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Prevalence and risk factors for trimethoprim–sulfamethoxazole-resistant *Escherichia coli* among women with acute uncomplicated urinary tract infection in a developing country

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SUMMARY

Background: Prospective studies from developing countries that have investigated risk factors for trimethoprim–sulfamethoxazole (TMP–SMX)-resistant *Escherichia coli* in women with uncomplicated urinary tract infection (UTI) remain scarce.

Methods: Women with acute uncomplicated UTI were enrolled prospectively. Urine was sent for antimicrobial susceptibility testing. Logistic regression analysis was used to identify risk factors for TMP–SMX resistance.

Results: Of 405 participants, 229 (56.5%) had bacteriuria (mean age 31.9 ± 9.5 years). In the previous 12 months, 77 (33.6%) had experienced at least one UTI episode and 106 (46.3%) reported antimicrobial use. The most common uropathogens were *E. coli* (75.8%) and *Staphylococcus saprophyticus* (8.9%). For the 179 *E. coli*, resistance rates were highest for ampicillin (64.3%) and TMP–SMX (41.3%). Resistance to cephalosporins, nitrofurantoin, and fluoroquinolones was much lower compared with the hospital laboratory-based surveillance data. Risk factors for TMP–SMX resistance were UTI in the last 6 months (odds ratio 2.22; $p = 0.04$) and the number of UTI episodes in the past year (odds ratio 2.06; $p = 0.004$). The number of UTI episodes (adjusted odds ratio 2.21; $p = 0.02$) remained significant on multivariate analysis.

Conclusions: TMP–SMX resistance was high. Number of previous UTI episodes was associated with increased risk of resistance; prior antimicrobial use was not. Hospital antibiograms should be used with caution when treating uncomplicated UTI.

1. Introduction

Urinary tract infection (UTI) remains one of the most common clinical entities necessitating antimicrobial therapy. The emergence and spread of drug-resistant uropathogens, particularly *Escherichia coli*, even among community-acquired UTI, has limited treatment choices.[1–3] This is of particular concern in developing countries where the capacity for resistance surveillance and access to healthcare are limited and over-the-counter drug purchase is rampant in the community.[4–6]

International surveillance reports of increasing resistance rates of community-acquired *E. coli* to trimethoprim–sulfamethoxazole (TMP–SMX), fluoroquinolones (FQs), and other frequently used drugs for the treatment of UTI are mostly derived from the laboratory- and hospital-based collection of urinary isolates.[7–9] The degree to which these rates reflect prevalence in the community is unknown. Additionally, reported risk factors for resistance among truly community-acquired uropathogens are limited to settings in the developed world.[10–16] The dearth of such information, particularly from Asian developing countries, is alarming in light of the emergence of highly drug-resistant community-associated strains in the region.[4,5,17]

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This study was conducted to prospectively determine the resistance rates of *E. coli* isolated from women with uncomplicated UTI in the Philippines and to compare these with data from parallel laboratory-based surveillance. It was further aimed to identify specific risk factors as independent predictors for resistance to TMP–SMX and other antimicrobials among this population.

2. Methods

2.1. Study site and participants

The Medical City is a 600-bed private, tertiary care teaching hospital in urban Metro Manila, with an estimated catchment population of more than two million. Each year approximately 37 600 patients are admitted to the hospital and more than 100 000 outpatient visits are recorded. UTI is among the 10 leading reasons for ambulatory consultation and hospital admission. The majority of adult patients are middle to upper class professionals and their family members, who use third party payer schemes through health maintenance organizations, or have private or government health insurance.

Women aged ≥18 years presenting to the emergency department or outpatient clinics or admitted to the hospital with dysuria, frequency, or urgency of less than 7 days duration, with or without fever and flank pain, were enrolled prospectively from July 2010 to October 2011. Exclusion criteria were pregnancy, diabetes, known anatomical or functional urologic abnormalities, urinary tract instrumentation, and immunosuppression. Patients were included only once in the study. All participants provided written informed consent and the hospital ethics committee approved the study (IRB Registry No. GCS IM 2010-030). The study was conducted in accordance with the Declaration of Helsinki and patient confidentiality was ensured.

Patients were interviewed at enrolment using a standardized form. Demographic and clinical data were collected, including potential risk factors for drug resistance such as a history of any antimicrobial use (excluding use for incident UTI), prior episodes of UTI, hospitalization within the past year, and use of contraception. Treatment decisions were left to the discretion of the attending physician who had access to the laboratory data.

