JOURNAL OF CLINICAL MICROBIOLOGY, Nov. 2002, p. 4332–4333 Vol. 40, No. 11
0095-1137/02/$04.00+0 DOI: 10.1128/JCM.40.11.4332–4333.2002

Impact of Modified Nonmeningeal *Streptococcus pneumoniae* Interpretive Criteria (NCCLS M100-S12) on the Susceptibility Patterns of Five Parenteral Cephalosporins: Report from the SENTRY Antimicrobial Surveillance Program (1997 to 2001)

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Received 17 May 2002/Accepted 19 August 2002

The revised interpretive criteria for *Streptococcus pneumoniae* recently published in the NCCLS M100-S12 informational supplement provide two sets of breakpoints for some cephalosporins: one set for meningeal infection isolates and a new set for nonmeningeal infection isolates. The net effect of these changes was to increase the reported rates of susceptibility of *S. pneumoniae* to the more active parenteral cephalosporins, such as cefepime, cefotaxime, and ceftriaxone, by 9.1 to 13.0%, bringing their in vitro rates much closer to those of amoxicillin (modified in an earlier NCCLS publication). These revised breakpoints will assist the rational prescribing of antimicrobial agents for the treatment of pneumococcal infections for specific types of infection and establish a greater correlation with clinical outcomes.

The revised interpretive MIC breakpoints for *Streptococcus pneumoniae* in NCCLS document M100-S10 (3) resulted in an anomalous situation in which more isolates would be reported as intermediate or resistant to broad-spectrum parenteral cephalosporins than to orally administered amoxicillin despite the twofold greater potency of agents such as ceftriaxone (6) and their superior bioavailability. This inconsistency was caused because the amoxicillin and amoxicillin-clavulanate breakpoints were based on their use in nonmeningeal infections, while those of the cephalosporins were set conservatively on the basis of their use in meningeal infections with limited associated bioavailability (4). Recently revised guidelines provide interpretive MIC breakpoints for some parenterally delivered cephalosporins for both meningeal and nonmeningeal (example: pneumonia with or without bacteremia) isolates of *S. pneumoniae* (5).

By using data covering the period of 1996 to 2000 from their surveillance network database, Sahm and colleagues (7) have estimated that the new guidelines will reduce the number of isolates reported as either intermediate or resistant to cefotaxime and ceftriaxone by 10% and 3 to 4%, respectively. However, other clinically usable parenteral cephalosporins were not addressed, including cefepime, a relatively new cephalosporin with an extended spectrum of activity that includes many species resistant to cefotaxime or ceftriaxone. Using five-year results (1997 to 2001) for the United States from the SENTRY Antimicrobial Surveillance Program, we were able to compare the rates of susceptibility to five cephalosporins (cefepime, cefotaxime, ceftazidime, ceftriaxone, and cefuroxime), penicillin, erythromycin, and vancomycin by applying the M100-S11 (4) and M100-S12 (5) criteria for nonmeningeal isolates of *S. pneumoniae*.

A total of 7,938 nonmeningeal infection isolates were selected for the period of 1997 to 2001 from the U.S. region of the SENTRY Antimicrobial Surveillance Program. These were consecutive prevalence study strains without preselection bias (7). The susceptibility criteria from M100-S11 and M100-S12 were identical for penicillin, erythromycin, and vancomycin (4, 5) and also remained unchanged for cefuroxime sodium (≤0.5 μg/ml). No criteria have been published for ceftazidime. All MIC results were obtained by using NCCLS reference methods (3) in a central monitoring laboratory with all quality control determinations within specified limits (5).

Table 1 compares the susceptibility rates of all of the antimicrobial agents by year of sampling, as well as by using summary data from Sahm et al. (7). The data show a clear trend toward decreasing susceptibility rates over the 5-year period for all of the agents except vancomycin. Vancomycin was also the only antimicrobial agent to which nonmeningeal infection isolates of *S. pneumoniae* remained completely susceptible. A comparison of the all-years SENTRY Antimicrobial Surveillance Program data with those from the earlier publication (7) shows a close concordance of the results for ceftriaxone but not of those for cefotaxime.

On the basis of our all-years results, the change in the MIC susceptibility criteria (5) for cefepime, cefotaxime, and ceftriaxone from 0.5 to 1.0 μg/ml (the cefuroxime breakpoint remains at 0.5 μg/ml) has a marked effect on the susceptibility rates, with increases ranging from 9.1% for cefotaxime to 11.2 and 13.0% for cefepime and ceftriaxone, respectively. Cefuroxime susceptibility rates were unchanged, and ceftazidime exhibited markedly less coverage (64.7 to 67.8%) of pneumococci on the basis of those breakpoints for the other agents tested.

