In vitro activity of cefepime against multidrug-resistant Gram-negative bacilli, viridans group streptococci and *Streptococcus pneumoniae* from a cross-Canada surveillance study

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OBJECTIVE: To determine the in vitro activity of cefepime against multidrug-resistant Gram-negative bacilli and Gram-positive cocci obtained from an ongoing cross-Canada surveillance study.

DESIGN: Clinical isolates of aerobic Gram-negative bacilli with inducible and constitutive chromosomally mediated cephalosporinases, viridans group streptococci and *Streptococcus pneumoniae* were collected from laboratories serving hospitals, nursing homes and physician offices in the community from across Canada during 1996 and 1997. Laboratories were asked to submit only clinically relevant nonduplicate isolates for susceptibility testing. In vitro antimicrobial susceptibility testing was carried out on all isolates of Gram-negative and viridans group streptococci. *S. pneumoniae* were characterized as penicillin susceptible, intermediately resistant or highly resistant. Nonsusceptible isolates were defined as being intermediately or highly resistant (minimal inhibitory concentrations [MIC] greater than 0.06 mg/L). Only isolates of *S. pneumoniae* that were nonsusceptible to penicillin were selected for further study. MICs were deter-

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mined using a microbroth dilution technique according to the National Committee of Clinical Laboratory Standards.

RESULTS: A total of 727 Gram-negative bacilli samples were collected. No resistance to cefepime was detected with *Citrobacter freundii*, *Serratia marcescens*, *Morganella morganii* and *Enterobacter* species. Of these strains, *Enterobacter* species and *C. freundii* were the most resistant to ceftazidime, cefotaxime and ceftriaxone with MIC_{90S} of 32 mg/L or greater and resistance rates of 6% or greater. Resistance rates of *Pseudomonas aeruginosa* and *Acinetobacter* species to cefepime were 4.8% and 3%, respectively. The two organisms had similar rates of resistance to ceftazidime. Less than 3% of the Gram-negative bacilli were resistant to imipenem and meropenem. There were 153 viridans group streptococci, of which 22 (14.4%) were resistant to penicillin. Of 1287 *S. pneumoniae* samples, 193 (15%) were nonsusceptible to penicillin. Cefepime, ceftriaxone and cefotaxime had comparable activity against all isolates of viridans group streptococci and *S. pneumoniae*.

CONCLUSIONS: Cefepime demonstrated excellent in vitro activity against Gram-negative bacilli with inducible and constitutive chromosomally mediated cephalosporinases, and had equal or superior activity versus comparator beta-lactams against all isolates of viridans group streptococci and *S. pneumoniae*.

Key Words: Antibiotic resistance, Cefepime, Gram-negative bacilli, In vitro susceptibility testing, Streptococcus pneumoniae, Surveillance, Viridans group streptococci

Activité *in vitro* du céfépime contre les bacilles gram-négatifs plurirésistants, les streptocoques du groupe *Viridans* et *Streptococcus pneumoniae* selon une étude épidémiologique pancanadienne

OBJECTIF : Déterminer l'activité *in vitro* du céfépime contre les bacilles gram-négatifs plurirésistants et les bacilles gram-positifs selon une étude épidémiologique pancanadienne en cours.

MODÈLE : Des spécimens cliniques de bacilles gram-négatifs aérobies présentant des céphalosporinases inductibles et constitutives à médiation chromosomique, de streptocoques du groupe *Viridans* et de *Streptococcus pneumoniae* ont été recueillis auprès de laboratoires desservant des hôpitaux, des établissements de soins prolongés et des cabinets médicaux dans la communauté d'un bout à l'autre du Canada en 1996 et 1997. Les laboratoires ont été invités à ne soumettre que des isolats non dupliqués et cliniquement pertinents pour antibiogrammes. Des antibiogrammes *in vitro* ont été effectués sur tous les isolats des streptocoques gram-négatifs et du groupe *Viridans*. Les spécimens de *S. pneumoniae* ont été classés selon qu'ils étaient sensibles, moyennement résistants ou très résistants à la pénicilline. Les isolats non sensibles ont été définis comme manifestant une résistance moyenne ou élevée (CMI, ou concentration minimale inhibitrice, supérieure à 0,06 mg/L). Seuls les isolats de *S. pneumoniae* qui n'étaient pas sensibles à la pénicilline ont été sélectionnés pour la suite de l'étude. Les CMI ont été calculées à l'aide d'une technique de microdilution, conformément aux directives du *National Committee of Clinical Laboratory Standards*.

