

# 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%), *Enterococcus* (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 (0.0-0.0%) for the most frequently isolated urinary pathogens. Susceptibility rates (%) for selected antimicrobial agents were:

	SXT	NTI	CIP	AMC	PTZ	CTR	CTZ	MER	GEN
EC	78	95	77	95	98	90	97	100	90
EN	NA	97	NA	NA	NA	NA	NA	NA	NA
KP	86	33	86	97	96	92	100	90	95
PM	84	0	85	95	100	98	100	100	97
PA	84	0	85	95	100	98	100	100	97

SXT-trimethoprim-sulfamethoxazole, NTI-nitrofurantoin, CIP-ciprofloxacin, AMC-amoxicillin-clavulanate, PTZ-piperacillin-tazobactam, CTR-ceftazidime, 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.

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### 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 where 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 ranged 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 GENURY 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 reported, 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-specified 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	% of 3,058 urine isolates collected in 2007-2009 <sup>a,b</sup>
1	<i>Escherichia coli</i>	55.5 (1,626)
2	<i>Enterococcus</i> spp.	13.4 (4,101)
3	<i>Klebsiella pneumoniae</i>	9.0 (2,744)
4	<i>Proteus mirabilis</i>	4.0 (1,222)
5	<i>Pseudomonas aeruginosa</i>	3.3 (1,000)
6	<i>Staphylococcus aureus</i>	2.6 (800)
7	<i>Enterobacter cloacae</i>	1.6 (544)
8	<i>Streptococcus agalactiae</i>	1.7 (522)
9	<i>Klebsiella oxytoca</i>	1.5 (464)
10	<i>Carbacter freundii</i>	1.0 (289)
11	<i>Morganella morganii</i>	0.8 (244)
12	<i>Staphylococcus saprophyticus</i>	0.5 (154)
13	<i>Carbacter koseri</i>	0.5 (154)
14	<i>Serratia marcescens</i>	0.4 (122)
15	<i>Enterobacter aerogenes</i>	0.3 (101)
16	Others <sup>c</sup>	4.0 (1,211)

a The collection of 3,058 isolates contained 1,326 isolates from 2007, 983 isolates from 2008, and 749 isolates from 2009.

b The other pathogen rank order of pathogens was consistent for 2007, 2008, and 2009 (data not shown).

c The Others pathogen category was composed of 56 coagulase-negative staphylococci and 83 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	Trimethoprim-Sulfamethoxazole	Ciprofloxacin	Nitrofurantoin	Amoxicillin-Clavulanate
Gender					
Female	1,305	22.7	20.4	3.5	5.7
Male	719	22.4	32.0	9.3	5.5
Age years					
<18	250	22.0	2.2	4.4	4.5
18-64	549	23.8	16.1	4.3	4.1
65+	727	24.8	34.1	7.3	5.8
Hospital Location					
Clinic/Office	491	25.5	19.8	4.5	4.9
Emergency Room	20.6	14.7	3.6	3.0	1.0
Intensive Care Unit	47	23.4	21.3	5.6	7.4
Medical Ward	520	26.1	31.5	6.2	5.4
Surgical Ward	113	23.9	38.0	6.4	15.6
Geographic Location <sup>d</sup>					
Western Canada	577	23.8	27.7	4.8	5.3
Ontario	549	23.7	20.9	4.6	4.3
Quebec	385	25.4	23.6	5.4	8.5
Eastern Canada	185	20.5	13.5	4.6	3.8

<sup>a</sup> For ciprofloxacin, nitrofurantoin, and amoxicillin-clavulanate, intermediate isolates were added to resistant isolates and reported as resistant for this analysis.

<sup>b</sup> Western Canada includes the provinces of British Columbia, Alberta, Saskatchewan, and Manitoba; eastern Canada includes Nova Scotia and New Brunswick.

<sup>c</sup> 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	% of co-resistant isolates	Percentage of all isolates
Ciprofloxacin, Trimethoprim-sulfamethoxazole	203	71.0	12.0
Ciprofloxacin, Amoxicillin-clavulanate	30	10.0	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

<sup>d</sup> For ciprofloxacin, nitrofurantoin, and amoxicillin-clavulanate, intermediate isolates were added to resistant isolates and reported as resistant for this analysis.

