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Antibiotic Resistance in Lower Respiratory Tract Infection (LRTI) Pathogens: A National Canadian Perspective: The CANWARD Study 2007-2009

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Abstract

Background: CANWARD is an ongoing national surveillance study that assesses pathogens causing infections in patients attending Canadian hospitals, as well as determines the prevalence of antimicrobial resistance in these isolates.

Methods: From January 2007 to December 2009, 10-15 sentinel hospitals across Canada submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. Susceptibility testing was performed using custom broth micro-dilution panels as recommended by CLSI.

Results: In total, 18,538 isolates were collected from blood, respiratory, urine and wound specimens; 6,559 (35.4%) isolates were from the LRTI. The in vitro activity of selected antimicrobials to the top 10 LRTI pathogens is shown below:

	% Resistant						
Organism (# Isolates)	A/C	CFT	LEV	TIG[b]	MER	P/T	T/S
S. pneumoniae (938)	0.8	0.3	1.1	2.1	1.3	NA	9.3
S. aureus MS (912)	0	0	9.5	0.1	0	0	0.8
S. aureus MR (293)	100[a]	100[a]	91.8	0.7	100[a]	100[a]	12
P. aeruginosa (870)	NA	33.2	26.4	NA	7.6	9.2	NA
E. coli (226)	2.9	8.4	31.4	0	0	2.7	27
H. influenzae (640)	0.2	0.2	0	ND	0.2	0.2	13.9
S. maltophilia (185)	NA	NA	20.5	NA	NA	NA	17.3
K. pneumoniae (201)	0.7	4.5	4	0	0	3	4.5
S. marcescens (116)	54.2	6	3.5	7.8	0.9	1.7	4.3
E. cloacae (121)	56	23.1	1.7	0.8	0	6.6	5

MS-methicillin susceptible; MR-methicillin-resistant; A/C-amoxicillin-clavulanate; CFT-ceftriaxone; LEV-levofloxacin; TIG-tigecycline; MER-meropenem, P/T-piperacillin-tazobactam; T/S-trimethoprim/sulfamethoxazole

[a] Based upon oxacillin resistance.

[b] FDA breakpoints

NA = breakpoints not available; ND= Not determined

Conclusions: Resistance rates in respiratory isolates in Canadian hospitals were pathogen-dependent. Overall, the lowest resistance rates were noted for MER, P/T and TIG.

Introduction

Infections hospitals is a worldwide escalating public health issue. Increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA); both hospital and community associated, vancomycin-resistant *Enterococcus faecium* (VRE), penicillin, macrolide and fluoroquinolone resistant *Streptococcus pneumoniae*, as well as, carbapenem-resistant Enterobacteriaceae pose significant management challenges and increasingly risk our infection control structures.

CANWARD is an ongoing national surveillance study in Canada whose goals are:

- Document pathogens associated with respiratory, blood stream, urinary tract and skin/skin structure infections each year and monitor pathogen shifts.
- Document the prevalence of resistance associated with these pathogens each year.

This study reports on the prevalence of resistance to common widely used antimicrobials used to treat LRTI caused by significant pathogens isolated in Canada in 2007-2009 as part of the larger CANWARD study.

Materials and Methods

Tertiary-care medical centres (12 in 2007, 10 in 2008, 15 in 2009) representing 8 of 10 provinces across Canada submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units.

From January 2007 to December 2009, each study site was asked to collect and submit pathogens (consecutive isolates, one per patient) using the following criteria:

(a) 100 isolates from patients with respiratory tract infections (community or nosocomial); (b) 50 isolates from patients with skin/skin structure infections (wound/IV site infections); (c) 50 isolates from patients with urinary tract infections (inpatients or outpatients); (d) 15 blood stream infection isolates/site/month.

All submitted isolates were deemed clinically significant by each site. All organisms were identified at each site using local site criteria and at the reference site, where indicated. At study sites, isolates were subcultured on appropriate solid media and incubated overnight. Isolates were shipped on Amies semi-solid transport media to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada), where isolates were subcultured on appropriate media, and stocked in skim milk at -80°C.

