

Antimicrobial Susceptibility of 36,607 Pathogens Isolated from Patients in Canadian Hospitals: CANWARD Study 2007-2014

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ABSTRACT

Background: CANWARD is a national, annual Health Canada endorsed surveillance study assessing pathogens causing infections in Canadian hospitals and their antimicrobial resistance patterns.

Methods: From 2007 to 2014, 36,607 pathogens were collected from tertiary-care hospitals across Canada. Antimicrobial susceptibility testing was performed using CLSI broth microdilution methods with >45 marketed and investigational agents.

Results: Specimen source composition of the 36,607 isolates was 44.1% blood, 32.0% respiratory, 13.7% urine and 10.2% wound specimens. Patient demographic characteristics were: 54.6/45.4% male/female; 13.0/44.6/42.4% patients aged ≤17/18-64/≥65 years; and 37.8/25.2/19.1/18.0% patients located in medical and surgical wards/emergency rooms/ICUs/clinics. The most common pathogens were: *E. coli* (EC 19.7%), *MSSA* (16.4%), *P. aeruginosa* (PA 8.7%), *S. pneumoniae* (SPN 6.5%), *K. pneumoniae* (KP 6.1%), *MRSA* (4.7%), *Enterococcus* spp. (4.0%), and *H. influenzae* (4.0%). Susceptibility rates (SR) for EC were: 99.9% for meropenem (MER) and tigecycline (TGC), 99.7% ertapenem (ERT), 97.7% piperacillin-tazobactam (PTZ), 92.5% ceftriaxone (CTR), 90.4% gentamicin (GEN), 77.2% ciprofloxacin (CIP) and 73.0% TMP-SMX (SXT). SR for PA were: 94.2% colistin, 84.3% PTZ, 83.3% ceftazidime (CAZ), 81.2% MER, 77.6% GEN and 74.1% CIP. SR for MRSA were: 100% for linezolid (LZD) and telavancin (TLV), 99.9% daptomycin (DAP), 99.4% TGC, 99.1% vancomycin, and 93.3% SXT. Rates of resistant organisms between 2007-2014 increased significantly for ESBL-producing EC (3.4%-11.6%) and KP (1.5%-6.5%) as well as VRE (1.8%-7.0%), whereas MRSA rates (26.1%-20.2%) significantly declined.

Conclusions: EC, MSSA, PA, SPN, KP, and MRSA are the most common pathogens in Canadian hospitals. SR for EC were highest for MER, TGC, ERT and PTZ. SR for PA were highest for colistin, PTZ, CAZ and MER. 99-100% of MRSA were susceptible DAP, LZD, TLV, and vancomycin.

INTRODUCTION

Infections caused by antibiotic resistant infections is a Canadian and global crisis (1,2). Resistant pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA), community associated-CA and healthcare-associated (HA), vancomycin-resistant *Enterococcus species* (VRE), penicillin-resistant *Streptococcus pneumoniae* (PRSP), extended spectrum β-lactamase (ESBL) producing *Escherichia coli* and *Klebsiella species* and fluoroquinolone-resistant and carbapenem-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* are increasing in prevalence in Canada and around the world (1,2). Available therapeutic options for the treatment of these antibiotic resistant organisms are severely limited as these organisms frequently display a multidrug resistant (MDR) phenotype.

The ongoing goal of the CANWARD study is to assess pathogens associated with and antimicrobial resistance patterns in respiratory, bacteremic, urinary, and wound/IV site infections in Canadian hospitalized patients on medical/surgical wards (W), emergency rooms (ER), outpatient clinics (C) and intensive care units (ICU).

PURPOSE

- To determine the pathogens associated with respiratory, urinary, bacteremic and wound/IV site infections in Canadian patients affiliated with hospitals from 2007-2014, inclusive.
- To determine the prevalence of antimicrobial resistance in pathogens associated with respiratory, urinary, bacteremic and wound/IV site infections in Canadian patients affiliated with hospitals from 2007-2014, inclusive.
- To assess the activity of antimicrobials against respiratory, urinary, bacteremic and wound/IV site pathogens in Canadian patients affiliated with hospitals from 2007-2014, inclusive.

