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Cefoperazone (T-1551), a New Semisynthetic Cephalosporin: Comparison with Cephalothin and Gentamicin

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The in vitro activity of cefoperazone (T-1551) against almost 9,000 recent clinical isolates at six institutions was tested and compared with that of cephalothin and gentamicin. The modal minimum inhibitory concentrations of cefoperazone were 16- and 4-fold less than those of cephalothin and gentamicin, respectively, against 5,503 strains of *Enterobacteriaceae*. Species normally resistant to cephalothin, such as indole-positive proteae and enterobacters, were almost universally susceptible to cefoperazone. Cefoperazone demonstrated activity comparable to gentamicin against *Pseudomonas aeruginosa* and other pseudomonads.

The emergence of antimicrobial resistance, particularly among endemic hospital gram-negative bacilli, has stimulted extensive research to find new antimicrobial agents. Several new cephalosporin-cephamycin compounds have been developed that have increased antibacterial activity, broadened spectrum, or resistance to hydrolyzing beta-lactamases (4, 9-10, 15, 17, 18; T. Yoshida, M. Narisada, S. Matsuura, W. Nagata and S. Kurahara, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 18th, Atlanta, Ga., abstr. no. 151, 1978). In addition, cefamandole, cefoxitin, and cefuroxime among the available compounds possess some of these features (1, 6, 8-10).

Cefoperazone (T-1551), sodium 7-[D(−)-α-(4-ethyl-2,3-dioxo-1-piperazinecarboxamido)-α-(4-hydroxyphenyl)acetamido]-3-[(1-methyl-1H-tetrazol-5yl)thiomethyl]-3-cephem-4-carboxylic acid, is a new semisynthetic cephalosporin structurally similar to cefamandole and piperacillin. This cephalosporin has a broad spectrum of antimicrobial activity against *Pseudomonas aeruginosa, Enterobacter* species, *Klebsiella* species, and indole-positive *Proteus* species as well as the usual organisms inhibited by this family of antimicrobial agents (S. Mitsuhashi, N. Matsubara, S. Minami, T. Muraoka, T. Yasuda, and T. Saikawa, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 18th, Atlanta, Ga., abstr. no. 153, 1978). In this collaborative study the in vitro antimicrobial activity of cefoperazone was compared with that of cephalothin and gentamicin. These current clinical organisms were tested at six clinical microbiology laboratories in five widely separate geographic areas.

Cefoperazone sodium was supplied by Pfizer Pharmaceuticals, New York, N.Y. Cephalothin laboratory-standard powder was provided by Eli Lilly Research Laboratories, Indianapolis, Ind. Schering Corp. kindly gave the gentamicin C complex sulfate. All three compounds were diluted in Mueller-Hinton broth supplemented with calcium (50 mg/liter) and magnesium (25 mg/liter) or included in Mueller-Hinton agar plates. A seven-dilution protocol was used for each antibiotic ranging from 0.25 to 64 μg/ml.

The organisms presented in this study were consecutive clinical strains isolated during a 30- to 45-day period. Participating institutions included the clinical microbiology laboratories of Kaiser Foundation Hospitals and St. Vincent Hospital and Medical Center (Portland, Ore.), Northwestern Memorial Hospital (Chicago, Ill.), Sacramento Medical Center (Sacramento, Calif.), St. Francis Hospital (Wichita, Kans.), and The Cleveland Clinic Foundation (Cleveland, Ohio). Nearly 9,000 aerobic and facultative anaerobic organisms were tested and identified by previously described procedures (5, 8, 9, 13). In addition, 248 anaerobic bacteria were tested by the National Committee for Clinical Laboratory Standards Wilkins-Chalgren reference procedure (Northwestern Memorial Hospital) or broth modifications (Kaiser Foundation Lab) and identification methods with gas-liquid chromatography in combination with microwell biochemical testing (5, 7-9, 12).

