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RESEARCH ARTICLE

Clinical Risk Factors and Multi-Antimicrobial Resistance Pattern in Community-Acquired Outpatient Urinary Tract Isolates of *Escherichia Coli*

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Abstract

Introduction: Urinary tract infections (UTIs) are one of the most commonly treated bacterial infections in ambulatory care clinics and emergency departments (ED). The management of UTIs has been complicated by the emergent resistance to most commonly prescribed antibiotics causing increased patient morbidity, cost of reassessment and retreatment, and rates of hospitalization.

Objective: To evaluate multi-antimicrobial resistance pattern of *Escherichia coli* (*E. coli*) urinary isolates and the risk factors associated with commonly prescribed antibiotics in emergency department and primary care clinics.

Method: This is a cross-sectional study of patients 18 to 65 years of age reported to have *E. coli* positive UTIs whose medical and laboratory records were systematically reviewed.

Results: Overall, 37.7% *E. coli* urinary isolates were resistant to ampicillin, 18.3% to trimethoprim/sulfamethoxazole (TMP/SMX), and 7.8% to ciprofloxacin. About 21% isolates were resistant to 2 or more antibiotics. Ciprofloxacin-resistant *E. coli* isolates from outpatient urine sample were frequently resistant to ampicillin (81.5%), and TMP/SMX (58.2%). The concurrent resistance rate of ciprofloxacin was about 8 times more frequent (24.8% vs. 3.1%) than nitrofurantoin among TMP/SMX-resistant *E. coli* urinary isolates. Patients with histories of genitourinary abnormalities were 1.59 times (*CI 1.27-1.98*) more likely have *E. coli* isolates resistant to TMP/SMX, and 2.35 times more likely (*CI 1.79-3.09*) to ciprofloxacin. Diabetic patients were at increased risk for resistance to TMP/SMX (*OR 1.37, CI 1.14-1.65*) and ciprofloxacin (*OR 2.51, CI 2.00-3.16*). Obesity is significantly associated with ciprofloxacin resistance (*OR 1.68, CI 1.34-2.09*). TMP/SMX and ciprofloxacin resistance rate increased gradually with the number of previous UTIs, hospitalizations, and antibiotic prescriptions.

Conclusions: Ciprofloxacin resistant isolates of *E. coli* from urine were frequently multi-drug resistant and TMP/SMX can induce ciprofloxacin resistances. In addition to demographic factors, history of genitourinary abnormalities, diabetes, obesity, number of hospitalizations, previous diagnosis of UTIs, antibiotic prescriptions in previous 6 months are risk factors for antimicrobial resistance.

Keywords

Urinary tract infection, Antibiotic resistance, Antibiotics, Risk factors, Ciprofloxacin, Fluoroquinolones, Ampicillin, Trimethoprim-sulfamethoxazole, Cefazolin, Obesity, Diabetes, *Escherichia coli*

Introduction

The management of *Escherichia coli* (*E. coli*) driven urinary tract infections (UTIs) has been complicated by the emergence of resistance to commonly prescribed antibiotics causing increases in patient morbidity, cost of reassessment and retreatment, and rates of hospitalization [1,2]. While resistance to amoxicillin has been established for years, trimethoprim/sulfamethoxazole (TMP/SMX) resistance became more prevalent in recent years. Studies have shown that TMP/SMX resistance rate varies by region ranging from 18% to 50% worldwide and from 18% to 25% in North America [3-6]. Recently revised published guidelines by the Infectious Disease Society of America (IDSA) recommended TMP/SMX therapy should not be used as empiric therapy in regions where the prevalence of TMP/SMX resistance rates exceed 20% [7]. Although emphasis has

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been given to prescribe more narrow-spectrum antibiotics for treating simple uncomplicated UTIs whenever possible, concerns about resistance have resulted in escalating use of broad-spectrum antibiotics, particularly cephalosporins, and fluoroquinolones. In recent years overall use of fluoroquinolones, particularly ciprofloxacin in ambulatory care, has dramatically increased [8-9]. Clinicians and researchers already began to observe an increasing trend in *E. coli* resistance urinary isolates for quinolones in addition to ampicillin and TMP/SMX [5,6,10]. The focus of this study was to identify common risk factors as well as the distribution and characteristics of multi-antimicrobial resistance patterns of commonly prescribed antibiotics among *E. coli* infected UTI patients in community ED and outpatient clinics.

