Antibiotic Resistance Rates by Geographic Region Among Ocular Pathogens Collected During the ARMOR Surveillance Study

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ABSTRACT

Introduction: The Antibiotic Resistance Monitoring in Ocular micRoorganisms (ARMOR) study is an ongoing nationwide surveillance program that surveys in vitro antibiotic resistance rates and trends among ocular bacterial pathogens. We report resistance rates by geographic region for isolates collected from 2009 through 2016.

Methods: Staphylococcus aureus, coagulase-negative staphylococci (CoNS), Streptococcus pneumoniae, Haemophilus influenzae, and Pseudomonas aeruginosa isolates from ocular infections were collected at clinical centers across the US and categorized by geographic region based on state. Minimum inhibitory concentrations (MICs) for various antibiotics were determined at a central laboratory, and isolates were classified as susceptible or resistant based on established breakpoints. Geographic differences in methicillin resistance among staphylococci were evaluated by \( \chi^2 \) test with multiple comparisons, whereas geographic differences in mean percentage antibiotic resistance were evaluated by one-way analyses of variance and Tukey’s test.

Results: Overall, 4829 isolates (Midwest, 1886; West, 1167; Northeast, 1143; South, 633) were evaluated. Across all regions, azithromycin resistance was high among S. aureus (49.4–67.8%), CoNS (61.0–62.8%), and S. pneumoniae (22.3–48.7%), whereas fluoroquinolone resistance ranged from 26.1% to 47.8% among S. aureus and CoNS. Across all regions, all staphylococci were susceptible to vancomycin; besifloxacin MICs were similar to those of vancomycin. Geographic differences were observed for overall mean resistance among S. aureus, S. pneumoniae, and P. aeruginosa isolates (\( p \leq 0.005 \)); no regional differences were found among CoNS and H. influenzae isolates. Methicillin resistance in particular was higher among S. aureus isolates from the South and CoNS isolates from the Midwest (\( p \leq 0.006 \)).

Conclusion: This analysis of bacterial isolates from the ARMOR study demonstrated geographic variation in resistance rates among ocular isolates, with greater in vitro resistance apparent in the South and Midwest for some organisms. These data may inform clinicians in

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selecting appropriate treatment options for ocular infections.

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**INTRODUCTION**

Bacteria, including commensal species, can be associated with ocular infections including conjunctivitis, keratitis, blepharitis, uveitis, and endophthalmitis [1]. If left untreated, such infections may result in potentially serious consequences, including permanent loss of vision [2–4]. While antibiotics are commonly used to treat ocular infections, resistance to antibiotics is well known among ocular pathogens [1, 5, 6]. Infections due to antibiotic-resistant pathogens are difficult to treat, and understanding resistance and/or susceptibility patterns may guide the empirical treatment of ocular infections [7–9]. Microbial resistance or susceptibility can show geographic variation, highlighting the need to identify antibiotic resistance patterns by geographic region [4, 6, 10, 11].

Common ocular pathogens in the US include *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae* [12]. The Antibiotic Resistance Monitoring in Ocular micRoorganisms (ARMOR) study is the only ongoing, prospective, multicenter, national surveillance study of antibiotic resistance patterns among bacterial isolates specific to ophthalmology in the US [9]. Each year since 2009, the ARMOR study has collected *S. aureus*, CoNS, *S. pneumoniae*, *H. influenzae*, and *P. aeruginosa* cultured from 1 January 2009 through 31 December 2016 as part of the ongoing ARMOR study. As this was a laboratory study, patient informed consent and institutional review board approval were not required, and Health Insurance Portability and Accountability Act compliance did not apply because samples were taken as part of routine medical care, unrelated to the study, and no patient-identifying information was collected. The current study was not registered as a clinical trial since it does not contain any studies with human participants or animals performed by any of the authors.

Detailed ARMOR study methodology has been published previously [9, 13, 14]. Briefly, minimum inhibitory concentrations (MICs) of various antibiotics were determined by broth microdilution at a central laboratory, and MICs for 90% of isolates (MIC90s) were calculated. Systemic breakpoints, where available, were used to categorize isolates as resistant (includes intermediate and full resistance) or susceptible. Staphylococci were classified as methicillin-resistant (MR) or methicillin-susceptible (MS) based on oxacillin susceptibility.

