CURRENT STATUS OF *IN VITRO* ANTIBACTERIAL ACTIVITIES OF CEFOTAXIME AND ELEVEN OTHER β-LACTAMS AGAINST RECENT CLINICALLY SIGNIFICANT PATHOGENS

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The present *in vitro* antibacterial activity of five third-generation cephalosporins (cefotaxime, latamoxef, cefmenoxime, cefpiramide, cefoperazone), four first- and second-generation agents (cefazolin, cefotiam, cefmetazole, cefamandole) and eight other antimicrobial agents were simultaneously compared against 384 strains of Gram-positive cocci, 595 strains of Enterobacteriaceae, 240 strains of non-fermenters and 143 strains of anaerobic bacteria and others. The agar dilution method was used to measure the minimum inhibitory concentration (MIC) and the results were expressed as MIC range, $MIC_{50\%}$ and $MIC_{90\%}$. Among β-lactams, cefotaxime and latamoxef exhibited the highest activity against a wide variety of Gram-positive and Gram-negative bacteria. Cefpiramide and cefoperazone were generally less active than these two agents, although cefpiramide showed good activity against *P. aeruginosa* strains. Ofloxacin, a new pyridone carboxylic acid derivative, inhibited the growth of over 80% of strains in all species tested, except *C. difficile* strains, at a concentration of 3.13 μg/ml. All the strains were tested for β-lactamase production by the Cefinase disc method and susceptibility to β-lactams evaluated in each of the species. We hope to have demonstrated the need for periodic susceptibility testing to provide guidance for empiric chemotherapy.

INTRODUCTION

Some new third-generation cephalosporins have become available in the last few years. These agents have potentially greater clinical usefulness because they possess : (a) a wider spectrum of antibacterial activity than do the older (first- and second-generation) cephalosporins and (b) lower toxicity than the aminoglycosides[1]. Since patterns of antibiotic resistance in a wide variety of pathogenic organisms may vary over even short periods and according to hospital environment, periodic evaluation of antibacterial activity is necessary for up-to-date information. The cephalosporin group is large and still growing, and it is impossible to simultaneously evaluate all available agents in any one test. We therefore limited our comparative studies to a few established β-lactams or to the latest developments in the field. In the present study, we chose cefotaxime as the standard with which other agents were compared, because it is the pioneer of the third-generation agents and is now available in over 90 countries. In addition, the total net world consumption of cefotaxime accounts for more than 10% of all cephalosporins. Cefotaxime, cefoperazone and latamoxef were introduced in Japan in 1981, and cefmenoxime and cefpiramide in 1983 and 1985. Despite increasing consumption of third-generation agents, little has been published documenting their antibacterial activity against recently significant pathogens freshly isolated from clinical specimens.

It is important to investigate whether the isolation frequencies of resistant organisms against these agents have increased after several years of use. We compared their present antibacterial activities with the results evaluated when they were first

introduced in Japan[2~6], and with those of other groups of drugs, including penicillin G, ampicillin, carbenicillin, gentamicin, tobramycin, minocycline, lincomycin and ofloxacin.

β-lactamase (EC 3.5.2.6) production is one of the major mechanisms by which organisms resist β-lactams. The contribution of β-lactamase may be qualitative and/or quantitative[7]. An awareness of the prevalence of β-lactamase in a species is valuable not only for physicians in choosing antibiotics but also for manufactures in assessing the relative merits of new agents. A novel cephalosporin nitrocefin, for example, has been reported as being very sensitive to hydrolysis by a wide variety of β-lactamases[8]. The present study was also designed to evaluate the relationship between susceptibility against β-lactams and β-lactamase production in each species tested.

MATERIALS AND METHODS

Strains tested. The organisms used were all recent clinical isolates in St. Marianna University Hospital and were routinely identified by the clinical microbiology laboratory. Species and numbers of strains tested are shown in Table 1. The identification was confirmed by the API 20 E microtube system (Analytab Products, Plainview, New York, USA) and Enteogram System[9] (Terumo, Tokyo) for Enterobacteriaceae, the Nonfergram system[10] (Terumo) for non-fermenters and the SP-18 system (Nissui, Tokyo) for staphylococci. Isolates were stored in 20% skim milk and kept frozen at −80°C until use. Before testing, the isolates were subcultured onto blood agar plates for facultative anaerobes and GAM agar plates (Nissui) for anaerobes.

Antibacterial agents. A total of 17 antibacterial agents were tested. They were kindly supplied by the following organizations : carbenicillin, cefoperazone and gentamicin (Pfizer Taito, Tokyo) ; latamoxef, cefamandole and tobramycin (Shionogi, Osaka) ; penicillin G and ampicillin (Meiji Seika, Tokyo) ; cefotiam and cefmenoxime (Takeda, Osaka) ; lincomycin and cefpiramide (Japan Upjohn, Tokyo) ; cefmetazole (Sankyo, Tokyo) ; cefazolin (Fujisawa, Osaka) ; cefotaxime (Roussel Medica, Tokyo) ; minocycline (Japan Lederle, Tokyo) ; ofloxacin (Daiichi, Tokyo). Solutions of antibacterial agents were freshly prepared for each test.

***In vitro* susceptibility testing.** The minimum inhibitory concentrations (MICs) were determined by the agar dilution method as defined by the Japanese Society of Chemotherapy[11]. Overnight cultures of test-organisms were diluted to a density of approximately 10^6 colony-forming units per ml in Mueller-Hinton broth (Difco, Michigan, USA) for facultative anaerobes and GAM broth (Nissui) for anaerobes and applied by means of a multiple inocula replicator (Sakuma, Tokyo) to the surface of modified Mueller-Hinton agar plates (Nissui) containing two-fold dilutions of antibacterial agents. For streptococci, modified Mueller-Hinton agar supplemented with 5% horse blood was used, and for *Haemophilus*, modified Mueller-Hinton agar supplemented with 2% Filde's Enrichment (Difco). *Streptococcus*, *Neisseria* and *Haemophilus* strains were incubated in 5% CO_2. For *Campylobacter*, modified Mueller-Hinton agar supplemented with 5% defibrinated sheep blood and 0.1% vitamin K-hemin (Difco) was used. Control plates without an antibacterial agent were also inoculated before and after each series of plates. *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were included as control strains in all susceptibility tests. The MICs were determined as the lowest concentrations inhibiting growth after overnight incubation at 37°C. A few slow growing strains were incubated for 48 hr. Results were expressed as the range of MIC (μg/ml), MIC_{50} and MIC_{90}.

β-lactamase detection. Production of β-lactamase was determined by testing 18-24 hr-old cultures by the Cefinase disc (BBL Microbiology System) method[12]. The characteristic of β-lactamase production of a species was evaluated as "+", "−" or "d", according to the description in Bergey's Manual of Systematic Bacteriology[13]. The meanings of symbols are : +, 90% or more of the strains positive ; −, 90% or more of the strains negative ; d, 11-89% of the strains positive.

