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Antibiotic Resistance Among Pediatric-Sourced Ocular Pathogens: 8-Year Findings From the Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) Surveillance Study

Sherman J. Alter, MD,* Christine M. Sanfilippo, PhD,† Penny A. Asbell, MD,‡ and Heleen H. DeCory, PhD†

Background: The Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study is a nationwide longitudinal antibiotic resistance surveillance program specific to bacterial pathogens commonly encountered in ocular infections. We evaluated in vitro resistance rates and trends among isolates obtained from pediatric patients (≤17 years of age).

Methods: 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* to a central laboratory. Minimum inhibitory concentrations for various antibiotic classes were determined by broth microdilution per Clinical and Laboratory Standards Institute guidelines and interpreted as susceptible, intermediate or resistant based on available breakpoints. Longitudinal trends were analyzed using a Cochran-Armitage test for linear trends in a proportion.

Results: Of 4829 isolates collected from January 2009 to December 2016, 995 isolates, sourced primarily from hospitals and referral centers, were obtained from pediatric patients (n = 286 *H. influenzae*, n = 284 *S. aureus,* n = 213 CoNS, n = 150 *S. pneumoniae* and n = 62 *P. aeruginosa*). With few exceptions, *P. aeruginosa* and *H. influenzae* were generally susceptible to the antibiotics tested. Of *S. aureus* and CoNS isolates, respectively, 56% and 72% were resistant to azithromycin and 24% and 47% were methicillin-resistant (MR); concurrent resistance to other drug classes and multidrug resistance (≥3 drug classes) were prevalent among MR staphylococci. Of *S. pneumoniae* isolates, 38% and 35% demonstrated resistance to azithromycin and penicillin, respectively. Besifloxacin had the lowest minimum inhibitory concentration against the Gram-positive isolates.

Conclusions: These in vitro data suggest antibiotic resistance is common among staphylococcal and pneumococcal isolates collected from pediatric patients with

ocular infections. Methicillin resistance was prevalent among staphylococci with many strains demonstrating multidrug resistance. These findings may not be representative of resistance trends in community-based practices.

Key Words: antibiotic resistance, surveillance, pediatric, ocular, methicillin resistance, multidrug resistance

Key Points

- Recent findings from the nationwide (United States) ARMOR study showed high, but apparently stabilizing, rates of in vitro antibiotic resistance, including multidrug resistance, among staphylococcal isolates sourced from ocular infections in patients 0–99 years of age.
- The current analysis focused specifically on isolates obtained from patients ≤17 years of age in the ARMOR study.
- This 8-year longitudinal analysis shows in vitro antibiotic resistance to be common, but generally not increasing, among staphylococcal and pneumococcal isolates collected from pediatric-sourced ocular infections.
- These data should be useful for clinicians tasked with choosing empiric therapy for pediatric ocular infections.

BACKGROUND

Bacterial eye infections are frequently encountered in pediatric medical care. Children can develop various types of ocular surface infections including keratitis, dacryocystitis, blepharokeratoconjunctivitis and conjunctivitis.[1–3] Gram-positive organisms, particularly coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus*, and the Gram-negative organism, *Pseudomonas aeruginosa*, are frequently implicated in pediatric keratitis.[1–4] Staphylococci are common pathogens in pediatric blepharokeratoconjunctivitis and dacryocystitis.[1,5–7] Common bacterial conjunctivitis pathogens in children include *Haemophilus influenzae*, *Streptococcus pneumoniae* and less frequently, *Moraxella catarrhalis*,[8–12] with *S. aureus* and *S. epidermidis* considered causative when present above quantitative thresholds.[13–20] Before initiating antibacterial therapy in any eye infection, identification of the causative bacterium along with its corresponding antibiotic resistance profile is ideal for guiding therapy. However, in real-world clinical practice, the utility of culture and sensitivity testing is lessened because of the delay involved in getting results. Thus, it is common for ocular infections to be treated empirically, a practice both possibly contributing to, and complicated by, the problem of antibiotic resistance among ocular bacterial pathogens.

Increased microbial resistance to antibiotic therapy has been a growing concern over recent decades, including among ocular pathogens.[21–25] There have been only 2 nationwide, prospective surveillance studies that have monitored resistance data among ocular pathogens specifically: the Ocular Tracking Resistance in US Today (TRUST) study, conducted between 2005 and 2008,[25–27] and the ongoing Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study initiated in 2009.[28–30] Both studies evaluated

antibiotic resistance among bacterial species common to ocular infections in general, namely *S. aureus*, CoNS (*S. epidermidis* in ocular TRUST), *H. influenzae, S. pneumoniae* and *P. aeruginosa* (ARMOR only), and both reported high rates of in vitro antibiotic resistance as well as multidrug resistance among bacterial isolates from clinically significant ocular infections, particularly among *S. aureus* and CoNS.[26,28–30]

While the ARMOR surveillance study is not specific to the pediatric population, there is no limit as to the age of the patient from whom isolates are obtained. The isolate database therefore includes a significant number of isolates obtained from ocular infections in pediatric patients (≤17 years of age). Herein, we report antibiotic resistance profiles and trends for the 995 ocular isolates obtained exclusively from pediatric patients in the ARMOR surveillance study as of December 2016.