MATERIALS & METHODS

Participating Sites:

From January 2007 to December 2014, sentinel hospital sites (12 in 2007, 10 in 2008, 15 in 2009, 14 in 2010, 15 in 2011, 12 in 2012, 15 in 2013, and 13 in 2014) in major population centres in 8 of the 10 provinces in Canada were recruited. These sites were geographically distributed in a population based fashion: (BC [1 site], Alberta [1 site], Saskatchewan [1 site], Manitoba [1 site], Ontario [3-5 sites], Quebec [2-4 sites], Maritimes [1-2 sites]).

Bacterial Isolates: Tertiary-care medical centres submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. Each study site was asked to submit clinical isolates (consecutive, one per patient, per infection site) from inpatients and outpatients with respiratory, urine, wound, and bloodstream infections. The medical centres submitted "clinically significant" isolates from patients with a presumed infectious disease. Surveillance swabs, eye, ear, nose and throat swabs, as well as anaerobes, were excluded. Isolate identification was performed by the submitting site and confirmed at the reference site as required, based on morphological characteristics and antimicrobial susceptibility patterns. Isolates were shipped on Amies semi-solid transport media to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada), subcultured onto appropriate media, and stocked in skin milk at -80°C until minimum inhibitory concentration (MIC) testing was carried out. In 2007, 2008, 2009, 2010, 2011, 2012, 2013 and 2014; 7714, 5283, 5374, 4960, 3788, 2803, 3511, and 3174 isolates were collected, respectively (1,2).

Antimicrobial Susceptibilities: Following 2 subcultures from frozen stock, the *in vitro* activity of selected antimicrobials was determined by broth microdilution in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2012 M7-A9). Antimicrobial MIC interpretive standards were defined according to CLSI breakpoints (M100-S24, 2014). Susceptibility testing could not be performed with all agents due to lack of space on the susceptibility panels. Antimicrobial agents were obtained as laboratory grade powders from their respective manufacturers. Stock solutions were prepared and dilutions made as described by CLSI (M7-A9, 2012). The MICs were determined using 96-well custom designed microtitre plates. These plates contained doubling antimicrobial dilutions in 100µl/well of cation adjusted Mueller-Hinton broth and inoculated to achieve a final concentration of approximately 5 x 10⁵ CFU/ml then incubated in ambient air for 24 hours prior to reading. Colony counts were performed periodically to confirm inocula. Quality control was performed using ATCC QC organisms including: *S. pneumoniae* 49619, *S. aureus* 29213, *E. faecalis* 29212, *E. coli* 25922, and *P. aeruginosa* 27853.

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Table 1. Antimicrobial activity against the most common Gram-positive cocci isolated from Canadian hospitals

