Comparative activity of cefepime with several antimicrobials against aerobic Gram-negative and Gram-positive organisms isolated from patients across Canada in 1993

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DE LOW, THE CANADIAN ANTIMICROBIAL RESISTANCE STUDY GROUP. Comparative activity of cefepime with several antimicrobials against aerobic Gram-negative and Gram-positive organisms isolated from patients across Canada in 1993. Can J Infect Dis 1995;6(5):258-262. To compare the activity of cefepime, a fourth-generation cephalosporin, with several available antimicrobials, in vitro susceptibility studies were carried out on bacteria commonly associated with various infections, including sepsis. Ten tertiary care hospital laboratories in six provinces provided 1276 clinically relevant isolates of aerobic Gram-negative bacilli and Gram-positive cocci during 1993. When the activity of each of the antimicrobials was determined against all isolates submitted, cefepime, piperacillin/tazobactam, imipenem and ciprofloxacin all had minimal inhibitory concentrations for 90% of the organisms (MIC_{90}) two or more dilutions below the MIC resistant category. Gentamicin's MIC_{90} against all organisms tested was one dilution below the MIC resistant category. The MIC_{90} s of the third-generation cephalosporins, piperacillin and ticarcillin/clavulanate, for *Enterobacter* species fell in the resistant category. This is presumably due to constitutive high level chromosomal cephalosporinase production. The MIC_{90} s of cefepime for *Enterobacter* species was three or more dilutions below the MIC resistant category. The MIC_{90} s of all antimicrobials against *Staphylococcus aureus*, with the exception of ceftazidime and piperacillin, had MIC_{90} categories two or more dilutions below the resistant category. The activity of cefepime, piperacillin/tazobactam, imipenem, ciprofloxacin and gentamicin make them excellent candidates for the empirical therapy of serious infections due to aerobic Gram-negative bacilli and *S aureus*. (*Pour le résumé, voir page 259*)

Key Words: Antimicrobial agents, Antimicrobial resistance, Cefepime, Surveillance

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Activité comparative de la céfépime et de divers antimicrobiens contre des organismes aérobies gram-négatifs et gram-positifs isolés chez des patients au Canada en 1993

RÉSUMÉ : Pour comparer l'efficacité de la céfépime, une céphalosporine de quatrième génération à celle des divers antimicrobiens offerts, des épreuves d'antibiogramme *in vitro* ont été effectuées sur les bactéries fréquemment associées à diverses infections, y compris la septicémie. Dix laboratoires d'hôpitaux de soins tertiaires, répartis dans six provinces, ont fourni 1 276 isolats cliniquement pertinents de bacilles aérobies gram-négatifs et de cocci gram-positifs au cours de 1993. Lorsque l'activité de chacun des antimicrobiens a été mesurée sur tous les isolats soumis, la céfépime, la piperacilline/tazobactame, l'imipénème et la ciprofloxacine ont tous présenté des concentrations inhibitrices minimales pour 90 % des organismes (CM_{I90}) à deux dilutions ou plus sous la catégorie de CM_{I} de la résistance. La CM_{I90} de la gentamycine contre tous les organismes testés était à une dilution sous la catégorie de CM_{I} de la résistance. Les CM_{I90} des céphalosporines de troisième génération, piperacilline et ticarcilline/clavulanate, pour *Enterobacter* sont tombées dans la catégorie de la résistance. Cela serait dû à une production inhérente de hauts taux de céphalosporinase chromosomique. Les CM_{I90} pour la céfépime à l'égard des *Enterobacter* a été de trois dilutions ou plus sous la catégorie de CM_{I} de la résistance. Les CM_{I90} de tous les antimicrobiens à l'égard de *Staphylococcus aureus*, à l'exception de la ceftazidime et de la piperacilline, étaient à deux dilutions ou plus sous la catégorie de la résistance. L'activité de la céfépime, de la piperacilline/tazobactame, de l'imipénème, de la ciprofloxacine et de la gentamycine en font d'excellents candidats pour le traitement empirique des infections graves attribuables aux bacilles gram-négatifs aérobies et à *S. aureus*.

SERIOUS BACTERIAL INFECTIONS RESULTING IN SEPSIS ARE ASSOCIATED with significant morbidity and mortality (1,2). Appropriate antibiotic therapy is critical in this condition and is considered the minimal standard of care (3). Since the initial choice of antimicrobial therapy is often empirical without the benefit of a culture report, let alone a susceptibility test result, it is essential to know what agents would be most effective in a given clinical diagnosis. This is especially important in the hospital setting where the patient is at risk of nosocomial infections due to antibiotic resistant pathogens. Patients with infections caused by bacteria resistant to the antimicrobial used for treatment have longer hospital stays and are at increased risk of death (4).

