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Outpatient Antibiotic Prescribing Practices for Uncomplicated Urinary Tract Infection in Women in the United States, 2002–2011

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Background. Urinary tract infection (UTI) is one of the most common diagnoses leading to an antibiotic prescription for women seeking ambulatory care. Understanding current national outpatient antibiotic prescribing practices will help ongoing stewardship efforts to optimize antibiotic use; however, information on recent national outpatient antibiotic prescribing trends for UTI is limited.

Methods. We analyzed the National Ambulatory Medical Care and National Hospital Ambulatory Medical Care Survey datasets from 2002 to 2011. Outpatient visits of women aged ≥18 years with a diagnosis of uncomplicated UTI were included for analysis. We conducted weighted descriptive analyses, examined time trends in antibiotic prescribing, and used multivariable logistic regression to identify patient and provider factors associated with fluoroquinolone prescribing.

Results. A total of 7111 visits were identified. Eighty percent of visits resulted in an antibiotic prescription; fluoroquinolones were the most frequently prescribed antibiotics throughout the study period (49% overall). Older patients (adjusted odds ratio [AOR] for adults aged ≥70 years = 2.5; 95% confidence interval [CI], 1.6–3.8) and patients treated by internists (AOR = 2.0; 95% CI, 1.1–3.3) were more likely than younger patients and those treated by family practitioners to receive fluoroquinolones. Outpatient visits in the West US Census region were less likely to be associated with fluoroquinolone prescribing (AOR = 0.6; 95% CI, .4–1.0) compared with visits in the Northeast.

Conclusions. Fluoroquinolones were the most frequently selected antibiotic treatment for uncomplicated UTI in women during the study period. Outpatient antibiotic stewardship initiatives should include efforts to reduce overuse of fluoroquinolones for uncomplicated UTI.

Keywords. adverse drug event; fluoroquinolone; outpatient antibiotic stewardship; uncomplicated urinary tract infection.

Each year, approximately 97 million outpatient visits are associated with antibiotic prescriptions, and urinary tract infection (UTI) is one of the most common diagnoses leading to an antibiotic prescription for women seeking ambulatory care [1, 2]. Increasing fluoroquinolone use for UTI [3–6] has coincided with increases in the incidence of fluoroquinolone resistance among uropathogens [7], including ciprofloxacin-resistant *Escherichia coli* among US outpatients [8]. The Infectious Diseases Society of America (IDSA) guideline published in 1999 recommended the use of trimethoprim-sulfamethoxazole as first-line therapy in the treatment of acute uncomplicated bacterial cystitis [9]. Although trimethoprim-sulfamethoxazole is still a first-line treatment option for acute uncomplicated cystitis

in the most recent guideline published in 2011, increases in antibiotic-resistant uropathogens since the 1999 guideline resulted in (1) the inclusion of nitrofurantoin among the first-line antibiotic options and (2) emphasis on using fluoroquinolones as an alternative, second-line option [10].

The increase in fluoroquinolone resistance has major implications for the treatment of more serious infections, such as community-acquired pneumonia, healthcare-associated pneumonia, and complicated UTIs [7]. An additional complication of fluoroquinolone use is subsequent infection with *Clostridium difficile*, manifesting as diarrhea that often recurs and can progress to sepsis and death; the Centers for Disease Control and Prevention (CDC) has estimated that there are approximately 450 000 *C difficile* infections in the United States each year [11]. Exposure to fluoroquinolone antibiotics has been well described as a risk factor for *C difficile* infection in the inpatient setting [12, 13]. A recent meta-analysis concluded that exposure to fluoroquinolones was associated with a more than 6-fold increased risk for developing community-acquired *C difficile* infections compared with those without fluoroquinolone exposure [14]. Comparatively, patients who received

sulfonamides/trimethoprim had a 2-fold higher risk of *C difficile* infection [14].

Understanding current national outpatient antibiotic prescribing practices will help ongoing stewardship efforts to optimize antibiotic use. However, limited information on recent national outpatient antibiotic prescribing trends for UTI is available [4, 5]. The objectives of this study were (1) to describe changes in ambulatory care antibiotic prescribing for uncomplicated UTI visits in women aged ≥18 years and (2) to identify factors associated with fluoroquinolone prescribing for uncomplicated UTI.