METHODS

Study Design

The ARMOR surveillance study design and methods have been described in detail elsewhere.[28] Here, we report antibiotic resistance among ocular isolates collected from January 1, 2009, to December 31, 2016, exclusively from pediatric patients ≤17 years of age. Briefly, participating eye care centers, community hospitals and academic or university hospitals across the United States were invited to submit a defined number of isolates: up to 65 ocular isolates (including 20 *S. aureus*, 20 CoNS, 5 *S. pneumoniae*, 5 *H. influenzae* and 15 *P. aeruginosa*) from 2009 to 2013 and up to 50 ocular isolates (with no more than 12 isolates per species) from 2014 to 2016. Sites were requested to submit clinically significant (ie, presumed causative) bacterial isolates from any eye infection sources. Not all sites submitted samples throughout all 8 years. Informed consent and institutional review board approval were not required for study conduct at any of the clinical sites, and Health Insurance Portability and Accountability Act compliance did not apply given initial ocular samples were taken as part of routine medical care unrelated to this study and no patient identifying information was provided.

Antibacterial Susceptibility Testing

Isolates were sent to an independent central laboratory [Eurofins Medinet, Chantilly, VA (2009–2013); IHMA, Schaumburg, IL (2014–2016)] for species confirmation and determination of the antibiotic resistance profile. Minimum inhibitory concentration (MIC) profiles were determined by broth microdilution according to Clinical and Laboratory Standards Institute (CLSI) defined methodology[31–33] using frozen antimicrobial microtiter panels (Thermo Fisher Scientific, Walthom, MA). Representative antibiotics from 12 different antibiotic classes (fluoroquinolone, macrolide, aminoglycoside, lincosamide, cephalosporin, penicillin, carbapenem, dihydrofolate reductase inhibitor, polypeptide, amphenicol, tetracycline and glycopeptide) were tested against isolates as appropriate based on species. Not all antibiotics were tested in each year. Where breakpoints were available, isolate MICs were interpreted as susceptible, intermediate or resistant according to the CLSI interpretive criteria in use during the collection year for a particular combination of species and antibiotic.[34–41] Staphylococci were classified as methicillin-resistant (MR) or methicillin-susceptible (MS) based on susceptibility to oxacillin. Susceptibility and resistance of *S. pneumoniae* isolates to penicillin were determined using the breakpoint for oral penicillin. For reporting purposes, resistant isolates were classified as those with intermediate or full resistance to an antibiotic. Multidrug resistance among isolates was defined as resistance to at least 3 classes of antibiotics.

Statistical Analysis

Logistic regression models for concurrent resistance to each antibiotic were used to obtain odds ratios based on MR. Confidence intervals for antibiotic resistance rates were computed using the Wilson score with a correction for continuity[42] using Statistix 10 software (Analytic Software, Tallahassee, FL). Changes in resistance rates over time were evaluated using a Cochran-Armitage test for linear trends in a proportion[43] with statistical significance defined as $P < 0.05$.

RESULTS

Isolates

A total of 4829 ocular isolates were collected from January 2009 to December 2016. Of these, 995 were specific to pediatric patients with ocular infections and were obtained from 67 sites (34 community hospitals, 24 university hospitals, 7 specialty centers, 2 reference laboratories). These included 286 *H. influenzae,* 284 *S. aureus,* 213 CoNS, 150 *S. pneumoniae* and 62 *P. aeruginosa* isolates. The 213 CoNS isolates included 154 *S. epidermidis,* 25 *S. hominis,* 12 unspeciated CoNS, 8 *S. capitis,* 6 *S. warneri,* 2 each *S. haemolyticus* and *S. lugdunensis* and 1 each *S. caprae, S. equorum, S. saprophyticus* and *S. simulans.*

Of the pediatric patients from whom samples were obtained, 429 (43.1%) were female, 527 (53.0%) were male and gender was not reported for 39 (3.9%). Stratification by patient age (Table 1) showed that the majority of *H. influenzae, S. aureus,* CoNS and *S. pneumoniae* isolates were obtained from pediatric patients ≤3 years of age, whereas approximately half of *P. aeruginosa* isolates were obtained from adolescent patients 11–17 years of age. The precise anatomical source of the ocular isolates was reported for only 373 (37.5%) isolates. In the subset of isolates with known ocular sources, the conjunctiva was the most common anatomical source for *H. influenzae*, *S. aureus*, CoNS and *S. pneumoniae* isolates, with 94.7%, 90.1%, 82.9% and 88.3% of isolates collected from that tissue, respectively. The most common anatomical source for *P. aeruginosa* isolates was the cornea (65.5%).

