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CANWARD 2012: Antimicrobial Resistance in Pathogens Isolated from Canadian Hospital Clinics, Emergency Rooms, Medical/Surgical Wards and Intensive Care Units

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REVISED ABSTRACT

Objectives: The CANWARD study assesses the pathogens causing infections in patients affiliated with Canadian hospitals and evaluates the prevalence of antimicrobial resistance in these isolates.

Methods: 12 tertiary-care centres across Canada submitted pathogens causing infections from patients attending clinics (C), emergency rooms (ER), medical and surgical wards (W) and intensive care units (ICU) in 2012. Susceptibility testing was performed by CLSI microdilution methods.

Results: 2,808 isolates were collected: 41.6%, 38.0%, 10.6%, and 9.8% from blood, respiratory, urine and wound/IV site specimens, respectively. Isolates were from patients on W 35.2%, ER 25.5%, ICU 22.1%, and C 17.2%. The most common pathogens were: *S. aureus* (MSSA) 20.1%, *E. coli* 17.8%, *P. aeruginosa* 9.4%, *K. pneumoniae* 6.0%, *H. influenzae* 5.3%, and *S. pneumoniae* 5.1%. Resistance rates (RR) for *E. coli* were: 0% for meropenem (MER), ertapenem (ERT) and tigecycline (TGC), 2.4% piperacillin/tazobactam (PTZ), 8.4% ceftriaxone (CTR), 8.8% gentamicin (GEN), 25.6% ciprofloxacin (CIP) and 27.0% trimethoprim-sulfamethoxazole (SXT). For *P. aeruginosa*, RR were 1.1% colistin (COL), 4.9% PTZ, 5.3% GEN, 9.1% MER, and 10.2% CIP. RR for MRSA were: 0% vancomycin (VAN) and linezolid (LZD), 0.8% daptomycin (DAP) (1/125 isolates; MIC-DAP 2, VAN 2µg/mL), 2.4% tigecycline, 4.0% SXT, 31.4% clindamycin, 73.4% CIP, and 79.0% clarithromycin. Overall, the prevalence of MRSA, VRE, and ESBL-*E. coli* was: 18.0%, 7.6%, and 7.8%, respectively.

Conclusions: RR for *E. coli* were lowest with MER, ERT, TGC and PTZ, while RR for *P. aeruginosa* were lowest with COL, PTZ, and GEN. For MRSA, no resistance occurred with VAN or LZD.

BACKGROUND

Infections caused by antimicrobial resistant pathogens are a serious issue in Canada, and many parts of the world. Resistant pathogens include methicillin-resistant *Staphylococcus aureus* (community and healthcare-associated), vancomycin resistant enterococci (VRE), *Escherichia coli* and *Klebsiella* species resistant to extended-spectrum β-lactams, penicillin-resistant *Streptococcus pneumoniae*, and carbapenem-resistant Enterobacteriaceae and *Pseudomonas aeruginosa*. Treatment options for these infections are often limited as these pathogens are frequently multidrug- resistant (MDR).

OBJECTIVES

The CANWARD study is a national, ongoing, population-based surveillance study. CANWARD, a study initiated in 2007, has three primary objectives:

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

MATERIALS & METHODS

Participating Sites: Twelve sentinel hospital sites in major population centres in 8 of the 10 provinces in Canada were recruited. These sites were geographically distributed in a population based fashion.

Bacterial Isolates: Tertiary-care medical centres submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. From January through October 2012, each study site was asked to submit clinical isolates (consecutive, one per patient, per infection site) from inpatients and outpatients with respiratory (100), urine (25), wound (25), and bloodstream (10/month x 10 months) infections. The medical centres submitted "clinically significant" isolates from patients with a presumed infectious disease. Surveillance swabs, eye, ear, nose and throat swabs were excluded. We also excluded anaerobic organisms. 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 skim milk at -80°C until minimum inhibitory concentration (MIC) testing was carried out. Characterization of MRSA isolates (*spa* typing) and putative VRE isolates (*van* PCR analysis) was performed at the National Microbiology Laboratory. In 2012, a total of 2,808 isolates were collected for the primary objectives of CANWARD.

