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Antimicrobial susceptibility of 22 746 pathogens from Canadian hospitals: results of the CANWARD 2007–11 study

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Objectives: The purpose of the CANWARD study was to assess the antimicrobial activity of a variety of available agents against 22 746 pathogens isolated from patients in Canadian hospitals between 2007 and 2011.

Methods: Between 2007 and 2011, 27 123 pathogens were collected from tertiary-care centres from across Canada; 22 746 underwent antimicrobial susceptibility testing using CLSI broth microdilution methods. Patient demographic data were also collected.

Results: Of the isolates collected, 45.2%, 29.6%, 14.8% and 10.4% were from blood, respiratory, urine and wound specimens, respectively. Patient demographics were as follows: 54.4%/45.6% male/female, 12.8% ≤17 years old, 45.1% 18–64 years old and 42.1% ≥65 years old. Isolates were obtained from patients in medical and surgical wards (37.8%), emergency rooms (25.7%), clinics (18.0%) and intensive care units (18.5%). The three most common pathogens were *Escherichia coli* (20.1%), *Staphylococcus aureus* [methicillin-susceptible *S. aureus* and methicillin-resistant *S. aureus* (MRSA)] (20.0%) and *Pseudomonas aeruginosa* (8.0%), which together accounted for nearly half of the isolates obtained. Susceptibility rates (SRs) for *E. coli* were 100% meropenem, 99.9% tigecycline, 99.7% ertapenem, 97.7% piperacillin/tazobactam, 93.7% ceftriaxone, 90.5% gentamicin, 77.9% ciprofloxacin and 73.4% trimethoprim/sulfamethoxazole. Twenty-three percent of the *S. aureus* were MRSA. SRs for MRSA were 100% daptomycin, 100% linezolid, 100% telavancin, 99.9% vancomycin, 99.8% tigecycline, 92.2% trimethoprim/sulfamethoxazole and 48.2% clindamycin. SRs for *P. aeruginosa* were 90.1% amikacin, 93.1% colistin, 84.0% piperacillin/tazobactam, 83.5% ceftazidime, 82.6% meropenem, 72.0% gentamicin and 71.9% ciprofloxacin.

Conclusions: The CANWARD surveillance study has provided important data on the antimicrobial susceptibility of pathogens commonly causing infections in Canadian hospitals.

Keywords: resistance, pathogens, medical wards, surgical wards, intensive care units, emergency rooms

Introduction

Hospitals worldwide are facing the growing presence of infections caused by antimicrobial-resistant and multidrug-resistant (MDR) pathogens.[1–5] Pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA) [both community-associated (CA-MRSA) and healthcare-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 Enterobacteriaceae, and *Pseudomonas aeruginosa* are growing in prevalence globally.[1–6] Treatment options for antimicrobial-resistant organisms can be severely limited, as these organisms frequently display an MDR phenotype.[1,7]

We recently reported on the prevalence of antimicrobial-resistant pathogens in Canadian hospitals[5] as well as the

antimicrobial susceptibility of a small collection of hospital pathogens.[6] The purpose of the CANWARD study was to assess the *in vitro* activity (MIC_{50} and MIC_{90}) of commonly used antimicrobials against 22746 isolates collected from 2007 to 2011 inclusive, from patients in hospitals across Canada.

Materials and methods

Bacterial isolates

As part of the CANWARD study, tertiary-care medical centres (12 in 2007, 10 in 2008, 15 in 2009, 14 in 2010 and 15 in 2011) representing 8 of the 10 provinces across Canada submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards and intensive care units (ICUs).[5,6] The specific CANWARD sites are as follows: Royal University Hospital, Saskatoon, Saskatchewan (Dr J. Blondeau); Children's Hospital of Eastern Ontario, Ottawa, Ontario (Dr F. Chan); Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia (Dr R. Davidson); Health Sciences Centre, Winnipeg, Manitoba (Dr D. Hoban/Dr G. Zhanel); London Health Sciences Centre, London, Ontario (Dr Z. Hussain); South East Health Care Corp., Moncton, New Brunswick (Dr M. Kuhn); Hôpital Maisonneuve-Rosemont, Montreal, Québec (Dr M. Laverdière); Montreal General Hospital, Montreal, Québec (Dr V. Loo); Royal Victoria Hospital, Montreal, Québec (Dr V. Loo); Mount Sinai Hospital, Toronto, Ontario (Dr S. Poutanen); University of Alberta Hospital, Edmonton, Alberta (Dr J. Fuller); Vancouver Hospital, Vancouver, British Columbia (Dr D. Roscoe); The Ottawa Hospital, Ottawa, Ontario (Dr M. Desjardins); St Michael's Hospital, Toronto, Ontario (Dr L. Matukas); and CHRTR Pavillon Ste Marie, Trois-Rivières, Québec (Dr M. Goyette). The sites were geographically distributed in a population-based fashion. From 2007 to 2011 inclusive, 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. By year, each centre was asked to provide the following: 2007—200 respiratory, 50 wound, 100 urinary and 30/month blood isolates; 2008—150 respiratory, 50 wound, 100 urinary and 20/month blood isolates; 2009–10—100 respiratory, 50 wound, 50 urinary and 15/month blood isolates; and 2011—100 respiratory, 25 wound, 25 urinary and 10/month blood isolates. The medical centres submitted clinically significant isolates, as defined by their individual hospital criteria. Surveillance swabs and eye, ear, nose and throat swabs were excluded. We also excluded anaerobic organisms and fungi, except yeast from bloodstream infections. Isolate identification was performed by the submitting site and confirmed at the reference site as required, based on morphological characteristics (e.g. Gram stain, colony morphology and haemolysis), automated susceptibility testing systems and antimicrobial susceptibility patterns. Isolates were shipped on Amies semi-solid transport media to the coordinating laboratory (Health Sciences Centre, Winnipeg, Manitoba, Canada), subcultured onto appropriate media and stocked in skimmed milk at −80°C until MIC testing was carried out. Isolate viability (including fastidious organisms such as *S. pneumoniae*) using these methods was >99%. Patient demographics collected included gender, age, hospital location and specimen source. Between 2007 and 2011, 27123 pathogens were collected (7714 in 2007, 5283 in 2008, 5372 in 2009, 4960 in 2010 and 3794 in 2011). The decline in isolates per year from 2007 to 2011 is mostly related to a decrease in the number of isolates requested from each participating institution and not related to extensive changes to the annual protocol.

The CANWARD study receives annual approval by the University of Manitoba Research Ethics Board (H2009:059).

Antimicrobial susceptibility testing

Following two subcultures from frozen stock, the *in vitro* activity of selected antimicrobials was determined by broth microdilution in accordance with CLSI guidelines.[8] Antimicrobial agents were obtained as laboratory-grade powders from their respective manufacturers. Stock solutions were prepared and dilutions made as described by CLSI.[8] The MICs for the isolates 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 were inoculated to achieve a final concentration of $\sim 5 \times 10^5$ cfu/mL. The plates were 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, including *S. pneumoniae* 49619, *S. aureus* 29213, *Enterococcus faecalis* 29212, *E. coli* 25922 and *P. aeruginosa* 27853.

Antimicrobial MIC interpretive standards were defined according to CLSI breakpoints.[9] The following interpretive breakpoints (FDA) were used for tigecycline [susceptible (S), intermediate (I) and resistant (R) isolates]: *S. aureus* [methicillin-susceptible (MSSA) and MRSA], ≤0.5 mg/L (S); *E. faecalis* (vancomycin susceptible), ≤0.25 mg/L (S); and Enterobacteriaceae, ≤2 mg/L (S), 4 mg/L (I) and ≥8 mg/L (R). The following interpretive breakpoints (FDA) were used for telavancin: *S. aureus* (MSSA and MRSA), ≤1.0 mg/L (S); and *Streptococcus pyogenes* and *Streptococcus agalactiae*, ≤0.12 mg/L (S).

Of the 27123 organisms collected, 22746 (83.9%) underwent susceptibility testing. Isolates selected for susceptibility testing included the top 20 pathogens [although not all coagulase-negative staphylococci (CoNS) or any viridans streptococci were tested] as well as a variety of less common Gram-negative bacilli. The development of a centralized database for the CANWARD study results was undertaken by International Health Management Associates, Schaumburg, IL, USA.