The plastic microdilution broth susceptibility

TABLE 1. *Comparative in vitro antimicrobial activity of cefoperazone, gentamicin, and cephalothin against 5,503 recent clinical isolates of Enterobacteriaceae*

Organisms (no. of strains)	Antibiotic	Cumulative % of isolates inhibited at MIC (μg/ml) of:						
		≤0.25	1	2	4	8	16	64
C. diversus (65)	Cefoperazone	**86**[a]	89	92	98		100	
	Gentamicin	**52**	92	94		95	98	100
	Cephalothin	2	24	**76**	85	97		98
C. freundii (98)	Cefoperazone	**65**	85	86	87	88	89	97
	Gentamicin	12	**94**		95		96	98
	Cephalothin	5	6	8	10	17	33	69
E. aerogenes (234)	Cefoperazone	**71**	85	90	92	94	98	100
	Gentamicin	11	**89**	95	97		98	99
	Cephalothin	4	5	7	11	12	15	44
E. agglomerans (24)	Cefoperazone	**71**	79	83	96	100		
	Gentamicin	46	**92**	100				
	Cephalothin		4	17	38	**63**	83	100
E. cloacae (300)	Cefoperazone	**70**	85	88	88	93	93	97
	Gentamicin	18	**95**	98	99			99
	Cephalothin		2		3	4	6	19
E. coli (2775)	Cefoperazone	**79**	92	95	97	98	98	99
	Gentamicin	7	**89**	96	98	98	99	99
	Cephalothin	3	5	14	**51**	79	92	97
K. oxytoca (170)	Cefoperazone	34	**69**	92	97	98		
	Gentamicin	11	**99**				99	100
	Cephalothin		15	**45**	71	86	92	94
K. pneumoniae (786)	Cefoperazone	**69**	88	94	97	98	99	99
	Gentamicin	11	**96**	98	99	99	99	99
	Cephalothin	3	11	**43**	**75**	88	91	97
M. morganii (116)	Cefoperazone	25	**81**	86	92	94	95	99
	Gentamicin	20	**96**					97
	Cephalothin	4	5	10			11	12
P. mirabilis (571)	Cefoperazone	36	**95**	98	99	99	99	99
	Gentamicin	10	**87**	97	99	99		100
	Cephalothin	2	7	33	**83**	94	97	98
P. vulgaris (46)	Cefoperazone	41	**87**	91		96	100	
	Gentamicin	37	**91**	93	98			
	Cephalothin			4			11	20
P. rettgeri (47)	Cefoperazone	**26**	47	62	74	85		100
	Gentamicin	21	**55**	74	83	89	91	
	Cephalothin			2	6	11	13	30
P. stuartii (30)	Cefoperazone	3	**40**	57	87		93	97
	Gentamicin	3	27	40	**57**	63	70	77
	Cephalothin		17			21	28	55
S. marcescens (184)	Cefoperazone	16	**64**	80	86	88	93	97
	Gentamicin	8	**79**	88	90	93		95
	Cephalothin	3				5	6	14
Other *Enterobacteriaceae* species (57)[b]	Cefoperazone	**44**	84	95	96			100
	Gentamicin	36	**95**	98				100
	Cephalothin	4	21	32	**49**	60	62	65

[a] Boldface value represents mode if within or below dilution range tested.

[b] Includes *Enterobacter sakazakii* (1 isolate), *E. coli* AD group (4 isolates), *H. alvei* (11 isolates), *K. ozaenae* (3 isolates), *Salmonella* species (15 isolates), *Serratia liquifaciens* (13 isolates), *Shigella* species (9 isolates), and *Yersinia enterocolitica* (1 isolate).

trays were prepared in three laboratories (Cleveland Clinic, Kaiser Foundation, and Sacramento Medical Center) with an MIC-2000 (Cooke Laboratory Products, Alexandria, Va.) and Mueller-Hinton broth (Difco) as previously described (5, 8, 9, 13). The trays were stored at or below −20°C until used. Trays were then thawed to room temperature and inoculated with an automatic replicating device said to deliver 1 μl to each well. The minimum inhibitory concentration (MIC) endpoint was defined as that lowest antimicrobial concentration totally inhibiting visible growth after 15 to 18 h of incubation at 35°C. Final inoculum size was adjusted to 10^5 colony-forming units per ml.

The agar dilution method was conducted in the three other centers by methods described by Ericsson and Sherris (3) with Mueller-Hinton agar and an inoculum replicating device of Steers (16). Media, inoculating methods, incubation, and interpretation were closely controlled with standardized performance characteristics, e.g., expected MIC modes on quality control organisms, thus bringing agar and broth methods to parity. Each inoculum spot contianed approximately 10^4 colony-forming units. The plates were incubated and interpreted as outlined in prior reports (13).

