

Antimicrobial Resistance and Ophthalmic Antibiotics

1-Year Results of a Longitudinal Controlled Study of Patients Undergoing Intravitreal Injections

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Objective: To determine antibiotic susceptibility patterns of conjunctival flora from patients undergoing intraocular injection for choroidal neovascularization after repeated exposure to ophthalmic antibiotics.

Methods: We conducted a randomized, controlled, longitudinal study of 48 eyes of 24 patients undergoing unilateral intraocular injection for choroidal neovascularization. Bilateral conjunctival cultures from the treated eye and untreated (control) fellow eye were taken at baseline and after each injection (before the application of povidone-iodine). Patients were randomized to ofloxacin, 0.3%; azithromycin, 1%; gatifloxacin, 0.3%; or moxifloxacin hydrochloride, 0.5% and used only their assigned antibiotic after each injection. Bacterial isolates were tested for antibiotic susceptibility to 16 different antibiotics, and analysis of bacteria DNA was performed using pulse-field gel electrophoresis. Main outcome measures included changes in antibiotic susceptibility patterns of conjunctival flora after 1 year.

Results: Coagulase-negative staphylococci (CNS) cultured from eyes repeatedly exposed to fluoroquinolone

antibiotics demonstrated significantly increased rates of resistance to older-generation ($P = .002$) and newer-generation ($P < .01$) fluoroquinolones. In contrast, CNS isolated from azithromycin-exposed eyes demonstrated significantly increased resistance to macrolides (95%; $P < .001$) and decreased resistance to older-generation ($P = .03$) and newer-generation ($P < .001$) fluoroquinolones. There were significant increases in multiple-drug resistance of CNS isolated from treated eyes, with 81.8% and 67.5% of isolates resistant to at least 3 ($P = .01$) and at least 5 ($P = .009$) antibiotics, respectively.

Conclusion: Repeated exposure of conjunctival flora to ophthalmic antibiotics selects for resistant strains.

Application to Clinical Practice: Repeated use of ophthalmic antibiotics after intraocular injection promotes the emergence of antimicrobial resistance.

Trial Registration: clinicaltrials.gov Identifier: NCT00831961

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AGE-RELATED MACULAR DEGENERATION is the leading cause of blindness among individuals older than 65 years in the United States and currently affects more than 8 million Americans.¹ Monthly intraocular injection of ranibizumab (Lucentis; Genentech, South San Francisco, California) or off-labeled use of bevacizumab (Avastin; Genentech) has become the standard of care for the treatment of neovascular age-related macular degeneration,^{2,3} and recent clinical trials⁴⁻⁶ have demonstrated the efficacy of these agents in treating macular edema secondary to retinal vein occlusions and diabetes mellitus. Consequently, the number of intraocular injections performed will continue to increase given the aging of the population and expanding applications.⁷

Endophthalmitis is the most severe complication after intraocular injection and results in substantial morbidity.⁸ If current trends continue, intraocular injection may

become the most common cause of endophthalmitis treated in clinical practice. Consequently, most treating eye specialists routinely prescribe ophthalmic antibiotics after each injection.⁹ Repeated exposure of ocular flora, however, may select for resistant bacterial strains and cultivate “superbugs” with multiple-drug resistance that may considerably affect the treatment of ocular infections.



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The Antibiotic Resistance of Conjunctiva and Nasopharynx Evaluation (ARCANE) Study is a prospective, randomized, longitudinal study designed to determine changes in antibiotic resistance after repeated exposure of ocular and nasopharyngeal flora to ophthalmic antibiotics. Baseline resistance patterns of our study cohort have already been published.¹⁰ Herein

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Table. Baseline Demographic Characteristics of 24 Patients Receiving Unilateral Intraocular Injection for Choroidal Neovascularization^a

Characteristic	Azithromycin (n=6)	Ofloxacin (n=6)	Gatifloxacin (n=6)	Moxifloxacin (n=6)
Age, mean (range), y	75 (42-86)	75 (64-83)	69 (49-86)	82 (68-97)
Indications for treatment, No. (%)				
AMD	5 (83)	5 (83)	4 (67)	6 (100)
Myopic degeneration	0	1 (17)	1 (17)	0
Ocular histoplasmosis	0	0	1 (17)	0
Idiopathic	1 (17)	0	0	0
Previous surgical procedure in treated eye, No. (%)				
Cataract surgery	4 (67)	3 (50)	3 (50)	3 (50)
Glaucoma surgery	0	0	0	0
Retinal surgery	0	0	0	0
Corneal surgery	0	0	0	0
Refractive surgery	0	1 (17)	0	0

Abbreviation: AMD, age-related macular degeneration.

^aPercentages have been rounded and may not total 100.

we report long-term results of antibiotic susceptibility and resistance of conjunctival flora after 1 year of repeated exposure to ophthalmic antibiotics in our cohort of patients undergoing serial unilateral injections for choroidal neovascularization.

METHODS

The Vanderbilt University institutional review board approved this study, and all participants gave informed consent before enrollment. The study adhered to all aspects of the Health Insurance Portability and Accountability Act.

Inclusion and exclusion criteria of the ARCANE Study have been previously published.¹⁰ In brief, all adult patients 18 years or older with choroidal neovascularization due to age-related macular degeneration or other causes in 1 eye only and planned treatment with intraocular injection were eligible for inclusion. Exclusion criteria consisted of a previous intraocular injection in either eye, long-term use of ophthalmic medication, contact lens wear, ocular surgery, use of ophthalmic medications in either eye or ocular infection within the past 3 months, use of systemic antibiotics within 30 days, and use of eye-drops (eg, artificial tears, saline solutions, and vasoconstrictors) in either eye within 3 days of enrollment.