RÉSULTATS : En tout, 727 échantillons de bacilles gram-négatifs ont été recueillis. On n'a décelé aucune résistance au céfépime avec *Citrobacter freundii*, *Serratia marcescens*, *Morganella morganii* et le groupe *Enterobacter*. De ces souches, celles d'*Enterobacter* et de *C. freundii* ont été les plus résistantes à la ceftazidime, au céfotaxime et au ceftriaxone avec des CMI₉₀ de 32 mg/L ou plus ou des taux de résistance de 6 % ou plus. Les taux de résistance de *Pseudomonas aeruginosa* et d'*Acinetobacter* au céfépime ont été de 4,8 % et de 3 %, respectivement. Les deux organismes ont présenté des taux similaires de résistance à la ceftazidime. Moins de 3 % des bacilles gram-négatifs se sont révélés résistants à l'imipénem et au méropénem. On a recensé 153 streptocoques du groupe *Viridans*, dont 22 (14,4 %) étaient résistants à la pénicilline. Parmi les 1 287 échantillons de *S. pneumoniae*, 193 (15 %) se sont révélés résistants à la pénicilline. Le céfépime a manifesté une activité comparable contre tous les isolats des streptocoques du groupe *Viridans* et *S. pneumoniae*.

CONCLUSIONS : Le céfépime a manifesté une excellente activité *in vitro* contre les bacilles gram-négatifs avec céphalosporinases inductibles et constitutives à médiation chromosomique et ont présenté une activité égale ou supérieure à celle des bêta-lactamines contre tous les isolats de streptocoques du groupe *Viridans* et *S. pneumoniae*.

The frequency of resistance in bacteria and the number of drugs to which they are resistant are a problem that compromises antimicrobial therapy for in-patients and out-patients. In the hospital setting, where the patient is at risk of nosocomial infections, there has been increased resistance among the Gram-negative bacilli with inducible chromosomally mediated beta-lactamases (1-3). These organisms include *Enterobacter* species, *Serratia marcescens*, indole-positive *Proteus* species, *Citrobacter freundii*, *Morganella morganii*, *Providencia* species, *Acinetobacter* species and *Pseudomonas aeruginosa*. In addition, high rates of multidrug-resistant viridans group streptococci have been documented in the hospital setting in the United States (4). In the community, we have witnessed the rapid emergence of multidrug-resistant *Streptococcus pneumoniae*, the most common bacterial cause of meningitis and community-acquired pneumonia (5). The consequence of increasing anti-

microbial resistance, both in the hospital and the community, include adverse patient outcomes, fewer alternative antimicrobials and increased health care costs (6-10).

Cefepime (Maxipime, Bristol-Myers Squibb Canada Inc) is a broad-spectrum cephalosporin with significant in vitro antimicrobial advantages over other beta-lactam antimicrobials (11-16). Cefepime is active in vitro against the major bacterial pathogens that cause infections of the lower respiratory tract, urinary tract, and skin and soft tissue, and bacteremia, including those caused by Gram-negative bacteria and Gram-positive bacteria (11,14,16). Isolates of aerobic Gram-negative bacilli with inducible and constitutive chromosomally mediated cephalosporinases, viridans group streptococci and *S. pneumoniae* were collected from across Canada as part of an ongoing surveillance program. The in vitro activity of cefepime and several other antimicrobials was determined against these isolates.

TABLE 1
Distribution of isolates from a cross-Canada surveillance study

Strains	Number of isolates
Penicillin nonsusceptible <i>Streptococcus pneumoniae</i>	193
Viridans group streptococci	153
<i>Pseudomonas aeruginosa</i>	262
<i>Enterobacter</i> species	246
<i>Citrobacter freundii</i>	67
<i>Serratia marcescens</i>	56
<i>Acinetobacter</i> species	68
<i>Morganella morganii</i>	28

METHODS

A network of 50 laboratories representing nine provinces, and serving hospitals, nursing homes and physician offices in the community participate in an ongoing cross-Canada surveillance study to determine resistance rates of various bacteria. Participating centres include private laboratories, and teaching and nonteaching hospitals. All isolates are sent to Mount Sinai Hospital, Toronto, Ontario, for testing.

For this study, each centre was asked to collect consecutive, clinically significant strains of *Enterobacter* species, *S. marcescens*, *C. freundii*, *M. morganii*, *Acinetobacter* species, and *P. aeruginosa* during 1996. During 1996, each centre was asked to submit all blood culture isolates of viridans group streptococci. In addition, up to 20 consecutive isolates of *S. pneumoniae* in 1996 and 1997 were collected from sterile or nonsterile sites. Participants were asked to provide nonduplicate strains isolated from patients. The bacteria were identified by standard methodologies (17).