Methods

Study design

We performed a retrospective cross-sectional study examining urinary *E. coli* isolates of patients aged 18 to 65-years-old collected in ED and primary care clinics. Laboratory data were matched with the corresponding individual's demographic information and medical record. The study was conducted at a university affiliated community hospital. Primary care clinics were defined as non-specialty care clinics within the Internal Medicine and Family Medicine departments. The medical records of these identified patients being evaluated were then reviewed to obtain demographics and clinical data. All medical information was in electronic format. Patients were excluded if their records were not available, if urine culture grew more than one organism, or if a urine contamination was suspected. Voided cultures with greater than 100,000 CFU/mL and cultures collected via catheterized specimen with greater than 10,000 CFU/mL were not considered contaminants [7]. Urine cultures positive for *E. coli* that were drawn from patients visiting in the primary care clinics and the ED from January 1, 2011 to December 31, 2012 were eligible for inclusion in the analysis. *E. coli* isolates with intermediate susceptibility were not classified as being resistant. The study was approved by the Carle Institutional Review Board (IRB).

Measurements variables

Demographic data included patient age, date of birth, gender, race, and insurance status. Clinical data consisted of date of encounters, height, weight, methods of specimen collection, urinalysis and culture and sensitivity results, history of genitourinary abnormality, chronic medical conditions, previous history of UTI, place of visit (primary care clinic, or ED), and history of antibiotic prescriptions in last 6 months.

All urinary tract isolates of *E. coli* were identified and subjected to susceptibility testing with the Vitek 2 automated system (Bio Merieux Vitek, Inc., Hazelwood, MO). Vitek 2 is an automated computerized instrument which provides specific quantitative results of urine cultures more rapidly when compared to conventional methods. It is highly sensitive (92.8%), and specific (99.4%) with average predictive value of 92% [11]. The breakpoints (microgram/mL) for *E. coli* isolates were based on Clinical Laboratory Standard Institute guidelines formerly known as the National Committee on Clinical Laboratory Standards [12]. The data set was then limited to the first isolate tested for antibiotic susceptibilities per patient to minimize potential bias resulting from repeat cultures.

Statistical Analysis

SAS Enterprise Guide for Windows Version 4.3 statistical software was used for data analysis. Summary statistics were performed for frequencies and proportions for categorical variables. Univariate statistics were calculated using χ^2 test at 5% significance level. Univariate and multivariate logistic regression models were analyzed to determine the association of predictor variables with commonly prescribed antibiotics. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

Results

During the study period 5,621 urinary tract isolates of *E. coli* from 4,236 different patients were examined for susceptibility patterns. The median patient age was 41-years-old and body mass index (BMI) was 27.8. Overall, 37.7% *E. coli* isolates were resistant to ampicillin, 18.3% to TMP/SMX, 13.5% to ampicillin/sulbactam, 7.8% to Cipro/levofloxacin, and 3.8% to cefazolin (Table 1). Ciprofloxacin and Levofloxacin reported identical susceptibility pattern in the study urinary isolates. Therefore, only ciprofloxacin was used in further analy-

Table 1: Antimicrobial susceptibility results for *Escherichia coli* urinary isolates.

Antimicrobial Agents	Total Number of isolates	Number of Isolates (%)	
		Resistant	Susceptible/Intermediate
Ampicillin	5609	2115 (37.7)	3494 (62.3)
Ciprofloxacin	5602	438 (7.8)	5164 (92.2)
Cefazolin	5611	214 (3.8)	5397 (96.2)
Ampicillin/sulbactam	5599	758 (13.5)	4841 (86.5)
Nitrofurantoin	5611	82 (1.5)	5529 (98.5)
Levofloxacin	5602	436 (7.8)	5166 (92.2)
TMP/SMX	5611	1027 (18.3)	4584 (81.7)

Abbreviation: TMP/SMX: Trimethoprim/Sulfamethoxazole.