For geographic analyses, isolates were categorized into Midwest, Northeast, South, and West regions based on the state of origin (Fig. 1). Differences in methicillin resistance among staphylococci by geography were determined by $\chi^2$ test followed by a multiple-comparisons test for proportions, using the $p < 0.05$ criterion for statistical significance. One-way analyses of variance (ANOVA) were performed by geographic region using the means of the percentage of drug classes to which each isolate was resistant. In most cases a single surrogate antibiotic was chosen to determine sensitivity or resistance to a drug class. Drug classes analyzed (and their representative antibiotic) included fluoroquinolones (ciprofloxacin),...
macrolides (azithromycin), aminoglycosides (tobramycin), lincosamides (clindamycin), penicillins (oxacillin/penicillin), folate pathway inhibitors (trimethoprim), polypeptides (polymyxin B), phenicols (chloramphenicol), glycopeptides (vancomycin), and tetracyclines (tetracycline), where applicable by species. Tukey’s honestly significant difference test for pairwise differences (using the $p < 0.1$ criterion for statistical significance unless otherwise indicated) was performed when ANOVAs showed significance at the $p < 0.05$ level.

RESULTS

A total of 4829 isolates were collected from 87 sites in 40 US states. Isolates included $S. aureus$ ($n = 1695$), CoNS ($n = 1475$, including $S. epidermidis$ [$n = 1119$]), $S. pneumoniae$ ($n = 474$), $H. influenzae$ ($n = 586$), and $P. aeruginosa$ ($n = 599$). Of the isolates collected, 1886 (39.1%) originated from 32 sites in the Midwest, 1167 (24.2%) from 14 sites in the West, 1143 (23.7%) from 20 sites in the Northeast, and 633 (13.1%) from 21 sites in the South (Fig. 1).

In vitro MIC$_{90}$s and resistance profiles by geography are presented in Tables 1, 2, and 3. Compared with other antibiotics, $S. aureus$ and CoNS isolates, especially the respective MR subsets, showed notable in vitro resistance to azithromycin and the fluoroquinolones (Tables 1 and 2). Among $S. pneumoniae$ isolates, resistance was observed for azithromycin and penicillin, whereas resistance was low overall among $P. aeruginosa$ isolates and negligible among $H. influenzae$ isolates. Of the fluoroquinolones tested, besifloxacin, a chlorofluoroquinolone for which susceptibility breakpoints are not available, had the lowest MIC$_{90}$ against staphylococcal (including MR isolates) and streptococcal isolates. Newer fluoroquinolones (besifloxacin, moxifloxacin, and gatifloxacin) generally had lower MIC$_{90}$s compared with older fluoroquinolones (ofloxacin, ciprofloxacin, and levofloxacin). Ciprofloxacin had the lowest MIC$_{90}$ against $P. aeruginosa$ and, along with gatifloxacin, the lowest MIC$_{90}$ against $H. influenzae$.

Among $S. aureus$ and CoNS, 621 and 717 isolates were MR (MRSA and MRCoNS), whereas 1074 and 758 isolates were MS (MSSA and MSCoNS), respectively. Resistance to methicillin varied by geographic region among both $S. aureus$ and CoNS isolates ($p \leq 0.006$; Fig. 2). Among $S. aureus$ isolates, the proportions of MRSA isolates were 48.5, 40.1%, 36.0%, and 24.4% in the South, Midwest, Northeast, and West, respectively, with pairwise differences observed between the South and Northeast and between the West and all other regions (Fig. 2A). The proportions of MRCoNS isolates were 53.8% in the Midwest, 51.1% in the South, 44.3% in the Northeast, and 44.1% in the West, with significant pairwise differences found between the South and Northeast and between the West and all other regions (Fig. 2B).

