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BRIEF REPORT

Epidemiology of Complicated Urinary Tract Infections due to Enterobacterales Among Adult Patients Presenting in Emergency Departments Across the United States

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In this multicenter study of adult patients who presented to the emergency department with an Enterobacterales complicated urinary tract infection (cUTI), high rates of resistance and co-resistance to commonly used oral antibiotics (fluoroquinolones, trimethoprim-sulfamethoxazole, nitrofurantoin, and third-generation cephalosporins) were observed.

Keywords. cUTI; epidemiology; resistance; urinary tract infection.

Complicated urinary tract infections (cUTI), which includes include cystitis (infection of the bladder/lower urinary tract) and pyelonephritis (infection of the kidney/upper urinary tract), are one of the most common bacterial infections encountered in the community and hospital setting and are associated with considerable morbidity and healthcare resource utilization [1–3]. A recent United States (US)–based cohort study indicated that there are 3 million newly diagnosed cUTIs annually among adults, resulting in 30-day healthcare costs in excess of 6 billion US dollars [4]. Fluoroquinolone and trimethoprim-sulfamethoxazole (TMP-SMX) have long been oral mainstay treatments for cUTIs but their use has been compromised by resistance among Enterobacterales [3, 5–10]. Resistance rates among common uropathogens remain lower for the oral β-lactams relative to the fluoroquinolones and TMP-SMX, but data indicate that the prevalence of community-acquired extended-spectrum β-lactamase–producing gram-negative urinary tract infections (UTIs) has sharply increased in recent years [8, 11]. Nitrofurantoin still remains highly active against *Escherichia coli* but it has limited microbiologic activity against other Enterobacterales and its use is restricted to cUTIs that only involve the lower genitourinary tract [9, 12]. This study sought to quantify the prevalence of resistance to the commonly used oral cUTI agents across US regions and co-resistance rates among adult patients who presented to the emergency department (ED) with an Enterobacterales cUTI.

METHODS

A retrospective multicenter analysis using data from the Premier Healthcare Database [13] was performed among adult cUTI patients from 2013 through 2018 who presented to the ED for their care. Patients presenting to the ED were included if they (1) were aged ≥18 years; (2) had a cUTI diagnosis based on previously published cUTI diagnostic code identification algorithms (Supplementary Appendix *A*) [14–16]; (3) had a positive blood or urine culture for an Enterobacterales between index ED/hospital days −5 to +2; and (4) were not a transfer patient transferred from another acute care facility. Patients meeting all study criteria were classified as "ED only" if they were discharged from the ED without a hospital admission or "inpatient" if admitted to the hospital. Because this study utilized already existing Health Insurance Portability and Accountability Act of 1996 (HIPAA)–compliant fully de-identified data, it was exempt from institutional review board review [13].

Hospital- and Patient-Level Covariates

Hospital-level covariates included US census regions, hospital size, teaching status, and location (urban vs rural). Demographics and baseline covariates at ED presentation included age, sex, race, admission source, Charlson Comorbidity Index and individual conditions [17], and baseline Enterobacterales. Susceptibility testing was performed at the local hospitals and presence of resistance to fluoroquinolones, TMP-SMX, nitrofurantoin, and third-generation cephalosporins (resistance to any 1 of the following: ceftibuten, cefixime, ceftriaxone, cefditoren, cefotaxime, ceftizoxime, cefpodoxime, cefoperazone, cefdinir, and ceftazidime) was recorded for each Enterobacterales among unique patients with the infecting pathogen. Antibiotic resistance was defined as the presence of resistant or intermediate susceptibility results. For patients with multiple urine or blood cultures, determination of resistance for each antibiotic was based on

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presence of at least 1 intermediate or resistant susceptibility result on any recovered Enterobacterales isolate(s). Patients with missing nitrofurantoin susceptibility data for *Proteus mirabilis*, *Providencia* sp, *Serratia marcescens*, *Morganella morganii*, *Proteus* sp, and *Serratia* sp were all classified as nitrofurantoin resistant due to its lack of in vitro activity against these pathogens [18].