In Vitro Antibiotic Resistance Rates

Resistance among *H. influenzae* isolates was minimal. Except for 2 isolates resistant to azithromycin and 3 isolates resistant to chloramphenicol, all *H. influenzae* isolates were susceptible to all antibacterials tested. The MIC that inhibits visible growth of 90% of isolates (MIC$_{90}$) against *H. influenzae* was no greater than 0.06 µg/mL for any fluoroquinolone tested, 2 µg/mL for azithromycin, 0.5 µg/mL for chloramphenicol, 0.03 µg/mL for ceftriaxone and 1 µg/mL for imipenem.

TABLE 1. Bacterial Isolates Collected From Pediatric Patients (January 2009 Through December 2016)

Organisms (Phenotype)	Total	No. of Isolates (%)		
		0–3 Years	4–10 Years	11–17 Years
Haemophilus influenzae	286	235 (82.2)	47 (16.4)	4 (1.4)
Staphylococcus aureus	284	169 (59.5)	72 (25.4)	43 (15.1)
MSSA	215	134 (62.3)	45 (20.9)	36 (16.7)
MRSA	69	35 (50.7)	27 (39.1)	7 (10.1)
CoNS	213	144 (67.6)	38 (17.8)	31 (14.6)
MSCoNS	112	64 (57.1)	25 (22.3)	23 (20.5)
MRCoNS	101	80 (79.2)	13 (12.9)	8 (7.9)
Streptococcus pneumoniae	150	97 (64.7)	41 (27.3)	12 (8.0)
Pseudomonas aeruginosa	62	29 (46.8)	4 (6.5)	29 (46.8)

Percentages may not equal 100 due to rounding.

Of the 284 *S. aureus* isolates, 69 (24.3%) were resistant to oxacillin (MR *S. aureus*, MRSA), 42 (14.8%) were resistant to ciprofloxacin and 158 (55.6%) were resistant to azithromycin. All *S. aureus* isolates were susceptible to vancomycin, and only a small proportion was resistant to clindamycin (13 of 284 [4.6%]), chloramphenicol (9 of 243 [3.7%]), tobramycin (10 of 284 [3.5%]) or trimethoprim (9 of 243 [3.7%]). Table 2 presents the MICs and resistance profiles for *S. aureus* isolates by MR phenotype. Among MRSA isolates, resistance was high for fluoroquinolones (range 40.6%–42.0%) and azithromycin (92.8%). Among MS *S. aureus* (MSSA), resistance was high only for azithromycin (43.7%).

Of the 213 CoNS isolates, 101 (47.4%), 33 (15.5%) and 153 (71.8%) were resistant to oxacillin, ciprofloxacin and azithromycin, respectively. Like *S. aureus*, all CoNS were susceptible to vancomycin, and all but one were susceptible to chloramphenicol. However, higher proportions were resistant to clindamycin (70 of 213 [32.9%]), tobramycin (34 of 213 [16.0%]) and trimethoprim (37 of 182 [20.3%]). Consistent with *S. aureus*, resistance was higher in the subset of CoNS isolates that were MR (MRCoNS) (Table 3), with 26.7%–30.8% resistant to fluoroquinolones and 88.1% resistant to azithromycin. Resistance among MRCoNS was also higher for clindamycin (43.6%), tobramycin (32.7%) and trimethoprim (34.6%).

Table 4 presents the MICs and resistance profiles for *S. pneumoniae* isolates. *S. pneumoniae* isolates appeared highly susceptible to the antibiotics tested with the exceptions being azithromycin and penicillin (resistance rates of 38.0% and 34.7%, respectively).

All *P. aeruginosa* isolates were susceptible to the fluoroquinolones tested; all but two isolates were susceptible to tobramycin, and all but one isolate was susceptible to polymyxin B (data provided in Additional File 1, Supplemental Digital Content 1, http://links.lww.com/INF/D305). Notably, about one fifth of *P. aeruginosa* isolates demonstrated resistance to the beta-lactam imipenem (10 of 52 [19.2%]). The MIC_{90} against *P. aeruginosa* was no greater than 2 μg/mL for the fluoroquinolones, 1 μg/mL for tobramycin, 4 μg/mL for imipenem and 2 μg/mL for polymyxin B.