Cefepime is a new broad spectrum fourth-generation cephalosporin with significant in vitro antimicrobial advantages over other beta-lactam antimicrobials (5-9). In addition to a broad antimicrobial spectrum, cefepime has a low binding affinity for the major inducible chromosomally mediated beta-lactamases and can resist hydrolysis by beta-lactamases (6,8,10,11). Cefepime is active in vitro against the major bacterial pathogens that cause infections of the lower respiratory tract, urinary tract, skin and soft tissue, and bacteremia, including those caused by Gram-negative bacteria and Gram-positive bacteria (5,8,11). Cefepime has limited activity against Gram-negative anaerobic bacilli (12). To determine the in vitro activity of cefepime and several available antimicrobials to bacterial strains isolated from hospitalized patients, 10 tertiary care hospital microbiology laboratories in six provinces were asked to provide clinically significant isolates for susceptibility testing.

MATERIALS AND METHODS

Participating laboratories were asked to collect approximately 100 consecutive bacterial isolates during 1993. Participants were asked to provide only nonduplicate isolates from specimens submitted from hospitalized patients that were considered clinically relevant and the source of which

was evenly distributed from various sites. They were asked to provide additional strains of *Enterobacter* species, *Serratia* species, indole-positive *Proteus* species, *Citrobacter freundii* and *Pseudomonas aeruginosa*. They were also asked to provide additional isolates of *Klebsiella* species. Isolates were identified by standard methodologies (13). All isolates were subcultured twice before susceptibility testing.

Susceptibility testing: Broth microdilution was performed according to National Committee for Clinical Laboratory Standards guidelines (14). Microdilution panels were prepared by dispensing cation-supplemented Mueller-Hinton broth containing twofold-concentration increments of antimicrobial agents in 100 μ L plastic, 96-well trays. Inoculum suspensions equal to a 0.5 McFarland standard were further diluted and added to the microdilution trays to achieve a final inoculum of 5×10^5 colony forming units (CFU)/mL. Colony counts were performed to confirm the final inoculum. Following inoculation, microdilution trays were incubated at 35°C in ambient air for 16 to 20 h. After incubation, the minimal inhibitory concentration (MIC) was defined as the lowest concentration of antimicrobial with no evidence of growth. Cefepime (Bristol-Myers Squibb, Connecticut), piperacillin (Lederle Laboratories, New Jersey), piperacillin/tazobactam (Lederle Laboratories), cefotaxime (Hoechst-Roussel Pharmaceuticals Inc, New Jersey), ceftazidime (Glaxo, North Carolina), ceftriaxone (Hoffman-La Roche, Inc, New Jersey), ticarcillin/clavulanate (Beecham Laboratories, Tennessee) and imipenem (Merck Sharp and Dohme, New Jersey) were obtained. Gentamicin and ciprofloxacin powders were obtained from Sigma (Sigma Chemical Co, Missouri). Tazobactam was combined with piperacillin at a fixed concentration of 4.0 mg/L. Clavulanic acid was combined with ticarcillin in a ratio of ticarcillin to clavulanate of 2:1. *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were used as control strains for broth microdilution testing.

The concentration of each antibiotic that inhibited 90% of the strains, MIC_{90} , was determined only when 10 or more iso-

TABLE 1
Interpretation of minimal inhibitory concentrations (MIC)
of each antibiotic tested

Antimicrobial	MIC (mg/L)		
	S	I	R
Cefepime	≤8	16	≥32
Ceftazidime	≤8	16	≥32
Cefotaxime	≤8	16-32	≥64
Ceftriaxone	≤8	16-32	≥64
Imipenem	≤4	8	≥16
Piperacillin			
when testing <i>Pseudomonas aeruginosa</i>	≤64	—	≥128
when testing other Gram-negative organisms	≤16	32-64	≥128
Piperacillin/tazobactam			
when testing <i>Pseudomonas aeruginosa</i>	≤64	—	≥128
when testing other Gram-negative organisms	≤16	32-64	≥128
when testing staphylococci	≤8		≥16
Ticarcillin/clavulanic acid			
when testing <i>Pseudomonas aeruginosa</i>	≤64	—	≥128
when testing other Gram-negative organisms	≤16	32-64	≥128
when testing staphylococci	≤8	—	≥16
Ciprofloxacin	≤1	2	≥4
Gentamicin	≤4	8	≥16

I Intermediate; R Resistant; S Susceptible. Adapted from reference 8

lates of a species were tested. The MIC interpretive standards for the antimicrobials tested are listed in Table 1 (15).

RESULTS

In total, 1276 isolates were submitted for testing. The number of isolates sent by each centre ranged from 88 to 192.