Table 2: Resistance to 1 or more antibiotics among 5,600 *Escherichia coli* urinary isolates against commonly prescribed antimicrobials.

Number of agents to which isolates were resistant	Total no. of isolates (%)	No. of Isolates (%) resistant to				
		Ampicillin	TMP/SMX	Cefazolin	Nitrofurantoin	Ciprofloxacin
0	3,276 (58.5)					
1	1,164 (20.8)	995 (85.5)	102 (8.8)	1 (0.1)	23 (2.0)	43 (3.7)
2	836 (14.9)	794 (95.0)	644 (77.0)	83 (9.9)	20 (2.4)	131 (15.7)
3*	266 (4.8)	266 (100.0)	224 (84.2)	75 (28.2)	26 (9.8)	207 (77.8)
4*	52 (0.9)	52 (100.0)	51 (98.1)	48 (92.3)	6 (11.5)	51 (98.1)
5*	6 (0.1)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)

Abbreviation: TMP/SMX: Trimethoprim/Sulfamethoxazole; *: In all, 5.8% (324 of 5600) of isolates were resistant to three or more antibiotics among the listed 5 antibiotics and defined as multidrug resistant.

Table 3: Factors associated with resistance to TMP/SMX and Ciprofloxacin *Escherichia coli* urinary isolates.

Risk factors	TMP/SMX				Ciprofloxacin			
	No. (%) of isolates		OR (95% CI)	P value	No. (%) of isolates		OR (95% CI)	P value
	S	R			S	R		
Overall	4584 (81.7)	1027 (18.3)			5164 (92.2)	438 (7.8)		
Gender								
Male	274 (6.0)	79 (7.7)	1.32 (1.01-1.69)	0.04	308 (6.0)	44 (10.0)	1.75 (1.27-2.44)	0.0008
Female	4310 (94.0)	948 (92.3)	1		4856 (94.0)	394 (90.0)	1	
Race								
Asian	70 (1.5)	43 (4.2)	3.15 (2.14-4.65)	< 0.0001	101 (2.0)	12 (2.7)	1.53 (0.83-2.82)	0.17
Black	480 (10.5)	142 (13.8)	1.52 (1.24-1.86)	< 0.0001	550 (10.6)	71 (16.2)	1.67 (1.27-2.19)	0.0002
White	3773 (82.3)	735 (71.6)	1		4178 (80.9)	324 (74.0)	1	
Health Insurance								
Yes	4255 (92.8)	957 (93.2)	1.06 (0.81-1.38)	0.68	4795 (92.9)	408 (93.2)	1.05 (0.71-1.54)	0.82
No	329 (7.2)	70 (6.8)	1		369 (7.1)	30 (6.8)	1	
Location								
Emergency Department	530 (11.6)	152 (14.8)	1.08 (0.79-1.46)	0.64	614 (11.9)	68 (15.5)	0.36 (0.26-0.51)	< 0.0001
Outpatient	3754 (81.9)	795 (77.4)	0.79 (0.61-1.03)	0.08	4259 (82.5)	281 (64.2)	0.22 (0.17-0.28)	< 0.0001
Inpatient	300 (6.5)	80 (7.8)	1		291 (5.6)	89 (20.3)	1	
History of Genitourinary Abnormality								
Yes	347 (7.6)	118 (11.5)	1.59 (1.27-1.98)	< 0.0001	393 (7.6)	71 (16.2)	2.35 (1.79-3.09)	< 0.0001
No	4237 (92.4)	909 (88.5)	1		4771 (92.4)	367 (83.8)	1	
History of Chronic Medication								
Yes	217 (4.7)	56 (5.5)	1.16 (0.86-1.57)	0.33	235 (4.6)	38 (8.7)	1.99 (1.39-2.85)	0.0002
No	4367 (95.3)	971 (94.5)	1		4929 (95.4)	400 (91.3)	1	
Mode of Urine Collection								
Catheterized	170 (3.7)	73 (7.1)	1.99 (1.50-2.64)	< 0.0001	175 (3.4)	68 (15.5)	5.24 (3.89-7.07)	< 0.0001
Void	4414 (96.3)	954 (92.9)	1		4989 (96.6)	370 (84.5)	1	
Diabetes								
Yes	579 (12.6)	170 (16.6)	1.37 (1.14-1.65)	0.0009	635 (12.3)	114 (26.0)	2.51 (2.00-3.16)	< 0.0001
No	4005 (87.4)	858 (83.4)	1		4529 (87.7)	324 (74.0)	1	
Cancer								
Yes	308 (6.7)	69 (6.7)	1.00 (0.76-1.31)	1	316 (6.1)	61 (13.9)	2.48 (1.85-3.33)	< 0.0001
No	4276 (93.3)	958 (93.3)	1		4848 (93.9)	377 (86.1)	1	
Age			0.99 (0.99-1.00)	0.0036			1.03 (1.02-1.04)	< 0.0001
Previous Diagnosis of UTI								
0 (reference)	2630 (57.4)	532 (51.8)	1		2996 (58.0)	160 (36.5)	1	
1	944 (20.6)	182 (17.7)	0.95 (0.79-1.15)	0.61	1044 (20.2)	80 (18.3)	1.44 (1.09-1.89)	0.01
2	298 (8.7)	92 (9.0)	1.14 (0.89-1.46)	0.29	446 (8.6)	44 (10.1)	1.85 (1.30-2.62)	0.0006
3	194 (4.2)	56 (5.5)	1.43 (1.05-1.95)	0.025	224 (4.3)	26 (5.9)	2.17 (1.41-3.36)	0.0005
4	111 (2.4)	40 (3.9)	1.78 (1.23-2.59)	0.0024	130 (2.5)	20 (4.6)	2.88 (1.75-4.74)	< 0.0001
05-Oct	213 (4.7)	82 (8.0)	1.90 (1.45-2.50)	< 0.0001	239 (4.6)	56 (12.8)	4.39 (3.15-6.11)	< 0.0001
> 10	94 (2.1)	43 (4.2)	2.26 (1.56-3.28)	< 0.0001	85 (1.7)	52 (11.9)	11.46 (7.83-16.75)	< 0.0001
Hospitalization								
0 (reference)	4415 (96.3)	966 (94.1)	1		5016 (97.1)	357 (81.5)	1	
1	102 (2.2)	38 (3.7)	1.70 (1.17-2.49)	0.006	89 (1.7)	51 (11.6)	8.05 (5.62-11.55)	< 0.0001
≥ 2	67 (1.5)	23 (2.2)	1.57 (0.97-2.53)	0.07	59 (1.1)	30 (6.9)	7.14 (4.54-11.23)	< 0.0001

