JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlac122

JAC-Antimicrobial Resistance

Antimicrobial resistance patterns of bacterial pathogens recovered from the urine of patients at Canadian hospitals from 2009 to 2020

Andrew Walkty[1,2], James A. Karlowsky[1,2], Philippe Lagace-Wiens[1,2], Melanie R. Baxter[1], Heather J. Adam[1,2] and George G. Zhanel[1]*

[1]*Max Rady College of Medicine, University of Manitoba, 502 Basic Medical Sciences Building, 745 Bannatyne Avenue, Winnipeg R3E 0J9, Manitoba, Canada;* [2]*Shared Health, Winnipeg, Manitoba, Canada*

*Corresponding author. E-mail: ggzhanel@pcsinternet.ca

Received 4 November 2022; accepted 13 November 2022

Objectives: To investigate in vitro susceptibility patterns of bacterial pathogens recovered from the urine of outpatients (isolates from outpatient clinics or emergency departments) and hospital inpatients across Canada from 2009 to 2020 as part of the CANWARD study

Methods: Canadian hospital microbiology laboratories submitted bacterial pathogens cultured from urine to the CANWARD study coordinating laboratory on an annual basis (January 2009 to December 2020). Antimicrobial susceptibility testing was performed by CLSI broth microdilution, with MICs interpreted by current CLSI breakpoints.

Results: In total, 4644 urinary pathogens were included in this study. *Escherichia coli* was recovered most frequently (53.3% of all isolates), followed by *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Together, these six species accounted for 84.2% of study isolates. Nitrofurantoin demonstrated excellent *in vitro* activity versus *E. coli*, with 97.6% of outpatient and 96.1% of inpatient isolates remaining susceptible. In contrast, *E. coli* susceptibility rates were lower for ciprofloxacin (outpatient 79.5%, inpatient 65.9%) and trimethoprim/sulfamethoxazole (outpatient 75.2%, inpatient 73.5%). The percentage of *E. coli* isolates that were phenotypically positive for ESBL production significantly increased from 4.2% (2009–11) to 11.3% (2018–20). A similar although less pronounced temporal trend was observed with ESBL-producing *K. pneumoniae*.

Conclusions: *E. coli* was the pathogen most frequently recovered from the urine of Canadian patients, and the proportion of isolates that were ESBL producers increased over time. Susceptibility data presented here suggest that ciprofloxacin and trimethoprim/sulfamethoxazole may be suboptimal for the empirical treatment of complicated urinary infections.

Introduction

Urinary tract infections (UTIs) are common. In the USA, UTIs were responsible for an estimated 8.6 million ambulatory care visits in 2007.[1] Further, in 2011, approximately 400 000 patients in the USA were hospitalized for a UTI, resulting in a total healthcare cost estimated at $2.8 billion.[2] UTIs that occur in young, otherwise healthy, non-pregnant, pre-menopausal, ambulatory women with no history suggestive of a functional or anatomical urinary tract abnormality are termed uncomplicated.[3] In contrast, UTIs in individuals with medical conditions or abnormalities of the urinary tract (anatomical or functional) that may increase the risk of treatment failure are considered complicated.[3] This latter group includes infections in pregnant women, children, males, immunocompromised patients, and patients with a urinary catheter.[3] *Escherichia coli* is the pathogen most frequently identified among patients presenting with uncomplicated cystitis and pyelonephritis.[3,4] For patients with complicated UTIs, including hospitalized patients, *E. coli* remains the most common organism but the spectrum of pathogens encountered is more diverse.[5–7] Of concern, ESBL producers are being detected with increasing frequency among urinary *E. coli* isolates, both in Canada and elsewhere in the world.[8–11] ESBL-producing *E. coli* often demonstrate phenotypic resistance to multiple antimicrobials used in

the empirical management of UTIs, complicating the selection of appropriate initial antimicrobial therapy.[8]

In the ambulatory care setting, women presenting with uncomplicated cystitis are often treated empirically with an oral agent and urine culture is not performed.[12–14] For patients with pyelonephritis or a complicated urinary tract infection, urine culture is recommended.[3,5] Initial therapy in this setting should be based on multiple factors including severity of illness, prior treatment history, previous microbiology results, and local or national antibiogram data. There has not been a large surveillance study describing the susceptibility patterns of common bacteria causing UTIs among Canadian patients published in recent years. The purpose of the current study was to investigate the *in vitro* susceptibility of pathogens frequently isolated from the urine of outpatients (persons attending outpatient clinics or seeking urgent care/emergency department services) and inpatients across Canada from 2009 to 2020, as well as to document changes in susceptibility to common antimicrobials over this time period.

Materials and methods

Bacterial isolates

The bacterial isolates tested here were obtained as part of the CANWARD surveillance study.[15] CANWARD is an ongoing, national Canadian Antimicrobial Resistance Alliance (CARA)/Health Canada partnered study assessing antimicrobial resistance patterns of pathogens causing infections among patients receiving care at hospitals across Canada. Isolates cultured from urine specimens submitted to sentinel hospital microbiology laboratories in nine of the ten Canadian provinces (geographically distributed in a population-based fashion) were forwarded on to the CANWARD coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) on an annual basis. Only clinically significant isolates were included, with significance determined based on local microbiology laboratory protocols. Isolates were shipped on Amies semi-solid transport medium, subcultured onto appropriate media, and stocked in skimmed milk at −80°C until MIC testing was performed. Species identities were confirmed biochemically or by MALDI-TOF MS (Bruker Daltonics, Billerica, MA, USA) at the coordinating laboratory as required (i.e. when the isolate morphology or susceptibility profile did not match the identification reported by the referring laboratory). For the purpose of this study, isolates were classified as outpatient if they were obtained from patients attending primary care and specialty medical clinics, and hospital emergency or urgent care departments. Isolates were considered inpatient if they were obtained from patients receiving care on medical, surgical or ICU wards.