Susceptibility testing: Broth microdilution was performed according to National Committee for Clinical Laboratory Standards guidelines (NCCLS) (18,19). NCCLS 1998 guidelines were used to determine susceptibility breakpoints (19). Microdilution panels were prepared by dispensing cation-supplemented Mueller-Hinton broth containing twofold-concentration increments of antimicrobial agents in 100 µL 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/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. In vitro susceptibility testing was carried out on all Gram-negative bacilli and viridans group streptococci. *S. pneumoniae* were characterized as penicillin susceptible, intermediately resistant or highly resistant. Those isolates characterized as being nonsusceptible were intermediately resistant or highly resistant (MIC greater than 0.06 mg/L). Only isolates of *S. pneumoniae* that were nonsusceptible to penicillin were selected for further study. All isolates were subcultured twice before susceptibility testing. Cefepime, cefotaxime (Claforan, Hoechst Marion Roussel), ceftazidime (Ceptaz, Glaxo wellcome Canada Inc), ceftriaxone (Rocephin, Roche), meropenem (Merrem, Zeneca Pharma Inc) and imipenem (Primaxin, MSD) were obtained from their respective manufacturers. Tobramycin, erythromycin, tetracycline, penicillin and ciprofloxacin powders were obtained from Sigma (Sigma Chemical Company, Michigan). Control organisms *Escherichia coli* ATCC 25922, *S. pneumoniae* ATCC 49619, *S. pneumoniae* ATCC 6303, *Enterococcus faecalis* 29212, *Staphylococcus aureus* ATCC 29213 and *P. aeruginosa* ATCC 27853 were used as control strains for broth microdilution testing.

RESULTS

A total of 727 Gram-negative bacilli, 153 viridans group streptococci and 1287 *S. pneumoniae* were submitted to Mount Sinai Hospital for susceptibility testing. The distribution of study isolates is shown in Table 1.

Sources of the Gram-negative isolates were urine (42%), wound (27%), lower respiratory tract (20%), blood (4%) and other sites (7%). Of the Gram-negative bacilli tested, cefepime, meropenem, imipenem and tobramycin were the most active antimicrobials with less than 5% resistance detected to these agents (Table 2). Eleven per cent or more of *Enterobacter* species and 6% or more of *C. freundii* demonstrated resistance to ceftriaxone, cefotaxime and ceftazidime. The MIC₅₀ and MIC₉₀ were both 0.5 mg/L or less for cefepime, whereas the MIC₉₀ for the other cephalosporins was more than six dilutions greater than the MIC₅₀. Less than 3% of *P. aeruginosa* and *Acinetobac-*

TABLE 2
In vitro activity of eight antimicrobial agents against aerobic Gram-negative isolates from across Canada in 1996

Organism (number)	MIC _{90s} (mg/L) (% resistant)							
	Cefepime	Ceftaz	Cefotax	Ceftriax	Imi	Mero	Tobr	Cipro
<i>Pseudomonas aeruginosa</i> (262)	16 (4.8)	8 (6.5)	>64 (27.2)	>64 (28.4)	4 (2.4)	2 (0)	2 (2.4)	1 (7.7)
<i>Enterobacter</i> species (246)	0.5 (0)	>32 (15.2)	64 (11)	64 (13.8)	2 (0)	0.5 (0)	2 (0.7)	0.5 (0)
<i>Citrobacter freundii</i> (67)	0.5 (0)	>32 (14.9)	32 (6)	64 (12)	1 (0)	0.5 (0)	2 (1.5)	0.5 (0)
<i>Serratia marcescens</i> (56)	0.5 (0)	0.5 (0)	1 (0)	1 (0)	2 (0)	0.5 (0)	4 (3.6)	2 (8.9)
<i>Acinetobacter</i> species (68)	16 (3)	16 (8.8)	32 (5.8)	32 (5.8)	0.5 (0)	0.5 (0)	2 (2.9)	1 (5.9)
<i>Morganella morganii</i> (28)	0.5 (0)	2 (7.2)	8 (3.6)	1 (0)	4 (0)	0.5 (0)	2 (0)	0.5 (0)

Cefotax Cefotaxime; Ceftaz Ceftazidime; Ceftriax Ceftriaxone; Cipro Ciprofloxacin; Imi Imipenem; Mero Meropenem; Tobr Tobramycin

TABLE 3

Results of susceptibility testing for selected antimicrobials against 153 viridans group streptococci expressed as minimum inhibitory concentration (MIC)₅₀ and MIC₉₀ (mg/L), range (mg/L), and percentage intermediate and resistant