Multidrug Resistance

MR staphylococcal isolates were more likely to be concurrently resistant to another drug class when compared with MS staphylococcal isolates, with $P \leq 0.018$ for resistance to representative antibiotics from the macrolide, fluoroquinolone, lincosamide and aminoglycoside classes (Fig. 1). The percentage of multidrug resistance among staphylococcal isolates is presented in Figure 2. Among all *S. aureus*

TABLE 2. Minimum Inhibitory Concentrations and Resistance Profiles for *Staphylococcus aureus* Isolates From Ocular Infections in Pediatric Patients 0–17 Years of Age

Antibacterial	No. of Isolates Tested	MIC (μg/mL)			Resistance Profile		
		Range	MIC_{50}	MIC_{90}	%S	%I	%R
Ofloxacin							
MSSA	181	0.12 to >8	0.25	0.5	96.1	0	3.9
MRSA	62	0.25 to >8	0.5	>8	58.1	0	41.9
Ciprofloxacin							
MSSA	215	≤0.002 to 64	0.25	0.5	94.0	0.9	5.1
MRSA	69	≤0.002 to 256	0.5	16	58.0	1.5	40.6
Levofloxacin							
MSSA	181	0.06 to 16	0.12	0.25	96.1	1.1	2.8
MRSA	62	0.06 to 256	0.25	4	58.1	3.2	38.7
Gatifloxacin							
MSSA	181	0.008 to 4	0.06	0.12	96.1	1.7	2.2
MRSA	62	0.03 to 64	0.12	2	58.1	6.5	35.5
Moxifloxacin							
MSSA	215	0.008 to 4	0.03	0.12	95.8	1.9	2.3
MRSA	69	0.015 to 32	0.06	4	59.4	20.3	20.3
Besifloxacin							
MSSA	215	≤0.008 to 0.5	0.03	0.06	NA	NA	NA
MRSA	69	≤0.008 to 2	0.03	0.5	NA	NA	NA
Azithromycin							
MSSA	215	≤0.25 to >512	2	>512	56.3	0.9	42.8
MRSA	69	1 to >512	128	>512	7.3	0	92.8
Clindamycin							
MSSA	215	≤0.03 to >16	0.12	0.25	97.2	0.5	2.3
MRSA	69	≤0.03 to >64	0.12	>2	89.9	0	10.2
Chloramphenicol							
MSSA	181	4 to 64	8	8	97.2	1.7	1.1
MRSA	62	2 to 128	8	8	93.6	3.2	3.2
Tobramycin							
MSSA	215	≤0.06 to 32	0.25	0.5	99.1	0	0.9
MRSA	69	≤0.06 to >256	0.5	16	88.4	1.5	10.2
Trimethoprim							
MSSA	181	0.25 to >256	2	4	96.1	0	3.9
MRSA	62	≤0.5 to 64	1	2	96.8	0	3.2
Vancomycin							
MSSA	215	≤0.25 to 2	0.5	1	100	0	0
MRSA	69	≤0.25 to 1	0.5	1	100	0	0

Percentages may not equal 100 due to rounding.

I indicates intermediate; MIC_{50}, MIC that inhibits visible growth of 50% of isolates; NA, CLSI interpretive breakpoints not available; R, resistant; S, susceptible.

TABLE 3. Minimum Inhibitory Concentrations and Resistance Profiles for CoNS Isolates From Ocular Infections in Pediatric Patients 0–17 Years of Age

Antibacterial	No. of Isolates Tested	MIC (µg/mL)			Resistance Profile		
		Range	MIC_{50}	MIC_{90}	%S	%I	%R
Ofloxacin							
MSCoNS	104	0.12 to 8	0.25	0.5	98.1	0	1.9
MRCoNS	78	0.12 to >256	0.5	>8	69.2	0	30.8
Ciprofloxacin							
MSCoNS	112	0.008 to 8	0.12	0.25	98.2	0	1.8
MRCoNS	101	≤0.06 to 256	0.25	32	69.3	5.0	25.7
Levofloxacin							
MSCoNS	104	0.008 to 4	0.12	0.25	98.1	0	1.9
MRCoNS	78	0.06 to 512	0.25	16	69.2	5.1	25.6
Gatifloxacin							
MSCoNS	104	0.008 to 2	0.06	0.12	98.1	1.0	1.0
MRCoNS	78	0.03 to 64	0.12	8	69.2	3.9	27.0
Moxifloxacin							
MSCoNS	112	0.008 to 1	0.06	0.12	98.2	1.8	0
MRCoNS	101	0.008 to 64	0.06	4	73.3	8.9	17.8
Besifloxacin							
MSCoNS	112	≤0.008 to 0.5	0.03	0.06	NA	NA	NA
MRCoNS	101	0.015 to 4	0.03	0.5	NA	NA	NA
Azithromycin							
MSCoNS	112	≤0.25 to >512	32	>512	42.9	0	57.1
MRCoNS	101	≤0.25 to >512	>512	>512	11.9	0	88.1
Clindamycin							
MSCoNS	112	≤0.03 to >64	0.06	8	76.8	6.3	17.0
MRCoNS	101	≤0.03 to >64	0.12	>64	56.4	2.0	41.6
Chloramphenicol							
MSCoNS	104	≤1 to 64	4	4	99.0	0	1.0
MRCoNS	78	2 to 8	4	8	100	0	0
Tobramycin							
MSCoNS	112	≤0.06 to 8	≤0.06	0.5	99.1	0.9	0
MRCoNS	101	≤0.06 to >256	0.5	32	67.3	6.9	25.7
Trimethoprim							
MSCoNS	104	≤0.12 to >256	0.5	8	90.4	0	9.6
MRCoNS	78	0.25 to >256	1	256	65.4	0	34.6
Vancomycin							
MSCoNS	112	≤0.25 to 2	1	2	100	0	0
MRCoNS	101	0.5 to 4	1	2	100	0	0