Antimicrobial susceptibility testing

Following two subcultures from frozen stock, MICs for clinically relevant antimicrobials were determined using the CLSI reference broth microdilution method, with 96-well custom-designed microtitre plates containing doubling dilutions of agents in volumes of 100 μL/well.[16] MICs were interpreted according to current CLSI breakpoints.[17] Quality control testing was performed each day that clinical isolates were tested, as specified by CLSI. Colony counts were performed periodically to confirm starting inocula. Susceptibility data in this report are only provided for the six pathogens most frequently recovered from the urine of Canadian patients. Cefazolin was tested as a surrogate for cefalexin, as permitted by the CLSI M100 standard.[17] Phenotypic screening and confirmation of ESBL-producing *E. coli* and *Klebsiella pneumoniae* was performed as described by CLSI.[17]

Statistical analysis

For the purpose of statistical analysis, isolates were defined as either susceptible or not susceptible (intermediate or resistant) to a tested antimicrobial agent using current CLSI breakpoints. The susceptible-dose-dependent category (cefepime and piperacillin/tazobactam tested against Enterobacterales) was included in the not-susceptible group. To estimate the change in antimicrobial susceptibility over time (from 2009 to 2020) in Canada, we performed a Cochrane–Armitage test of trend for four 3 year time periods (2009 to 2011, 2012 to 2014, 2015 to 2017, and 2018 to 2020) for the six most common pathogens isolated: *E. coli*, *K. pneumoniae*, *Enterococcus faecalis*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. *P* values ≤0.05 were considered statistically significant.

Results

This study included 4644 pathogens recovered from urine specimens obtained from Canadian patients between 2009 and 2020. Isolate demographics, stratified by bacterial species, are presented in Table S1. In total, 70.3% (3264/4644) of isolates were from female patients, while 29.7% (1380/4644) were from male patients. The distribution of isolates by patient age was as follows: 12.6% (587/4644) from patients ≤17 years of age, 37.6% (1747/4644) from patients 18 to 64 years of age, and 49.7% (2310/4644) from patients ≥65 years of age. The majority of isolates (3032; 65.3%) were classified as outpatient, with an almost even split between isolates obtained from clinic patients and isolates obtained from emergency room patients. The remaining 1612 isolates were classified as inpatient. The majority of these (1222; 75.8%) were from patients on medical wards. Isolates were obtained from across Canada, with roughly one-third from the eastern provinces, one-third from the western provinces, and one-third from Ontario (Canada's most populated province, located near the geographical centre of the country).

The six most frequently recovered urinary pathogens were *E. coli*, *E. faecalis*, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa* and *S. aureus* (Table S1). Together, these species accounted for 84.2% of all isolates in the study. *E. coli* was the most common urinary pathogen irrespective of inpatient or outpatient location, patient gender, patient age or region of Canada. However, the relative frequency of *E. coli* isolation was lower for inpatients (42.7% of all inpatient isolates) in comparison with outpatients (58.9% of all outpatient isolates). Pathogens other than *E. coli* made up a greater proportion of inpatient isolates. *E. faecalis* accounted for 14.1% of inpatient isolates but only 8.8% of outpatient isolates. Similarly, *P. aeruginosa* and *Enterobacter cloacae* accounted from 6.2% and 3.4% of inpatient isolates but only 2.1% and 1.6% of outpatient isolates, respectively. The relative proportions of isolates other than *E. coli* also tended to be higher among male patients and those ≥65 years of age.

Antimicrobial susceptibility data for the six most common pathogens isolated in this study are presented in Table 1. The most active oral antimicrobials versus outpatient *E. coli* urinary isolates were nitrofurantoin (97.6% susceptible), cefalexin (92% susceptible, extrapolated from cefazolin) and amoxicillin/clavulanate (85.1% susceptible). *In vitro* susceptibility to ciprofloxacin and trimethoprim/sulfamethoxazole, two other common antimicrobials for the treatment of urinary tract infections, was only 79.5% and 75.2%, respectively. Inpatient *E. coli* isolates were

Table 1. *In vitro* activities of antimicrobial agents against the six most common pathogens isolated from urine in the CANWARD 2009–20 study (split into outpatients and inpatients) (>100 isolates total)

