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Antimicrobial-Resistant Pathogens in Intensive Care Units in Canada: Results of the Canadian National Intensive Care Unit (CAN-ICU) Study, 2005-2006▽

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Between 1 September 2005 and 30 June 2006, 19 medical centers collected 4,180 isolates recovered from clinical specimens from patients in intensive care units (ICUs) in Canada. The 4,180 isolates were collected from 2,292 respiratory specimens (54.8%), 738 blood specimens (17.7%), 581 wound/tissue specimens (13.9%), and 569 urinary specimens (13.6%). The 10 most common organisms isolated from 79.5% of all clinical specimens were methicillin-susceptible *Staphylococcus aureus* (MSSA) (16.4%), *Escherichia coli* (12.8%), *Pseudomonas aeruginosa* (10.0%), *Haemophilus influenzae* (7.9%), coagulase-negative staphylococci/*Staphylococcus epidermidis* (6.5%), *Enterococcus* spp. (6.1%), *Streptococcus pneumoniae* (5.8%), *Klebsiella pneumoniae* (5.8%), methicillin-resistant *Staphylococcus aureus* (MRSA) (4.7%), and *Enterobacter cloacae* (3.9%). MRSA made up 22.3% (197/884) of all *S. aureus* isolates (90.9% of MRSA were health care-associated MRSA, and 9.1% were community-associated MRSA), while vancomycin-resistant enterococci (VRE) made up 6.7% (11/255) of all enterococcal isolates (88.2% of VRE had the *vanA* genotype). Extended-spectrum β-lactamase (ESBL)-producing *E. coli* and *K. pneumoniae* occurred in 3.5% (19/536) and 1.8% (4/224) of isolates, respectively. All 19 ESBL-producing *E. coli* isolates were PCR positive for CTX-M, with $bla_{\text{CTX-M-15}}$ occurring in 74% (14/19) of isolates. For MRSA, no resistance against daptomycin, linezolid, tigecycline, and vancomycin was observed, while the resistance rates to other agents were as follows: clarithromycin, 89.9%; clindamycin, 76.1%; fluoroquinolones, 90.1 to 91.8%; and trimethoprim-sulfamethoxazole, 11.7%. For *E. coli*, no resistance to amikacin, meropenem, and tigecycline was observed, while resistance rates to other agents were as follows: cefazolin, 20.1%; cefepime, 0.7%; ceftriaxone, 3.7%; gentamicin, 3.0%; fluoroquinolones, 21.1%; piperacillin-tazobactam, 1.9%; and trimethoprim-sulfamethoxazole, 24.8%. Resistance rates for *P. aeruginosa* were as follows: amikacin, 2.6%; cefepime, 10.2%; gentamicin, 15.2%; fluoroquinolones, 23.8 to 25.5%; meropenem, 13.6%; and piperacillin-tazobactam, 9.3%. A multidrug-resistant (MDR) phenotype (resistance to three or more of the following drugs: cefepime, piperacillin-tazobactam, meropenem, amikacin or gentamicin, and ciprofloxacin) occurred frequently in *P. aeruginosa* (12.6%) but uncommonly in *E. coli* (0.2%), *E. cloacae* (0.6%), or *K. pneumoniae* (0%). In conclusion, *S. aureus* (MSSA and MRSA), *E. coli*, *P. aeruginosa*, *H. influenzae*, *Enterococcus* spp., *S. pneumoniae*, and *K. pneumoniae* are the most common isolates recovered from clinical specimens in Canadian ICUs. A MDR phenotype is common for *P. aeruginosa* isolates in Canadian ICUs.

The global escalation in both community- and hospital-acquired antimicrobial-resistant bacteria is threatening the ability to effectively treat patients, underscoring the need for continued surveillance, more appropriate antimicrobial prescribing, prudent infection control, and new treatment alternatives (1, 10, 11, 14, 18, 27). Antimicrobial-resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) (community-associated [CA-MRSA] and health care-associated [HA-MRSA]), vancomycin-resistant *Enterococcus* species (VRE), penicillin-resistant *Streptococcus pneumoniae*, extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella* species, and fluoroquinolone-resistant and carbapenem-resistant members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa* are increasing in prevalence in all regions of Canada, in the United States, and globally (3–5, 8, 9, 13, 17–20, 22, 24, 28, 29, 31, 33). Available therapeutic options for antibiotic-resistant organisms are severely limited, as these organisms frequently display a multidrug-resistant (MDR) phenotype (18, 27, 31).

The purpose of this study was to assess the prevalence of pathogens, including the resistance genotypes of MRSA, VRE, and ESBL-producing bacteria, causing infections in patients in Canada intensive care units (ICUs), as well as their antimicrobial resistance patterns. The present report is the first national, prospective surveillance study assessing antimicrobial resistance in patients in ICUs in Canada.

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MATERIALS AND METHODS

Bacterial isolates. Study isolates were obtained as part of the *Ca*nadian *N*ational *I*ntensive Care *U*nit (CAN-ICU) study. The CAN-ICU study included 19 medical centers from all regions of Canada with active ICUs (see Acknowledgments and the website www.can-r.ca). From September 2005 to June 2006, inclusive, each center collected a maximum of 300 consecutive isolates recovered from clinical specimens, including blood, urine, wound/tissue, and respiratory specimens (one pathogen per cultured site per patient) of ICU patients. The 4,180 isolates obtained represented 2,580 patients (or 1.62 isolates/patient). Participating study sites were requested to obtain only "clinically significant" specimens from patients with a presumed infectious disease. Surveillance swabs, eye, ear, nose, and throat swabs, and duplicate swabs were excluded. We also excluded anaerobic organisms and fungal organisms. Isolates were shipped to the reference laboratory (Health Sciences Centre, Winnipeg, Canada) on Amies charcoal swabs, subcultured onto appropriate media, and stocked in skim milk at −80°C until MIC testing was carried out.