Percentages may not equal 100 due to rounding.
I indicates intermediate; MIC_{50}, MIC that inhibits visible growth of 50% of isolates; NA, CLSI interpretive breakpoints not available; R, resistant; S, susceptible.

TABLE 4. Minimum Inhibitory Concentrations and Resistance Profiles for *S. pneumoniae* isolates From Ocular Infections In Pediatric Patients 0–17 Years of Age

Antibacterial	No. of Isolates Tested	MIC (µg/mL)			Resistance Profile		
		Range	MIC_{50}	MIC_{90}	%S	%I	%R
Ofloxacin	122	≤0.015 to >8	1	2	99.2	0	0.8
Ciprofloxacin	150	0.06 to 2	0.5	1	NA	NA	NA
Levofloxacin	122	0.12 to 2	0.5	1	100	0	0
Gatifloxacin	122	0.015 to 0.5	0.12	0.25	100	0	0
Moxifloxacin	150	≤0.004 to 2	0.06	0.12	99.3	0.7	0
Besifloxacin	150	≤0.008 to 0.12	0.03	0.06	NA	NA	NA
Azithromycin	150	≤0.03 to >512	0.06	>128	62.0	0	38.0
Chloramphenicol	150	0.5 to 16	2	4	98.0	0	2.0
Ceftriaxone	122	≤0.015 to 2	≤0.03	0.5	98.4	1.6	0
Imipenem	94	≤0.008 to 0.5	≤0.008	0.12	93.6	6.4	0
Penicillin	150	≤0.015 to 4	≤0.03	1	65.3	24.7	10.0

Percentages may not equal 100 due to rounding.
I indicates intermediate; MIC_{50}, MIC that inhibits visible growth of 50% of isolates; NA, CLSI interpretive breakpoints not available; R, resistant; S, susceptible.
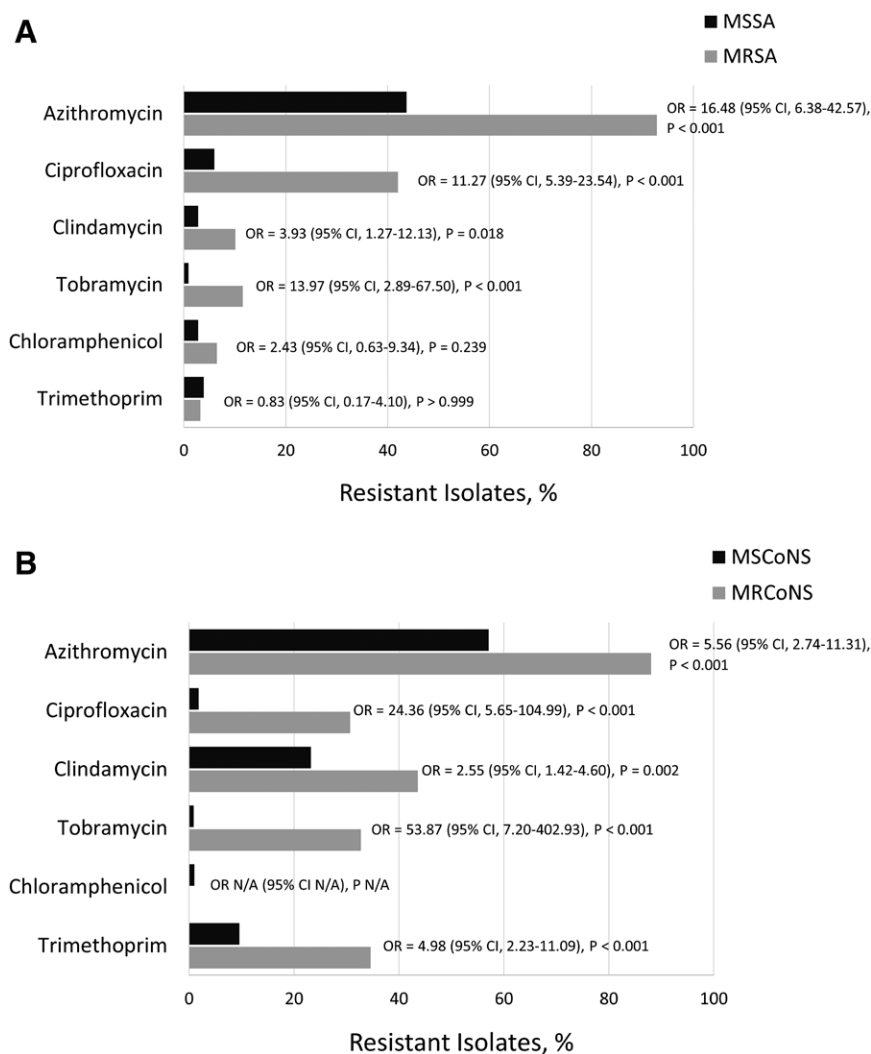
FIGURE 1. Resistance to antibacterial agents against staphylococcal isolates from pediatric patients collected in the ARMOR study. *Staphylococcus aureus* (A) and CoNS (B) isolates were tested for resistance to representative macrolide (azithromycin), fluoroquinolone (ciprofloxacin), lincosamide (clindamycin), dihydrofolate reductase inhibitor (trimethoprim) and aminoglycoside (tobramycin) antibacterials. Odds ratios (OR) and *P* values were obtained from logistic regression models.

