Risk Factors Associated with Colonization by Pneumococci with Reduced Susceptibility to Fluoroquinolones in Adult Outpatients

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We developed a case-control study in order to identify risk factors associated with pharyngeal colonization by Streptococcus pneumoniae with reduced susceptibility to fluoroquinolones (ciprofloxacin MIC, ≥4 μg/mL). A total of 400 patients were studied for colonization by quinolone-nonsusceptible S. pneumoniae (QNSP) isolates and risk factors for this colonization. Isolate susceptibility was determined by the agar dilution method. Forty patients were colonized by QNSP (case patients), and 360 patients were not colonized by QNSP (control patients). The MIC range of ciprofloxacin for QNSP isolates was 4 to 8 μg/mL. No isolates were resistant to levofloxacin or moxifloxacin. Risk factors significantly associated with QNSP colonization, according to univariate analysis, were recent hospitalizations (odds ratio [OR], 3.43; 95% confidence interval [CI], 1.6 to 7.2; P < 0.01) and prior exposure to fluoroquinolones (OR, 6.04; 95% CI, 3.0 to 12.0; P < 0.01). Other factors such as chronic obstructive pulmonary disease (OR, 1.94; 95% CI, 0.7 to 5.0), prior exposure to penicillins (OR, 1.68; 95% CI, 0.8 to 3.3) and prior exposure to macrolides (OR 2; 95% CI, 0.6 to 6.2) were more frequent among patients colonized with QNSP, but there was no statistical significance. Multivariate analysis showed that exposure to fluoroquinolones was the only independent factor associated with colonization by QNSP (OR, 4.2; 95% CI, 1.8 to 9.4; P < 0.01). Throat colonization by QNSP is becoming frequent, though most of these isolates (all the isolates in this case) remain susceptible to newer fluoroquinolones. Previous treatment with fluoroquinolones seems to be the main risk factor associated with colonization by QNSP.

The emergence and spread of drug-resistant Streptococcus pneumoniae are a major cause of concern in pneumococcal infection in recent years. More than 50% of isolates now found in several countries are resistant to penicillin (1, 7, 13, 14, 25), with Spain as one of the countries with the highest penicillin resistance rates (18). Among penicillin-resistant S. pneumoniae isolates, 60 to 80% are also resistant to cefuroxime, erythromycin, and clindamycin (13). Since the release in the late 1990s of newer fluoroquinolones (FQs) with enhanced activity against pneumococci, these drugs have been prescribed with increasing frequency for initial treatment of respiratory tract infections (10, 22). FQ resistance rates remain low in S. pneumoniae in most countries (3, 6, 17), though higher resistance rates have been reported occasionally in some countries (9, 12).

Recent studies have shown that 30% of S. pneumoniae isolates for which the ciprofloxacin (CIP) MIC is 4 μg/mL, and virtually all pneumococcal isolates for which the CIP MIC is >4 μg/mL harbor one or more topoisomerases mutations (2), though not all these strains are levofloxacin (LEV) or moxifloxacin (MOX) resistant. Another recent study (16) showed that 59% of S. pneumoniae isolates intermediate for LEV (MIC of 2 μg/mL) have a first-step mutation in parC. Thus, this group of strains with reduced susceptibility to CIP, despite their eventual susceptibility to newer FQs, might be the basis for a further development of resistance to the newer drugs.

To determine the prevalence of S. pneumoniae isolates for which the MICs of CIP are ≥4 μg/mL (quinolone nonsusceptible S. pneumoniae [QNSP]) and the epidemiological and clinical aspects of colonization by QNSP isolates, a study was conducted on risk factors for colonization by QNSP in a group of outpatients attending the Hospital Universitario de Salamanca (Salamanca, Spain).

MATERIALS AND METHODS

Setting. This study was conducted on adult outpatients attending the Emergency Service at the Hospital Universitario de Salamanca (Spain). This is a tertiary hospital with all the major medical and surgical specialties that offers health care to a community of about 300,000 inhabitants. The hospital also works as a reference center for bone marrow and kidney transplantsations, cardiac surgery, and some neurosurgery procedures. The Emergency Service admits all kind of patients (medical, surgical, pediatric, and acute psychiatric patients) from the whole province.

Study design and patient description. This was a prospective study that included a 6-month period from October 2002 through March 2003. A case-control study was developed to compare the frequency of exposure and the features of case patients with those of control patients and to identify and quantify potential risk factors associated with QNSP colonization.