			MIC (mg/L)			MIC interpretation (%)		
Organism	Patient location (*n*)	Antimicrobial agent	MIC_{50}	MIC_{90}	MIC range	Susceptible	Intermediate[a]	Resistant
E. coli	Outpatient (1786)	Amoxicillin/clavulanate	4	16	≤ 0.06 to > 32	85.1	11.3	3.6
		Cefalexin (urine)[b]	2	16	≤ 0.5 to > 128	92.0	NA[c]	8.0
		Cefepime	≤ 0.25	≤ 0.25	≤ 0.25 to > 64	95.6	1.8	2.5
		Cefoxitin	4	8	≤ 0.06 to > 32	92.9	4.5	2.6
		Ceftazidime	≤ 0.25	1	≤ 0.25 to > 32	95.6	0.5	3.9
		Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25 to > 64	93.7	0.3	6.0
		Ciprofloxacin	≤ 0.06	> 16	≤ 0.06 to > 16	79.5	1.1	19.4
		Colistin	0.25	0.5	≤ 0.06–8	NA	99.8	0.2
		Doxycycline	2	32	0.25 to > 32	77.3	5.0	17.7
		Gentamicin	≤ 0.5	1	≤ 0.5 to > 32	92.9	0.2	6.8
		Meropenem	≤ 0.03	≤ 0.03	≤ 0.03–1	100	0	0
		Nitrofurantoin	16	32	≤ 0.5 to > 512	97.6	1.3	1.1
		Piperacillin/tazobactam	2	4	≤ 1 to > 512	97.5	1.0	1.6
		Trimethoprim/ sulfamethoxazole	≤ 0.12	> 8	≤ 0.12 to > 8	75.2	NA	24.8
	Inpatient (689)	Amoxicillin/clavulanate	8	16	0.5 to > 32	76.8	16.5	6.7
		Cefalexin (urine)[b]	2	> 128	≤ 0.5 to > 128	84.6	NA	15.4
		Cefepime	≤ 0.25	4	≤ 0.25 to > 64	89.3	2.9	7.8
		Cefoxitin	4	16	0.5 to > 32	87.8	7.5	4.6
		Ceftazidime	≤ 0.25	8	≤ 0.25 to > 32	89.4	1.5	9.1
		Ceftriaxone	≤ 0.25	64	≤ 0.25 to > 64	86.8	0.1	13.1
		Ciprofloxacin	≤ 0.06	> 16	≤ 0.06 to > 16	65.9	0.7	33.4
		Colistin	0.25	0.5	≤ 0.06–4	NA	99.8	0.2
		Doxycycline	2	32	0.25 to > 32	71.1	5.8	23.1
		Gentamicin	≤ 0.5	32	≤ 0.5 to > 32	88.1	0.7	11.2
		Meropenem	≤ 0.03	≤ 0.03	≤ 0.03–0.12	100	0	0
		Nitrofurantoin	16	32	≤ 1–256	96.1	2.1	1.8
		Piperacillin/tazobactam	2	4	≤ 1–512	94.9	2.3	2.8
		Trimethoprim/ sulfamethoxazole	≤ 0.12	> 8	≤ 0.12 to > 8	73.5	NA	26.5
K. pneumoniae	Outpatient (295)	Amoxicillin/clavulanate	2	8	1 to > 32	92.1	4.7	3.2
		Cefalexin (urine)[b]	1	8	≤ 0.5 to > 128	92.5	NA	7.5
		Cefepime	≤ 0.25	≤ 0.25	≤ 0.25 to > 64	95.0	1.2	3.9
		Cefoxitin	4	8	0.5 to > 32	93.9	2.7	3.4
		Ceftazidime	≤ 0.25	0.5	≤ 0.25 to > 32	95.9	0.3	3.7
		Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25 to > 64	94.6	0	5.4
		Ciprofloxacin	≤ 0.06	0.5	≤ 0.06 to > 16	89.2	3.1	7.8
		Colistin	0.5	1	0.12 to > 16	NA	96.9	3.1
		Doxycycline	2	16	0.5 to > 32	84.5	5.0	10.5
		Gentamicin	≤ 0.5	≤ 0.5	≤ 0.5 to > 32	97.6	0	2.4
		Meropenem	≤ 0.03	0.06	≤ 0.03–0.5	100	0	0
		Nitrofurantoin	64	128	2–512	39.6	39.2	21.2
		Piperacillin/tazobactam	2	4	≤ 1–256	96.6	2.0	1.4
		Trimethoprim/ sulfamethoxazole	≤ 0.12	4	≤ 0.12 to > 8	89.5	NA	10.5
	Inpatient (172)	Amoxicillin/clavulanate	2	16	0.5 to > 32	88.8	6.5	4.7
		Cefalexin (urine)[b]	1	> 128	1 to > 128	86.6	NA	13.4
		Cefepime	≤ 0.25	1	≤ 0.25 to > 64	90.7	2.1	7.1
		Cefoxitin	2	8	0.5 to > 32	92.4	4.1	3.5
		Ceftazidime	≤ 0.25	8	≤ 0.25 to > 32	89.0	1.7	9.3

Continued

Table 1. *Continued*

Organism	Patient location (*n*)	Antimicrobial agent	MIC (mg/L)			MIC interpretation (%)		
			MIC_{50}	MIC_{90}	MIC range	Susceptible	Intermediate[a]	Resistant
		Ceftriaxone	≤ 0.25	8	≤ 0.25 to > 64	89.0	0	11.0
		Ciprofloxacin	≤ 0.06	4	≤ 0.06 to > 16	83.1	5.2	11.6
		Colistin	0.5	1	0.12 to > 16	NA	98.3	1.7
		Doxycycline	2	32	0.25 to > 32	73.9	5.2	20.9
		Gentamicin	≤ 0.5	≤ 0.5	≤ 0.5 to > 32	94.8	0	5.2
		Meropenem	≤ 0.03	0.06	≤ 0.03–0.25	100	0	0
		Nitrofurantoin	64	128	4 to > 512	38.8	34.1	27.1
		Piperacillin/tazobactam	2	8	≤ 1 to > 512	92.4	2.3	5.2
		Trimethoprim/ sulfamethoxazole	≤ 0.12	> 8	≤ 0.12 to > 8	82.0	NA	18.0
E. faecalis	Outpatient (268)	Ampicillin	0.5	1	0.12–2	100	NA	0
		Ciprofloxacin	1	> 16	0.12 to > 16	69.2	12.4	18.4
		Daptomycin	0.5	2	≤ 0.03–4	97.0	3.0	0
		Doxycycline	8	16	≤ 0.12–32	26.4	41.0	32.6
		Linezolid	2	2	0.5–4	93.5	6.5	0
		Nitrofurantoin	8	16	2–128	99.0	0.5	0.5
		Vancomycin	1	2	0.5–4	100	0	0
	Inpatient (228)	Ampicillin	0.5	1	0.12–8	100	NA	0
		Ciprofloxacin	1	> 16	0.25 to > 16	60.2	7.1	32.7
		Daptomycin	0.5	2	≤ 0.03–4	98.7	1.3	0.0
		Doxycycline	8	16	≤ 0.12–16	29.3	42.8	27.9
		Linezolid	2	2	0.5–4	90.3	9.7	0
		Nitrofurantoin	8	16	2–16	100	0	0
		Vancomycin	1	2	0.5–2	100	0	0
P. mirabilis	Outpatient (121)	Amoxicillin/clavulanate	1	4	0.5 to > 32	94.7	3.5	1.8
		Cefalexin (urine)[b]	4	8	2 to > 128	95.0	NA	5.0
		Cefepime	≤ 0.25	≤ 0.25	≤ 0.25–1	100	0	0
		Cefoxitin	4	4	2–32	97.5	1.7	0.8
		Ceftazidime	≤ 0.25	≤ 0.25	≤ 0.25–4	100	0	0
		Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25–1	100	0	0
		Ciprofloxacin	≤ 0.06	2	≤ 0.06 to > 16	86.0	0	14.0
		Gentamicin	1	2	≤ 0.5 to > 32	96.7	0.8	2.5
		Meropenem	0.06	0.12	≤ 0.03–0.25	100	0	0
		Nitrofurantoin	128	128	64–512	0	20.4	79.6
		Piperacillin/tazobactam	≤ 1	≤ 1	≤ 1–8	100	0	0
		Trimethoprim/ sulfamethoxazole	≤ 0.12	> 8	≤ 0.12 to > 8	80.2	NA	19.8
	Inpatient (76)	Amoxicillin/clavulanate	1	4	0.5 to > 32	93.3	1.3	5.3
		Cefalexin (urine)[b]	4	16	1 to > 128	93.4	NA	6.6
		Cefepime	≤ 0.25	≤ 0.25	≤ 0.25–16	96.8	1.6	1.6
		Cefoxitin	4	8	1 to > 32	96.1	1.3	2.6
		Ceftazidime	≤ 0.25	≤ 0.25	≤ 0.25–8	98.7	1.3	0
		Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25 to > 64	94.7	2.6	2.6
		Ciprofloxacin	≤ 0.06	2	≤ 0.06 to > 16	80.3	1.3	18.4
		Gentamicin	≤ 0.5	8	≤ 0.5 to > 32	89.5	2.6	7.9
		Meropenem	0.06	0.12	≤ 0.03–0.25	100	0	0
		Nitrofurantoin	128	128	64–256	0	17.6	82.4
		Piperacillin/tazobactam	≤ 1	≤ 1	≤ 1–32	97.4	1.3	1.3
		Trimethoprim/ sulfamethoxazole	≤ 0.12	> 8	≤ 0.12 to > 8	77.6	NA	22.4
P. aeruginosa	Outpatient (63)	Cefepime	4	16	0.5 to > 64	89.5	5.3	5.3

