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Canadian Ciprofloxacin Susceptibility Study: Comparative Study from 15 Medical Centers

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We tested 4,507 microorganisms, from 15 Canadian medical centers, against ciprofloxacin and several other antimicrobial agents to determine the in vitro susceptibilities. Overall, susceptibility of members of the family *Enterobacteriaceae* to ciprofloxacin was 97%; *Moraxella* and *Haemophilus* spp. had susceptibilities of 98 and 99%, respectively; and *P. aeruginosa* and *S. aureus* had susceptibilities of 79 and 96%, respectively.

Ciprofloxacin is a 4-fluoroquinolone antimicrobial agent that has been in use in Canada since 1989. It has a broad spectrum of activity against both gram-positive and gram-negative bacteria and is bacteriocidal by inhibiting the bacterial enzyme DNA gyrase (4, 8, 13). Antimicrobial resistance is a common concern worldwide (2, 13, 14), so that local and national surveys to identify and monitor the emergence of resistant isolates are a necessity. Parry et al. (8) reported that the level of resistance to ciprofloxacin was 0.6% of 1,454 isolates from a 300-bed community teaching hospital between 1984 and 1987. Following the release of ciprofloxacin in 1988, resistances to ciprofloxacin in *Pseudomonas aeruginosa* and *Staphylococcus* spp. increased to 6.5 and 4.2%, respectively, while members of the family *Enterobacteriaceae* remained exquisitely susceptible, with 0.3% resistance. Hoban and Jones, using data from five North American medical centers (5), reported that susceptibility of members of the family *Enterobacteriaceae* to ciprofloxacin ranged from 95 to 100%, that of *Staphylococcus aureus* ranged from 14 to 96%, that of coagulase-negative staphylococci ranged from 55 to 91%, that of *Streptococcus pneumoniae* was 85%, that of *P. aeruginosa* was 85%, and those of *Haemophilus influenzae* and *Moraxella catarrhalis* were 100%. We undertook a Canada-wide, 15-medical-center survey to determine the in vitro activities of ciprofloxacin and several other antimicrobial agents against gram-positive and gram-negative pathogens and compared these findings with those collected from previous surveys (1, 5, 6, 12).

A total of 15 medical centers representing all 10 Canadian provinces and nearly all major population areas in Canada were recruited to provide geographic organism sampling. Each center tested approximately 300 strains of bacteria: 100 each from patients with urinary tract infections, skin and soft tissue infections, and respiratory tract infections. In total 4,507 clinical isolates collected from October 1993 to April 1994 were examined. A maximum of 50 *Escherichia coli* isolates from urinary tract infections were collected from each site. Only fresh clinical isolates were eligible for inclusion in the study, and duplicate isolates from the same patient were not permitted. The clinical validity of the isolates was determined by local laboratory criteria, and organisms were identified by reference or comparable methods. Following testing, all isolates were stocked.

All sites used the same protocol for testing, and all supplies and media were provided by the study coordinator (J.M.B.). Following testing, the susceptibility results and the stocked microorganisms were shipped to the study coordinator. MICs were determined by using the Microscan MIC Plus Type 2 Panel. Testing was performed according to the manufacturer's instructions, and interpretation was in accordance with MIC interpretive criteria published in National Committee for Clinical Laboratory Standards no. M7-A2 (7). For *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*, and *Streptococcus* species, *Haemophilus* inoculum broth was used.

Table 1 shows the total number of microorganisms recovered and their susceptibilities to 10 antimicrobial agents. *S. aureus*, *E. coli*, *P. aeruginosa*, *Enterococcus* spp., *H. influenzae*, and *K. pneumoniae* were the most frequently recovered microorganisms. There were 4,507 isolates, with 1,507, 1,501, and 1,499 from patients with respiratory tract, skin and soft tissue, and urinary tract infections, respectively. There were 2,753 gram-negative and 1,754 gram-positive isolates tested; 2,890 were from inpatients, and 1,614 were from outpatients (patient location was not available for 3 isolates). *S. aureus* was the pathogen most frequently recovered from patients with respiratory tract and skin and soft tissue infections, while *E. coli* was

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TABLE 1. Antimicrobial susceptibilities of 4,482 microorganisms collected from 15 Canadian Medical Centers