and all CoNS isolates, rates of multidrug resistance (resistance to ≥3 classes of antibiotics) were 13.0% (37 of 284) and 36.6% (78 of 213), respectively, whereas among MRSA and MRCoNS rates were 49.3% (34 of 69) and 70.3% (71 of 101), respectively.

Resistance Rates Over Time

There were only two significant changes observed in resistance rates over the 8-year study period; among *S. aureus*, the percentage of isolates resistant to oxacillin decreased significantly from 17.1% in 2009 to 11.6% in 2016 (*P* = 0.014) and ciprofloxacin resistance also decreased significantly from 17.1% in 2009 to 4.7% in 2016 (*P* = 0.001). No other longitudinal trends were observed for any other ocular species/antibiotic class combination.

DISCUSSION

Surveillance data on antibiotic resistance patterns among common ophthalmic pathogens can inform clinical treatment decisions, particularly when instituting empiric therapy in the absence of culture and sensitivity data. The current analysis is the first to

specifically report on in vitro antibiotic resistance among isolates of *H. influenzae, S. aureus,* CoNS, *S. pneumoniae* and *P. aeruginosa* cultured from ocular infections specific to the pediatric population from a nationwide surveillance study. The analysis included data from nearly 1000 ocular isolates obtained from pediatric patients across 67 U.S. clinical sites. Although the precise ocular tissue source of the isolates was reported for only about one-third of isolates, where reported, the majority was collected from the conjunctiva suggesting a significant proportion of isolates evaluated may have originated from bacterial conjunctivitis cases. By organism, the majority of isolates were obtained from patients 0–3 years of age, the one exception being *P. aeruginosa* for which equal numbers of isolates were obtained from patients 0–3 years of age and patients 11–17 years of age. This observation likely reflects the fact that contact lens wear is a known risk factor for *P. aeruginosa* ocular infections (typically keratitis) and would be frequent among adolescent patients.[44–46]

