

Antibiotic resistance in isolates recovered from women with community-acquired urinary tract infections presenting to a tertiary care emergency department

Lyne Filiatrault, MD*[†]; Rachel M. McKay, MSc[‡]; David M. Patrick, MD, MHSc[§]; Diane L. Roscoe, MD^{||}#; Grahame Quan, BSc, BA**; Jeff Brubacher, MD*[†]; Ken M. Collins, BSc^{††}

ABSTRACT

Introduction: We sought to determine the antibiotic susceptibility of organisms causing community-acquired urinary tract infections (UTIs) in adult females attending an urban emergency department (ED) and to identify risk factors for antibiotic resistance.

Methods: We reviewed the ED charts of all nonpregnant, nonlactating adult females with positive urine cultures for 2008 and recorded demographics, diagnosis, complicating factors, organism susceptibility, and risk factors for antibiotic resistance. Odds ratios (ORs) and 95% confidence intervals (CIs) for potential risk factors were calculated.

Results: Our final sample comprised 327 UTIs: 218 were cystitis, of which 22 were complicated cases and 109 were pyelonephritis, including 22 complicated cases. *Escherichia coli* accounted for 82.3% of all UTIs, whereas *Staphylococcus saprophyticus* accounted for 5.2%. In uncomplicated cystitis, 9.5% of all isolates were resistant to ciprofloxacin and 24.0% to trimethoprim-sulfamethoxazole (TMP-SMX). In uncomplicated pyelonephritis, 19.5% of isolates were resistant to ciprofloxacin and 36.8% to TMP-SMX. In UTI (all types combined), any antibiotic use within the previous 3 months was a significant risk factor for resistance to both ciprofloxacin (OR 3.34, 95% CI 1.16–9.62) and TMP-SMX (OR 4.02, 95% CI 1.48–10.92). Being 65 years of age or older and having had a history of UTI in the previous year were risk factors only for ciprofloxacin resistance.

Conclusions: *E. coli* was the predominant urinary pathogen in this series. Resistance to ciprofloxacin and TMP-SMX was high, highlighting the importance of relevant, local antibiograms. Any recent antibiotic use was a risk factor for both ciprofloxacin and TMP-SMX resistance in UTI. Our findings should be confirmed with a larger prospective study.

RÉSUMÉ

Introduction: L'étude visait à déterminer la sensibilité aux antibiotiques des micro-organismes causant des infections urinaires (IU) extrahospitalières, chez des femmes adultes, vues à un service urbain des urgences, ainsi qu'à cerner des facteurs de risque de résistance aux antibiotiques.

Méthodes: Nous avons passé en revue les dossiers de toutes les femmes adultes, non enceintes et non allaitantes, vues à l'urgence en 2008 et ayant obtenu une uroculture positive, en plus de consigner les données démographiques, le diagnostic, les facteurs de complication, la sensibilité des micro-organismes, et les facteurs de risque de résistance aux antibiotiques. Nous avons calculé le risque relatif approché (RRA) et l'intervalle de confiance (IC) à 95% des facteurs de risque possibles.

Résultats: L'échantillon définitif totalisait 327 IU: 218 cystites, dont 22 avec complications, et 109 pyélonéphrites, dont 22 avec complications. *Escherichia coli* était responsable de 82.3% des IU, tandis que *Staphylococcus saprophyticus* en représentait 5.2%. Dans la cystite sans complications, 9.5% des isolats étaient résistants à la ciprofloxacine et 24.0% au triméthoprime-sulfaméthoxazole (TMP/SMX). Dans la pyélonéphrite sans complications, 19.5% des isolats étaient résistants à la ciprofloxacine et 36.8% au TMP/SMX. Dans les IU, tous types confondus, l'utilisation d'antibiotiques au cours des 3 mois précédents s'est révélée un facteur de risque important de résistance à la ciprofloxacine (RRA 3.34; IC à 95% 1.16–9.62) et au TMP/SMX (RRA 4.02; IC à 95% 1.48–10.92). Par ailleurs, le fait d'être âgé d'au moins 65 ans et d'avoir eu des antécédents d'IU au cours de l'année précédente se sont révélés des facteurs de risque de résistance à la ciprofloxacine seulement.

From the *§#**Department of Emergency Medicine, School of Population and Public Health, Department of Pathology and Laboratory Medicine, and School of Medicine, University of British Columbia, Vancouver, BC; †||Emergency Department and Division of Medical Microbiology and Infection Control, Vancouver General Hospital; ‡BC Centre for Disease Control, Vancouver, BC; ††School of Medicine, Queen's University, Kingston, ON.

Correspondence to: Dr. Lyne Filiatrault, VGH Emergency Department, 855 West 12th Avenue, Vancouver, BC V5Z 1M9; filiatra@interchange.ubc.ca.

This article has been peer reviewed.

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CJEM 2012;14(5):295-305

DOI 10.2310/8000.2012.120666

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CJEM • JCMU

2012;14(5) 295

Conclusions: Dans la présente série, *E. coli* était le principal agent pathogène des voies urinaires. La fréquence de la résistance à la ciprofloxacine et au TMP/SMX était élevée, d'où l'importance des antibiogrammes locaux, pertinents. Toute utilisation récente d'antibiotiques s'est révélée un facteur de risque de résistance à la ciprofloxacine et au TMP-SMX dans

les IU. Il faudrait confirmer les résultats de la recherche dans le cadre d'une étude prospective, menée à grande échelle.

