

Comparative activity of several antimicrobial agents against nosocomial Gram-negative rods isolated across Canada

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SR SCRIVER, CANADIAN ANTIMICROBIAL RESISTANCE STUDY GROUP, DE LOW. Comparative activity of several antimicrobial agents against nosocomial Gram-negative rods isolated across Canada. Can J Infect Dis 1995;6(2):76-82. In 1992, a surveillance study was performed in Canada to determine the susceptibility of nosocomial Gram-negative rods to several wide spectrum antimicrobials. Consecutive isolates from 10 institutions, as well as additional strains of selected species of Enterobacteriaceae that are known to possess the Bush group 1 beta-lactamase, were tested for susceptibility to 12 antimicrobials. Third-generation cephalosporin resistance was found to be as high as 29% in *Enterobacter cloacae* that possesses the Bush group 1 beta-lactamase and less than 4% in those isolates not possessing this enzyme. Cefepime equalled or exceeded the activity of the third-generation cephalosporins against the species of Enterobacteriaceae that demonstrated resistance to the third-generation cephalosporins.

Key Words: Antimicrobial resistance, Gram-negative rods

Activité comparative de plusieurs antibiotiques contre les souches nosocomiales gram-négatives isolées au Canada

RÉSUMÉ : En 1992, une étude épidémiologique a été effectuée au Canada afin de déterminer le degré de sensibilité des souches nosocomiales Gram-négatives à divers antibiotiques à large spectre. Des isolats consécutifs provenant de dix établissements, de même que d'autres souches d'espèces sélectionnées d'*Enterobacteriaceae* dont on sait qu'elles sont dotées de bêta-lactamases Bush de groupe 1 ont été soumis à des épreuves de sensibilité à 12 antimicrobiens. Une résistance de l'ordre de 29 % aux céphalosporines de troisième génération a été observée dans une souche d'*Enterobacter cloacae* dotée de bêta-lactamases Bush du groupe 1, et inférieure à 4 % dans les isolats dépourvus de cet enzyme. La céfépime a manifesté une activité égale ou supérieure aux céphalosporines de troisième génération contre les espèces d'*Enterobacteriaceae* qui manifestaient une résistance aux céphalosporines de troisième génération.

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THE INTRODUCTION OF THIRD-GENERATION CEPHALOSPORINS has improved our ability to treat serious infections caused by Gram-negative pathogens. However, increased use of these agents has been followed by the emergence of resistance to them. This resistance can be mediated by diminished outer membrane permeability, production of the chromosomally mediated inducible beta-lactamase, acquisition of plasmid mediated beta-lactamases or combinations of these mechanisms (1-3). Initially, extended spectrum cephalosporins were believed to be stable to both chromosomal and plasmid mediated enzymes. However, since 1985, outbreaks and sporadic cases of infections due to ceftazidime-resistant organisms with plasmid-mediated extended spectrum beta-lactamases have been described in Europe, the United States and elsewhere (4-8). Sporadic mutations leading to stable derepression of the chromosomally mediated inducible beta-lactamase also result in resistance to third-generation cephalosporins (1,9-12). These Bush group 1 (BGI) enzymes are generally identified in species of *Enterobacter*, *Citrobacter*, *Serratia*, *Providencia*, *Morganella*, indole-positive *Proteus* and *Pseudomonas aeruginosa*.

Cefepime is an extended spectrum cephalosporin that is considered to be a 'fourth-generation' cephalosporin. This group of cephalosporins has a slightly different penicillin-binding protein target-binding profile, lower affinity for chromosomally encoded beta-lactamases, particularly BGI, and a higher rate of penetration through outer membrane porins of Gram-negative bacteria compared with other cephalosporins. These differences enhance the spectrum of bactericidal activity of cefepime relative to all available cephalosporins (13). Other studies have demonstrated that Gram-negative isolates that are resistant to one or more third-generation cephalosporins are susceptible to cefepime (14,15). In a recent Canadian survey, it was determined that 23% of isolates of *Enterobacter cloacae* were ceftazidime resistant (16).

