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Madeline DeMarsh
Department of Pharmacy, Prisma Health Richland

P Brandon Bookstaver
University of South Carolina - Columbia, bookstaver@cop.sc.edu

Caroline Gordon
University of South Carolina - Columbia

Juanne Lim
University of South Carolina - Columbia

Nicole Griffith
University of South Carolina - Columbia

See next page for additional authors

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Prediction of trimethoprim/sulfamethoxazole resistance in community-onset urinary tract infections☆

Madeline DeMarsh[a,1], P. Brandon Bookstaver[a,b], Caroline Gordon[b], Juanne Lim[b,2], Nicole Griffith[b,3], Nicole K. Bookstaver[a], Julie Ann Justo[a,b], Joseph Kohn[a], Majdi N. Al-Hasan[c,d,*], the Prisma Health Antimicrobial Stewardship Support Team (PHASST)

[a] Department of Pharmacy, Prisma Health Richland, Columbia, SC, USA
[b] Department of Clinical Pharmacy & Outcomes Sciences, University of South Carolina College of Pharmacy, Columbia, SC, USA
[c] University of South Carolina School of Medicine, Columbia, SC, USA
[d] Department of Medicine, Division of Infectious Diseases, Prisma Health University of South Carolina Medical Group, Columbia, SC, USA

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ABSTRACT

Objectives: This study aimed to predict trimethoprim/sulfamethoxazole (SXT) resistance in patients with community-onset urinary tract infection (UTI) due to Enterobacteriaceae based on patient-specific risk factors.

Methods: This was a retrospective case–control study in Prisma Health facilities in central South Carolina, USA, including three community hospitals, affiliated emergency departments and ambulatory clinics, including adult patients with community-onset UTI due to Enterobacteriaceae (1 April 2015 to 29 February 2016). Multivariate logistic regression was used to examine risk factors for SXT resistance.

Results: Among 351 unique patients with community-onset UTI, 71 (20.2%) had SXT-resistant Enterobacteriaceae urinary isolates. Overall, median age was 64 years and 252 (71.8%) were female. A multivariate model identified prior urinary infection/colonisation with SXT-resistant Enterobacteriaceae (OR = 8.58, 95% CI 3.92–18.81; $P < 0.001$) and SXT use within past 12 months (OR = 2.58, 95% CI 1.13–5.89; $P = 0.02$) as predictors of SXT resistance among urinary isolates. Most patients with UTI (285; 81.2%) had no risk factors for SXT resistance. SXT resistance rates increased from 13% in the absence of risk factors to 31% in patients with prior SXT use, 66% in those with prior urinary infection/colonisation with SXT-resistant Enterobacteriaceae and 73% in the presence of both risk factors.

Conclusion: SXT resistance in Enterobacteriaceae urinary isolates may be predicted based on prior urine culture results and SXT use within the previous year. Utilisation of a patient-specific antibiogram may allow empirical SXT use in patients with community-onset UTI in the absence of risk factors for resistance.

1. Introduction

Urinary tract infections (UTIs) are among the most commonly encountered infections both in community and hospital settings [1]. Increasing antimicrobial resistance (AMR) rates among *Escherichia coli*, the predominant urinary pathogen, has limited oral antimicrobial treatment options for UTIs [2,3]. Although nitrofurantoin and fosfomycin remain the preferred agents for the treatment of uncomplicated cystitis, their use may be limited in many patients owing to, respectively, low creatinine clearance and concerns for reduced efficacy [4–8]. International management guidelines recommend against the use of trimethoprim/sulfamethoxazole (SXT) in acute cystitis if the resistance rate among local urinary isolates is ≥20% [4]. However, SXT resistance rates

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* Corresponding author at: University of South Carolina School of Medicine, Columbia, SC, USA.
E-mail address: majdi.alhasan@uscmed.sc.edu (M.N. Al-Hasan).
[1] Present address: Department of Pharmacy, Morton Plant Hospital, Clearwater, FL, USA.
[2] Present address: Department of Pharmacy, Novant Health Presbyterian Hospital, Charlotte, NC, USA.
[3] Present address: Department of Pharmacy, University of Virginia Health, Charlottesville, VA, USA.