Organism (*n*)	Amoxicillin-clavulanic acid				Aztreonam				Ceftazidime			
	MIC (μg/ml)[a]			% Susceptibility	MIC (μg/ml)			% Susceptibility	MIC (μg/ml)			% Susceptibility
	50%	90%	Range		50%	90%	Range		50%	90%	Range	
Acinetobacter spp. (49)	4/2[b]	16/8	<1/0.5–>32/16	88	16	32	<1–>32	33	4	16	<1–>32	88
Citrobacter spp. (84)	16/8	32/16	<1/0.5–>32/16	44	<1	32	<1–>32	85	<1	>32	<1–>32	82
Enterobacter spp. (181)	32/16	32/16	<1/0.5–>32/16	14	<1	16	<1–>32	84	<1	>32	<1–>32	83
E. coli (946)	2/1	8/4	<1/0.5–32/16	95	<1	<1	<1–>32	99	<1	<1	<1–>32	99
Haemophilus spp. (311)	<0.5/0.25	<0.5/0.25	<0.5/0.25–4/2	NA[c]	<0.5	<0.5	<0.5–>16	95	<0.5	<0.5	<0.5–8	100
Klebsiella spp. (355)	2/1	4/2	<1/0.5–8/4	99	<1	<1	<1–>32	98	<1	<1	<1–>32	99
Moraxella spp. (87)	<0.5/0.25	<0.5/0.25	<0.5/0.25–>16/8	99	<0.5	1	<0.5–>16	97	<0.5	<0.5	<0.5–2	100
Morganella spp. (39)	>32/16	>32/16	<1/0.5–>32/16	3	<1	<1	<1–4	100	<1	16	<1–>32	82
P. aeruginosa (390)	>32/16	>32/16	<1/0.5–>32/16	2	4	16	<1–>32	83	2	8	<1–>32	92
Proteus spp. (128)	<1/0.5	8/4	<1/0.5–>32/16	95	<1	<1	<1–>32	95	<1	<1	<1–>32	99
Providencia spp. (14)	32/16	>32/16	<1/0.5–>32/16	21	<1	<1	<1	100	<1	<1	<1	100
Pseudomonas spp. (26)[d]	>32/16	>32/16	<1/0.5–>32/16	27	4	>32	<1–>32	54	2	4	<1–>16	96
Serratia spp. (61)	>32/16	>32/16	<1/0.5–>32/16	11	<1	<1	<1–>32	93	<1	<1	<1–>32	98
S. maltophilia (57)	32/16	32/16	4/2–>32/16	4	>32	>32	2–>32	9	4	>32	<1–>32	58
Enterococcus spp. (307)	<1/0.5	<1/0.5	<1/0.5–>32/16	97	>32	>32	<1–>32	1	>32	>32	<1–>32	6
S. agalactiae (96)	<1/0.5	<1/0.5	<1/0.5–>32/16	99	>32	>32	<0.5–>32	8.3	<1	<1	<0.5–>16	99
S. aureus (955)	<1/0.5	<1/0.5	<1/0.5–>32/16	98	>32	>32	<1–>32	5.4	8	8	<1–>32	96
S. pneumoniae (118)	<0.5/0.25	<0.5/0.25	<0.5/0.25–>8/4	NA	>16	>16	<0.5–>16	7	<0.5	<0.5	<0.25–8	NA
S. pyogenes (86)	<0.5/0.25	<1/0.5	0.5/0.25–4/2	100	8	32	<0.5–>32	52	<0.5	1	<0.25–>16	95
Staphylococcus, coagulase negative (158)	<1/0.5	8/4	<1/0.5–>32/16	93	>32	>32	<1–>32	2	16	>32	<1–>32	45
Streptococcus spp. (28)	<0.5/0.25	<0.5/0.25	<0.5/0.25–2/1	100	>16	>16	>16	0	<0.5	8	<0.5–>16	96

[a] 50% and 90%, MICs at which 50 and 90% of the isolates are inhibited, respectively.
[b] The value before the slash is for amoxicillin, and the value after the slash is for clavulanic acid.
[c] NA, no approved National Committee for Clinical Laboratory Standards breakpoint.
[d] Includes two isolates of *Burkholderia cepacia.*

the isolate most frequently recovered from patients with urinary tract infections. A total of 25 miscellaneous microorganisms were collected: *Aeromonas* spp. (4 isolates), *Alcaligenes* spp. (2 isolates), *Chryseobacterium* spp. (4 isolates), *Hafnia alvei* (2 isolates), a *Kluyvera* sp. (1 isolate), *Neisseria meningitidis* (2 isolates), *Ochrobactrum onthropi* (1 isolate), *Providencia alcalifaciens* (1 isolate), *Pasteurella multocida* (3 isolates), a *Salmonella* sp. (1 isolate), *Shigella* spp. (2 isolates), and diphtheroids (2 isolates). Susceptibility data pertaining to these isolates are not shown.