Characterization of MRSA isolates

Screening for methicillin resistance was performed using CLSI-approved disc diffusion with cefoxitin[9] as well as by growth on MRSA Select chromogenic media (Bio-Rad Laboratories Ltd, Mississauga, Ontario, Canada). Potential MRSA isolates were confirmed by *mecA* PCR, as previously described.[10] All isolates of MRSA were typed using staphylococcal protein A (*spa*) typing to assess whether the isolates were CA or HA genotypes.[10,11] Isolates with a *spa* type associated with C(Canadian)MRSA7 or CMRSA10 were considered CA-MRSA. Isolates with a *spa* type associated with CMRSA1, CMRSA2, CMRSA4, CMRSA5, CMRSA3/6, CMRSA8 or CMRSA9 were considered HA-MRSA.[11]

Characterization of ESBL-producing E. coli isolates

Potential *E. coli* ESBL producers were identified as isolates with a ceftriaxone and/or ceftazidime MIC of ≥1 mg/L and confirmed using the CLSI double-disc diffusion method, as previously described.[12]

Characterization of VRE isolates

Potential VRE isolates were confirmed by *vanA* and *vanB* PCR, as previously described.[5,13]

Results

Patient demographics and specimen types

A total of 27123 organisms were collected between 2007 and 2011. There were 14744 (54.4%) obtained from males and 12379 (45.6%) from females. All isolates were obtained from bacteraemic (n=12261, 45.2%), urinary (n=4012, 14.8%), respiratory (n=8020, 29.6%) and wound (n=2830, 10.4%) specimens from hospitals across Canada. By age group, 3465 (12.8%),

12 234 (45.1%) and 11 424 (42.1%) isolates were received from patients 0–17, 18–64 and ≥65 years of age, respectively. With regard to hospital location, 4879 (18.0%), 6963 (25.7%), 5010 (18.5%), 7819 (28.8%) and 2452 (9.0%) isolates were received from patients in clinics, emergency rooms, ICUs, medical wards and surgical wards, respectively. The numbers of isolates referred from centres in different geographical locations were as follows: 4548 (16.8%) from British Columbia/Alberta, 4571 (16.9%) from Manitoba/Saskatchewan, 8021 (29.6%) from Ontario, 6903 (25.5%) from Quebec and 3080 (11.4%) from New Brunswick/Nova Scotia.

Most common organisms isolated

Of the 27 123 organisms collected, the 20 most common species accounted for 89.4% of the total ($n=24\,235$) (Table 1). The 20 most common isolated species comprised 11 193 (46.2%) Gram-positive cocci (MSSA, MRSA, CoNS/*Staphylococcus epidermidis*, *Streptococcus* spp. and *Enterococcus* spp.) as well as 13 042 (53.8%) Gram-negative species, including *E. coli*, *P. aeruginosa*, *Klebsiella* spp., *Haemophilus influenzae*, *Enterobacter* spp., *Proteus mirabilis*, *Serratia marcescens*, *Stenotrophomonas maltophilia* and *Moraxella catarrhalis* (Table 1). No significant changes occurred over the study period (2007–11) in the proportions of individual Gram-positive cocci and Gram-negative bacilli causing infections in Canadian hospitals. For example, *S. pneumoniae* continued to be the first or second most common pathogen causing respiratory tract infections and this did not change year to year.

Table 1. The 20 most common organisms isolated from Canadian hospitals

Rank	Organism	*n*	% of total
1	*E. coli*	5451	20.1
2	*S. aureus*	5443	20.0
3	*P. aeruginosa*	2183	8.0
4	*S. pneumoniae*	1881	6.9
5	*K. pneumoniae*	1659	6.1
6	CoNS/*S. epidermidis*	1180	4.4
7	*H. influenzae*	1038	3.8
8	*E. faecalis*	753	2.8
9	*E. cloacae*	637	2.3
10	*Enterococcus* spp.	578	2.1
11	*S. agalactiae*	432	1.6
12	*S. pyogenes*	424	1.6
13	*P. mirabilis*	415	1.5
14	*S. marcescens*	412	1.5
15	*K. oxytoca*	411	1.5
16	*S. maltophilia*	378	1.4
17	*M. catarrhalis*	293	1.1
18	*E. faecium*	271	1.0
19	viridans group streptococci	231	0.9
20	*E. aerogenes*	165	0.6
	other[a]	2888	10.6
	total	27 123	

CoNS, coagulase-negative staphylococci.
[a]Other: *Acinetobacter* spp., *Aeromonas* spp., *Alcaligenes* spp., *Bacillus* spp., *Brevibacterium* spp., *Candida* spp., *Cedecea* spp., *Chryseobacterium* spp., *Citrobacter* spp., *Corynebacterium* spp., *Enterobacter* spp., *Enterococcus* spp., *Escherichia* spp., *Gemella* spp., *Granulicatella* spp., *Haemophilus* spp., *Hafnia* spp., *Klebsiella* spp., *Listeria* spp., *Micrococcus* spp., *Moraxella* spp., *Morganella* spp., *Neisseria* spp., *Pantoea* spp., *Pasteurella* spp., *Proteus* spp., *Providencia* spp., *Pseudomonas* spp., *Ralstonia* spp., *Salmonella* spp., *Serratia* spp., *Staphylococcus* spp. and *Streptococcus* spp.

Antimicrobial activity against Gram-positive cocci

The *in vitro* activity of various antimicrobials against MSSA, MRSA (including HA-MRSA and CA-MRSA), *S. epidermidis* [including methicillin-susceptible (MSSE) and methicillin-resistant (MRSE)], *S. pneumoniae*, *S. agalactiae*, *S. pyogenes*, *E. faecalis* and *Enterococcus faecium* is displayed in Table 2. Limited resistance was observed among *S. aureus* (MSSA), with the exception of clarithromycin, the fluoroquinolones and clindamycin. Only 22 of the 4177 MSSA (0.5%) displayed vancomycin MICs of 2 mg/L. Resistance rates of MRSA isolates were 83.6%–85.9% for fluoroquinolones, 87.7% for clarithromycin, 51.7% for clindamycin and 7.8% for trimethoprim/sulfamethoxazole. The most active agents tested against MRSA were daptomycin, linezolid and telavancin (100% susceptibility), followed by vancomycin and tigecycline (99.9% and 99.8% susceptibility, respectively). Twenty-seven of 1266 (2.1%) MRSA displayed vancomycin MICs of 2 mg/L, while one (0.08%) MRSA isolate displayed a vancomycin MIC of 4 mg/L. The proportion of MRSA with vancomycin MICs of 2 mg/L was 1.0% (3/385) in 2007, 3.2% (9/274) in 2008, 6.1% (10/163) in 2009, 2.7% (6/223) in 2010 and 0% (0/154) in 2011 ($P>0.05$). Fluoroquinolones, clindamycin, clarithromycin and trimethoprim/sulfamethoxazole were more active against CA-MRSA than against HA-MRSA (Table 2). The activity of daptomycin, linezolid, tigecycline and vancomycin was comparable for HA-MRSA and CA-MRSA.

Among MSSE, resistance was observed with clarithromycin, clindamycin, gentamicin, fluoroquinolones and trimethoprim/sulfamethoxazole. The most active agents tested against MRSE were vancomycin, daptomycin and linezolid (100% susceptibility). Forty-five of the 85 MRSE (52.9%) displayed vancomycin MICs of 2 mg/L. Telavancin and tigecycline were active against MRSE, with MIC_{90} values of 0.5 and 0.25 mg/L, respectively.

With *S. pneumoniae*, limited resistance was observed, with the exception of cefuroxime (4.3%), clarithromycin (16%), clindamycin (6.2%), doxycycline (3.8%), penicillin (MIC_{90} of 0.25 mg/L, with 4.5% resistance) and trimethoprim/sulfamethoxazole (8.7%). Isolates were uniformly susceptible to linezolid and vancomycin. Telavancin was very active against *S. pneumoniae*, with an MIC_{90} of ≤0.06 mg/L. Susceptibility testing with clarithromycin and clindamycin suggested that ∼40% of isolates displayed altered target site resistance to macrolides, while ∼60% of *S. pneumoniae* demonstrated efflux-mediated resistance to macrolides. Both *S. pyogenes* and *S. agalactiae* were extensively susceptible to the tested antimicrobials, although clarithromycin resistance was noted in 9.7% and 25.4% of isolates, respectively.

