Update on the Epidemiology and Antibiotic Resistance of Ocular Infections

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Abstract:

PURPOSE: The purpose of this review is to provide an update on the epidemiology and current antibiotic-resistant threats in ophthalmology.

METHODS: Trends in frequency and antibiotic-nonsusceptible profiles during an 11 year-period (2005–2015) were evaluated and compared with the 5-year Antibiotic Resistance Monitoring in Ocular Microorganism (ARMOR) study.

RESULTS: Trends in the current review confirmed the continued high rates of fluoroquinolone nonsusceptibility circulating among ocular methicillin-susceptible Staphylococcus aureus, methicillin-susceptible Staphylococcus epidermidis, methicillin-resistant S. aureus, and methicillin-resistant S. epidermidis isolates as well as the detection of uncommon, but emerging resistance (<5%) for Streptococcus pneumoniae, Streptococcus viridans group, Haemophilus influenzae, and Pseudomonas aeruginosa. We documented significant differences in empirical fluoroquinolone and aminoglycoside coverage for the top three ocular pathogens (coagulase-negative staphylococci, S. aureus, and P. aeruginosa) in general and for corneal isolates between the Miami and the ARMOR studies. Collectively, the coverage for Miami was 74% versus 65.9% for ARMO (P < 0.0001, 5.3674–10.8042) for ciprofloxacin and 95.9% versus 84.2% for aminoglycosides (gentamicin/tobramycin) (P < 0.0001, 9.9925–13.3974). Monotherapy coverage for ciprofloxacin and levofloxacin for the most recent 5 years (2011–2015) was 76.6% and 77.1%, respectively. Combination therapy with a fluoroquinolone and vancomycin and/or vancomycin and an aminoglycoside provided coverage for 99% and 98% of the isolates, respectively.

CONCLUSION: The etiology of ocular pathogens is patient, source, and geography specific. The true incidence and/or prevalence are unknown. Fluoroquinolone monotherapy as standard therapy for common ocular infections needs to be reassessed. Ophthalmologists must become proactive and join the crusade to develop practical and prudent strategies for the administration of topical antibiotics.

Keywords:
Antibiogram, antibiotic resistance, diversity, nonsusceptibility

Introduction

Ocular infectious diseases (blepharitis, conjunctivitis, keratitis, and endophthalmitis) are responsible for a high degree of visual morbidity and blindness worldwide. Greater than 70% of all ocular infections are associated with Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Moraxella species, Pseudomonas aeruginosa, Candida albicans, Aspergillus species, and Fusarium species. The frequency and pathology may fluctuate depending on age, gender, climate, healthcare access, and culturing frequency.

Despite the higher drug concentrations obtained in ocular tissues when using topical antibiotics, there are increasing reports of clinical failure and/or less than optimal outcomes with empirical treatment with each new fluoroquinolone generation.[1,2]
Similar to nonocular isolates, there is an increasing threat to patient safety and poorer outcomes in the management of antibiotic-resistant or nonsusceptible isolates.

The true prevalence of antibiotic resistance and associated clinical failure, however, is unknown. The current standard of care is to treat first and culture later (if ever). There is no national or international clearing house to monitor antimicrobial resistance among common and uncommon bacterial and fungal ocular pathogens.

Regional and local trends in pathogen frequency and antibiotic resistance vary by time, geographic region, and patient population sampled. The Center for Disease Control and Prevention lists monitoring and tracking antibiotic resistance as one of the four cornerstones to reduce and protect against emerging antibiotic threats.[3] Current surveillance and tracking programs for ocular pathogens need to be expanded and coordinated.

The purpose of this review is to provide an update on the epidemiology in ocular pathogen trends and current antibiotic-resistant threats in ophthalmology.

Methods

The Miami Microbiology database was searched and data on trends in organism frequency, diversity, and antibiotic profiles extracted and reviewed for isolates collected between January 2005 and December 2015 with emphasis on the past 5 years (2011–2015). The study was performed with the approval of the University of Miami Institutional Review Board.

Isolates were identified using the Vitek 2 Compact System (BioMerieux, Durham, NC, USA) and a combination of rapid kits and standard microbiology protocols. Susceptibility data were compiled using the Vitek 2 computerized susceptibility database and E-test (BioMerieux, Durham, NC, USA).

Organism frequency and susceptibility profiles from our institute were compared with the Antibiotic Resistance Monitoring in Ocular Microorganism (ARMOR) 5-year study and/or comparable and appropriate national and international studies involving results of isolates collected and reported in literature between 2011 and 2015.

Statistics

Chi-square was used to evaluate differences in proportions. Significance, $P < 0.05$, 95 CI was determined using online software Med Calc, Belgium https://www.medcalc.org/and/or Microsoft 2013 Excel software.

Results

A total of 10,589 isolates were recovered and reviewed over the 11-year study period. There was a significant ($P < 0.0001$, 95 CI [1.8000–4.8083]) decline in the average number of organisms recovered from period I (2005–2010 $n = 5940$) average 990 per year versus period II (2011–2015, $n = 4649$) average 930.

Trends in organism group frequency over time are highlighted in Figure 1. Bacterial species were the predominant organism group for all time periods and ranged from 82% to 87.1%. There was a significant difference in bacterial recovery rates for period I (85.3%, $n = 5066$, 2005–2010) versus period II (87.1%, $n = 4049$, 2011–2015), ($P < 0.0136$, 95 CI 0.3583 – 3.2305).

A significant increase and crossover of Gram-positive bacteria versus Gram-negative bacteria occurred during the most recent 5 years. Compared to period I ($n = 2227$, 37.5%), the proportion of Gram-positive isolates increased by 8.4% ($P = 0.0001$).