Organism (n) / Antimicrobial Agent	% S % I % R			MIC (µg/mL)		Range
	MIC ₅₀	MIC ₉₀	MIC ₉₅	MIC ₉₀	MIC ₉₅	
Staphylococcus aureus, MSSA (n=5990)						
Amikacin	99.2	0.4	0.3	4	≤ 2	> 64
Cefoxitin	99.5	0.5	4	4	0.12	> 32
Ciprofloxacin	86.2	3.0	10.8	0.5	4	≤ 0.06 > 16
Clarithromycin	75.3	0.4	24.3	0.25	> 16	≤ 0.25 > 16
Clindamycin	93.0	0.4	6.8	≤ 0.25	≤ 0.25	> 8
Daptomycin	100.0			0.25	0.25	> 0.06 - 1
Dapsone *				128	128	32 - 256
Doxycycline	99.0	0.7	0.3	≤ 0.25	≤ 0.25	> 16
Ertapenem	97.9	0.1	2.0	≤ 0.5	≤ 0.5	> 32
Levofloxacin	90.1	0.3	9.8	0.25	1	≤ 0.06 > 32
Linezolid	99.98	0.02	2	2	≤ 0.12	> 8
Moxifloxacin	90.3	0.7	9.0	≤ 0.06	0.25	> 0.06 > 16
Nitrofurantoin	100.0			16	16	≤ 0.5 > 32
Tigecycline	99.9			0.12	0.25	> 0.03 > 32
Tobramycin	97.2	0.2	2.6	≤ 0.5	≤ 0.5	> 64
Trimethoprim Sulfamethoxazole	99.4	0.6	≤ 0.12	≤ 0.12	≤ 0.12	> 8
Vancomycin	100.0			1	1	≤ 0.25 > 2
Staphylococcus aureus, MRSA (n=1707)						
Amikacin	68.2	21.8	10.1	16	64	≤ 2 > 64
Cefoxitin	0.1		99.9	> 32	> 32	1 > 32
Ciprofloxacin	16.0	0.3	83.7	> 16	> 16	0.12 > 16
Clarithromycin	14.4	0.4	85.2	> 16	> 16	≤ 0.25 > 16
Clindamycin	52.8	0.1	47.2	≤ 0.25	> 8	0.06 > 8
Daptomycin	99.9	0.1	0.1	0.25	0.5	> 2
Dapsone *				128	256	16 - 512
Doxycycline	97.6	0.8	1.5	≤ 0.12	1	≤ 0.12 > 16
Gentamicin	92.2	0.3	7.5	≤ 0.5	1	≤ 0.5 > 32
Levofloxacin	14.1		85.9	> 32	> 32	0.12 > 32
Linezolid	100.0			2	2	≤ 0.12 > 4
Moxifloxacin	16.7	3.2	80.2	8	> 16	≤ 0.06 > 16
Nitrofurantoin	100.0			16	16	8 > 32
Tigecycline	99.1			0.25	0.5	> 0.03 > 32
Tobramycin	56.7	0.7	42.6	1	> 64	≤ 0.5 > 64
Trimethoprim Sulfamethoxazole	93.3	6.7	≤ 0.12	≤ 0.12	≤ 0.12	> 8
Vancomycin	99.9	0.1		1	1	≤ 0.25 > 4
Staphylococcus epidermidis (n=775)						
Amikacin	95.2	2.9	2.0	≤ 2	16	≤ 2 > 64
Amox-Clav				1	8	≤ 0.06 > 32
Cefazolin				1	64	≤ 0.5 > 128
Cefepime				4	> 32	> 1 > 32
Ceftriaxone				8	> 32	≤ 0.06 > 32
Cefuroxime				> 4	> 4	> 4 > 4
Ciprofloxacin	44.9	1.6	53.6	4	> 16	≤ 0.06 > 16
Clarithromycin	32.7	1.2	66.2	> 16	> 16	≤ 0.25 > 16
Clindamycin	55.0	1.3	43.8	≤ 0.25	> 8	0.25 > 8
Daptomycin	100.0			0.12	0.25	> 0.06 > 1
Dapsone *				128	512	32 > 512
Doripenem				1	16	≤ 0.12 > 32
Doxycycline	95.7	2.9	1.5	0.25	1	≤ 0.25 > 32
Ertapenem				4	> 32	≤ 0.06 > 32
Gentamicin				≤ 0.5	> 32	≤ 0.5 > 32
Levofloxacin	44.2	1.6	54.2	4	> 32	0.12 > 32
Linezolid	100.0			0.5	1	≤ 0.12 > 4
Meropenem				2	> 32	≤ 0.12 > 32
Moxifloxacin	46.9	6.9	46.2	1	> 16	≤ 0.06 > 16
Pip-Tazo				≤ 0.12	0.5	> 0.03 > 1
Tigecycline	99.3	12.8	27.8	2	64	≤ 0.5 > 64
Tobramycin	59.4	4.2	40.6	1	8	≤ 0.12 > 8
Trimethoprim Sulfamethoxazole	100.0			1	2	≤ 0.25 > 4
Vancomycin	100.0			1	1	≤ 0.25 > 4
Streptococcus pneumoniae (n=2366)						
Amox-Clav	97.8	1.2	0.9	≤ 0.06	0.12	≤ 0.06 > 16
Ceftriaxone *	99.3	0.5	0.2	≤ 0.12	≤ 0.12	≤ 0.12 > 4
Cefuroxime	93.6	1.8	4.6	≤ 0.25	0.5	≤ 0.25 > 16
Chloramphenicol	98.5	4.5	2	2	2	≤ 0.12 > 32
Ciprofloxacin	79.3	3.6	17.2	1	2	≤ 0.06 > 16
Clarithromycin	92.9	0.6	6.5	≤ 0.12	≤ 0.12	≤ 0.12 > 8
Daptomycin				0.06	0.12	> 0.06 > 16
Doripenem	99.9	0.1	0.1	≤ 0.06	0.06	≤ 0.06 > 2
Doxycycline	86.8	1.3	11.9	≤ 0.25	1	≤ 0.25 > 16
Ertapenem	98.9	1.1	0.0	≤ 0.06	0.12	≤ 0.06 > 4
Imipenem	93.6	4.2	2.3	≤ 0.03	≤ 0.03	> 1
Levofloxacin	98.9	0.2	0.9	≤ 0.03	0.25	≤ 0.03 > 32
Linezolid	100.0			1	1	≤ 0.12 > 2
Meropenem	95.1	3.0	1.9	≤ 0.06	≤ 0.06	> 2
Moxifloxacin	99.0	0.5	0.5	0.12	0.25	≤ 0.06 > 8
Nitrofurantoin	82.6	12.9	4.5	≤ 0.03	0.25	≤ 0.03 > 8
Pip-Tazo				≤ 1	≤ 1	> 8
Tigecycline	99.8			≤ 0.03	0.06	> 0.03 > 0.25
Trimethoprim Sulfamethoxazole	100.0	6.3	8.9	≤ 0.12	2	≤ 0.12 > 8
Vancomycin	84.9			≤ 0.25	0.25	≤ 0.25 > 1