Against *E. faecalis* and *E. faecium*, ciprofloxacin/levofloxacin resistance was seen in 33.6%/33.5% and 90.6%/89.2% of isolates, respectively. *E. faecalis* and *E. faecium* were 100% susceptible to daptomycin; additionally, linezolid and tigecycline were very active. Twenty-two percent (61/271) of *E. faecium* were

Table 2. Antimicrobial activity against most common Gram-positive cocci isolated from Canadian hospitals

Organism (no. tested)/antimicrobial agent	% S	% I	% R	MIC (mg/L)				
				MIC_{50}	MIC_{90}	range		
S. aureus, MSSA (n=4177)								
cefazolin	100[a]			≤0.5	1	≤0.5	–	32
ciprofloxacin	85.9	3.0	11.1	0.5	8	≤0.06	to	>16
clarithromycin	74.8	0.3	24.9	0.25	>32	≤0.12	to	>16
clindamycin	92.5	0.4	7.1	≤0.12	0.25	≤0.12	to	>8
daptomycin	100			0.12	0.25	≤0.03	–	1
gentamicin	97.8	0.1	2.1	≤0.5	1	≤0.5	to	>32
levofloxacin	90.1	0.3	9.6	0.25	1	≤0.06	to	>32
linezolid	100			2	2	≤0.12	–	4
moxifloxacin	90.1	0.6	9.3	≤0.06	0.25	≤0.06	to	>16
nitrofurantoin	100			16	16	≤0.5	–	32
telavancin	100			0.25	0.5	≤0.06	–	1
tigecycline	99.9			0.25	0.25	≤0.03	–	1
trimethoprim/sulfamethoxazole	99.5		0.5	≤0.12	0.12	≤0.12	to	>8
vancomycin	100			1	1	≤0.12	–	2
S. aureus, MRSA (n=1266)								
cefazolin			100[a]	64	>128	1	to	>128
ciprofloxacin	13.7	0.3	85.9	>16	>16	0.12	to	>16
clarithromycin	12.2	0.1	87.7	>32	>32	≤0.03	to	>32
clindamycin	48.2	0.1	51.7	>8	>8	≤0.12	to	>8
daptomycin	100			0.25	0.25	0.06	–	1
gentamicin	91.0	0.1	8.9	≤0.5	1	≤0.5	to	>32
levofloxacin	14.1		85.9	>32	>32	0.12	to	>32
linezolid	100			2	2	≤0.12	–	4
moxifloxacin	14.4	2.1	83.6	8	>16	≤0.06	to	>16
nitrofurantoin	100			16	16	8	–	32
telavancin	100			0.25	0.5	≤0.06	–	1
tigecycline	99.8			0.25	0.5	0.06	–	2
trimethoprim/sulfamethoxazole	92.2		7.8	≤0.12	0.5	≤0.12	to	>8
vancomycin	99.9	0.1		1	1	≤0.25	–	4
S. aureus, MRSA (HA) (n=868)								
cefazolin			100[a]	128	>128	1	to	>128
ciprofloxacin	2.8		97.2	>16	>16	0.25	to	>16
clarithromycin	4.6		95.4	>16	>16	≤0.03	to	>32
clindamycin	30.4	0.1	69.5	>8	>8	≤0.12	to	>8
daptomycin	100			0.25	0.25	0.06	–	1
gentamicin	87.6	0.1	12.3	≤0.5	>32	≤0.5	to	>32
levofloxacin	3.0		97.1	>32	>32	0.12	to	>32
linezolid	100			2	4	≤0.12	–	4
moxifloxacin	2.9	0.1	97.0	8	>16	≤0.06	to	>16
nitrofurantoin	100			16	16	8	–	32
telavancin	100			0.25	0.5	≤0.06	–	1
tigecycline	99.7			0.25	0.5	0.06	–	2
trimethoprim/sulfamethoxazole	88.6		11.4	≤0.12	8	≤0.12	to	>8
vancomycin	99.9	0.1		1	1	≤0.25	–	4
S. aureus, MRSA (CA) (n=366)								
cefazolin			100[a]	16	64	1	to	>128
ciprofloxacin	33.6	0.8	65.6	16	>16	0.12	to	>32
clarithromycin	24.7	0.3	75.0	32	>32	0.12	to	>32
clindamycin	87.1		12.9	≤0.12	>8	≤0.12	to	>8

Continued

Table 2. *Continued*

Organism (no. tested)/antimicrobial agent	% S	% I	% R	MIC (mg/L) MIC_{50}	MIC_{90}	range		
daptomycin	100			0.25	0.25	0.12	–	1
gentamicin	98.4		1.6	≤0.5	1	≤0.5	to	>32
levofloxacin	40.0		60.0	4	8	0.12	–	32
linezolid	100			2	2	1	–	4
moxifloxacin	35.3	6.8	57.9	2	2	≤0.06	–	16
nitrofurantoin	100			16	16	8	–	16
telavancin	100			0.25	0.5	0.12	–	1
tigecycline	100			0.25	0.25	0.06	–	0.5
trimethoprim/sulfamethoxazole	100			≤0.12	≤0.12	≤0.12	–	2
vancomycin	100			1	1	0.5	–	2
S. epidermidis, MSSE (*n*=475)								
cefazolin	100[a]			1	4	≤0.5	–	8
ciprofloxacin	51.4	1.5	47.2	0.5	>16	≤0.06	to	>16
clarithromycin	34.2	1.5	64.4	>16	>16	≤0.25	to	>16
clindamycin	61.6	0.8	37.6	≤0.25	>8	≤0.25	to	>8
daptomycin	100			0.12	0.25	≤0.06	–	1
gentamicin	60.8	4.4	34.7	≤0.5	>32	≤0.5	to	>32
levofloxacin	51.9	1.1	47.0	0.25	>32	0.12	to	>32
linezolid	100			0.5	1	≤0.12	–	4
moxifloxacin	53.1	8.0	39.0	0.12	8	≤0.06	to	>16
nitrofurantoin	100			8	16	2	–	16
telavancin				0.25	0.5	≤0.06	–	1
tigecycline				0.12	0.5	≤0.03	–	1
trimethoprim/sulfamethoxazole	66.1		33.9	≤0.12	8	≤0.12	to	>8
vancomycin	100			1	2	≤0.25	–	4
S. epidermidis, MRSE (*n*=85)								
cefazolin			100[a]	128	>128	32	to	>128
ciprofloxacin	2.4	1.2	96.5	>16	>16	0.12	to	>16
clarithromycin	15.3		84.7	>16	>16	≤0.25	to	>16
clindamycin	17.7		86.7	>8	>8	≤0.25	to	>8
daptomycin	100			0.12	0.25	≤0.06	–	0.5
gentamicin	14.1	7.1	78.8	>32	>32	≤0.5	to	>32
levofloxacin	2.2	2.2	95.6	>32	>32	1	to	>32
linezolid	100			1	1	≤0.12	–	2
moxifloxacin	3.5	2.4	94.1	>16	>16	0.06	to	>16
nitrofurantoin	100			16	16	4	–	16
telavancin				0.25	0.5	≤0.06	–	1
tigecycline				0.12	0.25	0.06	–	0.5
trimethoprim/sulfamethoxazole	20.0		80.0	4	8	≤0.12	–	>8
vancomycin	100			1	2	≤0.25	–	2
S. pneumoniae (*n*=1881)								
amoxicillin/clavulanic acid	98.2	1.0	0.9	≤0.06	0.12	≤0.06	–	16
ceftriaxone[b]	99.3	0.5	0.2	≤0.06	0.12	≤0.06	–	4
cefuroxime	93.7	2.0	4.3	≤0.25	0.5	≤0.25	to	>16
ciprofloxacin				1	2	≤0.06	to	>16
clarithromycin	80.3	3.7	16.0	≤0.03	4	≤0.03	to	>32
clindamycin	93.1	0.6	6.2	≤0.12	≤0.12	≤0.12	to	>64
doripenem	99.9		0.1	≤0.03	0.06	≤0.03	–	2
doxycycline[c]	93.1	3.1	3.8	≤0.25	1	≤0.25	to	>16
ertapenem	99.3	0.7	0.1	≤0.06	0.12	≤0.06	–	4
levofloxacin	99.1	0.2	0.7	0.5	1	≤0.06	–	32