<sup>e</sup> 60% (10/16) (100%) of isolates were uniformly susceptible to trimethoprim-sulfamethoxazole, nitrofurantoin, ciprofloxacin, and amoxicillin-clavulanate

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

Organism (no. susceptible/intermediate agent)	50% MIC Inhibitory	90% Range	Susceptible	Intermediate	Resistant
<i>Escherichia coli</i> (1696) <sup>a</sup>					
Trimethoprim-sulfamethoxazole	50	18-12	96.0	NA	34.0
Nitrofurantoin	16	32	95.0-106	78.0	2.7
Ciprofloxacin	50	16	90.0-116	77.0	0.4
Amoxicillin-clavulanate	4	8	90.0-112	77.4	0.7
Piperacillin-tazobactam	4	8	91.0-112	96.0	4.1
Ceftazidime	25	4	91.0-112	97.4	1.5
Ceftazidime	51	2	91.0-114	89.7	0.4
Mergempem	25	4	91.0-112	96.5	0.3
Gentamicin	11	2	91.0-112	100	0
Colistin	51	4	91.0-112	90.1	0.4
<i>Enterococcus</i> spp. (410) <sup>b</sup>					
Trimethoprim-sulfamethoxazole	10	4	91.0-116	NA	NA
Nitrofurantoin	10	4	91.0-116	97.4	0.7
Ciprofloxacin	2	16	90.0-116	39.9	2.1
Amoxicillin-clavulanate	2	16	90.0-116	89.7	0.5
Piperacillin-tazobactam	4	8	91.0-116	92.0	NA
Ceftazidime	4	8	91.0-116	92.0	NA
Ceftazidime	16	4	91.0-116	92.0	NA
Mergempem	16	4	91.0-116	92.0	NA
Gentamicin	4	16	91.0-116	92.0	NA
Colistin	2	20	90.0-116	90.0	0
<i>Klebsiella pneumoniae</i> (274) <sup>c</sup>					
Trimethoprim-sulfamethoxazole	10	16	91.0-116	86.1	NA
Nitrofurantoin	8	256	91.0-116	32.8	22.1
Ciprofloxacin	10	4	90.0-116	85.7	2.2
Amoxicillin-clavulanate	10	4	90.0-116	86.7	2.2
Amoxicillin-clavulanate	8	8	91.0-116	97.3	2.7
Ceftazidime	2	16	91.0-116	96.6	2.2
Ceftazidime	8	8	91.0-116	97.3	2.7
Ceftazidime	55.5	1	91.0-116	98.9	1.2
Mergempem	55.5	1	91.0-116	98.9	1.2
Gentamicin	11	2	91.0-116	98.9	0
Colistin	11	2	91.0-116	98.9	0
<i>Proteus mirabilis</i> (122) <sup>d</sup>					
Trimethoprim-sulfamethoxazole	10	16	91.0-116	84.4	NA
Nitrofurantoin	128	256	91.0-116	60.0	94.0
Ciprofloxacin	2	16	90.0-116	81.2	12.7
Amoxicillin-clavulanate	1	2	90.0-116	91.8	4.1
Piperacillin-tazobactam	1	8	90.0-116	94.8	2.6
Ceftazidime	1	8	90.0-116	94.8	2.6
Ceftazidime	1	8	90.0-116	94.8	2.6
Mergempem	1	8	90.0-116	94.8	2.6
Gentamicin	1	8	90.0-116	94.8	2.6
Colistin	1	8	90.0-116	94.8	2.6
<i>Pseudomonas aeruginosa</i> (100) <sup>e</sup>					
Trimethoprim-sulfamethoxazole	16	16	91.0-116	NA	NA
Nitrofurantoin	16	16	91.0-116	NA	NA
Ciprofloxacin	16	16	91.0-116	66.0	7.0
Amoxicillin-clavulanate	16	16	91.0-116	66.0	7.0
Amoxicillin-clavulanate	>12	>12	91.0-116	NA	NA
Piperacillin-tazobactam	>12	>12	91.0-116	NA	NA
Ceftazidime	4	64	91.0-116	92.0	NA
Ceftazidime	4	64	91.0-116	92.0	NA
Mergempem	4	8	91.0-116	90.0	48.0
Gentamicin	4	8	91.0-116	90.0	1.8
Colistin	4	8	91.0-116	90.0	1.8
Gentamicin	4	8	91.0-116	90.0	1.8
Colistin	4	8	91.0-116	90.0	1.8
<i>Staphylococcus aureus</i> (80) <sup>f</sup>					
Trimethoprim-sulfamethoxazole	50	12	91.0-116	92.5	NA
Nitrofurantoin	16	16	91.0-116	92.5	NA
Ciprofloxacin	8	16	91.0-116	41.8	0
Amoxicillin-clavulanate	8	16	91.0-116	41.8	0
Piperacillin-tazobactam	12	12	91.0-116	97.5	NA
Ceftazidime	11	12	91.0-116	62.5	NA
Ceftazidime	16	16	91.0-116	23.3	30.2
Mergempem	12	12	91.0-116	80.0	6.3
Gentamicin	12	12	91.0-116	80.0	6.3
Colistin	12	12	91.0-116	80.0	6.3
Vancomycin	1	1	98.0-116	100	0

<sup>a</sup> NA= not available.

<sup>b</sup> 84% of enterococci were susceptible to all antimicrobials.

<sup>c</sup> 38% isolates were methicillin-resistant. *S. aureus* (MRSA) 33 were healthcare-associated MRSA (PCE) genotypes and 47 were community-associated MRSA genotypes (including 161 community-associated MRSA (CAMSA) and 1