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Pathogens and Their Antimicrobial Resistance Patterns in Emergency Departments (EDs) across Canada: CANWARD 2007-2014

K.J. THOMPSON[1], H.J. ADAM[1,2], M. BAXTER[1], P.R.S. LAGACÉ-WIENS[1,2], J.A. KARLOWSKY[1,2], A. WALKTY[1,2], D.J. HOBAN[1,2], the CANADIAN ANTIMICROBIAL RESISTANCE ALLIANCE (CARA), and G.G. ZHANEL[1]

University of Manitoba[1] and Diagnostic Services Manitoba[2], Winnipeg, Manitoba, Canada

Dr. George Zhanel
MS673-820 Sherbrook Street
Winnipeg, MB, R3A 1R9
Phone: 204.787.4902
Email: ggzhanel@pcs.mb.ca

Health Sciences Centre Winnipeg

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ABSTRACT

Background: This study assessed the antimicrobial resistance patterns of pathogens causing infections in patients treated in Canadian EDs.

Methods: From 2007 to 2014 inclusive, tertiary care centres across Canada submitted 36,607 bacterial isolates as part of the Canadian Ward Surveillance Study (CANWARD). 9,222 (25.2%) were from patients presenting to EDs. Isolates were collected from blood, urine, wound, and respiratory specimens. Antimicrobial susceptibility testing and MIC breakpoint interpretation was carried out using Clinical and Laboratory Standards Institute (CLSI) guidelines.

Results: Of the 9,222 isolates, 63.4%, 15.5%, 12.2%, and 8.9% were from blood, urine, respiratory, and wound specimens, respectively. The most common organisms were: *E. coli* 29.8%, methicillin-susceptible *Staphylococcus aureus* (MSSA) 14.7%, *Streptococcus pneumoniae* 8.5%, *Klebsiella pneumoniae* 6.4%, *Pseudomonas aeruginosa* 4.3%, and methicillin-resistant *Staphylococcus aureus* (MRSA) 3.9%. 21.1% of *S. aureus* were MRSA (49.6%/45.7% CA/HA-MRSA genotypes). 3.9% of *E. coli* were extended spectrum β-lactamase-producing and 1.3% of *Enterococcus* spp. were vancomycin-resistant. Susceptibility rates (SR) for *E. coli* (blood) were: 100% meropenem (MER), 100% ertapenem (ERT), 98.8% piperacillin-tazobactam (PTZ), 94.0% ceftriaxone (CTR), 91.7% gentamicin, and 80.4% ciprofloxacin. SR for *S. pneumoniae* (respiratory) were: 99.3% CTR, 98.6% levofloxacin (LEV), 93.9% clindamycin (CLD), 90.0% doxycycline (DOX), 86.9% trimethoprim-sulfamethoxazole (SXT), 85.3% penicillin, and 81.4% clarithromycin. SR for MRSA were: 100% linezolid (LZD), 100% daptomycin (DAP), 99.4% vancomycin (VAN), 99.4% tigecycline (TGC), 97.2% SXT, and 54.7% CLD.

Conclusions: *E. coli*, MSSA, *S. pneumoniae, K. pneumoniae, P. aeruginosa,* and MRSA are the most common pathogens in Canadian EDs. MRSA represents 21.1% of all *S. aureus* infections in EDs (~50/50 split CA and HA genotypes). Against MRSA, SR of >99% were observed for LZD, DAP, VAN, and TGC. MER, ERT, PTZ, CTR were the most active intravenous agents against *E. coli* blood isolates (SR >94.0%). CTR, LEV, CLD, and DOX are the most active agents against respiratory *S. pneumoniae* isolates.

BACKGROUND

The treatment of infectious diseases remains a predominant aspect of care provision in emergency department settings. In addition to varying levels of acuity, limited information, and significant time constraints—the rising proportion of multidrug resistant organisms in the community represent an even further challenge to the ER physician when treating these infections (1,2,3). Antimicrobial stewardship in the ED is often hindered by the frequent need for empiric treatment; given the lack of initial culture data, undifferentiated infections, and/or those presenting with severe illness (1,2,3). CANWARD (an ongoing, annual, national, multicentre study) assesses pathogens causing infections in Canadian hospitals and their antimicrobial resistance patterns. This national surveillance data will hopefully guide and enable emergency room physicians to tailor empiric treatment, optimize clinical outcomes, and foster a culture conducive to antimicrobial stewardship (4).

The 3 main objectives of this study were [1] to determine the pathogens, [2] to assess the activity of antimicrobials, and [3] to determine the prevalence of antimicrobial resistance in these pathogens associated with respiratory, urinary, blood, and wound site infections in Canadian emergency department patients from 2007-2014.