Keywords: antibiotic resistance, community acquired, risk factors, urinary tract infection

After respiratory tract infections, urinary tract infections (UTIs) are the most common infections for which patients seek medical attention in the community.¹ In 2000, there were 6.3 million office visits and 1.3 million emergency department (ED) visits for UTIs in women in the United States.² An estimated 20% of women between 20 and 65 years will experience one UTI every year,³ and 50% of women have at least one UTI in their lifetime.⁴ Recurrences occur within 1 year in 48% of women.⁵

Treatment of a UTI with an antibiotic to which the organism is resistant results in high rates of microbiologic and clinical failure and leads to additional morbidity and costs.⁶⁻⁹ Resistance rates vary geographically,^{10,11} with the population studied, and according to whether or not the UTI is complicated¹²⁻¹⁴ (see Table 1 and Table 2 for definitions). Hospital laboratory surveillance studies have limited applicability to the ED outpatient population with community-acquired UTIs because young, healthy, premenopausal women with uncomplicated cystitis are typically treated empirically without urine cultures.¹² The hospital antibiogram—local susceptibility results of isolated bacterial strains based on laboratory testing—is based on urine cultures from patients with more severe infections, complicated UTIs, recurrent infections, or treatment failures and thus overestimates the prevalence of antibiotic resistance in the community.^{13,15,16}

Our primary goal was to describe the organisms responsible for community-acquired cystitis and pyelonephritis (PN) in the adult nonpregnant female ED population and their susceptibility to commonly prescribed antibiotics. Our secondary goal was to identify risk factors for antibiotic resistance in uncomplicated and complicated cystitis and PN. Visits (not admissions) to Vancouver General Hospital (VGH) within the last 4 weeks, antibiotic use within the last 3 months, and positive urine cultures in the previous year were investigated as potential risk factors for ciprofloxacin-resistant uropathogens, following the results of the VGH ED urosepsis study (personal communication, C Lowe, 2009). We also investigated age as a potential risk factor.

METHODS

Study setting

This study was conducted at VGH, an 800-bed tertiary care centre in Vancouver, British Columbia, with an annual ED census of 75,000 adult patients and an admission rate of 23%.

Ethics

This study was approved by the University of British Columbia's Clinical Research Ethics Board.

Definitions

UTIs can be either cystitis or PN (see Table 1 for definitions), and each of these can be considered uncomplicated or complicated, depending on the presence or absence of certain factors (see Table 2), based on the literature.^{12,14,17} Catheter samples were obtained from patients with complicated UTIs with a pre-existing indwelling catheter. In uncomplicated UTIs, samples were clean-catch midstream urine collection, with the rare in-and-out catheter sample.

Table 1. Definitions

Term	Defined as
Positive urine culture	Growing one or two uropathogens, either one $\geq 10^4$ CFU/mL ($\geq 10^7$ CFU/L)
Cystitis (infection of lower urinary tract or bladder)	Positive urine culture result as per above <i>and</i> One or more of dysuria, frequency, urgency, and/or hematuria
Pyelonephritis (infection of upper urinary tract)	Positive urine culture result <i>and</i> Flank pain and/or costovertebral angle tenderness; presence of a documented fever was not necessary

Table 2. Complicating factors

Anatomic/functional
Solitary kidney
Polycystic kidneys
Renal abscess
Duplicated collecting system
Instrumentation
Indwelling or intermittent catheterization
Ureteric stent
Nephrostomy tube
Recent cystoscopy
Vesicoureteral reflux
Surgical reconstruction
Ileal conduit
Bladder augmentation
Renal transplant
Neurogenic bladder
Urinary incontinence
Obstruction
Stone
Tumour
Stricture
Medical condition
Diabetes mellitus
Renal failure
Liver failure
Immunosuppression
Corticosteroid use
Human immunodeficiency virus (HIV)
Active cancer

Inclusion and exclusion criteria

We included adult (≥ 19 years) nonpregnant, nonlactating females who presented to the ED in 2008 with signs and symptoms consistent with cystitis or PN and who had a positive urine culture. We excluded long-term care or nursing home residents as well as patients who had been admitted to VGH or Vancouver Coastal Health Authority-affiliated hospitals (Richmond Hospital and University of British Columbia Hospital) in the previous 4 weeks. Patients with asymptomatic bacteriuria were excluded, as were patients with urosepsis. Patients were enrolled only once.

Data sources

We accessed the hospital microbiology and ED visit databases to identify all adult female ED patients with positive urine cultures (January 1 to December 31, 2008) who were discharged from the ED or admitted to hospital with a diagnosis of cystitis or PN (Appendix 1).

Data collection

Data were collected in accordance with recommendations for medical record reviews in emergency medicine.^{18,19} Two trained investigators determined eligibility and entered data from the medical record on a computer-based spreadsheet (Appendix 2). We used explicit definitions for each data category. The abstraction process was monitored by the first author. Coding uncertainties were resolved in weekly meetings. A random sample of 57 medical records was reviewed by both reviewers to determine interobserver agreement using the kappa (κ) statistic.