This shift was paralleled by a decrease in Gram-negatives by 7.4% (44.6%, $n = 2649$ vs. 37.5%, $n = 1743$) ($P < 0.001; 95 CI 31.3961–34.000$). There was no significant change in the recovery of Mycobacteria species (3.2%, $n = 190$ vs. 3.7, $n = 172$) between the two periods ($P = 0.1600$, 95 CI – 0.2104–1.2263).

Among the nonbacterial isolates, significant declines in recovery of molds (9%, $n = 535$ vs. 7.6%, $n = 353$) ($P = 0.0099$, 95 CI0.3268–2.4622) and Acanthamoeba species (2.2%, $n = 137$ vs 1%, $n = 46$) ($P < 0.0001$, 95 CI 0.7135–1.6850) were documented between period I and period II. Recovery of yeast isolates increased by 1.3% (3.5%, $n = 208$ vs. 4.8%, $n = 223$; $P = 0.0008$).

Table 1 outlines the trends in recovery rates between the two periods for the most common ocular bacteria pathogens. There were marginal increases in three of the four Gram-positive pathogens and ranged from 1.7% for the Streptococcus viridans group to 4.6% for S. aureus. The net increase for Gram-positive isolates was 8.8%. Significance was only observed for S. aureus. Significant decreases for two of the three Gram-negatives on the list were observed and ranged from 1.3% for Haemophilus influenzae to 2.2% for P. aeruginosa. The net decline for Gram-negative pathogens was 2.8%.

Abundance and diversity of the top five isolates differed by ocular sources and/or patient population sampled [Table 2]. Gram-positive isolates remain the most frequent isolates overall, but frequency was dependent on ocular source or patient population sampled.
Recovery rates by source for Gram-positive pathogens in descending order were endophthalmitis (90.9%, n = 180), conjunctivitis (62.8%, n = 402), and keratitis (26.4%, n = 395). Recovery rates for Gram-negatives isolates in descending order included keratitis (42.7%), conjunctivitis (37.3%), and endophthalmitis (11.0%). The ratio of Gram-positive to Gram-negative among the top ten most common ocular pathogens was 1.9:1. *S. aureus* remains the most common bacterial pathogen overall and ranged from 7.6% for endophthalmitis to 35.5% for conjunctivitis. *P. aeruginosa* was the most frequent pathogen recovered from patients’ samples submitted to rule out keratitis. Coagulase-negative staphylococci (CoNS; n = 71, 35.8%) remain the top patients recovered from patients with endophthalmitis.

Table 3 compares trends in conjunctiva isolates from three regions; Miami, FL, USA (2011–2015, n = 786), Pittsburg, PA, USA (1993–2011, n = 1320),[iv] and Lagos, Nigeria (2010, n = 155).[v] Spectrum and diversity were distinct for all other locations. Greater than two-thirds of the recovered isolates were Gram-positive for samples evaluated from populations in Pittsburg and Lagos. *S. aureus* was the most frequent pathogens in all three locations. Among the remaining isolates, only *Morganella* species was common to all three groups. Gram-positive
### Table 1: Trends in pathogen recovery and frequency

| Isolates                  | 2005-2010 (n=5940), n (%) | 2011-2015 (n=4649), n (%) | P     | Trend | Change (%) |
|---------------------------|---------------------------|---------------------------|-------|-------|------------|
| S. aureus                 | 1040 (17.5)               | 1027 (22.1)               | 0.0087| ↑     | 4.6        |
| P. aeruginosa             | 944 (15.9)                | 639 (13.7)                | 0.2294| ↓     | 2.2        |
| S. pneumoniae             | 226 (3.8)                 | 113 (2.4)                 | 0.4994| ↓     | 1.4        |
| H. influenzae             | 213 (3.6)                 | 108 (2.3)                 | 0.5301| ↓     | 1.3        |
| S. marcescens             | 187 (3.1)                 | 177 (3.8)                 | 0.7146| ↑     | 0.7        |
| S. viridans group         | 184 (3.1)                 | 222 (4.8)                 | 0.3865| ↑     | 1.7        |
| S. epidermidis            | 167 (2.8)                 | 312 (6.7)                 | 0.0704| ↑     | 3.9        |

**Note:** Staphylococcus aureus, P. aeruginosa, Pseudomonas aeruginosa, S. pneumoniae, Streptococcus pneumoniae, H. influenzae, Haemophilus influenzae, S. marcescens, Serratia marcescens, S. viridans, Streptococcus viridans, S. epidermidis, Staphylococcus epidermidis, S. aureus: Staphylococcus aureus, P. aeruginosa: Pseudomonas aeruginosa, S. viridans: Streptococcus viridans, C. trachomatis: Chlamydia trachomatis, S. pneumoniae: Streptococcus pneumoniae, E. coli: Escherichia coli, CoNS: Coagulase-negative staphylococci