Tazobactam is a recently studied penicillanic acid sulfone that inhibits a wide variety of lactamases (17-21). The combination of tazobactam with penicillins and broad spectrum cephalosporins has demonstrated broad antimicrobial activity (19,20).

The purpose of this study was to determine the in vitro activity of cefepime and piperacillin/tazobactam, two new antimicrobial agents, in addition to several other antimicrobials against a selected group of nosocomial Gram-negative isolates from several centres across Canada.

MATERIALS AND METHODS

Bacterial isolates: Approximately 100 consecutive nonduplicate nosocomial isolates of common Gram-negative bacterial pathogens were collected from 10 centres across Canada. Participating centres were asked to submit an additional 50 isolates of species known to harbour BGI beta-lactamases, specifically: *E. cloacae*, *Enterobacter* species, *Citrobacter freundii*, *Morganella morganii*, *Proteus vulgaris*, *Providencia* species, *Serratia marcescens* and *P. aeruginosa*. Isolates were identified using standard methodologies (22) and frozen

at -70°C in phosphate buffered glycerol. All isolates were sub-cultured twice before susceptibility testing.

Susceptibility testing: Broth microdilution was performed according to National Committee for Clinical Laboratory Standards guidelines (23). Microdilution panels were prepared by dispensation of cation-supplemented Mueller-Hinton broth containing twofold-concentration increments of antimicrobial agents in 100 μL aliquots into 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 minimum inhibitory concentration (MIC) was defined as the lowest concentration of antimicrobial agent with no visible evidence of growth. Cefepime (Bristol-Myers Squibb, Connecticut), piperacillin (Lederle Laboratories, New Jersey), tazobactam (Lederle Laboratories), cefotaxime (Hoechst-Roussel Pharmaceuticals Inc, New Jersey), ceftazidime (Glaxo, North Carolina), ceftriaxone (Hoffman-La Roche, Inc, New Jersey), ticarcillin (Beecham Laboratories, Tennessee), clavulanate (Beecham Laboratories) and imipenem (Merck Sharp and Dohme, New Jersey) were obtained from their respective manufacturers. Gentamicin, tobramycin, ciprofloxacin and trimethoprim-sulfamethoxazole powders were obtained from Sigma (Sigma Chemical Co, Missouri). Tazobactam was combined with piperacillin at a fixed concentration of 4.0 g/mL. 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.

RESULTS

From 10 centres across Canada, 1984 isolates of Enterobacteriaceae and *P. aeruginosa* were collected. The distribution of bacterial species collected was *E. cloacae* (27.7%), *E. coli* (18.8%), *Klebsiella pneumoniae* (12.4%), *P. aeruginosa* (11.5%), *S. marcescens* (9.5%), *C. freundii* (8.0%), *Enterobacter* species (6.7%), *M. morganii* (2.9%), *P. vulgaris* (1.2%), *P. mirabilis* (0.8%) and *Providencia* species (0.5%). Susceptibility results based on broth microdilution testing are presented in Table 1 as MIC₅₀, MIC₉₀, range and percentage resistance.

Third-generation cephalosporin resistance was rare in species where resistance would be characterized by the presence of plasmid-mediated extended spectrum beta-lactamases, specifically *E. coli* and *K. pneumoniae*. Rates of resistance to ceftazidime in these isolates were 1.1% and 2.9%, respectively. However, in isolates with BGI beta-lactamases, rates of resistance to the third-generation cephalosporins were significant. *E. cloacae* demonstrated the highest levels of resistance to ceftazidime (28.9%). Isolates resistant to ceftazidime also demonstrated cross-resistance to other third-generation cephalosporins. The most active cephalosporin tested against all isolates was cefepime.

