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A Seven-Day Course of Trimethoprim-Sulfamethoxazole May Be as Effective as a Seven-Day Course of Ciprofloxacin for the Treatment of Pyelonephritis

Miriam T. Fox,
The Johns Hopkins University School of Medicine, Department of Medicine

Michael T. Melia, MD,
The Johns Hopkins University School of Medicine, Department of Medicine, Division of Infectious Diseases

Rebecca G. Same, MD,
The Johns Hopkins University School of Medicine, Department of Pediatrics

Anna T. Conley, BA, and
The University of Maryland School of Medicine, Department of Medicine

Pranita D. Tamma, MD, MHS
The Johns Hopkins University School of Medicine, Department of Pediatrics, Division of Pediatric Infectious Diseases, 200 North Wolfe Street, Suite 3149, Baltimore, MD 21087, Tel (410) 614-1491

Abstract

Introduction—The Infectious Diseases Society of America guidelines recommend either 14 days of trimethoprim-sulfamethoxazole (TMP-SMX) or 7 days of ciprofloxacin for the treatment of pyelonephritis. Antibiotic courses of 7 days of TMP-SMX versus 7 days of ciprofloxacin for pyelonephritis have not been previously compared. We evaluated the odds of a subsequent, symptomatic urinary tract infection (UTI) for women with *E. coli* pyelonephritis receiving a 7-day course of TMP-SMX versus a 7-day course of ciprofloxacin.

Methods—Women ages 16 and older with *Escherichia coli* pyelonephritis presenting to 5 healthcare facilities in the greater Maryland area between 2010 and 2016 receiving either TMP-SMX or ciprofloxacin were included. Patients were excluded if they met any of the following criteria: (a) pregnancy, (b) dialysis dependency, (c) *E. coli* not susceptible to the treatment prescribed, (d) polymicrobial urine culture, or (e) greater than 48 hours of antibiotic therapy other than TMP-SMX or ciprofloxacin.

Results—Of 272 women meeting eligibility criteria, 81 (30%) and 191 (70%) received 7 days of TMP-SMX and 7 days of ciprofloxacin, respectively. In an adjusted model, the likelihood of a recurrent UTI within 30 days for the TMP-SMX and ciprofloxacin groups was similar (aOR: 2.30, 95% confidence interval: 0.72–7.42).

Correspondence to: Pranita D. Tamma.

None of the authors report any conflicts of interest.

Conclusions—Our findings suggest that 7 days of TMP-SMX therapy may result in similar clinical outcomes compared with 7 days of ciprofloxacin for the treatment of pyelonephritis. Considering the frequency of pyelonephritis and risks of antibiotic resistance and associated toxicities, decreasing the duration of antibiotic therapy for pyelonephritis may impact a large number of women.

Keywords

UTI; urine; *E. coli*; antibiotics; infection

Introduction

There are over 250,000 cases of pyelonephritis in the United States each year, resulting in direct and indirect costs approximating 2.1 billion US dollars per year [1,2]. Pyelonephritis is one of the most common reasons women visit emergency departments or ambulatory care clinics, frequently resulting in hospitalization [3,4].

The Infectious Diseases Society of America (IDSA) guidelines recommend treating pyelonephritis with either 14 days of oral trimethoprim-sulfamethoxazole (TMP-SMX) or 7 days of oral ciprofloxacin based on a randomized controlled trial that showed equivalence between these two regimens, when the causative pathogen was susceptible to these agents [5,6]. Data comparing the efficacy of a 7-day TMP-SMX regimen and a 7-day regimen of ciprofloxacin are lacking. If 7 days of TMP-SMX were to produce equivalent clinical outcomes to 7 days of ciprofloxacin, this shorter duration of therapy could have the potential to reduce TMP-SMX-associated adverse drug reactions, the emergence of antibiotic resistant organisms, and healthcare costs, while improving patient satisfaction. Our objective was to compare the odds of subsequent symptomatic urinary tract infections (UTIs) for women with pyelonephritis treated with a 7-day course of TMP-SMX versus a 7-day course of ciprofloxacin.

Methods

This was a multicenter, retrospective study of women at least 16 years of age who presented to the Johns Hopkins Hospital, Bayview Medical Center, Sibley Memorial Hospital, Howard County General Hospital, Suburban Hospital or their affiliated ambulatory care practices with *Escherichia coli* pyelonephritis between 2010 and 2016. Pyelonephritis was defined as the presence of fever (temperature ≥39°C), rigors, or costovertebral angle tenderness in addition to pyuria (>10 white blood cells/high powered field [WBC/hpf]) and ≥100,000 colony forming units per milliliter (CFU/mL) of *E. coli* in the urine.