A custom microtitre panel was designed with a variety of antimicrobials. Antimicrobials were obtained as laboratory grade powders from their respective manufacturers. Stock solutions were prepared and dilutions made as described by the Clinical and Laboratory Standards Institute (2009 CLSI). Following two subcultures from frozen stock, the MICs were determined by the CSLI-approved broth microdilution method (M07-A8, 2009). Briefly, 96-well custom designed microtitre plates containing doubling antibiotic dilutions in 100µl/well of cation adjusted Mueller-Hinton broth (eg. for Enterobacteriaceae) with or without lysed horse blood (2.5-5% V/V) (eg. for *S. pneumoniae*) was inoculated to achieve a final concentration of approximately $5x10^5$ CFU/ml and incubated in ambient air (35°C) for 20-24 hours prior to reading. Quality control was performed periodically using a variety of ATCC QC organisms including; *S. pneumoniae* 49619, *S. aureus* 29213, *E. faecalis* 29212, *E. coli* 25922 and *P. aeruginosa* 27853. For all antimicrobials tested, MIC interpretive standards were defined according to CLSI breakpoints (M100-S20, 2010). The following interpretive breakpoints (FDA) were used to tigecycline, susceptible (S), intermediate (I) and resistant (R) (µg/ml): *Staphylococcus aureus* (MSSA and MRSA) ≤0.5 (S); *Enterococcus faecalis*, ≤0.25 (S); Enterobacteriaceae, ≤2 (S), 4 (I), and ≥8 (R).

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Results

TABLE 1. Antimicrobial Resistance to the Top 10 LRTI Pathogens in Canada 2007-2009

***S. pneumoniae* (945)**

Antimicrobial	MIC50	MIC90	% S	% I	% R	Range
Amoxicillin/ Clavulanate	≤ 0.06	0.25	98.4	0.9	0.8	≤ 0.06 - 8
Ceftriaxone	≤ 0.12	0.12	99.2	0.5	0.3	≤ 0.12 - 4
Levofloxacin	1	1	98.7	0.2	1.1	≤ 0.06 - 32
Meropenem	≤ 0.06	0.12	95.2	3.5	1.3	≤ 0.06 - 2
Piperacillin Tazobactam	≤ 1	≤ 1		No BP		≤ 1 - 8
Tigecycline	0.03	0.06				≤ 0.03 - 0.5
Trimethoprim Sulfa	≤ 0.12	2	83.7	7	9.3	≤ 0.12 - > 8

***S. aureus*, MSSA (912)**

Antimicrobial	MIC50	MIC90	% S	% I	% R	Range
Amoxicillin/ Clavulanate	0.5	1	100			≤ 0.06 - 2
Ceftriaxone	4	4	99.6	0.4		≤ 1 - 16
Levofloxacin	0.25	2	89.8	0.7	9.5	≤ 0.06 - > 32
Meropenem	0.12	0.25	100			≤ 0.12 - 1
Piperacillin Tazobactam	≤ 1	≤ 1	100			≤ 1 - 8
Tigecycline	0.25	0.25				≤ 0.03 - 1
Trimethoprim Sulfa	≤ 0.12	≤ 0.12	99.2		0.8	≤ 0.12 - > 8

***P. aeruginosa* (870)**

Antimicrobial	MIC50	MIC90	% S	% I	% R	Range
Amoxicillin/ Clavulanate	> 32	> 32		No BP		1 - > 32
Ceftriaxone	32	> 64	27.1	39.7	33.2	≤ 1 - > 64
Levofloxacin	2	16	59	14.6	26.4	≤ 0.06 - > 32
Meropenem	0.5	8	87.6	4.8	7.6	≤ 0.12 - > 32
Piperacillin Tazobactam	4	64	90.8		9.2	≤ 1 - > 512
Tigecycline	> 16	> 16				0.25 - > 16
Trimethoprim Sulfa	8	> 8		No BP		≤ 0.12 - > 8

***H. influenzae* (640)**

Antimicrobial	MIC50	MIC90	% S	% I	% R	Range
Amoxicillin/ Clavulanate	0.5	2	99.8		0.2	≤ 0.06 - 8
Ceftriaxone	≤ 0.06	≤ 0.06	99.8		0.2	≤ 0.06 - > 4
Levofloxacin	≤ 0.015	0.03	100			≤ 0.015 - 0.5
Meropenem	≤ 0.06	0.12	99.8		0.2	≤ 0.06 - 2
Piperacillin Tazobactam	≤ 1	≤ 1	99.8		0.2	≤ 1 - 2
Tigecycline	0.12	2				≤ 0.03 - 4
Trimethoprim Sulfa	≤ 0.12	4	82.3	3.8	13.9	≤ 0.12 - > 8

