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Antimicrobial Susceptibility of Bacterial Pathogens Isolated from Canadian Intensive Care Units from 2007 to 2014: Results of the CANWARD Study

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UPDATED ABSTRACT

Objective: The purpose of this study was to assess the antimicrobial susceptibility patterns of bacterial pathogens isolated from Canadian ICUs from 2007 to 2014.

Methods: From 2007 to 2014 inclusive, tertiary care centres from across Canada submitted 36,607 bacterial isolates as part of the Canadian ward surveillance study (CANWARD). Of these, 6,978 (19.1%) were from patients on ICUs. Bacterial isolates were collected from blood, urine, wound, and respiratory specimens. Susceptibility testing was carried out using Clinical and Laboratory Standards Institute (CLSI) guidelines. Minimum inhibitory concentration interpretive criteria were defined by CLSI breakpoints.

Results: Of the 6,978 bacterial pathogens collected in this study, 57.1%, 37.1%, 3.2%, and 2.6% of isolates were from respiratory, blood, wound, and urine specimens, respectively. The top five organisms isolated from Canadian ICUs were: *Staphylococcus aureus* (21.0%), *Pseudomonas aeruginosa* (10.4%), *E. coli* (10.3%), *Streptococcus pneumoniae* (6.8%), and *Klebsiella pneumoniae* (6.3%). Susceptibility rates (SR) for MRSA were: 100% vancomycin (VAN), 100% televancin, 100% linezolid (LZD), 99.7% daptomycin (DAP), 99.7% tigecycline (TGC), and 49.5% clindamycin (CLD), respectively. SR for *E. coli* and *K. pneumoniae* were: 99.9% meropenem (MER), 98.8% ertapenem (ERT), 97.3% TGC, 94.8% piperacillin-tazobactam (PTZ), 91.2% gentamicin (GEN), 89.3% ceftriaxone, and 81.0% ciprofloxacin (CIP), respectively. SR for *P. aeruginosa* were: 95.4% amikacin, 94.4% colistin, 81.9% GEN, 76.9% ceftazidime, 75.9% PTZ, 74.9% CIP, and 74.1% MER, respectively. SR for *S. pneumoniae* were: 99.6% levofloxacin, 94.2% CLD, 87.4% doxycycline, 85.9% TMP-SMX, 83.3% penicillin, and 83.2% clarithromycin. Among the 1,453 *S. aureus* collected, 21.7% were MRSA, while 9.2% of 716 *E. coli* produced an ESBL, with the rate of ESBL-producing *E. coli* increasing from 2.5% in 2007 to 19.1% in 2014 ($P<0.001$).

Conclusions: MER, ERT, TGC, and PTZ were the most active agents against Gram-negative bacilli (susceptibility >94.8%). Against MRSA, SR of >99% were observed for VAN, LZD, TGC, and DAP. The proportion of ESBL-producing *E. coli* has increased significantly in Canadian ICUs since 2007.

BACKGROUND

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 a paucity of national surveillance data concerning antimicrobial susceptibility rates in Canadian ICUs. Antibiotic utilization and over-utilization both in hospitals and the community is a strong impetus for 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]. The ICU utilizes the most antibiotics and has the highest resistance rates. It is estimated that 70% of ICU patients are on antibiotics at any one time [6]. While available evidence suggests that antimicrobial stewardship interventions are effective in ICUs, stewardship is encumbered by the inherent severity of illness in ICU patients [7].

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MATERIALS & METHODS

Bacterial Isolates: A total of 36,607 bacterial isolates (isolated from blood, urine, wound, and respiratory specimens) were submitted by tertiary-care medical centres from January 2007 to December 2014, inclusive, as part of the ongoing CANWARD national surveillance study [2]. Of these, 6,978 (19.1%) were from patients admitted to an intensive care unit. The medical centres were asked to submit clinical isolates (consecutive, one per patient, per infection site) that were "clinically significant" (ie. from patients with a presumed infectious disease). Surveillance swabs, ear, eye, nose, and throat swabs were not included. Anaerobic organisms were not included. Isolates were shipped on Amies semi-solid transport media to the Health Sciences Centre laboratory in Winnipeg, MB, Canada. Isolates were subcultured onto appropriate media and stocked in skim milk at -80° C until minimum inhibitory concentration (MIC) testing was carried out.