Obesity								
BMI < 25	1887 (41.2)	422 (41.1)	1		2157 (41.8)	148 (33.8)	1	
BMI 25-29.9	1074 (23.4)	227 (22.1)	0.95 (0.79-1.13)	0.53	1215 (23.5)	84 (19.2)	1.01 (0.76-1.33)	0.96
BMI ≥ 30	1623 (35.4)	378 (36.8)	1.04 (0.89-1.22)	0.61	1792 (34.7)	206 (47.0)	1.68 (1.34-2.09)	< 0.0001
Antibiotic Prescribed in Past 6 Months								
0 (reference)	1190 (26.0)	185 (18.0)	1		1302 (25.2)	71 (16.2)	1	
1	1698 (37.0)	321 (31.3)	1.22 (1.00-1.48)	0.05	1930 (37.4)	85 (19.4)	0.81 (0.59-1.12)	0.19
02-Mar	1151 (25.1)	307 (29.9)	1.72 (1.41-2.10)	< 0.0001	1334 (25.8)	122 (27.9)	1.68 (1.24-2.27)	0.0008
04-May	310 (6.8)	107 (10.4)	2.22 (1.70-2.91)	< 0.0001	361 (7.0)	56 (12.8)	2.85 (1.97-4.12)	< 0.0001
> 5	235 (5.1)	107 (10.4)	2.93 (2.22-3.86)	< 0.0001	237 (4.6)	104 (23.7)	8.05 (5.77-11.22)	< 0.0001

