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

Antimicrobial Activity and Spectrum of Cefepime Tested Against 65,746 Clinical Strains from North American Medical Centers: Report from the SENTRY Antimicrobial Surveillance Program, 1998-2003



99.9/0.1 90.9/7.5 93.4/5.3

HS SADER, D BIEDENBACH, TR FRITSCHE, RN JONES
JMI Laboratories, North Liberty, IA, USA

AMENDED ABSTRACT

Objectives: To evaluate antimicrobial spectrum and potency of cefepime (CPM) and selected comparators against clinical bacterial strains collected in North America (NA) over a 6-year period (1998-2003).

Methods: Isolates were consecutively collected from bloodstream (44%), respiratory tract (41%), urinary tract (6%) and skin/soft tissue (5%) infections in 48 medical centers. 75% of isolates were from hospitalized patients. Isolates were susceptibility (S) tested by reference NCCLS broth microdilution methods in a central laboratory. Oxacillin-resistant (R) staphylococci (ORS) and enterococci were excluded.

Results: The activity of CPM against the key organisms tested is summarized in the Table.

	MIC (ı	MIC (mg/L)		Cumulative % inhibited at MIC (mg/L):				
Organism (no. tested)	50%	90%	≤0.5	1	2	4	8	16
E. coli (10,361)	≤0.12	≤0.12	98.5	99.1	99.4	99.6	99.7 ^a	99.8
Klebsiella spp. (KSP; 5,166)	≤0.12	0.25	94.4	96.0	97.5	98.6	99.3	99.7
Enterobacter spp. (2,836)	≤0.12	2	85.9	89.9	94.1	97.3	99.0	99.6
Serratia spp. (1,412)	≤0.12	0.25	95.6	97.2	98.5	99.0	99.3	99.6
P. mirabilis (1,225)	≤0.12	≤0.12	98.6	98.9	99.0	99.3	99.5	99.7
All Enterobacteriaceae (ENT; 22,860)	≤0.12	0.25	95.5	97.0	98.1	99.0	99.5	99.7
H. influenzae (7,975)	≤0.06	0.12	99.9	100.0	-	-		-
P. aeruginosa (PSA; 5,517)	4	16	1.9	13.8	45.1	67.0	85.2	94.5
Oxacillin-S S. aureus (OSSA; 10,835)	2	4	0.6	2.4	68.3	99.5	100.0	-
S. pneumoniae (9,249)	≤0.06	1	85.3	97.4	99.7	99.9	100.0	-
β-haemolytic strept. (2,703)	≤0.12	≤0.12	99.9	100.0	-	-	-	-
viridans gr. strept. (VGS; 783)	≤0.12	1	88.8	94.1	99.7	99.9	100.0	-

Overall, 99.8% of Gram-positive cocci (GP) tested were S to CPM. Imipenem (IMP; MIC $_{90}$, 1 mg/L; 99.9% S) was the most active compound tested against ENT, followed by CPM (MIC $_{90}$, 0.25 mg/L; 99.5% S) > amikacin (AMK; 99.4% S) > ceftriaxone (95.6% S) > aztreonam (95.1% S). The lowest S rate for ENT was observed with ciprofloxacin (CIPRO; 92.8%). IMP was also the most active compound against ESBL-producing KSP and *E. coli* (99.3 and 100% S, respectively), followed by AMK (81.4 and 97.2% S) and CPM (92.5 and 93.8% S). CPM activity against PSA (85.2% S) was similar to that of IMP (86.9% S). Against OSSA, CPM was 4-fold more potent than ceftazidime (CAZ; MIC $_{90}$, 16 mg/L, 86.4% S) and showed higher activity than CIPRO (93.2% S). CPM was the most active compound against SPN after gatifloxacin and levofloxacin (99.2% S). Against VGS, CPM was 8-fold more potent than CAZ and 4-fold more potent than piperacillin/tazobactam. The activity of CPM remained very stable during the period evaluated with the % S varying from 99.5 to 99.3% among ENT, 85.2 to 88.4% among PSA, 98.1 to 97.6% among SPN, and 94.4

Conclusions: CPM was very active against ENT, PSA and GP cocci (except ORS and enterococci) isolated in NA medical centers. CPM activity remained stable in the 7-year period of the study with low level of cross-R to third-generation cephalosporins. Continued R surveillance is necessary to monitor the effectiveness of widely used antimicrobials.

