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

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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 Staphylococcus aureus at the Francis I. Proctor Foundation microbiology laboratory from January 1, 2005, to December 31, 2008. The medical records of patients with positive Staphylococcus 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 analysis 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.

Results: Of 200 Staphylococcus aureus cultures, 41 were resistant to ciprofloxacin, moxifloxacin, and gatifloxacin (20.5%). Fluoroquinolone-resistant Staphylococcus aureus isolates were from older patients (mean [SD] age, 65.5 [25.0] years) compared with fluoroquinolone-susceptible isolates (mean [SD] patient age, 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 Staphylococcus aureus isolates from ocular cultures.

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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

<table>
<thead>
<tr>
<th>Year</th>
<th>Total <em>S aureus</em> Isolates, No.</th>
<th>Fluoroquinolone-Resistant Isolates, No. (%)</th>
<th>Methicillin-Resistant Isolates, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>56</td>
<td>8 (18)</td>
<td>8 (18)</td>
</tr>
<tr>
<td>2006</td>
<td>67</td>
<td>12 (22)</td>
<td>12 (22)</td>
</tr>
<tr>
<td>2007</td>
<td>38</td>
<td>7 (23)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>2008</td>
<td>87</td>
<td>14 (20)</td>
<td>9 (10)</td>
</tr>
</tbody>
</table>

Legend:
- **Total *S aureus* Isolates, No.**: Total number of *S aureus* isolates per year.
- **Fluoroquinolone-Resistant Isolates, No. (%)**: Number of fluoroquinolone-resistant isolates as a percentage of the total isolates.
- **Methicillin-Resistant Isolates, No. (%)**: Number of methicillin-resistant isolates as a percentage of the total isolates.

**COMMENT**

Antibiotic resistance due to widespread use of antibiotics is a major concern. 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, and systemic fluoroquinolone use has been associated with higher colony counts of nasal MRSA. 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. 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. Another study on *Escherichia coli* and *Klebsiella pneumoniae* from all sources...
blepharitis, meibomitis, conjunctivitis, and keratitis were ever, given the practice patterns at our center, cases of patients had received courses of topical antibiotics. How- severe ocular surface disease or ocular infections, so many occurred. The laboratory is located at a referral center, so admissions. This applies at least in our geographic area.

institutionalized patients or patients with recent hospital admission was a risk factor of empirical therapy when MRSA is suspected, such as in fourth-generation fluoroquinolones are not a suitable choice to either moxifloxacin or gatifloxacin, indicating that the 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 retrospec- tive 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 popula- tion. Our center cares for many patients with severe ocular surface disease or ocular infections, so many patients had received courses of topical antibiotics. How- ever, given the practice patterns at our center, cases of blepharitis, meibomitis, conjunctivitis, and keratitis were consistently cultured, so we do not believe there was selec- tion 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 suscepti- bility data has clinical relevance.

In addition, it has been reported that fluoroquino- lones do not induce resistance because they act on 2 sepa- rate topoisomerase isozymes and because they reach concentra- tions above the mutant prevention level in ocular applications. We were unable to analyze the ocular sur- face 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 hypothesized in their laboratory investigation into resistance induction of MRSA. In vitro resistance and made no attempt to study clinical suc- cess or failure. However, it is likely that in vitro suscepti- bility data has clinical relevance.

Table 3. Topical and Systemic Antibiotics Used

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Topical</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>Moxifloxacin, gatifloxacin, ofloxacin, ciprofloxacin, levofloxacin, 0.5% and 1.5%</td>
<td>Gatifloxacin</td>
</tr>
<tr>
<td>Nonfluoroquinolones</td>
<td>Bacitracin, polymyxin B/thrombomycin, erythromycin, tobramycin</td>
<td>Doxycycline, azithromycin, cephalaxin, penicillin</td>
</tr>
</tbody>
</table>

Table 4. Risk Factors for Fluoroquinolone Resistance After Backward Stepwise Regression

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

Abbreviations: CI, confidence interval; FO, fluoroquinolone.

demonstrated that both residence in a long-term care facili- ty and recent systemic fluoroquinolone use were asso- ciated with higher fluoroquinolone resistance. Similarly, we found that hospital admission was a risk factor for fluoroquinolone resistance in *S aureus* ocular iso- lates. Although the details of the hospitalizations were not reviewed, these may have involved administration of systemic antibiotics as well as systemic immunosuppres- sion and thus led to resistance in a similar fashion as in previous studies on systemic administration of fluoroquinolones. 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. In addition, systemic immunosuppression has been asso- ciated with bacterial resistance to antibiotics. 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. Recent nationwide surveillance of ocular bacterial isolates indicated that 1.5% of MRSA isolates were suscep- tible to fourth-generation fluoroquinolones. 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.

In conclusion, we found an association between fluoroquinolone use and fluoroquinolone resistance was statistically robust and consistent with findings from studies of monocular sites.

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Author Contributions: Dr Acharya had full access to all the data in the study and takes responsibility for the integ- rity of the data and the accuracy of the data analysis.

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REFERENCES


2. Gangopadhyay N, Daniell M, Wei L, Taylor HR. Fluoroquinolone and fortified...