Statistical Methods

Resistance to fluoroquinolones, TMP-SMX, nitrofurantoin, and third-generation cephalosporins for each Enterobacterales was reported among the unique number of cUTI patients with that pathogen. Within each cohort and US census region, the overall proportion of patients with resistance to fluoroquinolones, TMP-SMX, nitrofurantoin, and third-generation cephalosporins resistance was determined. The percentage of patients with resistant to 0, 1, 2, or ≥3 antibiotic classes was also quantified in each patient cohort and US census region. Co-resistance rates to fluoroquinolones, TMP-SMX, nitrofurantoin, and third-generation cephalosporins were determined overall and by study cohort. The χ^2 test was used for all statistical comparisons of categorical variables. We used the *t* test to compare means and the Mann-Whitney test to compare medians. All analyses were conducted using Stata/MP 15.1 for Windows software (StataCorp LLC, College Station, Texas).

RESULTS

Cohort derivation is shown in Supplementary Figure 1. There were 60 006 in the ED only cohort and 86 743 in the inpatient cohort. Hospital-level characteristics, demographics, and baseline covariates by admission status are shown in Supplementary Table 1. The ED only cohort were younger, less likely to be male, had fewer baseline comorbid conditions, and were less likely to be transferred from a non–acute care long-term care facility than the inpatient cohort. Across

Table 1. Resistance to Fluoroquinolones, Trimethoprim-Sulfamethoxazole, Nitrofurantoin, and Third-Generation Cephalosporins for Each Enterobacterales Among Patients With Complicated Urinary Tract Infection, by Hospital Admission Status

Organism	No. of Patients	FQ Resistance	TMP-SMX Resistance	NTF Resistance	Third-Generation Cephalosporin Resistance
ED only organisms					
Klebsiella pneumoniae	5281	7.0%	11.2%	59.9%	6.2%
Proteus mirabilis	3338	31.7%	25.3%	99.9%	4.7%
Escherichia coli	48 357	16.4%	27.8%	3.4%	5.0%
Enterobacter cloacae	896	8.5%	14.8%	65.2%	22.8%
Providencia sp	475	41.1%	19.4%	78.5%	10.5%
Serratia marcescens	390	7.2%	4.1%	100.0%	9.0%
Morganella morganii	375	40.5%	36.3%	100.0%	15.2%
Enterobacter aerogenes	819	2.0%	1.6%	82.5%	12.9%
Proteus spp	182	8.2%	9.9%	99.5%	24.2%
Citrobacter freundii	443	12.2%	17.8%	9.0%	21.0%
Klebsiella oxytoca	658	4.4%	6.4%	14.4%	5.0%
Enterobacter sp	89	5.6%	4.5%	40.5%	14.6%
Citrobacter sp	405	5.2%	5.4%	24.2%	4.2%
Serratia sp	44	9.1%	9.1%	95.5%	11.4%
Klebsiella sp	48	6.3%	12.5%	52.1%	6.3%
Inpatient organisms					
Klebsiella pneumoniae	14 024	14.3%	18.6%	60.4%	12.9%
Proteus mirabilis	9349	50.0%	37.2%	99.9%	7.5%
Escherichia coli	57 681	35.6%	33.2%	5.6%	12.5%
Enterobacter cloacae	2393	17.5%	19.7%	63.6%	33.9%
Providencia sp	1310	57.9%	20.5%	74.4%	12.2%
Serratia marcescens	995	9.2%	3.5%	99.7%	10.4%
Morganella morganii	1292	50.5%	48.6%	99.8%	19.7%
Enterobacter aerogenes	1213	5.6%	4.3%	78.1%	20.6%
Proteus spp	427	16.9%	16.2%	99.3%	24.1%
Citrobacter freundii	1038	14.6%	19.0%	10.3%	25.5%
Klebsiella oxytoca	1846	7.4%	8.4%	18.0%	8.2%
Enterobacter sp	174	11.5%	8.1%	34.5%	18.4%
Citrobacter sp	838	9.0%	9.1%	25.4%	10.6%
Serratia sp	88	25.0%	18.2%	86.4%	15.9%
Klebsiella sp	141	14.2%	17.0%	34.8%	8.5%

Abbreviations: ED, emergency department; FQ, fluoroquinolones; NFT, nitrofurantoin; TMP-SMX, trimethoprim-sulfamethoxazole.