As part of the study protocol, all enrolled patients received 4 consecutive monthly intraocular injections and follow-up treatment as needed. The study follow-up was for 1 year, and patients underwent reculturing of specimens after each injection. Patients were assigned by permuted block randomization to 1 of the following 4 ophthalmic antibiotics: ofloxacin, 0.3% (Ocuflox; Akorn Inc, Somerset, New Jersey); azithromycin, 1% (AzaSite; Inspire Pharmaceuticals, Inc, Durham, North Carolina); gatifloxacin, 0.3% (Zymar; Allergan Pharmaceuticals, Irvine, California); or moxifloxacin hydrochloride, 0.5% (Vigamox; Alcon, Fort Worth, Texas), and used only their assigned antibiotic for the duration of the study. Fluoroquinolone (ofloxacin, gatifloxacin, and moxifloxacin) and macrolide (azithromycin) antibiotics were chosen because they are frequently used systemically to treat respiratory infections; thus, emerging resistance of flora to these antibiotic classes has important clinical implications.

Before the application of any ophthalmic medication (including povidone-iodine), conjunctival cultures of both eyes were taken using a culture collection and transport system (BBL CultureSwab; Becton, Dickinson and Company, Sparks, Maryland) in accordance with manufacturer instructions. Conjunctival cul-

tures were obtained from the lower fornix in standardized fashion, with every effort made to minimize contamination from the lids, lashes, or skin. Conjunctival culture swabs were inoculated onto 5% sheep blood and chocolate agar plates and incubated with 5% carbon dioxide. All culture plates were incubated at 37°C for 3 days. Cultures were deemed positive if 1 or more colony-forming units was observed.

All intraocular injections were performed in standard fashion after obtaining informed consent. Briefly, subconjunctival or topical anesthesia was administered and povidone-iodine, 5% (Betadine), was applied to the ocular surface and lids. Povidone-iodine was reapplied and, immediately afterward, drug was injected approximately 3.5 mm from the limbus using a 32-gauge needle. Patients were administered 1 drop of their assigned antibiotic and carefully instructed to continue using their assigned antibiotic on the day of their injection and for the next 4 consecutive days. Ofloxacin, 0.3%; gatifloxacin, 0.3%; and moxifloxacin hydrochloride, 0.5%, were administered as 1 drop 4 times daily; azithromycin, 1%, was administered as 1 drop twice daily. All patients were given written instructions on the use of their antibiotic after each treatment and also new samples of their antibiotic to ensure adherence and to reduce the possibility of contamination.

After baseline cultures were taken (visit 0), the first injection was administered, and all patients returned in 4 weeks (visit 1), 8 weeks (visit 2), 12 weeks (visit 3), and 16 weeks (visit 4). At visits 1, 2, and 3, patients underwent reculturing and reinjection and then resumed use of their assigned ophthalmic antibiotic. At visit 4, all patients underwent reculturing, but continued treatment was determined on an individual basis. If patients underwent reinjection at visit 4, then they resumed use of their assigned antibiotic and underwent reculturing at their next appointment (visit 5). Some study participants received monthly injections throughout the year of follow-up and thus had as many as 13 cultures (baseline plus visits 1-12).

To test resistance, the Kirby-Bauer disc diffusion technique¹¹ was conducted in strict accordance with guidelines of the National Committee for Clinical Laboratory Standards.

The following antibiotics were tested on all cultures with positive results: a combination of amoxicillin and clavulanate potassium, cefazolin sodium, ceftiofur sodium, erythromycin, azithromycin, ofloxacin, levofloxacin, gatifloxacin, moxifloxacin, a combination of trimethoprim and sulfamethoxazole, rifampin, gentamicin sulfate, doxycycline hyclate, linezolid, clindamycin hydrochloride, and vancomycin hydrochloride. The diameter of the zone of inhibition was recorded and used to

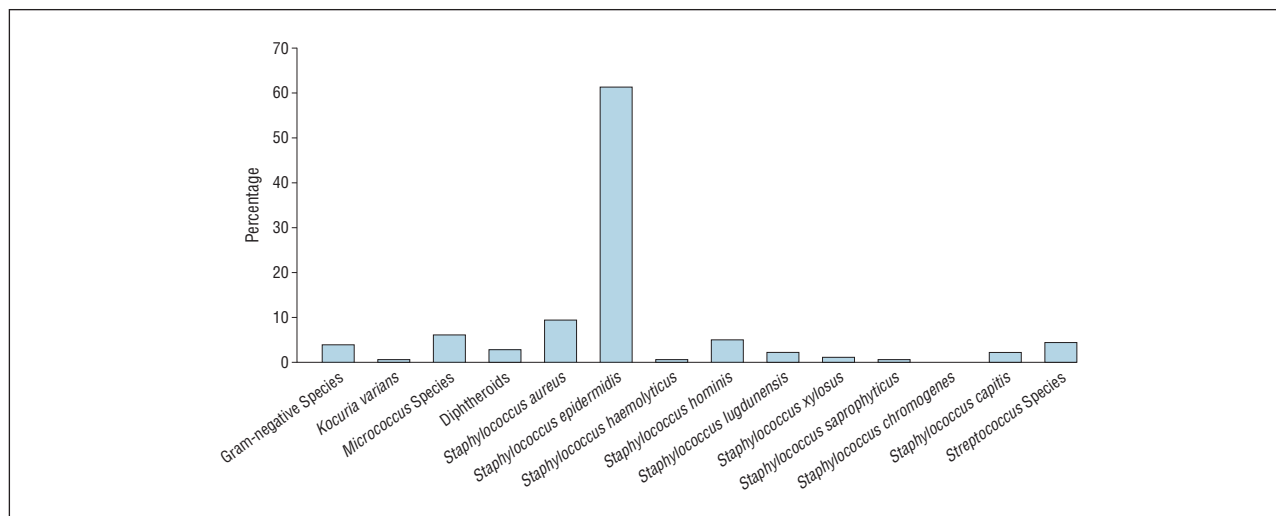


Figure 1. Different bacteria species cultured from untreated (control) eyes from visit 1 to the final visit (excludes baseline). *Staphylococcus epidermidis* accounted for 111 of 181 total isolates (61.3%).

