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Impact of Modified Nonmeningeal Interpretive Criteria (NCCLS M100-S12) for *S. pneumoniae* (SPN): Perceived Susceptibility Patterns of Five Parenteral Cephalosporins (CEPH)

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SENTRY ANTIMICROBIAL SURVEILLANCE

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ABSTRACT

Background: This report from the SENTRY Antimicrobial Surveillance Program summarizes results (1997-2001) for five parenteral CEPHs with significant potency and clinical indications against SPN. Modifications by the NCCLS of susceptibility (S) testing criteria (2002) into meningeal and nonmeningeal infection breakpoints has altered the perception of the clinical value for these agents.

Methods: All SPN non-meningeal isolates (7,938 strains) were tested by reference NCCLS methods using ceftriaxone (CTRI), cefotaxime (TAX), cefepime (CPIM), ceftazidime (CTAZ) and cefuroxime (CROX); and compared to penicillin (PEN), erythromycin (ER) and vancomycin (VAN). Results were interpreted by NCCLS criteria published in M100-S11 (2001) and -S12 (2002). Overall PEN-S and ER-S rates were 67.6 and 79.3%, respectively. No VAN-R was observed (MICs, - 1 µg/ml).

Results: Results were analyzed by year of isolation (1997-2001) and relationship to PEN category. All CEPHs showed decreased S over time using either NCCLS criteria, example: CROX S at 83.8 to 70.9% after 5 years. The most active agents exhibited an increase % S with the 2002 criteria of 9.1 - 13.0% (CTRI, 95.2% S; CTAX, 96.5%; CPIM, 96.5%). The spectrum of CTAZ (67.8% at - 1 µg/ml) and CROX (70.9%) were significantly inferior in the last year studied (2001). For meningeal infections, the former breakpoint (- 0.5 µg/ml) remains in force. Overall PEN-S, -I, and -R strains had S rates to CTRI, CTAX and CPIM of 99.8 - 99.9, 97.9 - 98.7 and 74.2 - 78.5%, respectively. CROX was only active versus PEN-S isolates regardless of criteria used.

Conclusions: These results from nearly 8,000 SPN tested by NCCLS methods confirm the wide coverage of CTAX and CTRI previously noted using commercial, non-reference products (Sahm et al., JCM 40:669-674, 2002); and expands experience to alternative CEPHs, namely CPIM, CROX and CTAZ. Only 2.9 (CPIM) to 8.7 (CTRI) % of PEN-R SPN would be R to the better parenteral agents tested.

INTRODUCTION

Revised MIC interpretive breakpoints for *Streptococcus pneumoniae* in National Committee for Clinical Laboratory Standards (NCCLS) document M100-S10 [1] resulted in an anomalous situation where more isolates would be reported as intermediate or resistant to broad spectrum parenteral cephalosporins than for orally administered amoxicillin despite two-fold greater potency advantages for agents such as ceftriaxone [2] and superior bioavailability. This inconsistency was caused because amoxicillin and amoxicillin/clavulanate breakpoints were based on their use in nonmeningeal mild-moderate infections, while those of the cephalosporins were set conservatively on their use in meningeal infections with limited associated bioavailability [3]. Recently revised guidelines now provide MIC interpretive breakpoints for some parenterally delivered cephalosporins for both meningeal and nonmeningeal (example: pneumonia with or without bacteremia) isolates of *S. pneumoniae* [4].

By using data covering the period of 1996 to 2000 from their surveillance network database, Sahm and colleagues [5] estimate 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 (1997-2001) for the United States (US) from the SENTRY Antimicrobial Surveillance Program, we were able to compare the susceptibility rates for five cephalosporins (cefepime, cefotaxime, ceftazidime, ceftriaxone and cefuroxime), penicillin, erythromycin, and vancomycin applying the M100-S11 [3] and M100-S12 [4] criteria for nonmeningeal isolates of *S. pneumoniae*.