Antimicrobial Susceptibility Testing: Following 2 subcultures from frozen stock, *in vitro* antimicrobial susceptibility testing was performed using the broth microdilution method in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI M07-A9). Minimum inhibitory concentration interpretive standards were defined by CLSI M100-S24 breakpoints. US Food and drug administration (FDA) breakpoints were used for colistin (S: ≤2, R: ≥4 μg/ml). Antimicrobial agents were obtained as laboratory grade powders from their respective manufacturers. Stock solutions were prepared and dilutions made as described by CLSI. The MICs were determined using 96-well custom designed microtitre plates. These plates contained doubling antimicrobial dilutions in 100 μl/well of cation adjusted Mueller-Hinton broth and inoculated to achieve a final concentration of approximately 5 x 10^5 CFU/ml. Microtitre panels were then incubated in ambient air at 35°C (±2°C) for 24 hours prior to reading. Colony counts were performed periodically to confirm inocula. Quality control was performed using ATCC organisms including;
S. aureus 29213, *E. faecalis* 29212, *E. coli* 25922, and *P. aeruginosa* 27853.

Statistical Analysis: Statistical significance was calculated by the chi-squared test or the Fisher exact test using the SPSS statistics (Version 20) program (IBM Corporation).

CONCLUSIONS

1. The most commonly isolated pathogens in Canadian ICUs were: *S. aureus*, *P. aeruginosa*, *E. coli*, *S. pneumoniae*, and *K. pneumoniae*.
   - ICU patients in this study were most commonly males ages 18-64 with respiratory tract infections.
2. Meropenem and piperacillin-tazobactam showed the greatest activity against Gram-negative bacilli in this study (susceptibility >94.6%). Against *P. aeruginosa*, susceptibility rates were greatest for amikacin (95.4%), colistin (94.5%), and gentamicin (81.9%)
3. Vancomycin, linezolid, tigecycline, and daptomycin demonstrated >99% susceptibility against MRSA isolates tested.
4. The prevalence of relevant antimicrobial-resistant organisms in Canadian ICUs was as follows:
   - MRSA reached peak incidence in 2008 (32.4%), however, from 2009 to 2014 MRSA rates declined and remained fairly constant between 17% and 20.4%.
   - Carbapenem-resistant Enterobacteriaceae are yet to emerge as a significant threat in Canadian ICUs.
   - While rates were somewhat variable, ESBL-producing *E. coli* now represent a significant proportion (2014: 18.6%) of *E. coli* isolated from the ICU.

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RESULTS

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

Organism (n)				MIC (μg/ml)			
Antimicrobial	%S	%I	%R	MIC_{50}	MIC_{90}	Min	Max
***P.aeruginosa* (724)**							
Amikacin	95.4	1.9	2.6	4	16	≤ 2	> 64
AMC				> 32	> 32	0.5	> 32
Cefazolin				> 128	> 128	≤ 0.5	> 128
Cefoxitin				> 32	> 32	4	> 32
Ceftazidime	77.0	6.6	16.4	4	32	≤ 0.5	> 32
Ceftriaxone				32	> 64	≤ 1	> 64
Ciprofloxacin	74.7	8.3	17.0	0.25	8	≤ 0.06	> 16
Colistin	94.5		5.5	1	2	≤ 0.06	> 16
Ertapenem				16	> 32	0.12	> 32
Gentamicin	81.9	7.5	10.6	2	16	≤ 0.5	> 32
Meropenem	74.0	8.3	17.7	1	16	≤ 0.12	> 32
Moxifloxacin				2	> 16	≤ 0.06	> 16
TZP	76.0	14.4	9.7	8	64	≤ 1	512
Tigecycline				16	> 16	0.25	> 16
SXT				8	> 8	≤ 0.12	> 8

