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Antimicrobial Activity of Broad Spectrum Parenteral Cephalosporins Tested Against Bacterial Isolates from Pediatric Patients: Report from the SENTRY Antimicrobial Surveillance Program

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SENTRY ANTIMICROBIAL SURVEILLANCE

AMENDED ABSTRACT

Background: Cephalosporins (CEP) are extensively used for empirical treatment of infections in pediatric patients.
Methods: 12,737 strains from patients < 18 y were utilized from >30 North American (NA) medical centers in 1998-2004. Cefepime (CPM), ceftriaxone (CTX), ceftazidime (CTZ) and many comparators were S tested by CLSI broth microdilution methods. The strains were from bacteremia (4,876; 38.3%), community-acquired respiratory tract infections (4,223; 33.2%), and nosocomial pneumonia (1,609; 12.6%).
Results: The most common pathogens were: *S. pneumoniae* (SPN; 1,975, 15.5%), *H. influenzae* (HI; 1,862, 14.6%), *S. aureus* (SA; 1,762, 13.8%), *M. catarrhalis* (MC, 1,022, 8.0%), coag.-neg. staphylococci (1,020, 8.0%), *E. coli* (EC; 988, 7.8%), *P. aeruginosa* (PSA; 661, 5.2%) and *Klebsiella* spp. (KSP; 615, 4.8%). The activities of CPM, CTX and CTZ against the main pathogens are shown in the table.

Organism	MIC₉₀ (µg/ml)/% S CPM	CTX	CTZ
S. pneumoniae	1/93.9	1/93.7	16/-
Oxacillin (OXA)-S *S. aureus*	4/100.0	4/99.8	16/86.7
E. coli	≤0.12/99.6	≤0.25/98.9	≤2/98.6
P. aeruginosa	8/90.8	>32/11.0	16/87.3
Klebsiella spp.	0.25/99.0	≤0.25/96.4	≤2/95.1

All 3 CEP were very active against HI and MC. Only slight variations were noted among results from 3 age groups evaluated (≤ 1, 1-5 and 6-17 y). CPM and CTX showed similar activities against all main pathogens, except PSA. CTZ showed limited activity against SPN and OXA-S SA. CPM was slightly more active than CTZ against PSA and KSP, mainly in the <1 y group. Decreased S to ciprofloxacin (MIC, ≥ 4 µg/ml) was detected in 21 (1.1%) SPN isolates, mainly in the 6-17 y age group and only 2 isolates were resistant (R) to levofloxacin. Imipenem-R among PSA varied from 3.6 to 7.7%.
Conclusions: CPM was clearly the most broad-spectrum CEP overall and remains very potent against bacteria collected from infected pediatric patients in NA. Only OXA-R staphylococci and enterococci were less S to the CEP agents.

INTRODUCTION

Any pediatric infection that requires admission to a hospital (e.g. community-acquired pneumonia, meningitis or febrile neutropenia) or is acquired in the hospital (e.g. nosocomial pneumonia) should be considered serious, because it can be life threatening and must be resolved promptly. However, the increased prevalence of resistance among bacterial pathogens poses a serious challenge to the immediate successful empiric treatment of these serious infections.

Despite the numerous antimicrobial agents available for use in the hospital setting, many of the commonly-used broad-spectrum agents are compromised by declining susceptibilities. Cefepime is a "fourth-generation" cephalosporin with activity against Gram-positive and Gram-negative aerobic bacteria, and it is indicated for the treatment of serious infections such as febrile neutropenia and moderate-to-severe pneumonia, including cases complicated by bacteremia.

In the present study, we evaluated the in vitro activity of cefepime in comparison to ceftriaxone, ceftazidime and selected broad-spectrum antimicrobial agents against bacterial strains collected from pediatric patients through the SENTRY Antimicrobial Surveillance Program (1998 - 2004).

MATERIALS AND METHODS

The SENTRY Antimicrobial Surveillance Program was established to monitor all prevalent pathogens and antimicrobial resistance patterns of nosocomial and community-onset infections via a broad network of sentinel hospitals distributed by geographical location and bed capacity. A total of 12,737 isolates were collected from pediatric patients (≤ 17 year-old) in North American medical centers in the 1998- 2004 period and utilized in the present study. The monitored core infections included bloodstream infections, community-acquired respiratory tract infections, pneumonia in hospitalized patients, wound or skin and soft tissue infections, and urinary tract infections in hospitalized or clinic patients. The pediatric population was divided into three age group subsets for comparison of antimicrobial activity and spectrum: < 1 year-old, 1-5 year-old and 6-17 year-old.