Analysis of the overall mean percentage of resistance showed variations based on the geographic region for $S. aureus$ ($p < 0.001$), $S. pneumoniae$ ($p < 0.001$), and $P. aeruginosa$ ($p = 0.005$), despite low overall resistance for $P. aeruginosa$ (Fig. 3). Among $S. aureus$ isolates, mean [standard error (SE)] percentage of resistance was highest in the South [28.1% (1.5%)] and lowest in the West [16.8% (1.1%); Fig. 3A]. Among $S. pneumoniae$ isolates, mean (SE)
| Organism | Antibiotic | Geographic region | West | Midwest | Northeast | South |
|----------|------------|-------------------|------|---------|-----------|-------|
|          |            | $n$ | %R | MIC$_{90}$ | $n$ | %R | MIC$_{90}$ | $n$ | %R | MIC$_{90}$ | $n$ | %R | MIC$_{90}$ |
| S. aureus | Vancomycin | 389 | 0.0 | 1 | 659 | 0.0 | 1 | 414 | 0.0 | 1 | 233 | 0.0 | 1 |
|          | Besifloxacin | 389 | NA | 0.5 | 659 | NA | 1 | 414 | NA | 1 | 233 | NA | 2 |
|          | Moxifloxacin | 389 | 26.5 | 4 | 659 | 33.7 | 4 | 414 | 33.8 | 8 | 233 | 45.1 | 8 |
|          | Gatifloxacin | 345 | 26.1 | 4 | 605 | 33.4 | 4 | 363 | 36.1 | 8 | 182 | 47.8 | 16 |
|          | Ciprofloxacin | 389 | 27.5 | 32 | 659 | 35.7 | 128 | 414 | 37.2 | 256 | 233 | 47.2 | 256 |
|          | Levofloxacin | 345 | 26.4 | 8 | 605 | 33.7 | 16 | 363 | 36.1 | 32 | 182 | 47.8 | 128 |
|          | Ofloxacin | 345 | 27.0 | > 8 | 605 | 34.1 | > 8 | 363 | 37.2 | > 8 | 182 | 47.8 | > 8 |
|          | Clindamycin | 389 | 15.7 | > 2 | 659 | 17.2 | > 2 | 414 | 13.8 | > 2 | 233 | 12.9 | > 2 |
|          | Chloramphenicol | 345 | 2.9 | 8 | 605 | 8.4 | 8 | 363 | 5.8 | 8 | 182 | 5.0 | 8 |
| MRSA     | Vancomycin | 95 | 0.0 | 1 | 264 | 0.0 | 1 | 149 | 0.0 | 1 | 113 | 0.0 | 1 |
|          | Besifloxacin | 95 | NA | 1 | 264 | NA | 1 | 149 | NA | 4 | 113 | NA | 2 |
|          | Moxifloxacin | 95 | 87.4 | 8 | 264 | 62.1 | 8 | 149 | 77.9 | 32 | 113 | 78.8 | 16 |
|          | Gatifloxacin | 81 | 85.2 | 8 | 241 | 62.2 | 8 | 135 | 79.3 | 64 | 86 | 83.7 | 16 |
|          | Ciprofloxacin | 95 | 88.4 | 256 | 264 | 65.5 | 256 | 149 | 80.5 | 256 | 113 | 81.4 | 256 |
|          | Levofloxacin | 81 | 86.4 | 32 | 241 | 62.7 | 32 | 135 | 80.0 | 256 | 86 | 83.7 | 128 |
|          | Ofloxacin | 81 | 86.4 | 64 | 241 | 63.5 | > 8 | 135 | 80.0 | > 8 | 86 | 83.7 | > 8 |
|          | Clindamycin | 95 | 37.9 | > 16 | 264 | 33.0 | > 2 | 149 | 29.5 | > 2 | 113 | 18.6 | > 2 |
|          | Chloramphenicol | 81 | 6.2 | 8 | 241 | 13.3 | 16 | 135 | 11.1 | 16 | 86 | 5.8 | 8 |
|          | Azithromycin | 95 | 87.4 | > 512 | 264 | 93.6 | > 512 | 149 | 95.3 | > 512 | 113 | 92.0 | > 512 |
|          | Tobramycin | 95 | 35.8 | > 256 | 264 | 38.6 | 256 | 149 | 49.0 | > 256 | 113 | 40.7 | 256 |
|          | Tetracycline | 30 | 6.7 | 0.5 | 57 | 12.3 | 16 | 15 | 6.7 | 4 | 1 | 0.0 | – |
|          | Trimethoprim | 81 | 0.0 | 2 | 241 | 2.9 | 2 | 135 | 8.2 | 4 | 86 | 16.3 | > 128 |

Table 1 In vitro MIC$_{90}$ (μg/ml) and resistance profiles for *Staphylococcus aureus*, MRSA, and MSSA.