Organism (n)				MIC (μg/ml)			
Antimicrobial	%S	%I	%R	MIC_{50}	MIC_{90}	Min	Max
***E. coli* (718)**							
Amikacin	99.0	1.0		≤ 2	4	≤ 2	32
AMC	77.4	13.0	9.6	8	16	0.5	> 32
Cefazolin	60.1	12.5	27.4	2	> 128	≤ 0.5	> 128
Cefoxitin	87.2	5.5	7.3	4	16	≤ 0.06	> 32
Ceftazidime	87.7	1.8	10.5	≤ 0.5	16	≤ 0.5	> 32
Ceftriaxone	86.2	0.6	13.2	≤ 1	16	≤ 1	> 64
Ciprofloxacin	72.7	0.4	26.8	≤ 0.06	> 16	≤ 0.06	> 16
Colistin	98.9		1.1	0.25	0.5	≤ 0.06	> 16
Ertapenem	98.6	0.6	0.8	≤ 0.06	0.06	≤ 0.06	> 32
Gentamicin	87.8	0.7	11.5	≤ 0.5	32	≤ 0.5	> 32
Meropenem	99.9		0.1	≤ 0.12	≤ 0.12	≤ 0.12	32
Moxifloxacin				≤ 0.06	> 16	≤ 0.06	> 16
TZP	94.6	1.7	3.8	2	8	≤ 1	> 512
Tigecycline	100.0			0.25	1	0.12	2
SXT	71.4		28.6	≤ 0.12	> 8	≤ 0.12	> 8

Organism (n)				MIC (μg/ml)			
Antimicrobial	%S	%I	%R	MIC_{50}	MIC_{90}	Min	Max
***K. pneumoniae* (439)**							
Amikacin	99.8		0.2	≤ 2	≤ 2	≤ 2	> 64
AMC	92.3	4.2	3.5	2	8	0.5	> 32
Cefazolin	79.7	6.4	13.9	2	16	≤ 0.5	> 128
Cefoxitin	89.1	4.0	6.9	4	16	0.5	> 32
Ceftazidime	94.7	0.6	4.7	≤ 0.5	1	≤ 0.5	> 32
Ceftriaxone	94.3		5.7	≤ 1	≤ 1	≤ 1	> 64
Ciprofloxacin	94.3	1.8	3.9	≤ 0.06	0.5	≤ 0.06	> 16
Colistin	97.5		2.5	0.5	1	≤ 0.06	> 16
Ertapenem	99.3	0.7		≤ 0.06	≤ 0.06	≤ 0.06	1
Gentamicin	96.8		3.2	≤ 0.5	≤ 0.5	≤ 0.5	> 32
Meropenem	100.0			≤ 0.12	≤ 0.12	≤ 0.12	0.25
Moxifloxacin				0.12	1	≤ 0.06	16
TZP	95.2	2.1	2.7	2	8	≤ 1	> 512
Tigecycline	92.9	5.5	1.6	1	2	0.25	8
SXT	93.6		6.4	≤ 0.12	1	≤ 0.12	> 8