TABLE 2
The activity of each of the 10 parenterally administered antimicrobial agents against the 1276 isolates submitted from 10 medical centres across Canada in 1993

Antimicrobial	Number of isolates for each MIC (mg/L) concentration											%resistant
	≤0.5	1	2	4	8	16	32	64	128	256	>256	
Cefepime	915*	62	109	60	35 [†]	24	22 [‡]	11	38	ND	ND	6
Ceftazidime	802*	62	61	28	118	37	43 ^{†‡}	29	96	ND	ND	13
Cefotaxime	772*	69	125	45	32	52	54 [†]	23 [‡]	104	ND	ND	10
Ceftriaxone	766*	47	93	73	29	56	52	47 ^{†‡}	113	ND	ND	13
Imipenem	923*	240 [†]	36	37	3	4 [‡]	33	ND	ND	ND	ND	3
Piperacillin	ND	ND	477	267*	153	86	53	50	47 [‡]	48 [†]	95	15
Piperacillin/tazobactam	ND	ND	835*	206	75	30	36 [†]	24	30 [‡]	19	21	5
Ticarcillin/clavulanic acid	ND	ND	495	287*	90	75	94	87	50 ^{†‡}	52	46	12
Ciprofloxacin	1105*	56 [†]	28	19 [‡]	22	10	36	ND	ND	ND	ND	7
Gentamicin	ND	1049*	32	35	47 [†]	68 [‡]	10	11	24	ND	ND	9

MIC Minimal inhibitory concentration; ND Not done. *MIC₅₀, concentration at which 50% of organisms inhibited; [†]MIC₉₀, concentration at which 90% of organisms inhibited; [‡]the MIC concentration that defines the resistant category

No specific pattern of resistance was noted in the individual hospitals participating in the study.

The activity of each of the antimicrobials tested against all isolates submitted is presented in Table 2. The most active compounds were imipenem, with a MIC₉₀ four dilutions below the resistance concentration breakpoint, and cefepime, piperacillin/tazobactam and ciprofloxacin, with MIC₉₀s two dilutions below the resistance concentration breakpoints. Cefepime was the most active cephalosporin when tested against all isolates, with a MIC₉₀ two dilutions below the resistance breakpoint.

The MIC₉₀ of each of the antimicrobials to some of the species of organisms tested is presented in Table 3. The MIC₉₀s of the third-generation cephalosporins were all 0.5 mg/L or less for *E coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca* and *Proteus mirabilis*, suggesting the absence of resistance due to extended spectrum plasmid-mediated beta-lactamase. Conversely, the high MIC₉₀s of the third-generation cephalosporins against *Enterobacter cloacae* and *Enterobacter aerogenes* suggests that constitutive production of chromosomal beta-lactamase has become a significant problem in Canada and limits the effectiveness of these agents to treat infections due to these strains. Cefepime, however, was very active against these organisms, with MIC₉₀ less than 1 mg/L.

The most resistant strains tested were *Staphylococcus haemolyticus* and *Staphylococcus epidermidis*. The traditional antipseudomonal agents, ceftazidime, piperacillin and gentamicin, and the newer agents, cefepime, piperacillin/tazobactam, imipenem and ciprofloxacin, demonstrated good activity against *P aeruginosa*.

DISCUSSION

The etiology of bloodstream infections were determined by Banerjee *et al* (16) from data reported by National Nosocomial Infections Surveillance system hospitals. They found that coagulase-negative staphylococci (CNST) were the most frequent cause of bloodstream infections, except in small

TABLE 3

The concentration of 10 parenterally administered antimicrobial agents that inhibit 90% of aerobic Gram-negative and Gram-positive isolates submitted from 10 medical centres across Canada in 1993*