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percentage of resistance was 14.5% (1.0%), 11.9% (1.8%), 9.9% (1.4%), and 7.6% (1.3%) in the Midwest, South, Northeast, and West, respectively, with pairwise differences observed between the Midwest and both the Northeast and West (Fig. 3B). For *P. aeruginosa* isolates, the mean (SE) percentage of resistance was 8.5% (1.1%), 5.4% (1.3%), 3.6% (1.6%), and 2.9% (1.4%) in the Midwest, Northeast, South, and West, with pairwise differences observed between the Midwest and both the South and West (Fig. 3C). No regional differences in overall mean resistance rates were observed among CoNS (Fig. 3D) or *H. influenzae* isolates (both \( p > 0.05 \); Fig. 3E).

**DISCUSSION**

The ARMOR study continues to provide important insights on in vitro antibiotic resistance among ocular pathogens in the US. The current analysis provides information on antibiotic resistance trends by geographic region among ARMOR pathogens isolated from ocular infections and expands upon the findings reported previously for the 5-year cumulative ARMOR data set through inclusion of an additional 1600 isolates collected in the 3 ensuing years from 15 additional clinical sites.

Overall, and consistent with previous reporting, analysis of the current cumulative data set highlights relatively high in vitro antibiotic resistance among staphylococci to methicillin, azithromycin, and fluoroquinolones across the various geographies [9, 13, 14]. Methicillin-resistant staphylococcal isolates showed the highest resistance rates, a finding that has been corroborated in other studies [6, 15, 16]. In contrast, but as expected based on the previous analysis, in vitro resistance among *S. pneumoniae* isolates appeared lower and largely limited to azithromycin and...
Table 2 In vitro MIC$_{90}$s (µg/ml) and resistance profiles for CoNS, MRCoNS, and MSCoNS