### Table 2: Diversity and distribution of ocular pathogens by source

| Rank | Top isolates 2011-2015 (n=876) | Top isolates | Keratitis 2011-2015 (n=1498) | Endophthalmitis 2011-2015 (n=198) | All ocular 2011-2015 (n=4649) |
|------|--------------------------------|--------------|-----------------------------|-----------------------------------|-----------------------------|
| 1    | S. aureus (35.5)                | S. aureus    | S. aureus                   | S. aureus                         |
| 2    | H. influenzae (7.4)             | H. influenzae| H. influenzae               | H. influenzae                     |
| 3    | P. aeruginosa (6.3)             | S. aureus    | S. aureus                   | S. aureus                         |
| 4    | Adenovirus (4.9)                | Fusarium     | Candida species             | S. epidermidis                    |
| 5    | S. viridans group (4.5)         | S. viridans  | CoNS, other                 | S. marcescens                     |
| 6    | C. trachomatis (3.8)            | S. epidermidis| CoNS, other                 | S. viridans group                 |
| 7    | S. pneumoniae (3.7)             | Herpes simplex virus | S. pneumoniae             |
| 8    | Candida species (2.5)           | S. pneumoniae| H. influenzae               | S. pneumoniae                     |
| 9    | Corynebacterium species (2.3)   | C. albicans  | C. albicans                 | C. albicans                       |
| 10   | Serratia species (2.3)          | Acanthamoeba spp. | S. aureus                   | S. aureus                         |

### Table 3: Comparison of conjunctivitis isolates by geography

| Conjunctivitis 2011-2015 (n=782)-Miami | Conjunctivitis 1993-2011 (n=1320)-Pittsburgh | Conjunctivitis 2010 (n=155)-Lago, Nigeria |
|----------------------------------------|----------------------------------------------|------------------------------------------|
| Top isolates                           | Top isolates                                 | Top isolates                             |
| S. aureus                              | S. aureus                                   | S. aureus                                |
| Haemophilus species                    | S. pneumoniae                               | CoNS                                     |
| P. aeruginosa                          | Haemophilus species                         | Corynebacterium species                  |
| S. viridans group                      | CoNS                                        | Moraxella species                        |
| C. trachomatis                         | Moraxella species                           | P. aeruginosa                            |
| S. pneumoniae                          | Acinetobacter species                       | E. coli                                  |
| Corynebacterium species                | Gram-positive, other                        | Gram-positive, other                     |
| Serratia species                       | Gram-negative, other                        | Gram-negative, other                     |
| Proteus species                        |                                              |                                          |
| Moraxella species                      |                                              |                                          |
| Gram-positive isolates, other          |                                              |                                          |
| Gram-negative isolates, other          |                                              |                                          |
| Percentage of all bacterial conjunctival isolates | 782 (101.3)                           | 1320 (100.0)                             |
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**Note:** S. aureus: Staphylococcus aureus, P. aeruginosa: Pseudomonas aeruginosa, S. viridans: Streptococcus viridans, C. trachomatis: Chlamydia trachomatis, S. pneumoniae: Streptococcus pneumonia, E. coli: Escherichia coli, CoNS: Coagulase-negative staphylococci
isolates were the dominant conjunctival pathogens, and recovery rates ranged from 57.1% to 72%.

Table 4 compares keratitis isolates from Bascom Palmer Eye Institute (BPEI, Miami, USA, 2011–2015, n = 1135) with isolates from King Khaled Eye Specialist Hospital (KKESH, Riyadh, SA, USA, 2011–2014, n = 2037).[6] and Hospital Universiti Sain Maylasia (HUSM, Malaysia, Malaysia, n = 1211).[7] Profiles were distinct for each location. Greater than 85% of isolates recovered from keratitis at KKESH were Gram-positive versus 42.6% and 40.5% for HUSM and Miami, respectively. S. aureus isolates ranged from 7.8% (HUSM) to 20.6% for Miami. Methicillin resistance was significantly higher (16.8%, \( P = 0.0001, 95 \text{ CI } 8.3935–24.9972 \)) among S. aureus rates from Miami versus KKESH (36.2%, \( n = 227 \) vs. 19.4%, \( n = 237 \)). The reported methicillin-resistant S. aureus (MRSA) rate for HUSM was the lowest at 7% (\( n = 94 \)).

The greatest contrast was observed for recovery rates for CoNS. These were the most frequent isolates recovered from keratitis at KKESH with a rate of 47.2%. The recovery rate for coagulase-negative isolates in Miami was 9-fold less at 5.2%. No CoNS were detected among the isolates from Malaysia.

Gram-negative bacteria were the predominant organism group recovered in two of the three studies and ranged from 12.5% (KKESH) to 57.4% for HUSM. Recovery rates for Miami were 2.4-fold greater than those for KKESH. Malaysia had the highest Gram-negative rates, 1.1-fold higher than the BPEI and 2.7-fold greater than the rate for KKESH. P. aeruginosa was the top pathogen for only one of these (Miami, 35.7%) but was the second most frequent pathogen in keratitis isolates from Malaysia at 16.0%. P. aeruginosa was recovered from the cornea at least 3.3 times more frequent than KKESH and 2.1 times more frequent than the recovery rate for HUSM.

Eighty-five percent of microorganisms recovered from vitreous samples during this period were Gram-positive, with S. epidermidis being the most frequent at 29.7%. Gram-negative bacteria were not among the top five pathogens for patients with endophthalmitis for this period.

**Antibiogram**

Table 5 provides a cumulative Antibiogram Report for Ocular Isolates collected for the most recent 5 years (2011–2015). It follows the recommendations of the Clinical Laboratory Standard Institute (M3-A2, CLSI document)[8] for preparation.[9,10]

**Fluoroquinolones**

Overall, empirical therapy with a fluoroquinolones (ciprofloxacin, 76.6%, \( n = 2383 \)) provided < 80% coverage for the top three (S. aureus, CoNS, and P. aeruginosa) pathogens in our study. Individual susceptibility was species specific.

