E-2032

Prevalence of Antimicrobial Resistance among Urinary Tract Pathogens Isolated in Canada from 2007 to 2009: Results from the CANWARD Surveillance Study

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ABSTRACT

Background: CANWARD is an annual national surveillance study assessing antimicrobial resistance in pathogens isolated from urinary, respiratory, skin and soft tissue, and bacteremic infections in sentinel hospitals across Canada. From January 2007 to December 2009, 18,538 isolates were collected, including 3,058 urinary culture pathogens.
Methods: Antimicrobial susceptibility testing was performed following CLSI guidelines using custom designed broth microdilution panels.
Results: The most frequently isolated urinary pathogens were *Escherichia coli* (EC, n=1696, 56%), *Enterococci* (EN, n=410, 13%), *Klebsiella pneumoniae* (KP, n=274, 9%), *Proteus mirabilis* (PM, n=122, 4%), and *Pseudomonas aeruginosa* (PA, n=100, 3%); the annual (2007, 2008, 2009) rank order of pathogens was consistent. Annual antimicrobial susceptibility rates from 2007 to 2009 remained unchanged (P>0.05) for the most frequently isolated urinary pathogens. Susceptibility rates (%S) for selected antimicrobial agents were:

	SXT	NIT	CIP	AMC	PTZ	CTR	CTZ	MER	GEN
EC	76	95	77	95	98	90	97	100	90
EN	NA	97	40	NA	NA	NA	NA	NA	NA
KP	86	33	86	97	96	92	97	100	95
PM	84	0	81	95	100	98	100	100	97
PA	NA	NA	66	NA	92	16	93	91	76

SXT-trimethoprim-sulfamethoxazole, NIT-nitrofurantoin, CIP-ciprofloxacin, AMC-amoxicillin-clavulanate, PTZ-piperacillin-tazobactam, CTR-ceftriaxone, CTZ-ceftazidime, MER-meropenem, GEN-gentamicin, NA- no breakpoints available.
Conclusion: Frequently prescribed empiric agents for urinary tract infections, such as SXT and CIP, demonstrate lowered in vitro susceptibilities when tested against recent clinical isolates.

ACKNOWLEDGMENTS

Funding for the CANWARD study was provided in part by the University of Manitoba. The medical centers (investigators) that participated in the CANWARD study from 2007 to 2009 were;

- Vancouver Hospital, Vancouver, British Columbia (Dr. D. Roscoe, 2007-2009)
- University of Alberta Hospitals, Edmonton, Alberta (Dr. R. Rennie, 2007-2009)
- Royal University Hospital, Saskatoon, Saskatchewan (Dr. J. Blondeau, 2007-2009)
- Health Sciences Centre, Winnipeg, Manitoba (Dr. D. Hoban, 2007-2009)
- London Health Sciences Centre, London, Ontario (Dr. Z. Hussain, 2007-2009)
- St. Joseph's Hospital, Hamilton, Ontario (Dr. C. Lee, 2007)
- Mount Sinai Hospital, Toronto, Ontario (Dr. S. Poutanen, 2007-2009)
- St. Michael's Hospital, Toronto, Ontario (Dr. L. Matukas, 2009)
- Children's Hospital of Eastern Ontario, Ottawa, Ontario (Dr. F. Chan, 2007-2009)
- The Ottawa Hospital Ottawa, Ontario (Dr. M. Desjardins, 2009)
- Royal Victoria Hospital, Montreal, Quebec (Dr. V. Loo, 2007, 2009)
- Montreal General Hospital, Montreal, Quebec (Dr. V. Loo, 2007-2009)
- Hôpital Maisonneuve-Rosemont, Montreal, Quebec (Dr. M. Laverdière, 2007-2009)
- Centre Hopitalier Régional de Trois Rivières, Pavillon Sainte Marie, Trois Rivières, Quebec (Dr. M. Goyette, 2009)
- South-East Regional Health Authority, Moncton, New Brunswick (Dr. M. Kuhn, 2009)
- Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia (Dr. R. Davidson, 2007-2009)