Antimicrobial Susceptibility Testing: Following 2 subcultures from frozen stock, the *in vitro* activity of antimicrobials was determined by broth microdilution in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines (M7-A9, 2012). Antimicrobial minimum inhibitory concentration (MIC) interpretive standards were defined according to CLSI breakpoints (M100-S22, 2012). 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 of the antimicrobial agents for the isolates 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 10^5 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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RESULTS

Table 1. Top Pathogens Isolated in Canadian Hospitals in 2012

Rank	Organism	n	% of Total
1	*Staphylococcus aureus*, MSSA	564	20.1
2	*Escherichia coli*	500	17.8
3	*Pseudomonas aeruginosa*	264	9.4
4	*Klebsiella pneumoniae*	169	6.0
5	*Haemophilus influenzae*	150	5.3
6	*Streptococcus pneumoniae*	143	5.1
7	*Staphylococcus aureus*, MRSA	125	4.5
8	*Enterococcus faecalis*	93	3.3
9	CNS / *Staphylococcus epidermidis*	85	3.0
10	*Enterobacter cloacae*	69	2.5
11	*Klebsiella oxytoca*	50	1.8
12	*Streptococcus agalactiae*	44	1.6
13	*Stenotrophomonas maltophilia*	43	1.5
14	*Serratia marcescens*	41	1.5
15	*Proteus mirabilis*	39	1.4
16	*Moraxella catarrhalis*	36	1.3
17	*Streptococcus pyogenes*	36	1.3
18	*Enterococcus faecium*	35	1.2
19	*Haemophilus parainfluenzae*	30	1.1
20	*Staphylococcus hominis*	26	0.9
	Other	266	9.5
		2,808	

Figure 1. Patient Demographics by Hospital Location, Specimen Source, Gender, and Age Group (% of Total)

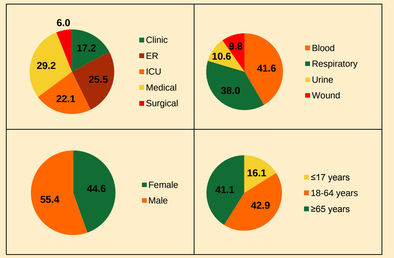
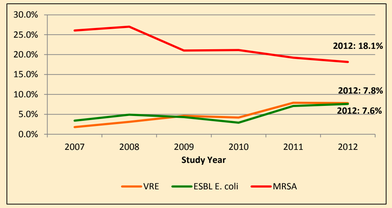


Figure 2. Prevalence (%) of MRSA, VRE and ESBL *E.coli* in CANWARD 2012



HA-MRSA: 54.4% (68/125); CA-MRSA: 38.4% (48/125)
VRE: 7.9% (10/128 [9 vanA, 1 vanB])

Tables 2-6. Antimicrobial Activities Against Common Gram Negative and Gram Positive Pathogens

