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Antimicrobial Susceptibility of Bacterial Pathogens Isolated from Canadian Intensive Care Units from 2007 to 2016: Results of the CANWARD Study

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Introduction

Subsequent to antimicrobial resistance data published from the Canadian National Intensive Care Unit (CAN-ICU) study (2005-2006) on 4,180 bacterial isolates from ICU patients (1), there has been little national surveillance data concerning antimicrobial susceptibility rates in Canadian ICUs. Antibiotic utilization and over-utilization, both in hospitals and the community, are important influences on the development of antibiotic-resistant pathogens such as MRSA, extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella* species, carbapenem-resistant *Enterobacteriaceae*, and multidrug-resistant *Pseudomonas aeruginosa* (1,2). It is estimated that 30-50% of antibiotic use in hospitals is unjustified (3). Each year in the United States, more than 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of resistant infections (4). Infections caused by antibiotic-resistant organisms are associated with longer hospital stays, costly or prolonged treatments, and increased morbidity and mortality when compared to antibiotic-susceptible infections (5). It is estimated that 70% of ICU patients are on antibiotics at any one time (6).

The purpose of this prospective surveillance study was to evaluate the prevalence of infectious organisms, including resistant pathogens, and antimicrobial resistance patterns in Canadian ICUs from 2007 to 2016.

Materials and Methods

Bacterial Isolates: A total of 42,938 bacterial isolates (isolated from blood, urine, wound, and respiratory specimens) were submitted by tertiary-care medical centres from January 2007 to December 2016, inclusive, as part of the ongoing CANWARD national surveillance study. The medical centres were asked to submit clinical isolates (consecutive, one per patient, per infection site) that were clinically significant. Isolates were shipped to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) where they were subcultured onto appropriate media and stocked in skim milk at -80˚ C. Of the isolates submitted, 8,130 (18.9%) were from patients admitted to an intensive care unit.

Antimicrobial Susceptibility Testing: Following 2 subcultures from frozen stock, *in vitro* antimicrobial susceptibility testing was performed using the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (7). Minimum inhibitory concentrations (MICs) were determined using custom, in-house prepared 96-well broth microdilution panels. Quality control was performed using CLSI recommended ATCC organisms. MIC interpretive criteria were defined according to CLSI breakpoints unless otherwise noted (8). Multidrug and extensive drug resistance (MDR, XDR) were defined as resistance to ≥3 or ≥5 antimicrobial agents, respectively.

Isolate Characterization: Potential MRSA isolates were confirmed by *mec*A PCR and further characterized by staphylococcal protein A (*spa*) typing to identify community-associated (CA-MRSA) and healthcare-associated (HA-MRSA) strains as previously described (9). Potential ESBL-producing isolates were confirmed by the CLSI confirmatory disc test. Potential vancomycin-resistant *Enterococcus* (VRE) isolates were confirmed by *van*/*van*B PCR, as previously described (10). *Streptococcus pneumoniae* isolates were serotyped using commercial antisera. All statistical analysis was performed using the Cochran-Armitage test of trend.

Results

Table 1. Antimicrobial susceptibility testing results of Gram-negative and Gram-positive pathogens collected from Canadian ICUs

Organism (n) / Antimicrobial	%S	%I	%R	MIC (μg/ml) MIC50	MIC90	Min	Max
***P. aeruginosa* (862)**							
Amikacin	96.1	1.7	2.2	4	16	≤ 1	> 64
Aztreonam	69.1	12.1	18.8	8	32	≤ 0.12	> 64
Cefepime	79.1	15.0	5.9	4	16	≤ 0.25	> 64
Ceftazidime	75.3	7.9	16.8	4	32	≤ 0.25	> 32
Ceftobiprole		NB		4	16	0.5	128
C/T	97.5	1.3	1.3	0.5	2	≤ 0.12	> 64
Ciprofloxacin	76.0	8.0	16.0	0.25	4	≤ 0.06	> 16
Colistin	94.7	-	5.3	1	2	≤ 0.06	> 16
Gentamicin	83.9	6.7	9.4	2	8	≤ 0.5	> 32
Imipenem	62.9	8.7	28.5	2	32	≤ 0.03	> 32
Meropenem	73.7	8.0	18.3	1	16	≤ 0.03	> 64
Tobramycin	93.3	0.7	6.0	≤ 0.5	2	≤ 0.5	> 64
TZP	75.8	14.4	9.9	8	64	≤ 1	512