Outcome measures

Antimicrobial susceptibility testing was performed according to Clinical and Laboratory Standards Institute (CLSI) procedures using the standardized disk diffusion or commercially available automated microdilution methods. Organisms were classified as “susceptible,” “intermediate,” or “resistant” to each of the antibiotics tested based on zones of inhibition (disk diffusion) or minimum inhibitory concentrations (automated microdilution methods). Applying the most conservative clinical interpretation, we defined “antibiotic resistance” as including both intermediate and resistant sensitivities. Any reference to resistance in the remainder of this article includes intermediate unless otherwise indicated. We excluded cultures growing more than two organisms (considered contaminated) and cultures with nonuropathogens.

Statistical analysis

Data were analyzed using SAS 9.2 for Windows (SAS Institute, Cary, NC) and SPSS 14 for Windows (SPSS Inc, Chicago, IL). We used the Mann-Whitney *U* test to compare for differences in continuous variables and the chi-square test or Fisher exact test, as appropriate, for categorical variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Statistical significance was set at $\alpha = 0.05$.

RESULTS**Patients' demographics and documented risk factors prevalence**

We identified 439 female ED patients with positive urine cultures and a diagnosis of cystitis or PN. Of

these, 112 were excluded and 327 were enrolled (Figure 1). Patient demographics are shown in Table 3.

Interobserver agreement was calculated for cystitis versus PN ($\kappa = 0.84$); history of previous UTI ($\kappa = 0.73$); antibiotics in the past 3 months ($\kappa = 0.63$); and hospital visit in the last 4 weeks ($\kappa = 0.53$).

Patients with uncomplicated cystitis and PN had similar median ages of 32 and 31 years, respectively ($p = 0.2$). By comparison, patients presenting with complicated cystitis and PN were older, with median ages of 65.5 and 48.5, years, respectively ($p < 0.001$ when compared to the respective uncomplicated diagnosis; see Table 3).

The prevalence of antibiotic use in the preceding 3 months, hospital visit in the last 4 weeks, and UTI in the previous year was similar for patients with uncomplicated cystitis and uncomplicated PN. The first two risk factors were more common in patients with complicated cystitis or complicated PN. A history of UTI in the previous year was most common in the complicated cystitis group (see Table 3).

Urine culture and sensitivities

Escherichia coli remains the predominant uropathogen across all diagnostic categories (Table 4). Extended-spectrum β -lactamases (ESBLs) were found in 6.7% (18 of 269) of *E. coli* isolates and were more prevalent in PN than in cystitis, irrespective of the presence of complicating factors.

Table 5 shows antibiotic resistance in all organisms by diagnosis and overall. Resistance to ciprofloxacin occurred in 14.7% of the sample, whereas resistance to trimethoprim-sulfamethoxazole (TMP-SMX) occurred in 27.5%. For uncomplicated cystitis, 24.0% of urine cultures demonstrated resistance to TMP-SMX, 9.5% to ciprofloxacin, and 6.8% to both antibiotics (data not shown). For uncomplicated PN, the rate of resistance was 36.8% for TMP-SMX, 19.5% for ciprofloxacin, and 13.8% for both antibiotics.

Although our numbers of complicated cystitis were low, ciprofloxacin (but not TMP-SMX) resistance was significantly higher in isolates causing complicated cystitis versus uncomplicated cystitis (Table 6). There was no significant difference in the prevalence of TMP-SMX or ciprofloxacin-resistant isolates in uncomplicated versus complicated PN.

Risk factors for antibiotic resistance in UTI (cystitis and PN combined)

Given that it is difficult to differentiate clinically between upper and lower tract urinary infections, cystitis and PN data were combined to evaluate the potential risk factors for antibiotic resistance. The results are not stratified by organism as empirical antibiotic treatment is generally initiated before this information is available.

Only 86 of the 327 charts (26.3%) had documentation as to whether antibiotics were used in the previous 3 months. Documentation of previous UTI in the past