Table 2. Resistance Rates by Drug Class and Hospital Admission Status

Drug Class	ED Only (n = 60 006)		Inpatient Only (n = 86 743)		*P* Value
Presence of at least 1 organism that is resistant to the following:					
Fluoroquinolones	9713	(16.2)	28 407	(32.8)	<.001
TMP-SMX	15 299	(25.5)	26 401	(30.4)	<.001
NFT	10 742	(18)	26 810	(30.9)	<.001
Third-generation cephalosporins	3516	(6)	11 720	(13.5)	<.001
Most resistant organism; resistant to FQ, TMP-SMX, NFT, or third-generation cephalosporins					
Resistant to 0	32 706	(54.5)	33 613	(38.8)	<.001
Resistant to 1	18 783	(31.3)	27 621	(31.8)	
Resistant to 2	5603	(9.3)	13 775	(15.9)	
Resistant to ≥3	2914	(4.9)	11 734	(13.5)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ED, emergency department; FQ, fluoroquinolones; NFT, nitrofurantoin; TMP-SMX, trimethoprim-sulfamethoxazole.

both cohorts, *E coli* was the predominant pathogen but a more diverse group of Enterobacterales was observed in the inpatient cohort.

Resistance to fluoroquinolones, TMP-SMX, nitrofurantoin, and third-generation cephalosporins for each Enterobacterales among cUTI patients by hospital admission status is shown in Table 1. The proportion of patients with resistance to fluoroquinolones, TMP-SMX, nitrofurantoin, and third-generation cephalosporins and percentage of patients with resistance to 0, 1, 2, or ≥3 antibiotic classes by patient cohort are shown in Table 2. Co-resistance among Enterobacterales between fluoroquinolones, TMP-SMX, nitrofurantoin, and third-generation cephalosporins are displayed in Table 3. Supplementary Table 2 displays resistance profiles by US census division and drug class. The proportions of patients with resistance to fluoroquinolones, TMP-SMX, nitrofurantoin, and third-generation cephalosporins were generally similar across the US census divisions. In the ED only cohort, 40%–50% of cUTIs in each region displayed resistance to at least 1 agent and 10%–18% in each region had resistance to ≥2 agents. In the inpatient cohort, 55%–65% of cUTIs in each region were resistant to at least 1 agent and 25%–35% in each region were resistant to ≥2 agents.

DISCUSSION

This US multicenter study of adult patients who presented to the ED with a cUTI due to an Enterobacterales assessed rates of resistance and co-resistance to the most commonly used oral antibiotics. Although no aggregate antibiotic resistance percentages to guide empiric antibiotic treatment decisions exist for cUTI patients, all US census divisions exceeded resistance thresholds cited for empiric use of TMP-SMX and fluoroquinolones for uncomplicated cystitis and pyelonephritis in women [19]. Not surprisingly, given the baseline differences between patients, resistance rates were more pronounced among patients in the inpatient cohort. Although resistance rates were lower in the ED only cohort, resistance to fluoroquinolones and nitrofurantoin exceeded 15% and exceeded 25% for TMP-SMX. Third-generation cephalosporin resistance was only approximately 6%, but there are bioavailability, dosing (ie, inability to achieve critical pharmacokinetic/pharmacodynamic exposure targets with standard approved regimens), and treatment failure concerns with the oral advanced-generation cephalosporins that limit their clinical utility [19, 20]. Co-resistance among agents was also found to be commonplace in both patient cohorts, especially between fluoroquinolones, TMP-SMX, and nitrofurantoin.