A case patient was defined as a patient whose throat was colonized by an S. pneumoniae isolate for which the CIP MIC was ≥4 μg/mL. A patient was considered a control patient when there was no pneumococcal colonization or when the CIP MICs of pneumococcal isolates were ≤2 μg/mL. Relevant clinical data were entered onto predesigned forms. The following data were obtained for all patients: age, sex, recent hospitalizations, residence in nursing homes, underlying diseases, and prior exposure to penicillins, cephalosporins, macrolides, and FQs.

Recent hospitalization was defined as any inpatient treatment lasting more than 1 day during the 6 previous months.
for categorical variables, and a Student’s t test for colonization. Either the chi-square test or Fisher’s exact test was used.

Telithromycin, and clindamycin were obtained from their respective manufacturers to NCCLS guidelines (20, 21).

bile solubility, susceptibility to optochin, and agglutination with specific sera lines (20). Pneumococci were identified by Gram staining, colony morphology, according to previous agar dilution tests performed according to NCCLS guidelines within 1 h after sampling. Every batch of CIP-containing plates was validated by clinical strains for which the CIP MICs were 1, 2, 4, and 8 μg/ml. The mean ages of case patients and control patients were very similar (42.7 versus 44.2 years). Overall, 82 (20.5%) patients were colonized by pneumococci. We found that 40 patients (10%) were colonized with QNSP isolates nonsusceptible to ciprofloxacin (Table 1). The susceptibilities of QNSP and susceptible isolates are given in Table 2. The MIC distribution of the three FQs tested for all the isolates is shown in Table 2.

Results of the study of potential risk factors are shown in Table 3. Nursing home residence was infrequent in both groups. Only 5% (2 of 40) of case patients resided in nursing homes versus 1.9% (7 of 360) of noncolonized patients. Smoking was less frequent among control patients (42.2%, or 152 of 360 patients) than among case patients (45%, or 18 of 40 patients), though the difference was not significant. Chronic obstructive pulmonary disease (COPD) was twofold more frequent among case patients (6 of 40 patients, or 15%) than among control patients (30 of 360 patients, or 8.3%). Recent hospitalization was significantly more frequent among case patients (12 of 40, or 30% versus 40 of 360, or 11.1%; P < 0.01).

A history of exposure to FQs was much more frequent among case patients (Fig. 1) and was the only antibiotic group significantly associated with QNSP colonization (P < 0.01). Eighteen case patients (45%) had received at least one FQ during the last 3 months versus 43 (11.9%) among the control group. If we study older FQs (norfloxacin, CIP, and ofloxacin) and newer respiratory FQs (LEV and MOX) separately, 9.7% of noncolonized patients and 27.5% of colonized patients had received older FQs (OR, 3.5; 95% CI, 1.6 to 7.7; P < 0.01), while 2.2% of noncolonized patients and 17.5% of colonized patients had received newer FQs (OR, 9.3; 95% CI, 3.2 to 27.4; P < 0.01).

We also compared the risk of colonization by QNSP when the patient had been treated with any one FQ versus the risk when treatment was with any other FQ. In this case, we found that the risk of colonization after treatment with MOX was similar to the risk after treatment with any other FQ; 3 patients out of 40 had received MOX.

Underlying diseases included any condition that might increase a patient’s predisposition to colonization or affect the patient’s life expectancy.

Previous exposure to antibiotics was defined as any antibiotic treatment during the previous 3 months and was categorized according to the class of agents (FQs, penicillins, cephalosporins, and macrolides).

Microbiological methods. Throat samples were collected by the usual microbiological methods. Samples were collected by using CultureSwabs (Becton-Dickinson) and transported in Stuart’s medium. Then, samples were spread onto blood agar plates and onto blood agar plates containing 2 μg of CIP per ml within 1 h after sampling. Every batch of CIP-containing plates was validated by using S. pneumoniae ATCC 49619 as a negative control and by using four S. pneumoniae clinical strains for which the CIP MICs were 1, 2, 4, and 8 μg/ml, according to previous agar dilution tests performed according to NCCLS guidelines (20). Pneumococci were identified by Gram staining, colony morphology, bile solubility, susceptibility to optochin, and agglutination with specific sera (Directigen S. pneumoniae; Becton-Dickinson).

Antibiotic susceptibility was determined by the agar dilution method, according to NCCLS guidelines (20, 21).

LEV, CIP, MOX, penicillin, cefazolin, cefuroxime, cefotaxime, erythromycin, telithromycin, and clindamycin were obtained from their respective manufacturers.

Statistical analysis. Univariate analysis was used for identifying potential risk factors for colonization. Either the chi-square test or Fisher’s exact test was used for categorical variables, and a Student’s t test or Mann-Whitney U test was used for continuous variables. Variables that were found to be significant by the univariate analysis were studied by logistic regression (forward conditional method). A P value of <0.05 was considered statistically significant. All the statistical tests were performed by using the SPSS statistical package.

