1088
ECCMID 2005
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax
319.665.3371
ronald-jones@jmilabs.com

Comparative Activity of Oral and Parenteral Cephalosporins Against Multidrug-Resistant *Streptococcus pneumoniae*: Report from the SENTRY Antimicrobial Surveillance Program (1997-2003)

S POTTUMARTHY, TR FRITSCHE, HS SADER, RN JONES
JMI Laboratories, North Liberty, IA, USA

SENTRY ANTIMICROBIAL SURVEILLANCE

ABSTRACT

Background: Multidrug-resistant (MDR) *S. pneumoniae* strains are increasing at an alarming rate worldwide. The therapy of respiratory tract infections due to these strains is challenging with an urgent need for antimicrobials with reliable activity against the MDR strains. Comparative activity of oral cephalosporins and parenteral cephalosporins against various pneumococcal MDR phenotypes was analyzed in a large, multi-year international collection of clinical strains of *S. pneumoniae.*

Methods: *S. pneumoniae* strains (21,605) collected during 1997-2003 from worldwide participants of the SENTRY Program were tested and interpreted using NCCLS (M7-A6, M100-S14) guidelines. The antimicrobial agents analyzed included penicillin (PEN), erythromycin (ER), clindamycin (CM), tetracycline (TET) and trimethoprim/sulfamethoxazole (TS); cephalosporins monitored included oral (cefpodoxime, cefuroxime) and parenteral (ceftriaxone, cefepime) agents.

Results: The rank order of occurrence rates of the various resistance phenotypes were: PEN only (32.0%) > PEN and ER (17.6%) > PEN, ER and CM (8.6%) > PEN, ER, CM and TET (7.6%) > PEN, ER, CM and TS (6.5%) > all five drugs (5.7%). The susceptibility rate of all strains to the orally administered cephalosporins, cefpodoxime (77.6%) and cefuroxime (77.3%), dropped to only 16.1% and 14.5% respectively, for the five-drug MDR phenotype. The parenteral cephalosporins retained excellent activity for all MDR phenotypes, with resistance rates being lower for cefepime than ceftriaxone (cefepime, 1.3 -1.9%; ceftriaxone, 3.0 - 4.4%) or the oral cephalosporins (cefpodoxime, 64.4 - 74.1%; cefuroxime, 69.3 - 79.1%) using respiratory infection breakpoints (NCCLS).

Conclusions: Our in vitro findings confirm that the parenteral cephalosporins, cefepime and ceftriaxone, retain excellent activity against the MDR phenotypes analyzed, and remain useful drugs in the armamentarium to treat MDR pneumococcal respiratory tract infections.

INTRODUCTION

Streptococcus pneumoniae remains the leading cause of community-acquired respiratory tract infections. While the "antibiotic era" saw the decline in mortality due to bacteremic pneumococcal disease from 80% to approximately 20%, the selective pressure from expanded antimicrobial usage has resulted in the emergence and global spread of multidrug-resistant (MDR) pneumococcal phenotypes.

Rates of resistance to all ß-lactam agents are known to increase in parallel with penicillin resistance, as does resistance to several other classes of antimicrobial agents. With the increasing resistance rates to pneumococci, the therapy of respiratory tract infections has become more problematic, resulting in the urgent need for antimicrobials with established activity against MDR strains.

To assess the anti-pneumococcal activity of orally and parenterally administered cephalosporins against various MDR phenotypes, 21,605 clinically significant *S. pneumoniae* isolates collected during 1997 to 2003 from over 70 medical centers participating in the global SENTRY Antimicrobial Surveillance Program were analyzed.

MATERIALS AND METHODS

Strain collection: The isolates were obtained from the following sources (strains/%): blood stream infections (4,208/19.5%), community-acquired respiratory tract infection (15,276/70.7%), patients hospitalized with pneumonia (2,035/9.4%), other infections (23/0.1%), and from various body sites in patients located in the intensive care unit (63/0.3%).

Susceptibility testing methods: MIC values were determined using the reference broth microdilution test as described in the National Committee for Clinical Laboratory Standards (NCCLS) approved standard and interpreted by NCCLS guidelines for *S. pneumoniae* [NCCLS, 2003 and 2004]. The antimicrobial agents analyzed included: penicillin, erythromycin, clindamycin, tetracycline, and trimethoprim/sulfamethoxazole; cephalosporins monitored included two commonly used oral agents (cefuroxime and cefpodoxime), and a third- and fourth-generation parenteral compound (ceftriaxone and cefepime, respectively).