Continued

Table 2. *Continued*

Organism (no. tested)/antimicrobial agent	% S	% I	% R	MIC (mg/L)				
				MIC_{50}	MIC_{90}	range		
linezolid	100			0.5	1	≤0.12	–	2
meropenem	95.6	2.8	1.6	≤0.06	≤0.06	≤0.06	–	2
moxifloxacin	99.1	0.4	0.6	0.12	0.25	≤0.06	–	8
penicillin[b]	81.7	13.9	4.5	≤0.03	0.25	≤0.03	to	>8
piperacillin/tazobactam				≤1	≤1	≤1	–	8
telavancin				≤0.03	≤0.06	≤0.03	–	0.12
telithromycin	99.9	0.1		0.008	0.03	≤0.008	–	2
tigecycline	99.7			0.03	0.06	≤0.015	–	0.25
trimethoprim/sulfamethoxazole	84.8	6.5	8.7	≤0.12	2	≤0.12	to	>8
vancomycin	100			≤0.25	0.25	≤0.12	–	1
S. agalactiae (*n*=432)								
amoxicillin/clavulanic acid				≤0.06	≤0.06	≤0.06	–	0.25
ceftriaxone	100			≤0.06	0.12	≤0.06	–	0.25
cefuroxime				≤0.25	≤0.25	≤0.25	–	0.5
ciprofloxacin				1	2	0.25	to	>16
clarithromycin	69.6	5.1	25.4	≤0.03	>32	≤0.03	to	>32
clindamycin	83.3	1.5	15.2	≤0.12	>8	≤0.12	to	>64
daptomycin	100			0.12	0.25	≤0.03	–	0.5
doripenem	100			≤0.06	≤0.06	≤0.03	to	≤0.06
doxycycline				8	16	≤0.25	to	>16
ertapenem	100			≤0.06	≤0.06	≤0.06	–	0.12
levofloxacin	97.8		2.2	1	1	0.25	to	>32
linezolid	100			1	1	≤0.12	–	2
meropenem	100			≤0.06	≤0.06	≤0.06	to	≤0.06
moxifloxacin				0.12	0.25	≤0.06	–	4
penicillin	99.3		0.7	0.12	0.12	≤0.03	–	0.25
piperacillin/tazobactam				≤1	≤1	≤1	to	≤1
telavancin	100			≤0.06	0.12	≤0.03	–	0.12
telithromycin				0.015	0.12	≤0.002	–	0.25
tigecycline	100			0.06	0.12	≤0.015	–	0.12
trimethoprim/sulfamethoxazole				≤0.12	≤0.12	≤0.12	–	0.5
vancomycin	100			0.5	0.5	≤0.25	–	0.5
S. pyogenes (*n*=424)								
amoxicillin/clavulanic acid				≤0.06	≤0.06	≤0.06	–	0.12
ceftriaxone	100			≤0.12	≤0.12	≤0.06	–	0.25
cefuroxime				≤0.25	≤0.25	≤0.25	to	≤0.25
ciprofloxacin				0.5	1	≤0.06	–	8
clarithromycin	84.5	2.8	9.7	≤0.03	0.5	≤0.03	to	>32
clindamycin	98.2		1.8	≤0.12	≤0.12	≤0.12	to	>64
daptomycin	100			≤0.03	0.06	≤0.03	–	0.25
doripenem				≤0.03	≤0.06	≤0.03	–	0.06
doxycycline				≤0.25	0.5	≤0.25	–	16
ertapenem	100			≤0.06	≤0.06	≤0.06	–	0.12
levofloxacin	99.7	0.3		0.5	1	≤0.06	–	4
linezolid	100			1	1	≤0.12	–	2
meropenem	100			≤0.06	≤0.06	≤0.06	–	0.12
moxifloxacin				0.12	0.25	≤0.06	–	0.5
penicillin	100			≤0.03	≤0.03	≤0.03	–	0.12
piperacillin/tazobactam				≤1	≤1	≤1	to	≤1
telavancin	100			0.06	0.06	≤0.03	–	0.12

Continued

Table 2. *Continued*

Organism (no. tested)/antimicrobial agent	% S	% I	% R	MIC (mg/L)				
				MIC_{50}	MIC_{90}	range		
telithromycin				0.008	0.015	≤0.002	–	2
tigecycline	100			0.03	0.06	≤0.015	–	0.25
trimethoprim/sulfamethoxazole				≤0.12	≤0.12	≤0.12	–	8
vancomycin	100			0.5	0.5	≤0.12	–	1
E. faecalis (*n*=753)								
amoxicillin/clavulanic acid				0.5	1	≤0.06	to	>32
cefazolin				32	64	0.5	to	>128
cefepime				>32	>64	≤0.25	to	>128
cefoxitin				>32	>32	≤0.06	to	>32
ceftriaxone				>64	>64	≤0.25	to	>256
ciprofloxacin	54.2	12.3	33.6	1	>16	0.25	to	>16
clarithromycin				2	>32	≤0.03	to	>32
clindamycin				>8	>8	≤0.12	to	>8
daptomycin	100			0.5	1	≤0.03	–	4
doripenem				4	8	≤0.06	to	>32
ertapenem				8	16	0.25	to	>32
gentamicin				8	>32	≤0.5	to	>32
levofloxacin	65.5	1.1	33.5	2	>32	0.25	to	>32
linezolid	99.5	4.5		2	2	0.5	–	4
meropenem				4	8	≤0.06	to	>32
moxifloxacin				0.5	16	≤0.06	to	>16
nitrofurantoin	99.5	0.6		8	8	2	–	64
piperacillin/tazobactam				4	8	≤1	to	>512
tigecycline	97.4			0.12	0.25	≤0.03	–	0.5
trimethoprim/sulfamethoxazole				≤0.12	0.5	≤0.12	to	>8
vancomycin	99.9		0.1	1	2	0.25	to	>32
E. faecium (*n*=271)								
amoxicillin/clavulanic acid				>32	>32	0.12	to	>32
cefazolin				>128	>128	2	to	>128
cefepime				>64	>64	2	to	>128
ceftriaxone				>64	>64	0.5	to	>256
ciprofloxacin	6.7	2.6	90.6	>16	>16	0.25	to	>16
clarithromycin				>32	>32	≤0.03	to	>32
clindamycin				>8	>8	≤0.12	to	>8
daptomycin	100			1	2	≤0.03	–	4
doripenem				>32	>32	1	to	>64
ertapenem				>32	>32	4	to	>32
gentamicin				8	>32	≤0.5	to	>32
levofloxacin	9.6	1.3	89.2	>32	>32	1	to	>32
linezolid	88.8	11.2		2	4	≤0.12	–	4
meropenem				>32	>32	2	to	>64
moxifloxacin				>16	>16	0.12	to	>16
nitrofurantoin	41.2	28.2	30.6	64	128	4	–	256
piperacillin/tazobactam				>512	>512	2	to	>512
tigecycline				0.12	0.12	≤0.03	–	0.5
trimethoprim/sulfamethoxazole				0.5	>8	≤0.12	to	>8
vancomycin	77.6		22.4	1	>32	≤0.12	to	>32

Continued

Table 2. *Continued*

Organism (no. tested)/antimicrobial agent	% S	% I	% R	MIC (mg/L) MIC_{50}	MIC_{90}	range		
VRE ($n=61$)								
amoxicillin/clavulanic acid				>32	>32	4	to	>32
cefazolin				>128	>128	2	to	>128
cefepime				>32	>32	>32	to	>32
ceftriaxone				>64	>64	>64	to	>64
ciprofloxacin			100	>16	>16	>16	to	>16
clarithromycin				>16	>16	1	to	>16
clindamycin				>8	>8	≤0.12	to	>8
daptomycin	100			1	2	≤0.03	–	2
doripenem				>32	>32	16	to	>32
ertapenem				>32	>32	>32	to	>32
gentamicin				8	>32	4	to	>32
levofloxacin			100	>32	>32	32	to	>32
linezolid	94.1	5.9		2	2	0.5	–	4
meropenem				>32	>32	>32	to	>32
moxifloxacin				>16	>16	16	to	>16
nitrofurantoin	32.7	24.6	42.7	64	128	4	–	128
piperacillin/tazobactam				>512	>512	64	to	>512
tigecycline				0.12	0.12	0.03	–	0.25
trimethoprim/sulfamethoxazole				0.5	>8	≤0.12	to	>8
vancomycin			100	>32	>32	32	to	>32

S, susceptible; I, intermediate; R, resistant; VRE, vancomycin-resistant enterococci (55 *vanA* and 6 *vanB*).
FDA-approved breakpoints used to interpret tigecycline and telavancin.
[a]Based upon oxacillin susceptibility.
[b]Interpreted with CLSI breakpoints: ceftriaxone (non-meningitis) and penicillin (oral penicillin V).
[c]Tetracycline breakpoints used to interpret MIC values.

vancomycin resistant (90.2% *vanA* and 9.8% *vanB*). The most active agents tested against VRE were daptomycin, linezolid and tigecycline, with MIC_{90} values of 2, 2 and 0.12 mg/L, respectively.