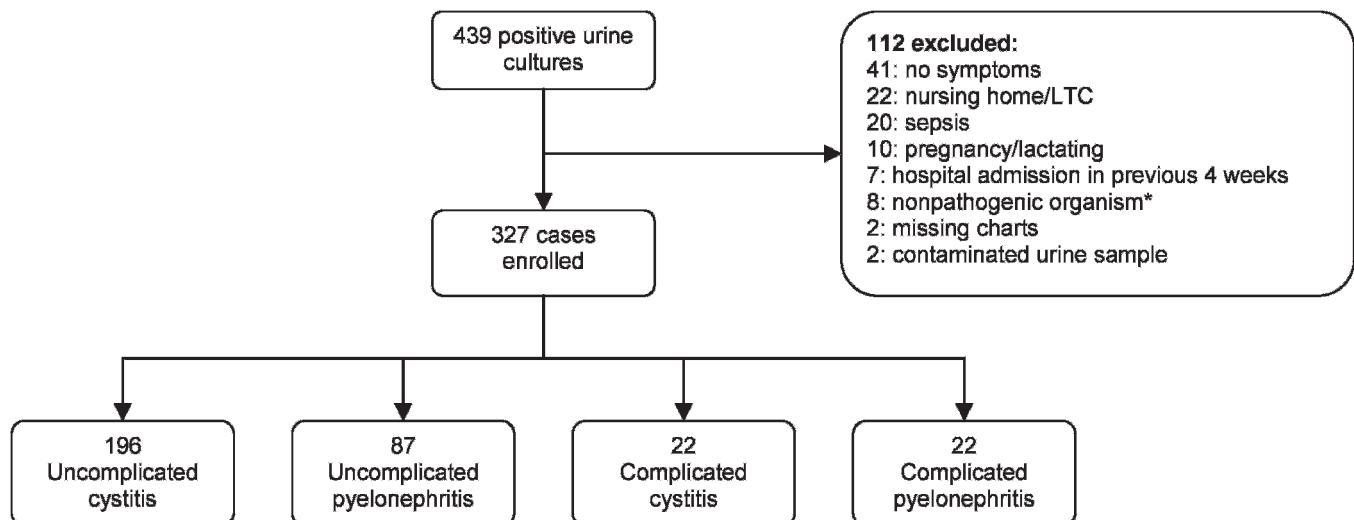


Figure 1. Case flow chart. LTC = long-term care. *Included *Streptococcus viridans*, lactose-fermenting gram-negative bacilli, diphtheroids, and yeast.

Table 3. Demographics

Demographics	Uncomplicated cystitis	Complicated cystitis	p value*	Uncomplicated PN	Complicated PN	p value*	p value comparing uncomplicated cystitis to uncomplicated PN	p value comparing complicated cystitis to complicated PN
Number of cases	196	22		87	22			
Age (yr)								
Mean	39.8	61.7	< 0.001	36.0	51.7	< 0.001	0.20	0.19
Median	32	65.5	< 0.001	31.0	48.5	< 0.001		
Range	19-94	25-97		19-78	27-83			
Previous antibiotic use within 3 mo (%)	20 (10.2)	10 (45.5)	< 0.001	10 (11.5)	7 (31.8)	0.019	0.75	0.35
Documented hospital visit in past 4 wk (%)	7 (3.6)	5 (22.7)	< 0.001	6 (6.9)	5 (22.7)	0.028	0.22	1.00
Documented history of UTI in the past year (%)	43 (21.9)	9 (40.9)	0.05	17 (19.5)	5 (22.7)	0.739	0.65	0.20
Age 65 yr or older	24 (12.2)	11 (50.0)	< 0.001	5 (5.8)	7 (31.8)	0.002	0.10	0.22

PN = pyelonephritis; UTI = urinary tract infection.

*The within-diagnosis p value refers to the Mann-Whitney U test for age comparisons and the Pearson chi-square for risk factors.

Table 4. Urine culture results by diagnosis

Organism	Uncomplicated cystitis n (%)	Complicated cystitis n (%)	Uncomplicated pyelonephritis n (%)	Complicated pyelonephritis n (%)	Uncomplicated UTI n (%)	Complicated UTI n (%)	Total n (%)
<i>Escherichia coli</i> without ESBL	160 (81.6)	16 (72.7)	59 (67.8)	16 (72.7)	219 (77.4)	32 (72.7)	251 (76.8)
<i>E. coli</i> with ESBL	8 (4.1)	1 (4.5)	7 (8.0)	2 (9.1)	15 (5.3)	3 (6.8)	18 (5.5)
<i>Staphylococcus saprophyticus</i>	4 (2.0)	0 (0.0)	13 (14.9)	0 (0.0)	17 (6.0)	0 (0.0)	17 (5.2)
Group B β-hemolytic streptococcus	6 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.1)	0 (0.0)	6 (1.8)
<i>Proteus mirabilis</i>	2 (1.0)	1 (4.5)	0 (0.0)	0 (0.0)	2 (0.7)	1 (2.3)	3 (0.9)
<i>Klebsiella pneumoniae</i>	3 (1.5)	1 (4.5)	1 (1.1)	1 (4.5)	4 (1.4)	2 (4.5)	6 (1.8)
<i>Klebsiella oxytoca</i>	1 (0.5)	0 (0.0)	0 (0.0)	1 (4.5)	1 (0.4)	1 (2.3)	2 (0.6)
<i>Enterococcus</i> spp.	1 (0.5)	1 (4.5)	1 (1.1)	1 (4.5)	2 (0.7)	2 (4.5)	4 (1.2)
<i>Enterobacter</i> spp.	1 (0.5)	0 (0.0)	1 (1.1)	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.6)
<i>Citrobacter</i> spp.	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Polymicrobial (2 uropathogens)	0 (0.0)	1 (4.5)	0 (0.0)	1 (4.5)	0 (0.0)	2 (4.5)	2 (0.6)
Polymicrobial (one of which is <i>E. coli</i>)	9 (4.6)	1 (4.5)	5 (5.7)	0 (0.0)	14 (4.9)	1 (2.3)	15 (4.6)
Total	196	22	87	22	283	44	327

ESBL = extended-spectrum β-lactamase; UTI = urinary tract infection.