RESULTS

The MIC range, MIC_{50} and MIC_{90} of nine β-lactams and eight other antibacterial agents are shown in Table 1. The reproducibility of the MIC determinations against control organisms was excellent for all agents and varied only within one two-fold dilution in separate measurements. Against staphylococci, all β-lactams were relatively

Table 1-1 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC (μg/ml)		
		range	MIC_{50}	MIC_{90}
I) Gram-positive cocci				
S. aureus (73)	Cefotaxime	0.1 - 50	3.13	25
	Latamoxef	0.2 - 100	6.25	25
	Cefmenoxime	0.1 - 50	3.13	50
	Cefpiramide	0.2 ->100	6.25	50
	Cefoperazone	0.2 - 50	6.25	25
	Cefamandole	0.2 - 100	3.13	50
	Cefmetazole	0.2 - 50	6.25	25
	Cefotiam	0.2 - 50	1.56	50
	Cefazolin	0.2 ->100	1.56	50
	Penicillin G	0.2 ->100	6.25	50
	Ampicillin	0.78 - 100	12.5	50
	Carbenicillin	0.39 50	3.13	25
	Gentamicin	0.05 - 100	3.13	50
	Tobramycin	0.025 100	1.56	25
	Minocycline	0.025 1.56	0.39	0.78
	Lincomycin	0.1 50	0.78	50
	Ofloxacin	0.1 - 6.25	3.13	6.25
Coagulase-negative, mannitol-negative staphylococci (55)	Cefotaxime	0.1 - 25	0.78	6.25
	Latamoxef	0.78 50	1.56	12.5
	Cefmenoxime	0.1 25	0.39	1.56
	Cefpiramide	0.2 - 12.5	1.56	6.25
	Cefoperazone	0.2 - 25	1.56	6.25
	Cefamandole	0.1 25	0.39	1.56
	Cefmetazole	0.39 - 12.5	0.78	6.25
	Cefotiam	0.2 - 1.56	0.39	0.78
	Cefazolin	0.2 - 100	0.78	3.13
	Penicillin G	0.39 - 100	0.78	50
	Ampicillin	0.78 ->100	3.13	50
	Carbenicillin	0.39 50	1.56	25
	Gentamicin	0.1 50	0.39	12.5
	Tobramycin	0.05 25	0.2	6.25
	Minocycline	0.025 - 1.56	0.05	0.1
	Lincomycin	0.2 - 50	0.39	0.78
	Ofloxacin	0.2 - 0.78	0.39	0.39
Coagulase-negative, mannitol-positive staphylococci (30)	Cefotaxime	0.2 - 50	1.56	50
	Latamoxef	0.78 100	6.25	100
	Cefmenoxime	0.39 100	3.13	25
	Cefpiramide	0.39 100	12.5	50
	Cefoperazone	0.39 50	12.5	50

Table 1-2 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC(μg/ml)		
		range	MIC_{50}	MIC_{80}
	Cefamandole	0.2 - 50	3.13	50
	Cefmetazole	0.39 - 50	1.56	25
	Cefotiam	0.78 - 100	3.13	25
	Cefazolin	0.2 ->100	3.13	50
	Penicillin G	0.05 ->100	12.5	100
	Ampicillin	0.39 ->100	25	100
	Carbenicillin	0.1 ->100	25	100
	Gentamicin	3.13 100	12.5	50
	Tobramycin	1.56 - 50	6.25	25
	Minocycline	0.39 - 3.13	1.56	1.56
	Lincomycin	0.78 - 50	3.13	50
	Ofloxacin	0.2 - 3.13	0.78	1.56
S. pneumoniae (46)	Cefotaxime	0.05 - 0.39	0.2	0.39
	Latamoxef	0.2 - 0.78	0.39	0.78
	Cefmenoxime	0.05 - 0.39	0.2	0.39
	Cefpiramide	0.1 - 1.56	0.39	1.56
	Cefoperazone	0.1 - 1.56	0.39	1.56
	Cefamandole	0.2 0.78	0.39	0.78
	Cefmetazole	0.2 - 3.13	0 78	0.78
	Cefotiam	0.2 - 0.78	0.2	0.39
	Cefazolin	0.05 - 1.56	0.2	0.78
	Penicillin G	≦0.025 - 0.2	0.1	0.2
	Ampicillin	0.1 - 0.78	0.39	0.39
	Carbenicillin	0.05 0.39	0.2	0.39
	Gentamicin	6.25 - 25	12.5	25
	Tobramycin	6.25 - 25	12.5	25
	Minocycline	0.39 3.13	1.56	3.13
	Lincomycin	0.39 3.13	0.78	3.13
	Ofloxacin	0.78 1.56	1.56	1.56
S. pyogenes (20)	Cefotaxime	0.05 0.2	0.1	0.2
	Latamoxef	0.2 0.39	0.39	0.39
	Cefmenoxime	≦0.025 - 0.39	0.39	0.39
	Cefpiramide	0.05 - 0.78	0.2	0.39
	Cefoperazone	0.1 - 0.78	0.39	0.39
	Cefamandole	0.1 - 0.78	0.2	0.39
	Cefmetazole	0.2 0.78	0.39	0.78
	Cefotiam	0.05 0.39	0.2	0.39
	Cefazolin	0.1 0.78	0.39	0.78

Table 1-3 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC(μg/ml) range	MIC_{50}	MIC_{80}
	Penicillin G	≤0.025 - 0.1	0.05	0.1
	Ampicillin	0.1 - 0.78	0.2	0.78
	Carbenicillin	0.2 - 0.78	0.39	0.78
	Gentamicin	3.13 - 25	6.25	6.25
	Tobramycin	3.13 - 25	6.25	12.5
	Minocycline	0.39 - 1.56	0.78	0.78
	Lincomycin	0.1 - 0.78	0.2	0.39
	Ofloxacin	1.56 - 6.25	3.13	6.25
S. agalactiae (20)	Cefotaxime	0.1 - 0.78	0.2	0.39
	Latamoxef	0.2 - 3.13	0.39	0.78
	Cefmenoxime	0.1 - 1.56	0.2	0.39
	Cefpiramide	0.2 - 1.56	0.2	0.78
	Cefoperazone	0.1 1.56	0.2	0.78
	Cefamandole	0.2 0.78	0.2	0.39
	Cefmetazole	0.39 1.56	0.39	1.56
	Cefotiam	0.1 - 0.78	0.39	0.78
	Cefazolin	0.2 - 0.78	0.2	0.39
	Penicillin G	0.05 - 0.2	0.1	0.2
	Ampicillin	0.2 - 0.78	0.39	0.78
	Carbenicillin	0.39 1.56	0.39	1.56
	Gentamicin	6.25 25	12.5	12.5
	Tobramycin	6.25 - 12.5	12.5	12.5
	Minocycline	0.39 3.13	0.78	1.56
	Lincomycin	0.05 3.13	0.78	1.56
	Ofloxacin	1.56 - 12.5	3.13	3.13
E. faecalis (50)	Cefotaxime	50 ->100	>100	>100
	Latamoxef	100 ->100	>100	>100
	Cefmenoxime	>100	>100	>100
	Cefpiramide	25 ->100	>100	>100
	Cefoperazone	100 ->100	>100	>100
	Cefamandole	100 ->100	>100	>100
	Cefmetazole	>100	>100	>100
	Cefotiam	>100	>100	>100
	Cefazolin	3.13 50	25	50
	Penicillin G	0.39 12.5	1.56	6.25
	Ampicillin	0.1 6.25	0.78	1.56
	Carbenicillin	0.1 12.5	0.78	3.13
	Gentamicin	6.25 ->100	25	>100
	Tobramycin	6.25 ->100	12.5	>100
	Minocycline	1.56 50	6.25	12.5
	Lincomycin	6.25 ->100	100	>100
	Ofloxacin	0.39 6.25	1.56	3.13