Antimicrobial susceptibilities. Following two subcultures from frozen stock, the in vitro activities of amikacin, cefazolin, ceftriaxone, cefepime, ciprofloxacin, clarithromycin, clindamycin, daptomycin, gentamicin, levofloxacin, linezolid, meropenem, moxifloxacin, piperacillin-tazobactam, tigecycline, trimethoprim-sulfamethoxazole (SXT), and vancomycin were determined by broth microdilution in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines (7). Antimicrobial agents were obtained as laboratory-grade powders from their respective manufacturers. Stock solutions were prepared, and dilutions were made according to the CLSI guidelines (7a). The MICs of the antimicrobial agents for the isolates were determined using 96-well custom-designed microtiter plates. These plates contained doubling antimicrobial dilutions in 100 μl/well of cation-adjusted Mueller-Hinton broth, and the wells were inoculated to achieve a final concentration of approximately 5×10^5 CFU/ml and then incubated in ambient air for 24 h prior to reading. Colony counts were performed periodically to confirm inocula. Quality control was performed using ATCC quality control organisms: *Streptococcus pneumoniae* 49619, *Staphylococcus aureus* 29213, *Enterococcus faecalis* 29212, *Escherichia coli* 25922, and *Pseudomonas aeruginosa* 27853.

For all antimicrobials tested, MIC interpretive standards were defined according to CLSI breakpoints (7). The following interpretive breakpoints (FDA) were used for tigecycline susceptible, intermediate, and resistant: *S. aureus* (MSSA and MRSA), ≤0.5 μg/ml (susceptible); *E. faecalis* (vancomycin susceptible), ≤0.25 μg/ml (susceptible); *Enterobacteriaceae*, ≤2 μg/ml (susceptible), 4 μg/ml (intermediate), and ≥8 μg/ml (resistant).

Characterization of MRSA, ESBL-producing members of the family *Enterobacteriaceae*, and VRE. (i) MRSA. Potential MRSA isolates were confirmed using the CLSI disk diffusion method and *mecA* PCR. All isolates of MRSA were tested for Panton-Valentine leukocidin and typed using pulsed-field gel electrophoresis following the Canadian standardized protocol to assess whether the isolates were community-associated or health care-associated MRSA (6, 21–23). Pulsed-field gel electrophoresis fingerprints were analyzed with BioNumerics v3.5 (Applied Maths, Austin, TX) using a position tolerance of 1.0 and an optimization of 1.0. Strain relatedness was determined as previously described (30). Fingerprints were compared to the national MRSA fingerprint database and were grouped into one of 10 Canadian MRSA epidemics (CMRSA-1, CMRSA-2, etc.) as previously described (22). In this study, CA-MRSA and HA-MRSA were defined genotypically and not epidemiologically. Any MRSA isolate with a CMRSA-7 (USA400/MW2) or CMRSA-10 (USA300) genotype was labeled as CA-MRSA, while all other genotypes (e.g., CMRSA-1 [USA600], CMRSA-2 [USA100], CMRSA-4 [USA200]) were labeled as HA-MRSA.

(ii) ESBL testing. Any *E. coli* isolate or *Klebsiella* isolate with a ceftriaxone MIC of ≥1 μg/ml was identified as a potential ESBL producer as specified by CLSI. ESBL producers were confirmed using the CLSI double disk diffusion method and retested for their MICs to both ceftriaxone and ceftazidime. PCR and DNA sequence analysis was used to identify bla_{SHV}, bla_{TEM}, and $bla_{CTX\text{-}M}$ genes among isolates as previously described (20, 24, 25).

(iii) VRE. Potential VRE isolates were confirmed using CLSI vancomycin disk diffusion testing and underwent *vanA* and *vanB* PCR as well as DNA fingerprinting to assess genetic similarity as previously described (2, 4, 33).

TABLE 1. The 20 most common organisms isolated from ICUs in Canada

Ranking	Organism[a]	No. of isolates	% of total
1	*Staphylococcus aureus* (MSSA)	687	16.4
2	*Escherichia coli*	536	12.8
3	*Pseudomonas aeruginosa*	419	10.0
4	*Haemophilus influenzae*	329	7.9
5	CoNS/*Staphylococcus epidermidis*	273	6.5
6	*Enterococcus* spp.	255	6.1
7	*Streptococcus pneumoniae*	244	5.8
8	*Klebsiella pneumoniae*	224	5.4
9	*Staphylococcus aureus* (MRSA)	197	4.7
10	*Enterobacter cloacae*	164	3.9
11	*Stenotrophomonas maltophilia*	108	2.6
12	*Serratia marcescens*	100	2.4
13	*Moraxella catarrhalis*	78	1.9
14	*Klebsiella oxytoca*	77	1.8
15	*Streptococcus pyogenes*	49	1.2
16	*Enterobacter aerogenes*	47	1.1
17	*Citrobacter freundii*	39	0.9
18	*Streptococcus agalactiae*	39	0.9
19	*Proteus mirabilis*	38	0.9
20	*Acinetobacter baumannii*	28	0.7
	Other[b]	249	6.0
Total		4,180	100.0

[a] CoNS, coagulase-negative staphylococci; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

[b] Includes *Acinetobacter, Burkholderia*, *Bacillus*, *Citrobacter*, *Corynebacterium*, *Enterobacter*, *Haemophilus*, *Micrococcus*, *Morganella*, *Neisseria*, *Pseudomonas, Salmonella*, *Serratia*, *Staphylococcus*, and *Streptococcus* spp.

