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Topical Fluoroquinolone Use as a Risk Factor for In Vitro Fluoroquinolone Resistance in Ocular Cultures

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Abstract

Objective—To determine whether recent use of topical fluoroquinolones is a risk factor for in vitro fluoroquinolone resistance in *Staphylococcus aureus* ocular isolates.

Methods—Disk diffusion susceptibility testing for ciprofloxacin, moxifloxacin, and gatifloxacin was performed for all ocular isolates of *S aureus* at the Francis I. Proctor Foundation microbiology laboratory from January 1, 2005, to December 31, 2008. The medical records of patients with positive *S aureus* cultures were reviewed to determine topical or systemic fluoroquinolone use within the 3 months prior to culture. The Fisher exact test was used to compare the proportion of patients who used topical fluoroquinolones in the past 3 months among fluoroquinolone-sensitive and -resistant cases. Logistic regression was used to determine risk factors for fluoroquino-lone resistance.

Results—Of 200 *S aureus* cultures, 41 were resistant to ciprofloxacin, moxifloxacin, and gatifloxacin (20.5%). Fluoroquinolone-resistant *S aureus* isolates were from older patients (mean [SD] age, 65.5 [25.0] years) compared with fluoroquinolone-susceptible isolates (mean [SD] patientage, 52.1 [22.1] years) (P=.003). Use of fluoroquinolones within the 3 months before testing was more frequent in resistant isolates (29%) than in susceptible isolates (11%) (P=.005), as was recent hospitalization (22% of resistant isolates, 0% of susceptible isolates) (P<.001). In the multivariate regression analysis, topical fluoroquinolone use within 3 months was a significant predictor of fluoroquinolone resistance (P=.046), along with age, systemic immunosuppression, and topical fluoroquinolone use between 3 and 6 months before testing.

Conclusion—Recent topical fluoroquinolone use is significantly associated with fluoroquinolone resistance in *S aureus* isolates from ocular cultures.

Topical fluoroquinolones, especially the fourth generation fluoroquinolones gatifloxacin and moxifloxacin,arecommonlyused in ophthalmology. Given their broad-spectrum activity, gatifloxacin and moxifloxacin are often used off-label as first-line monotherapy for corneal ulcers.[1-3] They are also frequently used in prophylaxis for cataract surgery.[4] Systemic use of

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fluoroquinolones has been associated with a higher incidence of resistance to these drugs.[5-7] Topical ocular antibiotics have been shown to induce bacterial resistance at extraocular sites,[8] but their effect on the resistance pattern of ocular bacteria is less clear. Herein, we report the association between topical fluoroquinolone use and subsequent in vitro resistance in ocular isolates of *Staphylococcus aureus*.

METHODS

We identified all ocular isolates of *S aureus* from the Francis I. Proctor Foundation at the University of California, San Francisco (UCSF) ocular microbiology laboratory database from January 1, 2005, to December 31, 2008. At our institution, bacterial cultures are routinely performed in cases of blepharitis, meibomitis, conjunctivitis, and keratitis. Disk diffusion susceptibility testing using clinical and laboratory standards institute (CLSI) break points[9] was performed for multiple antibiotics that are used topically in ophthalmology, including ciprofloxacin, moxifloxacin, and gatifloxacin. *Staphylococcus aureus* isolates were also classified as methicillin susceptible (MSSA) or methicillin resistant (MRSA) based on oxacillin susceptibility, using CLSI-defined break points.[9]

The medical records of patients with *S aureus* cultures were reviewed to determine topical or systemic fluoroquinolone use within the 3 months prior to culture. Patients could contribute multiple positive cultures to the study, but only the patient's first positive culture in any 3-month period was included. The Fisher exact test was used to compare the proportion of patients who used topical fluoroquinolone in the past 3 months among fluoroquinolone-sensitive and -resistant cases. Multivariate backward stepwise logistic regression was used to determine risk factors for fluoroquinolone resistance, using the following explanatory variables: age, sex, systemic fluoroquinolone use within the 3 months prior to culture, other topical antibiotic use, systemic immunosuppression, topical immunosuppression (use of topical corticosteroids), and hospitalization or nursing home admission within the 3 months prior to bacterial culture. Systemic immunosuppression was defined as IgE deficiency, human immunodeficiency virus (HIV) seropositivity, or systemic immunosuppressive therapy with agents such as oral prednisone, immunosuppressive agents, or systemic chemotherapy. Predictor variables with a Wald $P<.10$ were retained in the model. We used STATA software, version 9.2 (Stata Corporation, College Park, Texas) to conduct all of the statistical analyses. Approval for this study was obtained from the UCSF committee on human research.