Continued

Table 1. *Continued*

Organism	Patient location (*n*)	Antimicrobial agent	MIC (mg/L)			MIC interpretation (%)		
			MIC_{50}	MIC_{90}	MIC range	Susceptible	Intermediate[a]	Resistant
		Ceftazidime	4	16	1 to > 32	85.7	6.3	7.9
		Ceftolozane/tazobactam	1	2	0.25–8	98.4	1.6	0
		Ciprofloxacin	0.25	8	≤ 0.06 to > 16	76.2	6.3	17.5
		Colistin	1	2	0.5–4	NA	98.4	1.6
		Gentamicin	2	4	≤ 0.5 to > 32	92.1	4.8	3.2
		Meropenem	1	4	0.06 to > 32	84.1	6.3	9.5
		Piperacillin/tazobactam	8	32	2–512	88.9	6.3	4.8
	Inpatient (100)	Cefepime	2	16	0.5 to > 64	86.0	8.1	5.8
		Ceftazidime	4	32	0.5 to > 32	83.0	4.0	13.0
		Ceftolozane/tazobactam	0.5	2	≤ 0.12 to > 64	97.0	1.0	2.0
		Ciprofloxacin	0.25	16	≤ 0.06 to > 16	75.0	5.0	20.0
		Colistin	1	2	0.25–8	NA	96.0	4.0
		Gentamicin	2	8	≤ 0.5 to > 32	89.0	6.0	5.0
		Meropenem	1	4	≤ 0.03 to > 32	87.0	5.0	8.0
		Piperacillin/tazobactam	4	32	2–512	86.0	9.0	5.0
S. aureus	Outpatient (63)	Cefoxitin	4	> 32	0.5 to > 32	74.6	NA	25.4
		Ciprofloxacin	0.5	> 16	0.12 to > 16	54.0	1.6	44.4
		Clarithromycin	0.5	> 32	≤ 0.03 to > 32	52.4	0	47.6
		Clindamycin	≤ 0.12	> 8	≤ 0.12 to > 8	79.4	0	20.6
		Daptomycin	0.25	0.5	0.12–0.5	100	NA	NA
		Doxycycline	≤ 0.12	0.25	≤ 0.12–0.5	100	0	0
		Gentamicin	≤ 0.5	≤ 0.5	≤ 0.5–2	100	0	0
		Linezolid	2	4	1–4	100	NA	0
		Nitrofurantoin	16	16	4–32	100	0	0
		Trimethoprim/sulfamethoxazole	≤ 0.12	≤ 0.12	≤ 0.12–0.5	100	NA	0
		Vancomycin	1	1	0.25–1	100	0	0
	Inpatient (49)	Cefoxitin	4	> 32	2 to > 32	75.0	NA	25.0
		Ciprofloxacin	0.5	> 16	0.12 to > 16	60.4	0	39.6
		Clarithromycin	0.25	> 32	0.12 to > 32	62.5	0	37.5
		Clindamycin	≤ 0.12	> 8	0.12 to > 8	85.4	0	14.6
		Daptomycin	0.25	0.25	0.12–1	100	NA	NA
		Doxycycline	≤ 0.12	0.25	≤ 0.12–2	100	0	0
		Gentamicin	≤ 0.5	≤ 0.5	≤ 0.5–1	100	0	0
		Linezolid	2	4	1–4	100	NA	0
		Nitrofurantoin	16	16	8–16	100	0	0
		Trimethoprim/sulfamethoxazole	≤ 0.12	≤ 0.12	≤ 0.12–0.5	100	NA	0
		Vancomycin	1	1	0.5–2	100	0	0

[a]The % susceptible-dose dependent (SDD) value is given in the % intermediate box for cefepime and piperacillin/tazobactam tested against Enterobacterales; the CLSI does not published an intermediate MIC breakpoint for cefepime or piperacillin/tazobactam versus Enterobacterales.
[b]For cefalexin, cefazolin urine MIC breakpoints (16/—/32) were used for *E. coli*, *K. pneumoniae* and *P. mirabilis*.
[c]NA, not applicable.

less susceptible to oral antimicrobials than outpatient isolates, with susceptibility rates of 96.1% for nitrofurantoin, 84.6% for cefalexin, 76.8% for amoxicillin/clavulanate, 73.5% for trimethoprim/sulfamethoxazole and 65.9% for ciprofloxacin. Considering IV antimicrobials, meropenem was active *in vitro* versus 100% of *E. coli* isolates, while 97.5% and 94.9% outpatient and inpatient isolates, respectively, remained fully susceptible to piperacillin/tazobactam. Inpatient *E. coli* urinary isolates demonstrated reduced susceptibility to ceftriaxone (86.8% susceptible) relative to outpatient isolates (93.7% susceptible).