Antimicrobial activity against Gram-negative bacilli

The *in vitro* activity of various antimicrobials against *E. coli* (including ESBL-producing isolates), *P. aeruginosa*, *Klebsiella pneumoniae*, *H. influenzae*, *Enterobacter cloacae*, *P. mirabilis*, *Klebsiella oxytoca*, *S. marcescens*, *S. maltophilia*, *Enterobacter aerogenes*, *Citrobacter freundii* and *Acinetobacter baumannii* is displayed in Table 3. For *E. coli*, resistance rates >20% were noted for trimethoprim/sulfamethoxazole, ciprofloxacin and levofloxacin. The most active agents against *E. coli* were amikacin, cefepime, ceftazidime, doripenem, ertapenem, meropenem, nitrofurantoin, piperacillin/tazobactam and tigecycline. ESBL-producing *E. coli* displayed elevated resistance rates to ciprofloxacin, trimethoprim/sulfamethoxazole and gentamicin. All ESBL-producing *E. coli* were susceptible to doripenem and meropenem, while ertapenem (97.4% susceptible), amikacin (95.7% susceptible), nitrofurantoin (94.4% susceptible) and tigecycline (99.6% susceptible) were very active.

The most active agents tested against *P. aeruginosa* were colistin (polymyxin E), amikacin, doripenem, piperacillin/tazobactam, ceftazidime and meropenem. The resistance of *P. aeruginosa* to fluoroquinolones and gentamicin was high (15%–25%). For *K. pneumoniae*, meropenem, doripenem, ertapenem and amikacin demonstrated susceptibility rates >99%. All agents were active against *H. influenzae*, except ampicillin and trimethoprim/sulfamethoxazole with 17.2% and 13.1% resistance, respectively. With *E. cloacae*, >99% of isolates were susceptible to amikacin, meropenem, doripenem and cefepime. All *P. mirabilis* isolates were susceptible to cefepime, doripenem, ertapenem, meropenem and piperacillin/tazobactam. With *S. marcescens*, >98% of isolates were susceptible to meropenem, doripenem, ertapenem, cefepime, ceftazidime and amikacin. With *K. oxytoca*, all agents were very active, except cefazolin with 56.1% resistance. The most active agents tested against *S. maltophilia* were trimethoprim/sulfamethoxazole and levofloxacin, with 86.6% and 66.9% susceptibility, respectively. Tigecycline demonstrated good activity against *S. maltophilia*, with MIC_{50} and MIC_{90} values of 2 and 8 mg/L, respectively. The most active agents tested against *A. baumannii* were amikacin, meropenem, colistin and levofloxacin, with susceptibility rates >93% for all four agents.

Table 3. Antimicrobial activity against the most common Gram-negative bacilli isolated from Canadian hospitals

Organism (no. tested)/antimicrobial agent	% S	% I	% R	MIC (mg/L)				
				MIC_{50}	MIC_{90}	range		
E. coli (*n*=5451)								
amikacin	99.6	0.3	0.1	≤2	4	≤1	to	>64
amoxicillin/clavulanic acid	89.0	7.7	3.3	4	16	≤0.06	to	>32
cefazolin	70.2	13.1	16.7	2	16	≤0.5	to	>128
cefepime	97.7	1.2	1.1	≤0.25	1	≤0.25	to	>64
cefoxitin	91.9	4.1	4.0	4	8	≤0.06	to	>32
ceftazidime	95.2	0.6	4.2	≤0.25	1	≤0.25	to	>32
ceftriaxone	93.7	0.3	6.0	≤0.25	1	≤0.25	to	>256
ciprofloxacin	77.9	0.3	21.8	≤0.06	>16	≤0.06	to	>16
colistin				0.25	0.5	≤0.06	to	>16
doripenem	99.9[a]	0.1[a]		≤0.06	0.12	≤0.03	–	2
ertapenem	99.7	0.2	0.1	≤0.03	0.06	≤0.03	–	8
gentamicin	90.5	0.4	9.1	≤0.5	4	≤0.5	to	>32
levofloxacin	78.8	0.7	20.6	≤0.06	16	≤0.06	to	>32
meropenem	100			≤0.06	0.12	≤0.03	–	1
moxifloxacin	78.0	0.4	21.6	≤0.06	>16	≤0.06	to	>16
nitrofurantoin	96.7	2.3	1.1	16	32	≤0.5	to	>256
piperacillin/tazobactam	97.7	1.2	1.1	2	4	≤1	to	>512
tigecycline	99.9	0.1		0.25	0.5	0.06	–	4
trimethoprim/sulfamethoxazole	73.4		26.7	≤0.12	>8	≤0.12	to	>8
ESBL *E. coli* (*n*=231)								
amikacin	95.7	3.9	0.4	4	16	≤1	to	>64
amoxicillin/clavulanic acid	62.3	33.8	3.9	8	16	1	to	>32
cefazolin			100	>128	>128	16	to	>128
cefepime	53.2	24.9	21.9	8	>32	≤0.25	to	>64
cefoxitin	81.3	7.7	11.0	8	32	0.5	to	>32
ceftazidime	36.5	7.3	56.2	16	>32	≤0.5	to	>32
ceftriaxone	1.3	1.7	97.0	>64	>64	≤0.25	to	>64
ciprofloxacin	10.8	0.9	88.3	>16	>16	≤0.06	to	>16
colistin				0.5	1	≤0.06	–	4
doripenem	100			≤0.03	0.12	≤0.03	–	0.5
ertapenem	97.4	1.3	1.3	≤0.06	0.25	≤0.03	–	4
gentamicin	51.1	0.4	48.5	4	>32	≤0.5	to	>32
levofloxacin	12.9	1.3	85.8	16	32	≤0.06	to	>32
meropenem	100			≤0.06	0.12	≤0.03	–	1
moxifloxacin	10.8		89.2	16	>16	≤0.06	to	>16
nitrofurantoin	94.4	4.6	0.9	16	32	1	to	>256
piperacillin/tazobactam	93.1	4.8	2.2	4	16	≤1	to	>512
tigecycline	99.6	0.4		0.5	1	0.12	–	4
trimethoprim/sulfamethoxazole	29.9		70.1	>8	>8	≤0.12	to	>8
P. aeruginosa (*n*=2183)								
amikacin	90.1	4.5	5.4	4	16	≤1	to	>64
amoxicillin/clavulanic acid				>32	>32	0.5	to	>32
cefazolin				>128	>128	16	to	>128
cefepime	77.2	15.2	7.6	4	16	≤0.25	to	>128
cefoxitin				>32	>32	2	to	>32
ceftazidime	83.5	5.1	11.4	4	32	≤0.25	to	>32
ceftriaxone	25.3	43.2	31.6	16	>64	≤0.25	to	>32
ciprofloxacin	71.9	8.8	19.4	0.25	8	≤0.06	to	>16
colistin	93.1	5.9	1.1	2	2	≤0.06	to	>16