Abbreviation: TMP/SMX: Trimethoprim/Sulfamethoxazole; OR: Odds ratio.

ses. When multidrug resistance (MDR) rates were analyzed among the 5 most commonly prescribed antibiotics, 58.5% of total isolates were susceptible to all antimicrobials and 20.8% were resistant to at least 1 antimicrobial agent (Table 2). Approximately 15% urinary isolates were resistant to at least 2 agents, predominantly ampicillin (95%), and TMP/SMX (77%) followed by Ciprofloxacin (15.7%). MDR was defined if urinary isolates were resistant to at least one agent in three or more antimicrobial categories [13]. MDR isolates accounted for 5.8% (*n* = 324) of 5,600 isolates. The majority of MDR isolates were resistant to 3 antimicrobials, and these accounted for 4.8% (*n* = 266) of all isolates. Among all the MDR phenotypes, 82.1% (*n* = 266) isolates were concurrently resistant to at least 3 ≥ antibiotics.

When the risk of resistance to TMP/SMX and ciprofloxacin in relation to patient demographics and clinical variables were analyzed, men who were infected with *E. coli* uropathogen were found to be at increased risk for developing resistance to these antibiotics compared to women (Table 3). Black patients were at a significant risk for developing resistance to TMP/SMX (*OR = 1.52, CI 1.24-1.86*), and ciprofloxacin (*OR = 1.67, CI 1.27-2.19*) than their white counterparts. The odds of risk of resistance in Asians than to whites was significant for TMP/SMX (*OR = 3.15, CI 2.14-4.65*) but not for ciprofloxacin. Compared to inpatient, ciprofloxacin resistance was significantly lower for *E. coli* urinary isolates collected either from outpatient clinics (*OR = 0.36, CI 0.26-0.51*) or ED (*OR = 0.22, CI 0.17-0.28*). Urine samples collected via catheterization were significantly associated with *E. coli* resistance antibiotics*;* SMP/TMX: *OR = 1.99,* (*CI 1.50-2.64*)*;* and ciprofloxacin: *OR = 5.24,* (*CI 3.89-7.07*) than voided specimens. Patients with a history of genitourinary abnormality were 1.6 and 2.3 times more likely to have urinary isolates resistant to TMP/SMX ($P < 0.0001$) and ciprofloxacin ($P < 0.0001$), respectively. Patients who were on chronic medications ($P < 0.0002$) or who had cancer ($P < 0.0001$) were likely to have ciprofloxacin resistant *E. coli* urinary isolates than otherwise healthy adults. Compared to non-diabetic patients *E. coli* isolates from patients with diabetes appeared to be 2.51 times (*CI 2.00-3.16*) more likely to be resistant to ciprofloxacin, and 1.37 times (*CI 1.14-1.65*) to TMP/SMX. Although not significant, an overall increasing trend in resistance was observed against both antimicrobials when isolates were compared for overweight (BMI 25-29.9) and obese (BMI ≥ 30) patients to patients whom BMI was < 25. For ciprofloxacin, the odds of resistance were significantly higher among obese patients (*OR = 1.68, CI 1.34-2.09*). When ordinal variables were considered including previous diagnosis of UTIs, numbers of hospitalization and antibiotics prescribed in past 6 months, a clear increasing trend in risk of developing resistance against *E. coli* uropathogen was observed for both antibiotics. For patients who had 5-10 episodes of UTIs or who had ≥ 11 episodes of UTI, the odds of resistance increased to 1.90 ($P < 0.0001$) and 2.26 ($P < 0.0001$), respectively for TMP/SMX, and 4.39 ($P < 0.0001$) and 11.46 ($P < 0.0001$) for ciprofloxacin. Similarly, the risk of resistance to these two antimicrobials gradually increased among patients who were hospitalized ≥ 2 times (ciprofloxacin: *OR = 7.14, CI 4.54-11.23* TMP/SMX: *OR = 1.57, CI 0.97-2.53*) or who had ≥ 6 antibiotics prescriptions in last 6 months (ciprofloxacin: *OR = 8.05, CI 5.77-11.22* TMP/SMX: *OR = 2.93, CI 2.22-3.86*).