RESULTS

Of 624 positive cultures in the study timeframe, 248 grew *S aureus* (39.7%) (**Table 1**). Of these, 200 *S aureus* cultures from 166 patients (Table 1) were included in this study. Of *S aureus* isolates, 10 were from the conjunctiva alone (5%); 96 were from the conjunctiva and eyelids (48%); 80 were from the eyelids alone (40%); and 14 were from the cornea (7%) (**Table 2**). Fluoroquinolone resistance was documented in 41 isolates (20.5%). Methicillin-resistant *S aureus* accounted for 32 isolates (16%), all of which were resistant to ciprofloxacin, moxifloxacin, and gatifloxacin. The mean (SD) age of patients with resistant isolates was 65.5 (25.0) years, significantly higher than the mean age of patients with nonresistant isolates (52.1 [22.1] years) ($P=.003$). Use of fluoroquinolones in the 3 months before testing was more frequent in resistant isolates (29%) than in susceptible isolates (11%) ($P=.005$), as was recent hospitalization (22% of resistant isolates, 0% of susceptible isolates) ($P<.001$). Treatment with nonfluoroquinolone antibiotics in the 3 months before testing was more frequent in isolates that were resistant (44%) than in those that were susceptible (28%), although this difference did not reach statistical significance ($P=.06$). Use of systemic nonfluoroquinolone antibiotics or systemic immunosuppression did not differ

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between resistant and susceptible isolates. **Table 3** lists the topical and systemic antibiotics used.

In the multivariate regression analysis, age, topical fluoroquinolone use within 3 months, topical fluoroquinolone use between 3 and 6 months, and systemic immunosuppression were statistically significant risk factors for fluoroquinolone resistance (**Table 4**).

COMMENT

Antibiotic resistance due to widespread use of antibiotics is a major concern.[10-16] Fluoroquinolone use in particular is associated with a high rate of bacterial antibiotic resistance. Several studies have demonstrated an association between increased systemic fluoroquinolone use and resistance in *S aureus*. For example, the incidence of MRSA isolated from any body site increased with the use of systemic fluoroquinolones in a study of French hospitals,[17] and systemic fluoroquinolone use has been associated with higher colony counts of nasal MRSA.[18] While it has been speculated that previous use of topical fluoroquinolone in the eye should lead to an increase in resistance in ocular isolates, this has been difficult to demonstrate.[19] In the present study, we show that recent fluoroquinolone use is associated with in vitro resistance to fluoroquinolones in *S aureus* ocular isolates.

Various risk factors have been associated with antibiotic resistance in nonocular bacterial isolates. For example, hospital admission has been identified as a risk factor for nasal MRSA carriage.[20] Another study on *Escherichia coli* and *Klebsiella pneumoniae* from all sources demonstrated that both residence in a long-term care facility and recent systemic fluoroquinolone use were associated with higher fluoroquinolone resistance.[21] Similarly, we found that hospital admission was a risk factor for fluoroquinolone resistance in *S aureus* ocular isolates. Although the details of the hospitalizations were not reviewed, these may have involved administration of systemic antibiotics as well as systemic immunosuppression and thus led to resistance in a similar fashion as in previous studies on systemic administration of fluoroquinolones.[21] Older age was determined to be a predictor of resistance in these prior reports, and our study also found that patients with resistant isolates were more likely to be older than those with nonresistant isolates.[20,21] In addition, systemic immunosuppression has been associated with bacterial resistance to antibiotics.[22] Systemic immunosuppression was a significant risk factor in our study, although topical immunosuppression was not.

The incidence of MRSA in ocular isolates appears to be increasing.[23-25] Recent nationwide surveillance of ocular bacterial isolates indicated that 15% of MRSA isolates were susceptible to fourth-generation fluoroquinolones.[26] In our study, however, none of the MRSA isolates were sensitive to either moxifloxacin or gatifloxacin, indicating that the fourth-generation fluoroquinolones are not a suitable choice of empirical therapy when MRSA is suspected, such as in institutionalized patients or patients with recent hospital admissions. This applies at least in our geographic area.