Medium supplements were used to test several beta hemolytic streptococci, *Streptococcus pneumoniae* and *Haemophilus* species. These included a 5% Fildes reagent (peptic digest of horse cells) added to broth and 5% sheep erythrocytes in Mueller-Hinton agar.

Four or more quality control organisms with known reproducible MICs were run daily in parallel with the unknown clinical isolates. These included, but were not limited to, *Escherichia coli* ATCC 25922 or K380, *Staphylococcus aureus* ATCC 25923 or 29213, *Streptococcus faecalis* ATCC 29212, and *P. aeruginosa* ATCC 27853. Acceptable and comparable results were obtained between laboratories and methods. Only 1% of the endpoints were beyond the ±1 dilution limits from established modes, a finding consistent with other collaborative studies (5, 7, 9, 13). The statistical analysis of the differences in antimicrobial activity comparing the three antibiotics or six institutions was done by using the Kalmozorov-Smironov two-sample (points on cumulative percent curve) test. Three levels of significance were evaluated, i.e., $P < 0.05$, < 0.01 or < 0.001.

The cumulative percentages of *Enterobacteriaceae* inhibited by increasing concentrations of cefoperazone are compared with those inhibited by cephalothin and gentamicin in Table 1. Cefoperazone demonstrated significantly increased antimicrobial activity against these 5,503 isolates compared with cephalothin and gentamicin. The modal and median values were ≤0.25, 4, and 1 μg/ml for cefoperazone, cephalothin, and gentamicin, respectively. Gentamicin and cefoperazone had similarly broadened antimicrobial spectrum characteristics when compared with cephalothin. *Citrobacter freundii*, *Enterobacter aerogenes*, *E. cloacae*, *Morganella morganii*, *Proteus vulgaris*, *Providencia* species, and *Serratia* species were generally inhibited by ≤1 μg of cefoperazone per ml and not by cephalothin at ≤8 μg/ml. This represents a 17% (877 additional isolates susceptible) increase in spectrum among the *Enterobacteriaceae*, not counting the additional by weight activity advantages that cefoperazone had over cephalothin against *E. coli*, *Klebsiella* species, and *P. mirabilis*. Against no species group was cephalothin more active than cefoperazone. The in vitro efficacy of gentamicin against these organisms ranged from 57 to 100% (≤4 μg/ml) with lowest in vitro activity versus the *Providencia* species. Cefoperazone inhibited 85 to 100% of the *Enterobacteriaceae* species groups (≤16 μg/ml), but was also least active against providencia.

An endemic subpopulation of *S. marcescens* found in one of the participating institutions points out the not uncommon serious problem of multiresistant strains (Fig. 1). This organism possesses a plasmid-mediated aminoglycoside

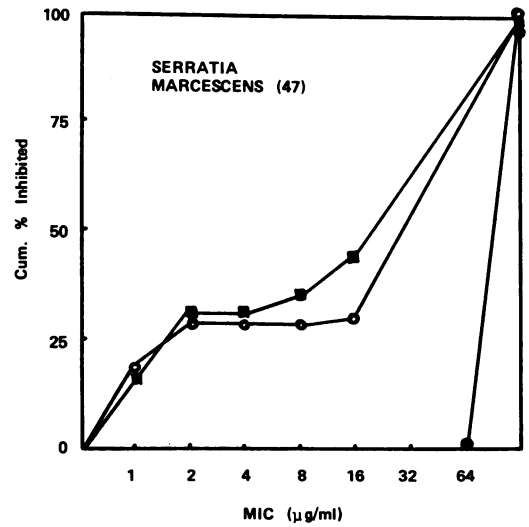

FIG. 1. *Cumulative percentage plots of forty-seven S. marcescens isolates inhibited by increasing concentrations of cefoperazone* (○—○), *gentamicin* (■—■) *and cephalothin* (●—●). *The endemic antibiotic-resistant strain accounts for 70% of isolates.*

TABLE 2. *In vitro comparison of cefoperazone and reference compounds against 868 non-Enterobacteriaceae gram-negative bacilli*