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among *E. coli* isolates across the USA and most of Europe have exceeded 20% [2,9,10]. Avoiding SXT use in patients with acute cystitis who may not be candidates for nitrofurantoin or fosfomycin therapy owing to either cost or the above clinical concerns may encourage utilisation of broader-spectrum and more toxic antimicrobial agents such as fluoroquinolones and cephalosporins.

Selection of an oral antimicrobial regimen for acute pyelonephritis is an even more complex decision owing to the greater severity of these infections and increasing AMR rates of *E. coli* isolates to all oral agents, including fluoroquinolones, SXT and β-lactams [2,3,9–11].

Several clinical tools for prediction of AMR based on patient-specific risk factors have recently been described in order to improve empirical antimicrobial selection in patients with bacterial infections [12–14]. More specifically, one study proposed the optimisation of ambulatory antimicrobial management of acute pyelonephritis by utilisation of a fluoroquinolone resistance score that predicts the probability of fluoroquinolone resistance based on patient-specific risk factors [15]. None the less, neither this approach nor the international management guidelines offer alternative oral options for treatment of acute pyelonephritis in patients with major risk factors for fluoroquinolone resistance [4,15].

The purpose of this retrospective case–control study was to develop a stratified antibiogram for prediction of SXT resistance among Enterobacteriaceae urinary isolates in patients with community-onset UTI.

2. Materials and methods

2.1. Setting

This study was conducted at Prisma Health inpatient and outpatient facilities in central South Carolina, USA, including three community hospitals, three emergency departments and several affiliated urgent treatment centres and ambulatory clinics. Prisma Health is the largest healthcare provider in the Midlands region of central South Carolina. The study was approved by the Institutional Review Board at Prisma Health, who waived informed consent.

2.2. Definitions

UTI was defined as the presence of urinary symptoms or signs and monomicrobial growth of bacteria in urine culture obtained during the index healthcare visit. Complicated UTI (cUTI) was defined as obstructive uropathy, indwelling urinary catheter, urinary retention due to neurological disease, or bladder outlet obstruction [16,17]. Patients with clinical manifestations of acute pyelonephritis, including temperature >38 °C, unilateral flank pain or costovertebral angle tenderness, were also considered to have cUTI [18]. Prior antimicrobial therapy was defined as using the respective antimicrobial agent or class for >24 h within the past 12 months from collection of the index urine culture. SXT-resistant (SXT-R) Enterobacteriaceae were defined as isolates with a minimum inhibitory concentration (MIC) ≥4/76 μg/mL according to the Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoint [19]. Nitrofurantoin susceptibility was also determined for 340 urinary isolates, with non-susceptible isolates being defined as those with an MIC ≥64 μg/mL [19].

2.3. Case ascertainment

All patients aged ≥18 years with growth of Gram-negative bacilli in urine culture obtained at ambulatory facilities or within 48 h of hospitalisation during the period 1 April 2015 to 29 February 2016 were retrospectively identified through an alert system that interfaced with the central microbiology laboratory at Prisma Health ($n = 1071$). Patients with asymptomatic bacteriuria ($n = 404$), polymicrobial growth of bacteria in urine culture ($n = 202$), growth of a lactose-non-fermenting bacterium in urine culture ($n = 103$) and recurrent episodes of positive urine cultures during the study period ($n = 11$) were excluded from the study. Thus, a total of 351 unique adults with community-onset UTI due to Enterobacteriaceae were included in the analysis. Patient demographics as well as microbiological and clinical data, including potential risk factors for AMR, were collected from the electronic medical records. Prior antimicrobial use was obtained from medication administration records, electronic prescriptions, external prescription records provided by community pharmacies and pharmacy benefit managers, and clinical notes from prior hospitalisations or visits to affiliated hospitals, emergency departments and other ambulatory settings.

2.4. Statistical analysis

Logistic regression was used to examine risk factors for SXT resistance in patients with UTI in a case–control design. Demographic and clinical variables were collected in patients with UTI due to SXT-R (cases) and SXT-susceptible (SXT-S) Enterobacteriaceae (controls). Collected variables included age, sex, ethnicity, diabetes mellitus, cancer, immunocompromised host [e.g. active cancer/receiving chemotherapy, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), solid-organ transplant recipient, documented immunosuppressive therapy], recent hospitalisation within 3 months, residence in a skilled nursing facility, ambulatory gastrointestinal or genitourinary procedure within 1 month, prior UTI or urinary colonisation with SXT-R bacteria within 12 months, and prior antimicrobial use within 12 months. Variables associated with SXT resistance in the univariate logistic regression model with $P < 0.10$ were included in the multivariate logistic regression model to identify independent risk factors for SXT resistance. The odds ratio with 95% confidence interval were reported to demonstrate the strength of association between each risk factor and SXT resistance.