BACKGROUND

There are an estimated 150 million urinary tract infections per annum worldwide (1). In the United States, urinary tract infections result in an approximately 8 million physician visits per year (2); they are the most common bacterial infections in women, and account for significant morbidity and health care costs (1, 3). Most visits to physicians for symptoms of acute cystitis do not result in urine culture and isolate antimicrobial susceptibility testing, rather urine culture is often reserved for patients failing empiric therapy and those with recurrent or complicated infections. Among both outpatients and inpatients, *Escherichia coli* is the primary urinary tract pathogen, accounting for 75-90% of uncomplicated urinary tract infection isolates (3, 4). *Staphylococcus saprophyticus*, *Klebsiella* spp., *Proteus* spp., *Enterococcus* spp. and *Enterobacter* spp., are pathogens less commonly isolated from outpatients.
The currently recommended empiric antimicrobial regimen for treating acute uncomplicated bacterial cystitis in otherwise healthy adult non-pregnant females is a three-day course of double-strength trimethoprim-sulfamethoxazole in settings where the prevalence of trimethoprim-sulfamethoxazole resistance is <10-20% (2, 5). Alternative therapy for uncomplicated urinary infections in settings with >10-20% trimethoprim-sulfamethoxazole resistance may include a fluoroquinolone, nitrofurantoin, or fosfomycin (2).
The IDSA also recommends that physicians obtain information on local resistance rates and that ongoing surveillance be conducted to monitor changes in susceptibility of uropathogens (2). Surveillance at the institutional and regional level is particularly important given that previous studies have reported that the activity of trimethoprim-sulfamethoxazole against urinary isolates of *E. coli* can vary considerably by geographic region (7, 8).
Recent in vitro studies specifically describing antimicrobial susceptibilities of urinary isolates of *E. coli* from female outpatients in Canada and the United States are limited (6, 8, 9, 11-13). In these studies, trimethoprim-sulfamethoxazole resistance increased from 7-9% in 1989-1992 (8, 9, 13, 14) to 17-18% in 1995-1999 (6, 8, 9, 12). Fluoroquinolone resistance was ≤1% in each of the aforementioned studies and nitrofurantoin resistance was reported to be ≤2% on national and regional levels in the United States. The 1998 SENTRY surveillance program, reporting on isolates of *E. coli* collected from 26 U.S. centers, found the overall prevalence of trimethoprim-sulfamethoxazole resistance to be 23.3% (15), very similar to the resistance rate found a year earlier (25.2%) by the same surveillance program (10).
In the current study, the in vitro activities of trimethoprim-sulfamethoxazole, ciprofloxacin, nitrofurantoin, and other comparator agents were evaluated against a recent Canadian collection of pathogens isolated from patients with urinary tract infections in 2007-2009.

MATERIALS & METHODS

Bacterial Isolates:
Tertiary-care medical centers (12 in 2007, 10 in 2008, 15 in 2009) in 8 of 10 Canadian provinces submitted pathogens from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. The sites were geographically distributed in a population-based manner. From January 2007 through December 2009, inclusive, each study site was asked to submit clinically significant isolates (consecutive, one per patient, per infection site), as defined by their site criteria, from inpatients and outpatients with respiratory, urine, wound, and bloodstream infections. Isolate identification was performed by the submitting site and confirmed at the reference site as required, based on morphological characteristics and antimicrobial susceptibility patterns. In 2007, 2008, and 2009, 7881, 5282, and 5375 isolates were collected, respectively.
Antimicrobial Susceptibility Testing:
The in vitro activities of antimicrobials were determined by broth microdilution in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines (17) with minimum inhibitory concentrations (MICs) interpreted according to CLSI breakpoints (18). Yeasts, non-speciated coagulase-negative staphylococci, *Streptococcus agalactiae*, viridans streptococci, *Moraxella catarrhalis*, and species with fewer than 10 isolates were not tested for antimicrobial susceptibilities.