| Organism | Antibiotic | Geographic region |
|----------|------------|-------------------|
|          |            | West | Midwest | Northeast | South |
|          | n         | % R | MIC$_{90}$ | n         | % R | MIC$_{90}$ | n         | % R | MIC$_{90}$ | n         | % R | MIC$_{90}$ |
| CoNS     | Vancomycin | 397 | 0.0 | 2 | 548 | 0.0 | 2 | 350 | 0.0 | 2 | 180 | 0.0 | 2 |
|          | Besifloxacin | 397 | NA | 2 | 548 | NA | 2 | 350 | NA | 2 | 180 | NA | 2 |
|          | Moxifloxacin | 397 | 27.2 | 8 | 548 | 30.8 | 16 | 350 | 31.4 | 16 | 180 | 40.0 | 16 |
|          | Gatifloxacin | 371 | 30.2 | 16 | 505 | 33.7 | 16 | 311 | 32.8 | 16 | 144 | 38.9 | 32 |
|          | Ciprofloxacin | 397 | 31.7 | 64 | 548 | 34.7 | 64 | 350 | 34.6 | 64 | 180 | 43.3 | 64 |
|          | Levofloxacin | 371 | 30.7 | 128 | 505 | 33.7 | 128 | 311 | 33.8 | 128 | 144 | 38.9 | 128 |
|          | Ofloxacin | 371 | 31.3 | > 8 | 505 | 34.3 | > 8 | 311 | 33.8 | > 8 | 144 | 38.9 | > 8 |
|          | Clindamycin | 397 | 25.4 | > 2 | 548 | 27.6 | 8 | 350 | 26.9 | > 2 | 180 | 21.7 | > 2 |
|          | Chloramphenicol | 371 | 1.9 | 4 | 505 | 1.2 | 8 | 311 | 0.6 | 4 | 144 | 0.7 | 8 |
|          | Azithromycin | 397 | 61.0 | > 512 | 548 | 61.0 | > 512 | 350 | 61.1 | > 512 | 180 | 62.8 | > 512 |
|          | Tobramycin | 397 | 17.1 | 8 | 548 | 17.7 | 16 | 350 | 15.7 | 8 | 180 | 16.7 | 8 |
|          | Tetracycline | 154 | 17.5 | > 16 | 157 | 10.2 | 8 | 68 | 14.7 | 8 | 2 | 0.0 | – |
|          | Trimethoprim | 371 | 27.5 | 256 | 505 | 26.1 | > 128 | 311 | 29.3 | > 128 | 144 | 32.6 | > 128 |
| MRCoNS   | Vancomycin | 175 | 0.0 | 2 | 295 | 0.0 | 2 | 155 | 0.0 | 2 | 92 | 0.0 | 2 |
|          | Besifloxacin | 175 | NA | 4 | 295 | NA | 4 | 155 | NA | 4 | 92 | NA | 4 |
|          | Moxifloxacin | 175 | 46.9 | 32 | 295 | 49.8 | 32 | 155 | 55.5 | 32 | 92 | 58.7 | 32 |
|          | Gatifloxacin | 162 | 53.1 | 32 | 269 | 55.0 | 32 | 135 | 58.5 | 64 | 75 | 60.0 | 32 |
|          | Ciprofloxacin | 175 | 55.4 | 64 | 295 | 56.3 | 64 | 155 | 60.7 | 64 | 92 | 64.1 | 64 |
|          | Levofloxacin | 162 | 54.3 | 256 | 269 | 55.4 | 128 | 135 | 60.0 | 256 | 75 | 60.0 | 128 |
|          | Ofloxacin | 162 | 54.3 | 16 | 269 | 56.1 | 32 | 135 | 60.0 | > 8 | 75 | 60.0 | > 8 |
|          | Clindamycin | 175 | 39.4 | > 16 | 295 | 35.3 | > 16 | 155 | 37.4 | > 16 | 92 | 30.4 | > 2 |
|          | Chloramphenicol | 162 | 1.2 | 8 | 269 | 1.9 | 8 | 135 | 1.5 | 8 | 75 | 1.3 | 8 |
|          | Azithromycin | 175 | 78.3 | > 512 | 295 | 77.6 | > 512 | 155 | 78.7 | > 512 | 92 | 79.4 | > 512 |
|          | Tobramycin | 175 | 28.0 | 16 | 295 | 28.5 | 32 | 155 | 28.4 | 32 | 92 | 23.9 | 16 |
|          | Tetracycline | 65 | 23.1 | > 16 | 87 | 16.1 | > 16 | 23 | 8.7 | 2 | 1 | 0.0 | – |
|          | Trimethoprim | 162 | 40.1 | > 256 | 269 | 40.5 | > 256 | 135 | 45.2 | > 128 | 75 | 42.7 | > 128 |
penicillin, and there was low-to-minimal in vitro resistance among *P. aeruginosa* and *H. influenzae* isolates. Specific analysis by geography showed that resistance to methicillin varied by region, with the highest resistance among *S. aureus* isolates in the South and CoNS isolates in both the Midwest and South. The findings for *S. aureus* isolates are consistent with those reported by Blanco et al., who observed higher methicillin resistance among *S. aureus* isolates from the South [17]. While the geographic trend for resistance among *S. aureus* isolates is consistent with the 5-year ARMOR results, methicillin resistance was slightly lower in *S. aureus* in the current analyses (36.6%) than in the 5-year analysis (42.2%) [14]. This decrease is not unexpected given that a decrease in methicillin resistance over time was observed in the 7-year ARMOR results [9]. Further differences by geography were found for overall mean percentage of resistance among *S. aureus*, *S. pneumoniae*, and *P. aeruginosa* isolates, with the highest rates in the South for *S. aureus* and the Midwest for both *S. pneumoniae* and *P. aeruginosa*. General geographic trends observed with *S. pneumoniae* and *P. aeruginosa* showed high resistance rates in the Midwest, similar to that reported in the 5-year findings [14].

Comparisons of cumulative MIC\textsubscript{90}s showed wide variations among fluoroquinolones, particularly against staphylococci, with newer fluoroquinolones having lower MIC\textsubscript{90}s than older fluoroquinolones and besifloxacin having an MIC\textsubscript{90} most comparable to that of vancomycin. Although not analyzed, MIC\textsubscript{90}s did not appear to differ by region and were consistent (within few dilutions) with the previous reports of ARMOR, other single-study reports of ocular isolates, and national systemic surveys [9, 13–15, 18–22]. Besifloxacin, a chlorofluoroquinolone for which interpretive breakpoints