METHODS

Data Sources

We used the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHMACS) to conduct this study. National Ambulatory Medical Care Survey and NHAMCS are publicly available datasets from the National Center for Health Statistics at the CDC [15]. In brief, NAMCS is a survey that conducts samples of visits to nonfederally employed office-based physicians. Anesthesiologists, pathologists, and radiologists are excluded from the survey. National Ambulatory Medical Care Survey has a 3-stage probability sampling design; (1) a probability sample based on geographic regions, (2) then stratified samples of practicing physicians, and lastly (3) patient visits within practices [16]. Physicians participating in NAMCS participate for a 1-week reporting period. At each visit, data are collected regarding patient demographics, symptoms, diagnoses, and medications provided. National Hospital Ambulatory Medical Care Survey is a survey of emergency departments, outpatient departments, and ambulatory surgery centers of noninstitutional general and short-stay hospitals [15]. National Hospital Ambulatory Medical Care Survey uses a 4-stage probability sampling design: the first stage samples geographic regions, the second stage is hospitals within the regions, the third stage is clinics within hospitals, and the last stage is patient visits [16]. All emergency departments and ambulatory care surgery centers within a selected hospital are included in the survey. During a 4-week reporting period, data for sampled visits are collected regarding patient demographics, complaints, diagnoses, and medical therapy. Data are weighted in both NAMCS and NHAMCS to produce national estimates. Unweighted response rates during the study period ranged from 54% to 71% for NAMCS, 67% to 75% for outpatient departments in NHAMCS, and 80% to 91% for emergency departments in NHAMCS.

Study Population

Women aged ≥18 years who presented to a healthcare facility with an acute or new-onset (ie, patient reason for visit "acute" problem or episode was labeled as "initial" visit to the emergency department) uncomplicated UTI during 2002–2011 were included. This study period was selected as 2011 was the most recent year available before changes in the survey sampling design. A diagnosis of uncomplicated UTI was defined as any visit assigned an *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis code of UTI (599.0) or acute cystitis (595.0 or 595.9). Exclusion criteria included visits with admission to the hospital, pregnancy (V22, 630), or presence of indwelling urinary catheter (996.64). Visits with a history of urinary stones (592.x), urinary neoplasm (189.0, 198.0, 223.0, 236.91, 188.x, 223.3, 236.7, 239.4), kidney transplant (996.81, V42.0), with coexisting infection as defined by Kallen et al [4] (ie, upper respiratory tract infection [460–466 and 473], pneumonia [480–488], otitis media [382], or cellulitis and abscess [680–686]), or those with upper UTI (590) were also excluded. In addition, visits associated with any intravenous antibiotic use were also excluded from the analysis. The flow chart summarizing the selection of visits is shown in Figure 1.

Definition

Each visit was associated with up to 6 medications and their corresponding drug classes. We determined antibiotic classes (eg, fluoroquinolones) and individual medications (eg, nitrofurantoin) using the Multum Lexicon therapeutic classification system [17].

Analysis

Descriptive analyses of demographics, insurance status, visit setting, provider specialty (available for NAMCS only), presence of midlevel provider (ie, nurse practitioners physician assistants, and midwives), and geographic location were performed on all eligible visits. The χ^2 tests were used to compare categorical variables. We performed logistic regression with 2-year time periods as a predictor variable to assess time trends in prescribing of each antibiotic or antibiotic class during the entire study period. Multivariable logistic regression was performed to determine factors associated with fluoroquinolone prescribing. All analyses were performed using Stata 12 software (StataCorp, College Station, TX) and were weighted to account for all components of the multistage probability survey design.

RESULTS

A total of 7111 uncomplicated UTI visits were included for analysis for the study period. Characteristics of the included visits are summarized in Table 1. The majority of visits were made by whites (82%), and approximately half of visits were covered by private insurance (53%) and were seen by a family or general practitioner (55%).