The influence of penicillin susceptibility patterns on the sus-

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TABLE 1. Comparison of rates of susceptibility to Five cephalosporins, penicillin, erythromycin, and vancomycin on the basis of NCCLS M100-S11 (4) and M100-S12 (3) interpretive criteria for 7,938 nonmeningeal infection isolates of *S. pneumoniae* in the United States

Yr(s) of sampling	% Susceptible at ≤0.5/≤1 μg/ml					% Susceptible[a]		
	Ceftriaxone	Cefotaxime	Cefepime	Ceftazidime[b]	Cefuroxime[c]	Penicillin	Erythromycin	Vancomycin
1997	NT[d]	88.6/99.6	89.7/98.1	NT	81.3/83.8	75.6	86.7	100.0
1998	NT	89.3/96.8	88.4/98.1	71.9/75.3	78.0/80.1	72.8	83.1	100.0
1999	87.4/97.3	83.0/96.0	86.9/98.1	68.4/72.5	72.2/74.4	70.4	78.4	100.0
2000	82.7/95.4	NT	84.8/97.4	68.0/70.4	69.8/73.0	68.2	75.1	100.0
2001	79.1/93.9	NT	79.7/95.9	NT	69.5/70.9	65.6	70.3	100.0
All years	82.2/95.2	87.4/96.5	85.3/96.5	64.7/67.8	75.3/77.7	67.6	79.3	100.0
2002[e]	82.7/95.9	79.2/93.5	NR[g]	NR	NR	53.2[f]	NR	NR

[a] The susceptibility criteria from NCCLS M100-S11 and M100-S12 were identical for these three antimicrobials (4, 5).
[b] Ceftazidime does not have published interpretive criteria and was consistently less potent by weight, than the other cephalosporins.
[c] The cefuroxime sodium susceptibility criterion was ≤0.5 μg/ml and is unchanged in M100-S12 (5).
[d] NT, not tested.
[e] Data from reference 7 for cefotaxime (10,777 strains) and ceftriaxone (9,863 strains) processed by various nonreference hospital-based methods from 1996 to 2000.
[f] Average of reported rates.
[g] NR, not reported.

ceptibilities of the four parenteral cephalosporins with interpretive criteria (cefepime, ceftriaxone, cefotaxime, and cefuroxime) and erythromycin is shown in Table 2. All penicillin-susceptible strains of *S. pneumoniae* were >99% susceptible to all of the cephalosporins listed. An activity of ≥97.9% was maintained for all of the cephalosporins except cefuroxime (52.2%) against penicillin-intermediate strains. Against penicillin-resistant strains, cefepime had the best activity (only 2.9% of the strains were resistant), with resistance rates of 8.3, 8.7, and 99.5% for cefotaxime, ceftriaxone, and cefuroxime, respectively. A previous study (7) used an *S. pneumoniae* isolate population with preselection bias toward penicillin resistance (46.8%), compared to the prevalence design reported here (32.4% penicillin resistance) for the SENTRY Antimicrobial Surveillance Program interval of 1997 to 2001.

TABLE 2. Influence of penicillin susceptibility patterns on susceptibilities to four parenteral cephalosporins and erythromycin on the basis of NCCLS M100-S12 interpretive criteria (5)

Antimicrobial and penicillin category (no. of isolates tested)	% by category		
	Susceptible	Intermediate	Resistant
Cefepime			
Susceptible (5,364)	99.9	0.1	0.0
Intermediate (1,408)	98.7	0.9	0.4
Resistant (1,166)	78.5	18.6	2.9
Cefotaxime			
Susceptible (3,060)	99.9	<0.1	<0.1
Intermediate (929)	98.1	1.1	0.8
Resistant (601)	76.7	15.0	8.3
Cefuroxime			
Susceptible (4,295)	99.2	0.5	0.3
Intermediate (1,216)	52.2	10.5	37.3
Resistant (992)	0.5	0.0	99.5
Ceftriaxone			
Susceptible (4,295)	99.8	0.1	0.1
Intermediate (479)	97.9	1.5	0.6
Resistant (565)	74.2	17.2	8.7
Erythromycin			
Susceptible (5,364)	93.4	0.7	5.9
Intermediate (1,408)	63.2	0.5	35.3
Resistant (1,166)	34.0	0.8	65.3

The in vitro activity of erythromycin was inferior to those of cefepime, cefotaxime, and ceftriaxone for all categories of penicillin susceptibility, with only 34% of penicillin-resistant isolates being susceptible to the macrolide. Rates of resistance to this antimicrobial class have increased alarmingly worldwide in the past few years, casting serious doubt on the continuing utility of macrolides in the treatment of serious pneumococcal infections (1).

Overall, our results confirm and significantly expand those of Sahm et al. (7) to all clinically relevant parenteral cephalosporins having potencies versus *S. pneumoniae*, with all tests using reference MIC methods (2). The implementation of the changes in MIC breakpoints published in NCCLS M100-S12 (5) will provide a clearer picture of the clinical merits of these cephalosporins and some other β-lactams and, on the basis of their true breadth of activity, will encourage the more rational use of these agents in the treatment of various types of pneumococcal infections. Continued surveillance of these declining susceptibility patterns, however, appears to be a prudent practice.

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