TABLE 1
Comparative activity of 12 antimicrobials against Gram-negative clinical isolates from 10 medical centres

Organism (number)	Antimicrobial agent	MIC ($\mu\text{g/mL}$)*			Resistant (%)
		50%	90%	Range	
<i>Escherichia coli</i> (373)	Cefotaxime	≤ 0.06	0.12	$\leq 0.06 - 1.0$	0
	Ceftazidime	≤ 0.50	≤ 0.50	$\leq 0.50 - 1.0$	1.1
	Ceftriaxone	≤ 0.50	≤ 0.50	$\leq 0.50 - 1.0$	0
	Cefepime	≤ 0.06	≤ 0.06	$\leq 0.06 - 0.25$	0
	Piperacillin	2.0	> 512.0	$\leq 1.0 - > 512.0$	19.0
	Piperacillin/tazobactam	2.0	16.0	$\leq 1.0 - > 256.0$	2.3
	Ticarcillin/clavulanate	2.0	64.0	$\leq 1.0 - > 256.0$	5.8
	Imipenem	0.25	0.50	$\leq 0.06 - 4.0$	0
	Gentamicin	≤ 4.0	≤ 4.0	$\leq 4.0 - > 16.0$	2.9
	Tobramycin	≤ 4.0	≤ 4.0	$\leq 4.0 - 8.0$	1.8
	Ciprofloxacin	≤ 0.06	≤ 0.06	$\leq 0.06 - 8.0$	1.1
	TMP/SMX	≤ 0.50	> 16.0	$\leq 0.50 - > 16.0$	12.2
<i>Klebsiella pneumoniae</i> (247)	Cefotaxime	≤ 0.06	0.12	$\leq 0.06 - > 64.0$	1.1
	Ceftazidime	≤ 0.50	≤ 0.50	$\leq 0.50 - > 128$	2.9
	Ceftriaxone	≤ 0.50	≤ 0.50	$\leq 0.50 - 128.0$	0.4
	Cefepime	≤ 0.06	0.12	$\leq 0.06 - 0.50$	0
	Piperacillin	16.0	512.0	$\leq 1.0 - > 512.0$	17.6
	Piperacillin/tazobactam	4.0	32.0	$\leq 1.0 - > 512.0$	6.9
	Ticarcillin/clavulanate	2.0	16.0	$\leq 1.0 - > 256.0$	2.7
	Imipenem	0.50	1.0	$\leq 0.06 - 4.0$	0
	Gentamicin	≤ 4.0	≤ 4.0	$\leq 4.0 - > 16.0$	0.4
	Tobramycin	≤ 4.0	≤ 4.0	≤ 4.0	0
	Ciprofloxacin	≤ 0.06	0.12	$\leq 0.06 - 0.50$	0
	TMP/SMX	2.0	4.0	$\leq 0.50 - > 16.0$	10.9
<i>Citrobacter freundii</i> (159)	Cefotaxime	0.25	16.0	$\leq 0.06 - > 64.0$	6.8
	Ceftazidime	≤ 0.50	32.0	$\leq 0.50 - > 128.0$	13.9
	Ceftriaxone	≤ 0.50	32.0	$\leq 0.50 - > 128.0$	7.8
	Cefepime	≤ 0.06	0.25	$\leq 0.06 - 2.0$	0
	Piperacillin	8.0	512.0	$\leq 1.0 - > 512.0$	18.4
	Piperacillin/tazobactam	4.0	64.0	$\leq 1.0 - 256.0$	5.1
	Ticarcillin/clavulanate	2.0	128.0	$\leq 1.0 - > 256.0$	12.9
	Imipenem	1.0	4.0	$\leq 0.06 - 4.0$	0
	Gentamicin	≤ 4.0	≤ 4.0	$\leq 4.0 - > 16.0$	2.6
	Tobramycin	≤ 4.0	≤ 4.0	$\leq 4.0 - > 16.0$	1.7
	Ciprofloxacin	≤ 0.06	≤ 0.06	$\leq 0.06 - 8.0$	1.7
	TMP/SMX	1.0	> 16.0	$\leq 0.50 - > 16.0$	21.6
<i>Proteus vulgaris</i> (23)	Cefotaxime	0.50	2.0	$\leq 0.06 - 8.0$	0
	Ceftazidime	≤ 0.50	≤ 0.50	$\leq 0.50 - 2.0$	0
	Ceftriaxone	≤ 0.50	64.0	$\leq 0.50 - 64.0$	12.7
	Cefepime	0.50	0.50	$\leq 0.06 - 0.50$	0
	Piperacillin	2.0	4.0	$\leq 1.0 - 128.0$	6.2
	Piperacillin/tazobactam	2.0	2.0	$\leq 1.0 - 4.0$	0
	Ticarcillin/clavulanate	2.0	> 256.0	$2.0 - > 256.0$	6.4
	Imipenem	2.0	2.0	$0.50 - 4.0$	0
	Gentamicin	≤ 4.0	≤ 4.0	$\leq 4.0 - > 16.0$	8.7
	Tobramycin	≤ 4.0	≤ 4.0	$\leq 4.0 - 8.0$	0
	Ciprofloxacin	≤ 0.06	≤ 0.06	$\leq 0.06 - 0.12$	0
	TMP/SMX	2.0	16.0	$\leq 0.50 - > 16.0$	22.7

