotic use by limiting overprescription of antibiotics, cycling between antibiotic classes, and using combination therapies have led to a decrease in resistance among bacteria involved in systemic infections and are likely having a similar impact among bacteria causing ocular infections. Finally, analysis by geographic region revealed small differences across the United States in susceptibility among S aureus, S pneumoniae, and P aeruginosa isolates. Resistance patterns varied by species, with gram-positive isolates from the West having the lowest rates of resistance. For S aureus isolates, the highest resistance was seen in the South.

Resistance rates observed in our study were similar to rates reported for nonocular isolates from systemic infections evaluated in recent US surveillance studies with similar methods. For instance, the cumulative MRSA prevalence in the AWARE (Assessing Worldwide Antimicrobial Resistance Evaluation) study for isolates collected from 2009 to 2013 was 49.7%, with no longitudinal change observed during the study period.

Likewise, the 2013 LEADER (Linezolid Experience and Accurate Determination of Resistance) study showed a MRSA rate of 47.9%. Although the MRSA rate for MRCoNS isolates was higher in the LEADER study than in our study (68.6% of 580 isolates in the LEADER study vs 49.7%), staphylococcal resistance rates for clindamycin and ciprofloxacin were analogous to those observed in our study. Penicillin resistance among S pneumoniae isolates was slightly higher in the LEADER and AWARE studies (17.6% of 1281 isolates in the LEADER study vs 21.1% of 3329 in the AWARE study) compared with a rate of 8.8% in our study based on oral penicillin break points. Further comparisons of S pneumoniae penicillin resistance between our study and nonocular surveillance studies were hampered by the fact that the break points used in those studies were often not specified.

Limitations of our study included potential sampling biases owing to the relatively infrequent practice of culturing bacterial pathogens, the use of systemic break points to interpret MIC data, and the choice of antibiotics tested. Systemic break points enable clinicians to choose an antibiotic for infections and to weigh the susceptibility of the bacterial pathogen against the systemic distribution of that antibiotic after oral or intravenous administration. The use of such break points may be of limited value when determining the antibiotic resistance status of ocular isolates exposed to topically applied antibiotics. However, systemic break points can be applied if one assumes that the concentration of antibiotic in the ocular tissue is equal to or greater than that achieved after systemic administration, although higher ocular tissue concentrations may lead to overreporting of resistance. We tried to include the most relevant ophthalmic antibiotics, but not all could be tested. For instance, bacitracin was not included because it is formulated as an ointment; sulfadiazine, ciprofloxacin, and tobramycin, did not have significant resistance, were not included due to infeasibility. Finally, our study was limited to those isolates submitted to a reference laboratory.

Figure 3. Resistance Among Ocular Isolates by Patient Age

With respect to MIC90, we found large differences consistent with other studies among fluoroquinolone class of antibiotics, in particular against staphylococci, with newer fluoroquinolones having a lower MIC90 compared with older fluoroquinolones. Besifloxacin, a chlorofluoroquinolone developed for ophthalmic use only, had the lowest MIC90 for gram-positive isolates; however, because no interpretive breakpoint is available for besifloxacin, the clinical relevance of this finding is unknown. Besifloxacin was as effective as moxifloxacin in the treatment of bacterial conjunctivitis but more effective at eliminating bacteria from the ocular surface before cataract surgery.

The large sample of isolates in this study allowed for analysis of resistance trends. Consistent with previous reports, antibiotic resistance among staphylococci isolates was highest among elderly patients. This finding was not unexpected given that elderly patients may spend more time in nursing homes and hospitals, which are known risk factors for carrying antibiotic-resistant bacteria. Based on the reported increase in antibiotic resistance among ocular staphylococci in the years before 2009, we hypothesized that staphylococcal resistance to methicillin and ciprofloxacin would continue to increase during the 5-year study period. However, no increase in methicillin resistance was observed among staphylococci isolates in our study, and, contrary to expectations, a small decrease occurred in resistance to ciprofloxacin among CoNS and MRCoNS isolates. These findings are promising and may reflect improved antibiotic stewardship. Indeed, programs advocating judicious antibiotic use by limiting overprescription of antibiotics, cycling between antibiotic classes, and using combination therapies have led to a decrease in resistance among bacteria involved in systemic infections and are likely having a similar impact among bacteria causing ocular infections. Finally, analysis by geographic region revealed small differences across the United States in susceptibility among S aureus, S pneumoniae, and P aeruginosa isolates. Resistance patterns varied by species, with gram-positive isolates from the West having the lowest rates of resistance. For S aureus isolates, the highest resistance was seen in the South.

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Facetamide was not included because of its known high resistance rates and limited clinical use. Within specific drug classes, alternate representative antibiotics may have been chosen.

Conclusions

Results from the ARMOR ocular surveillance study show that nationwide antibiotic resistance rates have not increased during the past 5 years; in fact, rates have decreased for some antibiotic and pathogen combinations. Although these trends are promising, resistance remains high for *Staphylococcus aureus* and CoNS isolates, with many strains demonstrating multidrug resistance consistent with reports for nonocular staphylococcal isolates in the literature. Until rapid diagnostic methods are available to guide treatment choices, clinicians should consider these data to guide the empirical treatment of ocular infections.
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42. McDonald MB, Protzko EE, Brunner LS, et al. Efficacy and safety of besifloxacin ophthalmic suspension 0.6% compared with moxifloxacin ophthalmic solution 0.5% for treating bacterial conjunctivitis. Ophthalmology. 2009;116(9):1616-1623.e1.