We have observed high collinearity among previous diagnosis of UTI, history of genitourinary abnormality, hospitalization, and antibiotic prescriptions in last 6 months. For instance, the *Pearson* correlation between hospitalization and previous diagnosis of UTI was 0.61, and the correlation between hospitalization and antibiotic prescriptions in past six months was 0.41. Such collinearity precludes us to use multivariate logistic regression including all variables simultaneously; however, when collinear variables were removed the results were similar to those from the univariate analysis.

Discussion

Both increasing trends in antimicrobial resistance of *E. coli* urinary isolates to TMP/SMX and the potential subsequent decreases in its efficacy as empiric therapy in treating uncomplicated UTIs in ambulatory care settings pose a serious challenge to our health care providers. Such resistance patterns and revised recommendations from the IDSA compel health care providers to take into consideration alternative therapies, like fluoroquinolones or nitrofurantoin. Therefore, knowledge of the multi-antimicrobial resistance pattern of commonly prescribed antibiotics and the associated risk factors in developing resistance in the local community is critical for practitioners to empirically select an effective

therapeutic agent and thereby reduce the risk of treatment failure.

Overall *in vitro* antimicrobial resistance rates among *E. coli* urinary isolates in our study is similar to the national benchmark reported in previous studies [14,15]. For example, except for ciprofloxacin, the resistances to ampicillin (37.7% vs. 39.1%) and TMP/SMX (18.3% vs. 18.6%) are consistent with the resistance prevalence reported in the USA 2000 national prevalence data used by Sahm, et al. [15]. Compared to that study the resistance rate has nearly doubled (3.7% to 7.8%) for ciprofloxacin while the TMP/SMX resistance rate has remained the same at 18%. We have also observed a marginal increase in nitrofurantoin resistance from 1% to 1.5%. Ciprofloxacin resistance in our study rose sharply from 15.7% to 77.8% compared to ampicillin (95% to 100%) and TMP/SMX (77% to 84.2%) when 3 antimicrobials phenotypes were considered (Table 2). Increase in provider use of fluoroquinolones may have contributed to rapid rising in antimicrobial resistance of *E. coli* to ciprofloxacin, as resistance to this agent has shown to correlate with the level of its use [16,17].

While previous retrospective studies that have inferred co-resistance of ciprofloxacin with other antimicrobials are unlikely in outpatient urinary *E. coli* isolates, our susceptibility data reported about 38% (n = 437/1160) of all MDR phenotypes which are resistant to ciprofloxacin were also resistant to 4 common antimicrobial phenotypes [6,15,18,19]. The co-resistance association between the ciprofloxacin resistant isolates with isolates resistant for TMP/SMX, nitrofurantoin, and cefazolins appeared to be significantly ($P < 0.0001$) strong (Table 4 and Table 5). Nearly 58% percent of cipro-resistant *E. coli* isolates were also resistant to TMP/SMX, 81% to ampicillin, 20% to cefazolin, and 5% to nitrofurantoin. The findings are in agreement with previous reports suggesting fluoroquinolones resistance typically arises in isolates of *E. coli* which already harbor ampicillin and/or TMP/SMX resistant mutants. The clonal expansion of MDR isolates may be amplified by exposure to any single agent for which resistance exists. Two recent European studies reported a strong positive correlation between the ciprofloxacin usage and the proportion of TMP/SMX resistance *E. coli* per year suggesting that the resistance to TMP/SMX might have been induced by ciprofloxacin treatment [20,21].

The activity of fluoroquinolones and nitrofurantoin against *E. coli* resistant uncomplicated UTIs may be of important consideration in communities where the TMP/SMX resistance rate exceeds the IDSA recommended threshold (20%). We have found concurrent resistance of ciprofloxacin about 8 times more frequent (24.8% vs. 3.1%) than resistance to nitrofurantoin among TMP/SMX-resistance *E. coli* urinary isolates (Table 5) which is in line with the findings from Karlowsky, et al. (9.5% vs. 1.7%, about 5 times more common) [18]. Yet, this apparent difference is minimal when overall susceptibility rate for ciprofloxacin (92.2%) cefazolin (96.2%), and nitrofurantoin (98.5%) were considered in our study. Furthermore, among the TMP/SMX-resistant *E. coli* urinary isolates 75% of the specimens were still sensitive to ciprofloxacin, 91% to cefazolin, and 97% to nitrofurantoin. Therefore, longitudinal monitoring of the course of TMP/SMX resistance as well as the susceptibility pattern of ciprofloxacin and nitrofurantoin are important as these alternative therapies become more widely prescribed.