The primary exposure was 7 days of TMP-SMX or 7 days of ciprofloxacin (± 2 days). Patients were excluded if they met any of the following criteria: (a) pregnancy, (b) dialysis dependency, (c) *E. coli* not susceptible to the treatment prescribed, (d) polymicrobial urine culture, or (e) greater than 48 hours of antibiotic therapy prior to conversion to TMP-SMX or ciprofloxacin. The primary outcome was a subsequent, symptomatic UTI (cystitis or pyelonephritis) with ≥100,000 CFU *E. coli* within 30 days of initiation of antibiotic therapy.

Cystitis was defined as dysuria, urgency, frequency, or suprapubic pain with pyuria (>10 WBC/hpf) and ≥100,000 CFU/mL of *E. coli*.

Demographic data, pre-existing medical conditions, hospital or ICU admission, microbiological data, treatment data, and outcomes were collected by electronic medical chart review. The EPIC Care Everywhere Network, which includes several hundred hospital networks nationwide (https://www.epic.com/CareEverywhere/) was used to determine whether patients presented to outside ambulatory care or acute care facilities with recurrent UTI symptoms subsequent to their initial pyelonephritis presentation. This study was approved by the Johns Hopkins University School of Medicine Institutional Review Board, with a waiver of informed consent.

Baseline categorical data were compared using Pearson χ^2 or Fisher's exact test, as appropriate. Continuous data were evaluated using the Wilcoxon rank-sum test. Unadjusted odds ratios and 95% confidence intervals were calculated for the analysis of a recurrent UTI within 30 days. Variables which changed the point estimate of the association between 7-days of TMP-SMX and UTI recurrence by at least 10% were included in a multivariable model. Statistical significance was defined as p-value <0.05. Statistical analysis was completed using STATA version 13.0.

Results

There were 272 women with pyelonephritis who met eligibility criteria. Of these, 81 patients (30%) received 7 days of TMP-SMX and 191 patients (70%) received 7 days of ciprofloxacin. Both groups were generally similar with respect to baseline characteristics (Table 1). Although the majority of women were otherwise healthy, the most common pre-existing condition in both groups was diabetes mellitus.

Fewer women in the TMP-SMX group had concomitant *E. coli* bloodstream infections (9% vs. 21%; p<0.01) or were hospitalized (22% vs. 36%; p=0.01). Overall, 43% of patients received intravenous (IV) antibiotics on day 1 and 57% received oral antibiotics on day 1 of therapy (Table 2). For women receiving TMP-SMX, 86% were infected with *E. coli* susceptible to ciprofloxacin. For women receiving ciprofloxacin, 69% were infected with *E. coli* susceptible to TMP-SMX.

There were 6 (7%) patients in the TMP-SMX group and 12 (6%) patients in the ciprofloxacin group with symptomatic UTIs within 30 days of starting antibiotic therapy; odds ratio (OR) 1.19 (95% CI 0.43–3.30). Adjustment for hospitalization and concomitant *E. coli* bloodstream infections yielded an aOR of 2.30 (95% CI 0.71–7.42). Two patients in the ciprofloxacin group developed *Clostridium difficile* infections at 7 days and 9 days, respectively, after initiating antibiotic therapy and both were readmitted to an acute care facility. One patient in the TMP-SMX group developed a pruritic rash after receiving 5 days of TMP-SMX.

Discussion

Our findings suggest that a 7-day course of TMP-SMX may be as effective as a 7-day course of ciprofloxacin for women with *E. coli* pyelonephritis. Previous data suggest that 14 days of TMP-SMX yielded similar outcomes to 7 days of ciprofloxacin, if the pathogen was susceptible *in vitro*, but a comparison of 7 days of each regimens for pyelonephritis has not been conducted [6]. Unlike the previous study [6], we included women with a variety of medical concerns in our analysis such as those with diabetes, immunocompromising conditions, urologic abnormalities, and severe sepsis. Clinicians appear more likely to prescribe ciprofloxacin to women requiring hospitalization or those with concomitant *E. coli* bloodstream infections, but even after adjustment for these variables, no differences in the outcomes between the groups was observed.