INTRODUCTION

Cephalosporins are currently the most prescribed class of antimicrobial agents in developed countries. The cephalosporins are very amenable to modifications in both their biological and pharmacologic properties. The "third-generation" cephalosporins usually incorporate the aminothiazolyl group (position 7) and iminomethoxy groups, which make the molecule more β-lactamase stable and enhance potency against Gram-negative bacilli when compared to earlier generation drugs. However, "third-generation" cephalosporins with anti-pseudomonal activity are generally less active against Gram-positive cocci. Additional synthetic modifications were incorporated in order to achieve a more balanced antimicrobial spectrum, and also a greater stability against β-lactamases, resulting in the "fourth-generation" cephalosporins.

"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 β-lactamases by preventing the approach of the enzymes to the main nucleus. Cefepime has demonstrated potent activity against Gram-negative pathogens, as well as Gram-positive cocci such as *Streptococcus pneumoniae* and oxacillin-susceptible *Staphylococcus aureus*. In contrast to other cephalosporins, cefepime is a weaker inducer of chromosomal β-lactamases, and it shows good stability against most chromosomal and plasmid-mediated β-lactamases. In the present study we evaluated the in vitro activity of cefepime and selected comparator antimicrobial agents tested against a large six year collection of clinical strains isolated in North American medical centers in the SENTRY Antimicrobial Surveillance Program (1998 - 2003).

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 4 major geographic regions: Asia-Pacific, Europe, Latin America, and the United States/Canada. We report here the antimicrobial susceptibility patterns of bacterial isolates collected in North American medical centers during a six-year period (1998-2003) of the SENTRY Program. The isolates were consecutively collected (prevalence format by infection site) from bloodstream (44%), respiratory tract (41%), urinary tract (6%) and skin/soft tissue (5%) infections. Approximately 75% of the isolates were from hospitalized patients. Oxacillin-resistant staphylococci and enterococci were excluded from the analysis since these organisms should be considered resistant to cefepime.

Individual, non-duplicate strains were collected consecutively from patients hospitalized in 48 participant SENTRY Program medical centers located in the United States (43) and Canada (5). All isolates were identified by the participant laboratories and confirmed by the monitoring facility (JMI Laboratories, North Liberty, Iowa). Each strain was tested by a reference broth microdilution method against more than 30 antimicrobial agents; only those with the widest potential clinical utility and in vitro activity are reported here in six tables. Interpretation of quantitative MIC results was in accordance with National Committee for Clinical Laboratory Standards (NCCLS) methods and criteria. Current quality control (QC) testing was performed using the following organisms: *S. pneumoniae* ATCC 49619, *S. aureus* ATCC 29213, *Escherichia coli* ATCC 25923, and *Pseudomonas aeruginosa* ATCC 27853. All QC results were within published ranges.

Proteus mirabilis (1.225)

Ceftriaxone

Ceftriaxone

Salmonella spp. (405)

Serratia spp. (1.412 strains)

Piperacillin/Tazobactam

Ceftriaxone

Shigella spp. (106)

Ceftriaxone

All enteric bacilli (22,860)

ndole-positive Proteae spp. (433)

- Oxacillin-susceptible *S. aureus* (OSSA; 10,835 strains, 16.5%) was the most frequent pathogen tested (Table 1), followed by *E. coli* (10,361 strains; 15.8%), *S. pneumoniae* (9,244 strains, 14.1%, *Haemophilus influenzae* (7,975 strains; 12.1%), *P. aeruginosa* (5,517 strains; 8.4%), and *Klebsiella* spp. (5,166 strains; 7.9%).
- The most active compound against Enterobacteriaceae (22,860 strains) was the carbapenem imipenem (MIC $_{90}$, 1 mg/L; 99.9% susceptible), followed by cefepime (MIC $_{90}$, 0.25 mg/L; 99.5%) and amikacin (MIC $_{90}$, 4 mg/L; 99.4%). The lowest susceptibility rate of presented agents was demonstrated by ciprofloxacin (92.8%; Table 2).
- All Enterobacteriaceae species evaluated were highly susceptible to cefepime (Table 2), with susceptibility rates ranging from 98.6% (indole-positive Proteae) to 100.0% (*Salmonella* and *Shigella*). Cefepime was also very active against ESBL-producing *E. coli* (MIC₉₀, 4 mg/L; 93.8% susceptible at ≤8 mg/L) and *Klebsiella pneumoniae* (MIC₉₀, 8 mg/L; 92.5% susceptibility).