*Minimum inhibitory concentration (MIC) for 50 and 90% of isolates tested. TMP/SMX Trimethoprim-sulfamethoxazole

TABLE 1 (continued)

Organism (number)	Antimicrobial agent	MIC ($\mu\text{g/mL}$)*			Resistant (%)
		50%	90%	Range	
<i>Proteus mirabilis</i> (16)	Cefotaxime	0.50	0.50	$\leq 0.06 - >64.0$	3.3
	Ceftazidime	≤ 0.50	≤ 0.50	$\leq 0.50 - 64.0$	1.4
	Ceftriaxone	≤ 0.50	≤ 0.50	$\leq 0.50 - 2.0$	0
	Cefepime	0.50	0.50	$\leq 0.06 - 1.0$	0
	Piperacillin	2.0	8.0	$\leq 1.0 - >512.0$	18.8
	Piperacillin/tazobactam	2.0	2.0	$\leq 1.0 - 2.0$	0
	Ticarcillin/clavulanate	2.0	2.0	$2.0 - >256.0$	1.4
	Imipenem	1.0	4.0	$0.50 - 8.0$	6.2
	Gentamicin	≤ 4.0	≤ 4.0	$\leq 4.0 - >16.0$	8.7
	Tobramycin	≤ 4.0	≤ 4.0	$\leq 4.0 - 8.0$	0
	Ciprofloxacin	≤ 0.06	≤ 0.06	$\leq 0.06 - 0.12$	0
	TMP/SMX	2.0	16.0	$\leq 0.50 - >16.0$	22.7
<i>Providencia</i> species (10)	Cefotaxime	1.0	4.0	$\leq 0.50 - 4.0$	0
	Ceftazidime	≤ 0.50	1.0	$\leq 0.50 - 16.0$	0
	Ceftriaxone	≤ 0.50	≤ 0.50	$\leq 0.50 - 4.0$	0
	Cefepime	≤ 0.06	0.50	$\leq 0.06 - 0.50$	0
	Piperacillin	2.0	32.0	$< 1.0 - 512.0$	10.0
	Piperacillin/tazobactam	≤ 1.0	4.0	$\leq 1.0 - 8.0$	0
	Ticarcillin/clavulanate	2.0	16.0	$\leq 1.0 - 16.0$	0
	Imipenem	1.0	8.0	$\leq 0.06 - 16.0$	10.0
	Gentamicin	8.0	> 16	$\leq 4.0 - >16.0$	40.0
	Tobramycin	≤ 4.0	≤ 4.0	≤ 4.0	0
	Ciprofloxacin	≤ 0.06	≤ 0.06	≤ 0.06	0
	TMP/SMX	16.0	> 16.0	$\leq 0.50 - >16.0$	40.0
<i>Enterobacter cloacae</i> (550)	Cefotaxime	1.0	> 64.0	$\leq 0.06 - >64.0$	16.8