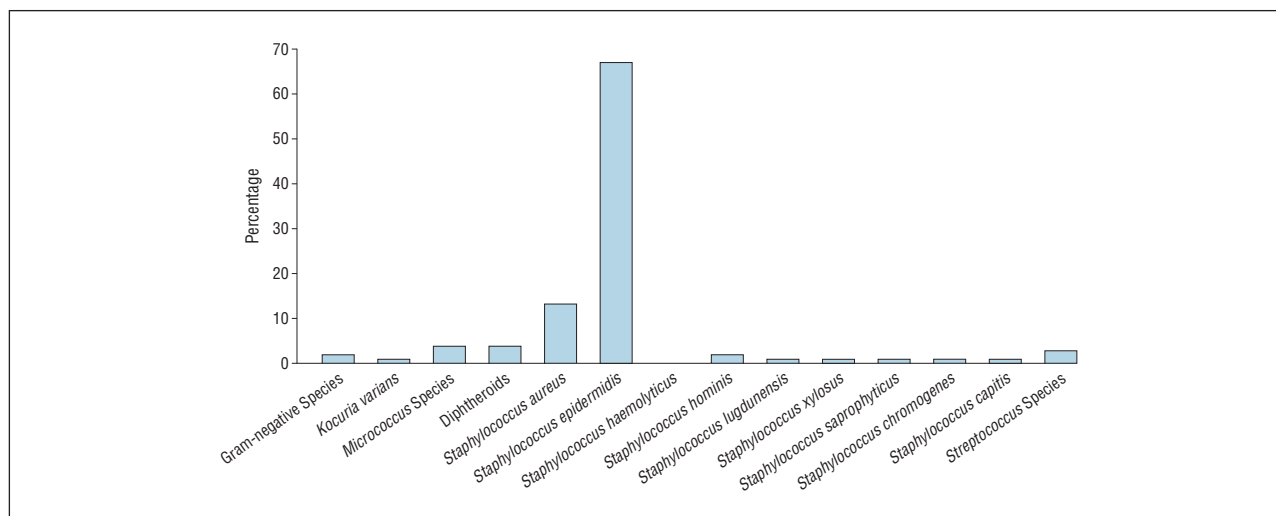


Figure 2. Different bacteria species cultured from treated eyes from visit 1 to the final visit (excludes baseline). *Staphylococcus epidermidis* accounted for 71 of 106 total isolates (67.0%).

determine susceptibility. Resistance to cefoxitin was considered equivalent to methicillin resistance.¹²

Identification of bacteria strains was performed by Gram staining and testing for the presence or absence of catalase and coagulase/agglutination. A *Staphylococcus* identification kit (API Staph kit; bioMérieux, Hazelwood, Missouri) was used to further speciate coagulase-negative staphylococci (CNS).

Genomic analysis was performed using the well-established technique of pulse-field gel electrophoresis after restriction digest with *Sma*I (ARUP Laboratories, Salt Lake City, Utah). Pulse-field gel electrophoresis involves use of restriction enzymes that selectively cleave (fragment) DNA at locations unique to each strain of bacteria, resulting in fragments of different lengths. The DNA fragments are then run on a gel to create a "fingerprint" of each strain of bacteria. Relatedness was based on criteria developed by Bannerman et al¹³ and Tenover et al.¹⁴

Descriptive statistics including means were calculated for case characteristics. Group comparisons were performed with the Fisher exact test. $P < .05$ was considered significant.

RESULTS

Baseline and demographic characteristics of the study cohort are summarized in the **Table**. A total of 24 patients were enrolled from February 1, to November 30, 2009, with a total of 6 patients randomized to each antibiotic. The average age of the cohort was 75 (range, 42-97) years. No patient had a history of intraocular injection in either eye. Most patients (20 [83%]) were undergoing treatment for age-related macular degeneration. The number of injections per patient during the course of 1 year ranged from 3 to 12. One patient died after the third injection. The remaining 23 patients all received 4 injections per study protocol and had a minimum of 5 cultures taken (baseline and 4 after injection). One patient elected to not receive additional treatment and 3 patients did not require additional treatment during the year of follow-up. The remaining 19 patients continued to re-

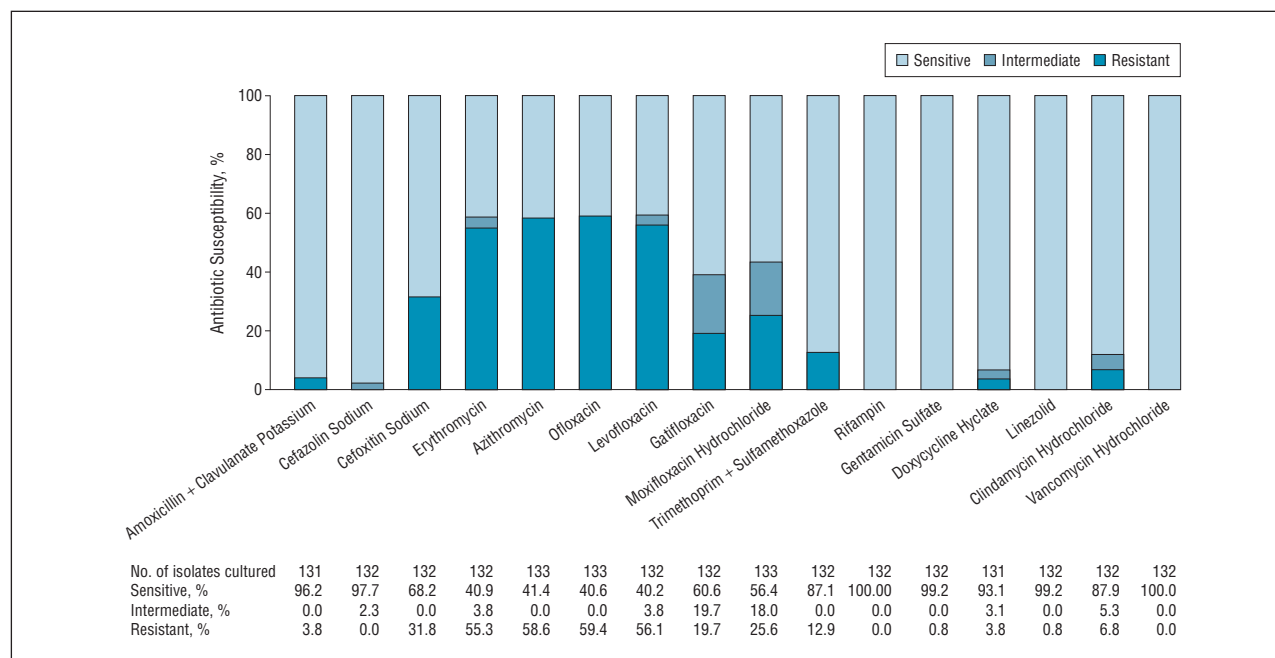


Figure 3. Antibiotic susceptibility of 133 coagulase-negative staphylococcus (CNS) isolates from the conjunctiva of control eyes from visit 1 to the final visit (excludes baseline). Antibiotic susceptibility was not significantly different compared with CNS cultured at baseline. Percentages have been rounded and might not total 100.