Table 5. Antibiotic susceptibility by diagnosis

Antibiotic	Susceptibility status	Diagnosis, n (%)								Total
		Uncomplicated cystitis	Complicated cystitis	Uncomplicated pyelonephritis	Complicated pyelonephritis	Uncomplicated UTI	Complicated UTI			
Ciprofloxacin	Susceptible	172 (90.5)	16 (72.7)	70 (80.5)	16 (72.7)	242 (87.4)	32 (72.7)	274 (85.4)		
	Intermediate	1 (0.5)	1 (4.5)	1 (1.1)	2 (9.1)	2 (0.7)	3 (6.8)	5 (1.6)		
	Resistant	17 (8.9)	5 (22.7)	16 (18.4)	4 (18.2)	33 (11.9)	9 (20.5)	42 (13.1)		
TMP-SMX	Susceptible	149 (76.0)	18 (81.8)	55 (63.2)	15 (68.2)	204 (72.1)	33 (75)	237 (72.5)		
	Intermediate									
Ampicillin	Resistant	47 (24.0)	4 (18.2)	32 (36.8)	7 (31.8)	79 (27.9)	11 (25)	90 (27.5)		
	Susceptible	116 (60.1)	11 (50.0)	28 (37.8)	7 (31.8)	144 (53.9)	18 (40.9)	162 (52.1)		
	Intermediate	1 (0.5)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (0.3)		
Cephalothin/cephalexin	Resistant	76 (39.4)	11 (50.0)	46 (62.2)	15 (68.2)	122 (45.7)	26 (59.1)	148 (47.6)		
	Susceptible	120 (62.8)	13 (61.9)	37 (50.7)	13 (61.9)	157 (59.9)	26 (61.9)	183 (59.8)		
	Intermediate	38 (19.9)	3 (14.3)	20 (27.4)	2 (9.5)	58 (22)	5 (11.9)	63 (20.6)		
	Resistant	33 (17.3)	5 (23.8)	16 (21.9)	6 (28.6)	49 (18.6)	11 (26.2)	60 (19.6)		
Cefazolin	Susceptible	170 (89.5)	15 (75.0)	62 (86.1)	17 (81.0)	232 (88.5)	32 (78)	264 (87.1)		
	Intermediate	5 (2.6)	3 (15.0)	1 (1.4)	0 (0)	6 (2.3)	3 (7.3)	9 (3.0)		
	Resistant	15 (7.9)	2 (10.0)	9 (12.5)	4 (19.0)	24 (9.2)	6 (14.6)	30 (9.9)		
Gentamicin	Susceptible	173 (93.5)	19 (95.0)	56 (77.8)	21 (100.0)	229 (89.1)	40 (97.6)	269 (90.3)		
	Intermediate	1 (0.5)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (0.3)		
	Resistant	11 (5.9)	1 (5.0)	16 (22.2)	0 (0)	27 (10.5)	1 (2.4)	28 (9.4)		
Nitrofurantoin*	Susceptible	192 (98.5)	19 (90.5)	84 (96.6)	21 (95.5)	276 (97.9)	40 (93)	316 (97.2)		
	Intermediate	0 (0)	1 (4.8)	3 (3.4)	0 (0)	3 (1.1)	1 (2.3)	4 (1.2)		
	Resistant	3 (1.5)	1 (4.8)	0 (0)	1 (4.5)	3 (1.1)	2 (4.7)	5 (1.5)		
Timentin	Susceptible	168 (91.3)	18 (90.0)	61 (83.6)	18 (85.7)	229 (89.1)	36 (87.8)	265 (88.9)		
	Intermediate	14 (7.6)	1 (5.0)	8 (11.0)	2 (9.5)	22 (8.6)	3 (7.3)	25 (8.4)		
	Resistant	2 (1.1)	1 (5.0)	4 (5.5)	1 (4.8)	6 (2.3)	2 (4.9)	8 (2.7)		
	Susceptible	121 (93.1)	15 (100.0)	46 (88.5)	13 (81.3)	167 (91.8)	28 (90.3)	195 (91.5)		
Piperacillin/tazobactam	Intermediate	2 (1.5)	0 (0)	0 (0)	0 (0)	2 (1.1)	0 (0)	2 (0.9)		
	Resistant	7 (5.4)	0 (0)	6 (11.5)	3 (18.8)	13 (7.1)	3 (9.7)	16 (7.5)		
	Susceptible	170 (91.9)	19 (95.0)	59 (80.8)	18 (85.7)	229 (88.8)	37 (90.2)	266 (89.0)		
Tobramycin	Intermediate	2 (1.1)	0 (0)	3 (4.1)	1 (4.8)	5 (1.9)	1 (2.4)	6 (2.0)		
	Resistant	13 (7.0)	1 (5.0)	11 (15.1)	2 (9.5)	24 (9.3)	3 (7.3)	27 (9.0)		
	Susceptible	7 (43.8)	1 (50.0)	1 (14.3)	0 (0)	8 (34.8)	1 (25)	9 (33.3)		
Cefuroxime	Intermediate	1 (6.3)	0 (0)	0 (0)	0 (0)	1 (4.3)	0 (0)	1 (3.7)		
	Resistant	8 (50.0)	1 (50.0)	6 (85.7)	2 (100.0)	14 (60.9)	3 (75)	17 (63.0)		

TMP-SMX = trimethoprim-sulfamethoxazole; UTI = urinary tract infection.
 *Nitrofurantoin is not an appropriate antibiotic for pyelonephritis.