Individual, non-duplicate strains were consecutively collected (prevalence format by infection site) according to a common protocol. All isolates were identified by the participant laboratories and confirmed by the monitoring facility (JMI Laboratories, North Liberty, Iowa). Oxacillin-resistant staphylococcal strains were excluded from the analyses since these isolates should be considered resistant to all ß-lactams. Each strain was tested by a reference broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) methods and criteria. Concurrent quality control testing was performed using the following organisms: *Escherichia coli* ATCC 25923, *Pseudomonas aeruginosa* ATCC 27853 and *Staphylococcus aureus* ATCC 29213. All QC results were within CLSI published ranges.

RESULTS

- *S. pneumoniae* was the most frequently isolated pathogen from pediatric patients monitored in the SENTRY Program and the vast majority of these isolates were from community-acquired respiratory infections.
- Levofloxacin (MIC_{90}, 1 µg/ml; 99.9% susceptible) was the most active compound against *S. pneumoniae* and decreased susceptibility to ciprofloxacin (MIC, ≥ 4 µg/ml) was detected in 21 strains (1.1%), mainly in the 6 - 17 year-old group.
- Both cefepime (MIC_{90}, 1 µg/ml; 93.9% susceptible) and ceftriaxone (MIC_{90}, 1 µg/ml; 93.7% susceptible) were highly active against *S. pneumoniae*. In contrast, only 56.6% of isolates were susceptible to penicillin (MIC, ≤ 0.06 µg/ml; Table 1), a surrogate for ceftazidime. Penicillin-susceptibility rates were lower in the < 1 year-old and 1 - 5 year-old age groups (52.4 - 54.9%) compared to the 6 - 17 year-old age group (67.7%; Table 2).
- *S. pneumoniae* also showed lower susceptibility rates to erythromycin (66.2%), tetracycline (71.4%) and trimethoprim/sulfamethoxazole (57.1%).
- *H. influenzae* strains were highly susceptible (100.0%) to cefepime (MIC_{90}, 0.12 µg/ml), ceftriaxone (MIC_{90}, 0.016 µg/ml) and levofloxacin (MIC_{90}, 0.5 µg/ml). Resistance to ampicillin (ß-lactamase production) was observed in 34.0% of *H. influenzae* and 99.2% of *M. catarrhalis* strains (Table 1).
- Cefepime (MIC_{90}, 4 µg/ml; 100.0% susceptible) and ceftriaxone (MIC_{90}, 4 µg/ml; 99.8% susceptible) showed excellent activity against oxacillin-susceptible *S. aureus*. In contrast, ceftazidime (MIC_{90}, 16 µg/ml) was active against only 86.7% of strains at the susceptible breakpoint of ≤ 8 µg/ml (Table 1).
- The three cephalosporins tested (cefepime, ceftriaxone and ceftazidime) were very active (98.6 - 99.6% susceptible) against *E. coli* (Table 1).
- Against *P. aeruginosa*, imipenem and piperacillin/tazobactam showed the highest susceptibility rates (94.4 and 93.3%, respectively) while imipenem and cefepime showed the lowest resistance rates (1.4 and 2.3%, respectively; Table 1). Ceftriaxone was not active against this non-fermentative bacillus.
- Cefepime (99.0% susceptible) was slightly more active than ceftriaxone (96.4% susceptible) and ceftazidime (95.1% susceptible) against *Klebsiella* spp. (Table 1).
- ß-haemolytic streptococci showed 100.0% susceptibility to penicillin, cefepime and ceftriaxone (Table 1).
- Cefepime was the most active ß-lactam tested against *Enterobacter* spp. (MIC_{90}, 2 µg/ml; 99.3% susceptible). The susceptibility rates of other broad-spectrum ß-lactams tested (ceftriaxone, ceftazidime and piperacillin/tazobactam) varied from 78.4 to 81.5%, a significantly lower level.
- Susceptibility rates to cephalosporins were very similar among isolates from the different age groups analyzed.

Table 1. Antimicrobial activity of cefepime and selected comparators against the 10 most frequently isolated pathogens from pediatric patients (SENTRY Antimicrobial Surveillance Program, 1998 - 2004).