Data analysis: Comparison of the anti-pneumococcal potency of the four cephalosporins was performed for all strains, including penicillin-resistant strains, and strains exhibiting various multidrug resistance phenotypes (MDR). MDR was defined as an isolate being intermediate or resistant to two or more of the following drug classes: ß-lactams, macrolides, lincosamides, tetracyclines or trimethoprim/sulfamethoxazole.

RESULTS

- Of the 21,605 isolates studied, over two-thirds were found to have one or more resistance markers. (Table 1).

Table 1. Activity of selected cephalosporins tested by reference methods against MDR *S. pneumoniae* phenotypes.

		MIC (mg/L)		% by category:[b]		
MDR phenotype (no. tested)[a]	Antimicrobial agent	Mode	90%	Susceptible	Intermediate	Resistant
PEN (6,907)	Cefepime	1	2	88.1	10.7	1.2
	Ceftriaxone	1	2	89.1	8.2	2.7
	Cefpodoxime	2	4	35.0	12.5	52.5
	Cefuroxime	4	8	33.4	8.9	57.7
PEN, ER (3,798)	Cefepime	1	2	85.0	13.7	1.3
	Ceftriaxone	1	2	86.9	10.0	3.0
	Cefpodoxime	2	4	22.7	12.3	65.0
	Cefuroxime	4	8	21.2	8.6	70.2
PEN, ER, CM (1,863)	Cefepime	1	2	83.8	14.6	1.6
	Ceftriaxone	1	2	85.0	11.6	3.4
	Cefpodoxime	2	4	24.5	11.1	64.4
	Cefuroxime	4	8	23.0	7.6	69.4
PEN, ER, CM, TET (1,633)	Cefepime	1	2	84.0	14.5	1.5
	Ceftriaxone	1	2	85.2	11.2	3.6
	Cefpodoxime	2	4	24.8	10.8	64.4
	Cefuroxime	4	8	23.6	7.1	69.3
PEN, ER, CM, TS (1,410)	Cefepime	1	2	80.8	17.3	1.9
	Ceftriaxone	1	2	82.4	13.4	4.2
	Cefpodoxime	2	4	15.6	10.3	74.1
	Cefuroxime	4	8	13.9	7.0	79.1
PEN, ER, CM, TET, TS (1,232)	Cefepime	1	2	80.8	17.3	1.9
	Ceftriaxone	1	2	82.7	12.9	4.4
	Cefpodoxime	2	4	16.1	10.3	73.6
	Cefuroxime	4,8	8	14.5	6.7	78.8
All strains (21,605)	Cefepime	≤0.12	1	96.2	3.5	0.3
	Ceftriaxone	≤0.25	1	96.5	2.6	0.9
	Cefpodoxime	≤0.03	2	77.6	4.4	18.0
	Cefuroxime	≤0.06	4	77.3	3.2	19.5

a. PEN = penicillin-resistant (MIC, ≥ 0.12 mg/L); ER = erythromycin-resistant (MIC, ≥ 0.5 mg/L); CM = clindamycin-resistant (MIC, ≥ 0.5 mg/L); TET = tetracycline-resistant (MIC, ≥ 4 mg/L); and TS = trimethoprim/sulfamethoxazole-resistant (MIC, ≥ 1/19 mg/L) [NCCLS, 2004].
b. Interpretive criteria of the NCCLS [2004] for respiratory tract infection isolates of *S. pneumoniae*.

- The rank order of the resistant rates among selected resistance phenotypes was as follows: penicillin alone (also other ß-lactams; 32.0%) > penicillin and erythromycin (17.6%) > penicillin, erythromycin and clindamycin (8.6%) > penicillin, erythromycin, clindamycin and tetracycline (7.6%) > penicillin, erythromycin, clindamycin and trimethoprim/sulfamethoxazole (6.5%) > and all 5 drugs (5.7%; Table 1).
- The susceptibility rate of all strains to cefpodoxime (77.6%) and cefuroxime (77.3%) decreased markedly to 16.1 and 14.5%, respectively, for the five drug MDR phenotype.
- This finding was in stark contrast to that of the parenteral third- and fourth-generation cephalosporins, where 96.2 and 96.5% of all strains were susceptible to cefepime and ceftriaxone, respectively, and decreased to 80.8 and 82.7% among the most resistant phenotype (five drugs).
- The modal MIC values of cefepime and ceftriaxone when examining all strains increased from ≤ 0.12 and ≤ 0.25 mg/L, respectively, to 1 mg/L for all MDR phenotypes; the MIC_{90} value only increased two-fold, from 1 to 2 mg/L (Tables 1 and 2).
- The cefepime versus ceftriaxone resistance rate ratio was approximately 1:2 for all resistance phenotypes analyzed (Table 2).

Table 2. MIC population distributions for the two parenteral cephalosporins having the greatest anti-pneumococcal potency indexed by MDR pattern (six types).