Table 2 (top) summarizes the proportion of visits that involved an antibiotic prescription during 2002–2011. Of all uncomplicated UTI visits, 80% (95% confidence interval [CI], 77%–82%) involved an antibiotic prescription, and there was no statistically significant change in this proportion during the study period. Among the antibiotics or antibiotic classes prescribed, fluoroquinolones were the most frequently prescribed (49% overall),
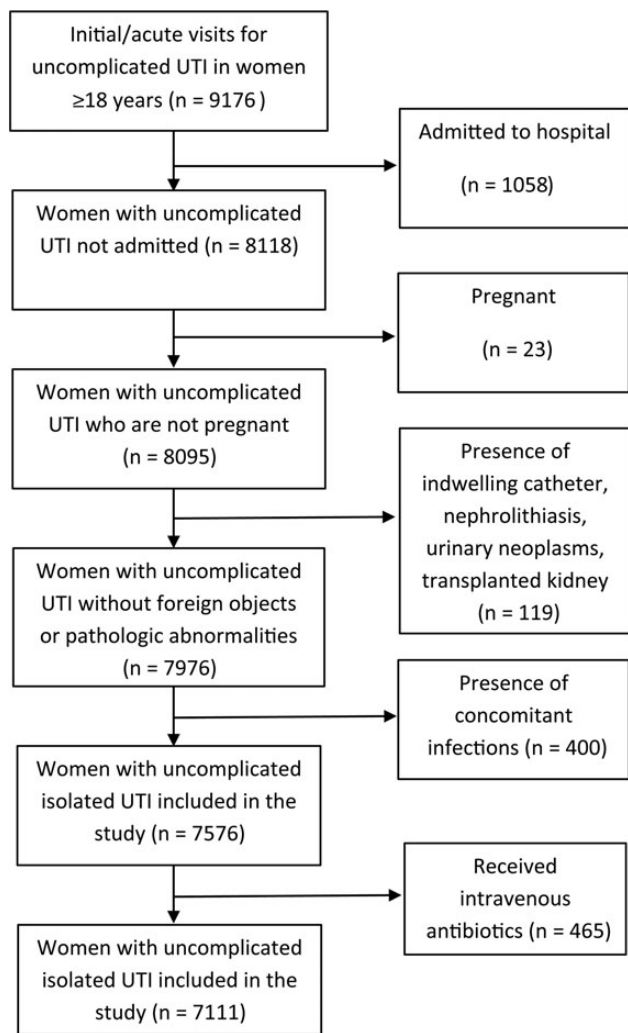
Figure 1. Flowchart describing the selection of outpatient visits, the National Ambulatory Medical Care Survey/National Hospital Ambulatory Medical Care Survey 2002–2011. Abbreviation: UTI, urinary tract infection.

Table 1. Characteristics of All Visits for Uncomplicated UTI in Women Aged ≥18 Years, NAMCS/NHAMCS 2002–2011 (N = 7111)

Characteristic	Percentage (95% CI)
Age group (years)	
18–29	26% (24%–29%)
30–49	35% (33%–38%)
50–69	22% (20%–24%)
≥70	17% (15%–19%)
Race	
White	82% (79%–84%)
Black	15% (13%–18%)
Other	3% (2%–4%)
Insurance status	
Private	53% (50%–56%)
Medicare/Medicaid	35% (32%–38%)
Other	12% (11%–14%)
Visit setting	
Physician's office	67% (64%–69%)
Hospital outpatient department	8% (7%–10%)
Emergency department	25% (23%–27%)
Provider specialty[a]	
Family/general practice	55% (50%–59%)
Internal medicine	24% (20%–29%)
Urology	7% (5%–8%)
Other	15% (11%–18%)
US Census region	
Northeast	15% (12%–19%)
Midwest	23% (18%–29%)
South	44% (38%–50%)
West	18% (14%–23%)
Metropolitan statistical area	
No	17% (11%–26%)
Yes	83% (74%–89%)
Midlevel provider present[b]	
No	90% (89%–92%)
Yes	10% (8%–11%)
Time period	
2002–2003	20% (17%–23%)
2004–2005	20% (17%–22%)
2006–2007	19% (17%–22%)
2008–2009	21% (19%–24%)
2010–2011	20% (18%–22%)

Abbreviations: CI, confidence interval; NAMCS, National Ambulatory Medical Care Survey; NHAMCS, National Hospital Ambulatory Medical Care Survey; UTI, urinary tract infection.

[a] Data available for NAMCS only.