Organisms (no. of strains)	Antibiotic	Cumulative % of isolates inhibited at MIC (μg/ml) of:						
		≤0.25	1	2	4	8	16	64
A. calcoaceticus subsp. *anitratus* (69)	Cefoperazone		1		3	12	33	**90**[a]
	Gentamicin	3	**53**	70	71	93	94	97
	Cephalothin	1			3		7	32
A. calcoaceticus subsp. *lwoffii* (23)	Cefoperazone			9	13		35	**70**
	Gentamicin	**52**	65	78	87	91	96	100
	Cephalothin	4			13	17	22	**83**
P. multocida (11)	Cefoperazone	**100**						
	Gentamicin		18	**82**	100			
	Cephalothin	**82**	100					
P. aeruginosa (718)	Cefoperazone	2	9	28	**65**	85	93	99
	Gentamicin	3	19	49	**80**	90	92	93
	Cephalothin		2	4	5	5	5	6
P. maltophilia (19)	Cefoperazone				**37**	47	68	84
	Gentamicin	16	26	37		42	**63**	79
	Cephalothin							16
Pseudomonas species (16)[b]	Cefoperazone	13	25	**50**	56	67	88	100
	Gentamicin	**25**	44	50	63	81	94	
	Cephalothin	6		13				31
Other nonenteric bacilli (12)[c]	Cefoperazone	**33**	42	50		58	75	100
	Gentamicin	**50**	67	83		92		100
	Cephalothin		8	17		25	**50**	**75**

[a] See Table 1.

[b] Includes *Pseudomonas* species, *P. cepacia* (2 isolates), *P. putida* (1 isolate), *P. putrifaciens* (1 isolate) and *Pseudomonas* species NOS (12 isolates).

[c] Includes *A. hydrophilia* (4 isolates), *Achromobacter* sp. (2 isolates), *A. denitrificans* (2 isolates), *Moraxella* species (3 isolates) and group IV-2 (1 isolate).

TABLE 3. *Modal and MICs[a] inhibiting 90% of 2,311 tested gram-positive cocci*

Organism (no. of strains)	Cefoperazone		Cephalothin		Gentamicin	
	Mode	MIC_{90}	Mode	MIC_{90}	Mode	MIC_{90}
S. aureus (924)	2	4	≤0.25	1	≤0.25	1
S. epidermidis (586)	1	4	≤0.25	1	≤0.25	8
Micrococci (18)	≤0.25	16	≤0.25	2	≤0.25	8
S. faecalis (588)	64	64	64	64	16	64
Group D, not *S. faecalis* (26)	>64	>64	≤0.25	>64	8, 16	16
S. agalactiae (39)	≤0.25	1	≤0.25	≤0.25	8	16
S. pyogenes (18)	≤0.25	1	≤0.25	≤0.25	8	16
Beta, not group A, B, D (27)	≤0.25	1	≤0.25	≤0.25	≤0.25	8
S. pneumoniae (17)	≤0.25	1	≤0.25	≤0.25	≤0.25	8
S. viridans group (37)	≤0.25	2	≤0.25	2	≤0.25	16
Other[b] (31)	≤0.25	4	≤0.25	8	≤0.25	8

[a] MIC in micrograms per milliliter.

[b] Includes various nonhemolytic, ungroupable streptococci.

resistance by two enzymes (13) and a broad-spectrum beta-lactamase inactivating cefoperazone, cephalothin, cefazolin, cefamandole, ampicillin, azlocillin, carbenicillin, mezlocillin, piperacillin, and ticarcillin. Only amikacin among the currently marketed compounds was effective at concentrations achievable in serum.

Table 2 shows the comparative susceptibility

of cefoperazone, cephalothin, and gentamicin to commonly isolated non-*Enterobacteriaceae* gram-negative bacilli. Cefoperazone was comparable to gentamicin in activity (by weight) against *Pseudomonas*, superior against *Pasteurella multocida*, and relatively inactive against acinetobacters. Cephalothin was generally ineffective against those bacteria listed in Table 2, except *P. multocida* (mode MIC ≤ 0.25 μg/ml).

Only 80% of current *P. aeruginosa* strains were inhibited by ≤4 μg of gentamicin per ml. However, cefoperazone inhibited 93% of these isolates at ≤16 μg/ml (mode = 4 μg/ml), a clinically achievable concentration. Similar findings were found for other pseudomonads. Acinetobacters were relatively resistant to both of the cephalosporins tested. Gentamicin was most active, inhibiting 71 and 87% of *A. calcoaceticus* subsp. *anitratus* and subsp. *lwoffii*, respectively.

