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Antimicrobial Activity of Cefepime Tested Against Ceftazidime-Resistant Gram-Negative Clinical Strains from North American Hospitals: Report from the SENTRY Antimicrobial Surveillance Program, 1998-2004

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SENTRY ANTIMICROBIAL SURVEILLANCE

ABSTRACT

Objectives: To evaluate antimicrobial spectrum and potency of cefepime (CPM) and selected comparators against ceftazidime (CAZ)-resistant (R; MIC >=16 mg/L) Gram-negative bacilli (GNB) collected in North American (NA) medical centers over a 7-year period (1998-2004).

Methods: Isolates were consecutively collected mainly from bloodstream (47%), respiratory tract (33%), urinary tract (9%) and skin/soft tissue (5%) infections in 48 major hospitals. Isolates were susceptibility (S) tested by reference CLSI broth microdilution methods in a central laboratory.

Results: A total of 42,061 GNB were collected during the study period. The most frequently isolated pathogens were *E. coli* (28.0%) > *P. aeruginosa* (PSA; 14.9%) > *Klebsiella* spp. (KSP; 14.0%) > *H. influenzae* (11.2%) > *Enterobacter* spp. (ESP; 7.8%) > *Serratia* spp. (4.0%). CAZ-R was observed in 8.5% of GNB and 5.6% of Enterobacteriaceae (ENT). The highest rates of CAZ-R were observed among *Acinetobacter* spp. (ASP; 40.3%) > ESP (20.9%) > PSA (16.9%) > *Citrobacter* spp. (CIT; 15.3%) > indol-pos. *Proteae* (10.0%). The activity of CPM against the most frequent CAZ-R organisms is summarized in the Table.

Organism (no. tested)	CPM MIC_{50} (mg/L)	%S	%R
Enterobacter spp. (690)	1	94	3
Klebsiella spp. (337)	2	86	8
E. coli (194)	1	79	17
Citrobacter spp. (122)	1	97	3
Indol-pos. *Proteae* (48)	0.25	90	4
All Enterobacteriaceae (1,471)	1	90	6
P. aeruginosa (1,059)	16	30	30
Acinetobacter spp. (500)	>16	16	57

Overall, 90% of CAZ-R ENT and 30% of CAZ-R PSA remained S to CPM. The activities (%S) of other antimicrobials tested against CAZ-R ENT and PSA were: amikacin 90 and 88%, ciprofloxacin 63 and 46%, ertapenem 93 and 6%, gentamicin 59 and 67%, imipenem 99 and 65%, levofloxacin 69 and 44% and piperacillin/tazobactam only 40 and 41%.

Conclusions: CAZ-R GNB exhibited high rates of R to other antimicrobials. CPM was very active against CAZ-R ENT, especially (>=90% S) ESP, CIT and indol-pos. *Proteae,* and showed activity similar to that of CAZ against all PSA and ASP isolated in NA medical centers. Continued R surveillance monitoring will be necessary to assess the effectiveness of widely used broad-spectrum antimicrobials.

INTRODUCTION

The cephalosporins are very amenable to modifications in both their biological and pharmacologic properties. “Fourth-generation” cephalosporins, such as cefepime and cefpirome, have a quaternary nitrogen that is positively charged at 3-position, creating the properties of a zwitterion. A 2-aminothiazolyl-acetamido group in the side chain at 7-position with an alpha-oxyimino substitution enhance stability against some ß-lactamases by preventing the approach of the enzymes to the main nucleus. In contrast to other cephalosporins, cefepime shows good stability against most chromosomal and plasmid-mediated ß-lactamases, especially those in the Amp-C group that can hydrolyze “third-generation” agents such as ceftazidime and ceftriaxone.

The SENTRY Antimicrobial Surveillance Program is a worldwide project, initiated in 1997, to monitor the prevailing patterns of resistance to a wide range of antimicrobial agents in over 80 sentinel hospitals and medical centers. We have utilized this program to assess the extent of contemporary resistance to ceftazidime among GNB received by the monitoring centers in North America. The antimicrobial spectrum and potency of cefepime and selected comparators were evaluated against these important nosocomial pathogens.

MATERIALS AND METHODS

The SENTRY Program has monitored the predominant pathogens and antimicrobial resistance patterns of nosocomial- and community-acquired infections via a broad network of sentinel hospitals in four major geographic regions: Asia-Pacific, Europe, Latin America and North America. We report here the antimicrobial susceptibility patterns of ceftazidime-resistant (MIC, ≥ 16 mg/L) GNB isolates collected in North American medical centers during a 7-year period (1998-2004). The isolates were consecutively collected (prevalence format by infected site) from bloodstream (47%), respiratory tract (33%), urinary tract (9%), and skin and soft tissue (5%) infections in 48 participating hospitals. Approximately 75% of the isolates were from hospitalized patients.