RESULTS

Patient demographics and specimen types. A total of 4,180 isolates recovered from clinical specimens were collected from intensive care units across Canada. The patient sex breakdown was as follows: 59.3% (2,479 of 4,180) of the isolates were collected from males, while 40.7% (1,701 of 4,180) were from females. The patient age breakdown was as follows: ≤17 years, 13.7% (572 of 4,180); 18 to 64 years, 46.7% (1,951 of 4,180); and ≥65 years, 39.6% (1,657 of 4,180). The isolates were obtained from the following specimens: 54.8% (2,292 of 4,180) of the organisms were obtained from respiratory specimens, 17.7% (738 of 4,180) were from blood specimens, 13.9% (581 of 4,180) were from wound/tissue specimens, and 13.6% (569 of 4,180) were from urine specimens.

Most common organisms isolated from ICUs. Table 1 shows the 20 most common organisms isolated from patients in ICUs across Canada. The most common gram-positive cocci included *S. aureus* (MSSA), coagulase-negative staphylococci/*Staphylococcus epidermidis*, *Enterococcus* spp., *S. pneumoniae*, and MRSA, which together represented 39.5% of all isolates. The most common gram-negative bacilli included *E. coli*, *P. aeruginosa*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Enterobacter cloacae*, *Stenotrophomonas maltophilia*, and *Serratia marcescens*, which together made up 45% of all organisms in ICUs.

Most common organisms isolated by specimen site. Table 2 shows the 10 most common isolates recovered from clinical specimens from the four specimen sites, including respiratory specimens, blood specimens, wound/tissue specimens, and specimens from the urinary tract. Within the respiratory tract, *S. aureus* (MSSA), *S. pneumoniae*, and MRSA were the most

TABLE 2. The 10 most common organisms isolated by specimen site in ICUs in Canada

Specimen site and ranking	Organism[a]	No. of isolates	% of total
Respiratory specimens (n = 2,292) (54.8%)			
1	*S. aureus* (MSSA)	467	20.5
2	*H. influenzae*	323	14.1
3	*P. aeruginosa*	289	12.6
4	*S. pneumoniae*	198	8.6
5	*E. coli*	122	5.3
6	*K. pneumoniae*	122	5.3
7	*S. aureus* (MRSA)	118	5.1
8	*E. cloacae*	107	4.7
9	*S. maltophilia*	95	4.1
10	*M. catarrhalis*	78	3.4
	Other[b]	373	16.3
Total		2,292	100.0
Blood specimens (n = 738) (17.7%)			
1	CoNS/*S. epidermidis*	166	22.5
2	*S. aureus* (MSSA)	87	11.8
3	*Enterococcus* spp.	74	10.0
4	*E. coli*	73	9.9
5	*S. aureus* (MRSA)	49	6.6
6	*S. pneumoniae*	40	5.4
7	*P. aeruginosa*	33	4.5
8	*K. pneumoniae*	26	3.5
9	*E. cloacae*	24	3.3
10	*S. pyogenes*	17	2.3
	Other[b]	149	20.2
Total		738	100.0
Wound/tissue specimens (n = 581) (13.9%)			
1	*S. aureus* (MSSA)	113	19.5
2	CoNS/*S. epidermidis*	85	14.6
3	*Enterococcus* spp.	72	12.4
4	*E. coli*	58	10.0
5	*P. aeruginosa*	52	9.0
6	*S. aureus* (MRSA)	27	4.6
7	*K. pneumoniae*	25	4.3
8	*S. pyogenes*	24	4.1
9	*E. cloacae*	17	2.9
10	*S. marcescens*	15	2.6
	Other[b]	93	16.0
Total		581	100.0
Urine specimens (n = 569) (13.6%)			
1	*E. coli*	283	49.7
2	*Enterococcus* spp.	78	13.7
3	*K. pneumoniae*	51	9.0
4	*P. aeruginosa*	45	7.9
5	*S. aureus* (MSSA)	20	3.5
6	*E. cloacae*	16	2.8
7	CoNS/*S. epidermidis*	14	2.5
8	*C. freundii*	11	1.9
9	*K. oxytoca*	8	1.4
10	*P. mirabilis*	8	1.4
	Other[b]	35	6.2
Total		569	100.0

[a] CoNS, coagulase-negative staphylococci.
[b] See Table 1, footnote *b*.

common gram-positive cocci, accounting for 34.2% of isolates. For gram-negative bacilli, *H. influenzae*, *P. aeruginosa*, *E. coli*, *K. pneumoniae*, *E. cloacae*, and *S. maltophilia* represented 46.1% of isolates obtained. Among blood culture isolates, gram-positive cocci, including coagulase-negative staphylococci/*S. epidermidis*, *S. aureus* (MSSA), *Enterococcus* spp., MRSA, *S. pneumoniae*, and *Streptococcus pyogenes*, made up 58.6% of the organisms isolated in ICUs. The most common gram-negative bacilli isolated from blood specimens included *E. coli*, *P. aeruginosa*, *K. pneumoniae*, and *E. cloacae*, which made up 21.2% of all isolates. For wound/tissue specimens, gram-positive cocci, including *S. aureus* (MSSA), coagulase-negative staphylococci/*S. epidermidis*, *Enterococcus* spp., MRSA, and *S. pyogenes*, made up 55.2% of the total isolates. The most common gram-negative bacilli isolated from wound/tissue specimens were *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *E. cloacae*, and *S. marcescens*, which made up 28.8% of all isolates. From the urinary tract, the most commonly isolated organisms were gram-negative bacilli, including *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *E. cloacae*, *Citrobacter freundii*, *Klebsiella oxytoca*, and *Proteus mirabilis*, which made up 75.1% of isolates. Gram-positive cocci obtained from the urinary tract most commonly included *Enterococcus* spp. and *S. aureus*, which made up 17.2% of isolates.