These findings have important clinical implications. Treatment decisions are largely empiric and based on symptoms, physical findings, and underlying perceived risk of resistance. Given the high observed rates of resistance observed in both cohorts, adult patients who present to the ED with a

Table 3. Co-resistance Rates by Drug Class and Hospital Admission Status

Admission Status	FQ Resistant	TMP-SMX Resistant	NFT Resistant	Third-Generation Cephalosporin Resistant
Emergency only				
FQ resistant	…	55.3%	26.7%	23.4%
TMP-SMX resistant	35.1%	…	16.9%	12.2%
NFT resistant	24.1%	24.1%	…	11.9%
Third-generation cephalosporin resistant	64.5%	53.1%	36.3%	…
Inpatient only				
FQ resistant	…	59.8%	37.7%	31.5%
TMP-SMX resistant	64.3%	…	34.1%	27.0%
NFT resistant	40.0%	33.6%	…	18.7%
Third-generation cephalosporin resistant	76.4%	60.7%	42.8%	…

Percentages in each cell represent the proportion of Enterobacterales that are resistant to the antibiotic listed in the column when resistance is present to the antibiotic in the row.

Abbreviations: FQ, fluoroquinolones; NFT, nitrofurantoin; TMP-SMX, trimethoprim-sulfamethoxazole.

cUTI have an elevated risk for receiving an inappropriate empiric agent if prescribed a fluoroquinolone, TMP-SMX, or nitrofurantoin. This is concerning as the deleterious outcomes associated with delayed appropriate therapy are well-documented for adult patients with community-onset UTIs [21–29]. The elevated risk of inappropriate empiric therapy highlights the need for clinicians to use institution-specific antibiotic resistance risk stratification tools to guide empiric antibiotic decisions among patients presenting to the ED with a cUTI. The high observed resistance rates among the oral cUTI options also indicate that many cUTI patients will require intravenous antibiotics for their entire treatment course. Thus, there is a clear unmet need for new oral options for patients with cUTI due to Enterobacterales.

Several issues should be considered when interpreting these findings. Patient and microbiologic data were extracted from an electronic database and the potential for inaccuracies exist. However, Premier has several validation processes in place to ensure the accuracy of the data [13]. Urinalysis results, physical examination findings, and physician notes were not available, and diagnosis of cUTIs were based on diagnostic and procedure codes. Although there was a potential for misclassification of cUTI (eg, classified asymptomatic bacteriuria as cUTI), the codes used to identify cUTIs have been previously validated to have high positive predictive value [30–34]. Resistance rates were stratified by US census regions, but local epidemiology and resistance should be considered when making empiric treatment decisions in the ED. Enterobacterales are not the only causative cUTI pathogens [16] and fluoroquinolones, TMP-SMX, nitrofurantoin, and third-generation cephalosporins have limited activity against many non-Enterobacterales uropathogens [9]. Thus, our reported resistance rates should be viewed as conservative estimates of resistance and co-resistance among adults presenting to the ED with a cUTI. Finally, amoxicillin-clavulanate and fosfomycin are potential oral cUTI Enterobacterales agents but were not included in this study given their limited use relative to the agents assessed [14]. Furthermore, susceptibility results were only available for these agents in approximately 1% of the Enterobacterales cUTIs in this study. Future studies should assess the viability of amoxicillin-clavulanate and fosfomycin as potential oral agents in adult patients with Enterobacterales cUTIs.

In conclusion, patients with cUTI infections presenting to EDs in the US are frequently resistant to many commonly used oral antibiotics. Institutions should consider developing specific antibiotic resistance risk stratification tools to best inform clinicians of the appropriate empiric antibiotic selection among patients presenting to the ED with a cUTI. The findings also highlight the clear need for new oral options for cUTI patients to address the growing challenge of antibiotic resistance.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Patient consent. The Premier Research Database only contained only de-identified patient records per 45 Code of Federal Regulations [C.F.R.] 164.506(d)(2)(ii)(B) through the "Expert Determination" method. Premier Research Database data are considered exempt from institutional review board oversight as dictated by Title 45 C.F.R. part 46 of the United States, specifically 45 C.F.R. 46.101(b)(4).

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Potential conflicts of interest. T. P. L. and T. C. are consultants for Spero Therapeutics. B. H. N.'s company, OptiStatim, LLC, had a consulting agreement with Spero Therapeutics. K. S. is a former employee of Spero Therapeutics. M. R. is an employee of Spero Therapeutics.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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