The most active oral antimicrobials versus outpatient urinary *K. pneumoniae* isolates were cefalexin (92.5% susceptible) and amoxicillin/clavulanate (92.1% susceptible), followed by trimethoprim/sulfamethoxazole (89.5% susceptible) and ciprofloxacin (89.2% susceptible). Susceptibility rates to oral antimicrobials for inpatient urinary *K. pneumoniae* isolates were approximately 3% to

7% lower than for outpatient isolates, depending on the antimicrobial. All *K. pneumoniae* isolates were susceptible to meropenem, while susceptibility to piperacillin/tazobactam was 96.6% among outpatient isolates and 92.4% among inpatient isolates. Ceftriaxone susceptibility was lower for inpatient urinary *K. pneumoniae* isolates than outpatient isolates (89% versus 94.6%).

Outpatient *P. mirabilis* urinary isolates were generally susceptible to amoxicillin/clavulanate (94.7%), cefalexin (95%), ceftriaxone (100%), meropenem (100%) and piperacillin/tazobactam (100%). Susceptibility rates for ciprofloxacin (86%) and trimethoprim/sulfamethoxazole (80.2%) were lower. Inpatient *P. mirabilis* urinary isolates were marginally less susceptible to all antimicrobials tested, relative to outpatient isolates (Table 1). For *P. aeruginosa* urinary isolates, ceftolozane/tazobactam was the most active antimicrobial *in vitro* (97% of inpatient isolates and 98.4% of outpatient isolates testing susceptible). Susceptibility versus other common antipseudomonal antimicrobials ranged from 83% to 92% depending on the agent. The notable exception was ciprofloxacin, for which only 76.2% of outpatient and 75% of inpatient *P. aeruginosa* urinary isolates tested susceptible.

All *E. faecalis* isolates were susceptible to ampicillin and vancomycin, and over 99% were susceptible to nitrofurantoin. Antimicrobial susceptibility rates for outpatient and inpatient *S. aureus* urinary isolates were similar. Approximately 75% of *S. aureus* isolates were methicillin-susceptible (inferred from cefoxitin) and 100% remained susceptible to daptomycin, doxycycline, linezolid, nitrofurantoin, trimethoprim/sulfamethoxazole and vancomycin.

Antimicrobial susceptibility trends over time for the six most frequently isolated urinary pathogens are presented in Table 2. For *E. coli*, the percentage of isolates that were phenotypically positive for ESBL production significantly increased from 4.2% (2009–11) to 11.3% (2018–20). Over the same time periods, a significant drop in the percentage of isolates testing susceptible to amoxicillin/clavulanate, cefazolin, cefepime, cefalexin, ceftazidime, ceftriaxone and piperacillin/tazobactam was observed, presumably secondary to the increased recovery of ESBL producers. A similar, although less pronounced, temporal trend was observed with *K. pneumoniae* isolates, with the proportion of ESBL producers increasing from 4.3% (2009–11) to 6.2% (2018–20). Again, this was associated with a reduction over time in susceptibility rates for several β-lactams including amoxicillin/clavulanate, cefalexin, cefepime, ceftazidime and ceftriaxone. Interestingly, there was no statistically significant change in susceptibility for ciprofloxacin, nitrofurantoin or trimethoprim/sulfamethoxazole versus *E. coli* and *K. pneumoniae* over the course of this study. Susceptibility rates for most antimicrobials remained relatively stable during the study for *E. faecalis* and *P. mirabilis*. For *P. aeruginosa*, susceptibility to cefepime, ceftazidime, ceftolozane/tazobactam and piperacillin/tazobactam declined over the course of the study. For *S. aureus*, methicillin susceptibility increased from 61.4% (2009–11) to 83.3% (2018–20), although this change did not reach statistical significance.

Discussion

Several recent studies have been published describing the *in vitro* susceptibilities of common urinary pathogens.[6,11,18] Aronin *et al.*[11] assessed the susceptibility of 546 716 *E. coli* urine isolates from patients hospitalized in the USA over a 10 year period (2011–20). Overall, 35.1% of isolates were not susceptible to fluoroquinolones, 30.6% were not susceptible to trimethoprim/sulfamethoxazole and 13.1% demonstrated an ESBL phenotype. Kaye *et al.*[18] investigated the *in vitro* susceptibilities of 1 513 882 *E. coli* urinary isolates from female outpatients in the USA obtained between 2011 and 2019. The percentage of isolates testing not susceptible to trimethoprim/sulfamethoxazole, fluoroquinolones and nitrofurantoin were 25.4%, 21.1% and 3.8%, respectively, and 6.4% were positive for ESBL production. Lodise *et al.*[6] evaluated the *in vitro* activity of common antimicrobials versus bacterial isolates obtained from patients presenting to emergency departments in the USA from 2013 to 2018 with a diagnosis of complicated UTI, stratified by whether the patient was admitted to hospital or in the emergency room (ER) only. Among 106 038 *E. coli* isolates, resistance rates to fluoroquinolones were 16.4% for ER patients and 35.6% for admitted patients, resistance rates to trimethoprim/sulfamethoxazole were 27.8% for ER patients and 33.2% for admitted patients, and resistance rates to nitrofurantoin were 3.4% for ER patients and 5.6% for admitted patients. In addition, 5.0% of isolates from ER patients demonstrated third-generation cephalosporin resistance versus 12.5% of isolates from admitted patients. Of concern, data from these publications, as well as the current study, have generally found >20% of *E. coli* urinary isolates are no longer susceptible to fluoroquinolones and trimethoprim/sulfamethoxazole. A resistance prevalence of 20% has been suggested as a threshold at which an agent is no longer recommended for the treatment of acute cystitis.[12] Nitrofurantoin typically remains active *in vitro* versus the majority of *E. coli* urinary isolates.[6,11,18]