Characteristics of MRSA. Of the 197 MRSA isolates (22.3% of all *S. aureus* isolates) isolated from ICUs, 179 (90.9%) were HA-MRSA isolates, while 18 (9.1%) were CA-MRSA isolates. Seventeen of 18 (94.4%) CA-MRSA isolates were positive for Panton-Valentine leukocidin using PCR. Eleven of 18 (61.1%) CA-MRSA isolates belonged to the Canadian MRSA epidemic 10 (CMRSA-10) (USA300) genotype, while the CMRSA-7 (USA400/MW2) genotype occurred in 38.9% (7/18) of CA-MRSA isolates. A thorough analysis of MRSA isolates, including HA-MRSA isolates from the CAN-ICU study, is available from reference 34.

Characteristics of ESBL-producing *E. coli*. ESBL-producing *E. coli* and *K. pneumoniae* occurred in 3.5% (19 of 536) and 1.8% (4 of 224) of isolates, respectively. The most common genotype of the ESBL-producing *E. coli* was CTX-M-15 at 73.7% (14/19), followed by CTX-M-2 at 10.5% (2/19), and CTX-M-1, CTX-M-9, and CTX-M-14 each at 5.3% (1/19 each). A thorough analysis of ESBL-producing *E. coli* isolates from the CAN-ICU study is available from reference 34.

Characteristics of VRE. Of the 17 VRE isolates, 76.5% (13/17) were *Enterococcus faecium*, while 23.5% (4/17) were *Enterococcus faecalis*. The most common genotype was *vanA* (88.2% [15/17]). A thorough analysis of VRE isolates from the CAN-ICU study is available from reference 34.

Antimicrobial susceptibility. The antimicrobials tested and percentages of isolates determined to be intermediate and resistant are listed in Table 3 (gram-positive cocci) and Table 4 (gram-negative bacilli). For MRSA, no resistance to daptomycin, linezolid, tigecycline, and vancomycin was observed. Resistance rates for MRSA were as follows: clarithromycin, 89.9%; clindamycin, 76.1%; fluoroquinolones, 90.1 to 91.8%; and SXT, 11.7% (Table 3). For methicillin-resistant *S. epidermidis* (MRSE), no resistance to daptomycin, linezolid, and vancomycin was observed. No FDA breakpoints are available for tigecycline and MRSE, but when MRSA breakpoints were applied, MRSE resistance to tigecycline was 0%. Resistance rates for MRSE were

TABLE 3. Resistance rates for the most common gram-positive cocci isolated from Canadian ICUs