Table 1-4 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC(μg/ml)		
		range	MIC_{50}	MIC_{90}
E. faecium (50)	Cefotaxime	>100	>100	>100
	Latamoxef	100 ->100	>100	>100
	Cefmenoxime	>100	>100	>100
	Cefpiramide	>100	>100	>100
	Cefoperazone	50 ->100	>100	>100
	Cefamandole	>100	>100	>100
	Cefmetazole	>100	>100	>100
	Cefotiam	100 ->100	>100	>100
	Cefazolin	>100	>100	>100
	Penicillin G	0.39 - 6.25	1.56	6.25
	Ampicillin	1.56 - 100	50	50
	Carbenicillin	1.56 - 100	50	50
	Gentamicin	1.56 ->100	>100	>100
	Tobramycin	1.56 ->100	>100	>100
	Minocycline	0.39 - 25	3.13	12.5
	Lincomycin	0.2 ->100	1.56	>100
	Ofloxacin	0.39 - 6.25	3.13	3.13
E.avium (40)	Cefotaxime	>100	>100	>100
	Latamoxef	>100	>100	>100
	Cefmenoxime	>100	>100	>100
	Cefpiramide	>100	>100	>100
	Cefoperazone	>100	>100	>100
	Cefamandole	>100	>100	>100
	Cefmetazole	>100	>100	>100
	Cefotiam	>100	>100	>100
	Cefazolin	>100	>100	>100
	Penicillin G	0.39 - 12.5	1.56	6.25
	Ampicillin	1.56 - 50	12.5	25
	Carbenicillin	1.56 - 50	12.5	25
	Gentamicin	0.39 ->100	1.56	>100
	Tobramycin	0.39 ->100	1.56	>100
	Minocycline	0.2 - 12.5	1.56	3.13
	Lincomycin	0.39 ->100	3.13	>100
	Ofloxacin	0.39 6.25	1.56	3.13
II) Enterobacteriaceae				
E. coli (72)	Cefotaxime	0.05 - 12.5	0.2	0.39
	Latamoxef	0.05 1.56	0.39	0.39
	Cefmenoxime	≦0.025 - 12.5	0.1	0.2
	Cefpiramide	0.2 - 50	0.78	12.5
	Cefoperazone	0.05 12.5	0.2	1.56

Table 1-5 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC(μg/ml) range	MIC_{50}	MIC_{90}
	Cefamandole	0.2 - 25	0.78	12.5
	Cefmetazole	0.39 - 50	1.56	3.13
	Cefotiam	0.39 - 100	0.78	1.56
	Cefazolin	0.78 - 100	3.13	25
	Penicillin G	12.5 - 100	25	100
	Ampicillin	3.13 - 100	6.25	50
	Carbenicillin	1.56 - 100	6.25	50
	Gentamicin	0.39 - 6.25	3.13	3.13
	Tobramycin	0.39 - 25	3.13	3.13
	Minocycline	0.78 - 25	3.13	12.5
	Lincomycin	25 ->100	50	>100
	Ofloxacin	0.1 - 0.78	0.2	0.78
C. freundii (50)	Cefotaxime	0.1 12.5	0.39	6.25
	Latamoxef	0.1 12.5	0.78	6.25
	Cefmenoxime	0.1 - 12.5	0.39	6.25
	Cefpiramide	0.1 12.5	3.13	6.25
	Cefoperazone	0.1 - 12.5	0.78	6.25
	Cefamandole	0.1 - 12.5	1.56	6.25
	Cefmetazole	3.13 - 50	12.5	50
	Cefotiam	0.2 - 12.5	1.56	6.25
	Cefazolin	3.13 100	25	50
	Penicillin G	25 ->100	50	>100
	Ampicillin	3.13 100	25	50
	Carbenicillin	3.13 100	12.5	50
	Gentamicin	0.78 - 12.5	1.56	3.13
	Tobramycin	0.78 - 12.5	1.56	3.13
	Minocycline	3.13 - 25	6.25	12.5
	Lincomycin	6.25 100	50	50
	Ofloxacin	0.1 - 3.13	0.39	0.78
C. diversus (11)	Cefotaxime	0.2 - 6.25	0.39	0.78
	Latamoxef	0.78 6.25	0.78	6.25
	Cefmenoxime	0.78 6.25	3.13	6.25
	Cefpiramide	0.39 3.13	3.13	3.13
	Cefoperazone	0.2 3.13	0.78	0.78
	Cefamandole	0.78 12.5	1.56	3.13
	Cefmetazole	3.13 50	6.25	50
	Cefotiam	1.56 25	3.13	6.25
	Cefazolin	3.13 50	12.5	50

Table 1-6 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC (μg/ml)		
		range	MIC_{50}	MIC_{80}
	Penicillin G	25 - 100	50	50
	Ampicillin	12.5 - 50	25	50
	Carbenicillin	6.25 - 50	25	50
	Gentamicin	1.56 - 6.25	3.13	6.25
	Tobramycin	0.78 - 6.25	3.13	3.13
	Minocycline	12.5 - 25	25	25
	Lincomycin	25 - 50	25	50
	Ofloxacin	0.78 - 6.25	3.13	3.13
K. pneumoniae (66)	Cefotaxime	0.05 - 12.5	0.2	0.78
	Latamoxef	0.1 - 12.5	0.39	0.78
	Cefmenoxime	0.05 - 3.13	0.78	1.56
	Cefpiramide	0.39 - 12.5	3.13	6.25
	Cefoperazone	0.1 - 12.5	0.78	6.25
	Cefamandole	0.2 12.5	1.56	6.25
	Cefmetazole	0.78 50	1.56	6.25
	Cefotiam	0.1 6.25	0.78	1.56
	Cefazolin	1.56 - 50	6.25	25
	Penicillin G	25 ->100	100	>100
	Ampicillin	6.25 - 100	50	100
	Carbenicillin	6.25 - 100	50	100
	Gentamicin	0.78 - 25	1.56	6.25
	Tobramycin	0.39 12.5	1.56	3.13
	Minocycline	3.13 50	12.5	25
	Lincomycin	6.25 100	50	100
	Ofloxacin	0.05 - 3.13	0.78	1.56
K. oxytoca (50)	Cefotaxime	0.05 6.25	0.1	0.39
	Latamoxef	0.05 6.25	0.2	0.39
	Cefmenoxime	0.05 - 12.5		1.56
	Cefpiramide	0.39 - 25	6.25	12.5
	Cefoperazone	0.2 - 25	0.78	12.5
	Cefamandole	0.39 25	0.78	12.5
	Cefmetazole	0.39 3.13	0.78	1.56
	Cefotiam	0.05 25	0.2	6.25
	Cefazolin	1.56 50	6.25	25
	Penicillin G	25 ->100	50	>100
	Ampicillin	6.25 100	50	100
	Carbenicillin	6.25 100	25	50
	Gentamicin	0.39 - 25	1.56	3.13
	Tobramycin	0.2 - 25	1.56	1.56
	Minocycline	1.56 25	3.13	6.25
	Lincomycin	6.25 ->100	50	100
	Ofloxacin	0.05 - 0.78	0.2	0.39

Table 1-7 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC(μg/ml) range	MIC_{50}	MIC_{90}
K. ozaenae (8)	Cefotaxime	0.05 - 0.1	0.05	0.1
	Latamoxef	0.05 - 0.1	0.1	0.1
	Cefmenoxime	≤0.025	≤0.025	≤0.025
	Cefpiramide	0.39 - 1.56	0.78	1.56
	Cefoperazone	0.1 - 0.2	0.1	0.2
	Cefamandole	0.39 - 0.78	0.78	0.78
	Cefmetazole	0.1 - 0.2	0.2	0.2
	Cefotiam	0.05 - 0.1	0.05	0.1
	Cefazolin	0.2 - 0.39	0.39	0.39
	Penicillin G	50 - 100	100	100
	Ampicillin	50	50	50
	Carbenicillin	50	50	50
	Gentamicin	0.05 - 0.1	0.1	0.1
	Tobramycin	0.05 - 0.2	0.05	0.2
	Minocycline	1.56 - 3.13	3.13	3.13
	Lincomycin	25	25	25
	Ofloxacin	0.1 - 0.39	0.1	0.39
E. aerogenes (50)	Cefotaxime	0.05 - 25	6.25	12.5
	Latamoxef	≤0.025 - 12.5	0.78	0.78
	Cefmenoxime	≤0.025 - 12.5	3.13	6.25
	Cefpiramide	0.2 - 50	12.5	50
	Cefoperazone	0.1 - 50	3.13	12.5
	Cefamandole	0.2 - 25	6.25	12.5
	Cefmetazole	3.13 - >100	100	>100
	Cefotiam	0.39 - >100	50	>100
	Cefazolin	3.13 - >100	100	>100
	Penicillin G	25 - >100	100	>100
	Ampicillin	6.25 - 100	25	50
	Carbenicillin	1.56 - 50	12.5	25
	Gentamicin	0.78 - 25	1.56	12.5
	Tobramycin	0.39 - 25	1.56	25
	Minocycline	1.56 - 25	3.13	6.25
	Lincomycin	12.5 - >100	50	>100
	Ofloxacin	0.05 - 0.78	0.1	0.39
E. cloacae (47)	Cefotaxime	≤0.025 - 12.5	0.78	6.25
	Latamoxef	≤0.025 - 12.5	0.39	12.5
	Cefmenoxime	0.05 - 12.5	0.39	6.25
	Cefpiramide	0.2 - 50	6.25	25
	Cefoperazone	0.1 - 50	0.78	25