Resistance rates were higher among inpatient isolates relative to outpatient isolates in the present study. It is speculated that this is related to more frequent antimicrobial exposure among inpatients, and potential acquisition of resistant pathogens in the hospital environment. Several studies have previously demonstrated that older patient age, male gender, recent hospitalization, prior use of antimicrobials and specific geographical locations are risk factors associated with increased antimicrobial resistance rates, including resistance to trimethoprim/sulfamethoxazole and fluoroquinolones.[19,20]

In our dataset, the proportion of *E. coli* and *K. pneumoniae* urinary isolates that were phenotypically positive for ESBL production increased from 2009–11 to 2018–20. Other investigators have similarly demonstrated an increase in the proportion of Enterobacterales urinary isolates that are ESBL producers over time.[8–11] This has been observed to a greater extent with *E. coli* and likely reflects, at least in part, successful dissemination of *E. coli* ST131, which possesses plasmid-mediated ESBL (CTX-M-14 or CTX-M-15) genes.[8] ESBL production likely accounts for the decline in β-lactam susceptibility among *E. coli* and *K. pneumoniae* isolates in our study from 2009–11 to 2018–20. Among the *P. aeruginosa* isolates included in our study, susceptibility to cefepime, ceftazidime, ceftolozane/tazobactam and piperacillin/tazobactam declined over time. These trends should be viewed with caution given the small number of *P. aeruginosa* isolates tested on an annual basis. Other North American publications have reported relatively stable susceptibility rates for *P. aeruginosa* over time versus common antipseudomonal antimicrobials.[21,22]

Table 2. Annual rates of *in vitro* susceptibility of oral and parenteral antimicrobial agents for urine isolates in Canada, 2009–20 (minimum 20 isolates/3 year group)[a]

		% of isolates susceptible				
Organism	Antimicrobial agent	2009–11	2012–14	2015–17	2018–20	*P* value
E. coli	Amoxicillin/clavulanate	86.42	82.46	77.76	75.23	<0.0001
	Cefazolin (systemic)	72.66	73.51	73.27	64.06	0.0121
	Cefalexin (urine)	92.46	91.23	88.22	84.35	<0.0001
	Cefepime	96.01	95.34	93.27	89.49	<0.0001
	Cefoxitin	90.65	94.78	90.84	89.98	0.6313
	Ceftazidime	95.98	94.22	92.52	90.22	<0.0001
	Ceftriaxone	94.17	92.54	90.47	86.80	<0.0001
	Ciprofloxacin	75.58	77.61	74.77	74.57	0.5894
	Colistin (I)	100	99.81	99.63	99.51	0.0538
	Doxycycline	75.53	75.56	76.64	74.33	0.7792
	Gentamicin	90.95	91.42	93.64	90.71	0.5148
	Meropenem	100	100	100	100	N/A
	Nitrofurantoin	97.28	96.98	97.76	97.28	0.9309
	Piperacillin/tazobactam	97.59	97.57	95.14	95.84	0.0306
	Trimethoprim/sulfamethoxazole	73.74	76.87	75.14	73.84	0.8465
	ESBL	4.22	6.90	8.22	11.25	<0.0001
K. pneumoniae	Amoxicillin/clavulanate	93.21	93.81	90.74	82.93	0.0138
	Cefazolin (systemic)	84.57	84.54	87.96	76.00	0.1983
	Cefalexin (urine)	92.59	91.75	93.52	82.00	0.0217
	Cefepime	97.87	95.88	93.52	87.00	0.0017
	Cefoxitin	94.44	92.78	93.52	92.00	0.4886
	Ceftazidime	96.91	95.88	93.52	85	0.0003
	Ceftriaxone	95.06	94.85	93.52	85.00	0.0061
	Ciprofloxacin	87.65	86.60	87.96	85.00	0.6407
	Colistin (I)	98.77	96.91	95.37	98.00	0.4113
	Doxycycline	86.67	77.32	85.19	78.00	0.6750
	Gentamicin	95.06	97.94	98.15	96.00	0.5089
	Meropenem	100	100	100	100	N/A
	Nitrofurantoin	29.27	43.40	42.59	38.00	0.5794
	Piperacillin/tazobactam	95.68	96.91	95.37	92.00	0.2079
	Trimethoprim/sulfamethoxazole	88.27	83.51	90.74	83.00	0.5077
	ESBL	4.32	4.12	5.56	6.21	0.0209
E. faecalis	Ampicillin	100	100	100	100	N/A
	Ciprofloxacin	62.33	70.91	64.52	64.86	0.6637
	Daptomycin	98.11	97.27	96.77	98.65	0.9237
	Doxycycline	17.07	34.55	27.96	22.97	0.7637
	Linezolid	91.04	97.27	82.80	98.65	0.6174
	Nitrofurantoin	98.15	100	100	98.65	0.8299
	Vancomycin	100	100	100	100	N/A
Proteus mirabilis	Amoxicillin/clavulanate	95.31	95.56	89.74	95.12	0.6493
	Cefazolin (systemic)	6.25	6.67	0	4.08	0.3328
	Cefalexin (urine)	95.31	91.11	89.74	100	0.4166
	Cefepime	100	100	94.87	100	0.5733
	Cefoxitin	98.44	95.56	94.87	97.96	0.7840
	Ceftazidime	100	100	97.44	100	0.5912
	Ceftriaxone	100	95.56	94.87	100	0.8238
	Ciprofloxacin	85.94	91.11	71.79	83.67	0.3126
	Gentamicin	98.44	95.56	87.18	91.84	0.0555
	Meropenem	100	100	100	100	N/A
	Nitrofurantoin	0	0	0	0	N/A