Organism[a] and specimen source	% of isolates intermediate/% of isolates resistant to the following antimicrobial[b]:														
	CFZ	CPM	CTR	CLR	CD	LZD	TGC	CIP	LEV	MXF	MER	PTZ	SXT	DAP	VAN
S. aureus															
MSSA															
All	0/0	0/0	0.4/0	0.3/20.1	0/4.4	0/0	0/0	1.3/7.9	0.2/7.3	0.9/6.4	0/0	0/0	0/0.6	0/0	0/0
Blood	0/0	0/0	1.2/0	0/16.1	0/4.6	0/0	0/0	1.2/6.9	0/6.9	0/6.9	0/0	0/0	0/0	0/0	0/0
Urine	0/0	0/0	0/0	0/30.0	0/10.0	0/0	0/0	0/20.0	0/20.0	5.0/15.0	0/0	0/0	0/0	0/0	0/0
Wound	0/0	0/0	0/0	0.9/23.9	0/3.5	0/0	0/0	1.8/8.0	0/7.1	0/7.1	0/0	0/0	0/1.8	0/0	0/0
Respiratory	0/0	0/0	0.4/0	0.2/19.5	0/4.3	0/0	0/0	1.3/7.5	0.2/6.9	1.1/5.8	0/0	0/0	0/0.4	0/0	0/0
MRSA															
All	0/100[c]	0/100[c]	0/100[c]	0/89.9	0/76.1	0/0	0/0	0/91.8	0/91.8	1.0/90.1	0/100[c]	0/100[c]	0/11.7	0/0	0/0
Blood	0/100[c]	0/100[c]	0/100[c]	0/93.9	0/79.6	0/0	0/0	0/91.8	0/91.8	2.0/89.8	0/100[c]	0/100[c]	0/4.1	0/0	0/0
Urine	0/100[c]	0/100[c]	0/100[c]	0/100	0/100	0/0	0/0	0/100	0/100	0/100	0/100[c]	0/100[c]	0/0	0/0	0/0
Wound	0/100[c]	0/100[c]	0/100[c]	0/96.3	0/81.5	0/0	0/0	0/92.6	0/92.6	3.7/88.9	0/100[c]	0/100[c]	0/14.8	0/0	0/0
Respiratory	0/100[c]	0/100[c]	0/100[c]	0/86.4	0/72.9	0/0	0/0	0/91.5	0/91.5	0/91.5	0/100[c]	0/100[c]	0/14.4	0/0	0/0
S. epidermidis															
MSSE															
All	2.3/0	2.3/16.3	23.3/8.1	1.2/77.4	0/54.8	0/0	–	3.5/54.7	4.7/52.3	8.3/41.7	9.3/9.3	0/1.2	0/35.7	0/0	0/0
Blood	0/0	1.8/8.9	17.9/1.8	1.8/74.6	0/43.6	0/0	–	5.4/44.6	5.4/42.9	7.3/34.6	8.9/1.8	0/0	0/34.6	0/0	0/0
Urine	0/0	20.0/20.0	60.0/0	0/100	0/100	0/0	–	0/80.0	0/80.0	0/80.0	40.0/0	0/0	0/20.0	0/0	0/0
Wound	8.3/0	0/33.3	29.2/25.0	0/79.2	0/70.8	0/0	–	0/70.8	4.2/66.7	12.5/50.0	4.2/29.2	0/4.2	0/41.7	0/0	0/0
Respiratory	0/0	0/0	0/0	ND	ND	ND	–	0/100	0/100	ND	0/0	0/0	ND	ND	0/0
MRSE															
All	0/100[c]	0/100[c]	0/100[c]	0/96.0	0/92.0	0/0	–	0/100	0/100	4.0/96.0	0/100[c]	0/100[c]	0/88.0	0/0	0/0
Blood	0/100[c]	0/100[c]	0/100[c]	0/100	0/100	0/0	–	0/100	0/100	16.7/83.3	0/100[c]	0/100[c]	0/83.3	0/0	0/0
Urine	0/100[c]	0/100[c]	0/100[c]	0/100	0/100	0/0	–	0/100	0/100	0/100	0/100[c]	0/100[c]	0/100	0/0	0/0
Wound	0/100[c]	0/100[c]	0/100[c]	0/94.1	0/88.2	0/0	–	0/100	0/100	0/100	0/100[c]	0/100[c]	0/88.2	0/0	0/0
Respiratory	NA	NA	NA	NA	NA	NA	–	NA	NA	NA	NA	NA	NA	NA	NA
S. pneumoniae															
All	–	0/0	0/0	3.4/15.9	0.4/5.6	0/0	–	0/2.1	0/1.7	0.4/1.3	4.3/0.4	–	7.3/8.6	–	0/0
Blood	–	0/0	0/0	0/13.2	0/2.6	0/0	–	0/0	0/0	0/0	8.1/0	–	5.3/10.5	–	0/0
Urine	–	NA	NA	NA	NA	NA	–	NA	NA	NA	NA	–	NA	–	NA
Wound	–	0/0	0/0	0/16.7	0/0	0/0	–	0/0	0/0	0/0	0/0	–	0/16.7	–	0/0
Respiratory	–	0/0	0/0	4.2/16.4	0.5/6.4	0/0	–	0/2.6	0/2.1	0.5/1.6	3.7/0.5	–	7.9/7.9	–	0/0
Enterococcus spp.															
All	–	–	–	16.8/65.9	–	11.1/1.8	0.4/0	8.0/53.4	1.2/51.0	–	–	–/21.1	–	0/0	0/6.8
Blood	–	–	–	18.6/68.6	–	17.1/2.9	0/0	9.5/58.1	0/56.8	–	–	–/27.0	–	0/0	0/5.4
Urine	–	–	–	11.9/70.1	–	3.0/1.5	0/0	4.0/54.7	2.7/52.0	–	–	–/17.3	–	0/0	0/4.0
Wound	–	–	–	20.6/60.3	–	14.3/1.6	1.4/0	11.1/50.0	1.4/45.8	–	–	–/22.2	–	0/0	0/12.5
Respiratory	–	–	–	15.4/61.5	–	7.7/0	0/0	6.7/46.7	0/46.7	–	–	–/13.3	–	0/0	0/3.3

[a] MSSE, methicillin-sensitive *S. epidermidis*; MRSE, methicillin-resistant *S. epidermidis*.
[b] Antimicrobial abbreviations: CFZ, cefazolin; CPM, cefepime; CTR, ceftriaxone; CLR, clarithromycin; CD, clindamycin; LZD, linezolid; TGC, tigecycline; CIP, ciprofloxacin; LEV, levofloxacin; MXF, moxifloxacin; MER, meropenem; PTZ-piperacillin-tazobactam; SXT, trimethoprim-sulfamethoxazole; DAP, daptomycin; VAN, vancomycin. CLSI breakpoints for *Enterococcus* spp. and ampicillin (sensitive [S], ≤8μg/ml; resistant [R], ≥16 μg/ml) were applied to piperacillin-tazobactam, and erythromycin breakpoints (S, ≤0.5 μg/ml; intermediate, 1 to 4 μg/ml; R, ≥ 6 μg/ml) were applied to clarithromycin. ND, no MIC data available; NA, no isolates within criteria; –, no defined breakpoints.
[c] Based on oxacillin susceptibility.

as follows: clarithromycin, 96.0%; clindamycin, 92.0%; fluoroquinolones, 96.0 to 100%; and SXT, 88.0% (Table 3). For *Enterococcus* spp., no resistance was observed to daptomycin and tigecycline (using *E. faecalis* breakpoints). Resistance rates for *Enterococcus* spp. were as follows: clarithromycin, 65.9%; fluoroquinolones, 51.0 to 53.4%; piperacillin-tazobactam, 21.1%; vancomycin, 6.8%; and linezolid, 1.8% (Table 3).