Table 1-8 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC(μg/ml)		
		range	MIC_{50}	MIC_{80}
	Cefamandole	0.39 - 25	3.13	12.5
	Cefmetazole	0.78 ->100	100	>100
	Cefotiam	0.39 ->100	50	>100
	Cefazolin	1.56 ->100	100	>100
	Penicillin G	50 ->100	100	>100
	Ampicillin	6.25 - 100	25	50
	Carbenicillin	0.78 - 25	12.5	25
	Gentamicin	0.78 - 12.5	3.13	12.5
	Tobramycin	0.78 - 25	1.56	25
	Minocycline	0.78 - 50	6.25	12.5
	Lincomycin	6.25 ->100	50	>100
	Ofloxacin	0.05 - 0.78	0.2	0.39
P. mirabilis (55)	Cefotaxime	0.05 - 1.56	0.2	0.39
	Latamoxef	0.2 - 0.78	0.39	0.78
	Cefmenoxime	0.05 - 0.39	0.2	0.39
	Cefpiramide	0.78 - 25	3.13	12.5
	Cefoperazone	0.39 - 25	1.56	25
	Cefamandole	0.39 - 25	1.56	6.25
	Cefmetazole	0.78 1.56	1.56	1.56
	Cefotiam	0.2 - 6.25	0.39	0.78
	Cefazolin	1.56 - 12.5	3.13	6.25
	Penicillin G	1.56 - 100	3.13	50
	Ampicillin	1.56 - 50	3.13	50
	Carbenicillin	1.56 - 50	3.13	50
	Gentamicin	1.56 - 25	3.13	25
	Tobramycin	0.78 - 25	1.56	12.5
	Minocycline	3.13 - 50	12.5	25
	Lincomycin	12.5 - 50	25	50
	Ofloxacin	0.05 - 0.78	0.2	0.39
P. vulgaris (40)	Cefotaxime	0.39 - 12.5	0.78	3.13
	Latamoxef	0.1 - 0.39	0.2	0.39
	Cefmenoxime	0.39 - 12.5	1.56	6.25
	Cefpiramide	1.56 - 50	6.25	25
	Cefoperazone	0.2 - 50	3.13	12.5
	Cefamandole	0.39 50	12.5	25
	Cefmetazole	0.78 6.25	0.78	0.78
	Cefotiam	0.39 - 100	50	100
	Cefazolin	12.5 100	50	100

Table 1-9 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC(μg/ml)		
		range	MIC_{50}	MIC_{90}
	Penicillin G	12.5 ->100	>100	>100
	Ampicillin	6.25 ->100	100	>100
	Carbenicillin	3.13 ->100	100	>100
	Gentamicin	0.78 - 50	1.56	3.13
	Tobramycin	0.78 - 50	1.56	1.56
	Minocycline	1.56 - 25	6.25	12.5
	Lincomycin	12.5 - 100	50	100
	Ofloxacin	0.1 - 0.78	0.39	0.78
M. morganii (50)	Cefotaxime	0.2 12.5	0.78	3.13
	Latamoxef	0.39 - 6.25	0.78	1.56
	Cefmenoxime	0.2 - 6.25	0.78	3.13
	Cefpiramide	3.13 - 50	12.5	25
	Cefoperazone	0.78 25	3.13	12.5
	Cefamandole	0.78 - 25	25	25
	Cefmetazole	0.78 - 12.5	3.13	6.25
	Cefotiam	0.2 - 25	12.5	25
	Cefazolin	6.25 ->100	>100	>100
	Penicillin G	25 ->100	100	>100
	Ampicillin	3.13 ->100	50	100
	Carbenicillin	3.13 - 50	12.5	25
	Gentamicin	1.56 - 6.25	3.13	6.25
	Tobramycin	1.56 25	3.13	6.25
	Minocycline	1.56 - 50	6.25	25
	Lincomycin	12.5 ->100	50	100
	Ofloxacin	0.2 - 1.56	0.78	1.56
P. rettgeri (17)	Cefotaxime	0.05 0.78	0.1	0.78
	Latamoxef	0.1 0.39	0.2	0.39
	Cefmenoxime	0.1 1.56	0.39	0.78
	Cefpiramide	0.78 - 25	25	25
	Cefoperazone	0.2 - 25	1.56	25
	Cefamandole	3.13 50	50	50
	Cefmetazole	0.39 25	3.13	25
	Cefotiam	0.39 - 12.5	1.56	12.5
	Cefazolin	6.25 ->100	100	>100
	Penicillin G	50 ->100	100	>100
	Ampicillin	6.25 ->100	50	100
	Carbenicillin	3.13 ->100	25	50
	Gentamicin	1.56 50	25	50
	Tobramycin	1.56 50	25	50
	Minocycline	3.13 50	25	50
	Lincomycin	25 ->100	100	100
	Ofloxacin	0.2 1.56	0.78	1.56

Table 1-10 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC(μg/ml)		
		range	MIC_{50}	MIC_{90}
S. marcescens (77)	Cefotaxime	0.2 - 12.5	3.13	12.5
	Latamoxef	0.2 - 25	0.78	12.5
	Cefmenoxime	0.2 - 12.5	0.78	6.25
	Cefpiramide	3.13 - 50	12.5	25
	Cefoperazone	0.78 - 50	12.5	25
	Cefamandole	3.13 - 50	6.25	25
	Cefmetazole	3.13 ->100	12.5	100
	Cefotiam	3.13 ->100	100	>100
	Cefazolin	3.13 ->100	>100	>100
	Penicillin G	50 ->100	>100	>100
	Ampicillin	25 ->100	100	>100
	Carbenicillin	6.25 ->100	100	>100
	Gentamicin	1.56 - 50	6.25	25
	Tobramycin	0.78 - 50	12.5	25
	Minocycline	1.56 - 25	6.25	12.5
	Lincomycin	3.13 - 100	50	100
	Ofloxacin	0.2 - 12.5	0.78	6.25
Salmonella spp. (21)	Cefotaxime	0.1 - 3.13	0.2	0.2
	Latamoxef	0.1 - 0.39	0.2	0.39
	Cefmenoxime	0.1 - 0.39	0.2	0.39
	Cefpiramide	0.78 - 6.25	0.78	6.25
	Cefoperazone	0.2 - 3.13	0.39	3.13
	Cefamandole	0.2 3.13	0.39	3.13
	Cefmetazole	0.1 6.25	0.2	0.39
	Cefotiam	0.1 6.25	0.2	0.2
	Cefazolin	0.2 - 1.56	0.39	1.56
	Penicillin G	0.39 - 50	1.56	25
	Ampicillin	0.39 - 50	1.56	25
	Carbenicillin	0.78 - 25	1.56	12.5
	Gentamicin	0.78 - 3.13	1.56	1.56
	Tobramycin	0.39 1.56	0.78	1.56
	Minocycline	0.78 12.5	3.13	12.5
	Lincomycin	25 - 100	50	100
	Ofloxacin	0.05 - 0.78	0.2	0.39
III) Nonfermenters	Cefotaxime	3.13 ->100	25	>100
P. aeruginosa (77)	Latamoxef	3.13 ->100	25	>100
	Cefmenoxime	1.56 ->100	12.5	>100
	Cefpiramide	0.2 100	1.56	12.5
	Cefoperazone	1.56 ->100	12.5	>100