**Gram-negatives**

Less than 10% resistance was reported for the most common Gram-negative isolates for ciprofloxacin and/or levofloxacin during the most recent 5-year test period. Percent susceptible
Table 5: Cumulative antibiogram

| Organism                        | Number of isolates | Cefazolin | Cefaclor | Cefadroxil | Cefditoren | Erythromycin | Ciprofloxacin | Levofloxacin | Moxifloxacin | Gentamicin | Tobramycin | Amikacin | Vancocin | Penicillin | Ampicillin | Trimethoprim-sulfamethoxazole |
|--------------------------------|--------------------|-----------|----------|------------|------------|--------------|---------------|--------------|--------------|------------|-------------|----------|----------|-----------|-----------|-----------------------------|
| **Gram-negative organisms**    |                    |           |          |            |            |               |                |              |              |            |            |          |          |           |           |                             |
| Enterobacter species           | 49                 | 0         | 98       | 100        | 100        | 98           | 98            | 100          |              |            |            | 70       |          |           |           |                             |
| Haemophilus species            | 124                | 87        | 99       | 100        |            |              |                |              |              |            |            |          |          |           |           |                             |
| Haemophilus influenzae         | 103                | 88        | 100      | 99         |            |              |                |              |              |            |            | 70       |          |           |           |                             |
| Klebsiella species             | 70                 | 98        | 97       | 100        | 100        | 100          | 96            | 96           | 100          |            |            |          |          |           |           |                             |
| Proteus species                | 62                 | 93        | 98       | 90         | 89         | 95           | 95            | 95           | 98           |            |            |          |          |           |           |                             |
| Pseudomonas aeruginosa         | 597                | 0         | 98       | 98         | 99         | 96           | 100           | 100          |              |            |            |          |          |           |           |                             |
| Serratia species               | 174                | 0         | 99       | 100        | 100        | 100          | 99            | 95           | 100          |            |            |          |          |           |           |                             |
| Serratia marcescens            | 162                | 0         | 99       | 100        | 100        | 100          | 99            | 92           | 100          |            |            |          |          |           |           |                             |
| Stenotrophomonas maltophilia   | 75                 |           |          |            |            |               |                |              |              |            |            |          |          | 96         |          |                             |
| **Gram-positive organisms**    |                    |           |          |            |            |               |                |              |              |            |            |          |          |           |           |                             |
| CoNS - all                     | 295                | 56        | 56       | 39         | 58         | 58           | 88            |              |              |            |            |          |          |           |           |                             |
| Staphylococcus epidermidis     | 287                | 54        | 54       | 37         | 51         | 54           | 54            | 99           |              |            |            |          |          |           |           |                             |
| Methicillin-susceptible        | 154                | 100       | 100      | 50         | 73         | 73           | 96            |              |              |            |            |          |          |           |           |                             |
| Methicillin-resistant (MRSE)   | 133                | 0         | 0        | 23         | 33         | 33           | 33            | 77           |              |            |            |          |          |           |           |                             |
| Staphylococcus aureus, all     | 967                | 58        | 58       | 37         | 58         | 59           | 59            | 95           |              |            |            |          |          |           |           |                             |
| Methicillin-susceptible        | 560                | 100       | 100      | 59         | 86         | 88           | 89            | 99           |              |            |            |          |          |           |           |                             |
| Methicillin-resistant (MRSA)   | 407                | 0         | 0        | 8          | 19         | 19           | 20            | 91           |              |            |            |          |          |           |           |                             |
| Enterococcus faecalis          | 42                 | 20        | 75       |            |            |              |                |              |              |            |            |          |          | 100       | 97        |                             |
| Streptococcus pneumoniae       | 97                 | 59        | 100      |            |            |              |                |              |              |            |            |          |          | 100       | 53        |                             |
| Streptococcus viridans group   | 266                | 39        | 91       |            |            |              |                |              |              |            |            |          |          | 100       | 81        |                             |

Percentage susceptible interpretations based on Clinical Laboratory Standards Institute breakpoints.\textsuperscript{2,3} Data in this document use PD/PK data for individual bug/drug combinations in serum and tissue to generate breakpoints. Duplicates were excluded, only isolates and/or species numbering 30 or more were included in the antibiogram. Statistical validity or estimates of percent susceptibility for organisms for which there are fewer than 30 isolates is limited and could lead to inappropriate selection of empirical therapy.

MRSA=42% Methicillin resistance was determined using the cefoxitin screen (Vitek 2) for the staphylococci. MRSA and CoNS are also resistant to penicillins, MRSE=44% cephalosporins, and carbapenems.

PNSSP (nonmeningitis breakpoints)=47%

Key: Empty Empty white space-inappropriate bug/drug testing combination and/or limited clinical data for this combination

Data White space with numbers-not primary choice for this organism. Clinical data are limited or may indicated increasing resistance (CLSI-MS 100-S21)

MRSE: Methicillin-resistant Staphylococcus epidermidis, PNSSP: Penicillin-nonsusceptible Streptococcus pneumoniae, CoNS: Coagulase-negative staphylococci, MRSA: Methicillin-resistant Staphylococcus aureus, BPEI: Bascom Palmer Eye Institute

ranged from 90% for Proteus species to 100% for common Enterobacteriaceae species (Serratia marcescens, Klebsiella oxytoca, Enterobacter cloacae, and H. influenzae). No significant differences were observed for in vitro susceptibilities to ciprofloxacin 98.5%, n = 940 versus 98%, n = 597, P = 0.4593 (95CI − 0.8492–1.6833) and/or levofloxacin 98.5%, n = 939 versus 99%, n = 597, P = 0.4002 (95CI − 0.8492–1.6838) from P. aeruginosa isolates recovered in 2005–2010 compared to 2011–2015.