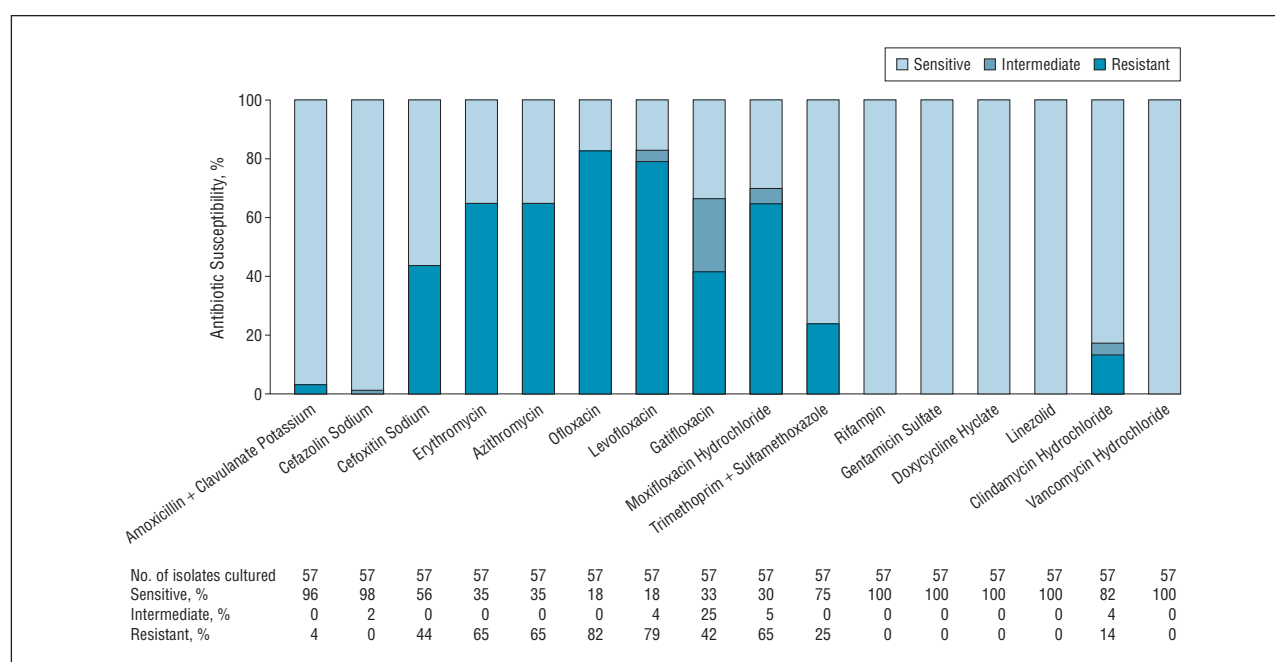


Figure 4. Antibiotic susceptibility of 57 coagulase-negative staphylococcus (CNS) isolates from the conjunctiva of fluoroquinolone-treated eyes from visit 1 to the final visit (excludes baseline). There was a significantly increased rate of resistance to older-generation (ofloxacin and levofloxacin [$P=.002$]) and newer-generation (gatifloxacin and moxifloxacin [$P<.01$]) fluoroquinolones when compared with control CNS isolates. Percentages have been rounded and might not total 100.

ceive injections, underwent reculturing, and resumed use of their assigned antibiotic after each treatment.

Fifty-seven bacteria were isolated at baseline from 48 eyes of 24 patients.¹⁰ A total of 181 bacteria were subsequently isolated from untreated (control) eyes during follow-up (visit 1 to the final visit). The most common bacteria was *Staphylococcus epidermidis* representing 61.3% of isolates, followed by *Staphylococcus aureus* (9.4%) and *Micrococcus* species

(6.1%; **Figure 1**). In contrast, only 106 bacteria (roughly 41% less than control eyes) were cultured in total from treated eyes during follow-up (**Figure 2**). Overall, *S epidermidis* (67.0%) and *S aureus* (13.2%) were the 2 most commonly isolated bacteria in treated eyes, but *S epidermidis* was more frequently isolated in azithromycin-exposed eyes (20 of 22 isolates [90.9%]) in contrast to fluoroquinolone-exposed eyes (51 of 84 isolates [61.0%]; $P=.01$), and *S aureus* was more