Table 1-11 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC(μg/ml) range	MIC_{50}	MIC_{90}
	Cefamandole	1.56 ->100	25	100
	Cefmetazole	>100	>100	>100
	Cefotiam	>100	>100	>100
	Cefazolin	>100	>100	>100
	Penicillin G	>100	>100	>100
	Ampicillin	100 ->100	100	>100
	Carbenicillin	0.78 ->100	50	>100
	Gentamicin	0.05 ->100	1.56	12.5
	Tobramycin	0.39 25	3.13	12.5
	Minocycline	1.56 ->100	25	50
	Lincomycin	12.5 ->100	100	>100
	Ofloxacin	0.1 - 12.5	0.78	3.13
P. cepacia (27)	Cefotaxime	0.78 25	6.25	12.5
	Latamoxef	3.13 - 100	25	50
	Cefmenoxime	0.78 - 25	12.5	25
	Cefpiramide	1.56 ->100	6.25	>100
	Cefoperazone	1.56 ->100	50	>100
	Cefamandole	25 ->100	50	100
	Cefmetazole	3.13 ->100	>100	>100
	Cefotiam	3.13 ->100	>100	>100
	Cefazolin	>100	>100	>100
	Penicillin G	>100	>100	>100
	Ampicillin	100 ->100	>100	>100
	Carbenicillin	3.13 ->100	>100	>100
	Gentamicin	25 ->100	>100	>100
	Tobramycin	6.25 ->100	>100	>100
	Minocycline	0.1 - 25	6.25	12.5
	Lincomycin	50 100	50	100
	Ofloxacin	0.2 - 25	3.13	6.25
P. putida (14)	Cefotaxime	1.56 100	6.25	50
	Latamoxef	6.25 ->100	50	>100
	Cefmenoxime	1.56 ->100	6.25	25
	Cefpiramide	0.78 ->100	6.25	25
	Cefoperazone	0.78 ->100	12.5	100
	Cefamandole	25 ->100	50	100
	Cefmetazole	12.5 ->100	>100	>100
	Cefotiam	>100	>100	>100
	Cefazolin	>100	>100	>100

Table 1-12 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC (μg/ml)		
		range	MIC_{50}	MIC_{90}
	Penicillin G	>100	>100	>100
	Ampicillin	12.5 ->100	50	>100
	Carbenicillin	25 ->100	100	>100
	Gentamicin	0.1 - 50	1.56	3.13
	Tobramycin	0.1 - 50	0.39	1.56
	Minocycline	0.78 - 25	1.56	6.25
	Lincomycin	50 - 100	50	100
	Ofloxacin	0.2 - 3.13	0.78	3.13
X. maltophilia (27)	Cefotaxime	1.56 ->100	50	100
	Latamoxef	0.39 ->100	3.13	6.25
	Cefmenoxime	1.56 ->100	50	100
	Cefpiramide	0.78 ->100	12.5	100
	Cefoperazone	0.39 ->100	12.5	100
	Cefamandole	6.25 ->100	50	100
	Cefmetazole	3.13 ->100	100	100
	Cefotiam	6.25 ->100	100	100
	Cefazolin	100	100	100
	Penicillin G	>100	>100	>100
	Ampicillin	6.25 ->100	>100	>100
	Carbenicillin	1.56 ->100	>100	>100
	Gentamicin	0.78 - 100	25	100
	Tobramycin	1.56 - 100	25	100
	Minocycline	0.1 - 0.78	0.2	0.39
	Lincomycin	12.5 100	50	100
	Ofloxacin	0.05 6.25	0.39	3.13
A. calcoaceticus (27)	Cefotaxime	3.13 100	12.5	50
	Latamoxef	6.25 - 100	50	100
	Cefmenoxime	3.13 - 100	25	100
	Cefpiramide	12.5 ->100	25	100
	Cefoperazone	12.5 ->100	50	100
	Cefamandole	50 ->100	50	>100
	Cefmetazole	6.25 ->100	100	>100
	Cefotiam	50 ->100	100	>100
	Cefazolin	>100	>100	>100
	Penicillin G	>100	>100	>100
	Ampicillin	6.25 ->100	25	>100
	Carbenicillin	3.13 ->100	12.5	>100
	Gentamicin	0.78 50	1.56	50
	Tobramycin	0.39 50	0.78	50
	Minocycline	0.05 0.39	0.1	0.2
	Lincomycin	6.25 50	12.5	25
	Ofloxacin	0.2 0.78	0.78	0.78

Table 1-13 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC (μg/ml)		
		range	MIC_{50}	MIC_{90}
A. lwoffii (15)	Cefotaxime	0.78 - 100	3.13	50
	Latamoxef	6.25 - 100	25	100
	Cefmenoxime	0.78 - 50	6.25	50
	Cefpiramide	3.13 ->100	12.5	100
	Cefoperazone	3.13 ->100	25	>100
	Cefamandole	1.56 - 100	25	100
	Cefmetazole	1.56 ->100	12.5	>100
	Cefotiam	3.13 ->100	12.5	>100
	Cefazolin	12.5 ->100	100	>100
	Penicillin G	0.78 ->100	6.25	>100
	Ampicillin	0.2 ->100	0.78	>100
	Carbenicillin	1.56 ->100	6.25	>100
	Gentamicin	0.2 25	1.56	12.5
	Tobramycin	0.2 - 50	0.78	25
	Minocycline	0.39 - 3.13	1.56	3.13
	Lincomycin	12.5 ->100	50	>100
	Ofloxacin	0.39 - 6.25	1.56	6.25
Flavobacterium spp. (18)	Cefotaxime	12.5 ->100	50	>100
	Latamoxef	12.5 ->100	50	100
	Cefmenoxime	6.25 25	25	25
	Cefpiramide	6.25 ->100	50	>100
	Cefoperazone	1.56 50	25	50
	Cefamandole	25 - 100	50	100
	Cefmetazole	12.5 ->100	25	>100
	Cefotiam	100 ->100	100	>100
	Cefazolin	>100	>100	>100
	Penicillin G	>100	>100	>100
	Ampicillin	25 ->100	>100	>100
	Carbenicillin	50 ->100	100	>100
	Gentamicin	12.5 - 50	12.5	25
	Tobramycin	12.5 - 50	12.5	50
	Minocycline	0.05 - 3.13	0.39	1.56
	Lincomycin	12.5 100	25	100
	Ofloxacin	0.39 6.25	0.78	6.25
A. xylosoxidans (25)	Cefotaxime	0.78 50	6.25	50
	Latamoxef	0.1 50	0.39	6.25
	Cefmenoxime	0.2 100	25	100
	Cefpiramide	0.78 - 100	3.13	50
	Cefoperazone	0.2 100	0.39	25

