JOURNAL OF CLINICAL MICROBIOLOGY, Nov. 2000, p. 4298–4299 Vol. 38, No. 11
0095-1137/00/$04.00+0

Macrolide and Fluoroquinolone (Levofloxacin) Resistances among *Streptococcus pneumoniae* Strains: Significant Trends from the SENTRY Antimicrobial Surveillance Program (North America, 1997–1999)

Chen et al. (1) compared the results of tests on 7,551 *Streptococcus pneumoniae* strains isolated in Canadian medical centers between 1988 and 1998. Strains with reduced susceptibility to fluoroquinolones (ciprofloxacin MIC, ≥4 μg/ml) dramatically increased between 1993 (0.0%) and 1997–1998 (1.7%), which corresponds to Canadian fluoroquinolone prescription increases (0.8 to 5.5 per 100 persons per year). These findings, confirmed by the experience of others (2; R. N. Jones, D. J. Biedenbach, D. M. Johnson, and the Trovafloxacin Study Group, Abstr. 99th Gen. Meet. Am. Soc. Microbiol. 1999; abstr. C-421, p. 191. 1999) prompted the SENTRY Antimicrobial Surveillance Program to query its North American (United States and Canada) pneumococcal testing experience for 1997 through 1999.

A total of 5,055 *S. pneumoniae* strains were isolated from eight sites in Canada and 28 sites in the United States. All strains were forwarded to the University of Iowa College of Medicine (Iowa City) for confirmation of organism identification and for testing against a large number of antimicrobial agents (≥30 drugs each year). Methods recommended by the National Committee for Clinical Laboratory Standards (NCCLS) were used, and the most recently published interpretive criteria were applied (4, 5). The validated, reference broth microdilution trays were prepared by MicroScan (West Sacramento, Calif.) or Sensititre/TREK Diagnostics (West Lake, Ohio).

Table 1 lists the percentages of pneumococcal strains found in the susceptible and resistant categories for strains isolated in 1997–1998 (combined) and in 1999. Among the 3,854 strains (703 from Canada; 3,151 from the United States) isolated in 1997–1998, penicillin-nonsusceptible rates varied from 25.6 to 34.7% for Canada and the United States, respectively. The penicillin susceptibility rate, however, for North American samples of *S. pneumoniae* remained relatively stable (67.0 versus 67.1%) over the three monitored years, with only a slight increase in the strains with penicillin MICs of ≥2 μg/ml (resistant).

In contrast to the cited penicillin resistance rates, greater macrolide (erythromycin, azithromycin, and clarithromycin) resistance emerged in both nations in 1999. The rate of macrolide susceptibility decreased from a range of 83.1 to 89.3% to 75.4% in only 1 year. The distribution of macrolide-nonsusceptible strains was dominated by the M phenotype (69.2 to 72.3% of isolates) without significant change between samples or nations. Similarly, the proportion of strains with reduced fluoroquinolone susceptibility also significantly ($P < 0.05$) increased. In 1997–1998, the percentage of pneumococci having ciprofloxacin MICs of ≥4 μg/ml was 1.7 to 2.4% (average, 1.9%), a rate very comparable to that reported by Chen et al. (1). This resistance rate increased slightly in 1999, but a commonly used fluoroquinolone, levofloxacin, showed a diminished spectrum of activity with high-level resistance (MIC, ≥8 μg/ml) rates increasing threefold or more (0.2 to 0.3 to 0.9%). Another longitudinal paired sample of *S. pneumoniae* strains (>6,000 total isolates from ≥200 laboratories in the United States) also demonstrated an increase in levofloxacin-resistant isolates from 0.2 to 0.8%, between the respiratory disease seasons of 1997–1998 and 1998–1999 (2; Jones et al., Abstr. 99th Gen. Meet. Am. Soc. Microbiol. 1999). The baseline rate for the SENTRY Program (1997–1998) documenting a lower levofloxacin resistance rate (0.2 to 0.3%) was also observed by others (6, 7).

This escalated occurrence of macrolide- and levofloxacin-resistant pneumococcal strains appears to be related to selective pressure by current drug use in each class of antimicrobials. The Canadian results clearly showed increasing fluoroquinolone (ciprofloxacin and levofloxacin) use as a contributing influence to the resistance (1). The fluoroquinolone (levofloxacin) resistance was most likely to emerge in strains that were either intermediate ($P < 0.05$; odds ratio [OR] = 5.8) or resistant ($P < 0.05$, OR = 7.0) to penicillin. The levofloxacin resistance rates were 0.1, 2.3, and 2.8% for the penicillin-susceptible, -intermediate, and -resistant *S. pneumoniae* strains, respectively. The levofloxacin-resistant strains also occurred in older patients but were widely distributed geographically within North America (nine institutions). These results confirm many of the findings in Canada (1, 7). Gyrase or topoisomerase gene sequence analysis of the 13 identified levofloxacin-resistant *S. pneumoniae* strains demonstrated numerous patterns of mutations and no clonality by automated ribotyping and pulsed-field gel electrophoresis.

The world-wide problem of β-lactam resistance in *S. pneumoniae* has been recently complicated by increasing resistances to the macrolides and some older fluoroquinolones (ciprofloxacin and levofloxacin). In North America, patterns of orally administered antimicrobial use have produced contemporary selective pressures that continue to expand resistance rates. Furthermore, sequential mutations of several gyrase or topoisomerase target sites occur more often with the less potent agents (ciprofloxacin and levofloxacin) than with the newer fluoroquinolones (gatifloxacin and moxifloxacin) that have improved pharmacodynamic properties (3). Lastly, clinical microbiology laboratories should offer accurate quantitative (wide dilution schedules) susceptibility tests for the fluoroquinolones

TABLE 1. Trends in resistance patterns among *S. pneumoniae* isolates in the SENTRY Antimicrobial Surveillance Program (1997–1999, North America)

Antimicrobial agent	% of isolates susceptible (resistant) in[a]:	
	1997–1998 (3,854 strains)	1999 (1,201 strains)
Penicillin	65.3–74.4 (7.5–13.5)[b]	67.1 (14.9)
Erythromycin	83.1–89.3 (9.8–15.9)	75.4 (23.7)[c]
Ciprofloxacin	NA [1.7–2.4][d]	NA[e] [2.0]
Levofloxacin	99.1–99.6 (0.2–0.3)	98.9 (0.9)[c]

[a] Susceptibility interpreted by NCCLS criteria (5).
[b] Range of percentages indicates the minimal variations between Canada and U.S. results for 1997–1998, with a greater susceptibility usually found in Canada.
[c] Significant increase in high-level resistance between the presented data samples ($P < 0.05$).
[d] Values in brackets indicate the percentages of strains meeting the resistance criteria suggested by Chen et al. (1).
[e] NA, no applicable criteria for susceptibility have been published by the NCCLS (5).

to facilitate the early identification of various resistance mutations in pneumococci.

We acknowledge the support of the following individuals in the manuscript preparation and performance of various technical work: K. Meyer, T. Granacher, D. J. Biedenbach, W. Wilke, and the SENTRY Monitor Staff.

The SENTRY Program was funded by an education/research grant from Bristol-Myers Squibb.

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