RESULTS

Table 1. Most common pathogens isolated from urine in the CANWARD Surveillance program, 2007-09

Rank	Pathogen	% (no.) of 3,058 urine isolates collected in 2007-2009[a,b]
1	*Escherichia coli*	55.5 (1,696)
2	*Enterococcus* spp.	13.4 (410)
3	*Klebsiella pneumoniae*	9.0 (274)
4	*Proteus mirabilis*	4.0 (122)
5	*Pseudomonas aeruginosa*	3.3 (100)
6	*Staphylococcus aureus*	2.6 (80)
7	*Enterobacter cloacae*	1.8 (54)
8	*Streptococcus agalactiae*	1.7 (52)
9	*Klebsiella oxytoca*	1.5 (46)
10	*Citrobacter freundii*	1.0 (29)
11	*Morganella morganii*	0.8 (24)
12	*Staphylococcus saprophyticus*	0.5 (14)
13	*Citrobacter koseri*	0.5 (14)
14	*Serratia marcescens*	0.4 (12)
15	*Enterobacter aerogenes*	0.3 (10)
86	Others[c]	4..0 (121)

a The collection of 3,058 isolates contained 1,326 isolates from 2007,983 isolates from 2008, and 749 isolates from 2009.
b The annual rank order of pathogens was consistent for 2007, 2008, and 2009 (data not shown).
c The Others pathogen category was composed of 58 coagulase-negative staphylococci and 63 isolates from 27 different species.

Table 3. Demographic characteristics of patients from whom *E. coli* was isolated from urine during CANWARD 2007-2009

Patient category	No of total isolates	Percentage of isolates resistant[a] to			
		Trimethoprim-Sulfamethoxazole	Ciprofloxacin	Nitrofurantoin	Amoxicillin-Clavulanate
Gender					
Female	1,305	22.7	20.4	3.5	5.7
Male	391	28.4	32.0	9.3	5.5
Age, years					
<18	250	22.0	5.2	3.4	4.5
18-64	719	23.9	18.1	2.3	4.3
>64	727	24.8	34.1	7.3	5.8
Hospital Location					
Clinic/Office	491	25.5	19.8	4.5	4.9
Emergency Room	525	20.6	14.7	3.6	3.0
Intensive Care Unit	47	23.4	21.3	5.6	7.4
Medical Ward	520	26.1	31.5	5.2	5.4
Surgical Ward	113	23.9	38.0	6.4	15.6
Geographic Location[b]					
Western Canada	577	25.8	27.7	4.8	5.3
Ontario	549	23.7	20.9	4.6	5.1
Quebec	385	23.4	23.6	5.4	8.5
Eastern Canada	185	20.5	13.5	4.6	3.8

[a] For ciprofloxacin, nitrofurantoin, and amoxicillin-clavulanate, intermediate isolates were added to resistant isolates and reported as resistant for this analysis.
[b] Western Canada includes the provinces of British Columbia, Alberta, Saskatchewan, and Manitoba; eastern Canada includes Nova Scotia and New Brunswick.

Table 4. Co-resistant phenotypes among 1,696 *E. coli* urinary isolates tested against amoxicillin-clavulanate ciprofloxacin, nitrofurantoin, and trimethoprim-sulfamethoxazole in 2007-2009

Co-resistant phenotype	No. of co-resistant isolates	Percentage of co-resistant isolates	Percentage of all isolates
Ciprofloxacin, Trimethoprim-sulfamethoxazole	203	71.0	12.0
Ciprofloxacin, Amoxicillin-clavulanate	30	10.5	1.8
Ciprofloxacin, Trimethoprim-sulfamethoxazole, Amoxicillin-clavulanate	17	5.9	1.0
Ciprofloxacin, Trimethoprim-sulfamethoxazole, Nitrofurantoin	14	5.0	0.8
Trimethoprim-sulfamethoxazole, Amoxicillin-clavulanate	10	3.5	0.6
Ciprofloxacin, Nitrofurantoin	7	2.4	0.4
Trimethoprim-sulfamethoxazole, Nitrofurantoin	3	1.0	0.2
Ciprofloxacin, Nitrofurantoin, Amoxicillin-clavulanate	2	0.7	0.1
Total	286	100	16.9

[a] For ciprofloxacin, nitrofurantoin, and amoxicillin-clavulanate, intermediate isolates were added to resistant isolates and reported as resistant for this analysis.
[b] 60.0% (1018/1696) of isolates were uniformly susceptible to trimethoprim-sulfamethoxazole, nitrofurantoin, ciprofloxacin, and amoxicillin-clavulanate

Table 2. In vitro activities of antimicrobial agents against the most common pathogens isolated from urine in the CANWARD Study 2007-2009