	Ceftazidime	8.0	> 128.0	$\leq 0.50 - >128.0$	28.9
	Ceftriaxone	≤ 0.5	> 128.0	$\leq 0.5 - >128.0$	18.5
	Cefepime	0.12	2.0	$\leq 0.06 - 8.0$	0.2
	Piperacillin	16.0	512.0	$\leq 1.0 - >512.0$	32.4
	Piperacillin/tazobactam	8.0	256.0	$\leq 1.0 - >512.0$	16.9
	Ticarcillin/clavulanate	32.0	> 256.0	$\leq 1.0 - >256.0$	43.6
	Imipenem	1.0	4.0	$\leq 0.06 - >64.0$	1.1
	Gentamicin	≤ 4.0	8.0	$\leq 4.0 - >16.0$	7.6
	Tobramycin	≤ 4.0	≤ 4.0	$\leq 4.0 - >16.0$	2.8
	Ciprofloxacin	≤ 0.06	0.12	$\leq 0.06 - 8.0$	0.9
	TMP/SMX	1.0	2.0	$\leq 0.50 - >16.0$	7.8
<i>Enterobacter</i> species [†] (132)	Cefotaxime	0.25	32.0	$\leq 0.06 - >64.0$	7.7
	Ceftazidime	≤ 0.50	128.0	$\leq 0.50 - >128.0$	18.9
	Ceftriaxone	0.50	64.0	$\leq 0.50 - >128.0$	10.3
	Cefepime	≤ 0.06	0.50	$\leq 0.06 - 32.0$	0.8
	Piperacillin	8.0	128.0	$< 1.0 - >512.0$	11.4
	Piperacillin/tazobactam	8.0	64.0	$\leq 1.0 - 256.0$	7.6
	Ticarcillin/clavulanate	4.0	256.0	$\leq 1.0 - 256.0$	22.2
	Imipenem	4.0	8.0	$\leq 0.06 - 16.0$	2.3
	Gentamicin	≤ 4.0	≤ 4.0	$\leq 4.0 - >16.0$	3.4
	Tobramycin	≤ 4.0	≤ 4.0	$\leq 4.0 - >16.0$	3.4
	Ciprofloxacin	≤ 0.06	1.0	$\leq 0.06 - 8.0$	5.1
	TMP/SMX	≤ 0.50	2.0	$\leq 0.50 - >16.0$	8.5

*Minimum inhibitory concentration (MIC) for 50 and 90% of isolates tested. [†]Includes 68 isolates of *Enterobacter aerogenes*, 27 isolates of *Enterobacter agglomerans* and 39 *Enterobacter* species. TMP/SMX Trimethoprim-sulfamethoxazole

TABLE 1 (continued)