REFERENCES

1. Acquisto N, et al. *Journal of Pharmacy Practice.* 2011. 24(2): 196-202.
2. Huang D, et al. *Annals of Emergency Medicine.* 2013. 62(1): 78-79.
3. May L, et al. *Annals of Emergency Medicine.* 2013. 62(1): 69-77.
4. Adam HJ, et al. *Diagnostic Microbiology and Infectious Disease.* 2011. 69:307-313.

RESULTS

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

Rank	Organism	n	% of Total
1	*Escherichia coli*	2749	29.8
2	*Staphylococcus aureus*, MSSA	1353	14.7
3	*Streptococcus pneumoniae*	786	8.5
4	*Klebsiella pneumoniae*	588	6.4
5	*Pseudomonas aeruginosa*	394	4.3
6	*Staphylococcus aureus*, MRSA	361	3.9
7	*Streptococcus pyogenes*	290	3.1
8	CNS / *Staphylococcus epidermidis*	262	2.8
9	*Haemophilus influenzae*	251	2.7
10	*Enterococcus faecalis*	244	2.6
11	*Streptococcus agalactiae*	197	2.1
12	*Proteus mirabilis*	174	1.9
13	*Klebsiella oxytoca*	124	1.3
14	*Enterobacter cloacae*	107	1.2
15	*Streptococcus viridans*	104	1.1
16	*Enterococcus spp.*	96	1.0
17	BHS Group G	82	0.9
18	*Staphylococcus hominis*	68	0.7
19	*Serratia marcescens*	63	0.7
20	*Moraxella catarrhalis*	49	0.5
	Other	880	9.5
		9222	

Table 2. Prevalence of common resistance phenotypes isolated from Canadian EDs

Prevalence (%)	n	%
MRSA	361/1714	21.1%
VRE	5/385	1.3%
ESBL *E.coli*	107/2749	3.9%
ESBL *K. pneumoniae*	10/578	1.7%

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

Table 3. Prevalence of MRSA phenotypes isolated from Canadian EDs

MRSA Phenotypes (n)	Region (n)				
	West	Ontario	Quebec	Maritimes	National
CA-MRSA	109	54	8	8	179
HA-MRSA	42	50	61	12	165
Unique	5	10	2	0	17
Grand Total	156	114	71	20	361
% CA	69.9%	47.4%	11.3%	40.0%	49.6%
% HA	26.9%	43.9%	85.9%	60.0%	45.7%

CA- community associated; HA- healthcare associated

Figure 1. Demographics of ED patients/isolates from CANWARD 2007-2014

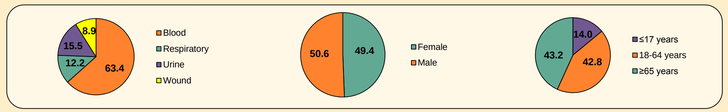

Table 4. Antimicrobial activity of top ED pathogens, by specimen source

Staphylococcus aureus, MSSA - WOUND (n=346)

Drug	MIC50	MIC90	MIC Range	% S	% I	% R
Cefoxitin	4	4	1 - 8	99.7		0.3
Ciprofloxacin	0.5	1	≤ 0.06 - > 16	93.6	0.6	5.8
Clarithromycin	0.25	> 16	≤ 0.25 - > 16	80.0	0.3	19.7
Clindamycin	≤ 0.25	≤ 0.25	≤ 0.25 - > 8	95.7		4.3
Daptomycin	0.25	0.25	0.06 - 0.5	100.0		
Gentamicin	≤ 0.5	≤ 0.5	≤ 0.5 - > 32	98.8		1.2
Linezolid	2	2	0.5 - 4	100.0		
Moxifloxacin	≤ 0.06	0.12	≤ 0.06 - > 16	94.2	0.9	4.9
Tigecycline	0.25	0.25	0.12 - 0.5	100.0		
SXT	≤ 0.12	≤ 0.12	≤ 0.12 - > 8	98.8		1.2
Vancomycin	1	1	≤ 0.25 - 1	100.0		

Staphylococcus aureus, MSSA - BLOOD (n=830)