Organism (n) / Antimicrobial	%S	%I	%R	MIC (μg/ml) MIC50	MIC90	Min	Max
***E. coli* (848)**							
Amikacin	99.2	0.8	-	≤ 2	4	≤ 2	32
AMC	75.4	15.4	9.2	8	16	0.5	> 32
Cefazolin (IV)	60.5	12.2	27.3	2	> 128	≤ 0.5	> 128
Cefoxitin	88.3	5.4	6.3	4	16	≤ 0.06	> 32
Ceftazidime	87.9	1.7	10.3	≤ 0.5	16	≤ 0.25	> 32
Ceftriaxone	85.4	0.7	13.9	≤ 0.25	32	≤ 0.25	> 256
Ciprofloxacin	72.0	0.4	27.7	≤ 0.06	> 16	≤ 0.06	> 16
Colistin [a]	99.7	-	0.3	0.25	0.5	≤ 0.06	8
Ertapenem	99.0	0.4	0.7	≤ 0.03	0.06	≤ 0.03	> 32
Gentamicin	87.5	0.7	11.8	≤ 0.5	32	≤ 0.5	> 32
Meropenem	99.9	-	0.1	≤ 0.03	0.12	≤ 0.03	32
Moxifloxacin		NB		≤ 0.06	> 16	≤ 0.06	> 16
TZP	94.2	1.9	3.9	2	8	≤ 1	> 512
Tigecycline [b]	100	-	-	0.25	0.5	0.12	2
SXT	70.5	-	29.5	≤ 0.12	> 8	≤ 0.12	> 8

Organism (n) / Antimicrobial	%S	%I	%R	MIC (μg/ml) MIC50	MIC90	Min	Max
***K. pneumoniae* (522)**							
Amikacin	99.8	-	0.2	≤ 1	2	≤ 1	> 64
AMC	91.8	4.5	3.7	2	8	0.5	> 32
Cefazolin	80.4	6.0	13.6	1	16	≤ 0.5	> 128
Cefoxitin	89.3	3.9	6.8	4	16	0.5	> 32
Ceftazidime	94.1	0.7	5.2	≤ 0.25	1	≤ 0.25	> 32
Ceftriaxone	93.7	-	6.3	≤ 0.25	1	≤ 0.25	> 64
Ciprofloxacin	93.7	1.9	4.4	≤ 0.06	0.5	≤ 0.06	> 16
Colistin [a]	97.7	-	2.3	0.5	1	≤ 0.06	> 16
Ertapenem	99.0	0.6	0.4	≤ 0.03	0.06	≤ 0.03	> 32
Gentamicin	96.7	-	3.3	≤ 0.5	≤ 0.5	≤ 0.5	> 32
Meropenem	99.6	0.2	0.2	≤ 0.03	0.06	≤ 0.03	16
Moxifloxacin		NB		0.12	1	≤ 0.06	16
TZP	95.0	2.1	2.9	2	8	≤ 1	> 512
Tigecycline [b]	93.7	5.0	1.3	1	2	0.25	8
SXT	92.7	-	7.3	≤ 0.12	1	≤ 0.12	> 8