Organism (number)	Antimicrobial agent	MIC ($\mu\text{g/mL}$)*			Resistant (%)
		50%	90%	Range	
<i>Serratia marcescens</i> (189)	Cefotaxime	0.25	2.0	$\leq 0.06 - 64.0$	0.7
	Ceftazidime	≤ 0.50	≤ 0.50	$\leq 0.50 - 32.0$	0.5
	Ceftriaxone	≤ 0.50	1.0	$\leq 0.50 - 32.0$	0
	Cefepime	≤ 0.06	0.25	$\leq 0.06 - 16.0$	0
	Piperacillin	8.0	> 512.0	$\leq 1.0 - > 512.0$	28.2
	Piperacillin/tazobactam	2.0	16.0	$\leq 1.0 - > 512.0$	1.6
	Ticarcillin/clavulanate	8.0	128.0	$\leq 1.0 - > 256.0$	14.0
	Imipenem	2.0	4.0	$\leq 0.06 - 8.0$	2.6
	Gentamicin	≤ 4.0	16.0	$\leq 4.0 - > 16.0$	26.2
	Tobramycin	≤ 4.0	16.0	$\leq 4.0 - > 16.0$	22.1
	Ciprofloxacin	≤ 0.06	0.50	$\leq 0.06 - 8.0$	2.7
TMP/SMX	2.0	8.0	$\leq 0.50 - > 16.0$	31.3	
<i>Morganella morganii</i> (57)	Cefotaxime	0.12	16.0	$\leq 0.06 - 16.0$	0
	Ceftazidime	≤ 0.50	32.0	$\leq 0.50 - > 128.0$	10.5
	Ceftriaxone	0.50	2.0	$\leq 0.50 - 32.0$	0
	Cefepime	≤ 0.06	0.12	$\leq 0.06 - 0.25$	0
	Piperacillin	4.0	256.0	$\leq 1.0 - > 512.0$	17.5
	Piperacillin/tazobactam	≤ 1.0	32.0	$\leq 1.0 - 256.0$	3.5
	Ticarcillin/clavulanate	4.0	32.0	$\leq 1.0 - 128.0$	4.2
	Imipenem	8.0	16.0	$\leq 0.06 - 16.0$	28.0
	Gentamicin	≤ 4.0	≤ 4.0	$\leq 4.0 - 8.0$	0
	Tobramycin	≤ 4.0	≤ 4.0	$\leq 4.0 - 16.0$	2.1
	Ciprofloxacin	≤ 0.06	0.12	$\leq 0.06 - 0.12$	0
TMP/SMX	2.0	> 16.0	$\leq 0.50 - > 16.0$	14.6	
<i>Pseudomonas aeruginosa</i> (228)	Cefotaxime	32.0	> 64.0	$\leq 0.06 - > 64.0$	43.2
	Ceftazidime	4.0	32.0	$\leq 0.50 - > 128.0$	11.7
	Ceftriaxone	32.0	> 128.0	$\leq 0.50 - > 128.0$	32.2
	Cefepime	2.0	16.0	$\leq 0.06 - 64.0$	28.6
	Piperacillin	16.0	512.0	$\leq 1.0 - > 512.0$	12.6
	Piperacillin/tazobactam	8.0	128.0	$\leq 1.0 - > 512.0$	10.9
	Ticarcillin/clavulanate	32.0	128.0	$\leq 1.0 - > 256.0$	10.3
	Imipenem	4.0	64.0	$\leq 0.06 - 64.0$	23.3
	Gentamicin	≤ 4.0	16.0	$\leq 4.0 - > 16.0$	15.1
	Tobramycin	≤ 4.0	≤ 4.0	$\leq 4.0 - > 16.0$	2.7
	Ciprofloxacin	0.25	2.0	$\leq 0.06 - 32.0$	4.8
TMP/SMX	> 16.0	> 16.0	> 16.0	100	

*Minimum inhibitory concentration (MIC) for 50 and 90% of isolates tested. TMP/SMX Trimethoprim-sulfamethoxazole

Isolates of *E coli*, *K pneumoniae* and *P mirabilis* were more susceptible to piperacillin/tazobactam (MIC₉₀ 32.0 g/mL) than those with type 1 cephalosporinases. Of the isolates of Enterobacteriaceae and *P aeruginosa* resistant to piperacillin alone, 290 (16.6%) and 34 (14.8%), respectively, became sensitive when piperacillin was combined with tazobactam.

For all isolates tested, the most active agents were the aminoglycosides, imipenem and ciprofloxacin. Ciprofloxacin resistance was less than 2.0% in all isolates of Enterobacteriaceae with the notable exception of *Enterobacter* species, in which 5.1% of isolates had MICs to ciprofloxacin of greater than 4.0 g/mL.