A stratified antibiogram of Enterobacteriaceae urinary isolates based on patient-specific risk factors for SXT resistance was developed to evaluate selection of SXT for empirical antimicrobial therapy in patients with UTI.

JMP Pro v.12.1 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis. The level of significance for statistical testing was defined as $P \leq 0.05$ (two-sided) unless otherwise specified.

3. Results

During the study period, 351 unique patients with UTI due to Enterobacteriaceae were identified and were included in the analysis. Overall, the median age was 64 years, 252 (71.8%) were female and 142 (40.2%) had a cUTI. *Escherichia coli* was the most common urinary isolate (214; 61.0%), followed by *Klebsiella* spp. (53; 15.1%), *Proteus mirabilis* (51; 14.5%), *Enterobacter* spp. (19; 5.4%), *Serratia* spp. (8; 2.3%) and other Enterobacteriaceae (6; 1.7%). Moreover, 71 patients (20.2%) had a UTI due to SXT-R bacteria and the remaining 280 (79.8%) had a UTI due to SXT-S bacteria.

The baseline demographic and clinical characteristics of the patients with community-onset UTI caused by SXT-S and SXT-R bacteria are shown in Table 1. Univariate logistic regression identified immunocompromised status, recent hospitalisation within previous 3 months, prior UTI or urinary colonisation with SXT-R bacteria, and prior use both of SXT and fluoroquinolones

Table 1
Demographic and clinical characteristics of patients with community-onset urinary tract infection and risk factors for trimethoprim/sulfamethoxazole (SXT) resistance in the univariate model.[a]

Characteristic	SXT-R (n = 71)	SXT-S (n = 280)	OR (95% CI)	P-value
Age (years) [median (IQR)]	64 (48–76)	64 (50–80)	0.99 (0.87–1.12)	0.84
Female sex	51 (71.8)	201 (71.8)	1.00 (0.56–1.79)	0.99
Ethnicity				
White	36 (50.7)	115 (41.1)	1.48 (0.88–2.49)	0.14
African-American	32 (45.1)	141 (50.4)		
Other	3 (4.2)	24 (8.6)		
Diabetes mellitus	29 (40.8)	88 (31.4)	1.51 (0.88–2.58)	0.13
Cancer	11 (15.5)	31 (11.1)	1.47 (0.70–3.10)	0.31
Immunocompromised status	10 (14.1)	19 (6.8)	2.24 (0.99–5.07)	0.05
Presence of Foley catheter	10 (14.1)	48 (17.1)	0.79 (0.38–1.66)	0.54
Residence at nursing facility	11 (15.5)	35 (12.5)	1.28 (0.62–2.67)	0.51
Recent hospitalisation[b]	29 (40.8)	70 (25.0)	2.07 (1.20–3.57)	0.009
Recent outpatient procedure[c]	4 (5.6)	8 (2.9)	2.03 (0.59–6.94)	0.26
Prior urinary infection/colonisation with SXT-R bacteria[d]	27 (38.0)	13 (4.6)	12.60 (6.05–26.27)	<0.001
Prior antimicrobial use[d]				
SXT	16 (22.5)	21 (7.5)	3.59 (1.76–7.32)	<0.001
Fluoroquinolones	22 (31.0)	32 (11.4)	3.48 (1.87–6.49)	<0.001
β-Lactams	12 (16.9)	66 (23.6)	0.66 (0.33–1.30)	0.23

SXT-R, SXT-resistant; SXT-S, SXT-susceptible; OR, odds ratio; CI, confidence interval; IQR, interquartile range.
[a] Data are n (%) unless otherwise stated.
[b] Within 3 months of infection.
[c] Within 1 month of infection.
[d] Within 12 months of infection.

within the previous 12 months of collection of the index urine culture as potential risk factors for SXT resistance.

After adjustments in the multivariate logistic regression, prior UTI or urinary colonisation with SXT-R bacteria and prior SXT use were the only two variables that were independently associated with SXT resistance (Table 2).

