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# Letters to the Editor

## Influences of Different Factors on Prevalence of Ciprofloxacin Resistance in *Streptococcus pneumoniae* in Spain

A role of the use of fluoroquinolones in the development of resistance to ciprofloxacin in *Streptococcus pneumoniae* in Canada has been recently suggested (2). We would like to contribute support for this hypothesis from three different perspectives.

First, we compared the levels of prevalence of ciprofloxacin resistance between macrolide- and β-lactam-susceptible and nonsusceptible *S. pneumoniae* strains. Then, we looked at differences in ciprofloxacin resistance among serotypes. Finally, ciprofloxacin resistance of strains isolated from children was compared to that of strains from adults. A total of 1,113 pneumococcal isolates were collected from patients with community-acquired respiratory tract infections in a 1-year period (1996–1997) in a nationwide Spanish prospective multicenter surveillance study (1). Susceptibility testing and breakpoints used followed NCCLS recommendations (4). A breakpoint for resistance to ciprofloxacin of ≥4 μg/ml was used for this analysis, as a ciprofloxacin breakpoint has not been approved for *S. pneumoniae* by NCCLS. Statistical significance was determined by the $\chi^2$ test.

Using an MIC >2 μg/ml, 59 strains were resistant to ciprofloxacin (5.3%). A significant difference in the prevalence of resistance to ciprofloxacin was found between the macrolide-susceptible and nonsusceptible pneumococci (4 versus 8%; $P < 0.01$) (Table 1). However, no differences in ciprofloxacin resistance (around 5%) were related to whether the strains were susceptible to amoxicillin, amoxicillin-clavulanic acid, or cefuroxime. Despite being high, the penicillin odds ratio (OR) did not reach statistical significance.

Ciprofloxacin resistance was more prevalent among ST-19 strains (9.9%), nontypeable strains (9.3%), and ST-3 strains (9.1%) than in other strains (ST-14, 6.7%; ST-9, 4.5%; ST-6, 1.8%; ST-23, 1.7%; other serotypes, 3.3%).

No strains for which the MIC of ciprofloxacin was ≥4 μg/ml were found among the 125 pneumococci from children, whereas there were 59 such strains among the 988 strains (6%) from adults. Interestingly, strains for which the MICs were ≥8 and ≥16 μg/ml accounted for 1.9 and 0.6% of the strains from adults. Using an MIC of ≥2 μg/ml for ciprofloxacin resistance, 224 resistant strains (22.6%) were found among those isolated from adults, in contrast with 9 strains (7.2%) from children (OR, 3.78; 95% confidence interval [CI], 1.83 to 8.1; $P < 0.01$).

The different prevalence of ciprofloxacin resistance in adults compared to children, even when a lower breakpoint is used (lower levels of resistance precede higher ones), appears to be consistent with the hypothesis of a link between fluoroquinolone consumption (extremely low in children, if any) and selection of resistance. Despite the fact that ST-19, together with ST-6, is recognized as the most prevalent serotype in children in Spain (3) and also the most prevalent ciprofloxacin-resistant serotype in our study, no resistant ST-19 strains were found in children, which suggests that phenotypic clusterization may be related to consumption as well. It is also noteworthy that ST-3, which has always been considered susceptible to penicillin and erythromycin, shows a high prevalence of ciprofloxacin resistance. Another important factor to bear in mind is the potential cross-selection of resistance to a drug by other, unrelated antibiotics. Our data show a tendency for ciprofloxacin-resistant pneumococci to cluster among the macrolide-nonsusceptible strains, suggesting that macrolide usage could select for ciprofloxacin resistance as well. All the aforementioned should be seriously taken into account in order to avoid the coselection of resistance and to preserve the value of present or future empirical antibiotics for use against community-acquired respiratory pathogens by using the therapy more likely to eradicate multiresistant pathogens.

TABLE 1. Prevalence of ciprofloxacin-resistant (MIC ≥4 μg/ml) *S. pneumoniae* strains

| Antibiotic[a] | No. of isolates (%) | | OR | 95% CI | *P* |
|---|---|---|---|---|---|
| | Nonsusceptible[b] | Susceptible[c] | | | |
| Penicillin | 42/669 (6.3) | 17/444 (3.8) | 1.68 | 0.92–3.12 | 0.074 |
| Amox | 23/460 (5) | 36/653 (5.5) | 0.94 | 0.53–1.67 | 0.83 |
| Amox-Clav | 24/451 (5.3) | 35/662 (5.3) | 1.01 | 0.57–1.77 | 0.98 |
| Cefuroxime | 30/559 (5.3) | 29/554 (5.2) | 1.03 | 0.59–1.79 | 0.92 |
| Erythromycin | 32/382 (8.5) | 27/731 (3.7) | 2.38 | 1.36–4.17 | 0.0015 |
| Clarithromycin | 32/357 (9) | 27/756 (3.6) | 2.66 | 1.52–4.66 | 0.0003 |
| Azithromycin | 32/385 (8.3) | 27/728 (3.7) | 2.35 | 1.35–4.12 | 0.0018 |

[a] Amox, amoxicillin; Clav, clavulanic acid.
[b] NCCLS MIC breakpoints for nonsusceptibility are as follows: penicillin, ≥0.12 μg/ml; amoxicillin and cefuroxime, ≥1 μg/ml; amoxicillin-clavulanic acid, ≥1/0.5 μg/ml; erythromycin and clarithromycin, ≥0.5 μg/ml; azithromycin, ≥1 μg/ml.
[c] NCCLS MIC breakpoints for susceptibility are as follows: penicillin, ≤0.06 μg/ml; amoxicillin and cefuroxime, ≤0.5 μg/ml; amoxicillin-clavulanic acid, ≤0.5/0.25 μg/ml; erythromycin and clarithromycin, ≤0.25 μg/ml; azithromycin, ≤0.5 μg/ml.

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**C. García-Rey**
**L. Aguilar***
*Medical Department*
*SmithKline Beecham Pharmaceuticals*
*Madrid, Spain*

**F. Baquero**
*Microbiology Department*
*Hospital Ramón y Cajal*
*Madrid, Spain*

**Spanish Surveillance Group for Respiratory Pathogens†**

*Phone: 34 91 334 5275
Fax: 34 91 334 5141
E-mail: lorenzo.aguilar-alfaro@sb.com


†E. Bouza, Madrid; M. Casal, Córdoba; R. Cisterna, Bilbao; R. Dal-Ré; Madrid; J. García-de-Lomas, Valencia; C. García-Riestra, Santiago de Compostela; J. A. García-Rodríguez, Salamanca; M. Gobernado, Valencia; C. Gómez-García, Badajoz; R. Gómez-Lus, Zaragoza; A. Gutiérrez, Madrid; T. Jiménez-de-Anta, Barcelona; M. Martín-Sánchez, Las Palmas; E. Perea, Sevilla; G. Prats, Barcelona; M. de la Rosa, Granada; and J. J. Granizo, Madrid.