Organism (n) / Antimicrobial	%S	%I	%R	MIC (μg/ml) MIC50	MIC90	Min	Max
***H. influenzae* (425)**							
AMC	99.5	-	0.5	0.5	2	≤ 0.06	8
Ampicillin	79.4	0.5	20.2	≤ 0.25	16	≤ 0.25	> 128
Cefepime	100	-	-	≤ 0.25	≤ 0.25	≤ 0.25	2
Ceftriaxone	100	-	-	≤ 0.06	≤ 0.06	≤ 0.06	1
Cefuroxime	97.2	2.3	0.5	1	2	≤ 0.25	> 16
Ciprofloxacin	100	-	-	≤ 0.015	≤ 0.015	≤ 0.015	0.03
Clarithromycin	89.7	9.3	1.0	4	16	≤ 0.03	32
Doxycycline		NB		0.5	1	≤ 0.25	4
Ertapenem	99.5	-	0.5	≤ 0.03	0.12	≤ 0.03	> 4
Gentamicin		NB		1	2	≤ 0.5	2
Meropenem	99.7	-	0.3	≤ 0.06	0.12	≤ 0.06	2
Moxifloxacin	100	-	-	≤ 0.015	0.03	≤ 0.015	0.25
TZP	100	-	-	≤ 1	≤ 1	≤ 1	≤ 1
SXT	82.6	4.0	13.4	≤ 0.12	4	≤ 0.12	> 8

Organism (n) / Antimicrobial	%S	%I	%R	MIC (μg/ml) MIC50	MIC90	Min	Max
MSSA (1385)							
Cefazolin		NB		≤ 0.5	1	≤ 0.5	8
Ceftobiprole [a]	100	-	-	0.5	≤ 1	0.06	2
Ciprofloxacin	90.0	2.2	7.8	0.5	1	≤ 0.06	> 16
Clarithromycin	78.9	0.6	20.6	0.25	> 32	≤ 0.03	> 32
Clindamycin	95.3	-	4.7	≤ 0.12	0.25	≤ 0.12	> 8
Daptomycin	100	-	-	0.25	0.25	≤ 0.06	1
Gentamicin	99.1	0.1	0.8	≤ 0.5	≤ 0.5	≤ 0.5	> 32
Linezolid	100	-	-	2	4	≤ 0.12	4
Moxifloxacin	93.0	0.4	6.6	≤ 0.06	0.12	≤ 0.06	> 16
Tigecycline [b]	99.9	-	0.1	0.12	0.25	≤ 0.03	1
SXT	99.7	-	0.3	≤ 0.12	≤ 0.12	≤ 0.12	> 8
Vancomycin	100	-	-	1	1	≤ 0.12	2

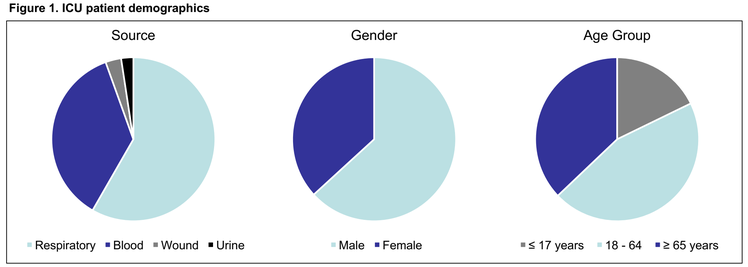
Organism (n) / Antimicrobial	%S	%I	%R	MIC (μg/ml) MIC50	MIC90	Min	Max
MRSA (361)							
Cefazolin		NB		64	> 128	≤ 0.5	> 128
Ceftobiprole [a]	100	-	-	1	2	0.5	2
Ciprofloxacin	18.3	0.6	81.2	> 16	> 16	0.25	> 16
Clarithromycin	16.7	0.3	83.1	> 32	> 32	≤ 0.03	> 32
Clindamycin	51.4	-	48.6	≤ 0.25	> 8	≤ 0.12	> 8
Daptomycin	99.7	-	0.3	0.25	0.5	0.06	2
Gentamicin	88.1	-	11.9	≤ 0.5	> 32	≤ 0.5	> 32
Linezolid	100	-	-	2	4	≤ 0.12	4
Moxifloxacin	19.1	3.1	77.8	8	> 16	≤ 0.06	> 16
Tigecycline [b]	99.7	-	0.3	0.25	0.5	0.12	1
SXT	89.8	-	10.3	≤ 0.12	8	≤ 0.12	> 8
Vancomycin	100	-	-	1	1	≤ 0.25	2