A stratified antibiogram was developed for Enterobacteriaceae urinary isolates based on the presence or absence of the aforementioned risk factors for SXT resistance. In the majority of patients without risk factors for resistance, the probability of SXT resistance among Enterobacteriaceae urinary isolates was 13%. This probability increased to 73% in patients with both risk factors for SXT resistance (Fig. 1).

Multidrug resistance was present in 82 isolates (23.4%) overall and was more common among SXT-R isolates (40/71; 56.3%) compared with SXT-S isolates (42/280; 15.0%) ($P < 0.001$). When examining nitrofurantoin susceptibility ($n = 340$ isolates), 107 isolates (31.5%) were nitrofurantoin-non-susceptible. Resistance to nitrofurantoin was uncommon among tested *E. coli* strains (10/210; 4.8%). There was no difference in nitrofurantoin resistance rates between SXT-R and SXT-S bacteria [21/68 (30.9%) vs. 86/272 (31.6%)]. However, nitrofurantoin resistance among *E. coli* isolates was more common in SXT-R compared with SXT-S isolates [8/52 (15.4%) vs. 2/158 (1.3%)].

4. Discussion

The study demonstrated that prior urinary infection or colonisation with a SXT-R bacteria and SXT use within the previous year were predictors of bacterial resistance to SXT in patients with community-onset UTI due to Enterobacteriaceae. The association between prior SXT use and resistance is consistent with the results of previous studies [20–24]. However, the finding that prior SXT use may increase the risk of SXT resistance up to 1 year from exposure is unique to the current study. The prolonged impact of SXT on the microbiome and the increased risk of AMR in patients with UTI for up to 1 year from exposure is not necessarily a feature unique to SXT. A recent study demonstrated that fluoroquinolone use increased the risk of cUTI due to fluoroquinolone-resistant bacteria up to 1 year from exposure, with the highest risk of resistance observed in patients who received fluoroquinolones within the past 3 months compared with 3–12 months from the index cUTI [15]. An exploratory analysis of the current study did not demonstrate a difference between timing of prior SXT use (i.e. within past 3 months vs. 3–6 months vs. 6–12 months, etc.) and the odds of SXT resistance, although this analysis may have been underpowered (results not shown). This highlights the importance of collecting prior antimicrobial use in patients with symptoms of UTI prior to making empirical antimicrobial treatment decisions.

The association between prior urinary infection or colonisation with SXT-R bacteria and SXT resistance in patients with UTI is conceivable. A recent study demonstrated that prior urine culture reports were useful in predicting current results in patients with recurrent UTI [25]. Utilisation of prior microbiology data to guide selection of empirical antimicrobial therapy of current infections prior to availability of new culture results has also been described in the setting of various infections [13,14,26].

Application of a patient-specific antibiogram for Enterobacteriaceae urinary isolates in the current study may improve SXT utilisation and antimicrobial management in patients with UTI.

Table 2
Independent risk factors for trimethoprim/sulfamethoxazole (SXT) resistance in the multivariate logistic regression model.

Risk factor	aOR (95% CI)	P-value
Immunocompromised status	1.59 (0.61–4.51)	0.34
Recent hospitalisation within past 3 months	1.14 (0.58–2.22)	0.71
Prior urinary infection/colonisation with SXT-R bacteria within past 12 months	8.58 (3.92–18.81)	<0.001
Prior SXT use within past 12 months	2.58 (1.13–5.89)	0.02
Prior fluoroquinolone use within past 12 months	1.83 (0.84–3.97)	0.13

aOR, adjusted odds ratio; CI, confidence interval; SXT-R, SXT-resistant.