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**Table 2 continued**

| Organism | Antibiotic | Geographic region | West | Midwest | Northeast | South |
|----------|------------|-------------------|------|---------|----------|-------|
|          |            |                   | *n* | %R      | MIC\textsubscript{90} | *n* | %R      | MIC\textsubscript{90} | *n* | %R      | MIC\textsubscript{90} | *n* | %R      | MIC\textsubscript{90} |
| MSCoNS   | Vancomycin |                   | 222 | 0.0     | 2        | 253 | 0.0     | 2        | 195 | 0.0     | 2        | 88  | 0.0     | 2        |
|          | Besifloxin |                   | 222 | NA      | 0.25     | 253 | NA      | 0.12     | 195 | NA      | 0.25     | 88  | NA      | 0.5     |
|          | Moxifloxin |                   | 222 | 11.7    | 1        | 253 | 8.7     | 0.25     | 195 | 12.3    | 1        | 88  | 20.5    | 2        |
|          | Gatifloxin |                   | 209 | 12.4    | 1        | 236 | 9.3     | 0.25     | 176 | 13.1    | 2        | 69  | 15.9    | 2        |
|          | Ciprofloxin|                   | 222 | 13.1    | 4        | 253 | 9.5     | 1        | 195 | 13.9    | 8        | 88  | 21.6    | 64       |
|          | Levofoxacin|                   | 209 | 12.4    | 4        | 236 | 8.9     | 0.5      | 176 | 13.6    | 4        | 69  | 15.9    | 8        |
|          | Ofloxacin  |                   | 209 | 13.4    | 8        | 236 | 9.3     | 1        | 176 | 13.6    | 8        | 69  | 15.9    | > 8      |
|          | Clindamycin|                   | 222 | 14.4    | 1        | 253 | 18.6    | > 2       | 195 | 18.5    | 2        | 88  | 12.5    | 1        |
|          | Chloramphenicol |           | 209 | 2.4     | 4        | 236 | 0.4     | 4        | 176 | 0.0     | 4        | 69  | 0.0     | 4        |
|          | Azithromycin|                   | 222 | 47.3    | > 512    | 253 | 41.5    | > 512    | 195 | 47.2    | > 512    | 88  | 45.5    | > 512    |
|          | Tobramycin  |                   | 222 | 8.6     | 4        | 253 | 5.1     | 2        | 195 | 5.6     | 4        | 88  | 9.1     | 4        |
|          | Tetracycline|                   | 89  | 13.5    | > 16     | 70  | 2.9     | 1        | 45  | 17.8    | 8        | 1   | 0.0     | –        |
|          | Trimethoprim |                 | 209 | 17.7    | 256      | 236 | 9.8     | 8        | 176 | 17.1    | 64       | 69  | 21.7    | > 128    |

*Note: - < 10 isolates, %R percentage resistance (refers to all non-susceptible isolates), CoNS coagulase-negative staphylococci, MIC\textsubscript{90} minimum inhibitory concentration at which 90% of the isolates were inhibited, MRCoNS methicillin-resistant CoNS, MSCoNS methicillin-susceptible CoNS, NA interpretive breakpoints not available/not applicable.*
Table 3  
In vitro MIC₉₀₉ (µg/ml) and resistance profiles for *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*  