**Gram-positives**

Overall, in vitro susceptibilities for the fluoroquinolones were <90% for both methicillin-susceptible and methicillin-resistant S. aureus and S. epidermidis. No significant difference in MSSA (n = 560) versus MRSA (n = 407) susceptibilities for moxifloxacin versus ciprofloxacin was documented.

Methicillin resistance was >40% for both S. aureus and S. epidermidis and ranged from 36.2% for keratitis (n = 224) to 43.8% for dacryocystitis (n = 73). Multidrug resistance was more likely to occur in MRSA and MRSE isolates [Table 6]. The highest level of nonsusceptibility to the fluoroquinolones among methicillin-susceptible isolates was observed for S. epidermidis (27%).

Levofloxacin remained above 90% susceptible for both S. pneumoniae (100%) and S. viridans (91%). While the
cumulative result for the *S. viridans* group was above 90%, values ranged from 88.8% in period I to 92% for period II.

**Aminoglycosides**

Non-susceptibility among the aminoglycosides (amikacin, gentamicin, and tobramycin) was <20% for all Gram-negative isolates tested during 2011–2015. Gentamicin susceptibility was <90% for all staphylococci excepted for MRSE which declined to < 80%. No significant differences in gentamicin susceptibility rates for *S. aureus* (94.5%, *n* = 1038 vs. 95%, *n* = 967) or *S. epidermidis* (82.5%, *n* = 165 vs. 86%, *n* = 287) were observed between periods. Tobramycin is not recommended for *in vitro* testing of staphylococci. Neither gentamicin nor tobramycin is recommended for *in vitro* testing of *Haemophilus* species and/or streptococcal species.

Susceptibilities for amikacin, gentamicin, and tobramycin were ≥90% for all Gram-negatives isolates tested. There was a significant difference in the susceptibility for gentamicin and tobramycin for both *S. marcescens* and *P. aeruginosa*. Higher susceptibility rates for gentamicin (99%) versus tobramycin (92%), *P* = 0.0024, 95 CI 2.2424–12.3802 to was documented for *S. marcescens*, while the opposite trend was observed for *P. aeruginosa* for both periods (I - 97% vs. 99%, *P* = 0.0019, 95 CI 0.6847—3.4035; II - 96% vs. 100%, *P* < 0.0001, 95 CI = 2.4588 to 5.9009).

**Table 6: Coresistance and trends in methicillin susceptible and methicillin resistant staphylococci**

(a) Trends for *Staphylococcus aureus*, MSSA=methicillin susceptible *S. aureus*, MRSA=methicillin resistant *S. aureus*

| *S. aureus* | Drugs | All ocular 2011-2015 | MSSA (*n*=560) | MRSA (*n*=407) |
|------------|-------|----------------------|----------------|----------------|
|            | n-tested | % susceptible | n-tested | % susceptible |
| Bacitracin  | 68     | 87                  | 42      | 40             |
| Ciprofloxacin | 560   | 86                  | 407     | 19             |
| Clindamycin | 560   | 74                  | 407     | 52             |
| Daptomycin  | 546    | 100                 | 396     | 100            |
| Doxycycline | 263    | 98                  | 168     | 94             |
| Erythromycin | 560   | 59                  | 407     | 8              |
| Gentamicin  | 560    | 99                  | 407     | 91             |
| Levofloxacin | 560   | 88                  | 407     | 19             |
| Linezolid   | 552    | 100                 | 400     | 100            |
| Moxifloxacin | 552   | 89                  | 405     | 20             |
| Tetracycline | 560   | 88                  | 407     | 90             |
| Tigecycline | 550    | 100                 | 402     | 100            |
| Trimethoprim-sulfamethoxazole | 560 | 97 | 406 | 92 |
| Vancomycin  | 560    | 99                  | 406     | 98             |
| Percent MRSA |       |                     |         | 42.10          |

(b) Trends for *Staphylococcus epidermidis*, MSSE=methicillin susceptible *S. epidermidis*, MRSE=methicillin resistant *S. epidermidis*

| *S. epidermidis* | Drug | All ocular 2011-2015 | MSSE (*n*=154) | MRSE (*n*=133) |
|------------------|------|----------------------|----------------|----------------|
|                  | n-tested | % susceptible | n-tested | % susceptible |
| Ciprofloxacin    | 154   | 73                  | 133   | 33             |
| Clindamycin      | 154   | 71                  | 133   | 59             |
| Daptomycin       | 142   | 100                 | 131   | 100            |
| Doxycycline      | 118   | 91                  | 75    | 81             |
| Erythromycin     | 154   | 50                  | 133   | 23             |
| Gentamicin       | 154   | 96                  | 133   | 77             |
| Levofloxacin     | 154   | 73                  | 133   | 33             |
| Linezolid        | 153   | 100                 | 133   | 100            |
| Moxifloxacin     | 153   | 73                  | 133   | 33             |
| Tetracycline     | 154   | 83                  | 133   | 73             |
| Tigecycline      | 149   | 100                 | 132   | 100            |
| Trimethoprim-Sulfamethoxazole | 154 | 84 | 133 | 55 |
| Vancomycin       | 154   | 99                  | 132   | 99             |
| Percent MRSE     |       |                     |         | 46.30          |
Cephalosporins
The first-generation cephalosporins (cefazolin and/or cefaclor) susceptibility was <20% for the staphylococci, Enterobacter species, Serratia species, and Haemophilus species. Greater than 90% susceptibility was observed for Klebsiella species and Proteus species. P. aeruginosa and Stenotrophomonas maltophilia are intrinsically resistant to the first generation cephalosporins.