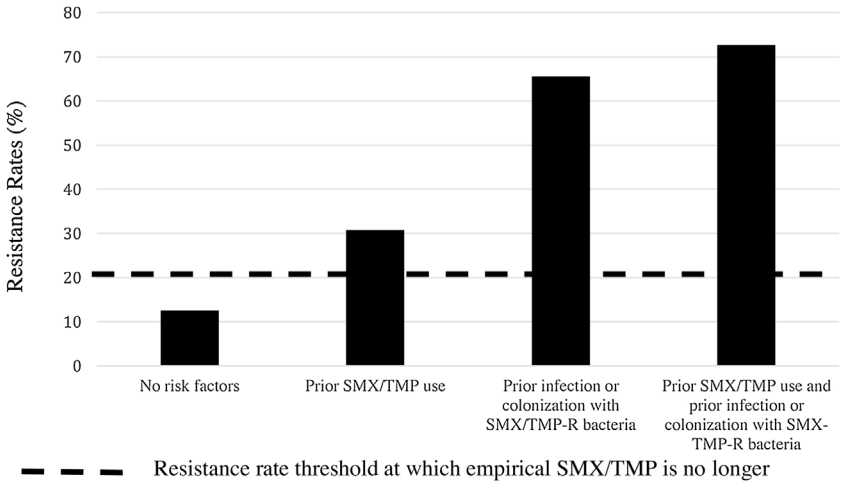

Fig. 1. Resistance rates to trimethoprim/sulfamethoxazole (SMX/TMP) in stratified antibiogram based on patient-specific risk factors.

The probability of SXT resistance was only 13% in the absence of prior urinary cultures for SXT-R bacteria and SXT use within the past year. This preserves SXT as a potential treatment option for acute cystitis in patients without risk factors since the probability of SXT resistance in these patients does not exceed 20% as recommended by the international management guidelines [4]. Although this threshold may seem arbitrary, a recent survey suggested that clinical pharmacists across the USA were comfortable with agents with ≥80% susceptibility when recommending empirical antimicrobial therapy for acute cystitis [27]. The low cost and inclusion of SXT as a preferred antimicrobial agent in most third-party insurers' plans make SXT an attractive option in many patients with acute cystitis. Moreover, this allows SXT use in patients who may not be ideal candidates for nitrofurantoin or fosfomycin therapy owing to low creatinine clearance, documented resistance in prior urine cultures or recent use of both agents.

The results of the current study also have clinical implications for patients with acute pyelonephritis in ambulatory settings. A recent study demonstrated that the probability of fluoroquinolone resistance exceeded 50% in patients who used fluoroquinolones within the past 3 months and exceeded 30% if fluoroquinolones were used within the past 3–12 months [15]. Based on the current results, SXT may be a better empirical option than fluoroquinolones in these patients if they did not use SXT and did not have prior UTI or urinary colonisation with SXT-R bacteria within the past year. However, since the probability of SXT resistance still exceeds 10% even in the absence of risk factors, patients with pyelonephritis should receive one injection of ceftriaxone prior to empirical SXT therapy [4].

In the era of increasing AMR, selection of empirical antimicrobial therapy based on overall antibiogram data has become incredibly challenging. A patient-specific antibiogram that predicts the probability of AMR in each individual based on their own risk factors may improve empirical antimicrobial selection in patients with bacterial infections. The current study adds one more clinical tool for prediction of AMR in patients with UTI.

This study has several limitations. First, it shares common limitations of retrospective studies of missing undocumented variables in electronic medical records or from hospitals outside of the health system, and potentially failing to adjust for unknown confounders. Second, the patient sample may have been biased to a higher acuity population, as many of the patients were seeking care at the emergency department. Approximately 30% of the patients had a previous hospitalisation in the past 3 months, which may have increased the likelihood of hospital-acquired bacteria. However, hospitalisation alone without the receipt of antibiotics is less likely to drive resistance. In addition, the study includes patients from multiple facilities within the same healthcare system in one geographic location. Multicentre studies may offer a broader scale of microbiology and patient populations. External validation of this SXT resistance tool may increase the generalisability of the current study results.

In summary, SXT remains an important option for treatment of community-onset cystitis and pyelonephritis. Stratification of patients with UTI based on the probability of SXT resistance allows using this antimicrobial agent in patients with a low probability of resistance, such as those without prior urinary infection/colonisation with SXT-R bacteria or SXT use in the previous year. This allows the expansion of oral antimicrobial treatment options for acute cystitis and pyelonephritis, which is particularly helpful in patients who may not be eligible for treatment with first-line agents.

Competing interests

PBB has been an advisory board member for CutisPharma and Melinta Therapeutics, has served on the speaker's bureau for Melinta Therapeutics and has been a research advisor for Synthetic Biologics; NKB has been an advisory board member for CutisPharma. All other authors declare no competing interests.

Ethical approval

The study was approved by the Institutional Review Board at Prisma Health, who waived informed consent.

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