Drug	MIC50	MIC90	MIC Range	% S	% I	% R
Cefoxitin	4	4	0.12 - 8	99.7		0.3
Ciprofloxacin	0.5	2	≤ 0.06 - > 16	88.9	2.0	9.0
Clarithromycin	0.25	> 16	≤ 0.25 - > 16	79.8	0.1	20.1
Clindamycin	≤ 0.25	≤ 0.25	≤ 0.25 - > 8	95.4	0.4	4.2
Daptomycin	0.25	0.25	≤ 0.06 - 0.5	100.0		
Gentamicin	≤ 0.5	≤ 0.5	≤ 0.5 - > 32	99.3		0.7
Linezolid	2	2	≤ 0.12 - 4	100.0		
Moxifloxacin	≤ 0.06	0.25	≤ 0.06 - > 16	91.6	0.7	7.7
Tigecycline	0.12	0.25	≤ 0.03 - 1	99.9		-
SXT	≤ 0.12	≤ 0.12	≤ 0.12 - > 8	99.4		0.6
Vancomycin	1	1	≤ 0.25 - 2	100.0		

Staphylococcus aureus, MRSA - WOUND (n=123)

Drug	MIC50	MIC90	MIC Range	% S	% I	% R
Cefoxitin	32	> 32	8 - > 32			100.0
Ciprofloxacin	16	> 16	0.25 - > 16	32.5	0.8	66.7
Clarithromycin	> 16	> 16	≤ 0.25 - > 16	18.0	0.8	81.1
Clindamycin	≤ 0.25	> 8	≤ 0.25 - > 8	81.1		18.9
Daptomycin	0.25	0.25	0.12 - 1	100.0		
Gentamicin	≤ 0.5	1	≤ 0.5 - > 32	93.5	0.8	5.7
Linezolid	2	2	1 - 4	100.0		
Moxifloxacin	2	8	≤ 0.06 - > 16	33.3	5.7	61.0
Tigecycline	0.25	0.25	0.12 - 1	99.2		-
SXT	≤ 0.12	≤ 0.12	≤ 0.12 - > 8	97.6		2.4
Vancomycin	1	1	0.5 - 1	100.0		

Staphylococcus aureus, MRSA - BLOOD (n=179)

Drug	MIC50	MIC90	MIC Range	% S	% I	% R
Cefoxitin	32	> 32	8 - > 32			100.0
Ciprofloxacin	> 16	> 16	0.12 - > 16	22.3	0.6	77.1
Clarithromycin	> 16	> 16	≤ 0.25 - > 16	15.6		84.4
Clindamycin	≤ 0.25	> 8	≤ 0.25 - > 8	54.7		45.3
Daptomycin	0.25	0.5	0.06 - 0.5	100.0		
Gentamicin	≤ 0.5	1	≤ 0.5 - > 32	98.3		1.7
Linezolid	2	2	0.5 - 4	100.0		
Moxifloxacin	2	> 16	≤ 0.06 - > 16	23.5	5.6	70.9
Tigecycline	0.25	0.25	0.12 - 1	99.4		-
SXT	≤ 0.12	≤ 0.12	≤ 0.12 - > 8	97.2		2.8
Vancomycin	1	1	≤ 0.25 - 4	99.4	0.6	

Enterococcus spp. - URINE (n=146)

Drug	MIC50	MIC90	MIC Range	% S	% I	% R
A/C	0.5	1	0.12 - > 32	-	-	-
Ciprofloxacin	1	> 16	0.25 - > 16	64.4	13.0	22.6
Clarithromycin	2	> 16	≤ 0.25 - > 16	-	-	-
Daptomycin	0.5	2	≤ 0.06 - 4	100.0		
Doripenem	4	4	0.12 - > 32	-	-	-
Ertapenem	> 4	> 4	1 - > 4	-	-	-
Levofloxacin	1	> 32	0.5 - > 32	79.7		20.3
Linezolid	2	2	1 - 4	96.5	3.5	
Meropenem	4	8	0.12 - > 32	-	-	-
Moxifloxacin	0.25	16	≤ 0.06 - > 16	-	-	-
Nitrofurantoin	8	8	4 - 64	99.2	0.8	
PTZ	4	4	≤ 1 - > 512	-	-	-
Tigecycline	0.12	0.25	≤ 0.03 - 0.25	-	-	-
Vancomycin	1	2	≤ 0.25 - > 32	99.3		0.7

' – ' indicates no defined CLSI breakpoints
Tigecycline breakpoints defined by US FDA
A/C – amoxicillin-clavulanate
PTZ – piperacillin-tazobactam
SXT – trimethoprim-sulfamethoxazole

Streptococcus pneumoniae - BLOOD (n=466)