Organism (n) / Antimicrobial	%S	%I	%R	MIC (μg/ml) MIC50	MIC90	Min	Max
***S. pneumoniae* (527)**							
AMC	97.6	1.8	0.6	≤ 0.06	0.25	≤ 0.06	8
Ceftobiprole [a]	100	-	-	≤ 0.03	0.06	≤ 0.03	0.5
Ceftriaxone	99.4	0.4	0.2	0.12	0.12	≤ 0.06	4
Cefuroxime	91.7	3.2	5.1	≤ 0.25	0.5	≤ 0.25	> 16
Clarithromycin	82.1	3.4	14.6	≤ 0.03	2	≤ 0.03	> 32
Clindamycin	94.1	0.2	5.7	≤ 0.12	≤ 0.12	≤ 0.12	> 64
Doxycycline	87.4	1.2	11.4	≤ 0.25	1	≤ 0.25	> 16
Levofloxacin	99.6	0.2	0.2	1	1	≤ 0.06	8
Linezolid	100	-	-	1	1	≤ 0.12	2
Moxifloxacin	99.6	0.4	-	0.12	0.25	≤ 0.06	2
Penicillin	83.5	11.9	4.6	≤ 0.03	0.5	≤ 0.03	4
SXT	85.4	4.9	9.7	≤ 0.12	2	≤ 0.12	> 8

Organism (n) / Antimicrobial	%S	%I	%R	MIC (μg/ml) MIC50	MIC90	Min	Max
***E. faecalis* (198)**							
AMC		NB		0.5	1	0.12	32
Ceftobiprole		NB		0.5	1	≤ 0.06	> 32
Ciprofloxacin	60.7	8.7	30.6	1	> 16	0.25	> 16
Daptomycin	100	-	-	0.5	1	0.06	4
Levofloxacin	63.2	-	36.8	2	> 32	1	> 32
Linezolid	91.2	8.8	-	2	2	0.5	4
Meropenem		NB		4	8	1	> 32
TZP		NB		4	8	≤ 1	512
Tigecycline [b]	97.9	-	2.1	0.12	0.25	0.06	0.5
Vancomycin	100	-	-	1	2	0.5	4

[a], percent susceptibility interpreted using EUCAST breakpoints. [b], percent susceptibility interpreted using FDA breakpoints. MSSA: methicillin-susceptible *S. aureus*, MRSA: methicillin-resistant *S. aureus*, AMC: amoxicillin/clavulanate, C/T: ceftolozane/tazobactam, TZP: piperacillin/tazobactam, SXT: trimethoprim/sulfamethoxazole, NB: no breakpoints available.

Figure 1. ICU patient demographics



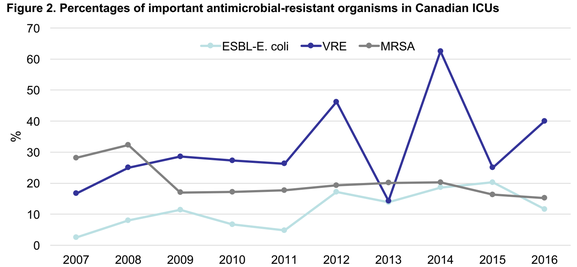
This study identified MDR/XDR in the following: 19.0/2.3% of *S. aureus*, 5.1/1.9% of *S. pneumoniae*, 15.0/2.0% of *P. aeruginosa*, 26.3/14.9% of *E. coli* and 8.6/5.4% of *K. pneumoniae*. The proportion of MDR/XDR *E. coli* increased significantly over the study period, from 13.4/3.2% in 2007 to 30.4/18.8% in 2016 (*P*<0.0001). MDR/XDR *K. pneumoniae* also increased significantly in prevalence, from 2.5/0% in 2007 to 13.6/12.8% in 2016 (*P*=0.022). The most common *S. pneumoniae* serotypes isolated from Canadian ICUs were 3 (9.1%) and 11A (8.0%), predominantly associated with respiratory infections.