Organism (n)				MIC (μg/ml)			
Antimicrobial	%S	%I	%R	MIC_{50}	MIC_{90}	Min	Max
***H. influenzae* (351)**							
AMC	99.4		0.6	0.5	2	≤ 0.06	8
Ampicillin	80.1	0.6	19.3	≤ 0.25	16	≤ 0.25	> 128
Cefepime	100.0			≤ 0.25	≤ 0.25	≤ 0.25	2
Ceftriaxone	100.0			≤ 0.06	≤ 0.06	≤ 0.06	1
Cefuroxime	97.2	2.1	0.6	0.5	2	≤ 0.25	> 16
Ciprofloxacin	100.0			≤ 0.015	≤ 0.015	≤ 0.015	0.03
Clarithromycin	89.4	9.4	1.2	4	16	≤ 0.03	32
Doxycycline				≤ 0.25	1	≤ 0.25	4
Ertapenem	99.7		0.3	≤ 0.03	0.12	≤ 0.03	> 4
Gentamicin				1	2	≤ 0.5	2
Meropenem	99.7		0.3	≤ 0.06	0.12	≤ 0.06	2
Moxifloxacin	100.0			≤ 0.015	0.03	≤ 0.015	0.25
TZP	100.0			≤ 1	≤ 1	≤ 1	≤ 1
SXT	85.9	3.4	10.7	≤ 0.12	4	≤ 0.12	> 8

Organism (n)				MIC (μg/ml)			
Antimicrobial	%S	%I	%R	MIC_{50}	MIC_{90}	Min	Max
MSSA (1149)							
Cefazolin				≤ 0.5	1	≤ 0.5	8
Ciprofloxacin	89.7	2.3	8.0	0.5	2	≤ 0.06	> 16
Clarithromycin	77.8	0.5	21.6	0.25	> 16	≤ 0.25	> 16
Clindamycin	94.6		5.4	≤ 0.25	≤ 0.25	≤ 0.25	> 8
Daptomycin	100.0			0.25	0.25	≤ 0.06	1
Gentamicin	99.0	0.2	0.9	≤ 0.5	≤ 0.5	≤ 0.5	> 32
Linezolid	99.9		0.1	2	2	≤ 0.12	8
Moxifloxacin	93.0	0.3	6.8	≤ 0.06	0.12	≤ 0.06	> 16
Tigecycline	99.9		0.1	0.12	0.25	≤ 0.03	1
SXT	99.7		0.3	≤ 0.12	≤ 0.12	≤ 0.12	> 8
Vancomycin	100.0			1	1	≤ 0.25	2

Organism (n)				MIC (μg/ml)			
Antimicrobial	%S	%I	%R	MIC_{50}	MIC_{90}	Min	Max
MRSA (317)							
Cefazolin				128	> 128	1	> 128
Ciprofloxacin	15.8	0.3	83.9	> 16	> 16	0.25	> 16
Clarithromycin	16.1	0.3	83.5	> 16	> 16	≤ 0.25	> 16
Clindamycin	49.4		50.6	> 8	> 8	≤ 0.25	> 8
Daptomycin	99.7		0.3	0.25	0.5	0.06	2
Gentamicin	86.4		13.6	≤ 0.5	> 32	≤ 0.5	> 32
Linezolid	100.0			2	2	≤ 0.12	4
Moxifloxacin	16.4	3.2	80.4	8	> 16	≤ 0.06	> 16
Tigecycline	99.7		0.3	0.25	0.5	0.12	1
SXT	88.3		11.7	≤ 0.12	8	≤ 0.12	> 8
Vancomycin	100.0			1	1	≤ 0.25	2

Organism (n)				MIC (μg/ml)			
Antimicrobial	%S	%I	%R	MIC_{50}	MIC_{90}	Min	Max
***S. pneumoniae* (474)**							
AMC	97.3	2.0	0.7	≤ 0.06	0.25	≤ 0.06	8
Ceftriaxone	99.3	0.4	0.2	≤ 0.12	0.12	≤ 0.12	4
Cefuroxime	91.5	3.1	5.4	≤ 0.25	0.5	≤ 0.25	> 16
Clarithromycin	83.2	3.8	13.0	≤ 0.03	2	≤ 0.03	> 32
Clindamycin	94.2	0.2	5.6	≤ 0.12	≤ 0.12	≤ 0.12	> 8
Doxycycline	87.5	1.3	11.2	≤ 0.25	1	≤ 0.25	> 16
Levofloxacin	99.6	0.2	0.2	1	1	≤ 0.06	8
Linezolid	100.0			1	1	≤ 0.12	2
Moxifloxacin	99.6	0.4		0.12	0.25	≤ 0.06	2
Penicillin	83.3	11.4	5.3	≤ 0.03	0.5	≤ 0.03	4
SXT	85.9	4.9	9.2	≤ 0.12	2	≤ 0.12	> 8