Continued

Table 2. *Continued*

Organism	Antimicrobial agent	% of isolates susceptible				*P* value
		2009–11	2012–14	2015–17	2018–20	
	Piperacillin/tazobactam	100	100	94.87	100	0.4467
	Trimethoprim/sulfamethoxazole	85.94	84.44	56.41	83.67	0.1883
P. aeruginosa	Cefepime	94.29	93.10[b]	89.19	76.19	0.0141
	Ceftolozane/tazobactam	100	100[b]	97.30	92.86	0.0228
	Ceftazidime	90.91	86.21[b]	89.19	69.05	0.0097
	Ciprofloxacin	69.09	68.97[b]	86.49	78.57	0.1208
	Colistin (I)	94.55	100[b]	100	95.24	0.6973
	Gentamicin	87.27	93.10[b]	91.89	90.48	0.5855
	Meropenem	89.09	86.21[b]	86.49	80.95	0.2848
	Piperacillin/tazobactam	90.91	96.55[b]	89.19	73.81	0.0146
S. aureus	Cefoxitin	61.36	95.65[b]	73.08[b]	83.33[b]	0.0954
	Ciprofloxacin	47.73	60.87[b]	61.54[b]	66.67[b]	0.1327
	Clarithromycin	38.64	65.22[b]	73.08[b]	66.67[b]	0.0069
	Clindamycin	70.45	82.61[b]	92.31[b]	94.44[b]	0.0069
	Daptomycin	100	100[b]	100[b]	100[b]	N/A
	Doxycycline	100[b]	100[b]	100[b]	100[b]	N/A
	Gentamicin	100	100[b]	100[b]	100[b]	N/A
	Linezolid	100	100[b]	100[b]	100[b]	N/A
	Nitrofurantoin	100[b]	100[b]	100[b]	100[b]	N/A
	Trimethoprim/sulfamethoxazole	100	100[b]	100[b]	100[b]	N/A
	Vancomycin	100	100[b]	100[b]	100[b]	N/A

[a]Number of isolates/year group: 2009–11: 995 *E. coli*, 162 *K. pneumoniae*, 218 *E. faecalis*, 64 *P. mirabilis*, 55 *P. aeruginosa* and 44 *S. aureus*. 2012–14: 536 *E. coli*, 97 *K. pneumoniae*, 110 *E. faecalis*, 45 *P. mirabilis*, 29 *P. aeruginosa* and 23 *S. aureus*. 2015–17: 535 *E. coli*, 108 *K. pneumoniae*, 94 *E. faecalis*, 39 *P. mirabilis*, 37 *P. aeruginosa* and 26 *S. aureus*. 2018–20: 409 *E. coli*, 100 *K. pneumoniae*, 74 *E. faecalis*, 49 *P. mirabilis*, 42 *P. aeruginosa* and 19 *S. aureus*.
[b]Fewer than 30 isolates in this block were tested against drug. *S. aureus* had <30 isolates for three out of four of the time periods. *P. aeruginosa* had 29 isolates in the 2012–14 time period.

There are several important limitations to the data presented here that deserve attention. The CANWARD study does not obtain clinical details on the patients from whom the isolates are obtained. Clinical significance of the urinary isolates included here was based on local microbiology laboratory protocols. As such, it is likely that some of the included isolates were from patients with asymptomatic bacteriuria. Urine cultures are often not obtained for women presenting with acute, uncomplicated cystitis. Hence, the susceptibility data presented here do not necessarily apply to this patient population. It is likely that the urine specimens submitted to the microbiology laboratory in our study were from patients with complicated UTIs, patients who had failed prior therapy and/or patients with more severe illness (e.g. pyelonephritis). However, our data do represent real-world isolates that can be expected to be grown from outpatient and inpatient urine specimens submitted to clinical microbiology laboratories for culture and antimicrobial susceptibility testing. Antimicrobial susceptibility rates in countries other than Canada may differ from what is presented here, due to differences in the prevalence of various resistance mechanisms. Fosfomycin susceptibility was not assessed because this antimicrobial must by tested by disc diffusion or agar dilution rather than broth microdilution (the method used here). Hospital laboratories participating in the CANWARD study varied slightly from year to year. This may have influenced susceptibility trends observed over time. Finally, for several pathogens (*P. aeruginosa*, *S. aureus*), the number of isolates obtained on an annual basis was relatively small and changes in susceptibility over time for these species should be regarded with caution.

In conclusion, the most common bacterial pathogen isolated from urine specimens of Canadian outpatients and inpatients submitted to sentinel hospital laboratories between 2009 and 2020 was *E. coli*, followed in descending order by *E. faecalis*, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa* and *S. aureus*. In general, susceptibility rates for urinary pathogens were lower for inpatient isolates, relative to outpatient isolates. Over 20% of urinary *E. coli* isolates were not susceptible to ciprofloxacin and trimethoprim/sulfamethoxazole, while the majority remained susceptible to nitrofurantoin. These data suggest that ciprofloxacin and trimethoprim/sulfamethoxazole may not be optimal as empirical therapy for UTIs among Canadian patients with complicated UTIs and/or severe infection requiring hospitalization. However, use of local antibiogram data is highly encouraged when making treatment decisions. An increase in the proportion of *E. coli* and *K. pneumoniae* urinary isolates that were ESBL producers was observed over the course of this study. Consideration should be given to empirical coverage of ESBL producers among patients presenting with severe illness due to a UTI. Nitrofurantoin remains a reasonable option for cystitis caused by *E. coli* based on the data presented here.

Acknowledgements

We would like to thank staff in the following hospital laboratories that participated in the CANWARD Surveillance Study: Vancouver Hospital, Vancouver, British Columbia; University of Alberta Hospital, Edmonton, Alberta; Royal University Hospital, Saskatoon, Saskatchewan; Health Sciences Centre, Winnipeg, Manitoba; London Health Sciences Centre, London, Ontario; Hamilton Health Sciences Centre, Hamilton, Ontario; University Health Network/Mount Sinai Hospital, Toronto, Ontario; Children's Hospital of Eastern Ontario, Ottawa, Ontario; Cité de la Santé de Laval, Laval, Québec; Jewish General Hospital, Montréal, Québec; CHRTR Pavillon Ste. Marie, Trois-Rivières, Québec; Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Québec; L'Hôtel-Dieu de Québec, Québec City, Québec; South East Regional Health Authority, Moncton, New Brunswick; and Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia.

Funding

The CANWARD Surveillance Study was supported in part by the Health Sciences Centre (Winnipeg, Manitoba, Canada) and the University of Manitoba (Winnipeg, Manitoba, Canada), the Public Health Agency of Canada—National Microbiology Laboratory (Winnipeg, Manitoba, Canada), Avir, Iterum, Merck and Verity.