***Escherichia coli* (n=500)**

Antimicrobial Agent	Susceptibility % S	% I	% R	MIC_{50}	MIC_{90}	Range Min	Max
Amikacin	99.6	0.4		≤ 1	4	≤ 1	32
Amoxicillin Clav	77.0	16.2	6.8	4	16	0.5	> 32
Cefazolin	70.6	11.2	18.2	2	32	≤ 0.5	> 128
Cefepime	96.8	2.2	1.0	≤ 0.25	≤ 0.25	≤ 0.25	> 64
Cefoxitin	92.6	4.0	3.4	4	8	1	> 32
Ceftazidime	93.0	1.0	6.0	≤ 0.25	1	≤ 0.25	> 32
Ceftriaxone	91.2	0.4	8.4	≤ 0.25	≤ 0.25	≤ 0.25	> 64
Ciprofloxacin	74.0	0.2	25.8	≤ 0.06	> 16	≤ 0.06	> 16
Colistin				0.25	0.5	≤ 0.06	> 16
Doripenem	100.0			≤ 0.03	≤ 0.03	≤ 0.03	0.25
Ertapenem	100.0			≤ 0.03	0.06	≤ 0.03	0.5
Gentamicin	90.8	0.4	8.8	≤ 0.5	2	≤ 0.5	> 32
Meropenem	100.0			≤ 0.03	≤ 0.03	≤ 0.03	0.12
Moxifloxacin				≤ 0.06	> 16	≤ 0.06	> 16
Piperacillin Tazo	97.0	0.6	2.4	≤ 1	4	≤ 1	> 512
Tigecycline *	100.0			0.25	0.5	0.12	2
Trimethoprim Sulfa	73.0		27.0	≤ 0.12	> 8	≤ 0.12	> 8

* FDA breakpoints used for tigecycline

***Pseudomonas aeruginosa* (n=264)**

Antimicrobial Agent	Susceptibility % S	% I	% R	MIC_{50}	MIC_{90}	Range Min	Max
Amikacin	94.7	3.0	2.3	4	8	≤ 1	> 64
Cefepime	90.2	6.8	3.0	4	8	≤ 0.25	64
Ceftazidime	86.0	4.9	9.1	4	16	≤ 0.25	> 32
Ceftriaxone	20.5	53.0	26.5	16	> 64	1	> 64
Ciprofloxacin	83.3	6.4	10.2	0.25	4	≤ 0.06	> 16
Colistin	98.5	0.4	1.1	1	1	0.25	> 16
Doripenem	89.4	5.7	4.9	0.5	4	≤ 0.03	32
Gentamicin	90.5	4.2	5.3	1	4	≤ 0.5	> 32
Meropenem	81.4	9.5	9.1	0.5	4	≤ 0.03	> 32
Piperacillin Tazo	87.5	7.6	4.9	4	32	≤ 1	512

***Streptococcus pneumoniae* (n=136)**

Antimicrobial Agent	Susceptibility % S	% I	% R	MIC_{50}	MIC_{90}	Range Min	Max
Amoxicillin Clav [a]	96.3	1.5	2.2	≤ 0.06	≤ 0.06	≤ 0.06	8
Ceftriaxone	100.0			≤ 0.12	≤ 0.12	≤ 0.12	1
Cefuroxime [a]	93.4		6.6	≤ 0.25	≤ 0.25	≤ 0.25	8
Ciprofloxacin	97.8		2.2	1	2	0.12	> 16
Clarithromycin	76.5	1.5	22.1	≤ 0.03	4	≤ 0.03	> 32
Clindamycin	90.4		9.6	≤ 0.12	≤ 0.12	≤ 0.12	> 64
Doripenem	100.0			≤ 0.03	≤ 0.03	≤ 0.03	1
Doxycycline [b]	86.0	1.5	12.5	≤ 0.25	1	≤ 0.25	16
Ertapenem	95.6	4.4		≤ 0.06	0.12	≤ 0.06	2
Levofloxacin	98.5		1.5	1	1	≤ 0.06	16
Linezolid	100.0			1	1	≤ 0.12	2
Meropenem	94.1	2.2	3.7	≤ 0.06	≤ 0.06	≤ 0.06	1
Moxifloxacin	98.5	0.7	0.7	0.12	0.25	≤ 0.06	4
Penicillin [c]	88.9	7.1	4.0	≤ 0.03	0.12	≤ 0.03	4
Telithromycin	100.0			0.008	0.12	≤ 0.002	0.5
Tigecycline *	100.0			≤ 0.015	0.03	≤ 0.015	0.03
Trimethoprim Sulfa	89.0	5.1	5.9	0.25	1	≤ 0.12	8
Vancomycin	100.0			0.25	0.25	≤ 0.12	0.5