Organism (n)				MIC (μg/ml)			
Antimicrobial	%S	%I	%R	MIC_{50}	MIC_{90}	Min	Max
***E. faecalis* (179)**							
AMC				0.5	1	0.12	32
Ciprofloxacin	59.9	7.3	32.8	1	> 16	0.25	> 16
Clarithromycin				> 16	> 16	≤ 0.25	> 16
Daptomycin	100.0			0.5	1	0.06	4
Ertapenem				16	16	2	> 32
Levofloxacin	63.2		36.8	2	> 32	1	> 32
Linezolid	97.7	2.3		2	2	0.5	4
Meropenem				4	8	1	> 32
TZP				4	8	≤ 1	512
Tigecycline	97.7		2.3	0.12	0.25	0.06	0.5
Vancomycin	100.0			1	2	0.5	4

MSSA: methicillin-susceptible *S. aureus*, MRSA: methicillin-resistant *S. aureus*, AMC: amoxicillin-clavulanate, TZP: piperacillin-tazobactam, SXT: trimethoprim-sulfamethoxazole.

Table 2. Top 20 bacterial pathogens isolated from Canadian ICUs.

RANK	ORGANISM	N	% TOTAL
1	*Staphylococcus aureus*	1466	21
2	*Pseudomonas aeruginosa*	724	10.4
3	*Escherichia coli*	718	10.3
4	*Streptococcus pneumoniae*	474	6.8
5	*Klebsiella pneumoniae*	439	6.3
6	*Haemophilus influenzae*	351	5
7	*Enterobacter cloacae*	317	4.5
8	*Staphylococcus epidermidis*	226	3.2
9	*Serratia marcescens*	192	2.8
10	*Stenotrophomonas maltophilia*	192	2.8
11	*Enterococcus faecalis*	179	2.6
12	*Klebsiella oxytoca*	151	2.2
13	*Enterococcus faecium*	110	1.6
14	*Moraxella catarrhalis*	105	1.5
15	*Enterobacter aerogenes*	93	1.3
16	*Acinetobacter baumannii*	61	0.9
17	*Proteus mirabilis*	60	0.9
18	*Morganella morganii*	26	0.4
19	*Citrobacter freundii*	25	0.4
20	Other	1068	15.3

Figure 1. Patient demographics.

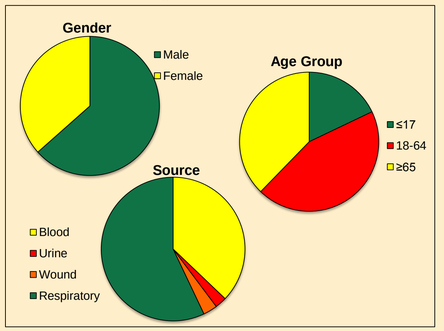
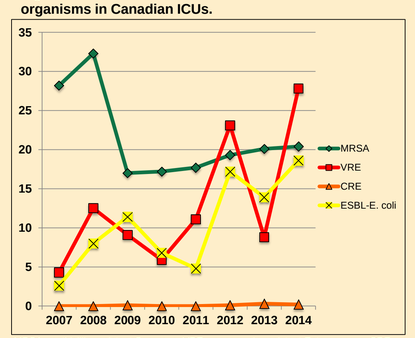


Figure 2. The prevalence of relevant antibiotic-resistant organisms in Canadian ICUs.



MRSA: methicillin-resistant S. aureus, VRE: vancomycin-resistant Enterococcus, CRE: carbapenem-resistant Enterobacteriaceae, ESBL: extended-spectrum β-lactamase