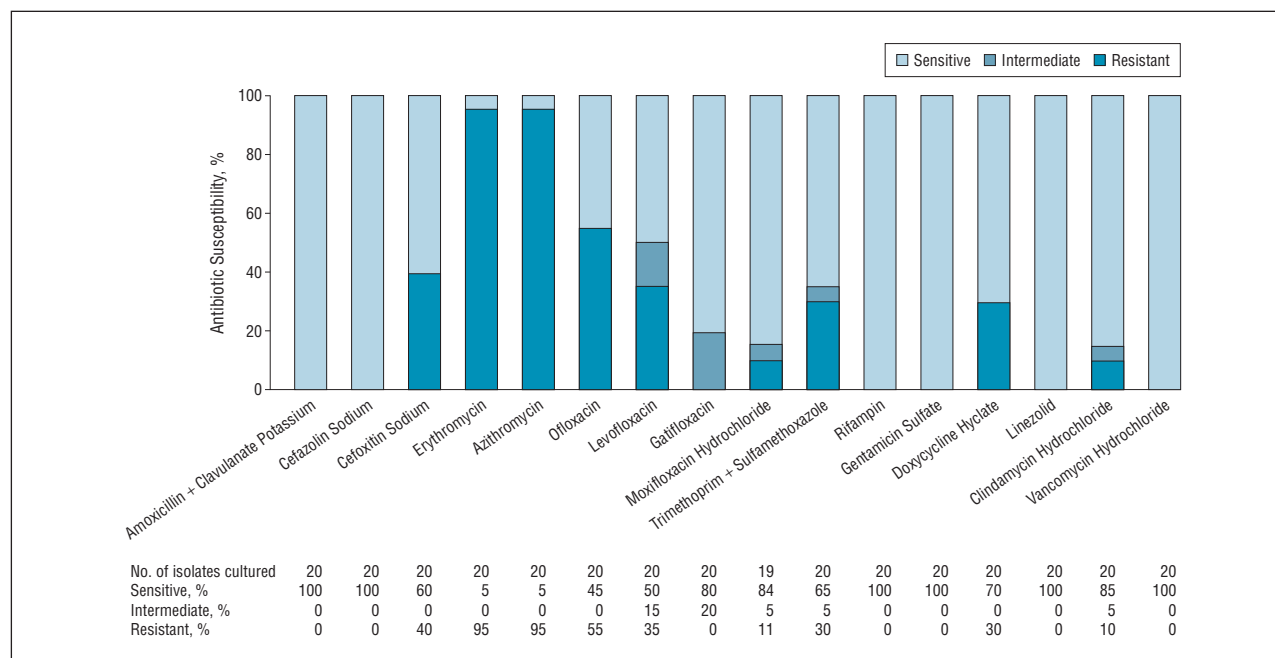


Figure 5. Antibiotic susceptibility of 20 coagulase-negative staphylococcus (CNS) isolates from the conjunctiva of azithromycin-treated eyes from visit 1 to the final visit (excludes baseline). There were significantly increased rates of resistance to erythromycin and azithromycin ($P < .001$) when compared with control CNS isolates and significantly decreased resistance to older- and newer-generation fluoroquinolones when compared with fluoroquinolone-exposed CNS isolates.

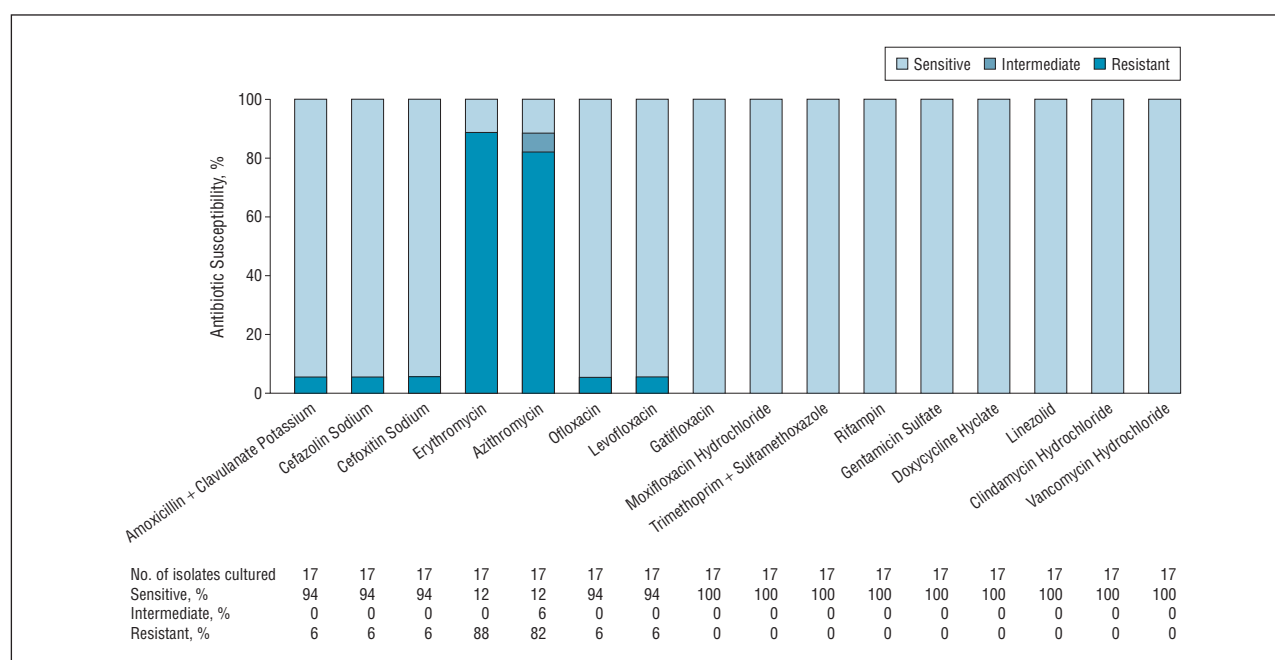


Figure 6. Antibiotic susceptibility of *Staphylococcus aureus* isolated from the conjunctiva of control eyes from visit 1 to the final visit (excludes baseline). There was no observed resistance to fourth-generation fluoroquinolones.

frequently recovered in fluoroquinolone-exposed eyes (13 isolates [15.5%]) than in azithromycin-exposed eyes (1 isolate [4.5%]).

A total of 133 of the 181 isolates (73.4%) cultured from control eyes during follow-up were CNS. The antibiotic susceptibility of these CNS isolates are shown in **Figure 3**. Resistance to erythromycin and azithromycin was 55.3% and 58.6%, respectively, and resistance to ofloxacin and levofloxacin was 59.4% and 56.1%, respectively. Resistance to gatifloxacin and moxifloxacin was 19.7% and

25.6%, respectively. Overall, these 133 CNS isolates did not demonstrate significant differences in fluoroquinolone or macrolide resistance when compared with CNS isolated at baseline.