Table 3. Nursing home residence was infrequent in both groups. Only 5% (2 of 40) of case patients resided in nursing homes versus 1.9% (7 of 360) of noncolonized patients. Smoking was less frequent among control patients (42.2%, or 152 of 360 patients) than among case patients (45%, or 18 of 40 patients), though the difference was not significant. Chronic obstructive pulmonary disease (COPD) was twofold more frequent among case patients (6 of 40 patients, or 15%) than among control patients (30 of 360 patients, or 8.3%). Recent hospitalization was significantly more frequent among case patients (12 of 40, or 30% versus 40 of 360, or 11.1%; P < 0.01).

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We also compared the risk of colonization by QNSP when the patient had been treated with one FQ versus the risk when treatment was with any other FQ. In this case, we found that the risk of colonization after treatment with MOX was similar to the risk after treatment with any other FQ; 3 patients out of 40 had received MOX.

### RESULTS

We studied 400 patients (211, or 52.8%, male and 189, or 47.2%, female). Overall, 82 (20.5%) patients were colonized by pneumococci. We found that 40 patients (10%) were colonized by pneumococcal isolates for which the CIP MICs were ≥4 μg/ml. The mean ages of case patients and control patients were very similar (42.7 ± 25.4 versus 44.2 ± 17.8 years, respectively). The CIP MIC range for QNSP isolates was 4 to 8 μg/ml. No strains were resistant to LEV and MOX, and only one isolate was intermediate for LEV (Table 1). The susceptibilities of QNSP and susceptible isolates are given in Table 2. The MIC distribution of the three FQs tested for all the isolates is shown in Table 2.

### Table 2. Antibiotic susceptibility of 40 S. pneumoniae isolates nonsusceptible to ciprofloxacin

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Meq50 (μg/ml)</th>
<th>Meq90 (μg/ml)</th>
<th>Range (μg/ml)</th>
<th>% Intermediate</th>
<th>% Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>0.06</td>
<td>8</td>
<td>0.03–16</td>
<td>26.8</td>
<td>24.4</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>0.5</td>
<td>16</td>
<td>&lt;0.1–32</td>
<td>2.4</td>
<td>31.7</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>1</td>
<td>8</td>
<td>&lt;0.1–32</td>
<td>14.6</td>
<td>43.9</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>0.5</td>
<td>2</td>
<td>0.1–8</td>
<td>14.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Eritromycin</td>
<td>0.5</td>
<td>32</td>
<td>0.1–32</td>
<td>17.1</td>
<td>41.5</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.5</td>
<td>128</td>
<td>0.1–128</td>
<td>9.8</td>
<td>46.3</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>≤0.008</td>
<td>≤0.008–0.03</td>
<td>≤0.008–0.1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>CIP</td>
<td>4</td>
<td>4</td>
<td>0.2–1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>MOX</td>
<td>0.2</td>
<td>2</td>
<td>0.2–1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>LEV</td>
<td>1</td>
<td>2</td>
<td>1–4</td>
<td>2.5</td>
<td>0.0</td>
</tr>
</tbody>
</table>

MIC50, MIC90, and CIP. Nonsusceptible isolates are those for which the CIP MIC is ≥4 μg/ml. MIC50, MIC at which 50% of strains are inhibited; MIC90, MIC at which 90% of strains are inhibited. ND, not done; there are no interpretative guidelines for S. pneumoniae and CIP.
who had received MOX were colonized (33.3%), versus 15 out of 43 (34.9%) who had been treated with any other FQ (OR, 1.2; 95% CI, 0.3 to 5.6; \( P \), not significant). The risk of colonization after treatment with LEV versus treatment with any other FQ was higher. Four of 6 patients (66.7%) who were treated with LEV were colonized versus 14 of 55 (25.5%) who were treated with CIP or MOX (OR, 5.9; 95% CI, 1.0 to 35.5; \( P < 0.03 \)).

Of the case group 42.5% (17 of 40) of patients had received penicillins, and 30.6% (110 of 360) of the control patients had also received penicillins. The use of macrolides was less frequent overall but was twofold more frequent among case patients (4 of 40, or 10%) than among the control group (19 of 360 patients, or 5.3%). For both groups, the use of cephalosporins was the least frequent treatment (2 of 40, or 5%, of case patients and 25 of 360, or 6.9%, of control patients).

Multivariate analysis showed that the only factor independently associated with colonization by QNSP was the exposure to FQs (OR, 4.2; 95% CI, 1.8 to 9.4; \( P < 0.01 \)).