Drug	MIC50	MIC90	MIC Range	% S	% I	% R
A/C	≤ 0.06	≤ 0.06	≤ 0.06 - 8	98.1	1.3	0.6
Ceftriaxone	≤ 0.12	≤ 0.12	≤ 0.12 - 2	99.8	0.2	
Cefuroxime	≤ 0.25	≤ 0.25	≤ 0.25 - 16	95.7	1.1	3.2
Ciprofloxacin	1	2	≤ 0.06 - 4	99.4		0.6
Clarithromycin	≤ 0.03	4	≤ 0.03 - > 32	79.7	2.4	17.9
Clindamycin	≤ 0.12	≤ 0.12	≤ 0.12 - > 8	94.0	0.4	5.6
Doripenem	≤ 0.06	≤ 0.06	≤ 0.06 - 1	100.0		
Doxycycline	≤ 0.25	0.5	≤ 0.25 - > 16	89.8	0.6	9.5
Ertapenem	≤ 0.06	≤ 0.06	≤ 0.06 - 2	99.1	0.9	
Levofloxacin	0.5	1	≤ 0.06 - 2	100.0		
Linezolid	1	1	≤ 0.12 - 2	100.0		
Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 - 1	97.4	0.9	1.7
Moxifloxacin	0.12	0.25	≤ 0.06 - 0.5	100.0		
Penicillin	≤ 0.03	0.12	≤ 0.03 - 4	88.2	9.1	2.7
PTZ	≤ 1	≤ 1	≤ 1 - 4	-	-	-
Tigecycline	≤ 0.03	0.06	≤ 0.03 - 0.06	100.0		
SXT	≤ 0.12	1	≤ 0.12 - > 8	88.0	6.4	5.6
Vancomycin	≤ 0.25	0.25	≤ 0.25 - 1	100.0		

Streptococcus pneumoniae - RESPIRATORY (n=282)

Drug	MIC50	MIC90	MIC Range	% S	% I	% R
A/C	≤ 0.06	0.12	≤ 0.06 - 8	98.6	0.7	0.7
Ceftriaxone	≤ 0.12	≤ 0.12	≤ 0.12 - 2	99.3	0.7	
Cefuroxime	≤ 0.25	≤ 0.25	≤ 0.25 - 16	95.4	1.4	3.2
Ciprofloxacin	1	2	≤ 0.06 - > 16	96.4		3.6
Clarithromycin	≤ 0.03	2	≤ 0.03 - > 32	81.4	5.4	13.2
Clindamycin	≤ 0.12	≤ 0.12	≤ 0.12 - > 8	93.9	1.1	5.0
Doripenem	≤ 0.06	≤ 0.06	≤ 0.06 - 2	99.3		0.7
Doxycycline	≤ 0.25	≤ 0.25	≤ 0.25 - > 16	90.0	1.1	8.9
Ertapenem	≤ 0.06	≤ 0.06	≤ 0.06 - 2	99.6	0.4	
Levofloxacin	1	1	≤ 0.06 - 32	98.6		1.4
Linezolid	0.5	1	≤ 0.12 - 2	100.0		
Meropenem	≤ 0.06	≤ 0.06	≤ 0.06 - 1	96.8	1.4	1.8
Moxifloxacin	0.12	0.25	≤ 0.06 - 8	98.2	0.4	1.4
Penicillin	≤ 0.03	0.25	≤ 0.03 - 8	85.3	10.4	4.3
PTZ	≤ 1	≤ 1	≤ 1 - 8	-	-	-
Tigecycline	≤ 0.03	0.06	≤ 0.03 - 0.25	99.3		0.7
SXT	≤ 0.12	1	≤ 0.12 - > 8	86.9	6.7	6.4
Vancomycin	≤ 0.25	0.25	≤ 0.25 - 0.5	100.0		

Escherichia coli - BLOOD (n=1810)