A total of 77 of the 106 isolates (72.6%) cultured from treated eyes during follow-up were CNS. Fifty-seven of these CNS isolates were from eyes exposed to fluoroquinolone antibiotics and demonstrated significantly increased rates of resistance to fluoroquinolones when compared with control CNS isolates (**Figure 4**). Resistance

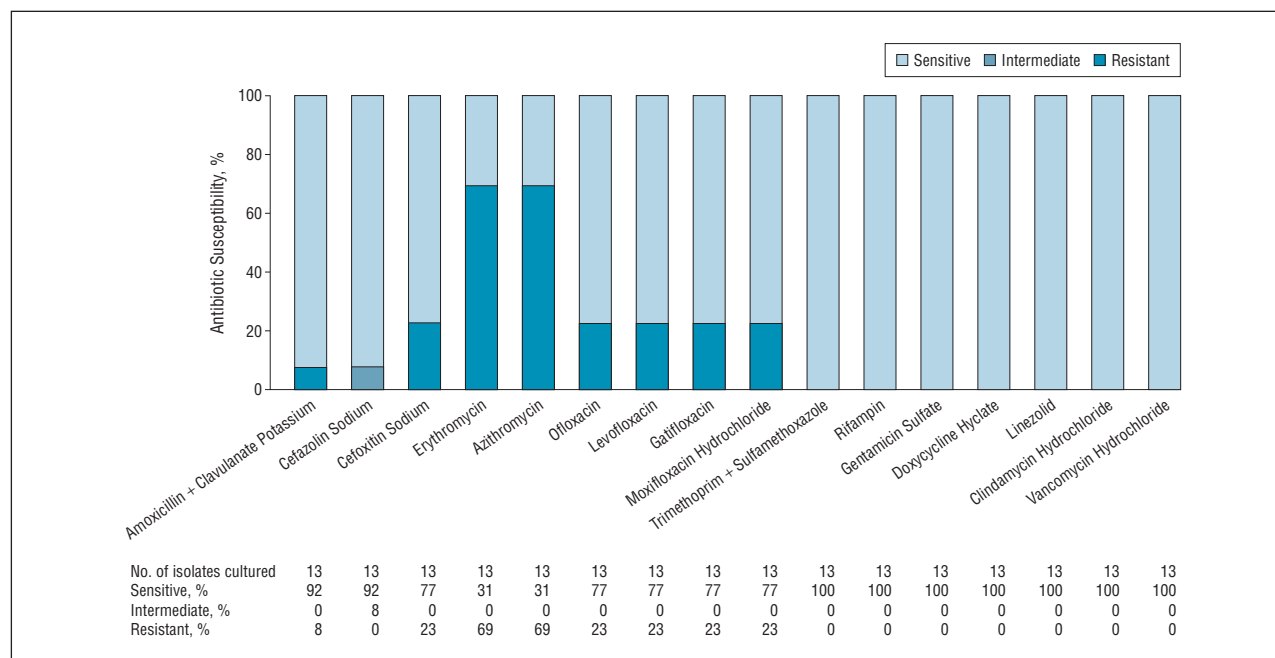


Figure 7. Antibiotic susceptibility of *Staphylococcus aureus* isolated from the conjunctiva of fluoroquinolone-treated eyes from visit 1 to the final visit (excludes baseline). There was a trend of increased resistance (23%) to both older- and newer-generation fluoroquinolones and methicillin (cefoxitin) resistance.

to ofloxacin and levofloxacin was 82% ($P=.002$) and 79% ($P=.002$), respectively, and resistance to gatifloxacin and moxifloxacin was 42% ($P=.004$) and 65% ($P<.001$), respectively. In contrast, 20 CNS isolates from eyes exposed to azithromycin demonstrated significantly increased resistance to macrolides (95%; $P<.001$) when compared with control CNS isolates and decreased resistance to ofloxacin (55%; $P=.03$), levofloxacin (35%; $P<.001$), gatifloxacin (0%; $P<.001$), and moxifloxacin (11%; $P<.001$) when compared with fluoroquinolone-exposed CNS isolates (**Figure 5**).

A total of 17 isolates cultured from control eyes during follow-up were *S aureus*. The antibiotic susceptibility of these 17 isolates is shown in **Figure 6**. Resistance to erythromycin and azithromycin was 88% and 82%, respectively, and resistance to ofloxacin and levofloxacin was 6% each. There was no observed resistance to gatifloxacin or moxifloxacin. Overall, these 17 isolates did not demonstrate significant differences in fluoroquinolone or macrolide resistance when compared with *S aureus* isolated at baseline. In contrast, 13 *S aureus* isolates were cultured during follow-up from eyes exposed to fluoroquinolones (**Figure 7**) and demonstrated a trend toward increased resistance to ofloxacin (23%; $P=.30$), levofloxacin (23%; $P=.30$), gatifloxacin (23%; $P=.07$), and moxifloxacin (23%; $P=.07$).

There were significant increases in rates of multiple-drug resistance among CNS isolated from treated eyes when compared with control eyes (**Figure 8**). Approximately one-quarter of CNS isolates from the control eye (24.8%) were sensitive to all 16 antibiotics, but only 10.4% of CNS isolates from treated eyes were similarly pansensitive ($P=.01$). Furthermore, 64.7% and 81.8% of CNS isolates from control and treated eyes were resistant to at least 3 antibiotics, respectively ($P=.01$), and 48.2% and 67.5% were resistant to at least 5 antibiotics, respectively ($P=.009$).