Organism (no. tested)/antimicrobial agent	MIC (µg/mL)			%	%	%
	50%	90%	Range	Susceptible	Intermediate	Resistant
***Escherichia coli* (1696)[a,b]**						
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12->8	76.0	NA[c]	24.0
Nitrofurantoin	16	32	≤0.5->256	95.4	2.7	1.9
Ciprofloxacin	≤0.06	>16	≤0.06->16	77.0	0.4	22.7
Levofloxacin	≤0.06	16	≤0.06->32	77.4	0.9	21.7
Amoxicillin-clavulanate	4	8	≤0.06->32	95.0	4.1	0.9
Piperacillin-tazobactam	2	4	≤1->512	97.5	1.5	0.9
Ceftriaxone	≤1	2	≤1->64	89.7	0.4	9.9
Ceftazidime	≤0.5	1	≤0.5->32	96.5	0.3	3.2
Meropenem	≤0.12	≤0.12	≤0.12	100	0	0
Gentamicin	≤0.5	4	≤0.5->32	90.1	0.4	9.6
***Enterococcus* spp. (410)[a]**						
Trimethoprim-sulfamethoxazole	≤0.12	0.5	≤0.12->8	NA	NA	NA
Nitrofurantoin	8	8	≤0.5-256	97.4	0.7	2.0
Ciprofloxacin	2	>16	≤0.06->16	39.9	21.1	39.1
Levofloxacin	2	>32	≤0.06->32	61.7	0.5	37.8
Amoxicillin-clavulanate	0.5	1	≤0.06->32	NA	NA	NA
Piperacillin-tazobactam	4	8	≤1->512	NA	NA	NA
Ceftriaxone	>64	>64	≤1->64	NA	NA	NA
Ceftazidime	>32	>32	≤0.5->32	NA	NA	NA
Meropenem	4	16	≤0.06->32	NA	NA	NA
Gentamicin	16	>32	≤0.5->32	NA	NA	NA
Vancomycin	1	2	≤0.5->32	99.0	NA	1.0
***Klebsiella pneumoniae* (274)[a]**						
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12->8	86.1	NA	13.9
Nitrofurantoin	64	256	8->256	32.8	22.1	45.1
Ciprofloxacin	≤0.06	4	≤0.06->16	85.7	2.2	12.1
Levofloxacin	≤0.06	4	≤0.06->32	89.7	2.9	7.3
Amoxicillin-clavulanate	2	8	0.5-16	97.3	2.7	0
Piperacillin-tazobactam	2	16	≤1-512	95.6	2.2	2.2
Ceftriaxone	≤1	≤1	≤1->64	91.9	1.5	6.6
Ceftazidime	≤0.5	1	≤0.5->32	96.9	1.2	1.9
Meropenem	≤0.12	≤0.12	≤0.12-0.25	100	0	0
Gentamicin	≤0.5	≤0.5	≤0.5->32	94.5	0.4	5.1
***Proteus mirabilis* (122)[a]**						
Trimethoprim-sulfamethoxazole	≤0.12	>8	≤0.12->8	84.4	NA	15.6
Nitrofurantoin	128	256	64-256	0	6.0	94.0
Ciprofloxacin	≤0.06	2	≤0.06->16	81.2	10.7	8.2
Levofloxacin	0.12	2	≤0.06->32	91.8	4.1	4.1
Amoxicillin-clavulanate	1	8	0.5->32	94.8	2.6	2.6
Piperacillin-tazobactam	≤1	≤1	≤1-8	100	0	0
Ceftriaxone	≤1	≤1	≤1-4	97.5	0.8	1.6
Ceftazidime	≤0.5	≤0.5	≤0.5-4	100	0	0
Meropenem	≤0.12	≤0.12	≤0.12-0.25	100	0	0
Gentamicin	1	2	≤0.5->32	96.7	1.6	1.6
***Pseudomonas aeruginosa* (100)**						
Trimethoprim-sulfamethoxazole	>8	>8	1->8	NA	NA	NA
Nitrofurantoin	>256	>256	>256	NA	NA	NA
Ciprofloxacin	0.5	>16	≤0.06->16	66.0	7.0	27.0
Levofloxacin	1	>32	0.12->32	60.0	8.0	32.0
Amoxicillin-clavulanate	>32	>32	>32	NA	NA	NA
Piperacillin-tazobactam	4	64	2-512	92.0	NA	8.0
Ceftriaxone	32	>64	4->64	16.0	46.0	38.0
Ceftazidime	4	8	1->32	93.0	1.8	5.3
Meropenem	0.5	4	≤0.12->32	91.0	2.0	7.0
Gentamicin	4	16	≤0.5->32	76.0	10.0	14.0
***Staphylococcus aureus* (80)[a]**						
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12->8	92.5	NA	7.5
Nitrofurantoin	16	16	Aug-32	100	0	0
Ciprofloxacin	>16	>16	0.12->16	41.3	0	58.8
Levofloxacin	8	>32	0.12->32	43.8	0	56.3
Amoxicillin-clavulanate	1	32	0.12-32	57.5	NA	42.6
Piperacillin-tazobactam	≤1	128	≤1->512	62.5	NA	37.5
Ceftriaxone	4	>64	1->64	57.5	7.5	35.0
Ceftazidime	16	>32	8->32	23.3	30.2	46.5
Meropenem	0.12	16	≤0.12->32	80.0	6.3	13.8
Gentamicin	≤0.5	2	≤0.5->32	90.0	0	10.0
Vancomycin	1	1	≤0.25-1	100	0	0