Organism/antimicrobial agent (no. tested)	MIC (µg/ml) 50%	90%	Range	% category:[a] Susceptible	Resistant
S. pneumoniae (1,975)					
Cefepime	≤0.12	1	≤0.12-8	93.9	0.9
Ceftriaxone	≤0.25	1	≤0.25-16	93.7	3.1
Penicillin	≤0.03	2	≤0.03-8	56.6	24.2
Erythromycin	≤0.25	32	≤0.25->32	66.2	33.3
Clindamycin	≤0.25	>2	≤0.25->2	89.4	10.4
Levofloxacin	1	1	≤0.03->4	99.9	0.1
Tetracycline	≤2	>16	≤2->16	71.4	18.9
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5->4	57.1	33.9
H. influenzae (1,862)					
Cefepime	≤0.06	0.12	≤0.06-2	100.0	-[b]
Ceftriaxone	≤0.008	0.016	≤0.008-0.5	100.0	-
Ceftazidime	≤0.25	≤0.25	≤0.25-8	99.9	-
Ampicillin[c]	≤2	>4	≤1->4	66.0	34.0
Clarithromycin	8	16	≤0.25->32	87.0	0.5
Levofloxacin	≤0.5	≤0.5	≤0.5	100.0	-
Tetracycline	≤2	≤2	≤2->16	94.0	0.4
Trimethoprim/sulfamethoxazole	≤0.5	>4	≤0.5->4	79.1	16.1
Oxacillin-susceptible *S. aureus* (1,313)					
Cefepime	2	4	0.25-8	100.0	0.0
Ceftriaxone	4	4	≤0.25-16	99.8	0.0
Ceftazidime	8	16	0.25->16	86.7	0.5
Erythromycin	0.5	>8	≤0.06->8	71.5	25.5
Clindamycin	0.12	0.25	≤0.06->8	97.2	2.3
Levofloxacin	0.12	0.25	≤0.03->4	98.4	1.4
Tetracycline	≤4	≤4	≤4->8	95.7	3.6
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	99.5	0.5
M. catarrhalis (1,022)					
Cefepime	0.5	2	≤0.06-4	-	-
Ceftriaxone	0.25	1	≤0.008-2	-	-
Ceftazidime	≤0.25	0.5	≤0.25-8	-	-
Ampicillin[c]	2	>4	≤1->4	0.8	99.2
Clarithromycin	≤0.25	≤0.25	≤0.25-0.5	-	-
Levofloxacin	≤0.5	≤0.5	≤0.5	-	-
Tetracycline	≤2	≤2	≤2-16	-	-
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5-8	-	-
E. coli (988)					
Cefepime	≤0.12	≤0.12	≤0.12->16	99.6	0.3
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	98.9	0.7
Ceftazidime	≤2	≤2	≤2->16	98.6	0.7
Piperacillin/tazobactam	2	4	≤0.12->64	97.1	1.3
Levofloxacin	≤0.5	≤0.5	≤0.5->4	97.4	2.0
Gentamicin	≤2	≤2	≤2->16	95.7	3.2
P. aeruginosa (661)					
Cefepime	2	8	≤0.12->16	90.8	2.3
Ceftriaxone	>32	>32	0.5->32	11.0	62.8
Ceftazidime	2	16	0.5->16	87.3	8.8
Piperacillin/tazobactam	4	64	≤0.5->64	93.3	6.7
Imipenem	1	2	≤0.5->8	94.4	1.4
Levofloxacin	0.5	2	≤0.5->4	91.4	3.9
Ciprofloxacin	≤0.25	1	≤0.25->4	92.9	4.2
Gentamicin	≤2	4	≤2->16	91.4	4.4
Klebsiella spp. (615)					
Cefepime	≤0.12	0.25	≤0.12->16	99.0	0.5
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	96.4	1.6
Ceftazidime	≤2	≤2	≤2->16	95.1	4.1
Piperacillin/tazobactam	2	8	≤0.5->256	94.6	2.6
Levofloxacin	≤0.5	≤0.5	≤0.5->4	99.0	0.2
Gentamicin	≤2	≤2	≤2-16	94.1	3.9
ß-haemolytic streptococci[d] (556)					
Cefepime	≤0.12	≤0.12	≤0.12-0.5	100.0	-
Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0	-
Penicillin	≤0.016	0.06	≤0.016-0.12	100.0	-
Erythromycin	≤0.06	2	≤0.06->32	84.4	15.5
Clindamycin	≤0.25	≤0.25	≤0.25->8	93.7	6.1
Levofloxacin	0.5	1	≤0.03->4	99.8	0.2
Tetracycline	≤4	>8	≤4->8	9.3	42.8
Enterobacter spp. (459)					
Cefepime	≤0.12	2	≤0.12->16	99.3	0.4
Ceftriaxone	≤0.25	>32	≤0.25->32	81.0	10.7
Ceftazidime	≤1	>16	≤1->16	78.4	18.1
Piperacillin/tazobactam	2	64	≤0.5-128	81.5	8.4
Levofloxacin	≤0.5	≤0.5	≤0.5->4	99.3	0.4
Gentamicin	≤2	≤2	≤2->16	93.7	5.0
Oxacillin-susceptible CoNS (182)					
Cefepime	1	2	≤0.12-4	100.0	0.0
Ceftriaxone	2	4	≤0.25->32	98.3	0.6
Ceftazidime	8	8	≤1->16	94.0	1.1
Erythromycin	>8	>8	≤4->8	47.3	51.1
Clindamycin	0.12	>8	≤0.06->8	86.8	12.6
Levofloxacin	0.12	0.25	0.06->4	98.3	0.8
Tetracycline	≤4	>8	≤4->8	86.8	13.2
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	94.5	5.5