Antimicrobial	MIC ₅₀	MIC ₉₀	Range	Percentage intermediate	Percentage resistant
Cefepime	0.25	2	0.03 - >16	NA	NA
Ceftriaxone	0.25	4	0.03 - >4	12.4	18.2
Cefotaxime	0.25	2	0.03 - >4	12.4	17
Ciprofloxacin	2	4	0.12 - >4	NA	NA
Erythromycin	0.5	8	0.12 - >8	2	49.7
Tetracycline	1	>32	1 - >32	3.3	28.1
Imipenem	0.12	1	0.03 - >2	NA	NA
Meropenem	0.12	2	0.03 - >2	NA	NA
Penicillin	0.25	4	0.03 - >4	54.9	14.4

NA Category breakpoints not available

ter species were resistant to imipenem, meropenem and tobramycin. A total of 4.8% and 3% of *P aeruginosa* and *Acinetobacter* species, respectively, were resistant to cefepime.

The results of the present study revealed high rates of resistance of blood culture isolates of viridans group streptococci to beta-lactam and nonbeta-lactam antimicrobials (Table 3). Resistance rates were greater than 14% for all antibiotics tested for which NCCLS antimicrobial breakpoints are available. A total 14.4%, 49.7% and 28.1% of isolates were resistant to penicillin, erythromycin and tetracycline, respectively. The MIC₉₀ values for the beta-lactams was the same or one dilution higher than the MIC breakpoints for resistance, whereas the MIC₉₀ values for erythromycin and tetracycline were three dilutions higher than the MIC breakpoints for resistance. The MIC₉₀ values of cefepime, ceftriaxone, cefotaxime, imipenem and meropenem were similar (2 to 4 mg/L).

Of the 1287 *S pneumoniae* submitted, 193 (15%) were non-susceptible to penicillin, of which 6.4% were highly resistant (2 mg/L or more). The activity of each of the antimicrobials tested against the isolates of penicillin-resistant *S pneumoniae* is presented in Table 4. Of the penicillin-nonsusceptible strains, 10.8%, 30.6% and 31.8% were highly resistant to ceftriaxone, erythromycin and tetracycline, respectively. Within the cephalosporin and carbapenem groups, the activity was comparable. However, the percentage of nonsusceptible isolates was much less for cefepime, ceftriaxone and cefotaxime (less than 22%) than imipenem and meropenem (greater than 42%). Cefotaxime was the most active of the beta-lactams, with only 13% of the isolates being nonsusceptible. The sources of the majority of isolates were blood (30%), lower respiratory tract (34.7%) and upper respiratory tract (31%).

DISCUSSION

The results of this study confirm the results of other investigators regarding the resistance rates of selected *Enterobacteriaceae* strains isolated in Canada. The high rates of multidrug resistance among viridans group streptococci and the increasing rates of multidrug resistance in *S pneumoniae* demonstrated in this study have not been previously recognized.

The Gram-negative species that were chosen for this study

TABLE 4

Results of susceptibility testing for selected antimicrobials against 193 penicillin-nonsusceptible *Streptococcus pneumoniae*, expressed as minimum inhibitory concentration (MIC)₅₀ and MIC₉₀ (mg/L), range (mg/L) and percentage nonsusceptible

Antimicrobial	MIC ₅₀	MIC ₉₀	Range	Percentage non-susceptible
Cefepime	0.5	1	0.03 - 2	21.8
Ceftriaxone	0.5	1	0.03 - 2	18.1
Cefotaxime	0.12	1	0.03 - 2	13.0
Ciprofloxacin	1	1	0.12 - >4	NA
Erythromycin	0.03	8	0.03 - >16	16.6
Tetracycline	2	32	2 - 32	26.9
Imipenem	0.25	0.5	0.03 - 0.5	58.5
Meropenem	0.25	0.5	0.03 - 1	42.2

NA Category breakpoints not available

were selected because of the previous reports of high rates of beta-lactam resistance due to the presence of chromosomal beta-lactamases (20-22). These bacteria can undergo single-step mutations to become constitutive high level producers of this enzyme, which is capable of hydrolyzing cephalosporins (1,3,23-25). However, the constitutive expression of this mechanism of resistance can vary from genus to genus, and, thus, resistance to cephalosporins can vary. *S marcescens* was not resistant to ceftriaxone, cefotaxime and ceftazidime, whereas more than 11% of *Enterobacter* species were resistant. The Gram-negative resistance rates found in this study were comparable with other previous cross-Canada surveillance studies. For example, in previous studies, ceftazidime resistance in *Enterobacter* species varied between 16% and 27%, whereas ciprofloxacin resistance was 3% or less, results very similar to this study (20,22,26).