		% at each MIC (mg/L):						
MDR phenotype (no. tested)[a]	Antimicrobial agent	≤0.12	0.25	0.5	1	2	4	≥8
PEN (6,907)	Cefepime	18.9	11.0	18.7	39.4	10.7	0.9[b]	0.3
	Ceftriaxone	-	30.7	15.1	43.4	8.2	2.2	0.4
PEN, ER (3,798)	Cefepime	9.9	7.9	19.6	47.6	13.7	1.0[b]	0.3
	Ceftriaxone	-[c]	22.1	14.3	50.5	10.0	2.4	0.6
PEN, ER, CM (1,863)	Cefepime	12.0	7.8	17.0	47.1	14.5	1.3	0.3
	Ceftriaxone	-	22.7	12.7	49.6	11.6	2.6	0.8
PEN, ER, CM, TET (1,633)	Cefepime	11.8	8.3	17.1	46.7	14.6	1.3	0.2
	Ceftriaxone	-	22.8	12.3	50.1	11.3	2.6	1.0
PEN, ER, CM, TX (1,410)	Cefepime	6.2	6.0	16.6	52.1	17.3	1.7	0.2
	Ceftriaxone	-	12.9	13.1	56.4	13.4	3.1	1.1
PEN, ER, CM, TET, TS (1,232)	Cefepime	6.1	6.4	17.0	51.4	17.3	1.8	0.1
	Ceftriaxone	-	13.4	12.8	56.5	12.9	3.2	1.2
All strains (21,605)	Cefepime	72.5	4.6	6.3	12.8	3.5	0.3	0.1
	Ceftriaxone	-	77.8	5.1	13.6	2.6	0.7	0.1

a. PEN = penicillin-resistant (MIC, ≥ 0.12 mg/L); ER = erythromycin-resistant (MIC, ≥ 0.5 mg/L); CM = clindamycin-resistant (MIC, ≥ 0.5 mg/L); TET = tetracycline-resistant (MIC, ≥ 4 mg/L); and TS = trimethoprim/sulfamethoxazole-resistant (MIC, ≥ 1/19 mg/L) [NCCLS, 2004].
b. Underlined values are the proportions of isolates at resistant MIC levels.
c. - = untested MIC.

CONCLUSIONS

- The higher anti-pneumococcal potency and wider spectrum of the parenteral compared to the orally administered cephalosporins against MDR phenotypes was confirmed in this large international sample of *S. pneumoniae* isolates (21,605) collected over a 7-year period as a part of the SENTRY Antimicrobial Surveillance Program.
- Among the parenteral cephalosporins, cefepime exhibited greater anti-pneumococcal activity against the various MDR drug phenotypes, by having significantly lower resistance rates ($p < 0.05$) compared to ceftriaxone (1.3 - 1.9% versus 3.0 - 4.4%, respectively).
- Our findings confirm that the parenteral cephalosporins (cefepime and ceftriaxone) retain acceptable activity against the MDR phenotypes analyzed.
- In contrast, orally administered cephalosporins had limited value against the emerging MDR phenotypes for *S. pneumoniae*.

SELECTED REFERENCES

Aspa J, Rajas O, Rodriguez de Castro F, Blanquer J, Zalacain R, Fenoll A, de Celis R, Vargas A, Rodriguez Salvanes F, España PP, Rello J, & Torres A. (2004). Drug-Resistant pneumococcal pneumonia: Clinical relevance and related factors. *Clinical Infectious Diseases* 38:787-798.

Mandell LA, Bartlett JG, Dowell SF, File Jr TM, Musher DM, & Whitney C. (2003). Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clinical Infectious Diseases* 37:1405-1433.

Mera RM, White A, & Weil J. (2003) Increasing prevalence of multidrug-resistant *S. pneumoniae* in the USA over a 10-year period: Alexander Project, abstr. 202. In: *Programs and Abstracts of the 41st Annual Meeting of the Infectious Diseases Society of America*. San Diego, CA, October 9 - 12, 2003.

National Committee for Clinical Laboratory Standards. (2003). *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A6.* Wayne, PA:NCCLS.

National Committee for Clinical Laboratory Standards. (2004). *Performance standards for antimicrobial susceptibility testing, 14th informational supplement M100-S14.* Wayne, PA:NCCLS.

Whitney CG, Farley MM, Hadler J, Harrison LH, Lexau C, Reingold A, Lefkowitz L, Cieslak PR, Cetron M, Zell ER, Jorgensen J, & Schuchat A, for the Active Bacterial Core Surveillance Program of the Emerging Infections Program Network. (2000). Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. *The New England Journal of Medicine* 343:1917-1924.