Table 1-14 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC(μg/ml) range	MIC_{50}	MIC_{90}
	Cefamandole	3.13 - 100	12.5	50
	Cefmetazole	1.56 ->100	100	>100
	Cefotiam	1.56 ->100	100	>100
	Cefazolin	25 ->100	>100	>100
	Penicillin G	25 ->100	>100	>100
	Ampicillin	0.39 ->100	3.13	100
	Carbenicillin	0.1 ->100	0.39	100
	Gentamicin	1.56 100	50	100
	Tobramycin	0.2 - 100	50	100
	Minocycline	0.2 - 50	1.56	12.5
	Lincomycin	25 ->100	50	100
	Ofloxacin	0.05 - 50	12.5	25
A. faecalis (10)	Cefotaxime	0.1 1.56	0.78	0.78
	Latamoxef	0.1 - 0.78	0.1	0.39
	Cefmenoxime	0.1 - 1.56	0.39	0.78
	Cefpiramide	1.56 - 50	6.25	50
	Cefoperazone	0.78 25	1.56	12.5
	Cefamandole	0.1 0.39	0.2	0.39
	Cefmetazole	0.2 - 1.56	0.78	0.78
	Cefotiam	0.39 1.56	1.56	1.56
	Cefazolin	12.5 50	12.5	12.5
	Penicillin G	6.25 ->100	12.5	100
	Ampicillin	1.56 100	12.5	100
	Carbenicillin	6.25 100	25	100
	Gentamicin	0.39 12.5	1.56	6.25
	Tobramycin	0.2 25	0.39	12.5
	Minocycline	0.39 - 12.5	0.78	6.25
	Lincomycin	25 100	50	100
	Ofloxacin	0.2 6.25	1.56	3.13
IV) Miscellaneous	Cefotaxime	0.05 - 0.1	0.05	0.1
N. gonorrhoeae (3)	Latamoxef	0.05 0.39	0.2	0.39
	Cefmenoxime	0.05 0.1	0.05	0.1
	Cefpiramide	0.05 0.39	0.2	0.39
	Cefoperazone	0.05 0.39	0.2	0.39
	Cefamandole	0.05 0.1	0.05	0.1
	Cefmetazole	0.2 0.39	0.39	0.39
	Cefotiam	0.39 0.78	0.39	0.78
	Cefazolin	0.2 0.39	0.2	0.39

Table 1-15 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC(μg/ml)		
		range	MIC_{50}	MIC_{90}
	Penicillin G	0.05 - 0.1	0.1	0.1
	Ampicillin	0.2 - 0.39	0.39	0.39
	Carbenicillin	0.1 - 0.39	0.2	0.39
	Gentamicin	12.5	12.5	12.5
	Tobramycin	12.5	12.5	12.5
	Minocycline	0.1 - 0.2	0.2	0.2
	Lincomycin	0.2 - 0.39	0.2	0.39
	Ofloxacin	0.05 - 3.13	0.1	3.13
influenzae (23)	Cefotaxime	0.05 - 0.78	0.2	0.2
	Latamoxef	0.1 - 0.39	0.39	0.39
	Cefmenoxime	0.05 - 0.39	0.2	0.39
	Cefpiramide	0.2 - 6.25	0.39	1.56
	Cefoperazone	0.2 - 3.13	0.39	1.56
	Cefamandole	0.39 3.13	0.78	0.78
	Cefmetazole	0.78 - 1.56	1.56	1.56
	Cefotiam	0.39 - 1.56	0.39	0.78
	Cefazolin	1.56 - 12.5	6.25	12.5
	Penicillin G	0.39 - 25	1.56	3.13
	Ampicillin	1.56 25	3.13	6.25
	Carbenicillin	0.78 - 25	1.56	6.25
	Gentamicin	1.56 - 12.5	6.25	12.5
	Tobramycin	1.56 6.25	3.13	6.25
	Minocycline	0.78 - 3.13	1.56	3.13
	Lincomycin	3.13 50	12.5	25
	Ofloxacin	0.39 - 3.13	0.78	1.56
H. parahaemolyticus (23)	Cefotaxime	0.1 3.13	0.2	3.13
	Latamoxef	0.2 - 0.78	0.39	0.78
	Cefmenoxime	0.1 - 1.56	0.2	1.56
	Cefpiramide	0.39 - 6.25	0.78	6.25
	Cefoperazone	0.2 - 3.13	0.39	3.13
	Cefamandole	0.2 - 3.13	0.78	3.13
	Cefmetazole	0.39 - 3.13	1.56	3.13
	Cefotiam	0.39 - 1.56	0.78	1.56
	Cefazolin	1.56 - 12.5	6.25	12.5
	Penicillin G	0.78 6.25	1.56	6.25
	Ampicillin	3.13 - 25	3.13	25
	Carbenicillin	1.56 - 12.5	1.56	12.5
	Gentamicin	3.13 - 12.5	6.25	12.5
	Tobramycin	3.13 - 6.25	6.25	6.25
	Minocycline	1.56 3.13	3.13	3.13
	Lincomycin	6.25 - 50	12.5	50
	Ofloxacin	0.39 0.78	0.39	0.78

Table 1-16 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC(μg/ml) range	MIC_{50}	MIC_{90}
C. jejuni (18)	Cefotaxime	3.13 - 100	12.5	50
	Latamoxef	12.5 ->100	50	>100
	Cefmenoxime	6.25 ->100	25	>100
	Cefpiramide	50 ->100	>100	>100
	Cefoperazone	>100	>100	>100
	Cefamandole	6.25 - 100	25	50
	Cefmetazole	12.5 ->100	50	>100
	Cefotiam	6.25 - 100	25	100
	Cefazolin	>100	>100	>100
	Penicillin G	0.39 - 25	6.25	25
	Ampicillin	0.05 - 6.25	1.56	6.25
	Carbenicillin	0.05 - 12.5	1.56	6.25
	Gentamicin	≦0.025 - 0.39	0.1	0.2
	Tobramycin	≦0.025 - 0.2	0.1	0.2
	Minocycline	0.1 - 12.5	0.78	6.25
	Lincomycin	0.05 - 1.56	0.2	0.78
	Ofloxacin	0.1 - 3.13	0.39	1.56
V) Anaerobes				
Bacteroides spp. (20)	Cefotaxime	0.39 - 100	6.25	100
	Latamoxef	0.39 - 25	1.56	3.13
	Cefmenoxime	1.56 - 100	25	100
	Cefpiramide	3.13 ->100	12.5	100
	Cefoperazone	0.78 ->100	12.5	100
	Cefamandole	6.25 ->100	50	100
	Cefmetazole	0.78 ->100	3.13	100
	Cefotiam	12.5 ->100	50	>100
	Cefazolin	1.56 ->100	25	>100
	Penicillin G	0.78 ->100	50	100
	Ampicillin	6.25 - 100	50	100
	Carbenicillin	0.39 100	12.5	50
	Gentamicin	50 ->100	100	>100
	Tobramycin	50 ->100	100	>100
	Minocycline	0.05 - 6.25	0.78	1.56
	Lincomycin	0.78 ->100	50	>100
	Ofloxacin	0.39 - 12.5	1.56	3.13
Fusobacterium spp. (15)	Cefotaxime	<0.025 - 0.1	0.05	0.1
	Latamoxef	<0.025 0.1	0.05	0.1
	Cefmenoxime	<0.025 - 0.2	0.05	0.2
	Cefpiramide	<0.025 - 0.2	0.1	0.2
	Cefoperazone	<0.025 - 0.39	0.1	0.2
	Cefamandole	<0.025 - 0.2	0.1	0.2
	Cefmetazole	<0.025 - 0.78	0.2	0.39
	Cefotiam	<0.025 - 0.78	0.1	0.39
	Cefazolin	<0.025 - 0.39	0.1	0.39