For *E. coli*, no resistance to amikacin, meropenem, and tigecycline was observed (Table 4). Resistance rates for *E. coli* were as follows: cefazolin, 20.1%; cefepime, 0.7%; ceftriaxone, 3.7%; gentamicin, 3.0%; fluoroquinolones, 21.1%; piperacillin-tazobactam, 1.9%; and SXT, 24.8% (Table 4). Resistance rates for *P. aeruginosa* were as follows: amikacin, 2.6%; cefepime, 10.2%; gentamicin, 15.2%; fluoroquinolones, 23.8 to 25.5%; meropenem, 13.6%; and piperacillin-tazobactam, 9.3% (Table 4). With *K. pneumoniae*, no resistance was observed to amikacin, cefepime, gentamicin, and meropenem (Table 4). Resistance rates for *K. pneumoniae* were as follows: cefazolin, 6.2%; ceftriaxone, 0.4%; fluoroquinolones, 3.6 to 4.0%; piperacillin-tazobactam, 1.3%; tigecycline, 0.4%; and SXT, 8.9%.

MDR. Multidrug resistance (MDR) was assessed only in gram-negative organisms, as no accepted definition exists for gram-positive organisms (Table 5). MDR for gram-negative organisms was defined as resistance to three or more of the following: cefepime, piperacillin-tazobactam, meropenem, amikacin or gentamicin, and ciprofloxacin (adapted from reference 18). The MDR phenotype was most common in *P. aeruginosa* at 12.6%. A MDR phenotype occurred in 0.2% of *E. coli* and 0.6% of *E. cloacae* (Table 5). No MDR phenotype was obtained with *K. pneumoniae* or *H. influenzae*.

DISCUSSION

The CAN-ICU study was the first national, prospective surveillance study assessing antimicrobial resistance in patients in

TABLE 4. Resistance rates for the most common gram-negative bacilli isolated from Canadian ICUs

Organism and specimen source	% of isolates intermediate/% of isolates resistant to the following antimicrobial[a]:										
	CFZ	CPM	CTR	AMK	GEN	CIP	LEV	MER	PTZ	TGC	SXT
E. coli											
All	8.4/20.1	0.9/0.7	4.8/3.7	0.2/0	4.7/3.0	0.6/21.1	0/21.1	0/0	0.9/1.9	0/0	0/24.8
Blood	2.7/21.9	2.7/1.4	1.4/5.5	0/0	2.7/6.9	0.0/23.3	0/23.3	0/0	1.4/6.9	0/0	0/35.6
Urine	11.3/25.8	0.7/0.4	8.5/4.2	0/0	5.7/1.1	0.4/19.8	0/19.8	0/0	0.7/1.1	0/0	0/23.3
Wound	10.3/8.6	0/1.7	1.7/1.7	0/0	3.5/6.9	0/24.1	0/24.1	0/0	3.5/0	0/0	0/27.6
Respiratory	4.1/11.5	0.8/0.8	0/2.5	0.8/0	4.1/3.3	1.6/21.3	0/21.3	0/0	0/1.6	0/0	0/20.5
P. aeruginosa											
All	–	11.0/10.2	44.1/30.0	1.2/2.6	17.1/15.2	5.7/23.8	6.4/25.5	5.2/13.6	0/9.3	–	0/95.2
Blood	–	9.1/9.1	33.3/51.5	3.0/0	12.1/9.1	0/24.2	12.1/24.2	9.1/9.1	0/6.1	–	0/100
Urine	–	11.1/17.8	46.7/33.3	0/6.7	15.6/22.2	4.4/37.8	2.2/40.0	8.9/17.8	0/13.3	–	0/95.6
Wound	–	9.4/18.9	49.1/30.2	1.9/1.9	20.8/18.9	11.3/28.3	1.9/35.9	1.9/18.9	0/18.9	–	0/98.1
Respiratory	–	11.4/7.6	43.9/27.0	1.0/2.4	17.3/14.2	5.5/20.8	7.3/21.5	4.8/12.5	0/7.3	–	0/94.1
K. pneumoniae											
All	0.4/6.2	0/0	1.8/0.4	0.4/0	1.3/0	0.9/4.0	0.9/3.6	0/0	1.3/1.3	4.4/0.4	0/8.9
Blood	0/7.7	0/0	7.7/0	0/0	3.9/0	3.9/3.9	3.9/3.9	0/0	0/0	3.9/0	0/7.7
Urine	0/7.8	0/0	2.0/0	0/0	0/0	2.0/0	0/0	0/0	2.0/0	2.0/0	0/13.7
Wound	0/7.7	0/0	3.9/3.9	3.9/0	7.7/0	0/11.5	0/11.5	0/0	3.9/0	11.5/3.9	0/11.5
Respiratory	0.8/4.9	0/0	0/0	0/0	0/0	0/4.1	0.8/3.3	0/0	0.8/2.5	4.1/0	0/6.6
E. cloacae											
All	4.2/89.7	0/1.2	7.9/13.9	0/0	0/3.0	1.8/1.8	0/1.8	0/0	10.3/4.9	0.6/0.6	0/8.3
Blood	4.2/83.3	0/8.3	8.3/29.2	0/0	0/8.3	0/4.2	0/4.2	0/0	16.7/4.2	0/0	0/0
Urine	0/100	0/0	12.5/25.0	0/0	0/6.3	0/6.3	0/6.3	0/0	18.8/12.5	6.3/6.3	0/0
Wound	5.9/94.1	0/0	23.5/5.9	0/0	0/0	0/5.9	0/5.9	0/0	11.8/0	0/0	0/0
Respiratory	4.6/88.9	0/0	4.6/10.2	0/0	0/1.9	2.8/0	0/0	0/0	7.4/4.6	0/0	0/12.0
H. influenzae											
All	–	0/0	0/0.3	–	–	0/0	0/0	0/0	0/0.3	–	0/12.0
Blood	–	0/0	0/0	–	–	0/0	0/0	0/0	0/0	–	0/0
Urine	–	NA	NA	–	–	NA	NA	NA	NA	–	NA
Wound	–	0/0	0/0	–	–	0/0	0/0	0/0	0/0	–	0/0
Respiratory	–	0/0	0/0.3	–	–	0/0	0/0	0/0	0/0.3	–	0/12.5