Results of antibiotic resistance testing showed low resistance among ocular *H. influenzae* from pediatric patients to the antibiotics tested, consistent with reports of low level resistance against these antibiotics among *H. influenzae* from other sources (ear, nose and/or
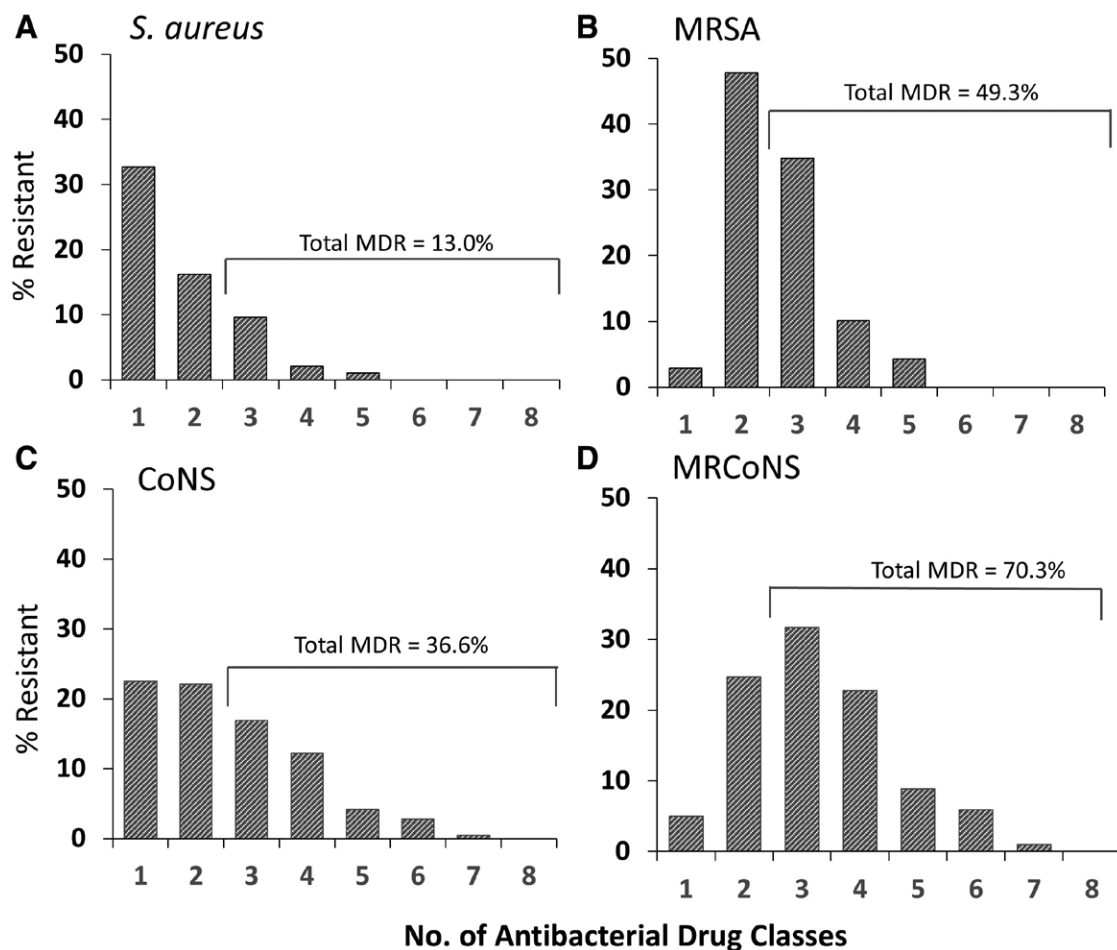
FIGURE 2. Multidrug resistance among ocular isolates collected from pediatric patients in the ARMOR study. Isolates were tested against ciprofloxacin, azithromycin, clindamycin, chloramphenicol, tobramycin, oxacillin, vancomycin, tetracycline and trimethoprim. The percentage of resistance includes intermediate resistance. MDR indicates multidrug resistant.

throat).[47–49] However, we did not test for ampicillin resistance, which has been shown among both ocular[50–52] and nasopharyngeal[49,52–54] isolates. In contrast, we found significant in vitro resistance among staphylococci. Approximately 1 in 2 *S. aureus* and 3 in 4 CoNS isolates demonstrated in vitro resistance to azithromycin; as well, approximately 1 in 4 *S. aureus* and 1 in 2 CoNS isolates demonstrated in vitro resistance to oxacillin (ie, MR). Among *S. pneumoniae,* approximately 2 in 5 isolates demonstrated resistance to azithromycin and to penicillin, whereas little in vitro antibiotic resistance was noted among *P. aeruginosa,* with the exception of some resistance to imipenem. Of note, nearly identical rates of resistance were found when data from the subset of isolates obtained from pediatric patients 0 to 3 years of age were analyzed (data not shown), emphasizing that within the pediatric population as a whole, antibiotic resistance patterns were consistent regardless of age subgrouping.

In general, our findings specific to ocular isolates from pediatric patients were consistent with findings for the 2009–2015 full ARMOR dataset[30] with few exceptions. Notable among these was the finding of an approximately 2-fold higher resistance to imipenem among pediatric *P. aeruginosa* isolates and a lower resistance to methicillin among pediatric *S. aureus* isolates (24.3% vs. 36.6%, respectively), which was expected given the reported greater prevalence of ocular MRSA among older patients.[29,51] Again, consistent with prior reporting,[30] all staphylococcal isolates in the pediatric dataset were susceptible to vancomycin; this finding is reassuring given

that compounded vancomycin is commonly utilized by ophthalmologists when treating particularly resistant ocular infections. As reported previously, MR significantly increases the likelihood of concurrent resistance to other antibiotic classes.[29] However, for reasons that are unclear, the percentage of multidrug-resistant *S. aureus* isolates was lower in the pediatric isolate subset as compared with the full ARMOR dataset (13.0% vs. 33.5%, respectively) as was the percentage of multidrug-resistant MRSA (49.3% vs. 76.4%, respectively).[30]