[b] Midlevel providers included nurse practitioners, physician assistants, and midwives. Midwives were not present in emergency department settings.

followed by sulfonamides (27%), and nitrofurantoin (19%) (Table 2, bottom). The proportion of visits associated with sulfonamide prescribing decreased during the study period (35% in 2002–2003 to 23% in 2010–2011; $P = .02$), whereas an increase was observed for nitrofurantoin prescribing (14% in 2002–2003 to 24%; $P < .01$). There were no statistically significant changes in prescribing of fluoroquinolones and other antibiotic classes. Of all visits associated with a fluoroquinolone prescription, ciprofloxacin was prescribed in the greatest proportion of visits (78%; 95% CI, 73%–81%), followed by levofloxacin (21%; 95% CI, 17%–25%).

Results of the multivariable analysis assessing factors associated with fluoroquinolone prescribing are summarized in Table 3. Compared with the youngest age group (ages 18–29), older age groups were associated with increased odds of fluoroquinolone prescribing (adjusted odds ratio [AOR] for ages 30–49 = 1.7, 95% CI, 1.3–2.2; AOR for ages 50–69 = 1.8, 95% CI, 1.3–2.4; AOR for those aged ≥70 = 2.5, 95% CI, 1.6–3.8), and

visits to an internist were associated with increased odds of prescribing fluoroquinolones compared with visits to family or general practitioners (AOR = 2.0; 95% CI, 1.1–3.3). Visits in the West US Census region were associated with lower odds of fluoroquinolone prescribing compared with the Northeast (AOR = 0.6; 95% CI, .4–1.0).

DISCUSSION

During 2002–2011, fluoroquinolones were the most frequently selected antibiotics for the management of uncomplicated

Table 2. Antibiotic[a] Prescribing for Uncomplicated UTI in Women Aged ≥18 Years, NAMCS/NHAMCS 2002–2011

Antibiotic/Antibiotic Class	2002–2003	2004–2005	2006–2007	2008–2009	2010–2011	All Years	P Value[b]
Percentage of Visits Resulting in Antibiotic Prescription by Year (N = 7111)							
Any antibiotic	77%	83%	82%	81%	77%	80%	.76
Fluoroquinolones	36%	46%	37%	38%	37%	39%	.47
Sulfonamides	27%	19%	26%	19%	18%	22%	.02
Nitrofurantoin	11%	15%	14%	17%	18%	15%	<.01
Cephalosporins	3%	2%	3%	4%	3%	3%	.34
Other	2%	2%	3%	3%	2%	3%	.41
Percentage of Selected Antibiotic Classes Prescribed of All Prescribed Antibiotics (N = 5722)							
Fluoroquinolones	47%	56%	46%	47%	48%	49%	.53
Sulfonamides	35%	23%	31%	24%	23%	27%	.02
Nitrofurantoin	14%	18%	17%	21%	24%	19%	<.01
Cephalosporins	4%	3%	4%	5%	4%	4%	.32
Other	2%	3%	4%	4%	3%	3%	.38

Abbreviations: NAMCS, National Ambulatory Medical Care Survey; NHAMCS, National Hospital Ambulatory Medical Care Survey; UTI, urinary tract infection.

[a] Antibiotics included penicillins, cephalosporins, macrolides, fluoroquinolones, lincomycin derivatives, tetracyclines, sulfonamides, and nitrofurantoin. Intravenous antibiotics were excluded. These were as follows: aminoglycosides, carbapenems, nafcillin, oxacillin, penicillin G, ticarcillin/clavulanic acid, piperacillin, piperacillin/tazobactam, vancomycin, and daptomycin.

[b] The P value for trend is based upon unadjusted logistic regression with time period as a predictor variable.

UTI in women in the outpatient setting. National Ambulatory Medical Care Survey data from 1989 to 1998 showed that fluoroquinolone prescribing surpassed trimethoprim-sulfamethoxazole for uncomplicated UTI in women [18]. Therefore, fluoroquinolones have remained the most frequently prescribed antibiotic class for uncomplicated UTI in US outpatients [4, 5]. At the same time, a decrease in sulfonamide prescribing and an increase in nitrofurantoin prescribing was observed. Although some of this change may be attributed to the latest IDSA guideline encouraging use of nitrofurantoin as a first-line agent [10], the decrease in sulfonamide prescribing is likely due to the increase in the proportion of sulfonamide-resistant uropathogens [8], which, as a result, made nitrofurantoin a preferred treatment option [19].