North America for the years 1998-2003 (65,746 strains)

Citrobacter spp. (717)

Imipenem Ciprofloxacin Amikacin

Ceftriaxone

Ciprofloxacin

Escherichia coli (10.361)

Ceftriaxone

Aztreonam Piperacillin/Tazobactam

Piperacillin/Tazobactam

E. coli (ESBL-producing; 386)

Aztreonam
Piperacillin/Tazobactam

Piperacillin/Tazobactam

Aztreonam Piperacillin/Tazobactam

According to criteria published by the NCCLS (2005).

Klebsiella spp. (ESBL-producing; 442)

Ceftazidime Ceftriaxone

Ciprofloxacin Amikacin

Klebsiella spp. (5,166)

Ceftazidime

Ciprofloxacin

Ceftriaxone Cefoxitin

Cefepime
Ceftazidime
Ceftriaxone
Aztreonam
Piperacillin/Tazobactam

Frequency of occurrence for bacterial isolates in the SENTRY Antimicrobial Surveillance Program medical centers in

 Table 2.
 In vitro activity of cefepime and selected comparators against Enterobacteriaceae collected in North America (SENTRY Program, 1998 - 2003).

Category:^a

% susceptible

Organism or group	No. of occurrences	% of all isolates
1. S. aureus oxacillin-susceptible	10,835	16.5
2. E. coli	10,361	15.8
3. S. pneumoniae	9,244	14.1
4. H. influenzae	7,975	12.1
5. P. aeruginosa	5,517	8.4
6. Klebsiella spp.	5,166	7.9
7. M. catarrhalis	3,565	5.4
8. Enterobacter spp.	2,836	4.3
9. ß-haemolytic streptococci	2,703	4.1
10. Serratia spp.	1,412	2.2
11. P. Mirabilis	1,225	1.9
12. Coagneg. staphylococci oxacillin-susceptible	1,177	1.8
13. Acinetobacter spp.	1,046	1.6
14. viridans group streptococci	783	1.2
15. Citrobacter spp.	717	1.1
16. Indole-positive Proteus spp.	433	0.7
17. Salmonella spp.	405	0.6
18. Shigella spp.	106	0.2
19. Other species	240	0.4
a. Oxacillin-resistant Staphylococcus spp. and Enterococcus s	pp. isolates were not included.	

RESULTS was the most active compound

- Amikacin (MIC₉₀, 8 mg/L; 96.2% susceptible) was the most active compound against *P. aeruginosa* (5,517 strains tested) with only 2.0% resistant isolates identified (Table 3). Cefepime (MIC₉₀, 16 mg/L; 85.2% susceptible and 5.5% resistance) and imipenem (MIC₉₀, 8 mg/L; 86.9% susceptible and 7.6% resistance) showed similar activity against *P. aeruginosa*. Piperacillin/tazobactam (MIC₉₀, >64 mg/L) showed a slightly higher susceptibility rate (89.0%) overall, but a higher resistance rate (11.0%) when compared to cefepime and imipenem.
- Acinetobacter spp. isolates had higher rates of resistance to most antimicrobial agents tested. The most active compounds against this pathogen were imipenem (MIC₉₀, 4 mg/L; 92.5% susceptible) and amikacin (MIC₉₀, 32 mg/L; 85.2%). Cefepime, ceftazidime, piperacillin/tazobactam, gatifloxacin, and gentamicin showed similar activity against Acinetobacter spp., with susceptibility rates ranging from 62.0 to 64.6% (Table 3).
- All Haemophilus influenzae isolates tested (7,975) were susceptible to cefepime (MIC₉₀, 0.12 mg/L), ceftriaxone (MIC₉₀, ≤0.25 mg/L), levofloxacin (MIC₉₀, ≤0.5 mg/L) and gatifloxacin (MIC₉₀, ≤0.03 mg/L). Production of β-lactamase was detected in 31.5% of *H. influenzae* and 96.5% of *Moraxella catarrhalis* strains (Table 4).