Individual non-duplicate strains were collected consecutively from patients hospitalized in participant SENTRY Program medical centers located in the United States (43 centers) and Canada (5 centers). All isolates were identified by the participant laboratories and confirmed by the monitoring facility (JMI Laboratories, North Liberty, Iowa, USA). Each strain was tested by a reference broth microdilution method against more than 30 antimicrobial agents; only those with the widest potential clinical activity and spectrum against GNB are reported here. Interpretation of quantitative MIC results was in accordance with Clinical and Laboratory Standards Institute (CLSI) methods and interpretive criteria. Concurrent quality control (QC) testing was performed using the following organisms: *Escherichia coli* ATCC 25933 and *Pseudomonas aeruginosa* ATCC 27853. All QC results were within published ranges.

Table 1. Frequency of occurrence and of resistance to ceftazidime among Gram-negative clinical isolates in SENTRY Antimicrobial Surveillance Program medical centers in North America for the years 1998 – 2004 (N = 42,061 strains).

			Resistance to ceftazidime[a]	
Organism or group	No. of occurrences	% of all isolates	No. of isolates	% of organism or group
E. coli	11,791	28.0	194	1.6
Klebsiella spp.	5,893	14.0	337	5.7
Enterobacter spp.	3,299	7.8	690	20.9
Serratia spp.	1,667	4.0	43	2.6
Citrobacter spp.	796	1.9	122	15.3
Indole positive *Proteae*	477	1.1	48	10.1
All Enterobacteriaceae	25,571	60.8	1,471	5.7
P. aeruginosa	6,284	14.9	1,059	16.9
Acinetobacter spp.	1,240	2.9	500	40.3
All others	8,966	21.4		
Total	42,061	100.0		

a. Ceftazidime resistance defined as MIC ≥ 16 mg/L.

RESULTS

- A total of 42,061 clinical GNB isolates, including 25,571 strains of Enterobacteriaceae; 6,284 strains of *P. aeruginosa*; and 1,240 strains of *Acinetobacter* spp., were collected from North American medical centers, and the frequency of occurrence of various analyzed genus and species groups is shown in Table 1.
- The rank order of species resistant to ceftazidime was *P. aeruginosa* > *Enterobacter* spp. > *Acinetobacter* spp. > *Klebsiella* spp. > *E. coli* > *Citrobacter* spp. > indole-positive *Proteae* > *Serratia* spp. (Table 1).
- Cefepime was very active against ceftazidime-resistant Enterobacteriaceae strains with an overall resistance rate of only 6.3% (range 2.5 to 17%; Table 2). Notably, cefepime was highly active against ceftazidime-resistant strains of *Enterobacter* spp. (2.6% resistance) and *Klebsiella* spp. (7.7% resistance).
- Cefepime had the lowest resistance rate among the ceftazidime-resistant enteric GNB of all the ß-lactams, and was markedly superior to the aminoglycosides (except amikacin) and the fluoroquinolones. Among the 13 broad-spectrum agents tested, only reserved drugs, the carbapenems and amikacin, were more active than cefepime against ceftazidime-resistant enteric bacilli.
- Amikacin had the highest susceptibility rate (932/1,059, 88.0%) against ceftazidime-resistant *P. aeruginosa*, followed by tobramycin (81.7%), meropenem (67.6%), gentamicin (66.7%) and imipenem (65.0%). Fewer isolates were resistant to cefepime (321, 30.3%) compared to the fluoroquinolones (482-510, 45.5-48.2%) and piperacillin/tazobactam (622, 58.7%).
- Only imipenem (81.8%S/10.8%R) demonstrated usable activity against ceftazidime-resistant strains of *Acinetobacter* spp.

Table 2. Antimicrobial activity and susceptibility rates for cefepime and other broad-spectrum agents tested against ceftazidime-resistant Gram-negative bacilli isolated in North American medical centers (SENTRY Antimicrobial Surveillance Program, 1998-2004)[a].