[a] Antimicrobial abbreviations: CFZ, cefazolin; CPM, cefepime; CTR, ceftriaxone; AMK, amikacin; GEN, gentamicin; CIP, ciprofloxacin; LEV, levofloxacin; MER, meropenem; PTZ, piperacillin-tazobactam; TGC, tigecycline; SXT, trimethoprim-sulfamethoxazole. NA, no isolates within criteria; –, indicates no defined breakpoints.

ICUs in Canada. This national surveillance study involving 19 medical centers in major population centers in 9 of the 10 provinces in Canada found that more than half of all isolates recovered from clinical specimens in the ICUs were respiratory in origin (Table 2). This was the case in all ICUs across Canada, irrespective of patient age and gender. The remaining half of all specimens from ICUs were from blood specimens, wound/tissue specimens, and urine specimens. The observation that more than half of all infections in the ICU are respiratory in origin, followed by blood, wound/tissue and urinary tract infections has previously been documented (10, 32). Klevens et al. reported that of the deaths associated with health care-associated infections in U.S. hospitals (National Nosocomial Infections Surveillance [NNIS] in 2002), approximately 36.3% were respiratory infections, 31.0% were bloodstream infections, 13.2% were urinary tract infections, and 8.3% were surgical site (wound) infections (15). We report that the 10 most common isolates recovered from 80% of all clinical specimens in the ICU were MSSA, *E. coli*, *P. aeruginosa*, *H. influenzae*, coagulase-negative staphylococci/*S. epidermidis*, *Enterococcus* spp., *S. pneumoniae*, *K. pneumoniae*, MRSA, and *E. cloacae* (Table 1). This observation that gram-positive cocci, including MSSA, *Enterococcus* spp., *S. pneumoniae*, and MRSA, are the most common gram-positive isolates recovered from clinical specimens in ICUs has been previously documented (12). The recent finding by Lockhart et al. (18) that of the gram-negative bacilli reported to cause infections in ICUs in the United States from 1993 to 2004, *P. aeruginosa* (22.2%), *E. coli* (18.8%), *K. pneumoniae* (14.2%), and *E. cloacae* (9.1%) were the most common organisms isolated is consistent with our findings.

TABLE 5. Multidrug-resistant phenotypes in Canadian ICUs[a]

Organism	No. of MDR isolates/ total no. of isolates	% of MDR isolates
E. coli	1/536	0.2
P. aeruginosa	53/420	12.6
K. pneumoniae	0/225	0
E. cloacae	1/165	0.6
H. influenzae	0/329	0

[a] Multidrug resistance for gram-negative bacilli was defined as resistance to three or more of the following antimicrobials: cefepime, piperacillin-tazobactam, meropenem, amikacin or gentamicin, and ciprofloxacin.

The CAN-ICU study documented that MSSA and MRSA are important isolates recovered from clinical specimens, including respiratory tract specimens, bacteremia, and wound/

tissue specimens in all ICUs in Canada. MRSA made up 22.3% of all staphylococci, and surprisingly, 9.1% of all MRSA in the ICU were CA-MRSA. This has not been previously documented in Canada and shows the rapid evolution of CA-MRSA in ICUs across Canada. All 18 of the CA-MRSA were made up of either USA400/MW2 (CMRSA-7) or USA300 (CMRSA-10) genotypes. These two genotypes are the two primary genotypes that have been reported across North America (4, 6, 13, 22). The CAN-ICU study also showed that VRE made up 6.7% of all enterococci, with the *vanA* genotype (mostly *E. faecium*) making up 88.2% of all VRE. Previous data have suggested that *E. faecium* with the *vanA* genotype is the predominant genotype in North America (8, 33). This relatively low level of VRE across Canada has been documented previously and shows the lack of spread of VRE across the country (33). The low level of VRE in Canadian ICUs may reflect the ubiquitous active surveillance programs in Canadian hospitals that have been reported to prevent VRE colonization and bacteremia (14, 29).

This study is the first to document that ESBL-producing *E. coli* bacteria are becoming more common than ESBL-producing *Klebsiella* spp. in Canadian ICUs. ESBL-producing *E. coli* isolates made up 3.5% of all *E. coli* isolates, whereas ESBL-producing *K. pneumoniae* represented 1.8% of all *Klebsiella* species. All 19 of the ESBL-producing *E. coli* isolates displayed a MDR phenotype, with 84.2% demonstrating concomitant resistance to fluoroquinolones and 63.2% demonstrating resistance to SXT. This study has shown that $bla_{\text{CTX-M-15}}$ was the predominant genotype (73.7%) of ESBL-producing *E. coli* in Canada. Other studies assessing ESBL-producing *E. coli* have shown that the CTX-M genotype is spreading rapidly in both community and hospital settings (3, 17, 19, 20, 24, 25). Pitout et al. investigated the molecular epidemiology of ESBL-producing *E. coli* isolates collected from 2000 to 2005, inclusive, in the Calgary Health Region in Canada (25). These investigators reported that 64% (354 of 552) of ESBL-producing *E. coli* isolates were positive for $bla_{\text{CTX-M}}$ genes by PCR, with CTX-M-14 (59.6%) and CTX-M-15 (36.2%) reported most commonly. This study highlights the rapid spread of MDR ESBL-producing CTX-M-15 *E. coli* in Canadian ICUs. This genotype may be spreading rapidly due to the extensive use of expanded-spectrum cephalosporins and fluoroquinolones.