Caution must be considered, however, when choosing ciprofloxacin over nitrofurantoin or vice versa. There was 5.5% of ciprofloxacin-resistant urinary isolates which were also resistant to nitrofurantoin. On the other hand, 29.3% of the nitrofurantoin-resistant isolates were resistant to ciprofloxacin. It was 10.4% vs. 29.8% in the Karlowsky, et al. study [18]. Hence, emphasizing the rationality of prescribing nitrofurantoin over ciprofloxacin as a second-line agent when TMP/SMX cannot be used for uncomplicated UTIs. Unlike ciprofloxacin

Table 4: Association between ciprofloxacin and four common antibiotics.

	No. of Isolates	Ciprofloxacin No. (%)		p-value
		S*	R**	
TMP/SMX				
S	4,575	4,392 (85.1)	183 (41.8)	< 0.0001
R	1,027	772 (14.9)	255 (58.2)	
Ampicillin				
S	3,487	3,406 (66.0)	81 (18.5)	< 0.00001
R	2,113	1,756 (34.0)	357 (81.5)	
Nitrofurantoin				
S	5,520	5,106 (98.9)	414 (94.5)	< 0.0001
R	82	58 (1.1)	24 (5.5)	
Cefazolin				
S	5,388	5,036 (97.5)	352 (80.4)	< 0.0001
R	214	128 (2.5)	86 (19.6)	

Abbreviation: TMP/SMX: Trimethoprim/Sulfamethoxazole; S*: Susceptible; R**: Resistant.

Table 5: Association between TMP/SMX and four common antibiotics.

No. of Isolates		TMP/SMX No. (%)		p-value
		S*	R**	
Ciprofloxacin				
S	5164	4,392 (96.0)	772 (75.2)	< 0.0001
R	438	183 (4.0)	255 (24.8)	
Ampicillin				
S	3,494	3,354 (73.2)	140 (13.6)	< 0.0001
R	2,115	1,228 (26.8)	887 (86.4)	
Nitrofurantoin				
S	5,529	4,534 (98.9)	995 (96.9)	< 0.0001
R	82	50 (1.1)	32 (3.1)	
Cefazolin				
S	5,397	4,465 (97.4)	932 (90.7)	< 0.0001
R	214	119 (2.6)	95 (9.3)	

Abbreviation: TMP/SMX: Trimethoprim/Sulfamethoxazole; S*: Susceptible; R**: Resistant.

and cefazolin which are broader in spectrum and have a wide variety of indications, nitrofurantoin is a unique drug for treatment of uncomplicated UTIs in outpatient areas because of its narrow spectrum bactericidal activity and its limited contact with bacteria outside the urinary tract. B-lactams, including second generation cephalosporin, are generally less effective and have more adverse effects. Therefore, they are not an option for first-line treatment for uncomplicated UTIs.

Our study also reported men are at significant risk of developing resistant *E. coli* urinary isolates to TMP/SMX and ciprofloxacin than women. A similar trend was observed in our pediatric study as well as the NAUTICA surveillance study of outpatient UTIs [1,14]. The NAUTICA study reported greater antibiotic resistance to ciprofloxacin, and TMP/SMX among all urinary isolates from US and Canadian male patients. Despite the fact of higher prevalence of UTIs among women due to their anatomic and physiologic factors, the etiology of men being more prone to have antibiotic resistance *E. coli* isolates was not clearly understood. One likely explanation could be men are likely to present with complicated UTIs hence more at risk of developing antimicrobial resistant pathogens. In addition to patient age, gender, and race, we found a strong association and trend in developing TMP/SMX and ciprofloxacin resistant isolates with increasing frequency of UTI infections and number of antibiotic prescriptions filled in last 6 months. Ciprofloxacin resistant risk increased exponentially for patients who had > 4 UTIs or had > 5 antibiotic prescriptions in last 6 months. Patients' age, severity of illness, history of multiple hospitalizations, uropathological disorders, comorbidities including obesity, and diabetes are potential explanations for developing such resistance [1,3,6,7].

