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BRIEF REPORT

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 χ^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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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*, *P. aeruginosa*, and *H. influenzae* isolates from participating centers for antibiotic resistance monitoring. Overall 1-, 5-, and 7-year study outcomes have been reported [9, 13, 14].

The purpose of this analysis was to determine if the antibiotic susceptibility profiles of common ocular isolates vary by geography in the US. Here, we report antimicrobial resistance rates across the Northeast, Midwest, South, and West regions among isolates collected from 2009 through 2016 as part of the ARMOR study.

METHODS

Participating centers across the US were invited to submit ocular isolates of *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 (MIC_{90}s) 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 χ^2 test followed by a multiple-comparisons test for proportions, using the $p < 0.05$ criterion for statistical significance. One-way analyses of variance (ANOVAs) 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),

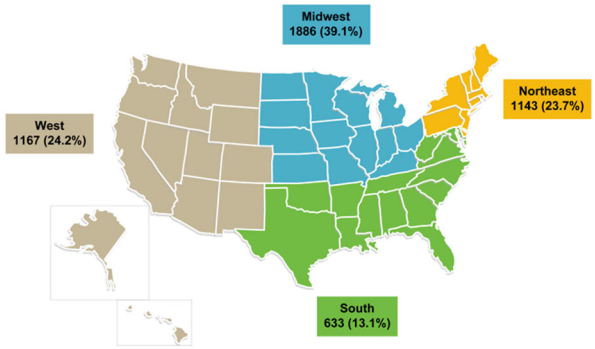

Fig. 1 Distribution of ARMOR isolates by geographic region. Northeast: Connecticut, Delaware, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont. Midwest: Illinois, Indiana, Iowa, Kansas, Kentucky, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin. South: Alabama, Arkansas, Florida, Georgia, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia. West: Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, and Wyoming

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 Midwest and both the Northeast and West (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)

Table 1 In vitro MIC_{90}s (μg/ml) and resistance profiles for *Staphylococcus aureus*, MRSA, and MSSA

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
	Azithromycin	389	49.4	> 512	659	62.5	> 512	414	64.0	> 512	233	67.8	> 512
	Tobramycin	389	11.6	32	659	17.8	256	414	19.6	256	233	22.3	256
	Tetracycline	148	2.0	0.5	188	6.9	0.5	74	2.7	0.5	9	0.0	–
	Trimethoprim	345	2.6	2	605	3.6	4	363	4.1	2	182	10.4	16
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 continued

Organism	Antibiotic	Geographic region											
		West			Midwest			Northeast			South		
		n	%*R*	MIC_{90}	*n*	%*R*	MIC_{90}	*n*	%*R*	MIC_{90}	*n*	%*R*	MIC_{90}
MSSA	Vancomycin	294	0.0	1	395	0.0	1	265	0.0	1	120	0.0	1
	Besifloxacin	294	NA	0.06	395	NA	0.25	265	NA	0.25	120	NA	0.25
	Moxifloxacin	294	6.8	0.12	395	14.7	2	265	9.1	0.5	120	13.3	1
	Gatifloxacin	264	8.0	0.25	364	14.3	2	228	10.5	1	96	15.6	2
	Ciprofloxacin	294	7.8	1	395	15.7	8	265	12.8	4	120	15.0	8
	Levofloxacin	264	8.0	0.5	364	14.6	4	228	10.1	2	96	15.6	8
	Ofloxacin	264	8.7	1	364	14.6	8	228	11.9	8	96	15.6	> 8
	Clindamycin	294	8.5	0.25	395	6.6	0.25	265	4.9	0.12	120	7.5	0.25
	Chloramphenicol	264	1.9	8	364	5.2	8	228	2.6	8	96	4.2	8
	Azithromycin	294	37.1	> 512	395	41.8	> 512	265	46.4	> 512	120	45.0	> 512
	Tobramycin	294	3.7	0.5	395	3.8	0.5	265	3.0	1	120	5.0	1
	Tetracycline	118	0.9	0.5	131	4.6	0.5	59	1.7	0.5	8	0.0	–
	Trimethoprim	264	3.4	2	364	4.1	4	228	1.8	2	96	5.2	2