Overall, 97% of isolates of the family *Enterobacteriaceae* were susceptible to ciprofloxacin: *Providencia* spp. and *Citrobacter* spp. had susceptibility rates of 82 and 88%, respectively. For the remaining agents tested, rates of susceptibility of *Enterobacteriaceae* to all but cefamandole and ticarcillin were 96% or greater. Imipenem and netilmicin were the most effective against *Enterobacteriaceae* (99 and 98% susceptibilities, respectively). For all gram-negative isolates tested, susceptibility to ciprofloxacin was 93% while susceptibility percentages for aztreonam, ceftazadime, imipenem, and netilmicin were 91% or greater. Imipenem and ceftazadime were the most active agents against all gram-negative isolates (95% susceptibility). Ceftazadime (91%), imipenem (90%), and ticarcillin (90%) were the most active agents against *P. aeruginosa*, followed by aztreonam (83%), ciprofloxacin (79%), and netilmicin (78%). Susceptibilities of *Haemophilus* and *Moraxella* species to all agents tested were nearly uniform (98% or greater; ticarcillin activity against *Haemophilus* species was 88%). *Acinetobacter* species and *Stenotrophomonas maltophilia* were the least susceptible microorganisms, with susceptibilities to ciprofloxacin of 78 and 18%, respectively, and susceptibilities to other agents tested ranging from 16 to 98% and 2 to 80%, respectively. Susceptibility of *S. maltophilia* to ticarcillin-clavulanic acid was 95%. Imipenem was the most active agent against Acinetobacter spp. (98%). Amoxicillin-clavulanic acid and imipenem were the most active agents (98 and 96% susceptibility, respectively) against gram-positive isolates. Susceptibilities to cefamandole, cefotaxime, netilmicin, and ticarcillin were 81 to 88%. Ceftazadime and cefotetan were less active, with 76 and 77% of isolates susceptible, respectively. Susceptibility of *S. aureus* to all agents, including ciprofloxacin, was 96% or greater. Ciprofloxacin was the least active agent against *S. pneumoniae* and *Streptococcus agalactiae* (76 and 74% susceptibility, respectively), but its activity was comparable to those of other agents against *S. pyogenes*. Coagulase-negative *Staphylococcus* and *Enterococcus* spp. were the most resistant groups tested. Susceptibility of coagulase-negative *Staphylococcus* spp. to ciprofloxacin was 68%, while higher susceptibility rates were seen for cefotaxime (70%), netilmicin (82%), cefamandole (88%), and amoxicillin-clavulanic acid (92%). For *Enterococcus* spp., susceptibility to ciprofloxacin was 63% while higher rates were seen for amoxicillin-clavulanic acid and imipenem (96%).

On the basis of the results of a 15-medical-center survey using fresh clinical isolates, susceptibilities of *S. aureus* and *Enterobacteriaceae* to ciprofloxacin were similar to susceptibility data determined by Hoban et al. (6) in a previous Canadian survey. Additionally, susceptibility rates reported here are similar to those determined in previous studies of isolates from Canadian medical centers and reported by Toye et al. (12) for *Klebsiella* and *Enterobacter* spp. and by Chamberland et al. (1) for gram-negative pathogens. Likewise, susceptibility rates have not changed for *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*, and *Enterococcus* spp. Similarly, Tillotson et al. (11) reported the cumulative susceptibility rates of gram-negative pathogens collected over a 6-year period and tested against ciprofloxacin in 14 laboratories in the United Kingdom. Susceptibility rates for *Enterobacteriaceae* ranged from 92.1% for