Drug	MIC50	MIC90	MIC Range	% S	% I	% R
Amikacin	≤ 2	4	≤ 2 - > 64	99.7	0.2	0.1
A/C	4	16	0.25 - > 32	89.8	7.6	2.6
Aztreonam	≤ 0.12	0.25	≤ 0.12 - > 64	93.8	0.9	5.3
Cefazolin	2	8	≤ 0.5 - > 128	74.4	12.7	12.9
Cefepime	≤ 1	≤ 1	≤ 1 - > 32	96.2	2.0	1.7
Cefoxitin	4	8	0.25 - > 32	95.0	2.5	2.4
Ceftazidime	≤ 0.5	0.5	≤ 0.5 - > 32	94.9	0.4	4.7
Ceftriaxone	≤ 1	≤ 1	≤ 1 - > 64	94.0	0.2	5.7
Ciprofloxacin	≤ 0.06	> 16	≤ 0.06 - > 16	80.4	0.1	19.4
Colistin	0.25	0.5	≤ 0.06 - > 16	-	-	-
Doripenem	≤ 0.12	≤ 0.12	≤ 0.12 - 0.25	100.0		
Ertapenem	≤ 0.06	≤ 0.06	≤ 0.06 - 2	99.8	0.1	0.1
Gentamicin	≤ 0.5	1	≤ 0.5 - > 32	91.7	0.2	8.2
Meropenem	≤ 0.12	≤ 0.12	≤ 0.12 - 0.25	100.0		
Moxifloxacin	≤ 0.06	16	≤ 0.06 - > 16	-	-	-
Nitrofurantoin	16	32	≤ 1 - 256	96.3	2.6	1.0
PTZ	≤ 1	4	≤ 1 - 512	98.8	0.8	0.4
Tigecycline	0.25	0.5	0.12 - 2	100.0		
SXT	≤ 0.12	> 8	≤ 0.12 - > 8	72.8		27.2

Escherichia coli - URINE (n=878)

Drug	MIC50	MIC90	MIC Range	% S	% I	% R
Amikacin	≤ 2	4	≤ 2 - 16	100.0		
A/C	4	16	≤ 0.06 - > 32	88.8	8.9	2.3
Aztreonam	≤ 0.12	0.5	≤ 0.12 - > 64	93.4	1.5	5.1
Cefazolin	2	8	≤ 0.5 - > 128	77.0	9.9	13.1
Cefepime	≤ 1	≤ 1	≤ 1 - > 32	96.9	1.3	1.8
Cefoxitin	4	8	≤ 0.06 - > 32	94.0	2.6	3.4
Ceftazidime	≤ 0.5	0.5	≤ 0.5 - > 32	96.1	0.3	3.7
Ceftriaxone	≤ 1	≤ 1	≤ 1 - > 64	95.7	0.2	4.1
Ciprofloxacin	≤ 0.06	> 16	≤ 0.06 - > 16	85.3		14.7
Colistin	0.25	0.5	≤ 0.06 - > 16	-	-	-
Doripenem	≤ 0.12	≤ 0.12	≤ 0.12 - 0.25	100.0		
Ertapenem	≤ 0.06	≤ 0.06	≤ 0.06 - 0.25	100.0		
Gentamicin	≤ 0.5	1	≤ 0.5 - > 32	93.1	0.3	6.6
Meropenem	≤ 0.12	≤ 0.12	≤ 0.12 - 0.12	100.0		
Moxifloxacin	≤ 0.06	16	≤ 0.06 - > 16	-	-	-
Nitrofurantoin	16	32	≤ 1 - 256	97.9	1.4	0.7
PTZ	≤ 1	4	≤ 1 - > 512	98.7	0.7	0.6
Tigecycline	0.25	0.5	0.06 - 4	99.9	0.1	
SXT	≤ 0.12	> 8	≤ 0.12 - > 8	78.2		21.8

MATERIALS & METHODS

Bacterial isolates: From January 2007 through December 2014, participating tertiary-care medical centres submitted 36,607 bacterial isolates from patients presenting to hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. 9,222 (25.2%) of these isolates were from patients presenting to emergency departments. Each study site was asked to submit clinical isolates (consecutive, one per patient, per infection site) from patients with respiratory, urine, wound, and bloodstream infections. The medical centres submitted clinically significant isolates from patients with a presumed infectious disease. 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.

Antimicrobial susceptibility testing: 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 minimum inhibitory concentration (MIC) interpretive standards were defined according to CLSI breakpoints (M100-S24, 2014). 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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CONCLUSIONS

- *E. coli*, MSSA, *S. pneumoniae, K. pneumoniae, P. aeruginosa, and* MRSA are the most common pathogens isolated from Canadian emergency departments.
- MRSA represents 21.1% of all *S. aureus* infections in EDs (with a nearly 50/50 split between community-acquired and hospital acquired genotypes).
- Against MRSA, susceptibility rates of >99% were observed for LZD, DAP, VAN, and TGC. Wound MRSA isolates exhibited 18.9% resistance to CLD and 2.4% resistance to SXT.
- MER, ERT, PTZ, CTR were the most active intravenous agents against *E. coli* blood isolates (susceptibility >94.0%), while urinary *E. coli* isolates exhibited 21.8% resistance to SXT and 14.7% resistance to CIP—both common empiric oral agents prescribed in the ED.
- CTR, LEV, A/C, and DOX are the most active agents against respiratory *S. pneumoniae* isolates.