a. Criteria as published by the CLSI [2005].
b. - = no breakpoints have been established by the CLSI.
c. Susceptibility and resistance rates based on ß-lactamase test results.
d. Includes: ß-haemolytic streptococci (two strains), group A streptococci (300 strains), group B streptococci (228), group C streptococci (six strains), group F streptococci (five strains) and group G streptococci (15 strains).

Table 2. Comparison of the spectrum of activity of ß-lactams tested against the most frequently isolated pathogens from pediatric patients according to age groups (SENTRY Antimicrobial Surveillance Program, 1998 - 2004).

Organism/antimicrobial agent	% susceptible (no tested)[a] < 1 years	1 - 5 years	6 - 17 years
S. pneumoniae			
All strains	(512)	(1,009)	(452)
Penicillin	54.9	52.4	67.7
Cefepime	94.3	93.1	95.4
Ceftriaxone	93.3	92.6	96.6
Penicillin-susceptible	(281)	(529)	(306)
Cefepime	100.0	100.0	100.0
Ceftriaxone	100.0	100.0	100.0
Penicillin-intermediae	(105)	(204)	(70)
Cefepime	96.2	98.5	95.7
Ceftriaxone	98.7	100.0	100.0
Penicillin-resistant	(126)	(276)	(76)
Cefepime	80.2	76.1	76.3
Ceftriaxone	74.4	74.6	81.7
H. influenzae	(500)	(850)	(512)
Ampicillin[b]	66.5	64.7	68.0
Cefepime	100.0	100.0	100.0
Ceftriaxone	100.0	100.0	100.0
Ceftazidime	99.6	100.0	100.0
S. aureus			
Oxacillin-susceptible	(486)	(268)	(559)
Cefepime	100.0	100.0	100.0
Ceftriaxone	99.8	99.6	100.0
Ceftazidime	86.8	90.7	84.6
E. coli	(490)	(191)	(307)
Cefepime	99.8	99.5	99.3
Ceftriaxone	99.4	97.9	98.7
Ceftazidime	99.4	96.9	98.4
Klebsiella spp.	(375)	(109)	(131)
Cefepime	99.7	98.2	97.7
Ceftriaxone	97.6	93.6	95.4
Ceftazidime	96.3	93.6	93.1
P. aeruginosa	(250)	(177)	(234)
Cefepime	91.6	94.4	87.2
Ceftriaxone	6.4	7.9	18.4
Ceftazidime	84.8	91.0	87.2
Piperacillin/tazobactam	93.4	94.4	92.7
Imipenem	96.4	94.4	92.3
Enterobacter spp.	(272)	(79)	(108)
Cefepime	100.0	97.5	99.1
Ceftriaxone	81.3	75.9	84.3
Ceftazidime	78.3	72.2	83.3
CoNS			
oxacillin-susceptible	(100)	(36)	(46)
Cefepime	100.0	100.0	100.0
Ceftriaxone	98.0	97.2	100.0
Ceftazidime	93.0	94.4	95.7

a. Criteria as published by the CLSI [2005].
b. Susceptibility and sesistance rates based on ß-lactamase test results.

CONCLUSIONS

- *S. pneumoniae* isolated from pediatric patients in the SENTRY Program (1998 - 2004) showed high rates of resistance to penicillin, but the cephalosporins, cefepime and ceftriaxone, remained very active (93.7 - 93.9% susceptible) against this pathogen.
- Enterobacteriaceae, *H. influenzae*, oxacillin-susceptible staphylococci and ß-haemolytic streptococci isolated from pediatric patients in North American medical centers remained most susceptible (> 99.0%) to cefepime among tested cephalosporins.
- Cefepime exhibited the broadest spectrum among cephalosporins and remained highly potent against 12,737 bacterial isolates from pediatric patients in North America.

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