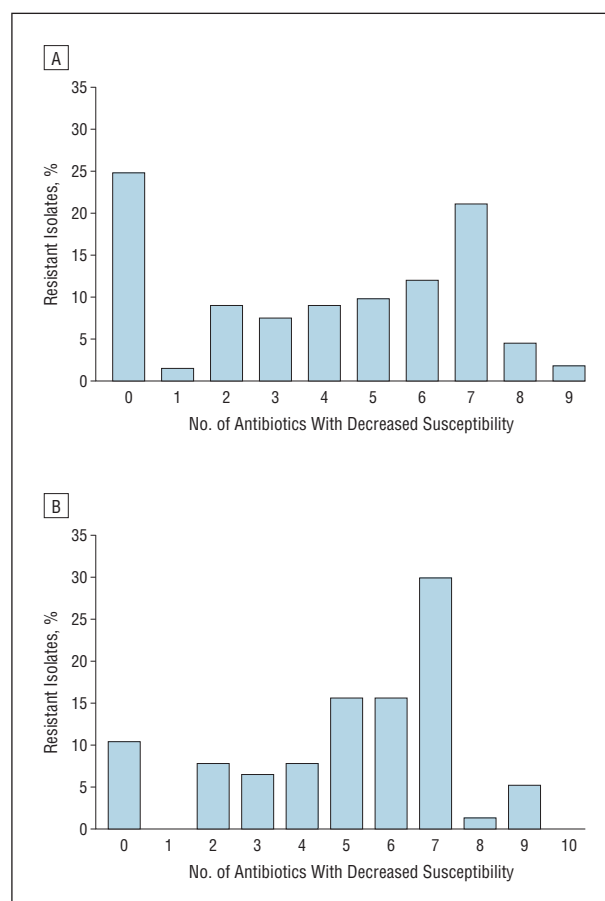


Figure 8. Percentage of coagulase-negative staphylococcus from control (A) and treated (B) eyes from visit 1 to the final visit (excludes baseline) resistant to the corresponding number of antibiotics. Intermediate resistance was included in the definition of resistance.

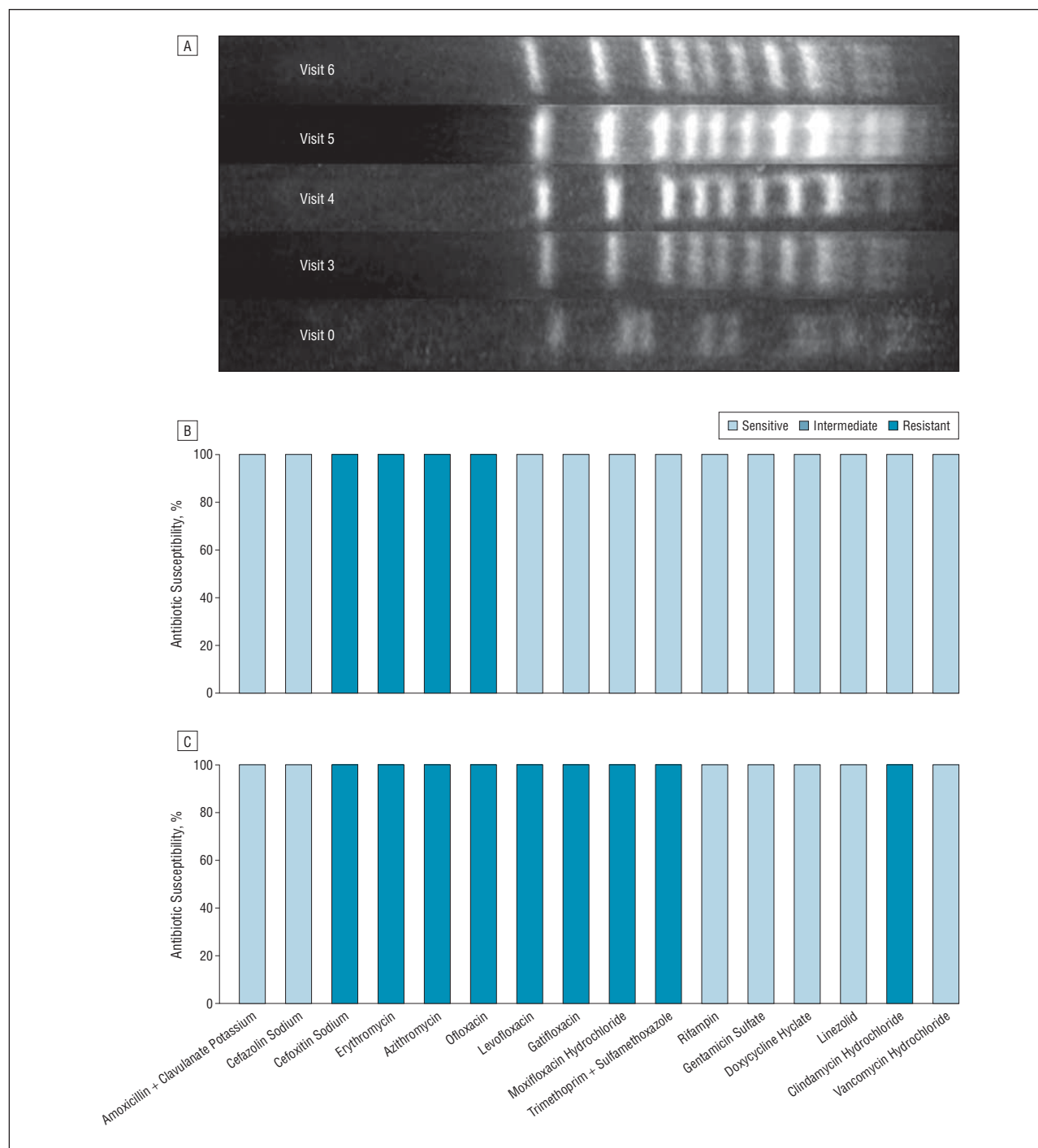


Figure 9. Antibiotic susceptibility and DNA strain analysis of coagulase-negative staphylococcus (CNS) isolates from the treated eye of a representative patient randomized to moxifloxacin. At baseline (visit 0), a CNS strain sensitive to levofloxacin, moxifloxacin hydrochloride, and gatifloxacin (B) was subsequently supplanted with a different strain by visit 3 (change is noted in the DNA fingerprint pattern [A]) that was resistant to all fluoroquinolones tested and resistant to combined trimethoprim and sulfamethoxazole and clindamycin hydrochloride (C). This was the only strain reisolated at visits 4, 5, and 6.