MATERIALS AND METHODS

A total of 7,938 nonmeningeal infection isolates were selected for the period from 1997 to 2001 from the US region of the SENTRY Program. These were consecutive, prevalence study strains without pre-selection bias [5]. The susceptibility criteria from M100-S11 and M100-S12 were identical for penicillin, erythromycin and vancomycin [3, 4], and also remained unchanged for cefuroxime sodium (-0.5 µg/ml). No criteria have been published for ceftazidime. All MIC results were performed by reference NCCLS [6] methods in a central monitoring laboratory with all quality control determinations within specified limits [4].

RESULTS

- Table 1 compares the susceptibility rates for each of the antimicrobial agents by year of sample as well as using summary data from Sahm et al. [3]. The data show a clear trend toward decreasing susceptibility rates over the 5-year period for all agents except vancomycin. A comparison of the 'All years' SENTRY Program data with that from the earlier publication [5] shows a close concordance in the results for ceftriaxone but not for cefotaxime.

- Using our 'All year' results, the change in the MIC susceptibility criteria [NCCLS, 2002] for cefepime, cefotaxime and ceftriaxone from 0.5 to 1.0 µg/ml (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 a markedly lower coverage (64.7 - 67.8%) of pneumococci utilizing those breakpoints for the other tested agents.

- The influence of penicillin susceptibility patterns (susceptible-S, intermediate-I, resistant-R) on the susceptibilities of the four parenteral cephalosporins with interpretive criteria (cefepime, ceftriaxone, cefotaxime and cefuroxime) and erythromycin is shown in Table 2. All penicillin-S strains of *S. pneumoniae* were > 99% susceptible to all listed cephalosporins. An activity of • 97.9% was maintained for all cephalosporins except cefuroxime (52.2%) against penicillin-I strains. Against penicillin-R strains, cefepime had the best activity (only 2.9% of strains being resistant) with resistance rates of 8.3, 8.7, and 99.5% for cefotaxime, ceftriaxone and cefuroxime, respectively.

- The in vitro activity of erythromycin was inferior to cefepime, cefotaxime and ceftriaxone for all categories of penicillin susceptibility, with only 34% of penicillin-R isolates being susceptible to the macrolide. Resistance rates 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 [7].

Table 1. Comparison of susceptibility rates for five cephalosporins, penicillin, erythromycin and vancomycin using NCCLS M100-S11 and M100-S12 interpretive criteria for 7,938 non-meningeal infection isolates of *S. pneumoniae* in the US.

	% susceptible at - 0.5/- 1 µg/ml					% susceptible[a]		
Year of sample	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
Sahm et al. [2002][e]	82.7/95.9	79.2/93.5	NR	NR	NR	53.2[f]	NR	NR

a. Susceptibility criteria from NCCLS M100-S11 and M100-S12 were identical for these three antimicrobials.
b. Ceftazidime *does not* have published interpretive criteria, and consistently was less potent by weight compared to other cephalosporins.
c. The cefuroxime sodium susceptibility criteria was - 0.5 µg/ml, unchanged in M100-S12.
d. NR = not reported, NT = not tested.
e. From Sahm et al. [5] for cefotaxime (10,777 strains) and ceftriaxone (9,863 strains) processed by various, non-reference hospital-based methods from 1996-2000.
f. Average of reported rates.

Table 2. Influence of penicillin susceptibility patterns on the susceptibilities of four parenteral cephalosporins and erythromycin using NCCLS M100-S12 interpretive criteria.

		% by category		
Antimicrobial	Penicillin category (no. tested)	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

CONCLUSIONS

- Overall, our results confirm and significantly expand those reported earlier [5] to all clinically relevant parenteral cephalosporins having potencies versus S. pneumoniae, with all tests using reference MIC methods. The implementation of the changes in MIC breakpoints published in NCCLS M100-S12 [4] will provide a clearer picture of the clinical merits of these cephalosporins and some other ß-lactams, and based on 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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