Table 1-17 Antibacterial activity of seventeen antimicrobial agents

Species	Antimicrobial agent	MIC(μg/ml) range	MIC_{50}	MIC_{90}
	Penicillin G	<0.025	<0.025	<0.025
	Ampicillin	<0.025 - 0.2	0.05	0.2
	Carbenicillin	<0.025 - 0.39	0.05	0.2
	Gentamicin	50 ->100	100	>100
	Tobramycin	50 ->100	100	>100
	Minocycline	<0.025 - 0.2	0.05	0.2
	Lincomycin	0.05 - 0.2	0.1	0.2
	Ofloxacin	0.78 - 25	3.13	12.5
Gram-positive cocci(11)	Cefotaxime	<0.025 - 0.78	0.2	0.39
	Latamoxef	<0.025 - 0.78	0.2	0.39
	Cefmenoxime	0.05 - 1.56	0.2	0.78
	Cefpiramide	<0.025 - 1.56	0.39	0.78
	Cefoperazone	<0.025 - 0.78	0.2	0.78
	Cefamandole	<0.025 - 0.78	0.2	0.78
	Cefmetazole	<0.025 0.78	0.2	0.39
	Cefotiam	<0.025 - 1.56	0.39	0.78
	Cefazolin	0.05 - 1.56	0.39	0.78
	Penicillin G	<0.025 - 1.56	0.39	1.56
	Ampicillin	<0.025 - 1.56	0.2	0.78
	Carbenicillin	0.1 3.13	0.39	3.13
	Gentamicin	3.13 ->100	12.5	>100
	Tobramycin	3.13 ->100	12.5	>100
	Minocycline	<0.025 - 12.5	0.78	6.25
	Lincomycin	<0.025 - 0.78	0.1	0.39
	Ofloxacin	0.2 - 6.25	0.39	3.13
C. difficile(30)	Cefotaxime	12.5 ->100	25	100
	Latamoxef	12.5 ->100	50	100
	Cefmenoxime	12.5 ->100	25	100
	Cefpiramide	6.25 ->100	25	>100
	Cefoperazone	6.25 ->100	25	25
	Cefamandole	25 ->100	100	>100
	Cefmetazole	3.13 ->100	>100	>100
	Cefotiam	>100	>100	>100
	Cefazolin	1.56 - 25	6.25	12.5
	Penicillin G	0.39 6.25	0.78	1.56
	Ampicillin	0.2 - 6.25	0.78	1.56
	Carbenicillin	0.39 25	6.25	12.5
	Gentamicin	50 ->100	100	100
	Tobramycin	50 ->100	100	100
	Minocycline	0.2 100	0.39	100
	Lincomycin	0.78 - 100	6.25	>100
	Ofloxacin	3.13 - 25	12.5	25

[a] Number in parentheses indicates number of strains tested.

Table 2 Antibacterial activity of five third-generation cephems

Species against which MIC_{80} of all third-generation cephems are		
less than 6.25 μg/ml	more than 12.5 μg/ml	variable[a]
CNS, Mannit(−)[b]	*S. aureus*	CNS, Mannit(+)[c]
S. pneumoniae	*E. faecalis*	
S. pyogenes	*E. faecium*	*E. aerogenes*
S. agalactiae	*E. avium*	*E. cloacae*
		K. oxytoca
E. coli		*P. vulgaris*
C. freundii		*M. morganii*
C. diversus		*P. rettgeri*
K. pneumoniae		*S. marcescens*
K. ozaenae	*P. cepacia*	
H. alvei	*P. putida*	
P. mirabilis	*A. calcoaceticus*	*P. aeruginosa*
Salmonella spp.	*A. lwoffii*	*X. maltophilia*
	F. indologenes	*A. faecalis*
H. influenzae	*F. meningosepticum*	*A. xylosoxidans*
H. parahaemolyticus		
N. gonorrhoeae	*C. jejuni*	
Anaerobic Gram-positive cocci		
Fusobacterium spp.	*C. difficile*	*Bacteroides* spp.

[a] MIC_{80} varies considerably, depending on the cephem involved.
[b] Coagulase-negative, mannitol-nonfermentative staphylococci.
[c] Coagulase-negative, mannitol-fermentative staphylococci.

inactive, the $MICs_{90}$ being 25 μg/ml or more. Against coagulase-negative staphylococci (CNS), a significant difference in susceptibility was observed between mannitol-fermentative CNS and mannitol-nonfermentative CNS. The former group consisted mainly of *S. haemolyticus* and a small number of *S. sciuri*, *S. capitis* and *S. cohnii*. The latter group consisted mainly of *S. epidermidis* and a few *S. hominis*. In general, all cephalosporins were inactive against the latter group, with $MICs_{90}$ of 25 μg/ml or more ; but active against the former, with $MICs_{90}$ ranging 0.78 μg/ml (cefotiam) to 12.5 μg/ml (latamoxef). The significance of the difference in susceptibility of CNS necessiates accurate identification of species and precise testing in a clinical microbiology laboratory. The third-generation agents had less activity than the older agents against mannitol-nonfermentative CNS. Against streptococci, all β-lactams showed good activity and MIC_{90} of these agents were 1.56 μg/ml or less. No significant difference in susceptibility to β-lactams was observed among *S. pneumoniae*, *S. pyogenes* and *S. agalactiae* strains. Against enterococci, all cephalosporins were inactive and $MICs_{90}$ were more than 100 μg/ml. A significant difference in susceptibility to penicillins was observed, however, between strains of *E. faecalis* and of *E. faecium* and *E. avium*. $MICs_{90}$ of ampicillin and carbenicillin against *E. faecalis* strains were 1.56 and 3.13 μg/ml respectively, whereas those against *E. faecium* and *E. avium* strains were 25 μg/ml or more.

Against Enterobacteriaceae, the third-generation agents were more effective than the older ones, especially against *C. freundii*, *C. diversus*, *E. aerogenes*, *E. cloacae*, indole-positive *Proteus* (including *P. vulgaris*, *M. morganii* and *P. rettgeri*), and *S. marcescens*. The Enterobacteriaceae were roughly divided into two groups according to their susceptibility to the third-generation agents (Table 2). The Group 1, which included strains of *E. coli*, *C. freundii*, *C. diversus*, *K. pneumoniae* ssp. *pneumoniae*, *K. pneumoniae* ssp. *ozaenae*, *H. alvei*, *P. mirabilis* and *Salmonella* species, was normally sensitive to these agents. Amounts ranging from 0.025–6.25 μg/ml of these agents were sufficient to inhibit 80% of strains of all species in this group. Group 2, however, which included strains of *E. aerogenes*, *E. cloacae*, *K. oxytoca*, *P. vulgaris*, *M. morganii*, *P. rettgeri* and *S. marcescens*, showed

Table 3 Detection of β-lactamase by Nitrocefin disc

Characteristic of β-lactamase production in species of		
+[a]	−	d
CNS, Mannit(−)[b]		*S. aureus* CNS, Mannit(+)[c]
	S. pneumoniae *S. pyogenes* *S. agalactiae* *E. faecalis*	*E. faecium* *E. avium*
E. coli *C. freundii* *K. pneumoniae* *K. oxytoca* *E. aerogenes* *E. cloacae* *P. vulgaris* *M. morganii* *P. rettgeri* *H. alvei* *S. marcescens*	*K. ozaenae* *P. mirabilis*	*C. diversus* *Salmonella* spp.
P. aeruginosa *P. cepacia* *P. putida* *A. calcoaceticus* *F. meningosepticum* *F. indologenes* *A. faecalis* *A. xylosoxidans*	*X. maltophilia* *N. gonorrhoeae*	*A. lwoffii* *H. influenzae* *H. parahaemolyticus*
	Anaerobic Gram (+) cocci[d] *Fusobacterium* spp. *C. difficile*	*Bacteroides* spp.