***S. aureus*, MRSA (293)**

Antimicrobial	MIC50	MIC90	% S	% I	% R	Range
Amoxicillin/ Clavulanate	16	32	6.5		93.6	1 - > 32
Ceftriaxone	> 64	> 64	0.3	12.6	87	8 - > 64
Levofloxacin	> 32	> 32	8.2		91.8	0.12 - > 32
Meropenem	8	> 32	37.9	20.1	42	0.25 - > 32
Piperacillin Tazobactam	64	128	9.6		90.4	≤ 1 - 512
Tigecycline	0.25	0.5				0.12 - 1
Trimethoprim Sulfa	≤ 0.12	8	88.1		12	≤ 0.12 - > 8

***E. coli* (226)**

Antimicrobial	MIC50	MIC90	% S	% I	% R	Range
Amoxicillin/ Clavulanate	4	16	87.9	9.3	2.9	Jan-32
Ceftriaxone	≤ 1	2	88.9	2.7	8.4	≤ 1 - > 64
Levofloxacin	≤ 0.06	32	67.7	0.9	31.4	≤ 0.06 - > 32
Meropenem	≤ 0.12	≤ 0.12	100			≤ 0.12 - ≤ 0.12
Piperacillin Tazobactam	2	8	96	1.3	2.7	≤ 1 - 256
Tigecycline	0.5	1				0.25 - 2
Trimethoprim Sulfa	≤ 0.12	> 8	73		27	≤ 0.12 - >8

***K. pneumoniae* (201)**

Antimicrobial	MIC50	MIC90	% S	% I	% R	Range
Amoxicillin/ Clavulanate	2	8	94	5.3	0.7	Jan-32
Ceftriaxone	≤ 1	≤ 1	95	0.5	4.5	≤ 1 - > 64
Levofloxacin	≤ 0.06	1	95	1	4	≤ 0.06 - > 32
Meropenem	≤ 0.12	≤ 0.12	100			≤ 0.12 - ≤ 0.12
Piperacillin Tazobactam	4	16	94.5	2.5	3	≤ 1 - > 512
Tigecycline	1	2				0.25 - 4
Trimethoprim Sulfa	≤ 0.12	0.5	95.5		4.5	≤ 0.12 - > 8

***S. maltophilia* (186)**

Antimicrobial	MIC50	MIC90	% S	% I	% R	Range
Amoxicillin/ Clavulanate	> 32	> 32		No BP		2 - > 32
Ceftriaxone	> 64	> 64		No BP		8 - > 64
Levofloxacin	2	8	67.6	11.9	20.5	0.12 - > 32
Meropenem	> 32	> 32		No BP		≤ 0.12 - > 32
Piperacillin Tazobactam	256	> 512		No BP		16 - > 512
Tigecycline	2	8				0.25 - 16
Trimethoprim Sulfa	0.5	8	82.7		17.3	≤ 0.12 - > 8

***E. cloacae* (121)**

Antimicrobial	MIC50	MIC90	% S	% I	% R	Range
Amoxicillin/ Clavulanate	32	> 32	19.8	24.2	56	2 - > 32
Ceftriaxone	≤ 1	> 64	72.7	4.1	23.1	≤ 1 - > 64
Levofloxacin	≤ 0.06	0.25	95.9	2.5	1.7	≤ 0.06 - 16
Meropenem	≤ 0.12	≤ 0.12	100			≤ 0.12 - 2
Piperacillin Tazobactam	2	64	85.1	8.3	6.6	≤ 1 - 512
Tigecycline	1	1				0.25 - 8
Trimethoprim Sulfa	≤ 0.12	0.5	95		4.9	≤ 0.12 - >8

***S. marcescens* (116)**

Antimicrobial	MIC50	MIC90	% S	% I	% R	Range
Amoxicillin/ Clavulanate	32	> 32	1.4	44.4	54.2	8 - > 32
Ceftriaxone	≤ 1	≤ 1	94		6	≤ 1 - > 64
Levofloxacin	0.12	2	92.2	4.3	3.5	≤ 0.06 - 16
Meropenem	≤ 0.12	≤ 0.12	99.1		0.9	≤ 0.12 - > 32
Piperacillin Tazobactam	2	8	95.7	2.6	1.7	≤ 1 - 128
Tigecycline	2	4				1 - > 16
Trimethoprim Sulfa	0.5	2	95.7		4.3	≤ 0.12 - > 8

Conclusions

1. LRTI pathogens accounted for 29% of all pathogens submitted.
2. The 5 most common lower respiratory tract infection pathogens were *S. pneumoniae*, *Staphylococcus aureus, Pseudomonas aeruginosa*, MSSA and *E. coli*.
3. Highest antimicrobial resistance rates occurred with MRSA, *P. aeruginosa* and *E. cloacae*.
4. Overall resistance in LRTI pathogens in Canada continues to increase.

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