Table 3 compares the modal and MIC_{90}s of cefoperazone, cephalothin, and gentamicin against 2,284 gram-positive cocci. Cephalothin

TABLE 4. *Comparative in vitro antimicrobial activity of cefoperazone and other antibiotics against B. fragilis group and other anaerobes*

Organism (no. of strains)	Antibiotic	MIC (μg/ml)		
		Range	MIC_{50}	MIC_{90}
B. fragilis group[a] (94)	Cefoperazone	≤1->32	16	>32
	Cefoxitin	≤1-16	2	8
	Carbenicillin	≤8-128	≤8	64
	Chloramphenicol	2-16	4	8
	Clindamycin	≤0.25-8	≤0.25	1
Bacteroides species (48)	Cefoperazone	≤1->32	8	>32
	Cefoxitin	≤1-32	2	8
	Carbenicillin	≤8->128	≤8	32
	Chloramphenicol	≤0.5-16	2	8
	Clindamycin	≤0.25-2	≤0.25	1
Clostridium species (22)	Cefoperazone	≤1->32	2	>32
	Cefoxitin	≤1->32	≤1	>32
	Carbenicillin	≤8	≤8	≤8
	Chloramphenicol	≤0.5-16	4	16
	Clindamycin	≤0.25-16	≤0.25	8
Eubacterium species (17)	Cefoperazone	≤1->32	2	>32
	Cefoxitin	≤1->32	2	8
	Carbenicillin	≤8-32	≤8	32
	Chloramphenicol	≤0.5-16	2	4
	Clindamycin	≤0.25->16	≤0.25	>16
Fusobacterium species (16)	Cefoperazone	≤1	≤1	≤1
	Cefoxitin	≤1-2	≤1	2
	Carbenicillin	≤8	≤8	≤8
	Chloramphenicol	≤0.5-1	≤0.5	1
	Clindamycin	≤0.25	≤0.25	≤0.25
Gram-positive anaerobic cocci (46)	Cefoperazone	≤1->32	2	>32
	Cefoxitin	≤1->32	1	>32
	Carbenicillin	≤8->128	≤8	128
	Chloramphenicol	≤0.5-4	2	4
	Clindamycin	≤0.25->16	≤0.25	1
Other anaerobes (6)[b]	Cefoperazone	≤1	≤1	≤1
	Cefoxitin	≤1-8	2	8
	Carbenicillin	≤8	≤8	≤8
	Chloramphenicol	≤0.5-8	2	8
	Clindamycin	≤0.25-2	≤0.25	2

[a] Includes blood culture or deep wound infection isolates of *B. fragilis* (68 isolates), *B. thetaiotaomicron* (8 isolates), *B. distasonis* (4 isolates), *B. ovatus* (2 isolates) and *B. vulgatus* (12 isolates).

[b] Includes *Lactobacillus* species (4 isolates) and one strain each of *Bifidobacterium* species and *Viellonella* species.

was more active than cefoperazone or gentamicin against staphylococcal isolates, although all three drugs were highly effective at clinically obtainable concentrations. None of the compounds was active against the serogroup D streptococci, i.e., *S. faecalis*, *S. faecium*, *S. durans*, and *S. bovis*. Only a limited number strains of *S. durans* and *S. bovis* were tested; for few of these was the cefoperazone MIC ≤8 μg/ml. Cefoperazone and cephalothin were highly inhibitory against all other tabulated *Streptococcus* species, but gentamicin MIC_{90}s were consistently within the resistant range. Twenty-two gram-positive bacilli and neisseria were not presented in tabular form. Cefoperazone inhibited 100% of these strains of corynebacteria (including *C. diphtheriae*), *Bacillus* species, and *Neisseria* at ≤8 μg/ml. The modal MIC was ≤0.25 μg/ml.

Cefoperazone inhibited 75% of *Bacteroides fragilis* group isolates at ≤32 μg/ml (Table 4). Comparable figures for other antimicrobial agents include: clindamycin (96% at ≤2 μg/ml), chloramphenicol (97% at ≤8 μg/ml) and cefoxitin (100% at ≤16 μg/ml). All five tested antibiotics were generally active against the other anaerobe species. Endemic differences in cefoperazone MICs were found for the bacteroides isolated at the two participating laboratories. Nearly all *B. fragilis* group isolates (98% at ≤32 μg/ml) were susceptible at Kaiser Foundation Laboratories, and only half were susceptible at Northwestern Memorial Hospital.