America (SENTRY Progra	ım, 1998 - 2003).				
	MIC (mg/L)		Category: ^a		
Organism/antimicrobial agent (no. tested)	50%	90%	% susceptible	% resistant	
Pseudomonas aeruginosa (5,517)					
Cefepime	4	16	85.2	5.5	
Ceftazidime	2	>16	82.8	12.8	
Aztreonam	8	>16	63.7	21.5	
Piperacillin/Tazobactam	8	>64	89.0	11.0	
Imipenem	1	8	86.9	7.6	
Ciprofloxacin	0.25	>2	75.2	19.0	
Amikacin	4	8	96.2	2.0	
Acinetobacter spp. (1,046) ^b					
Cefepime	4	>16	63.0	22.7	
Ceftazidime	8	>16	62.0	28.2	
Ceftriaxone	16	>32	32.2	29.3	
Aztreonam	>16	>16	9.6	73.1	
Piperacillin/Tazobactam	8	>64	62.7	20.3	
Imipenem	0.25	4	92.5	4.6	
Ciprofloxacin	0.25	>4	60.6	37.9	
Amikacin	4	32	85.2	9.6	

Category:^a

aeruginosa (5,517 strains tested) with Cefepime was very active against oxacillin-susceptible S. aureus (MIC₅₀, 2 mg/L and MIC₉₀, 4 mg/L) with 100% of isolates susceptible and 5.5% resistance) and Susceptible (Table 5). Cefepime was four-fold more potent than ceftazidime (MIC₅₀, 16 mg/L, 86.4% susceptible) and two-fold

The fluoroquinolones, gatifloxacin (MIC₉₀, 0.5 mg/L) and levofloxacin (MIC₉₀, 1 mg/L) were the most active compounds against S. pneumoniae (99.2% susceptibility), followed by cefepime (MIC₉₀, 1 mg/L; 97.4% susceptible) and ceftriaxone (MIC₉₀, 1 mg/L; 96.5%). Penicillin was active against only 69.9% of isolates at the susceptible breakpoint (\leq 0.06 mg/L), while 95.2% of isolates were considered susceptible to amoxicillin/clavulanate. Cefepime was also very active against β-haemolytic (MIC₉₀, \leq 0.12 mg/L) and viridans group streptococci (MIC₉₀, 1 mg/L; Table 5).

more active against oxacillin-susceptible CoNS (MIC₅₀, 0.5 mg/L and MIC₉₀, 2 mg/L) when compared to OSSA results.

more potent than ceftriaxone (MIC₅₀, 4 mg/L, 99.6% susceptible) against this staphylococcal pathogen. Cefepime was slightly

• Cefepime activity remained stable during the 1998-2003 period (Table 6). Against *P. aeruginosa*, susceptibility/resistance rates varied from 85.6%/4.6% in 1998 to 88.4%/3.5% in 2003 (improved spectrum); while against Enterobacteriaceae susceptibility/resistance rates remained essentially unchanged (99.4%/0.3% in 1998 to 99.3%/0.3% in 2003).

				•	
	MIC (mg/L)		Category: ^a		
Organism/antimicrobial agent (no. tested)	50%	90%	% susceptible	% resistant	
Haemophilus influenzae (7,975)					
Cefepime	≤0.06	0.12	100.0	_b	
Ceftriaxone	≤0.008	≤0.25	100.0	-	
Cefuroxime	1	2	98.7	0.2	
Ampicillin	≤0.5	>4	68.5 ^c	31.5 ^c	
Amoxicillin/Clavulanate	0.5	≤2	99.9	0.1	
Azithromycin	1	2	86.8	-	
Levofloxacin	≤0.5	≤0.5	100.0	-	
Tetracycline	≤4	≤4	86.9	0.5	
Trimethoprim/Sulfamethoxazole	≤0.5	>4	79.5	15.9	
Moraxella catarrhalis (3,565)					
Cefepime	0.5	2	-	-	
Ceftriaxone	0.25	0.5	-	-	
Cefuroxime	1	2	-	-	
Ampicillin	≤2	4	4.4 ^c	95.6 ^c	
Amoxicillin/Clavulanate	≤0.25	0.5	-	-	
Azithromycin	≤0.12	≤0.12	-	-	
Levofloxacin	≤0.5	≤0.5	-	-	
Tetracycline	≤2	≤2	-	-	
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	-	-	