	MIC (mg/L)		%	
Organism (no. tested)/ Antimicrobial agent	50%[b]	90%[b]	S[c]	R[c]
Enterobacter spp. (690)				
Cefepime	1	8	94.3	2.6
Ceftriaxone	32	>32	19.4	44.1
Piperacillin/tazobactam	64	128	21.9	30.7
Imipenem	0.5	1	99.3	0.3
Amikacin	2	8	97.4	0.4
Tobramycin	0.5	>16	73.3	20.1
Ciprofloxacin	0.25	4	75.9	18.7
Levofloxacin	0.5	>4	81.2	12.5
Klebsiella spp. (337)				
Cefepime	2	16	86.4	7.7
Ceftriaxone	16	>32	36.8	22.8
Piperacillin/tazobactam	16	128	51.9	28.5
Imipenem	0.12	0.5	96.7	2.4
Amikacin	2	>32	69.4	16.9
Tobramycin	16	>16	17.5	64.4
Ciprofloxacin	2	>4	44.5	45.7
Levofloxacin	2	>4	53.1	31.8
E. coli (194)				
Cefepime	1	>16	78.9	17.0
Ceftriaxone	16	>32	33.0	30.9
Piperacillin/tazobactam	8	128	70.6	12.9
Imipenem	0.25	0.5	100.0	0.0
Amikacin	2	16	93.8	1.5
Tobramycin	4	>16	52.6	37.6
Ciprofloxacin	4	>4	44.3	53.6
Levofloxacin	4	>4	46.4	50.0
Citrobacter spp. (122)				
Cefepime	1	2	96.7	2.5
Ceftriaxone	32	>32	16.4	40.2
Piperacillin/tazobactam	64	128	32.0	24.6
Imipenem	0.5	1	100.0	0.0
Amikacin	2	4	99.2	0.0
Tobramycin	1	16	81.1	16.4
Ciprofloxacin	0.25	4	73.8	18.0
Levofloxacin	0.5	>4	76.2	13.1
Indole-positive *Proteae* (48)				
Cefepime	0.25	16	89.6	4.2
Ceftriaxone	4	32	77.1	6.3
Piperacillin/tazobactam	4	64	72.9	6.3
Imipenem	2	4	95.8	0.0
Amikacin	4	16	93.8	4.2
Tobramycin	2	>16	70.8	25.0
Ciprofloxacin	4	>4	45.8	52.1
Levofloxacin	4	>4	47.9	50.0
Serratia spp. (43)				
Cefepime	4	>16	72.1	16.3
Ceftriaxone	32	>32	48.8	27.9
Piperacillin/tazobactam	16	>128	53.5	23.3
Imipenem	1	2	97.7	2.3
Amikacin	4	16	93.0	4.7
Tobramycin	16	>16	20.9	67.4
Ciprofloxacin	1	>4	58.1	27.9
Levofloxacin	1	>4	74.4	18.6
All Enterobacteriaceae (1,471)				
Cefepime	1	16	89.7	6.3
Ceftriaxone	32	>32	27.1	34.9
Piperacillin/tazobactam	32	128	39.5	26.1
Imipenem	0.5	1	98.7	0.7
Amikacin	2	16	90.3	4.7
Tobramycin	2	>16	57.2	33.6
Ciprofloxacin	0.5	>4	63.0	30.8
Levofloxacin	0.5	>4	68.5	23.4
P. aeruginosa (1,059)				
Cefepime	16	>16	29.9	30.3
Ceftriaxone	>32	>32	0.6	95.8
Piperacillin/tazobactam	128	128	12.0	58.7
Imipenem	2	>8	65.0	23.1
Amikacin	4	32	88.0	6.7
Tobramycin	1	>16	81.7	16.3
Ciprofloxacin	2	>4	45.6	45.5
Levofloxacin	4	>4	44.2	45.5
Acinetobacter spp. (500)				
Cefepime	>16	>16	16.2	56.6
Ceftriaxone	>32	>32	2.6	75.4
Piperacillin/tazobactam	128	128	17.8	52.9
Imipenem	1	>8	81.8	10.8
Amikacin	8	>32	67.6	22.8
Tobramycin	4	>16	52.2	41.0
Ciprofloxacin	4	>4	15.2	83.4
Levofloxacin	>4	>4	19.6	73.0

a. Ceftazidime resistance defined as MIC ≥ 16 mg/L.
b. 50% and 90%; MIC encompassing 50% and 90% of isolates tested, respectively.
c. Susceptible (S) and resistant (R) categories as published by the CLSI.

CONCLUSIONS

- The overall rank order of activity of the tested antimicrobial agents against this exceptionally challenging set of organisms as measured by the percentage of resistant to each agent was: amikacin > imipenem > cefepime > tobramycin > levofloxacin > piperacillin/tazobactam > ciprofloxacin > ceftriaxone.
- Cefepime remains highly active against ceftazidime-resistant Enterobacteriaceae collected in North American medical centers.
- The high levels of resistance to both fluoroquinolones and aminoglycosides, with the exception of amikacin, underscore the multidrug-resistant nature of many of these isolates.
- The well documented spread of resistant GNBs in both hospital and long-term care settings makes the choices of initial empiric therapy even more difficult. Rigorous enforcement and adherence to infection control guidelines are the foundation of any effort to control the spread of antimicrobial resistance.
- There is a continuing need to not only develop new antimicrobials that are active against resistant GNB, but also to continue to monitor the efficacy of available, safe antimicrobial agents to ensure that appropriate agents are selected for use in early empirical therapy.

SELECTED REFERENCES

Clinical and Laboratory Standards Institute. (2005). *Performance standards for antimicrobial susceptibility testing, 15th informational supplement M100-S15.* Wayne, PA: CLSI.

Cosgrove SE, Kaye KS, Eliopoulous GM, Carmeli Y (2002). Health and economic outcomes of the emergence of third-generation cephalosporin resistance in *Enterobacter* species. *Arch Intern Med* 162: 185-190.

Cosgrove SE (2006). The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis* 42 Suppl 2: S82-89.

Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH (2000). The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 118: 146-155.

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

Sader HS, Fritsche TR, Jones RN (2005). Potency and spectrum trends for cefepime tested against 65,746 clinical bacterial isolates collected in North American medical centers: results from the SENTRY Antimicrobial Surveillance Program (1998-2003). *Diagn Microbiol Infect Dis* 52: 265-273.