Ceftazidime nonsusceptibility ranged from 1% to 3% with the highest rate of extended spectrum beta-lactamases being documented for Klebsiella species. Susceptibility for the staphylococci was < 60%.

Ampicillin/penicillins
There was a high rate of resistance to penicillin among the streptococci. Penicillin nonsusceptible S. pneumoniae rate using nonmeningitis interpretation was 47%. Penicillin susceptibility for the S. viridans group was 81%. Ampicillin susceptibility for the Haemophilus species was <80% for isolates recovered during 2011–2015.

Carbapenem (imipenem/meropenem) nonsusceptibility among the Enterobacteriaceae was rare. Rates for P. aeruginosa during the last 5 years was 3% (n = 461/473).

Fluoroquinolone monotherapy provided less than 80% coverage (levofloxacin - 77.1%) for gram positive isolates. Combination therapy with a fluoroquinolone and vancomycin coverage was 99.1% (vancomycin and levofloxacin) or (98.9%) vancomycin and ciprofloxacin. Vancomycin plus gentamicin coverage was 98.3%.

Our corneal isolates differed from those recovered from KKESH. No moxifloxacin resistance was documented for KKESH S. aureus isolates (n = 237, 100%). The rate for Miami corneal S. aureus isolates was 55% (n = 225). This 45% difference was significant (P < 0.0001, 95 CI 38.2037–51.7519).

Antibiotic Resistance Monitoring in Ocular Microorganism Study
Table 7 compares fluoroquinolones, gentamicin, vancomycin, and/or imipenem general susceptibility results for S. aureus, CoNS, and P. aeruginosa collected from 2009 to 2013 versus the same isolates from the cumulative ARMOR study.

In general, there were significant differences in empirical fluoroquinolone and aminoglycoside coverage for the top three ocular pathogens (CoNS, S. aureus, and P. aeruginosa) between the Miami and the ARMOR isolates. Collectively, the coverage for Miami was 74% versus 65.9% for ARMOR (P < 0.0001, 5.3674–10.8042) for ciprofloxacin and 95.9% versus 84.2% for aminoglycosides (gentamicin/tobramycin), (P < 0.0001, 9.9925–13.3974).

Individually, different, but not significant differences in fluoroquinolones susceptibilities for MSSA and/or MRSA isolates were documented between the two studies. Higher susceptibility rates were observed among Miami MSSA isolates, range (87%–89%) compared to those from the ARMOR study (85.8%–88%). MRSA rates were slightly higher, but not significantly for Miami versus ARMOR (43.6% vs. 42.2%) among isolates collected during 2009–2013. No difference in rates (42.2% vs. 42.1%) was observed for 2011–2015.

Fluoroquinolone susceptibilities for MRSA were <30% for both studies.

There were no significant differences in fluoroquinolones susceptibilities for Miami isolates collected during 2009–2013 versus those collected during 2011–2015.

Susceptibilities for the fluoroquinolones for isolates recovered from the conjunctiva (n = 234) during 2009–2013 were distinct, but not significantly different than MSSA or MRSA isolates from the general ARMOR study. Corneal isolates were both distinct and significantly lower for all three fluoroquinolones. A >4-fold difference was observed for ciprofloxacin, 4.4×, 17.7%, P < 0.0001 (95 CI 10.1711–22.9450), levofloxacin, 4.6×, 18.9%, P < 0.0001 (95 CI 11.1059–24.5509) and moxifloxacin, 4.6×, 20.3%, P < 0.0001 (95 CI 12.3865–25.8800).

A significant difference was documented for moxifloxacin when comparing S. epidermidis isolates from Miami (n = 150, 33.3%) versus CoNS ARMOR isolates (n = 992 67.7%) (P < 0.0001, 95 CI 25.7122–42.4195). Nonsusceptible trends for the aminoglycosides were slightly higher, but not significant for Miami isolates (17.3% vs. 15%).

No significant differences were observed for CoNS in the Miami versus ARMOR study during (2011–2015) with the exception of lower susceptibility profile for moxifloxacin (58% vs. 65%, P = 0.0318, 95 CI 0.3425–13.2072). Methicillin resistance was 44% (n = 130/295) for BPEI isolates versus 49.7% (n = 493/992) for the ARMOR study. This difference was not significant (P = 0.0856).

Vancomycin susceptibilities were 100% for all Gram-positive isolates for both time periods.
P < 0.0001 (95 CI 2.3846–8.4684 in 2009–2013 and highest for levofloxacin during 2011–2015, [99% vs. 93.1%], 5.9%,  

No significant differences were observed for fluoroquinolones susceptibility among conjunctival P. aeruginosa isolates versus isolates in the ARMOR study. Significant differences and higher susceptibilities were observed for Miami P. aeruginosa corneal isolates for both ciprofloxacin (6.4%,  P < 0.0001, 95 CI 3.1577–10.2405) and levofloxacin (7.4%,  P < 0.00001, 95 CI 4.3335–11.1585). Eighty-one percent of the indefinable (n = 216) P. aeruginosa isolates from the ARMOR study were from the cornea.[11] BPEI data for 2011-2015 mirrored these results. Aminoglycoside susceptibility (gentamicin-Miami, tobramycin-ARMOR) profiles were >90% for all MSSA and MRSA isolates from Miami with significantly higher rates for both groups compared to ARMOR. MSSA, (98.5% vs. 95.6%,  P = 0.0055, 95 CI 0.6995–4.5573) and MRSA (90.9% vs. 55.8%),  

There was a 32.1% difference in aminoglycoside susceptibility for isolates from the conjunctiva (87.8% vs. 55.8%,  P < 0.0001, 95 CI 23.0648–39.7981. Tobramycin susceptibilities were distinct and significantly higher for isolates from Miami versus those in the ARMOR study. The difference was 2.9% ( P < 0.0001, 95 CI 1.2586–5.1976) in 2009–2013 and up to 7.7% in 2011–2015 ( P < 0.001, 95 CI 5.1771–10.8127).
No significant differences were documented for *P. aeruginosa* isolates to ciprofloxacin among isolates corneal from KKESH \((n = 123, 95\% )\) versus isolates from the ARMOR study \((n = 389, 92.3\% )\).