Table 5 shows the results of testing two populations of antibiotic-resistant bacteria. Cefoperazone was very active against cephalothin- and aminoglycoside-resistant clinical isolates. Amikacin was the most effective compound against the cephalothin-resistant isolates. The rank order of activity was as follows: amikacin (92% at ≤16 μg/ml) > cefoperazone (87% at ≤32 μg/ml) > piperacillin (85% at ≤32 μg/ml) > cefoperazone (78% at ≤16 μg/ml) > gentamicin (77% at ≤4 μg/ml) > cefoxitin (42% at ≤16 μg/ml) > cefamandole (33% at ≤16 μg/ml) > cefazolin (17% at ≤16 μg/ml). Similarly, cefoperazone was very active against aminoglycoside-resistant organisms. It was markedly superior to currently available cephalosporins and the semisynthetic pseudomonas-active penicillins and comparable to enzyme-resistant aminoglycosides (amikacin). Cefoperazone inhibited 68 and 88% of this more resistant population at 16 and 64 μg/ml.

This study shows that cefoperazone (T-1551) is a markedly active cephalosporin against recent clinical bacterial isolates including anaerobes, *P. aeruginosa*, and antibiotic-resistant subpopulations. Principal among the favorable features observed in the present study was the expanded antimicrobial spectrum against *Enter-*

TABLE 5. *In vitro comparison of cefoperazone (T-1551) and eight other antimicrobial agents against two populations of resistant bacteria*

Organism (no. of strains)	Antibiotic	Cumulative % of strains inhibited at MIC (μg/ml) of:								
		≤0.5	1	2	4	8	16	32	64[a]	128
Cephalothin resistant[b] (100)	Cefoperazone	27	37	45	68	77	**78**[c]	**87**	**91**	94
	Cefamandole	7	11	18	25	29	**33**	34	49	
	Cefazolin			10	11	14	**17**	20	22	
	Cefoxitin	2	8	8	21	30	**42**	44	45	
	Piperacillin	34	60	24	56	70	78	**85**	86	89
	Gentamicin		14	72	**77**	88	91	92	94	
	Amikacin			40	68	82	**92**	96	97	98
Aminoglycoside resistant[d] (50)	Cefoperazone	14	20	28	46	60	**68**	**74**	**88**	94
	Cefamandole	18	24	26	28	32	**36**	38	42	
	Cefoxitin	4	12	24	36	38	**42**	50	54	
	Carbenicillin	6	10	12	18	22	30	44	56	**62**
	Piperacillin	8	16	20	28	44	54	**64**	68	72
	Ticarcillin	8	14	16	20	26	36	54	**54**	64
	Amikacin	0	8	16	36	44	**54**	72	78	88

[a] Highest tested concentration of cefamandole, cefazolin, cefoxitin, and gentamicin.

[b] Cephalothin-resistant (MIC ≥ 32 μg/ml) organisms adjusted by species to that incidence found in clinical isolate study.

[c] Boldface percent is that MIC usually considered the highest susceptible concentration. Three possible levels are boldfaced for cefoperazone.

[d] Aminoglycoside-resistant bacteria (kanamycin, ≥ 64 μg/ml or gentamicin, ≥16 μg/ml or tobramycin, ≥16 μg/ml), many with previously determined resistance mechanisms (13).

obacteriaceae, i.e., *Enterobacter* species, *Providencia* species, *P. vulgaris*, *Serratia* species, and *C. freundii*. In addition, *P. aeruginosa* and other pseudomonads were inhibited by concentrations comparable to the related semisynthetic penicillin piperacillin (11, 14) and four- to eightfold lower than those of ticarcillin or carbenicillin (5, 11, 14).

The antimicrobial spectrum of cefoperazone appears similar to those of cefotaxime (HR756) and 6059S (4, 15; Yoshida et al., 18th ICAAC, abstr. no. 151). Also cefoperazone has a significant in vitro spectrum and activity advantage when compared to currently available (1, 4, 6, 8) and some investigational cephalosporins (17, 18). To date only three extensively studied investigational beta-lactams, e.g., cefotaxime, moxallactam (LY127935), and piperacillin, have shown comparably broad in vitro characteristics.

The only uniformly resistant organisms detected were serogroup D *Streptococcus* species and acinetobacters. These two groups account for two-thirds of all resistant (>16 μg/ml) strains by in vitro testing.

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