| Organism          | Antibiotic          | Geographic region | West          | Midwest         | Northeast       | South          |
|-------------------|---------------------|-------------------|---------------|-----------------|-----------------|----------------|
|                   |                     |                   | *n* | %R | MIC₉₀₉ | *n* | %R | MIC₉₀₉ | *n* | %R | MIC₉₀₉ | *n* | %R | MIC₉₀₉ |
| *S. pneumoniae*   | Besifloxacin        |                  | 121 | NA | 0.06 | 191 | NA | 0.06 | 103 | NA | 0.12 | 59 | NA | 0.06 |
|                   | Moxifloxacin        |                  | 121 | 0.0 | 0.12 | 191 | 0.0 | 0.25 | 103 | 1.0 | 0.25 | 59 | 0.0 | 0.12 |
|                   | Gatifloxacin        |                  | 105 | 1.0 | 0.25 | 171 | 0.0 | 0.25 | 86  | 0.0 | 0.25 | 37 | 0.0 | 0.25 |
|                   | Ciprofloxacin       |                  | 121 | NA | 1    | 191 | NA | 1    | 103 | NA | 2    | 59 | NA | 1    |
|                   | Levoflaxcin         |                  | 105 | 0.0 | 1    | 171 | 0.0 | 1    | 86  | 0.0 | 1    | 37 | 0.0 | 1    |
|                   | Ofloxacin           |                  | 105 | 0.0 | 2    | 171 | 0.0 | 2    | 86  | 1.2 | 2    | 37 | 2.7 | 2    |
|                   | Chloramphenicol     |                  | 121 | 4.1 | 4    | 191 | 2.1 | 4    | 103 | 2.9 | 4    | 59 | 0.0 | 2    |
|                   | Penicillin<sup>a</sup> |                | 121 | 22.3| 0.25 | 191 | 41.9| 1    | 103 | 30.1| 1    | 59 | 33.9| 2    |
|                   | Azithromycin        |                  | 121 | 22.3| 16   | 191 | 48.7| 256  | 103 | 29.1| 256  | 59 | 33.9| 32   |
|                   | Tobramycin          |                  | 121 | NA | 32   | 191 | NA | 32   | 103 | NA | 32   | 59 | NA | 32   |
|                   | Tetracycline        |                  | 28  | 3.6 | 0.25 | 45  | 17.8| > 4  | 18  | 5.6 | 0.25 | 1  | 0.0 | –    |
|                   | Trimethoprim        |                  | 105 | NA | 128  | 171 | NA | 128  | 86  | NA | 64   | 37 | NA | 32   |
| *P. aeruginosa*   | Vancomycin          |                  | 120 | NA | > 16 | 186 | NA | > 16 | 133 | NA | > 16 | 60 | NA | > 16 |
|                   | Besifloxacin        |                  | 138 | NA | 2    | 215 | NA | 4    | 154 | NA | 4    | 92 | NA | 4    |
|                   | Moxifloxacin        |                  | 138 | NA | 4    | 215 | NA | 4    | 154 | NA | 4    | 92 | NA | 4    |
|                   | Gatifloxacin        |                  | 120 | 3.3 | 1    | 186 | 7.5 | 2    | 133 | 4.5 | 2    | 60 | 8.3 | 2    |
|                   | Ciprofloxacin       |                  | 138 | 4.3 | 0.5  | 215 | 8.8 | 1    | 154 | 3.3 | 0.25 | 92 | 6.5 | 0.5  |
|                   | Levoflaxcin         |                  | 120 | 2.5 | 1    | 186 | 7.5 | 1    | 133 | 3.0 | 1    | 60 | 8.3 | 1    |
|                   | Ofloxacin           |                  | 120 | 3.3 | 1    | 186 | 9.7 | 2    | 133 | 6.8 | 2    | 60 | 10.0| 2    |
|                   | Azithromycin        |                  | 138 | NA | 512  | 215 | NA | 512  | 154 | NA | 512  | 92 | NA | 512  |
|                   | Chloramphenicol     |                  | 138 | NA | 128  | 215 | NA | 128  | 154 | NA | 128  | 92 | NA | 128  |
|                   | Polymyxin B         |                  | 120 | 1.7 | 2    | 186 | 12.4| 4    | 133 | 12.0| 4    | 60 | 3.3 | 2    |
|                   | Tetracycline        |                  | 50  | NA | > 16 | 57  | NA | 16   | 36  | NA | 16   | 2  | NA | –     |
|                   | Tobramycin          |                  | 138 | 1.5 | 1    | 215 | 4.2 | 1    | 154 | 2.0 | 1    | 92 | 1.1 | 1    |

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are not available, was approved by the US Food and Drug Administration for use in 2009 [19], and in vitro MIC\textsubscript{90}s have not varied substantially since its introduction [9, 13, 14, 19]. Compared with other fluoroquinolones, besifloxacin has more balanced targeting of DNA gyrase and topoisomerase IV; this, in turn, results in the need for multistep mutations and reduces the possibility of spontaneous resistance [23–25]. Furthermore, besifloxacin may have a lower incidence of resistance development due to its use being limited to topical ophthalmic infections only, although cross-resistance from other fluoroquinolones is possible [26].

Although the literature contains antibiotic resistance data by geography for systemic infections [11, 27, 28], very few studies are available that describe geographic differences in antibiotic resistance rates among ocular pathogens [14, 16]. A prospective cohort study of systemic MRSA infections from 20 sites across the US suggested that meteorologic factors and geographic location play a role in MRSA colonization [17]. The study results indicated a negative association between latitude and colonization (p = 0.001), with MRSA colonization being higher in the South than in the North [17]. It follows that these factors may be associated with colonization of other microorganisms as well. Overuse and inappropriate prescribing have been associated with the crisis of antibiotic resistance [29]. Variations in the prescribing patterns of antibiotics may be associated with the differences in antibiotic resistance rates across geographies.