Considering the incidence of pyelonephritis, decreasing the length of antibiotic therapy could have widespread implications beyond simply reducing antibiotic use. Every additional day of antibiotics prescribed has been associated with an increased risk of *C. difficile* infections, adverse drug events, and antibiotic resistance. The prevalence of resistance to both TMP-SMX and ciprofloxacin in uropathogens continues to rise globally [7,8]. Reducing the duration of TMP-SMX treatment may help slow the development of resistance to this agent. In addition, shorter antibiotic regimens decrease healthcare costs and may increase patient compliance and satisfaction with medical care. Furthermore, a 7-day course of TMP-SMX provides an attractive alternative to fluoroquinolone therapy, which has been associated with a high risk of community-acquired *C. difficile* infections, amongst other negative sequelae [9]. In July 2016, the US Food and Drug Administration disseminated the results of a safety review outlining the association between fluoroquinolones and a number of disabling side effects involving tendons, muscles, nerves, and the central nervous system [10]. Although fluoroquinolones have an excellent track-record for treating UTIs, providing an alternative antibiotic for the same duration of therapy may prevent some of these potentially incapacitating side effects, particularly in high-risk populations.

There are several limitations to our study. First, as this was an observational study, it is possible that there were important differences influencing the decision to prescribe TMP-SMX or ciprofloxacin that we failed to consider in our analysis. Additionally, our sample size may have precluded the ability to effectively evaluate for differences in adverse events between the groups. Third, despite our best attempt to capture subsequent symptomatic UTIs across health networks in the Epic Care Everywhere network, we were not able to capture visits to primary care physicians, urgent care centers, and emergency rooms that do not use the Epic system. To our knowledge, however, missing data should have similarly impacted both groups.

Despite the limitations of this study, our findings suggest that a 7-day course of TMP-SMX may produce equivalent clinical outcomes to a 7-day course of ciprofloxacin for women with pyelonephritis and provide support for re-evaluation of the recommended 14-day regimen of TMP-SMX. A randomized controlled trial comparing outcomes associated with these two regimens would be helpful to validate our findings. With the large number of pyelonephritis cases annually, a 50% reduction in the duration of antibiotic treatment could

result in an important decrease in antibiotic use and the downstream effects associated with antibiotic overuse.

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Table 1

Baseline Characteristics of 272 Women with *Escherichia coli* Pyelonephritis Treated with 7 Days of Trimethoprim-Sulfamethoxazole (TMP-SMX) versus 7 Days of Ciprofloxacin from 2010 to 2016

Variable	TMP-SMX (n=81; 30%)	Ciprofloxacin (n=191; 70%)	p-value
Age (median, IQR)	37 (29–48)	41 (26–59)	0.33
Race/Ethnicity			
Caucasian	36 (43%)	77 (40%)	1.00
African American	37 (46%)	80 (42%)	0.59
Latino	2 (2%)	8 (4%)	0.73
Asian/Pacific Islander	2 (2%)	13 (7%)	0.24
Multiracial/Unknown	6 (7%)	13 (7%)	0.80
Pre-existing conditions			
Diabetes	12 (15%)	30 (16%)	1.00
Human immunodeficiency virus	2 (2%)	6 (3%)	1.00
Chemotherapy in past 6 months	1 (1%)	4 (2%)	1.00
Renal transplant	1 (1%)	4 (2%)	1.00
End-stage liver disease	1 (1%)	4 (2%)	1.00
Immunomodulators within the past 30 days	2 (2%)	11 (6%)	1.00
Indwelling or intermittent urinary catheterization	2 (2%)	6 (3%)	1.00
Serum creatinine on day of positive urine culture (median, IQR)	1 (0.7–1)	1 (0.8–1)	0.22
Escherichia coli bacteremia	7 (9%)	40 (21%)	<0.01
Hospitalized	18 (22%)	69 (36%)	0.01
Extended spectrum beta-lactamase producing *E. coli*	3 (4%)	4 (2%)	0.43

Table 2

Antibiotics Prescribed on Day One of Therapy for 272 Women with Pyelonephritis

Antibiotic Prescribed on Day 1	Final Antibiotic: TMP-SMX (n=81)	Final Antibiotic: ciprofloxacin (n=191)
Ceftriaxone	19 (24%)	53 (28%)
Ciprofloxacin	0	105 (55%)
Trimethoprim-sulfamethoxazole	57 (70%)	0
Piperacillin-tazobactam	1 (1%)	4 (2%)
Cefepime	4 (5%)	19 (10%)
Aztreonam	0	10 (5%)