The fluoroquinolone besifloxacin was developed exclusively for topical ocular administration, and as such, no systemic susceptibility breakpoints are available to interpret bacterial isolates as resistant or susceptible to besifloxacin. However, besifloxacin demonstrated the lowest MIC_{90} values of all ophthalmic antibiotics tested against *S. aureus* and CoNS, including MR isolates and *S. pneumoniae*. This is consistent with previous studies where the MIC_{90} of besifloxacin was lower compared with other fluoroquinolones for these species, including those with substantial resistance[13,55,56] and suggests a potential for improved efficacy with besifloxacin, especially against MR staphylococcal infections on the ocular surface. Besifloxacin had an MIC_{90} comparable to that of other newer generation fluoroquinolones tested against *P. aeruginosa* (MIC_{90} = 2), while the older generation fluoroquinolone ciprofloxacin had the lowest MIC_{90} in this class against that organism (MIC_{90} = 0.25).

The longitudinal nature of this study allowed for analysis of resistance trends over the 8-year study period. Contrary to the

reported increase in antibiotic resistance observed among ocular bacteria in the years before 2009, and most notably for MR among staphylococci,[25–27,57] there were no significant increases in resistance rates of any ocular bacterial species to the tested antibiotics in the current dataset, consistent with findings in the full ARMOR dataset. In fact, there was a small but significant decrease in in vitro resistance to oxacillin and ciprofloxacin among *S. aureus* pediatric isolates. Consistent with the decrease in MRSA prevalence over time that was observed in the current study, a previous retrospective analysis of *S. aureus* isolates from infections (not limited to any anatomical site, mostly skin and soft tissue) in over 39,000 pediatric patients found that oxacillin resistance declined from 41% in 2005 to 32% in 2014 ($P < 0.001$).[58] Further longitudinal data are needed to determine whether this decreasing trend persists among pediatric ocular isolates. Nonetheless, the lack of any increases in resistance over time is a welcome finding, and one that hopefully will be sustained and even improved upon over coming years. To this end, careful adherence to treatment guidelines and implementation of antibiotic stewardship strategies such as those advocated by the Pediatric Infectious Diseases Society[59] and the American Academy of Pediatrics[60] may minimize antimicrobial resistance development among bacteria causing ocular infections. Empiric coverage against MRSA is encouraged by many experts as long as prevalence of the organism exceeds 10%–15%.[61,62]

The pediatric ARMOR data are subject to several limitations. The isolate collection was limited to U.S. sites, thus possibly limiting generalizability of the data to other global regions. There is potential for sampling biases as ocular pathogens are not routinely cultured in community-based practices. Indeed the majority of participating centers were hospitals and referral centers, and investigators were instructed to supply isolates for ocular infections that were considered to be of clinical significance, thus the pediatric isolate dataset analyzed here may be skewed toward more difficult cases and may not reflect resistance patterns in community-based practices. The precise ocular source was known for only one-third of isolates, and information on diagnosis was not collected, limiting application of findings to specific ocular infections. Relevant ophthalmic antibiotics were included, but not all agents could be tested. Chloramphenicol, no longer available as a topical formulation in the United States because of its apparent association with systemic adverse drug reactions, is still widely used in other countries as the first line for the treatment of bacterial conjunctivitis and was therefore included[63]; vancomycin was also included as it is often compounded for ophthalmic use and may be available in a commercial formulation for use in bacterial conjunctivitis in the future.[64] Finally, bacterial susceptibility and resistance to tested antibiotics were interpreted using MIC data for systemic breakpoints, which may be of limited value for determining ocular susceptibility given the expected differences in achievable drug concentrations in the eye compared with systemic administration. Nevertheless, if concentrations in ocular tissues after topical administration are assumed to be at least equal to that found in systemic tissues after systemic administration, application of systemic breakpoints is an appropriate method to compare antibiotic susceptibilities among ocular bacterial pathogens.

In summary, in vitro antibiotic resistance appears common among staphylococcal and pneumococcal isolates collected from pediatric patients with ocular infections, but such resistance does not appear to be increasing. MR was prevalent among staphylococci with many strains demonstrating multidrug resistance. Despite limitations in MIC interpretation for topically administered ocular antibiotics, these data may be of interest to clinicians tasked with choosing empiric therapy for pediatric ocular infections and can serve as a benchmark for future surveillance of resistance among pediatric ocular isolates.

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