– < 10 isolates, *%R* percentage resistance (refers to all non-susceptible isolates), MIC_{90} minimum inhibitory concentration at which 90% of the isolates were inhibited, *MRSA* methicillin-resistant *S. aureus*, *MSSA* methicillin-susceptible *S. aureus*, *NA* interpretive breakpoints not available/not applicable

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

Table 2 continued

Organism	Antibiotic	Geographic region											
		West			Midwest			Northeast			South		
		n	%*R*	MIC_{90}	*n*	%*R*	MIC_{90}	*n*	%*R*	MIC_{90}	*n*	%*R*	MIC_{90}
MSCoNS	Vancomycin	222	0.0	2	253	0.0	2	195	0.0	2	88	0.0	2
	Besifloxacin	222	NA	0.25	253	NA	0.12	195	NA	0.25	88	NA	0.5
	Moxifloxacin	222	11.7	1	253	8.7	0.25	195	12.3	1	88	20.5	2
	Gatifloxacin	209	12.4	1	236	9.3	0.25	176	13.1	2	69	15.9	2
	Ciprofloxacin	222	13.1	4	253	9.5	1	195	13.9	8	88	21.6	64
	Levofloxacin	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

– < 10 isolates, *%R* percentage resistance (refers to all non-susceptible isolates), *CoNS* coagulase-negative staphylococci, *MIC_{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

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_{90}s showed wide variations among fluoroquinolones, particularly against staphylococci, with newer fluoroquinolones having lower MIC_{90}s than older fluoroquinolones and besifloxacin having an MIC_{90} most comparable to that of vancomycin. Although not analyzed, MIC_{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

Table 3 *In vitro* MIC_{90}s (μg/ml) and resistance profiles for *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*

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. 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
	Levofloxacin	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[a]	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
	Levofloxacin	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

Table 3 continued

Organism	Antibiotic	Geographic region											
		West			Midwest			Northeast			South		
		n	%*R*	MIC_{90}	*n*	%*R*	MIC_{90}	*n*	%*R*	MIC_{90}	*n*	%*R*	MIC_{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_{90} minimum inhibitory concentration at which 90% of the isolates were inhibited, *NA* interpretive breakpoints not available/not applicable

[a] Oral penicillin breakpoints applied

are not available, was approved by the US Food and Drug Administration for use in 2009 [19], and in vitro MIC_{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