Imipenem exhibited excellent in vitro activity. Resistance

was detected only in *P aeruginosa* (23.3%) and *Enterobacter* species (2.3%). The highest incidence of aminoglycoside resistance was found in isolates of *S marcescens*, in which 26.2% and 22.1% of isolates were gentamicin- and tobramycin-resistant, respectively. In all other species tested, including *P aeruginosa*, aminoglycoside resistance was less than 10%. Tobramycin was much more effective against isolates of *P aeruginosa* than gentamicin, because only 2.7% were resistant to this aminoglycoside whereas 15.1% of isolates were resistant to gentamicin.

DISCUSSION

The rapid initiation of effective antimicrobial therapy for the

management of infections caused by Gram-negative bacilli can significantly improve outcome (24). Treatment is often empirical and based primarily on knowledge of the antimicrobial susceptibility of the most common bacteria encountered. It is therefore crucial to conduct broadly based surveillance studies to generate susceptibility data that can help predict susceptibility of a species to an antimicrobial or group of antimicrobials. However, it is also necessary to know or highly suspect what species are responsible for the disease syndrome in a given patient population.

In light of the increasing importance of *Enterobacter* species as important nosocomial pathogens, changes in the beta-lactam susceptibility profile of these isolates are of great concern. Sanders (12) found that, although all isolates of *E. cloacae* will produce a BGI beta-lactamase on induction, 28.9% of these isolates have become constitutive producers.

Cefepime, a fourth-generation cephalosporin, is structurally similar to cefotaxime, ceftriaxone and ceftizoxime. However, a quaternary nitrogen-containing substitution on the positively charged third carbon and the negative charge on position four of the cephalosporin nucleus gives cefepime zwitterionic properties that allow cefepime to penetrate very rapidly through the outer membrane of Gram-negative bacteria. As well, cefepime, like other fourth-generation cephalosporins, is stable against BGI beta-lactamases (13).

For all isolates, the most active cephalosporin tested was cefepime. Among Enterobacteriaceae, more than 98% of all isolates were susceptible to this agent. The activity of cefepime equalled or exceeded that of third-generation cephalosporins. Isolates demonstrating resistance to third-generation cephalosporins remained susceptible to cefepime. Major differences in activity between cefepime and the third-generation cephalosporins were found in isolates with BGI beta-lactamases, ie, *E. cloacae*, *Enterobacter aerogenes*, *C. freundii*, *M. morgani* and *S. marcescens*. Against *P. aeruginosa*, cefepime and ceftazidime were more active than cefotaxime, but these differences are likely the result of different permeabilities for these agents (25) as opposed to beta-lactamase stability.

For all isolates tested, the activity of piperacillin was highly potentiated when combined with the beta-lactamase inhibitor tazobactam. The beta-lactam/beta-lactamase inhibitor combination of piperacillin/tazobactam was more effective than ticarcillin/clavulanate against isolates possessing BGI beta-lactamases, isolates found in this study and others to be increasingly resistant to traditional third-generation therapeutic agents.

Antimicrobial resistance among isolates of *K. pneumoniae* and *E. coli* occurred infrequently. Resistance to third-generation cephalosporins was rare, which contrasts sharply with reports from Europe and specific areas of the United States, where the prevalence of resistance is high with the occurrence of nosocomial outbreaks (7,8).

CONCLUSIONS

This study demonstrated that third-generation cephalosporin resistance is a clinically relevant problem in isolates

known to possess BGI beta-lactamases. Although cross-resistance to other third-generation cephalosporins was seen, cefepime and nonbeta-lactam agents retained their activity. Plasmid-mediated extended spectrum beta-lactamase was not a significant finding. Traditional nonbeta-lactam agents were found to have retained their activity against nosocomial Gram-negative rods. As well, aminoglycosides are still highly active against the majority of isolates tested, with the notable exception of *S. marcescens*.

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