DISCUSSION

The correlation between topoisomerase mutations and FQ resistance is not as homogeneous in \( S. pneumoniae \) strains as in other gram-positive strains, such as staphylococci (4, 15). The number of mutations that can be found in \( S. pneumoniae \) clinical isolates varies more widely than in other gram-positive strains (4, 15, 19), and the relationship to FQ resistance is not clear for some mutations. Moreover, isolates with the same mutation profile can have different susceptibilities, and, since the main target in \( S. pneumoniae \) is not the same for all FQs (23), the importance of each mutation may change depending on the FQ being studied.

Mutations in some key positions, such as Ser\(^79\) and Ser\(^83\) in \( parC \) and Ser\(^81\) in \( gyrA \) seem to be decisive in FQ resistance of \( S. pneumoniae \) (1, 24), and the usual pattern of acquiring successive alternate mutations, such as \( parC \), then \( gyrA \), and then \( parC \) or vice versa, remains the rule in FQ resistance emergence.

Previously studies have shown that, although a number of the \( S. pneumoniae \) isolates for which the MIC of CIP is \( \geq 4 \mu g/ml \) remain susceptible to newer FQs (LEV, MOX, and gatifloxacin), at least 20% of these isolates harbor topoisomerase mutations (2, 16). Therefore, the probability that these isolates will acquire a second mutation and become fully FQ resistant are probably higher in comparison to wild-type isolates. Thus, an increasing frequency of pharyngeal colonization by these FQ nonsusceptible isolates might herald an increase in FQ resistance in the near future, which the study of risk factors associated with this colonization might help to prevent.

Results obtained in this study show that, in our area, 10% of adult outpatients attending the Emergency Service for any reason harbor QNSP in their throats. Though most of the isolates remain LEV and MOX susceptible, this high frequency is a cause of concern, since this group might form the basis for a further increase in FQ resistance in pneumococci. Other authors (2, 16) have shown that a significant proportion of this type of isolate harbors topoisomerase mutations; if QNSP isolates become widespread, then the possibility of the

### TABLE 3. Potential risk factors associated with colonization by the QNSP isolates studied and the significance of each factor (univariate analysis)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Case patients (( n = 40 ))</th>
<th>Control patients (( n = 360 ))</th>
<th>OR (95% CI)</th>
<th>( P^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46 ± 25.4</td>
<td>46.2 ± 17.8</td>
<td>2.65 (0.5–13.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Nursing home residence</td>
<td>2 (5%)</td>
<td>7 (1.9%)</td>
<td>1.25 (0.6–2.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>18 (45%)</td>
<td>142 (52.2%)</td>
<td>1.94 (0.7–5)</td>
<td>NS</td>
</tr>
<tr>
<td>COPD</td>
<td>6 (15%)</td>
<td>30 (8.3%)</td>
<td>3.42 (1.6–7.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Recent hospitalization</td>
<td>12 (30%)</td>
<td>40 (11.1%)</td>
<td>4.04 (1.5–9.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Recent treatment with: Fluoroquinolones</td>
<td>18 (45%)</td>
<td>43 (11.9%)</td>
<td>6.04 (3–12)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Penicillins</td>
<td>17 (42.5%)</td>
<td>110 (30.6%)</td>
<td>1.68 (0.8–3.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>2 (5%)</td>
<td>25 (6.9%)</td>
<td>0.7 (0.16–3.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Macrolides</td>
<td>4 (10%)</td>
<td>19 (5.3%)</td>
<td>2.04 (0.64–6.18)</td>
<td>NS</td>
</tr>
</tbody>
</table>

\(^a\) NS, nonsignificant. Only recent exposure to FQs was found significant in multivariate analysis (OR, 4.2; 95% CI, 1.8 to 9.4; \( P < 0.01 \)).
emergence of high-level FQ-resistant isolates increases, since they are only one mutation step away from this.