[a] No significant change in % susceptibility for *E. coli* by year (2007, 2008, 2009; P>0.05).
[b] ESBL rates for *E. coli* , *K. pneumoniae* , and *P. mirabilis* were 3.1% (52/1,696), 2.9% (8/274), and 0% (0/122).
[c] NA – not available.
[d] Included 4 vancomycin-resistant isolates (all *vanA* positive).
[e] 35 isolates were methicillin-resistant *S. aureus* (MRSA); 33 were healthcare-associated MRSA PFGE genotypes (one of the 10 Canadian MRSA epidemic pulsed-field gel electrophoresis patterns excluding CMRSA7 [USA400] and CMRSA10 [USA300]), 1 was a community-associated MRSA genotype (CMRSA7 [USA400] or CMRSA10 [USA300]), and 1 was a unique MRSA PFGE type (not one of the 10 Canadian MRSA epidemic types).

CONCLUSIONS

- The most frequently isolated urinary pathogens tested by the CANWARD study in 2007-2009 were *E. coli* (56%), enterococci (13%), *K. pneumoniae* (9%), *P. mirabilis* (4%), *P. aeruginosa* (3%), and *S. aureus* (3%). These six pathogens accounted for ~90% of all isolates collected from urinary tract infections (Table 1).
- 76%, 86%, 84%, and 92.5% of *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *S. aureus* were susceptible to trimethoprim-sulfamethoxazole, a frequently prescribed empiric therapy. Enterococci and *P. aeruginosa* are intrinsically resistant to trimethoprim-sulfamethoxazole (Table 2).
- 95%, 97%, 33%, and 100% of *E.coli*, enterococci, *K. pneumoniae* and *S. aureus* were susceptible to nitrofurantoin, a frequently prescribed empiric therapy. *P. mirabilis* and *P. aeruginosa* are intrinsically resistant to nitrofurantoin (Table 2).
- 77%, 40%, 86%, 81%, 66%, and 41% of *E.coli*, enterococci, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*, and *S. aureus* were susceptible to ciprofloxacin, a frequently prescribed empiric therapy in adults (Table 2).
- For isolates of *E. coli*, patient gender and age influenced rates of resistance to ciprofloxacin and nitrofurantoin; hospital location and geographic location influenced rates of resistance to ciprofloxacin and amoxicillin-clavulanate (Table 3).
- 286 of 1696 (16.9%) isolates of *E. coli* were resistant to two or more frequently prescribed antimicrobial agents; 95.5% (273/286) and 86.4% (247/286) of co-resistant isolates were resistant to ciprofloxacin and trimethoprim-sulfamethoxazole, respectively (Table 4).
- Frequently prescribed empiric agents for urinary tract infections, such as trimethoprim-sulfamethoxazole and ciprofloxacin, demonstrate lowered in vitro susceptibilities when tested against recent clinical isolates.

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ICAAC Interscience Conference on Antimicrobial Agents and Chemotherapy, Boston MA, September 12-15, 2010