There are several limitations to our study. It was a retrospective analysis, so misclassification errors could have occurred. The laboratory is located at a referral center, so the results may not be directly applicable to the general patient population. Our center cares for many patients with severe ocular surface disease or ocular infections, so many patients had received courses of topical antibiotics. However, given the practice patterns at our center, cases of blepharitis, meibomitis, conjunctivitis, and keratitis were consistently cultured, so we do not believe there was selection bias within our practice. We documented only in vitro resistance and made no attempt to study clinical success or failure. However, it is likely that in vitro susceptibility data has clinical relevance.[27,28]

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In addition, it has been reported that fluoroquinolones do not induce resistance because they act on 2 separate topoisomerase isozymes and because they reach concentrations above the mutant prevention level in ocular applications. We were unable to analyze the ocular surface concentration in our patients because the data on the exact treatment frequency were not available for all patients. It seems, however, that the separate sites of action of fluoroquinolones do not prevent induction of resistance, as Allen and Deshpande[29] hypothesized in their laboratory investigation into resistance induction of MRSA using mutant prevention concentration (MPC) testing. Given the retrospective nature of this study, it is not possible to determine whether fluoroquinolone resistance was present in the isolates prior to the use of antibiotics or whether it was induced by fluoroquinolone use.

Finally, with multiple predictors in a regression model, there is always the possibility of finding a false association. However, the association we found between topical fluoroquinolone use and fluoroquinolone resistance was statistically robust and consistent with findings from studies of nonocular sites.

In conclusion, we found an association between fluoroquinolone use and fluoroquinolone resistance in ocular *S aureus*. Other risk factors associated with fluoroquinolone resistance included older age, systemic immunosuppression, and recent hospital or nursing home admission. Further research will be important to determine whether our finding of an association between topical fluoroquinolone use and fluoroquinolone resistance is generalizable to other ocular infections or other antibiotics.

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Table 1

Antibiotic-Resistant *Staphylococcus aureus* isolated at the Francis I. Proctor Foundation for Research in Ophthalmology From 2005 to 2008

Year	Total *S Aureus* Isolates, No.	Fluoroquinolone-Resistant Isolates, No. (%)	Methicillin-Resistant Isolates, No. (%)
2005	56	8 (18)	8 (18)
2006	67	12 (22)	12 (22)
2007	38	7 (23)	7 (23)
2008	87	14 (20)	9 (10)

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Table 2

Characteristics of Patients With Fluoroquinolone-Resistant and -Susceptible *Staphylococcus aureus* Isolates[a]

Baseline Characteristics	Resistant (n=41)	Susceptible (n=159)	*P* Value
Age, mean (SD), y	65.5 (25.0)	52.1 (22.1)	.003
Male	39.0	46.5	.48
Culture site			
Eyelid	48.8	37.1	.11
Conjunctiva	4.9	5.0	
Eyelid and conjunctiva	34.2	51.6	
Cornea	9.8	6.3	
Lacrimal sac	2.4	0.00	
Eye			
Right	36.6	29.6	
Left	12.2	24.5	0.21
Both	51.2	45.9	
MRSA	78.1	0.00	<.001
Topical FQ use within 3 mo	29.3	10.7	.005
Topical FQ use >3 mo ago	4.9	0.6	.11
Oral FQ	4.9	0.6	.11
Other topical antibiotic	43.9	27.7	.06
Other systemic antibiotic	7.3	5.7	.71
Systemic immunosuppression	22.0	15.7	.36
Topical immunosuppression	19.5	25.8	.54
Recent hospitalization	22.0	0.00	<.001

Abbreviations: FQ, fluoroquinolone; MRSA, methicillin-resistant *S aureus*.

[a]Unless otherwise indicated, data are reported as percentage of isolates.

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Table 3

Topical and Systemic Antibiotics Used

Antibiotic	Topical	Systemic
Fluoroquinolones	Moxifloxacin, gatifloxacin, ofloxacin, ciprofloxacin, levofloxacin, 0.5% and 1.5%	Gatifloxacin
Nonfluoroquinolones	Bacitracin, polymyxin B/trimethoprim, erythromycin, tobramycin	Doxycycline, azithromycin, cephalexin, penicillin

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Table 4

Risk Factors for Fluoroquinolone Resistance After Backward Stepwise Regression

Risk Factor	Odds Ratio (95% CI)	*P* Value
Age, y	1.03 (1.01-1.05)	.007
Use of topical FQs in past 3 mo	2.8 (1.0-7.6)	.046
Use of topical FQs more than 3 mo ago	13.2 (1.1-162.2)	.04
Use of other topical antibiotic	1.9 (0.8-4.4)	.15
Use of systemic immunosuppression	3.2 (1.1-9.1)	.03

Abbreviations: CI, confidence interval; FQ, fluoroquinolone.