Transparency declarations

The authors have no conflicts of interest to disclose related to this work. G.G.Z. received research funding from Avir Pharma, Iterum Therapeutics, Merck Canada and Verity Pharma.

Supplementary data

Table S1 is available as Supplementary data at *JAC-AMR* Online.

References

1 Schappert SM, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2007. National center for health statistics. *Vital Health Stat* 2011; **169**: 1–38.

2 Simmering JE, Tang F, Cavanaugh JE *et al*. The increase in hospitalizations for urinary tract infections and the associated costs in the United States, 1998–2011. *Open Forum Infect Dis* 2017; **4**: ofw281. https://doi.org/10.1093/ofid/ofw281

3 Hooton TM. Uncomplicated urinary tract infection. *N Engl J Med* 2012; **366**: 1028–37. https://doi.org/10.1056/NEJMcp1104429

4 Hooton TM, Roberts PL, Cox ME *et al*. Voided midstream urine culture and acute cystitis in premenopausal women. *N Engl J Med* 2013; **369**: 1883–91. https://doi.org/10.1056/NEJMoa1302186

5 Nicolle LE. Complicated urinary tract infection in adults. *Can J Infect Dis Med Microbiol* 2005; **16**: 349–60. https://doi.org/10.1155/2005/385768

6 Lodise TP, Chopra T, Nathanson BH *et al*. Epidemiology of complicated urinary tract infections due to Enterobacterales among adult patients presenting in emergency departments across the United States. *Open Forum Infect Dis* 2022; **9**: ofac315. https://doi.org/10.1093/ofid/ofac315

7 Zhanel GG, DeCorby M, Adam H *et al*. Prevalence of antimicrobial-resistant pathogens in Canadian hospitals: results of the Canadian ward surveillance study (CANWARD 2008). *Antimicrob Agents Chemother* 2010; **54**: 4684–93. https://doi.org/10.1128/AAC.00469-10

8 Denisuik AJ, Karlowsky JA, Adam HJ *et al*. Dramatic rise in the proportion of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* among clinical isolates identified in Canadian hospital laboratories from 2007 to 2016. *J Antimicrob Chemother* 2019; **74** Suppl 4: iv64–71. https://doi.org/10.1093/jac/dkz289

9 Peirano G, Pitout JDD. Extended-spectrum β-lactamase-producing Enterobacteriaceae: update on molecular epidemiology and treatment options. *Drugs* 2019; **79**: 1529–41. https://doi.org/10.1007/s40265-019-01180-3

10 McDanel J, Schweizer M, Crabb V *et al*. Incidence of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella* infections in the United States: a systematic literature review. *Infect Control Hosp Epidemiol* 2017; **38**: 1209–15. https://doi.org/10.1017/ice.2017.156

11 Aronin SI, Dunne MW, Yu KC *et al*. Increased rates of extended-spectrum beta-lactamase isolates in patients hospitalized with culture-positive urinary Enterobacterales in the United States: 2011–2020. *Diagn Microbiol Infect Dis* 2022; **103**: 115717. https://doi.org/10.1016/j.diagmicrobio.2022.115717

12 Gupta K, Hooton TM, Naber KG *et al*. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the infectious diseases society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011; **52**: e103–20. https://doi.org/10.1093/cid/ciq257

13 Bent S, Nallamothu BK, Simel DL *et al*. Does this woman have an acute uncomplicated urinary tract infection? *JAMA* 2002; **287**: 2701–10. https://doi.org/10.1001/jama.287.20.2701

14 Wagenlehner F, Nicolle L, Bartoletti R *et al*. A global perspective on improving patient care in uncomplicated urinary tract infection: expert consensus and practical guidance. *J Glob Antimicrob Resist* 2022; **28**: 18–29. https://doi.org/10.1016/j.jgar.2021.11.008

15 Zhanel GG, Adam HJ, Baxter MR *et al*. 42 936 pathogens from Canadian hospitals: 10 years of results (2007–16) from the CANWARD surveillance study. *J Antimicrob Chemother* 2019; **74** Suppl 4: iv5–iv21. https://doi.org/10.1093/jac/dkz283

16 CLSI. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically—Eleventh Edition: M07*. 2018.

17 CLSI. *Performance Standards for Antimicrobial Susceptibility Testing—Thirty-Second Edition: M100*. 2022.

18 Kaye KS, Gupta V, Mulgirigama A *et al*. Antimicrobial resistance trends in urine *Escherichia coli* isolates from adult and adolescent females in the United States from 2011 to 2019: rising ESBL strains and impact on patient management. *Clin Infect Dis* 2021; **73**: 1992–9. https://doi.org/10.1093/cid/ciab560

19 Lob SH, Nicolle LE, Hoban DJ *et al*. Susceptibility patterns and ESBL rates of *Escherichia coli* from urinary tract infections in Canada and the United States, SMART 2010–2014. *Diagn Microbiol Infect Dis* 2016; **85**: 459–65. https://doi.org/10.1016/j.diagmicrobio.2016.04.022

20 Chin TL, McNulty C, Beck C *et al*. Antimicrobial resistance surveillance in urinary tract infections in primary care. *J Antimicrob Chemother* 2016; **71**: 2723–8. https://doi.org/10.1093/jac/dkw223

21 Sader HS, Huband MD, Castanheira M *et al*. *Pseudomonas aeruginosa* antimicrobial susceptibility results from four years (2012 to 2015) of the international network for optimal resistance monitoring program in the United States. *Antimicrob Agents Chemother* 2017; **61**: e02252-16. https://doi.org/10.1128/AAC.02252-16

22 Shortridge D, Gales AC, Streit JM *et al*. Geographic and temporal patterns of antimicrobial resistance in *Pseudomonas aeruginosa* over 20 years from the SENTRY antimicrobial surveillance program, 1997–2016. *Open Forum Infect Dis* 2018; **6** Suppl 1: S63–8. https://doi.org/10.1093/ofid/ofy343