**Discussion**

Both culture-independent and culture-dependent methods identify a diversity of microorganisms at the ocular surface in health and disease.\(^{[12,15]}\) The top pathogens remain *S. aureus*, *S. pneumoniae*, CoNS, *H. influenzae*, *P. aeruginosa*, *Chlamydia trachomatis*, *C. albicans*, *Fusarium* species, and *Aspergillus* species. In general, now including Miami, Gram-positive bacteria remain the most common microbial agents recovered from ocular infections worldwide.\(^{[1,16]}\)

A 2011 report by Iwalokun *et al.* identified *S. aureus* as the most common bacteria pathogen among 155 isolates recovered from 83 conjunctiva samples collected during an 8-month period (February–September 2010). Gram-positive isolates constituted 72% of the isolates. *P. aeruginosa* was the most frequent Gram-negative pathogen \((n = 15, 9.7\% )\).\(^{[9]}\)

Worldwide, the etiology and frequency in microbial keratitis is greatly influenced by climate and patient population. Bacterial pathogens are the most common in industrialized countries, while fungi and parasites are more frequent in developing nations.\(^{[17-19]}\)

Staphylococci species and *S. pneumoniae* are among the leading bacteria cause of microbial keratitis. Gram-negative isolates, predominately *P. aeruginosa*, may be increasing and have been reported more frequently from Miami, East Kent, and Saudi Arabia.\(^{[20,21]}\)

Reports from the Middle East and Africa are scarce. A recent report by Burton *et al.* identified microbial keratitis as a significant burden of disease and cause of blindness in East Africa.\(^{[19]}\) Prevalence estimates range from 113/100,000 to 789/100,000. Filamentous fungi were the most common pathogens, compounded by underlying HIV diseases. Gebremariam in a small series of 24 isolates documented *P. aeruginosa* (41.7%) as the most common pathogen.

Al-Dhaheri *et al.* documented staphylococci (91.4%) as the leading cause in a recent series documenting trends in keratitis from KKESH from 2011 to 2014. *P. aeruginosa* was recovered in <10% of isolates. The diversity and spectrum of pathogens might reflect the dry climate and the small number of contact lens wearers.\(^{[6]}\)

Data from Malaysia documented *S. aureus* as the predominant pathogen;\(^{[17]}\) however, recovery rate for Gram-negatives was 57.4% versus 46.6% for Gram-positive isolates. *P. aeruginosa* was the top Gram-negative isolate at 16.0%. No CoNS were recovered in this series.\(^{[7]}\)

Kowalski (2013) identified *S. aureus* and *S. pneumoniae* as the top pathogens recovered from samples submitted to the Campbell laboratory over a 19-year period.\(^{[4]}\) Gram-negative isolates were recovered in less than a third of the isolates (30%). This was significantly different than current and historical trends from Miami and might demonstrate the influence of geography and climate on pathogen recovery.

Gram-negative isolates remain the top bacteria pathogens (42.7% vs. 30.7%) in the current Miami series. There was a significant decline, however, in the number and percent of *P. aeruginosa* recovered between earlier years (2005–2010) compared with frequency and numbers for the later 5 years (2011–2015).

**Endophthalmitis**

Gram-positive isolates, predominantly CoNS, remain the most common isolates recovered from endophthalmitis.\(^{[22-24]}\) The spectrum and diversity is expanding and varies dependent on endophthalmitis category.

**Susceptibility tests**

Comparing susceptibility results across cities and nations are difficult. Data are hindered by testing standards, interpretation, methodology, and expertise. We limited our *in vitro* comparison to the ARMOR cumulative study (2009–2013) and data from reports with similar methodology (MIC breakpoints).

**Fluoroquinolones**

The fluoroquinolones remain the most frequently dispensed class of topical antibiotics in the treatment ocular infections.\(^{[1,2,25]}\) Susceptibility is driven by availability and frequency of use. In areas such as the United States, Brasil, and India, where use is high, emerging and nonsusceptible rates are as high as 70% for the staphylococi (both methicillin sensitive and methicillin resistant) and ranged from 1% to 29% for *P. aeruginosa* and the Enterobacteriaceae.\(^{[26-28]}\)

In regions where use is limited and/or minimal, Australia, Africa, and the Middle East, rates are as low as 1%.\(^{[6,19,29]}\)

Cross resistance among the fluoroquinolones are high, but reported lower minimal inhibitory concentrations are observed for besifloxacin.\(^{[26,30,31]}\) In a study by Miller *et al.*, besifloxacin MICs was 2-4 times lower than ciprofloxacin, levofloxacin, and moxifloxacin for fluoroquinolone susceptible and or resistant staphylococcal ocular isolates.\(^{[32]}\) Similar results are observed for both *S. aureus* and CoNS in the cumulative ARMOR surveillance data and the original ARMOR study.\(^{[31]}\)
Differences in the current Miami study and the ARMOR 5-year report was “bug and drug” specific. This study confirmed the continued rise in nonsusceptibility among the staphylococci (both methicillin susceptible and resistant) among the fluoroquinolones and the associated multidrug co-resistance. Emerging fluoroquinolone resistance among the alpha hemolytic streptococci and ceftazidime resistance among P. aeruginosa is worrisome.