Organism (number)	MIC ₉₀ (mg/L) [†]									
	Cefep	Ceftaz	Cefotax	Ceftriax	Imi	Pip	P/T	T/C	Cipro	Gent
<i>Escherichia coli</i> (200)	≤0.5	≤0.5	≤0.5	≤0.5	≤0.5	>256 [‡]	4	64	≤0.5	≤1
<i>Klebsiella pneumoniae</i> (131)	≤0.5	≤0.5	≤0.5	≤0.5	≤0.5	16	8	8	≤0.5	≤1
<i>Klebsiella oxytoca</i> (19)	≤0.5	≤0.5	≤0.5	≤0.5	≤0.5	256 [‡]	8	16	≤0.5	≤1
<i>Proteus mirabilis</i> (24)	≤0.5	≤0.5	≤0.5	≤0.5	2	>256 [‡]	≤2	≤2	≤0.5	8
<i>Enterobacter cloacae</i> (236)	1	64 [‡]	>64 [‡]	>64 [‡]	1	>256 [‡]	64	256 [‡]	≤0.5	≤1
<i>Enterobacter aerogenes</i> (49)	≤0.5	64	32	64 [‡]	1	128 [‡]	64	256 [‡]	2	≤1
<i>Serratia marcescens</i> (101)	≤0.5	1	8	4	1	32	32	64	1	≤1
<i>Citrobacter freundii</i> (61)	≤0.5	16	16	16	1	256 [‡]	32	256 [‡]	≤0.5	≤1
<i>Citrobacter diversus</i> (11)	2	2	4	1	≤0.5	16	≤2	4	≤0.5	≤1
<i>Morganella morganii</i> (37)	≤0.5	16	16	4	4	128 [‡]	≤2	32	≤0.5	≤1
<i>Proteus vulgaris</i> (27)	≤0.5	1	16	64 [‡]	4	128 [‡]	≤2	≤2	≤0.5	2
<i>Pseudomonas aeruginosa</i> (52)	8	4	>64 [‡]	>64 [‡]	1	32	16	128 [‡]	2	4
<i>Staphylococcus aureus</i> (106)	4	16	4	4	≤0.5	256 [‡]	4	4	1	≤1
<i>Staphylococcus epidermidis</i> (53)	16	64 [‡]	16	32	8	64	8	64 [‡]	>16 [‡]	16 [‡]
<i>Staphylococcus haemolyticus</i> (10)	>64 [‡]	>64 [‡]	>64 [‡]	>64 [‡]	>16 [‡]	256 [‡]	256 [‡]	>256 [‡]	>16 [‡]	16 [‡]

Cefep Cefepime; Cefotax Cefotaxime; Ceftaz Ceftazidime; Ceftriax Ceftriaxone; Cipro Ciprofloxacin; Gent Gentamicin; Imi Imipenem; MIC Minimal inhibitory concentration; Pip Piperacillin; P/T Piperacillin/tazobactam; T/C Ticarcillin/clavulanic acid. *MIC₉₀ was determined only when 10 or more isolates of a species were available; [†]MIC₉₀, the concentration at which 90% of the organisms are inhibited; [‡]MIC₉₀, concentrations that are in the resistant category

nonteaching hospitals, followed by aerobic Gram-negative bacilli and *Staphylococcus aureus*. Although CNST are often multiresistant, requiring vancomycin for effective therapy, waiting until a CNST is isolated and identified from a blood culture does not affect outcome (17,18). However, it is essential that appropriate therapy be initiated as soon as possible for bloodstream infections due to aerobic Gram-negative bacilli and *S aureus*. Chamberland et al (19) determined the susceptibility of 941 aerobic Gram-negative bacilli isolated from the blood from septic patients in 10 Canadian hospitals during 1988. The most frequent species isolated were *E coli* (52.5%), *K pneumoniae* (11.2%), *P aeruginosa* (8.2%), *Serratia marcescens* (4.3%), *P mirabilis* (3.9%), *K oxytoca* (3.7%) and *E cloacae* (3.6%). The other 24 species each made up less than 2%.

Even though aminoglycosides have been used clinically for four decades, they continue to have excellent in vitro activity. In Canada, Chamberland et al (19) in their 1988 study found rates of resistance of aerobic Gram-negative bacilli to gentamicin to be 2%. In the present study, we continued to find similar rates of resistance in Enterobacteriaceae.

Following the introduction of extended spectrum cephalosporins, cephamycins, monobactams and carbapenems, increased resistance among the Gram-negative bacilli with inducible chromosomally mediated beta-lactamases were found (20,21). These strains included *Enterobacter* species, *Serratia* species, indole-positive *Proteus* species, *C freundii* and *P aeruginosa*. These bacteria can undergo single-step mutations to constitutive high level production of this enzyme, which is capable of hydrolyzing second- and third-generation cephalosporins (22,23). Although in our study we found MIC₉₀s in the resistance range only among third-generation

cephalosporins, piperacillin and ticarcillin/clavulanate against *E cloacae*, *E aerogenes* and *P vulgaris*, other species with inducible chromosomally mediated beta-lactamase had reduced activity against these antimicrobials compared with those Gram-negative bacilli without this inducible beta-lactamase.

Resistance was not found with cefepime because of the low binding affinity of these beta-lactamases and its resistance to hydrolysis. In addition, cefepime has a slightly different penicillin binding protein target profile and a higher rate of penetration through outer membrane porins of Gram-negative bacteria compared with other cephalosporins. This and other studies have demonstrated that Gram-negative isolates that are resistant to one or more third-generation cephalosporins are susceptible to cefepime (24,25).

CONCLUSION

Cefepime demonstrated excellent in vitro activity against those pathogens often causing serious bacterial infections and sepsis in the hospitalized patient and retained excellent activity to those isolates that demonstrated resistance to other antimicrobials, including third-generation cephalosporins.

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