Selection of resistant strains occurred rapidly in the conjunctiva in susceptible but not resistant flora. One representative patient, randomized to moxifloxacin, had a fluoroquinolone-sensitive strain of *S epidermidis* at baseline (visit 0) that became rapidly supplanted by a fluoroquinolone-resistant strain of *S epidermidis* (**Figure 9**) by visit 3. Furthermore, only this fluoroquinolone-resistant strain was recultured on subsequent visits. In contrast, 1 representative patient randomized to azithro-

mycin had an azithromycin-resistant strain of *S epidermidis* at baseline, and cultures continued to yield this same strain on subsequent visits (data not shown).

All CNS isolates resistant to gatifloxacin or moxifloxacin were also resistant to ofloxacin and levofloxacin, indicating high levels of cross-resistance between newer- and older-generation fluoroquinolone antibiotics. This high level of cross-resistance explains the increasing rate of levofloxacin resistance observed in this study despite absence of exposure.

Intraocular injections are the fastest growing procedure in ophthalmology and, if trends continue, may become the most common cause of endophthalmitis seen in clinical practice. For this reason, topical antibiotics are frequently used before and after each injection despite their unproven efficacy.^{9,10} Nevertheless, there is rationale to support their application. Prospective studies have confirmed that topical antibiotics administered 1 hour before injection significantly reduce conjunctival bacteria flora,^{15,16} and in vitro studies using fourth-generation fluoroquinolones demonstrate eradication of causative organisms of endophthalmitis in 5 to 15 minutes.¹⁷ In addition, topical antibiotics would seem to have benefit given the presumed mechanisms of postinjection endophthalmitis, which involves direct inoculation of ocular flora at the time of injection or subsequent entry through a wound track.¹⁰ Finally, medicolegal concerns and patient expectations favor their use in some circumstances. For these reasons and others, topical antibiotics will continue to be commonly used in relation to intraocular injections.

Emerging resistance of CNS ocular flora to third- and fourth-generation fluoroquinolones has been observed by recent surveillance studies^{10,18,19}; however, to our knowledge, this is the first controlled longitudinal study to directly establish ophthalmic antibiotic use with emergence of resistance and to determine its relationship with different classes of antibiotics. Our results demonstrate that macrolide- and fluoroquinolone-resistant conjunctival CNS emerge rapidly after exposure to their respective antibiotic and are maintained by periodic reexposure. This finding has considerable implications because conjunctival flora are presumed to be the predominant source of postinjection endophthalmitis and because at least 1 study has suggested that antibiotic-resistant *S epidermidis* is associated with greater intraocular inflammation than antibiotic-susceptible strains.²⁰

We also observed increasing fluoroquinolone resistance among conjunctival *S aureus*. There was no observed resistance to gatifloxacin or moxifloxacin of *S aureus* isolated at baseline or from control eyes at any time during follow-up, but resistance rates increased in fluoroquinolone-exposed eyes and approached statistical significance ($P=.07$). Equally concerning was the observation of increased methicillin resistance among fluoroquinolone-resistant *S aureus*. No methicillin-resistant *S aureus* was observed at baseline, and only 1 of 17 *S aureus* isolates (6%) from the conjunctiva of control eyes during follow-up was methicillin resistant. In contrast, 23% of *S aureus* isolates cultured from fluoroquinolone-exposed eyes during follow-up were methicillin resistant.

Rapid emergence of fluoroquinolone-resistant *S aureus* was observed in several US hospitals after the introduction of ciprofloxacin in the 1980s, with reported resistance rates as high as 80% and more common in methicillin-resistant strains.²¹ The association of fluoroquinolone and methicillin resistance in *S aureus* observed in our study has been reported by others²² and is a potential concern given the possibility of greater viru-

lence and morbidity with methicillin-resistant *S aureus* infections.^{23,24}

Our results also demonstrate increasing multiple-drug resistance among conjunctival flora repeatedly exposed to ophthalmic antibiotics. In a recent prospective but cross-sectional study, Ta and colleagues²⁵ reported that 53% and 28% of CNS isolates were resistant to at least 3 and at least 5 antibiotics, respectively. Of the 16 antibiotics that were tested in our longitudinal study, 82% and 68% of CNS isolated during follow-up from treated eyes were resistant to at least 3 and at least 5 antibiotics, respectively. This finding is concerning because multiple-drug-resistant strains of CNS may increase the risk of treatment failure.^{20,23}

In contrast to fluoroquinolones, for which there were already substantial rates of baseline resistance among ocular CNS, susceptibility of CNS to gentamicin in our series remained approximately 97%. Although aminoglycosides may have less intraocular penetration than fluoroquinolones, they still provide targeted coverage of conjunctival CNS. However, repeated use of this class of antibiotic may also select for resistant strains.

As with all observational studies, our results should be taken with caution. Resistance found in vitro does not always correlate with clinical resistance. A combination of pharmacokinetics and pharmacodynamics of drug, infection site, and minimum inhibitory concentration is needed to properly predict in vivo efficacy of antibiotics against target pathogens. Although the Kirby-Bauer disc diffusion technique is a well-established and widely used method of susceptibility testing, the results are qualitative (eg, classification as susceptible, intermediate, and resistant) and subject to interpretation. Resistant strains may also be less virulent than sensitive strains, but fluoroquinolone-resistant strains of *S aureus* show increased expression of fibronectin, which facilitates their attachment and spread, and appear to have greater concomitant methicillin resistance.^{21,26} Despite our small sample size, we believe our results are convincing because of the controlled nature of our data and longitudinal follow-up, but we strongly encourage independent verification of our results.

In conclusion, the repeated use of ophthalmic antibiotics selects for resistant strains. Our findings indicate the need for more judicious use of ophthalmic antibiotics after intraocular injection to reduce the potential emergence and spread of antimicrobial resistance.

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Correction

Error in Table. In the Epidemiology article titled "Prevalence of Age-Related Macular Degeneration in the United States" by Friedman et al, published in the April 2004 issue of the *Archives* (2004;122[4]:564-572), Table 2 has 2 incorrect values. The confidence intervals for prevalence per 100 individuals among white female participants aged ≥ 80 years with geographic atrophy age-related macular degeneration should be 8.53 to 10.29, not 8.53 to 1.29, and for white male participants aged 80 years or older with neovascular age-related macular degeneration should be 6.76 to 10.12, not 6.76 to 1.12.