Table 6. Percentage resistance (including intermediate susceptibility) to ciprofloxacin and TMP-SMX by diagnosis

	Ciprofloxacin resistance	TMP-SMX resistance
Uncomplicated cystitis (%)	9.5	24.00
Complicated cystitis (%)	27.3	18.20
Fisher exact test, one sided, <i>p</i> value	0.02	0.38
Uncomplicated PN (%)	19.5	36.8
Complicated PN (%)	27.3	31.8
Fisher exact test, one sided, <i>p</i> value	0.30	0.43
Uncomplicated UTI (%)	12.60	27.90
Complicated UTI (%)	27.30	25.00
Fisher exact test, one sided, <i>p</i> value	0.01	0.42

PN = pyelonephritis; TMP-SMX = trimethoprim-sulfamethoxazole; UTI = urinary tract infection.

year was also incomplete, being mentioned in 154 (47%) charts. Therefore, for our risk factor analysis, we combined all UTIs (cystitis, PN, complicated and

uncomplicated). Any antibiotic use in the previous 3 months was a statistically significant risk factor for ciprofloxacin and TMP-SMX resistance (Table 7). A history of UTI and age over 65 were statistically significant risk factors for ciprofloxacin resistance but not TMP-SMX resistance. Due to sparse data, adjusted ORs are not reported.

Further stratification by uncomplicated/complicated UTI did not demonstrate any statistically significant risk factors, although our numbers were small.

DISCUSSION

With the emergence of antibiotic resistance, the treatment of UTIs has become complex. Neither outpatient laboratory studies that use consecutive mid-stream samples without patient clinical presentation nor hospital antibiograms can adequately guide management

Table 7. Risk factors for ciprofloxacin and TMP-SMX resistance in all UTIs combined (cystitis, PN, complicated and uncomplicated)

	Ciprofloxacin resistance, <i>n</i> (%)	Ciprofloxacin sensitivity, <i>n</i> (%)	OR (95% CI)
Antibiotic use	<i>n</i> = 23	<i>n</i> = 61	
Have not used antibiotics in the previous 3 mo	6 (26.1)	33 (54.1)	3.34 (1.16–9.62)
Have used antibiotics in the previous 3 mo	17 (73.9)	28 (45.9)	
Hospital visit	<i>n</i> = 47	<i>n</i> = 274	
No documented history of hospital visit in the past 4 wk	41 (87.2)	258 (94.2)	2.36 (0.87–6.38)
Documented history of hospital visit in the past 4 wk	6 (12.8)	16 (5.8)	
History of UTI	<i>n</i> = 25	<i>n</i> = 126	
No documented history of a UTI in the past year	8 (32.0)	70 (55.6)	2.66 (1.07–6.61)
Documented history of UTI in the past year	17 (68.0)	56 (44.4)	
Age	<i>n</i> = 47	<i>n</i> = 274	
< 65 yr	35 (74.5)	241 (88.0)	2.50 (1.18–5.30)
≥ 65 yr	12 (25.5)	33 (12.0)	
	TMP-SMX resistance	TMP-SMX sensitivity	OR (95% CI)
Antibiotic use	<i>n</i> = 29	<i>n</i> = 57	
Have not used antibiotics in the previous 3 mo	7 (24.1)	32 (56.1)	4.02 (1.48–10.92)
Have used antibiotics in the previous 3 mo	22 (75.9)	25 (43.9)	
Hospital visit	<i>n</i> = 90	<i>n</i> = 237	
No documented history of hospital visit in the past 4 wk	83 (92.2)	220 (92.8)	1.09 (0.44–2.73)
Documented history of hospital visit in the past 4 wk	7 (7.8)	17 (7.2)	
History of UTI	<i>n</i> = 46	<i>n</i> = 108	
No documented history of a UTI in the past year	24 (52.2)	56 (51.9)	0.99 (0.50–1.97)
Documented history of UTI in the past year	22 (47.8)	52 (48.1)	
Age	<i>n</i> = 90	<i>n</i> = 237	
< 65 yr	76 (84.4)	204 (86.1)	
≥ 65 yr	14 (15.6)	33 (13.9)	1.14 (0.58–2.24)

PN = pyelonephritis; UTI = urinary tract infection; TMP-SMX = trimethoprim-sulfamethoxazole.

of community-acquired UTI. Appropriate treatment should rest on valid information about local resistance rates, ideally derived from community-based isolates linked to presenting symptomatology. Our study sought to describe such a community-based sample.

The uropathogens associated with uncomplicated community-acquired cystitis and PN are consistent with previous studies,^{20,21} with *E. coli* accounting for 82.7% of uncomplicated infections followed by *Staphylococcus saprophyticus* at 6% and group B streptococcus at 2.1%, and the rest made up of enterococci and other gram-negative rods (see Table 4). The low number of complicated UTIs overall makes it hard to establish a valid trend in terms of their causative uropathogens, but, as expected, *Proteus mirabilis* and *Klebsiella* species (*pneumoniae* and *oxytoca*), as well as *Enterococcus* species, were more commonly encountered.^{13,17}

The 2010 Infectious Diseases Society of America (IDSA) guidelines on uncomplicated cystitis in women suggest that fluoroquinolones should be avoided unless other options have been exhausted. Nitrofurantoin and TMP-SMX, if resistance prevalence is known to be lower than 20%, are the recommended antimicrobial therapies.²²

The high rates of TMP-SMX resistance in this study (24% for uncomplicated cystitis and 36.8% for uncomplicated PN) make TMP-SMX an unreliable choice for uncomplicated community-acquired UTI in our ED adult female population. Our results are similar to those of a 2004 study of community-acquired UTIs in adult women in British Columbia, which also found a high TMP-SMX resistance rate (20.5%) in isolates growing *E. coli*.²³