TABLE 1—*Continued*

Cefamandol				Cefotaxime				Ciprofloxacin				Cefotetan			
MIC (μg/ml)			% Susceptibility	MIC (μg/ml)			% Susceptibility	MIC (μg/ml)			% Susceptibility	MIC (μg/ml)			% Susceptibility
50%	90%	Range		50%	90%	Range		50%	90%	Range		50%	90%	Range	
>32	>32	<4–>32	16	8	64	<2–>64	60	<0.25	4	<0.25–>4	78	>32	>32	<4–>32	12
≤4	>32	<4–>32	62	<2	32	<2–>64	83	<0.25	2	<0.25–>4	88	<4	32	<2–>32	86
16	>32	<4–>32	48	<2	64	<2–>64	80	<0.25	<0.25	<0.25–>4	97	<4	>32	<4–>32	68
<4	8	<4–>32	88	<2	<2	<2–>64	99	<0.25	<0.25	<0.25–>4	99	<4	<4	<1–>32	NA
<2	<2	<2–>16	NA	<1	<1	<1–4	100	<0.125	<0.125	<0.125–2	99	<2	<2	<1–16	NA
<4	<4	<4–>32	94	<2	<2	<2–32	99	<0.25	<0.25	<0.25–>4	96	<4	<4	<1–>32	99
<2	<2	<2–>16	99	<1	<1	<1–8	100	<0.125	<0.125	<0.125–>2	99	<2	<2	<2–>16	99
32	>32	<4–>32	8	<2	8	<2–16	92	<0.25	<0.25	<0.25–>4	97	<4	<4	<4–32	99
>32	>32	<4–>32	2	16	>64	<2–>64	24	<0.25	4	<0.25–>4	79	>32	>32	<4–>32	5
<4	>32	<4–>32	84	<2	<2	<2–>64	96	<0.25	<0.25	<0.25–>4	98	<4	<4	<4–>32	95
<4	16	<4–>32	79	<2	<2	<2	100	<0.25	>4	<0.25–>4	62	<4	<4	<4	100
>32	>32	<4–>32	12	16	64	<2–>64	42	<0.25	1	<0.25–>4	89	>32	>32	<4–>32	39
>32	>32	<4–>32	10	<2	<2	<2–32	93	<0.25	1	<0.25–>4	92	<4	<4	<4–>32	97
>32	>32	<4–>32	4	32	>64	<2–>64	9	4	>4	0.5–>4	18	8	32	<4–>32	81
16	32	<4–>32	6	>64	>64	<2–>64	13	1	>4	<0.25–>4	63	>32	>32	<4–>32	2
<4	<4	<2–16	99	<2	<2	<1–32	99	0.5	2	<0.12–>4	81	<4	8	<2–>16	99
<4	<4	<4–>32	99	<2	<2	<1–>64	98	<0.25	0.5	<0.25–>4	96	<4	<4	<2–>32	98
<2	<2	<2	NA	<1	<1	<1	NA	1	2	<0.125–>2	NA	<2	<2	<2–>16	NA
<2	<4	<2–>32	97	<1	<2	<1–>32	99	0.5	2	<0.125–>4	81	<4	8	<2–32	93
<4	8	<4–32	90	<2	>64	<2–>64	71	<0.25	>4	<0.25–>4	63	16	>32	<4–>32	53
<2	<2	<2	100	<1	<1	<1–16	96	0.5	2	<0.125–>2	71	<2	>16	<2–>16	86

Serratia species to 99.8% for *E. coli. H. influenzae* and *M. catarrhalis* had susceptibility rates of 99.6 and 97.5%, respectively. Tillotson et al. (11) concluded that after 6 years of ciprofloxacin use, little resistance has emerged among *Enterobacteriaceae* and *H. influenzae*. The results of their study appear to be similar to those of the current study. The reduction in susceptibility of coagulase-negative staphylococci observed in this study is similar to that found by Hoban et al. (6). Overall, susceptibility to ciprofloxacin was 90%, and this was identical to the rate reported by Hoban and Jones (5) and Hoban et al. (6).

Chamberland et al. (1) did not find any ciprofloxacin-resistant *P. aeruginosa* isolates, while Hoban et al. (6) found a 4 to 10% incidence of resistance in isolates from Canadian medical centers. Coronado et al. (3) reported that 4.7% of 8,517 *P. aeruginosa* isolates collected between 1989 and 1992 and reported to the National Nosocomial Infections Surveillance System were resistant to ciprofloxacin, and Tillotson et al. (11) reported an increase (1.4 to 11.1%) in the occurrence of ciprofloxacin-resistant *P. aeruginosa* in the United Kingdom over a 6-year period. In the study of Coronada et al. (3), a higher level of resistance was found in respiratory tract isolates versus those from other sites, in teaching versus nonteaching institutions, and in the period 1991 to 1992 versus 1989 to 1990.