Limitations of this study include potential sampling bias owing to the practice of infrequent culturing of bacteria involved in ocular infections. In the absence of specific breakpoints for ocular isolates, systemic criteria were used to interpret MIC data, which may be of limited value given expected differences in antibiotic concentrations achieved following

### Table 3 continued

| Organism       | Antibiotic | Geographic region | West | Midwest | Northeast | South |
|----------------|------------|-------------------|------|---------|-----------|-------|
|                |            |                   | n    | %R      | MIC\textsubscript{90} | n    | %R      | MIC\textsubscript{90} | n    | %R      | MIC\textsubscript{90} |
| *H. influenzae*| Besifloxacin| 122 NA 0.03       | 273  NA 0.03 | 122 NA 0.03 | 69 NA 0.03 |
|                | Moxifloxacin| 122 0.8 0.03      | 273 0.0 0.06 | 122 0.0 0.06 | 69 0.0 0.03 |
|                | Gatifloxacin| 108 0.9 0.015     | 252 0.0 0.015 | 108 0.0 0.015 | 45 0.0 0.015 |
|                | Ciprofloxacin| 122 0.8 0.015   | 273 0.0 0.015 | 122 0.0 0.015 | 69 0.0 0.015 |
|                | Levofloxacin| 108 0.9 0.03      | 252 0.0 0.03 | 108 0.0 0.03 | 45 0.0 0.015 |
|                | Ofloxacin   | 108 0.9 0.06      | 252 0.0 0.03 | 108 0.0 0.06 | 45 0.0 0.03 |
|                | Azithromycin| 122 0.0 2         | 273 1.1 2    | 122 0.0 2    | 69 0.0 2 |
|                | Chloramphenicol| 122 0.0 0.5     | 273 0.7 0.5  | 122 0.8 0.5  | 69 0.0 1 |
|                | Penicillin  | 122 NA > 4        | 273 NA > 4  | 122 NA > 4  | 69 NA > 4 |
|                | Polymyxin B | 108 NA 1          | 252 NA 2    | 108 NA 2    | 45 NA 2 |
|                | Tetracycline| 53 0.0 0.5        | 89 2.3 0.5  | 11 18.2 8   | 7 0.0 – |
|                | Tobramycin  | 122 NA 2          | 273 NA 2    | 122 NA 2    | 69 NA 4 |

- < 10 isolates, %R percentage resistance (refers to all non-susceptible isolates), MIC\textsubscript{90} minimum inhibitory concentration at which 90% of the isolates were inhibited, NA interpretive breakpoints not available/not applicable

* Oral penicillin breakpoints applied
topical versus systemic administration. Moreover, not all topical ophthalmic antibiotics could be included, and one may debate the choice of antibiotics tested. Identification of the reasons for underlying geographic variability in resistance rates was outside the scope of this study.

**Fig. 2** Methicillin resistance by geographic region for **A** *Staphylococcus aureus* and **B** CoNS. Horizontal lines represent significant pairwise comparisons. CoNS coagulase-negative staphylococci

**Fig. 3** Mean percentage resistance by geographic region for **A** *Staphylococcus aureus*, **B** *Streptococcus pneumoniae*, **C** *Pseudomonas aeruginosa*, **D** CoNS, and **E** *Haemophilus influenzae*. *Tukey’s test performed using a *p* < 0.05 criterion for statistical significance; bars sharing the same letter (a, b, c) are not significantly different. ANOVA analysis of variance; CoNS coagulase-negative staphylococci; SEM standard error of the mean.
study. A limitation specific to this analysis is the subjective delineation of the geographic regions, implemented for comparison with previously published data [14]. Alternate regional divisions were possible with more evenly matched numbers of participating sites, further lessening potential sampling bias.

CONCLUSIONS

Findings from the ARMOR study suggest that in vitro antibiotic resistance rates among ocular S. aureus, S. pneumoniae, and P. aeruginosa isolates vary across different regions of the US, with the South and Midwest identified as regions of potential resistance concerns. Data related to geographic distribution of resistant ocular microorganisms may be useful during empirical prescription of antibiotics.

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Compliance with Ethics Guidelines. This article does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. The data sets from the current study are available from the corresponding author on reasonable request.

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