Ten percent is a high proportion of colonization by QNSP and means that, in our study, one-half of the patients colonized by \textit{S. pneumoniae} harbored QNSP isolates. FQ resistance rates in Spain are very variable, as reported in previous studies. In a nationwide study of 1,684 clinical isolates obtained from 1998 to 1999 \cite{19}, 7\% of pneumococci were quinolone nonsusceptible. Recent studies on isolates obtained in 2002 and sent to a reference laboratory show that the CIP MIC for only 2.6\% of isolates was \textgreek{g}/ml \cite{5}. This high proportion of colonization by QNSP is probably associated with the widespread use of FQs in Spain. The use of FQs in the community in Spain has increased by 19.2\% from 1997 to 2003 (4,501,929 \textgreek{U} in 1997 versus 5,368,358 \textgreek{U} in 2003). This increase derives mainly from the increasing use of newer FQs. The use of CIP remains almost unchanged since 1997 (2,575,526 \textgreek{U} in 1997; 2,525,680 \textgreek{U} in 2003; range, 2,715,935 [2001] to 2,475,751 \textgreek{U} [2002]). Meanwhile, LEV use in the community has increased from 125,184 \textgreek{U} in 1999 (LEV was released in Spain in late 1998) to 299,764 \textgreek{U} in 2003 (13\%), and MOX use has increased from 477,420 \textgreek{U} in 2000, when it was released in Spain, to 1,034,412 \textgreek{U} in 2003 (116.7\%). Nevertheless, the highest proportion of FQs used in the community in Spain are still the older FQs. CIP, norfloxacin, ofloxacin, and pefloxacin (the four older FQs now available in Spain) represent, overall, 75.2\% of the total amount of FQs used in the community. Thus, though the consumption of older FQs remains stable, the selective pressure exercised by them should not be undervalued.

Moreover, the use of newer FQs in Spain differs in the community and in the hospital. Use of MOX was 3.5-fold greater than use of LEV in the community in 2003, while in the nosocomial setting, use of LEV was 9-fold greater than use of MOX (1,715,663 versus 18,399 \textgreek{U} in 2003). In both community and nosocomial settings together, the use of LEV was around twofold greater than the use of MOX in 2003 (2,015,427 and 1,052,811 \textgreek{U}, respectively).

A study published on the risk factors of colonization or infection by LEV-resistant \textit{S. pneumoniae} \cite{12} shows that old age, residence in a nursing home, history of previous hospitalizations, COPD, and previous antibiotic treatments may be risk factors; COPD, nosocomial origin of bacteria, residence in nursing homes, and exposure to FQs were independent risk factors by multivariate analysis.

Other studies show that COPD is very frequent (63\%) among patients harboring FQ-resistant pneumococci and suggest that elderly COPD patients might be the main reservoir for FQ-resistant pneumococci in the same way that children are a main reservoir for penicillin-resistant strains \cite{12}. In this study we do not find this correlation (only 15\% of colonized patients had COPD), probably because the mean ages of our patients and controls (42.7 ± 25.4 and 44.2 ± 17.8 years, respectively) were much lower than in the study by Ho et al. (median ages of 75 and 72.5 years, respectively) \cite{12}. Frequency of COPD in colonized patients was double that in control patients (OR, 1.94), suggesting that this group might be important as a QNSP reservoir.

The high frequency of COPD in the colonized patients group has been associated with high airway \textit{S. pneumoniae} bacterial counts (around 10^7 CFU/ml), both in periods of exacerbation and remission in these patients \cite{11,12}. These high counts would correlate with a higher probability of the emergence of mutant strain. Nevertheless, according to our results, colonization by QNSP frequently happens in the absence of these high counts, since 85\% of our colonized patients did not have COPD or any other conditions suggesting high airway bacterial counts.

According to our results, age and nursing home residence would not be risk factors among our patients. This can be explained because nursing home residence was very infrequent in both groups; as a matter of fact, nursing home residence of elderly patients is less frequent in Spain than in other European countries.

Other studies suggest that patient-to-patient spread is the most likely mechanism of the spread of FQ-resistant strains, mainly in the hospital \cite{8}. In this study, hospitalization is a significant risk factor in the univariate analysis, though multivariate analysis does not confirm it as an independent risk factor.

Among patients harboring pneumococci for which the MICs of CIP were \textgreek{g}/ml, recent FQ treatments were more frequent, and recent FQ treatment was the only risk factor confirmed both by univariate and multivariate analysis. This association has been shown in LEV-resistant isolates by other investigators \cite{12,23}. Some studies have shown an increase of FQ resistance in pneumococci for the same years that others have shown an increasing consumption of FQs \cite{3,11–13}. In the present study, this association is significant both for older and newer FQs.

Of interest is the finding that colonization by QNSP is more frequent in patients who have been treated with penicillins and macrolides (ORs of 1.68 and 2.0, respectively) and is probably associated with the high frequency of penicillin, macrolide, and FQ coreistance.

In conclusion, throat colonization by QNSP is frequent in our area, and almost 50\% of adult patients with pharyngeal colonization by pneumococci harbor QNSP. Though in most cases these isolates remain susceptible to newer FQs, this may be a serious first step toward a further increase in the number of fully resistant strains. Hospitalization and exposure to FQs are significant risk factors according to the univariate analysis, and the multivariate analysis shows that exposure both to older and newer FQs is the only factor independently associated with colonization by QNSP.

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