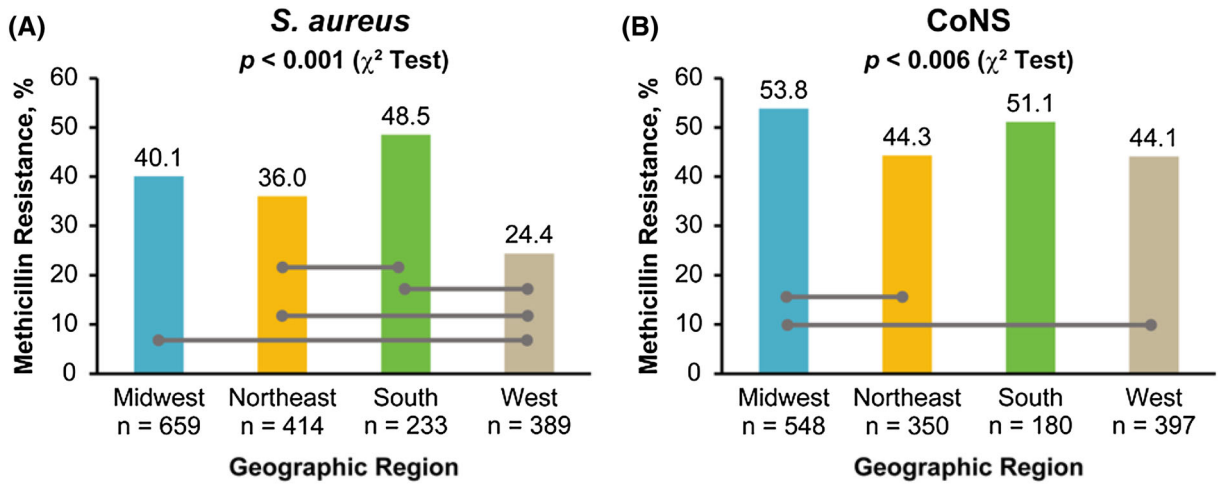

Fig. 2 Methicillin resistance by geographic region for **A** *Staphylococcus aureus* and **B** CoNS. Horizontal lines represent significant pairwise comparisons. *CoNS* coagulase-negative staphylococci

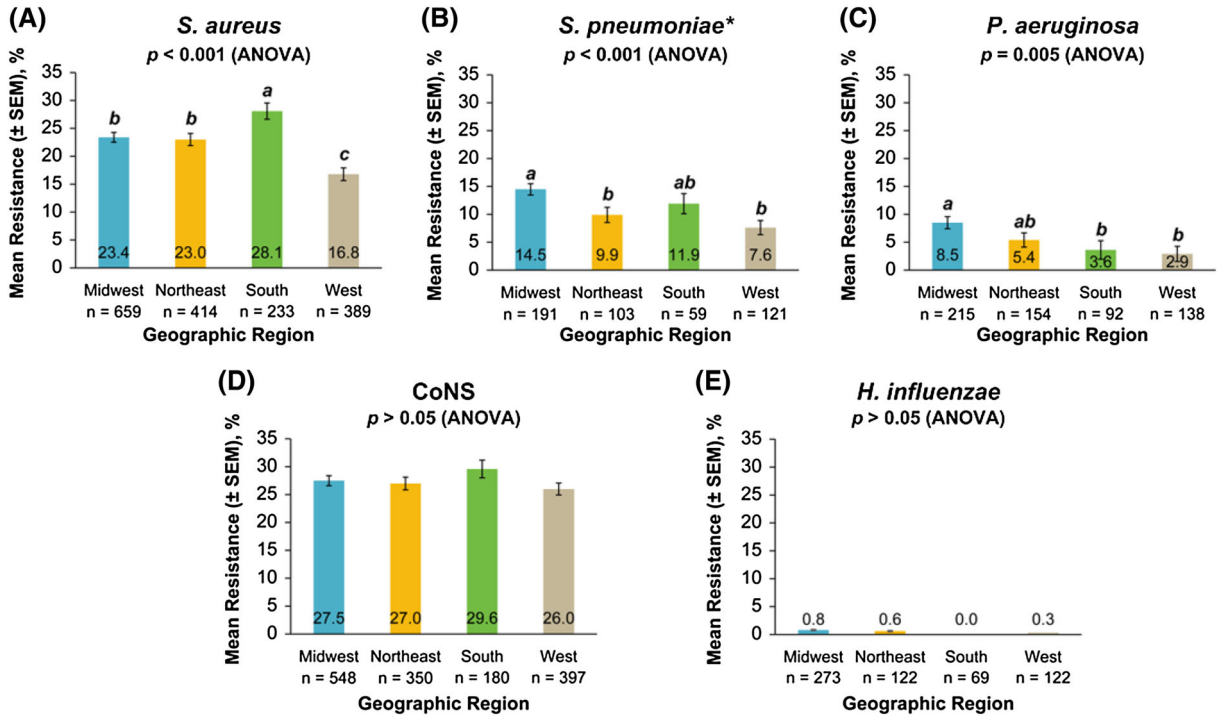

Fig. 3 Mean percentage resistance by geographic region for **A** *Staphylococcus aureus*, **B** *Streptococcus pneumoniae*, **C** *Pseudomonas aeruginosa*, **D** CoNS, and **E** *Haemophilus influenzae*. *Tukey's test performed using a $p < 0.05$ criterion for statistical significance; bars sharing the same letter (a, b, c) are not significantly different. *ANOVA* analysis of variance; *CoNS* coagulase-negative staphylococci; *SEM* standard error of the mean

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. 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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