Continued

Table 3. *Continued*

Organism (no. tested)/antimicrobial agent	% S	% I	% R	MIC (mg/L)				
				MIC_{50}	MIC_{90}	range		
doripenem	84.2	6.3	9.5	0.5	4	≤0.03	to	>64
ertapenem				8	>32	0.06	to	>32
gentamicin	72.0	13.2	14.9	4	16	≤0.5	to	>32
levofloxacin	63.5	12.1	24.5	1	16	≤0.06	to	>32
meropenem	82.6	6.3	11.1	0.5	8	≤0.03	to	>64
moxifloxacin				4	>16	≤0.06	to	>16
nitrofurantoin				>256	>256	16	to	>256
piperacillin/tazobactam	84.0	8.6	7.4	4	64	≤1	to	>512
tigecycline				>16	>16	0.25	to	>16
trimethoprim/sulfamethoxazole				8	>8	≤0.12	to	>8
K. pneumoniae (*n*=1659)								
amikacin	99.6	0.1	0.3	≤2	≤2	≤1	to	>64
amoxicillin/clavulanic acid	94.8	3.1	2.1	2	8	0.5	to	>32
cefazolin	82.3	6.7	11.0	2	8	≤0.5	to	>128
cefepime	98.2	0.4	1.4	≤0.25	1	≤0.25	–	128
cefoxitin	91.9	4.5	3.6	4	8	0.12	to	>32
ceftazidime	96.8	0.3	3.0	≤0.25	1	≤0.25	to	>32
ceftriaxone	95.7	1.3	6.5	≤0.25	0.5	≤0.25	to	>256
ciprofloxacin	92.2	1.3	6.5	≤0.06	0.5	≤0.06	to	>16
colistin				0.5	1	≤0.06	to	>16
doripenem	99.9		0.1	≤0.06	0.12	≤0.03	–	4
ertapenem	99.6	0.3	0.1	≤0.03	0.06	≤0.03	–	16
gentamicin	97.0	0.3	2.7	≤0.5	≤0.5	≤0.5	to	>32
levofloxacin	93.8	1.8	4.5	≤0.06	1	≤0.06	to	>32
meropenem	99.9		0.1	≤0.06	0.12	≤0.03	–	4
moxifloxacin	92.8	2.5	4.8	0.12	1	≤0.06	to	>16
nitrofurantoin	36.1	32.0	31.8	64	128	2	to	>256
piperacillin/tazobactam	96.9	1.2	1.9	2	8	≤1	to	>512
tigecycline	95.3	3.9	0.8	1	2	0.06	–	16
trimethoprim/sulfamethoxazole	90.8		9.2	≤0.12	2	≤0.12	to	>8
H. influenzae (*n*=1038)								
amoxicillin/clavulanic acid	99.9		0.1	0.5	2	≤0.06	–	8
ampicillin	81.2	1.6	17.2	≤0.25	8	≤0.25	to	>128
cefepime	100			≤0.25	≤0.25	≤0.25	–	2
ceftriaxone	99.7		0.3	≤0.06	≤0.06	≤0.06	to	>4
cefuroxime	96.5	2.7	0.9	1	4	≤0.25	to	>16
ciprofloxacin	100			≤0.015	≤0.015	≤0.015	to	>0.5
clarithromycin	86.8	11.2	2.0	4	16	≤0.03	to	>32
doripenem	98.1		1.9	≤0.06	0.25	≤0.06	–	2
doxycycline				0.5	1	≤0.25	–	8
ertapenem	99.7		0.3	≤0.03	0.12	≤0.03	to	>4
gentamicin				1	2	≤0.5	–	16
levofloxacin	100			≤0.015	0.03	≤0.015	–	0.5
meropenem	99.6		0.4	≤0.06	0.12	≤0.06	–	2
moxifloxacin	100			≤0.015	0.03	≤0.015	–	0.5
piperacillin/tazobactam	99.5		0.5	≤1	≤1	≤1	–	8
telithromycin	98.2	1.2	0.7	1	4	≤0.03	to	>32
trimethoprim/sulfamethoxazole	83.3	3.5	13.1	≤0.12	4	≤0.12	to	>8

Continued

Table 3. *Continued*

Organism (no. tested)/antimicrobial agent	% S	% I	% R	MIC (mg/L) MIC_{50}	MIC_{90}	range		
E. cloacae (*n*=637)								
amikacin	100			≤2	2	≤2	–	16
amoxicillin/clavulanic acid	12.7	18.1	69.2	32	>32	2	to	>32
cefazolin	2.0	1.1	96.9	128	>128	1	to	>128
cefepime	99.8	0.2		≤0.25	2	≤0.25	–	16
cefoxitin	11.4	6.5	82.1	>32	>32	2	to	>32
ceftazidime	80.7	1.1	18.3	0.5	>32	≤0.25	to	>32
ceftriaxone	74.3	2.0	23.7	≤0.25	64	≤0.25	to	>256
ciprofloxacin	93.9	1.6	4.6	≤0.06	0.25	≤0.06	to	>16
colistin				0.5	>16	≤0.06	to	>16
doripenem	99.7	0.2	0.2	≤0.06	0.12	≤0.03	–	8
ertapenem	92.6	4.2	3.1	≤0.06	0.5	≤0.06	–	16
gentamicin	97.3	0.2	2.5	≤0.5	≤0.5	≤0.5	to	>32
levofloxacin	94.8	3.8	1.4	≤0.06	0.5	≤0.06	–	32
meropenem	99.7	0.3		≤0.06	0.12	≤0.03	–	2
moxifloxacin	94.5	2.4	3.1	≤0.06	0.5	≤0.06	to	>16
nitrofurantoin	47.9	39.8	12.4	64	128	2	to	>256
piperacillin/tazobactam	85.7	8.0	6.3	2	64	≤1	–	512
tigecycline	94.4	4.1	1.6	1	1	0.25	–	16
trimethoprim/sulfamethoxazole	92.5		7.5	≤0.12	1	≤0.12	to	>8
P. mirabilis (*n*=415)								
amikacin	99.8	0.2		2	4	≤1	–	32
amoxicillin/clavulanic acid	96.4	2.1	1.5	1	4	0.5	to	>32
cefazolin	3.4	50.7	45.9	4	8	1	to	>128
cefepime	100			≤0.25	1	≤0.25	–	2
cefoxitin	97.0	2.1	0.9	4	4	1	to	>32
ceftazidime	99.0		1.0	≤0.25	0.5	≤0.25	–	32
ceftriaxone	98.3	0.5	1.2	≤0.25	1	≤0.25	–	16
ciprofloxacin	85.5	6.5	8.0	≤0.06	2	≤0.06	to	>16
colistin				>16	>16	0.5	to	>16
doripenem	100			0.12	0.25	≤0.03	–	1
ertapenem	100			≤0.03	0.06	≤0.03	–	0.25
gentamicin	95.2	1.0	3.9	1	2	≤0.5	to	>32
levofloxacin	90.3	3.8	5.9	0.12	2	≤0.06	to	>32
meropenem	100			0.06	0.12	≤0.03	–	0.5
moxifloxacin	81.9	1.7	16.4	0.5	16	≤0.06	to	>16
nitrofurantoin		7.6	92.4	128	256	64	to	>256
piperacillin/tazobactam	100			≤1	≤1	≤1	–	8
tigecycline	8.2	32.1	59.7	8	16	1	to	>16
trimethoprim/sulfamethoxazole	84.1		15.9	≤0.12	>8	≤0.12	to	>8
K. oxytoca (*n*=411)								
amikacin	99.8		0.2	≤2	2	≤1	to	>64
amoxicillin/clavulanic acid	91.5	4.1	4.4	2	8	1	to	>32
cefazolin	25.4	18.5	56.1	8	128	≤0.5	to	>128
cefepime	99.7	0.3		≤0.25	1	≤0.25	–	16
cefoxitin	97.1	1.8	1.2	2	4	1	to	>32
ceftazidime	98.7		1.3	≤0.25	0.5	≤0.25	to	>32
ceftriaxone	92.0	1.2	6.8	≤0.25	≤1	≤0.25	–	64
ciprofloxacin	96.6	1.2	2.2	≤0.06	0.12	≤0.06	to	>16