In a recent surveillance study involving seven European countries (France, Germany, Italy, Poland, Slovak Republic, Spain, and the UK, January–August 2011), susceptibility results for S. aureus ocular isolates (n = 252) ranged from 0% to 31.1% for moxifloxacin and 5.3%–31.1% for ciprofloxacin. The average rate was 14.7% for ciprofloxacin and 12.7% for moxifloxacin.

Among the countries who submitted 30 or more isolates, the lowest fluoroquinolone resistant or nonsusceptible rates were documented for France (n = 53, 7.5% for ciprofloxacin and moxifloxacin) and the UK (n = 46, 8.7% for ciprofloxacin and 6.5% for moxifloxacin). Highest rates were documented in isolates collected from Germany (n = 45), with a 31.1% for both drugs [33]. Methicillin resistance was only 9.1% for this group with the highest rates reported for Germany at 20.0%. These rates were significantly lower than those reported in the current study and/or those highlighted in the ARMOR study.

Methicillin resistance among coagulase-negative isolates (n = 313) averaged 55%. The highest rates were observed in Spain at 75% (n = 32) and lowest in the UK at 48% (n = 50). Fluoroquinolone resistance ranged from 6.0% to 48.5%.

A total of 70, S. pneumoniae, 64 H. influenzae, and 39 P. aeruginosa isolates were submitted during the 20 months test period. All isolates were 100% susceptible to moxifloxacin and/or ciprofloxacin, except P. aeruginosa. Nonsusceptibility to ciprofloxacin among P. aeruginosa in the European study was 10.8%. This rate was 5-fold higher than the 2% rate reported in this study and 3-fold higher than for isolates in the ARMOR study.

Results for S. pneumoniae and H. influenzae were in line with the results for the current and ARMOR studies. Comparative result should be viewed, however, with caution due to the low numbers in the European study.

Aminoglycosides

Worldwide, susceptibility to the aminoglycosides is also impacted by use, availability, and disease profile. In areas where fluoroquinolone monotherapy has supplanted traditional use of the aminoglycosides with a cefazolin for dual therapy, in vitro susceptibilities rates are higher [34].

Sanfilippo et al. documented differences in nonsusceptibility for gentamicin and tobramycin among S. aureus, CoNS, and P. aeruginosa in a recent surveillance study from Europe [33]. Nonsusceptibility rates for gentamicin among the staphylococci ranged from 2.0% to 28.4%, with highest rates for coagulase-negative isolates. In contrast, the rates for tobramycin against the same isolates ranged from 9.5% to 39.9%, again with rates highest among the coagulase-negative strains. Rate for P. aeruginosa was 2.7% for both gentamicin and tobramycin.

Cephalosporins

Cephalosporins remain treatment options for treating bacterial conjunctivitis, keratitis, and endophthalmitis. In areas with high MRSA, MRSE, and MRCoNS rates, their use are limited. Nonsusceptibility among the cephalosporins (cefazolin, cefuroxime, and ceftazidime) is correlated with methicillin resistance. Isolates resistant to methicillin confer resistance to all beta lactams [25,39].

The second-generation cephalosporins have varying activity against members of the Enterobacteriaceae and the streptococci and are ineffective against P. aeruginosa [25].

Ceftazidime susceptibility among Gram-negatives retains >95% for Gram-negative Enterobacteriaceae and P. aeruginosa in this study.

Vancomycin

Vancomycin susceptibility remains >95% for the most common Gram-positive ocular isolates with ranges from 99% to 100%. No true vancomycin-resistant S. aureus and/or S. epidermidis have been documented among ocular isolates in any of the surveillance studies in the United States. Reports of VRSA using disk diffusion are inappropriate and unreliable. Disk diffusion is not an acceptable method for detection of vancomycin intermediate and or resistant isolates.

Vancomycin-resistant enterococci have been recovered from cases of posttraumatic endophthalmitis. The majority of these have been Enterococcus faecalis and/or Enterococcus faecium associated with previous ocular surgery and immunosuppression. Hillier et al. describes a case of Enterococcus gallinarum following trauma [38].

Limitations of this study include its retrospective nature and current issues of patient sampling frequency, in vitro susceptibility testing and interpretation. Our center is a tertiary referral center and isolates and susceptibility profiles may reflect recovery of pathogens with a different pathology and susceptibility profile. The use of the Clinical Laboratory Standards Institute susceptibility breakpoints for serum and tissues may not accurately.
reflect the pharmacokinetics and pharmacodynamics of antibiotics in ocular tissues and fluids.

Spectrum and diversity of ocular pathogens along with their in vitro susceptibility patterns are influenced by climate, geographic region, patient populations, and prior antibiotic exposure. These factors may compromise extrapolation and application of these and similar surveillance data to other regions.

**Conclusion**

The spectrum and diversity of ocular pathogens have not changed significantly, over the last 10 years. What has changed is the declining rate of the in vitro efficacy of fluoroquinolone as coverage for the most common ocular pathogens, worldwide.

Fluoroquinolone monotherapy as standard therapy for common ocular infections should be reassessed. Ophthalmologists must become proactive and join the crusade to develop practical, prudent, and collaborative efforts in antibiotic stewardship for improved patient safety and optimal visual outcomes.

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**Conflicts of interest**

There are no conflicts of interest.

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