Bacterial Isolates Collected

36,607 clinical isolates were collected for CANWARD 2007-2014.

- 16,150 (44.1%) were from blood, 11,712 (32.0%) from respiratory sources, 5,001 (13.7%) were from urine and 3,744 (10.2%) were from wounds
- 19,977 (54.6%) collected from male patients; 16,627 (45.4%) female patients

Organism (n) / Antimicrobial Agent	% S % I % R			MIC (µg/mL)		Range
	MIC ₅₀	MIC ₉₀	MIC ₉₅	MIC ₉₀	MIC ₉₅	
Streptococcus agalactiae (n=599)						
Amox-Clav				≤ 0.06	≤ 0.06	≤ 0.06 > 0.25
Ceftriaxone	100.0			≤ 0.12	≤ 0.12	≤ 0.12 > 0.25
Cefuroxime				≤ 0.25	≤ 0.25	≤ 0.25 > 0.5
Chloramphenicol	77.2	2.8		4	4	0.5 > 8
Ciprofloxacin	90.5	4.3	25.3	0.5	1	0.25 > 16
Clarithromycin	90.3	1.0	15.7	≤ 0.12	> 8	≤ 0.12 > 8
Clindamycin	83.3			0.25	0.25	≤ 0.06 > 0.5
Daptomycin	100.0			≤ 0.06	≤ 0.06	≤ 0.06 > 256
Dapsone *				16	16	256 > 16
Doxycycline	100.0			0.06	≤ 0.06	≤ 0.06 > 0.06
Ertapenem	100.0			≤ 0.06	≤ 0.06	≤ 0.06 > 0.12
Imipenem				≤ 0.03	0.03	≤ 0.03 > 0.12
Levofloxacin	97.1		3.0	1	1	≤ 0.25 > 32
Linezolid	100.0			1	2	≤ 0.12 > 2
Meropenem				≤ 0.06	≤ 0.06	≤ 0.06 > 0.12
Moxifloxacin				0.12	0.25	≤ 0.06 > 4
Nitrofurantoin	100.0			0.06	0.12	≤ 0.03 > 0.12
Penicillin	100.0			0.12	0.25	≤ 0.03 > 0.12
Pip-Tazo				≤ 1	≤ 1	≤ 1 > 512
Tigecycline	99.7			0.06	0.12	≤ 0.12 > 51
Trimethoprim Sulfamethoxazole	100.0			≤ 0.12	0.25	≤ 0.12 > 1
Vancomycin	100.0			0.5	0.5	≤ 0.25 > 1
Streptococcus pyogenes (n=547)						
Amox-Clav				≤ 0.06	≤ 0.06	≤ 0.06 > 0.5
Ceftriaxone	99.8	0.2		≤ 0.12	≤ 0.12	≤ 0.12 &