In British Columbia, there is a well-documented trend of increasing ciprofloxacin resistance in uropathogens, with the rate of resistance increasing from 2.5% in 1998 to over 20% in 2007; this correlates with the increased use of fluoroquinolone antibiotics.²⁴ In our ED, ciprofloxacin was the most commonly prescribed antibiotic for uncomplicated cystitis during our study period, accounting for 52.7% of prescriptions (data not shown). This may not be wise, and, when possible, preference should be given to nonfluoroquinolone alternatives, such as nitrofurantoin (see Table 5). However, nitrofurantoin has limited activity against non-*E. coli* urinary pathogens, which are more commonly encountered with complicated cystitis.

The 2010 IDSA guidelines for acute uncomplicated PN in women also suggest that an oral fluoroquinolone is appropriate outpatient therapy “where the prevalence

of community uropathogens to fluoroquinolones is not known to exceed 10%.”²² When the resistance exceeds 10%, expert opinion recommends “an initial one-time long-acting parenteral antimicrobial” in addition to the prescription of oral ciprofloxacin. In our study, resistance to ciprofloxacin for uncomplicated PN was 19.5%, well above that number. This suggests the need for a 24-hour dose of an aminoglycoside or an intravenous dose of ceftriaxone. Unfortunately, the IDSA guidelines make no recommendation as to what fluoroquinolone resistance level mandates altogether an “alternative agent either in conjunction” or as replacement of an oral fluoroquinolone for the outpatient treatment of PN.

Our results of antibiotic susceptibility (see Table 5) for uncomplicated PN in the face of high prevalence of in vitro ciprofloxacin resistance do not allow us to offer an oral antibiotic alternative. Too few isolates were tested against cefuroxime to draw any valid conclusion, and nitrofurantoin is not acceptable for PN because it does not achieve sufficient serum levels.

Any antibiotic use in the previous 3 months was the only significant risk factor for both TMP-SMX and ciprofloxacin resistance in UTI. This finding is in keeping with previous studies of community-acquired cystitis,^{25,26} although our results are based on all UTIs combined. In our ED, patients with UTI who had been on antibiotics in the last 3 months were more than three times as likely to have an isolate resistant to ciprofloxacin than those who had not taken any recent antibiotic. Similarly, women were four times as likely to have an isolate resistant to TMP-SMX than those who had not taken any recent antibiotic. Patients with a history of UTI within the previous year were 2.7 times more likely and those over age 65 were 2.5 times more likely to have a urinary isolate resistant to ciprofloxacin.

Limitations

Several limitations should be taken into account when evaluating our results. Medical record reviewers were not blinded to the study hypothesis; however, strict adherence to recommendations for chart reviews^{18,19} helped minimize potential bias in this regard.

Common pitfalls of medical record reviews (e.g., illegibility, incomplete documentation) may account for the low frequency of potential risk factors for antibiotic resistance and, ultimately, lack of significance. The small number of risk factors documented meant that

stratifying by type of diagnosis (complicated and uncomplicated) was not feasible. A clinician will not always have the patient's full history available to assign a diagnosis of uncomplicated or complicated UTI, so interpreting the risk factors for all UTIs combined is clinically relevant.

There is a lack of standardization in the literature of various UTI-related definitions including "positive urine culture," making comparisons difficult. Our definitions (see Table 1) are consistent with those in the literature and have face validity. Our criteria for both cystitis and PN are symptom based, which would exclude paraplegics (4 cases were excluded), patients with altered sensation (2 multiple sclerosis patients), and the elderly with UTI presenting with delirium, general weakness, and vague symptoms (28 cases). These were among the 41 asymptomatic patients excluded in Figure 1. Unlike some studies,^{6,27} we did not require a documented fever as a criterion for PN. We made this decision because immunosuppressed patients, the elderly, and patients who take antipyretics prior to their ED visit may have PN without a documented fever. The low numbers of patients with complicated UTI in our study limit our ability to draw conclusions in this category. These low numbers may be due to our exclusion criteria.

We took a conservative approach and classified organisms with intermediate antibiotic resistance as resistant. We recognize that patients may improve despite being treated with an antibiotic to which the organism has only intermediate resistance. However, we found that any antibiotic use in the prior 3 months was a risk factor for both ciprofloxacin and TMP-SMX resistance regardless of whether intermediate results were classified as resistant or not. Similarly, a history of UTI in the last year and age over 65 remained risk factors for ciprofloxacin regardless of the classification. These findings increase our confidence in our conclusions.

Our findings are limited to the population we studied, that is, adult women, age 19 or greater, nonpregnant and nonlactating, who presented to our tertiary care Vancouver ED with community associated-UTI and had a positive urine culture. With ED overcrowding, nurse-initiated investigations at our institution have led to urine cultures being sent on most UTI patients; however, patients with UTIs without a urine culture were not included or tracked to ensure that they were similar to our study subjects.

Finally and most importantly, our study was not an outcome study; thus, we can only comment on in vitro resistance to antibiotic or microbiologic failure rather than clinical failure.