Continued

Table 3. *Continued*

Organism (no. tested)/antimicrobial agent	% S	% I	% R	MIC (mg/L)				
				MIC_{50}	MIC_{90}	range		
colistin				0.5	1	0.12	to	>16
doripenem	100			≤0.06	0.12	≤0.03	–	1
ertapenem	99.7		0.3	≤0.03	0.06	≤0.03	–	2
gentamicin	98.1	0.5	1.5	≤0.5	≤0.5	≤0.5	to	>32
levofloxacin	97.8	0.7	1.5	≤0.06	0.25	≤0.06	to	>32
meropenem	100			≤0.03	0.12	≤0.03	–	1
moxifloxacin	96.8	1.2	2.0	0.12	0.25	≤0.06	to	>16
nitrofurantoin	77.8	20.4	1.9	32	64	4	–	128
piperacillin/tazobactam	89.8	0.5	9.8	2	32	≤1	to	>512
tigecycline	99.3	0.5	0.2	0.5	1	0.06	–	8
trimethoprim/sulfamethoxazole	94.9		5.1	≤0.12	0.25	≤0.12	to	>8
S. marcescens (*n*=412)								
amikacin	99.5	0.2	0.2	≤2	4	≤1	to	>64
amoxicillin/clavulanic acid	2.6	21.1	76.3	>32	>32	≤0.06	to	>32
cefazolin	0.7		99.3	>128	>128	2	to	>128
cefepime	100			≤0.25	1	≤0.25	–	8
cefoxitin	21.9	48.3	29.8	16	>32	4	to	>32
ceftazidime	99.3		0.7	≤0.5	1	≤0.25	to	>32
ceftriaxone	93.7	1.0	5.4	≤0.25	1	≤0.25	to	>64
ciprofloxacin	89.8	4.1	6.1	≤0.06	2	≤0.06	to	>16
colistin				>16	>16	0.5	to	>16
doripenem	99.5	0.2	0.2	≤0.12	0.12	≤0.03	to	>32
ertapenem	99.1	0.3	0.6	≤0.06	0.06	≤0.03	–	4
gentamicin	95.1	2.4	2.4	≤0.5	1	≤0.5	to	>32
levofloxacin	93.3	2.8	4.0	0.12	2	≤0.06	–	16
meropenem	99.5	0.5		≤0.06	0.12	≤0.06	–	2
moxifloxacin	87.8	5.8	6.3	0.5	4	≤0.06	to	>16
nitrofurantoin		1.8	98.2	256	>256	64	to	>256
piperacillin/tazobactam	95.9	3.2	1.0	≤1	4	≤1	–	256
tigecycline	71.0	24.9	4.2	2	4	0.12	to	>16
trimethoprim/sulfamethoxazole	95.6		4.4	0.5	1	≤0.12	to	>8
S. maltophilia (*n*=378)								
amikacin				>64	>64	≤2	to	>64
amoxicillin/clavulanic acid				>32	>32	2	to	>32
cefazolin				>128	>128	128	to	>128
cefepime				>32	>32	≤0.25	to	>128
cefoxitin				>32	>32	8	to	>32
ceftazidime	25.8	9.0	65.3	>32	>32	1	to	>32
ceftriaxone				64	256	8	to	>256
ciprofloxacin				2	16	≤0.06	to	>16
colistin				8	>16	0.25	to	>16
doripenem				>32	64	≤0.12	to	>64
ertapenem				>32	>32	0.12	to	>32
gentamicin				32	>32	≤0.5	to	>32
levofloxacin	66.9	12.8	20.3	2	8	≤0.06	to	>32
meropenem				>32	64	≤0.06	to	>64
moxifloxacin				1	4	≤0.06	to	>16
nitrofurantoin				>256	>256	32	to	>256
piperacillin/tazobactam				256	>512	16	to	>512

Continued

Table 3. *Continued*

Organism (no. tested)/antimicrobial agent	% S	% I	% R	MIC (mg/L) MIC_{50}	MIC_{90}	range		
tigecycline				2	8	0.25	–	16
trimethoprim/sulfamethoxazole	86.6		13.4	0.5	4	≤0.12	to	>8
E. aerogenes (*n*=163)								
amikacin	100			≤2	2	≤1	–	8
amoxicillin/clavulanic acid	7.8	17.6	74.7	32	>32	2	to	>32
cefazolin	5.5	6.1	88.3	64	>128	1	to	>128
cefepime	99.2	0.8		≤0.25	1	≤0.25	–	16
cefoxitin	7.7	3.5	88.8	>32	>32	0.25	to	>32
ceftazidime	77.0	1.6	21.4	0.5	>32	≤02.5	to	>32
ceftriaxone	75.5	1.2	23.3	≤0.25	16	≤0.25	to	>64
ciprofloxacin	95.1		4.9	≤0.06	0.25	≤0.06	to	>16
colistin				0.5	1	0.12	–	16
doripenem	99.4	0.6		0.06	0.12	≤0.03	–	2
ertapenem	94.4	4.9	0.7	0.06	0.5	≤0.03	–	16
gentamicin	99.4		0.6	≤0.5	≤0.5	≤0.5	–	32
levofloxacin	94.4	2.2	3.3	≤0.06	0.5	≤0.06	–	16
meropenem	99.4	0.6		≤0.06	0.12	≤0.03	–	2
moxifloxacin	94.5	1.2	4.3	0.12	1	≤0.06	–	16
nitrofurantoin	8.1	51.4	40.5	64	128	32	–	256
piperacillin/tazobactam	89.5	8.6	1.9	4	32	≤1	–	128
tigecycline	95.7	3.1	1.2	1	2	0.25	–	8
trimethoprim/sulfamethoxazole	98.2		1.9	≤0.12	0.5	≤0.12	to	>8
C. freundii (*n*=123)								
amikacin	100			≤2	2	≤1	–	8
amoxicillin/clavulanic acid	32.0	28.9	39.2	16	>32	0.5	to	>32
cefazolin	2.4	1.6	95.9	32	>128	1	to	>128
cefepime	100			≤0.25	1	≤0.25	–	4
cefoxitin	9.3	7.2	83.5	>32	>32	2	to	>32
ceftazidime	83.5		16.5	0.5	>32	≤0.25	to	>32
ceftriaxone	82.9	1.6	15.5	≤0.25	32	≤0.25	to	>64
ciprofloxacin	91.9	1.6	6.5	≤0.06	0.25	≤0.06	to	>16
colistin				0.5	0.5	0.12	–	1
doripenem	100			≤0.06	0.12	≤0.03	–	0.5
ertapenem	99.0		1.0	≤0.03	0.12	≤0.03	–	2
gentamicin	91.9	0.8	7.3	≤0.5	1	≤0.5	to	>32
levofloxacin	94.1		5.9	≤0.06	1	≤0.06	to	>32
meropenem	100			≤0.06	0.12	≤0.03	–	0.5
moxifloxacin	89.4	2.4	8.1	0.12	4	≤0.06	to	>16
nitrofurantoin	97.5		2.5	16	32	8	–	128
piperacillin/tazobactam	89.4	8.1	2.4	2	32	≤1	–	256
tigecycline	93.5	5.7	0.8	0.5	1	0.25	–	8
trimethoprim/sulfamethoxazole	87.8		12.2	≤0.12	>8	≤0.12	to	>8
A. baumannii (*n*=104)								
amikacin	94.2		5.8	≤2	4	≤1	to	>64
amoxicillin/clavulanic acid				16	32	0.5	to	>32
cefazolin				>128	>128	64	to	>128
cefepime	84.2	4.0	11.8	4	32	0.5	–	128
cefoxitin				>32	>32	8	to	>32
ceftazidime	78.8	3.8	17.5	8	32	1	to	>32

Continued

Table 3. *Continued*

Organism (no. tested)/antimicrobial agent	% S	% I	% R	MIC (mg/L)				
				MIC_{50}	MIC_{90}	range		
ceftriaxone	49.0	40.4	10.6	16	64	2	to	>256
ciprofloxacin	89.4	1.9	8.7	0.25	2	≤0.06	to	>16
colistin	96.8		3.2	1	2	0.25	to	>16
doripenem				0.25	1	≤0.06	to	>32
ertapenem				4	16	0.12	to	>32
gentamicin	92.3	1.0	6.7	1	2	≤0.5	to	>32
levofloxacin	93.7		6.4	0.12	0.5	≤0.06	–	16
meropenem	95.2		4.8	0.5	2	≤0.12	to	>32
moxifloxacin				≤0.06	0.5	≤0.06	to	>16
nitrofurantoin				>256	>256	128	to	>256
piperacillin/tazobactam	81.7	8.7	9.6	≤1	64	≤1	to	>512
tigecycline				0.5	1	0.12	to	>16
trimethoprim/sulfamethoxazole	86.5		13.5	0.25	8	≤0.12	to	>8

S, susceptible; I, intermediate; R, resistant.
FDA-approved breakpoints were used for tigecycline.
[a]Non-rounded values: 99.98% S (n=5450/5451) and 0.02% I (n=1/5451).