Studies have been equivocal in finding the role of diabetes as independent risk factors for *E. coli* resistance isolates, particularly in ambulatory care settings [22-24]. In our study diabetes remained strong risk factors for TMP/SMX (*OR* = 1.39; *P* < 0.001), and ciprofloxacin (*OR* = 2.03; *P* < 0.0001) even when urinary isolates were excluded for patients who were admitted in hospital from ambulatory care clinics and ED. Advanced age, poor compliance, frequent infections leading to more use of antibiotics, and hospitalization could be some of the mechanisms by which this subgroup of population acquires resistant uropathogens.

Unlike other studies, our study also found a significant association between increasing antimicrobial trend in resistance to TMP/SMX and ciprofloxacin with obesity. The data clearly indicates the ordinal increase in risk of developing resistance when BMI goes over 25. In particular, the risk was found to be significantly high for ampicillin and ciprofloxacin. A complex relationship has been suggested in literature among dietary habit, use of frequent antimicrobials leading to change in gut flora which ultimately contributes to increasing the risk of developing obesity later in life [25-28]. Although the actual causality and the temporal associations among these variables remain to be elucidated, repeated or early exposure of antibiotics might be playing a critical role in modulation of intestinal microbes which in turn influence host metabolism and lead to fat accumulation.

Contrasting surveillance data provides a snap shot of antimicrobial susceptibility patterns of different geographical locations; the current study strength is that it is uniquely able to examine the relationship of demographical and clinical variables as risk factors against antimicrobials at an individual level. Patient age, gender, race, previous history of UTIs, number of antibiotic prescriptions in the last 6 months, and comorbidities, such as obesity and diabetes, are found to be independent risk factors for antimicrobial resistance to urinary *E. coli* infections. The study was also able to evaluate the resistant and concurrent resistant patterns of different antimicrobials at outpatient community settings. All urinary samples were analyzed in one central location and the laboratory data was merged with an electronic clinical dataset which was later validated systematically with individual patients' medical records.

The results of our investigation, however, must be interpreted in light of the following considerations. When a narrower spectrum agent would suffice, empiric broad spectrum antibiotic selection, without routine urine cultures, are common health care practice for patients with uncomplicated UTI. Hence, there is a potential for overestimating the resistance rates in the community by selectively ordering urine cultures for patients whose UTIs are either serious, recurrent, not responding to empiric therapy, or requiring hospitalization. Despite our efforts in collaborating urinary isolates data systematically with patient demographics and clinical history, certain family history such as history of hospitalization or antimicrobial use in a family member, contact with pets and livestock, having a child in daycare, and dietary habits information are deficient. While the study results are useful to our health care practitioners at the local level, caution must be made for its applicability to other geographic areas.

In summary, our study demonstrates the importance of monitoring TMP/SMX, ciprofloxacin, and nitrofurantoin susceptibility patterns and the association of MDR phenotypes in *E. coli* urinary isolates. Because the emergence of resistance to ciprofloxacin and its propensity of inducing co-resistance to nitrofurantoin, and TMP/SMX phenotypes, the use of ciprofloxacin should be discouraged as it will undermine the efficacy in treating more serious infections. Alternative antimicrobials, such as nitrofurantoin which is narrow in coverage and mostly stays in urinary tract, should be preferred in the treatment of TMP/SMX-resistant UTIs (exceeds 20%). Further longitudinal studies are warranted to identify

specific risk factors and virulence of organisms at broader geographic locations for better understanding of the potential forces that trigger the resistance. Meanwhile, a multidisciplinary, educational partnership incorporating patients, health care providers, and local leaders are recommended at community and national levels to promote judicious use of antimicrobials in order to prolong the clinical effectiveness of existing agents.

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Declaration of Conflicting Interests

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

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