In this study, we found that 21% of *P. aeruginosa* isolates were resistant to ciprofloxacin. However, occurrence of resistance was not uniformly distributed as four centers (data not shown) recorded individual resistance rates from 28 to 40% and these centers contributed 31% of the 391 isolates tested. The study design incorporated no selection process that would increase the likelihood of collecting resistant isolates. One difficulty in the interpretation of these results is that the number of *P. aeruginosa* isolates from individual centers ranged from 16 to 39, making comparisons between teaching and nonteaching institutions difficult. We found that resistant isolates were more commonly recovered from inpatients than from outpatients (21 versus 16%) with respiratory tract infections, from inpatients than from outpatients (15 versus 12%) with skin and soft tissue infections, and from outpatients than from inpatients (37 versus 32%) with urinary tract infections; however, these differences were not significant. The occurrences of ceftazadime-, imipenem-, and netilmicin-resistant *P. aeruginosa* isolates reported here are similar to those reported by Chamberland et al. (1). Resistance to aztreonam and ticarcillin appears to have decreased. These comparisons need to be interpreted with caution, since the numbers of isolates tested (47 to 78 versus 391) and institutions (10 versus 15) participating were less than in the current study.

Our study data do not indicate increasing resistance of *S. aureus* to ciprofloxacin in comparison with data in previous reports. Raviglione et al. (9) and Shalit et al. (10) have reported a higher rate of resistance to ciprofloxacin among methicillin-resistant *S. aureus* (MRSA) strains than among methicillin-susceptible *S. aureus* strains. In our study, only 4 of the 959 isolates of *S. aureus* tested were specifically identified (by the participating center) as MRSA. The overall high susceptibility rates for other beta-lactam antibiotics (96 to 99%) reported in this study suggest that the number of isolates likely to be MRSA is small.

On the basis of the results of a 15-center study and comparison of our results with those of previous surveys, we conclude that the occurrence of resistance to ciprofloxacin and other broad-spectrum antimicrobial agents among *Enterobacteriaceae* and *S. aureus* appears stable in Canadian medical centers. An unexpectedly high number of ciprofloxacin-resistant (21%) *P. aeruginosa* isolates appears to be related more to some institutions than to others and may represent focal outbreaks of resistant isolates or the dissemination of resistant strains.

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TABLE 1—*Continued*

Imipenem				Netilmicin				Ticarcillin			
MIC (μg/ml)			% Susceptibility	MIC (μg/ml)			% Susceptibility	MIC (μg/ml)			% Susceptibility
50%	90%	Range		50%	90%	Range		50%	90%	Range	
<0.5	1	<0.5–16	98	<2	>16	<2–>16	84	<16	<16	<16–>128	90
<0.5	2	<0.5–2	100	<2	<2	<2–>16	95	<16	>128	<16–>128	56
<0.5	2	<0.5–16	99	<2	<2	<2–>16	97	<16	128	<16–>128	70
<0.5	<0.5	<0.25–<16	99	<2	<2	<2–>16	99	<16	>128	<16–>128	72
<0.25	0.5	<0.25–8	100	<1	<2	<1–>8	NA	<8	16	<8–>64	NA
<0.5	1	<0.25–4	100	<2	<2	<2–>16	98	128	>128	<16–>128	9
<0.25	<0.25	<0.25–0.5	100	<1	<1	<1–4	100	<8	<8	<8–16	100
4	4	1–8	92	<2	<2	<2–>16	97	<16	32	<16–>128	85
1	8	<0.5–>16	89	4	16	1–>16	78	<16	64	<16–>128	66
2	8	<0.25–>16	86	<2	<2	<2–>16	99	<16	64	<16–>128	85
2	4	<0.5–4	100	4	>16	<2–>16	79	<16	<16	<16–>128	93
1	4	<0.5–>16	89	<2	>16	<2–>16	81	128	>128	<16–>128	42
<0.5	2	<0.5–4	100	<2	4	<2–>16	98	<16	32	<16–>128	84
>16	>16	<0.5–>16	2	>16	>16	<2–>16	21	32	>128	<16–>128	35
1	2	<0.25–>16	96	16	>16	<2–32	48	32	32	<16–>128	NA
<0.5	<0.5	<0.25–1	100	8	>16	<1–>16	73	<16	<16	<8–32	NA
<0.5	<0.5	<0.5–>16	98	<2	<2	<2–>16	99	<16	<16	<4–>128	NA
<0.25	<0.25	<0.25	NA	2	8	<1–>8	NA	<8	<8	<8–>64	NA
<0.25	<0.5	<0.125–4	100	4	8	<1–>16	92	<8	<16	<8–64	NA
<0.5	>16	<0.5–>16	70	<2	2	<2–>16	98	<16	>128	<16–>128	NA
<0.25	<0.25	<0.25	100	4	8	<1–>8	79	<8	<8	<8–>64	NA

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