[a] + : more than 90% strains positive.
− : more than 90% strains negative.
d : 11-89% strains positive.
[b] Coagulase-negative, mannitol-nonfermentative staphylococci.
[c] Coagulase-negative, mannitol-fermentative staphylococci.
[d] Peptococci and peptostreptococci.

varying susceptibility to each of the five third-generation agents. A significant difference in species susceptibility to the older agents, however, was observed between indole-positive and -negative *Proteus* strains. *P. mirabilis* strains were sensitive to the first- and second-generation agents with $MIC_{s_{90}}$ ranging from 0.78-6.25 μg/ml. However, indole-positive strains were generally resistant to the older agents and $MIC_{s_{90}}$ ranged from 6.25 μg/ml (cefmetazole) to more than 100 μg/ml (cefazolin). $MIC_{s_{90}}$ of the older agents to indole-positive *Proteus* strains were 4 (cefmetazole) to 128 (cefotiam)-times higher than those to *P. mirabilis* strains. The third-generation agents, however, showed equally good activity against indole-negative and -positive *Proteus* strains.

Against non-fermenters, the relative activities of β-lactams varied by species tested. Strains of *P. aeruginosa*, *P. cepacia*, *P. putida*, *Flavobacterium* species and *Acinetobacter* species were resistant to cephalosporins, whereas strains of *A. faecalis* were normally sensitive, the $MIC_{s_{90}}$ of cefotaxime and latamoxef being 0.78 and 0.39 μg/ml respectively. Strains of *X. maltophilia*(formerly *P. maltophilia*) were generally highly resistant to cephalosporins, despite their lack of β-lactamase produc-

tion. Against *Haemophilus* and *Neisseria* species, cephalosporins were generally highly effective. They were inactive against strains of *Campylobacter*, although some penicillins showed good activity. Against anaerobic bacteria, the relative activities of β-lactams varied by species tested. Against Gram-positive cocci (peptococci and peptostreptococci) and *Fusobacterium*, all β-lactams showed good activity, their $MIC_{s_{90}}$ being 0.78 μg/ml or less. Against *Bacteroides* (mainly *B. fragilis*) and *C. difficile* strains, cephalosporins were generally ineffective. Ofloxacin, one of the newer pyridone carboxylic acid derivatives, inhibited growth of over 80% of strains in all species tested except *C. difficile* strains, at a concentration of 3.13 μg/ml.

An apparently close relationship between susceptibility to β-lactams and β-lactamase production was observed in *Proteus* species (Table 3). Strains of indole-positive *Proteus* produced β-lactamase and were resistant to the older cephalosporins, whereas strains of *P. mirabilis* did not produce β-lactamase and were susceptible to the older cephalosporins. Both groups of *Proteus* strains, however, were equally susceptible to the third-generation cephalosporins which are generally β-lactamase resistant. On the other hand, a controversial relationship was observed in *Klebsiella* species : although *K. pneumoniae* ssp. *pneumoniae* produced β-lactamase, whereas *K. pneumoniae* ssp. *ozaenae* did not, the susceptibility profiles of both species were quite similar. These results indicate that β-lactamase production is not an absolute determinant of susceptibility to β-lactams, so that alternative mechanism(s) of resistance should be considered in each case.

DISCUSSION

The antibacterial activity of cephalosporins was summarized in a recent paper[1]. Enormous progress in cephalosporins has been effected of late by the development of a large number of potent semisynthetic derivatives. The pioneer of the newer, third-generation cephalosporins is cefotaxime, which combines high β-lactamase stability with a markedly improved intrinsic bactericidal activity and extends the antibacterial spectrum to almost all species of Enterobacteriaceae and also to some Gram-positive and Gram-negative organisms. From the present *in vitro* comparison of activities of third-generation agents against recent clinical isolates, cefotaxime and latamoxef appear to be the most widely active against Enterobacteriaceae, some non-fermenters and Gram-positive cocci. Although there was a slight difference in activity against some species, this difference seems to be clinically irrelevant when the low MICs are considered. Their insufficient activity in comparison with cefpiramide against *P. aeruginosa* may constitute a slight handicap in clinical infections if microbiological diagnosis has not excluded a *P. aeruginosa* infection[14]. Nevertheless, it should be noted that cefpiramide is definitely less active than cefotaxime and latamoxef against a wide variety of species. Cefoperazone and cefmenoxime were less active than cefotaxime and latamoxef against Enterobacteriaceae *in vitro*. Cefotiam and cefamandole were generally less active than the third-generation agents, and might become obsolete as soon as the latter becomes generally more available.

Our results were compared with those previously evaluated when the third-generation agents were first introduced in Japan[2-6], and are in general agreement with the previously reported susceptibilities of a wide variety of clinical isolates. No significant increase in resistant organisms to any of the agents was observed in the species tested, although continued increase in the resistance of organisms to the older cephalosporins has been demonstrated[14]. There were, however, some differences between the present results and those reported from other researchers[15-19] in the susceptibility patterns of bacterial isolates. Regional variations, origins of strains tested, and extent of consumption of antibacterial agents may account for some of these differences.

No apparently close relationship was observed between β-lactamase production and resistance to β-lactams in *Klebsiella* species or the *Pseudomonas-Xanthomonas* group. We demonstrated that β-lactamase production was not an absolute predictor of susceptibility, as some of the β-lactamase producing strains were susceptible to cefazolin and, contrariwise, some of the β-lactamase nonproducing strains were resistant to cefazolin and cefotaxime. In these cases, alternative mechanism(s) of resistance, for example, the existence of a permeability barrier in the outer membrane or alteration of the properties of the target enzymes, should

be considered.

Staphylococci and streptococci are Gram-positive bacteria which play important roles in infectious diseases. Gram-positive cocci are notoriously susceptible to β-lactams. Enterococci, however, are an exception to this rule, showing susceptibility to some penicillins but usually high resistance to cephalosporins. This differential susceptibility suggests that streptococci and enterococci may possess different penicillin-binding proteins.

β-lactams have been thought to be more reliable and safe than other groups of antibacterial agents. Nevertheless, serious problems have emerged with wide use of some of third-generation agents. Latamoxef and cefoperazone, both of which have a methyltetrazolethiol side chain, have been reported to cause coagulation abnormalities, clinical bleeding and disulfiram-like reactions. In addition, an unusually high incidence of diarrhea has been associated with administration of cefoperazone. Cefotaxime, however, does not have this side chain and has not caused the symptoms described above[17]. In conclusion, their broad spectrum and highly potent *in vitro* activity and other *in vivo* characteristics make cefotaxime and some other third-generation agents potentially useful therapeutic agents ; but continued periodic evaluation of their *in vitro* activity and *in vivo* therapeutic efficacy is necessary.

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新鮮臨床分離菌に対する Cefotaxime および8種の β-ラクタム系薬剤の抗菌力の検討

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臨床材料から分離されたグラム陽性球菌 384 株，腸内細菌科菌群 595 株，ブドウ糖非発酵菌 240 株，嫌気性菌その他 143 株を用いて，第3世代セフェム系薬剤5種 (Cefotaxime, Latamoxef, Cefmenoxime, Cefpiramide, Cefoperazone)，第1，第2世代セフェム系薬剤4種 (Cefazolin, Cefotiam, Cefmetazole, Cefamandole) および他の8種の抗菌性物質の *in vitro* 抗菌力を検討した。化療標準法により MIC を測定し，MIC range, MIC_{50}, MIC_{90} で表示した。β-ラクタム剤の中で Cefotaxime と Latamoxef は広範な菌種に対し最も優れた抗菌力を示した。Cefpiramide と Cefoperazone は前二者より抗菌力は劣った。Ofloxacin は *C. difficile* を除いて，全菌種において 3.13 μg/ml の濃度で 80% 以上の菌株の増殖を阻害した。Cefinase ディスク法により全菌株の β-lactamase 産生能を測定し，β-ラクタム剤に対する感受性との関連を検討した。有効な化学療法を実施するために，新鮮分離菌株に対する抗菌活性を定期的に検討し把握しておくことが必要である。