This study, along with previous studies, highlights that antimicrobial resistance is high in patients in ICUs and based on other studies is higher in patients in the ICU than in patients in other regions of the hospital, such as medical/surgical wards, emergency rooms, and outpatient clinics (1, 10, 16, 18, 26). Resistance rates for MRSA were very high with fluoroquinolones, macrolides (such as clarithromycin), as well as clindamycin (range, 76.1% to 91.8%), and lower with SXT (11.7%). These resistance rates are consistent with previous reports (22). Thus, SXT still represents a reasonable empirical treatment for mild to moderate infections (e.g., skin and soft tissue infections) caused by CA-MRSA or HA-MRSA. All MRSA isolates were susceptible to vancomycin, linezolid, tigecycline, and daptomycin. Likewise, all MRSE isolates were susceptible to vancomycin, linezolid, tigecycline, and daptomycin, while no *Enterococcus* spp. proved to be resistant to tigecycline and daptomycin. As in previous studies, we document the lowest rates of resistance for gram-negative bacilli with cefepime, meropenem, and piperacillin-tazobactam (18, 26). Although only limited comparative data are available, we also report low resistance rates in gram-negative bacilli from ICUs with amikacin (18). This likely reflects the declining usage of aminoglycosides in favor of increasing fluoroquinolone usage. Fluoroquinolone resistance, on the other hand, was high in *E. coli* (21.1%) and *P. aeruginosa* (23.8 to 25.5%), which is consistent with other reports (18, 26), and reflects extensive fluoroquinolone usage (16). Lockhart et al. (18) documented increasing prevalence of MDR gram-negative bacilli in U.S. ICUs. Although our definition of multidrug resistance for gram-negative bacilli (resistance to three or more of the following: cefepime, piperacillin-tazobactam, meropenem, amikacin or gentamicin, and ciprofloxacin), was slightly more restrictive, our MDR resistance rates of 12.6% with *P. aeruginosa* were somewhat higher than Lockhart et al. (18) at 9.3%. In contrast, MDR rates in Canadian ICUs of 0.2% with *E. coli*, 0.6% with *E. cloacae*, and 0% with *K. pneumoniae* are lower than those in U.S. ICUs at 2.0%, 5.9%, and 13.3%, respectively. Why MDR rates are higher in Canada with *P. aeruginosa* and lower with members of the family *Enterobacteriaceae* (*E. coli*, *E. cloacae*, and *K. pneumoniae*) is unclear but may be due to the lower prevalence of ESBL-producing *Enterobacteriaceae* in Canada (34). MDR ESBL-producing *E. coli* isolates were all susceptible to the carbapenems, ertapenem and meropenem, as well as tigecycline. As nosocomial infections in the ICU are frequently MDR (a characteristic often associated with prior antimicrobial use) (16), some have suggested that involvement of an infectious diseases specialist may help to improve cure and minimize further resistance development (10).

Our study has several limitations including the fact that we cannot be certain that all clinical specimens represented active infection. In the CAN-ICU study, we asked centers to obtain "clinically significant" specimens from patients with a presumed infectious disease. Although all of the isolates may not represent actual infection from patients, we believe that most do because we excluded all surveillance swabs, duplicate swabs, and eye, ear, nose, and throat swabs and genital cultures. In addition, we do not have admission date data for each patient/clinical specimen, so we were not able to provide a more accurate description of community versus nosocomial onset. In this study, CA-MRSA and HA-MRSA were defined genotypically and not epidemiologically. Any MRSA with a CMRSA-7 (USA400/MW2) or CMRSA-10 (USA300) genotype was labeled as CA-MRSA, while all other genotypes (e.g., CMRSA-1 [USA600], CMRSA-2 [USA100], and CMRSA-4 [USA200]) were labeled as HA-MRSA. It is known epidemiologically that CA-MRSA genotypes can be associated with HA infections and that HA-MRSA can be associated with CA infections (6). In this study, we screened all *E. coli* and *K. pneumoniae* isolates for potential ESBL production using only ceftriaxone, which although consistent with CLSI guidelines, may have missed some SHV-producing *K. pneumoniae* strains by not also testing ceftazidime. Whether this accounted for the reduced number of ESBL-producing *K. pneumoniae* bacteria versus ESBL-producing *E. coli* bacteria is unclear.

In conclusion, *S. aureus* (MSSA and MRSA), *E. coli*, *P. aeruginosa*, *H. influenzae*, *Enterococcus* spp., *S. pneumoniae*, and *K. pneumoniae* are the most common isolates recovered from clinical specimens in Canadian ICUs. Respiratory tract

specimens represent over 50% of all the specimens collected in the ICU. A MDR phenotype is common with *P. aeruginosa* in Canadian ICUs.

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CAN-ICU data are also displayed at www.can-r.ca.

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