Tigecycline was active, with MIC_{50} and MIC_{90} values of 0.5 and 1 mg/L, respectively.

Discussion

The CANWARD study is the first national, ongoing, prospective, Health Canada-endorsed surveillance study assessing antimicrobial activity against pathogens from Canadian hospitals, including hospital clinics, emergency rooms, medical and surgical wards and ICUs.[5,6] A total of 27123 pathogens were collected between 2007 and 2011 inclusive, 83.9% of which underwent susceptibility testing (Table 1). The most active antimicrobial agents (based upon MIC data only) against Gram-positive organisms were vancomycin, linezolid, daptomycin, telavancin and tigecycline. It should be mentioned that listing agents as most active based solely upon MIC is not accurate, as potency depends upon both the agent's pharmacokinetics as well as *in vitro* susceptibility (i.e. pharmacodynamics). However, as an *in vitro* susceptibility study, the activity of antimicrobial agents was evaluated in this fashion.

In this study, vancomycin was active against MSSA and MRSA, with only one isolate (0.08%) of MRSA displaying a vancomycin MIC of 4 mg/L. This is consistent with previous data reporting that vancomycin continues to be active against MSSA and MRSA in Canada, the USA and internationally.[5,6,14–17] Vancomycin MIC creep was not observed in this study. Vancomycin was less active against MSSE and MRSE compared with MSSA and MRSA, which is consistent with previous reports.[5,6,16,18–20] In this study, as well as with previous data, vancomycin continues to be very active against all *Streptococcus* spp.[5,6,16,18,20] Vancomycin was less active against *E. faecalis* and *E. faecium*, with 0.1% and 22.4% of strains demonstrating resistance, respectively. As has been reported elsewhere, the predominant (~90% in this study) VRE genotype in North America continues to be *vanA*.[5,13]

Linezolid was active against MSSA, MRSA, MSSE, MRSE and *Streptococcus* spp., with all isolates demonstrating linezolid susceptibility. Linezolid's continued excellent activity against these isolates is consistent with the current literature.[6,15,18,19] Linezolid was less active against *E. faecalis* and *E. faecium*, with 4.5% and 11.2% of strains demonstrating intermediate resistance, respectively. This low rate of linezolid non-susceptibility in *E. faecalis* and *E. faecium* is consistent with previous reports.[6,15,18–20]

Daptomycin was active against MSSA, MRSA, MSSE and MRSE, with all isolates demonstrating daptomycin MICs ≤1 mg/L. Daptomycin's excellent activity against MSSA/MRSA and MSSE/MRSE has been previously documented.[6,14,16,17,21] In addition, it has been recently reported that daptomycin displays excellent activity (MIC_{90} of 0.5 mg/L) and maintains bactericidal activity against MRSA with vancomycin MICs of 2 mg/L, many of which are heteroresistant vancomycin-intermediate–resistant *S. aureus*.[22] As has been previously reported, daptomycin was active against *Streptococcus* spp.[6,16,18] Daptomycin was also very active against *E. faecalis*, *E. faecium* and VRE. Daptomycin-resistant *Enterococcus* spp. continue to be rare[16,17] and have not been documented in Canada. From these data, it is clear that daptomycin is a very active agent against all Gram-positive organisms causing infections in Canadian hospitals.

In this study, both telavancin and tigecycline were active against MSSA, MRSA, MSSE, MRSE and *Streptococcus* spp., as has been demonstrated previously.[6,14,23–25] Tigecycline was also very active against *E. faecalis*, *E. faecium* and VRE. Thus, both of these agents show good activity against Gram-positive pathogens causing infections in Canadian hospitals.

The most active (based upon MIC) agents against the Gram-negative bacilli obtained from Canadian hospitals were amikacin, cefepime, doripenem, ertapenem (excluding *P. aeruginosa*), meropenem, piperacillin/tazobactam and tigecycline (excluding *P. aeruginosa*) (Table 3).

In this study, amikacin was very active against *E. coli* (including ESBL-producing strains). Likewise, amikacin proved to be very active against all other Enterobacteriaceae tested (Table 3). Against *P. aeruginosa* and *A. baumannii*, amikacin was one of the most active agents tested. The excellent activity of amikacin and other aminoglycosides against both Enterobacteriaceae as well as non-fermenters isolated from patients in hospitals, including in the ICU, is not surprising, as the reduced usage of aminoglycosides in favour of fluoroquinolones over the last 15 years has resulted in maintained or even increased activity of aminoglycosides in the setting of increasing fluoroquinolone resistance.[3,26] Thus, amikacin represents a potential option for the treatment of infections caused by Gram-negative bacilli resistant to other less toxic agents.

In this study, we report that cefepime, doripenem, ertapenem, meropenem and piperacillin/tazobactam were very active against Gram-negative bacilli isolated from patients in Canadian hospitals. These agents were active against Enterobacteriaceae, including *E. coli* (only doripenem, ertapenem and meropenem were active against ESBL-producing strains, due to the presence of multiple β-lactamases per bacterial cell). Among *P. aeruginosa*, resistance rates for piperacillin/tazobactam, meropenem and cefepime were less than ∼10%. Previous investigators have reported the ongoing excellent activity of these agents against Gram-negative bacilli isolated from hospitalized patients.[3,27] In this study, the activity of doripenem was similar to that of meropenem, except that it was more active against *P. aeruginosa* and *A. baumannii*. This is consistent with previous data.[6]

Colistin was found to be very active against *E. coli* (including ESBL-producing strains). Colistin was also very active against *Klebsiella* spp., *P. aeruginosa* and *A. baumannii*. These data are consistent with other recent reports of the promising potential of polymyxins for Gram-negative bacilli such as *P. aeruginosa* and *A. baumannii*.[28,29]

In this study, tigecycline demonstrated excellent activity against *E. coli* (including ESBL-producing strains) and was also active against other Enterobacteriaceae, including *K. pneumoniae*, *E. cloacae*, *S. marcescens* and *K. oxytoca* (Table 3). These data are consistent with recent studies showing the excellent activity of tigecycline against Gram-negative bacilli, including MDR strains.[30,31] Tigecycline was not active against *P. mirabilis* and *P. aeruginosa*. As with previous studies, tigecycline displayed good activity against *S. maltophilia* and *A. baumannii*, organisms frequently resistant to other antimicrobial classes (Table 3).[31,32] These data support the potential use of this agent for the treatment of infections caused by non-*Pseudomonas* Gram-negative bacilli in hospitalized patients.[30–32]

The CANWARD study has several limitations, including the fact that we cannot be certain that all clinical specimens represented active infection. In the CANWARD study, the medical centres were asked to submit only clinically significant specimens from patients with a presumed infectious disease; however, this interpretation cannot be rigorously controlled by the coordinating site. Although not all of the isolates may represent actual infection, we believe the vast majority were clinically significant isolates as all surveillance swabs, duplicate swabs, eye, ear, nose and throat swabs and genital cultures were specifically excluded from the study, and the primary medical centres agreed to the study criteria. Another limitation is that we do not have admission date data for each patient/clinical specimen; thus we are not able to provide a more accurate description of community versus nosocomial onset. Finally, antimicrobial susceptibility testing was not performed for all commercially available antimicrobial agents due to lack of space on the custom-designed susceptibility panels utilized. It is recognized that data on antimicrobials such as cefotaxime, imipenem, tobramycin and others would be beneficial, as different hospital formularies stock these and other antimicrobials not tested in this study.

In conclusion, *E. coli*, *S. aureus*, *P. aeruginosa*, *S. pneumoniae*, *K. pneumoniae* and *Enterococcus* spp. are the most common pathogens in Canadian hospitals. Susceptibility rates for *E. coli* were highest with meropenem, ertapenem, piperacillin/tazobactam and tigecycline. Susceptibility rates for *P. aeruginosa* were highest with amikacin, colistin, meropenem, piperacillin/tazobactam and ceftazidime. All MRSA were susceptible to daptomycin, linezolid and telavancin and 99.9% were susceptible to vancomycin.

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CANWARD data are also displayed at www.can-r.ca, the official web site of the Canadian Antimicrobial Resistance Alliance (CARA).

Members of the Canadian Antimicrobial Resistance Alliance (CARA)

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