Cefepime resistance was unusual in the *Enterobacteriaceae* species tested as has been reported in other studies (11-16).

This is thought to be due to the low binding affinity of the beta-lactamases to cefepime 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 versus other cephalosporins. This and other studies have demonstrated that Gram-negative isolates that are resistant to ceftriaxone, cefotaxime and/or ceftazidime often maintain susceptibility to cefepime (27-29). Consistent with previous reports, greater cross-resistance between cefepime and ceftazidime was detected among the *P aeruginosa* and *Acinetobacter* species (30).

Other than immunocompromised patients, viridans group streptococci isolated in other clinical settings have been assumed to be susceptible to penicillin. The patient characteristics from whom the blood culture isolates of viridans group streptococci were not obtained. However, resistance was not associated with the type or size of the hospital (data not shown). Surveillance data regarding the in vitro susceptibility of the viridans group streptococci are limited. In 1979, Bourgault (31) found low rates of resistance in the viridans group streptococci isolated from patients with endocarditis in the United States. Only two of 63 isolates were resistant to penicillin (MIC 4.0 mg/L). Subsequent reports found high rates of penicillin resistance in isolates from neutropenic patients (32,33). The emergence of multidrug resistance among the viridans group isolated from non-neutropenic patients has only been recently reported (4,34). Doern et al (4) carried out a study of 352 blood culture isolates of viridans group streptococci from 43 American medical centres during 1993 and 1994. The results were very similar to the results of the present study. The clinical importance of these organisms as a cause of bacteremia in the neutropenic host and endocarditis emphasizes the importance of knowing the local resistance rates of these organisms, especially when routine susceptibility testing is not performed and vancomycin is not part of the treatment regimen. The results of this study suggest that many of the oral antimicrobials with Gram-positive activity may have limited value as prophylactic and therapeutic agents.

Antimicrobial resistance in *S pneumoniae* has only been recognized in Canada during the past two decades. In 1979, two cases of *S pneumoniae* disease due to isolates that were nonsusceptible to penicillin were reported in Canada (35,36). Until recently, Canadian surveys have found the rates of resistance of *S pneumoniae* strains nonsusceptible to penicillin to be 3% or less (36-39). However, since 1988, increased resistance has been reported in different regions. A survey of clinical isolates from community and hospital laboratories in Toronto during 1993 and 1994 found that 7% of *S pneumoniae* were nonsusceptible to penicillin (40). In a cross-Canada study carried out by Davidson et al (5) between 1994 and 1996, there was a significant increase in the number of isolates of *S pneumoniae* nonsusceptible to penicillin found that during the two time periods. Overall, Davidson et al (5) found 10.7% of isolates were nonsusceptible to penicillin. A similar survey of clinical isolates obtained from 39 hospitals and community laboratories across Canada during 1994 and 1995

found that 12% of *S pneumoniae* were nonsusceptible to penicillin (41). In a study carried out by Kellner et al (42) in 1995, 16% of nasopharyngeal isolates and 11% of invasive isolates from a survey of children in Toronto were nonsusceptible to penicillin. The present survey documents the continued increase in multidrug-resistant *S pneumoniae* in Canada as has occurred in the United States and elsewhere.

The use of beta-lactams and carbapenems for the treatment of penicillin-resistant, nonmeningeal, invasive pneumococcal infections is controversial (43-46). The MIC breakpoint, above which such therapies are likely to be ineffective for nonmeningeal infections, is unknown, but a *S pneumoniae* MIC of 4.0 mg/L or greater to penicillin or the broader spectrum parenteral cephalosporins tested in this study is likely. Such strains are rare in North America.

CONCLUSIONS

This study has documented that the resistance in Gram-negative rods due to presumed inducible and constitutive chromosomal cephalosporinases has remained at relatively constant rates compared with rates reported in similar previous studies. There is a dramatic increase in the rates of multidrug resistance among viridans group streptococci and the continuing increase in the rates of resistance of *S pneumoniae* strains nonsusceptible to penicillin. Cefepime, a new broad-spectrum beta-lactam, has excellent in vitro activity against Gram-negative bacilli with inducible and constitutive chromosomally mediated beta-lactamases and has equal or superior activity than comparator agents against viridans group streptococci and *S pneumoniae* that are nonsusceptible to penicillin (27,34). Thus, cefepime may be an alternative agent for the treatment of suspected or proven infections due to such organisms.

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