Table 2. Top 20 most common organisms isolated from Canadian ICUs.

Rank	Organism	N	% Total
1	*Staphylococcus aureus*	1746	21.5
2	*Pseudomonas aeruginosa*	862	10.6
3	*Escherichia coli*	848	10.4
4	*Streptococcus pneumoniae*	527	6.5
5	*Klebsiella pneumoniae*	520	6.4
6	*Haemophilus influenzae*	425	5.2
7	*Enterobacter cloacae*	379	4.7
8	*Stenotrophomonas maltophilia*	238	2.9
9	*Serratia marcescens*	223	2.7
10	*Enterococcus faecalis*	198	2.4
11	*Klebsiella oxytoca*	182	2.2
12	*Candida albicans*	174	2.1
13	*Enterococcus faecium*	127	1.7
14	*Moraxella catarrhalis*	113	1.4
15	*Enterobacter aerogenes*	105	1.3
16	*Streptococcus agalactiae*	87	1.1
17	*Enterococcus*, unspeciated	73	0.9
18	*Proteus mirabilis*	71	0.9
19	*Acinetobacter baumannii*	68	0.8
20	*Streptococcus pyogenes*	57	0.7
	Total	7023	86.4
	Other [a]	1107	13.6

[a] Includes *Staphylococcus epidermidis* and coagulase-negative *staphylococci* (419, 5.2%).

Figure 2. Percentages of important antimicrobial-resistant organisms in Canadian ICUs



ESBL: extended-spectrum β-lactamase; VRE: vancomycin-resistant *Enterococcus faecium*; MRSA: methicillin-resistant *S. aureus*.

Figure 3. Prevalence of HA- and CA-MRSA in Canadian ICUs

MRSA: methicillin-resistant *S. aureus*; HA: healthcare-associated; CA: community-associated.

Conclusions

1. The most commonly isolated pathogens in Canadian ICUs were *S. aureus*, *P. aeruginosa*, *E. coli*, *S. pneumoniae*, and *K. pneumoniae*. ICU specimens were most commonly obtained from respiratory samples, males and patients aged 18-64.
2. Meropenem, ertapenem and piperacillin-tazobactam showed the greatest activity against *E. coli* and *K. pneumoniae* in this study. Against *P. aeruginosa*, susceptibility rates were greatest for ceftolozane/tazobactam, amikacin, colistin and tobramycin.
3. Ceftobiprole, vancomycin, linezolid, tigecycline, and daptomycin demonstrated >99% susceptibility against MRSA isolates tested.
4. This study identified MDR/XDR in the most common ICU pathogens, including 19.0/2.3% of *S. aureus*, 5.1/1.9% of *S. pneumoniae*, 15.0/2.0% of *P. aeruginosa*, 26.3/14.9% of *E. coli* and 8.6/5.4% of *K. pneumoniae*. The proportion of both MDR and XDR *E. coli* and *K. pneumoniae* increased significantly from 2007 to 2016 (*P*<0.0001 and *P*≤0.022, respectively).
5. Overall, 63.4% of MRSA were hospital-associated genotypes. Community-associated genotypes increased significantly in prevalence from 2007 to 2016 (*P*<0.001).
6. ESBL-producing *E. coli* now represent a significant proportion (2016: 11.5%) of *E. coli* isolated from the ICU. Though rates were somewhat variable, there was a statistically significant increase from 2007 to 2016 (*P*=0.008).

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