CONCLUSION

E. coli was the predominant uropathogen across all UTI categories in the adult nonpregnant women with community-acquired UTIs who presented to our ED in 2008. Fifteen percent of all UTIs were caused by isolates resistant to ciprofloxacin and 27.5% by those resistant to TMP-SMX. Any antibiotic use in the previous 3 months was a significant risk factor for both ciprofloxacin and TMP-SMX uropathogen resistance. Being 65 years of age or older and having had a history of UTI in the previous year were risk factors only for ciprofloxacin resistance. Future prospective outcome studies, with emphasis on clinical cure rather than microbiologic cure, as well as patient-specific risk factors associated with antibiotic resistance, are needed to guide UTI management.

Competing interests: Dr. Brubacher's research is supported by a scholar award from the Michael Smith Foundation for Health Research.

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Appendix 1. ICD-9 and ICD-10-CA codes

ICD-9 codes

- 590.0 Chronic pyelonephritis
- 590.1 Acute pyelonephritis
- 590.2 Renal and perinephric abscess
- 590.3 Pyeloureteritis cystica
- 590.8 Other pyelonephritis or pyonephrosis, not specified as acute or chronic
- 590.80 Pyelonephritis, unspecified
- 590.81 Pyelitis or pyelonephritis in diseases classified elsewhere
- 590.9 Infection of kidney, unspecified
- 595 Cystitis
- 595.0 Acute cystitis
- 595.2 Other chronic cystitis
- 595.4 Cystitis in diseases classified elsewhere
- 595.8 Other specified types of cystitis
- 595.9 Cystitis, unspecified
- 599.0 Urinary tract infection, site not specified
- 599.7 Hematuria
- 599.9 Unspecified disorder of urethra and urinary tract

ICD-10-CA codes

- N30.0 Acute cystitis
- N30.2 Other chronic cystitis
- N30.8 Other cystitis
- N30.9 Cystitis, unspecified
- N39.8 Other specified disorders of the urinary system
- N39.9 Disorder of the urinary system, unspecified
- R31.0 Gross hematuria
- R31.1 Microscopic hematuria
- R31.8 Other and unspecified hematuria

Appendix 2. Database structure

Demographics
 Age
 Postal code
 Primary care physician (Y/N)

Current visit
 Visit date
 Diagnosis (cystitis or pyelonephritis)

Laboratory results
 Urine culture and sensitivity
 Sample type (catheterized, Y/N)
 Organism
 Culture (million CFU/L)
 Antibiotic susceptibilities
 Ampicillin, cephalothin/cephalexin, cefazolin, cefuroxime, ciprofloxacin, gentamicin, nitrofurantoin, tetracycline, ticarcillin-clavulanic acid, piperacillin/tazobactam, tobramycin, TMP-SMX

Urinalysis and microscopy
 Hemoglobin
 Nitrite
 Leukocytes
 White blood cells
 Red blood cells
 Epithelial cells

Antibiotic resistance and risk factors
 Previous antibiotics (within 3 months of current visit, Y/N)
 Antibiotic prescribed
 Dosage
 Indication
 Start date
 Duration
 Previous positive urine culture (within 1 yr of current visit, Y/N)
 Sample date
 Sample type (catheterized, Y/N)
 Organism
 Culture (CFU/L)
 Antibiotic susceptibilities
 Ampicillin, cephalothin/cephalexin, cefazolin, cefuroxime, ciprofloxacin, gentamicin, nitrofurantoin, tetracycline, ticarcillin-clavulanic acid, piperacillin/tazobactam, tobramycin, TMP-SMX

Positive history of UTIs (within 1 year of current visit, Y/N)
 Number of VGH visits, excluding admission (within 1 mo of current visit)

Complicating factors
 Anatomic/functional
 Solitary kidney, polycystic kidneys, renal abscess, duplicated collecting system, indwelling catheterization, intermittent catheterization, ureteric stent, nephrostomy tube, recent cystoscopy (within 2 wk), vesicoureteral reflux, ileal conduit, bladder augmentation, renal transplant, neurogenic bladder (any history)

Obstructive
 Stone, tumour, stricture (any history), bladder outlet obstruction

Appendix 2. Continued

Medical conditions
 IDDM, NIDDM, renal failure (SCr > 200 µmol/L, GFR < 30 mL/min), hepatic failure, immunosuppression, corticosteroid use, HIV, active cancer (within 6 mo)

Antibiotic allergies
 Penicillins, cephalosporins, sulphas, fluoroquinolones, nitrofurantoin

Disposition
 Admitted
 Admission date
 Admission length
 Discharged
 Antibiotic prescribed
 Dosage
 Duration
 IV fast track
 Antibiotic prescribed
 Dosage
 Duration

Additional UTIs
 Additional cystitis cases (2008)
 Additional pyelonephritis cases (2008)

Return visit
 Visit date
 Reason(s) for return
 Disposition
 Admitted
 Admission date
 Admission length
 Discharged
 Antibiotic prescribed
 Dosage
 Duration
 IV fast track
 Antibiotic prescribed
 Dosage

GFR = glomerular filtration rate; HIV = human immunodeficiency virus; IDDM = insulin-dependent diabetes mellitus; IV = intravenous; NIDDM = non-insulin-dependent diabetes mellitus; SCr = serum creatinine; TMP-SMX = trimethoprim-sulfamethoxazole; UTI = urinary tract infection; VGH = Vancouver General Hospital.