	MIC (mg/L)	Category: ^a		
Organism/antimicrobial agent (no. tested)	50%	90%	% susceptible	% resistant	
Staphylococcus aureus (10,835) ^b					
Cefepime	2	4	100.0	0.0	
Ceftazidime	8	16	86.4	0.4	
Ceftriaxone	4	4	99.7	0.0	
Piperacillin/Tazobactam	1	2	99.8	0.2	
Imipenem	≤0.5	≤0.5	100.0	0.0	
Ciprofloxacin	0.25	1	93.2	5.4	
Clindamycin	0.12	0.25	95.8	4.0	
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	98.7	1.3	
Vancomycin	_1	_1	100.0	0.0	
Coagulase-negative staphylococci (1,177) ^b					
Cefepime	0.5	2	100.0	0.0	
Ceftazidime	4	8	94.1	0.6	
Ceftriaxone	2	4	99.2	0.1	
Piperacillin/Tazobactam	≤0.5	1	100.0	0.0	
Imipenem	≤0.06	≤0.5	99.8	0.2	
Ciprofloxacin	≤0.25	>2	86.5	12.4	
Clindamycin	0.12	0.25	90.7	9.0	
Trimethoprim/Sulfamethoxazole	≤0.5	>2	89.7	10.3	
Vancomycin	1	2	100.0	0.0	
Streptococcus pneumoniae (9,244)					
Cefepime	≤0.06	1	97.4	0.3	
Ceftriaxone	0.06	1	96.5	1.4	
Penicillin	≤0.03	2	69.9	15.2	
Amoxicillin/Clavulanate	≤0.25	2	95.2	2.5	
Erythromycin	≤0.25	8	76.6	22.5	
Clindamycin	≤0.25	≤0.25	92.2	7.0	
Levofloxacin	1	1	99.2	0.7	
Tetracycline	≤2	>16	67.0	14.1	
Trimethoprim/Sulfamethoxazole	≤0.5	4	70.0	22.5	
ß-haemolytic streptococci (2,703) ^с				d	
Cefepime	≤0.12	≤0.12	100.0	_"	
Ceftriaxone	0.06	0.06	100.0	-	
Penicillin	0.03	0.06	>99.9	-	
Amoxicillin/Clavulanate	≤2	≤2	-	-	
Erythromycin	≤0.06	2	80.3	18.8	
Clindamycin	≤0.06	≤0.06	93.2	6.6	
Levofloxacin	0.5	1	99.6	0.3	
Tetracycline	>8	>8	43.7	54.1	
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5		-	
viridans group streptococci (783)	<0.12	4	04.1	0.0	
Cefepime Ceftriaxone	≤0.12 0.12	1 0.5	94.1 93.6	2.3 2.7	
Penicillin	0.12		93.6 75.7		
		1		4.2	
Amoxicillin/Clavulanate	≤2 ≤0.25	≤2 8	- 58.0	38.2	
Erythromycin					
Clindamycin	≤0.06	0.12	92.2	7.8	
Levofloxacin	1	2	96.9	2.1	
Tetracycline Trimethoprim/Sulfamethoxazole	≤4 ≤0.5	>8 2	68.3	31.7	

a. Criteria as published by the NCCLS (2005).
b. Includes only oxacillin-susceptible strains.
c. Includes: β-haemolytic streptococci (52 strains), *S. dysgalactiae* (one strain), *S. equisimilis* (two strains), group A β-haemolytic streptococci (900 strains), group B β-haemolytic streptococci (1,328 strains), group C β-haemolytic streptococci (77 strains), group F β-haemolytic streptococci (31 strains), group G β-haemolytic streptococci (301 strains), and *Streptococcus* spp. (11 strains).
d. - = no breakpoint has been established by the NCCLS.