[a] CLSI non-meningitis breakpoints used; [b] tetracycline breakpoints used; [c] penicillin V breakpoints used, [d] cefuroxime oral breakpoints used * FDA breakpoints used for tigecycline

***Staphylococcus aureus*, MSSA (n=563)**

Antimicrobial Agent	% S	% I	% R	MIC_{50}	MIC_{90}	Range Min	Max
Cefazolin	100.0			≤ 0.5	≤ 0.5	≤ 0.5	2
Ciprofloxacin	87.6	2.0	10.5	0.5	4	≤ 0.06	> 16
Clarithromycin	75.7	0.2	24.2	0.25	> 32	≤ 0.03	> 32
Clindamycin	94.8	0.2	5.0	≤ 0.12	≤ 0.12	≤ 0.12	> 8
Daptomycin	100.0			0.25	0.5	≤ 0.03	0.5
Gentamicin	97.9	0.4	1.8	≤ 0.5	≤ 0.5	≤ 0.5	> 32
Linezolid	100.0			2	2	≤ 0.12	4
Moxifloxacin	90.8	0.5	8.7	≤ 0.06	0.25	≤ 0.06	> 16
Tigecycline *	100.0			0.12	0.25	0.06	0.5
Trimethoprim Sulfa	98.9		1.1	≤ 0.12	≤ 0.12	≤ 0.12	> 8
Vancomycin	100.0			1	1	0.25	1

* FDA breakpoints used for tigecycline

***Staphylococcus aureus*, MRSA (n=125)**

Antimicrobial Agent	Susceptibility % S	% I	% R	MIC_{50}	MIC_{90}	Range Min	Max
Cefazolin			100.0 [a]	32	128	1	> 128
Ciprofloxacin	27.2		72.8	16	> 16	0.25	> 16
Clarithromycin	21.6		78.4	> 32	> 32	0.12	> 32
Clindamycin	68.8		31.2	≤ 0.12	> 8	≤ 0.12	> 8
Daptomycin	99.2		0.8	0.25	0.5	0.12	2
Gentamicin	98.4	0.8	0.8	≤ 0.5	≤ 0.5	≤ 0.5	> 32
Linezolid	100.0			2	2	0.5	4
Moxifloxacin	27.2	3.2	69.6	2	> 16	≤ 0.06	> 16
Tigecycline *	97.6			0.12	0.5	0.06	1
Trimethoprim Sulfa	96.0		4.0	≤ 0.12	≤ 0.12	≤ 0.12	> 8
Vancomycin	100.0			1	1	0.5	2

[a] based upon oxacillin susceptibility; * FDA breakpoints used for tigecycline

CONCLUSIONS

- Of the 2,808 pathogens obtained, the most common were: *S. aureus* (MSSA) 20.1%, *E. coli* 17.8%, *P. aeruginosa* 9.4%, *K. pneumoniae* 6.0%, *H. influenzae* 5.3%, *S. pneumoniae* 5.1%, and MRSA 4.5%.
- For *E. coli*, resistance was lowest with meropenem, ertapenem, doripenem, and tigecycline 100% susceptible (S), amikacin 99.6%S, piperacillin-tazobactam 97.0%S, and 96.8%S for cefepime.
- For *P. aeruginosa*, resistance was lowest with colistin 98.5%S, amikacin 94.7%S, gentamicin 90.5%S, cefepime 90.2%S, and 89.4%S for doripenem.
- For MRSA, no resistance occurred with vancomycin or linezolid, however, 1 isolate (1/125 or 0.8%) was found to be non-susceptible to daptomycin with an MIC of 2 µg/mL and vancomycin MIC 2 µg/mL.
- Statistical analysis revealed that rates of VRE and ESBL *E. coli* increased, while MRSA rates declined over time.