2.2. Microbiological examinations

Midstream, clean-catch urine samples were sent to the laboratory for standard urinalysis and culture. Bacterial growth of $\geq 10^4$ CFU/ml urine was considered positive. Susceptibility testing was performed using the Vitek 2 system (bioMérieux). Minimum inhibitory concentration (MIC) breakpoints and quality control protocols were based on the Clinical and Laboratory Standards Institute (CLSI) recommendations.[18] Intermediate and resistant strains were categorized together as resistant. Less than 1% of the resistant strains demonstrated intermediate susceptibility. Extended-spectrum β-lactamase (ESBL) strains were detected phenotypically in accordance with the CSLI recommendations.

The hospital's continuous surveillance program monitors and reports rates of resistance of various sentinel pathogens among which are urine *E. coli*. Surveillance data on resistance rates of urine *E. coli* isolates from ambulatory patients during the study period were compared with *E. coli* resistance rates in the isolates from women enrolled in the study.

2.3. Statistical analyses

Data were analysed using Stata Statistical Software, version 12.0 (StataCorp., College Station, TX, USA). Descriptive statistics were used to summarize patient characteristics and the prevalence of antimicrobial resistance. Univariate and multivariate analyses for putative risk factors for TMP–SMX-resistant *E. coli* were conducted. Variables with $p < 0.10$ on univariate analysis were included in the multivariate analysis. The level of significance was set at $p < 0.05$, using two-sided comparisons. Risk factors included age, history or presence of fever and hospitalization for incident UTI, prior antimicrobial use within 3 and 12 months (excluding use for the incident UTI), and history and number of UTI episodes in the past 6 and 12 months.

3. Results

Of 405 patients enrolled, 229 (56.5%) had growth on urine culture ($\geq 10^4$ CFU/ml). Only 11 (4.8%) of them had taken an antimicrobial for the incident UTI prior to consultation compared to 28 (15.9%) of those who had no growth on urine culture.

The mean age of the 229 patients with positive urine cultures was 31.9 ± 9.5 years. Twenty (8.7%) were hospitalized for the incident UTI and 68 (29.7%) were febrile or had a history of fever. Seventy-seven (33.6%) had experienced a UTI in the previous 12 months; 33 (42.8%) of these UTI episodes occurred within 3 months prior to consultation and 15 (19.5%) within 3 to 6 months prior to consultation. Fifteen patients (5%) had experienced more than one UTI episode in the past year; only five had had at least three preceding UTI episodes. Almost half (106, 46.3%) reported antimicrobial use in the past year; 51 (22.3%) had taken an antimicrobial for prior UTI. Antimicrobials previously taken were predominantly β-lactams (38.2%), followed by FQs (19.5%) and TMP–SMX (6.3%); 26.6% could not recall the specific antimicrobial class. Data regarding the time elapsed between prior antimicrobial use for any indication and the incident UTI episode were available for 83 of the 106 patients; 43 (18.8%) reported intake in the preceding 3 months. The duration of antimicrobial use could not be obtained. A history of prior hospitalization in the previous year was practically nil. Of the 229 patients, 28 (12.2%) had used an oral contraceptive; no patients had used spermicides or intrauterine devices.

Of 229 patients with growth on culture, six had mixed pathogens. The most common organisms isolated were *E. coli* (76.2%), *Staphylococcus saprophyticus* (8.9%), and *Klebsiella pneumoniae* (3.4%) (Table 1). Four samples (2%) with ≥10 000 CFU/ml of coagulase-negative staphylococci as pure growth ($n = 3$) or mixed with *S. saprophyticus* ($n = 1$), with significant pyuria (>5/high-power field), were considered to have true pathogens. The

Table 1
Pathogens in acute uncomplicated urinary tract infection[a]

	Number ($n = 235$)	Percent (%)
Pathogen		
Gram-negative		
Escherichia coli	179	76.2
Klebsiella pneumoniae	8	3.4
Enterobacter aerogenes	4	1.7
Citrobacter	3	1.3
Proteus mirabilis	3	1.3
Edwardsiella tarda	1	0.4
Gram-positive		
Staphylococcus saprophyticus	21	8.9
Staphylococcus aureus	7	3.0
Streptococcus agalactiae	3	1.3
Staphylococcus hominis	2	0.9
Enterococcus faecalis	2	0.9
Staphylococcus haemolyticus	1	0.4
Staphylococcus warneri	1	0.4

[a] Six patients had mixed infections: *S. hominis* and *S. saprophyticus*; *K. pneumoniae* and *E. faecalis*; *E. coli* and *S. saprophyticus*; *S. saprophyticus* and *S. aureus*; *E. coli* and *K. pneumoniae*; and *E. faecalis* and *S. aureus*.