Organism		9	% susceptible/resistant by	year (no. of isolates tester	:(E	
	1998	1999	2000	2001	2002	2003
Klebsiella spp.	(918)	(876)	(944)	(757)	(915)	(756)
Cefepime	99.3/0.3	99.2/0.2	99.7/0.2	99.6/0.4	99.2/0.2	98.9/0.7
Ceftazidime	95.8/4.0	86.1/3.8	96.4/3.3	94.2/5.0	92.0/7.2	92.7/6.2
Piperacillin/Tazobactam	93.0/3.2	95.9/2.6	93.2/2.1	94.5/3.3	93.4/5.4	94.0/3.7
Imipenem	99.9/0.1	100.0/0.0	100.0/0.0	99.7/0.0	99.9/0.1	99.9/0.1
Ciprofloxacin	95.1/4.0	95.3/3.4	95.8/3.4	83.5/5.0	93.4/4.0	89.8/9.1
Gentamicin	95.1/2.7	96.3/2.2	96.3/2.6	93.9/4.4	91.6/7.7	93.0/5.8
Enterobacter spp.	(511)	(526)	(520)	(475)	(475)	(329)
Cefepime	99.4/0.2	98.7/1.0	99.4/0.0	99.2/0.6	99.2/0.6	97.3/0.3
Ceftazidime	77.1/19.8	73.8/21.9	80.8/16.7	78.9/17.5	78.9/17.5	83.6/14.0
Piperacillin/Tazobactam	79.5/8.2	79.7/10.5	82.1/4.8	84.4/4.8	84.4/4.8	87.8/4.9
Imipenem	100.0/0.0	99.8/0.0	100.0/0.0	99.4/0.6	99.4/0.6	99.7/0.0
Ciprofloxacin	93.9/3.9	94.5/3.2	95.4/3.3	92.4/6.5	92.4/6.5	90.9/7.3
Gentamicin	94.1/4.5	93.3/5.3	95.2/3.5	93.5/5.9	93.5/5.9	91.5/5.8
Enterobactereaceae	(4,307)	(3,751)	(4,188)	(3,518)	(3,682)	(3,414)
Cefepime	99.4/0.3	99.4/0.3	99.8/0.1	99.5/0.3	99.5/0.3	99.3/0.3
Ceftazidime	94.6/4.6	94.1/4.8	95.4/3.9	93.9/4.7	93.8/5.0	95.1/3.7
Piperacillin/Tazobactam	92.7/2.5	94.4/2.6	92.9/1.6	94.8/2.1	95.0/2.7	95.7/2.3

able 6. Antimicrobial spectrum of cefepime and selected comparators by year.

95.1/3.9 95.6/3.2

81.1/13.5 89.9/10.0 84.7/10.2 77.3/17.2 86.6/8.8

? aeruginosa Cefepime Ceftazidime Piperacillin/Tazobactam

CONCLUSIONS

- The results of this study clearly demonstrated that cefepime, a "fourth-generation" cephem, remained highly active against Enterobacteriaceae (22,860 strains tested) with >99% susceptibility consistently shown during the study period (1998 2003).
- Amikacin, cefepime, and imipenem provided the best coverage against *P. aeruginosa* (2.0 7.6% resistance rates). Although piperacillin/tazobactam showed reasonable susceptibility rate (89.0%), the resistance rate was relatively high (11.0%) compared to other potential regimens.
- Cefepime was also highly active against bacterial pathogens isolated from community-acquired respiratory tract infections, including all *H. influenzae* isolates. Only 0.3% of *S. pneumoniae* isolates were resistant (MIC, ≥4 mg/L). Thus, cefepime appears to be an excellent therapeutic option for the treatment of community-acquired respiratory infection cases that require hospitalization, especially community-acquired pneumonia.
- Cefepime spectrum, as well as that of several other antimicrobial agents evaluated, remained stable against the main bacterial pathogens from 1998 - 2003. However, the activity of ciprofloxacin against Enterobacteriaceae species declined continuously during the same period.
- In summary, the results of the present study showed that cefepime was very active against Enterobacteriaceae, *P. aeruginosa* and the most prevalent Gram-positive cocci (except oxacillin-resistant staphylococci and enterococci) isolated in North American medical centers (1998 2003 period) with very minor temporal variation.

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