Concerns for increases in fluoroquinolone resistance are not only a problem associated with uropathogens. Given the broad spectrum of activity, high potency, good oral bioavailability, and the ability to reach high drug concentrations in most target tissues [20], fluoroquinolones are one of the most frequently prescribed antibiotic classes in the outpatient setting [2]. Results from a national surveillance study conducted in Canada showed that ciprofloxacin-resistant *Streptococcus pneumoniae* rates increased significantly during the 9-year study period, in conjunction with increased ciprofloxacin consumption [21]. In 2013, the CDC published a report in which antibiotic resistance threats of each bacteria were categorized as urgent, serious, or concerning public health threats [22]. In the report, *C difficile* is categorized as an urgent public health threat given the burden in the United States and its association with antibiotic use [22].

Fluoroquinolones have also been associated with severe adverse events, such as rate-corrected electrocardiographic QT interval prolongation, tendinitis and tendon rupture, and seizures [23]. On May 12, 2016, the US Food and Drug Administration advised that serious side effects associated with fluoroquinolone use "generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options" [24].

Given these compelling reasons, nitrofurantoin and trimethoprim-sulfamethoxazole should be chosen for outpatient treatment of uncomplicated cystitis, whenever appropriate as determined by local resistance patterns; although resistance to trimethoprim-sulfamethoxazole is variable, the prevalence of nitrofurantoin-resistant uropathogens has remained low. In addition, due to its relatively narrow spectrum of activity and limited effect on fecal flora, nitrofurantoin is considered to have less potential for adverse events and collateral damage compared with other antibiotics used for UTI, such as *C difficile* colitis or selection of drug-resistant organisms [10, 25–27].

In our study, older patients were more likely than younger patients to receive fluoroquinolones, and internists were more likely to prescribe fluoroquinolones compared with family practitioners. Similar findings have been reported previously [4, 18]. Increased fluoroquinolone prescribing among older adults may be driven by higher frequency of trimethoprim-sulfamethoxazole resistance among older age groups [28]. In addition, nitrofurantoin is not recommended in individuals with decreased renal function (previously creatinine clearance ≤60 mL/minute, now revised to <30 mL/minute) [29], which is more likely to be present among older adults. Moreover, the Star Ratings system, introduced by the Centers for Medicare and Medicaid Services in 2007 for Medicare Advantage programs [30], listed nitrofurantoin as a high-risk medication for older adults and

Table 3. Characteristics Associated With Fluoroquinolone Prescribing for Uncomplicated UTI in Women Aged ≥18 Years Involving Antibiotic Prescription, NAMCS/NHAMCS 2002–2011 (N = 5686)

Characteristic	Percentage of Visits That Involved Fluoroquinolone Prescription	P Value*	AOR (95% CI) for Fluoroquinolone Prescribing
Age group (years)		<.001	
18–29	39%		1.00
30–49	51%		**1.67 (1.26–2.21)**
50–69	52%		**1.75 (1.28–2.37)**
≥70	58%		**2.47 (1.62–3.77)**
Race		.57	
White	49%		1.00
Black	48%		0.99 (.69–1.41)
Other	41%		0.73 (.39–1.38)
Insurance		.28	
Private	50%		1.00
Medicare/Medicaid	49%		0.83 (.63–1.10)
Other	43%		0.83 (.58–1.21)
Visit setting		.27	
Physician's office	50%		1.00
Hospital outpatient department	45%		0.91 (.68–1.22)
Emergency department	47%		1.07 (.84–1.36)
Provider specialty[a]		.01	
Family/general practice	48%		1.00
Internal medicine	62%		**1.95 (1.14–3.31)**
Urology	42%		0.72 (.42–1.24)
Other	39%		0.70 (.39–1.27)
US Census region		.24	
Northeast	54%		1.00
Midwest	47%		0.73 (.45–1.18)
South	50%		0.81 (.52–1.27)
West	43%		**0.61 (.38–1.00)**

The number in bold fonts indicate *P* < .05.

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; NAMCS, National Ambulatory Medical Care Survey; NHAMCS, National Hospital Ambulatory Medical Care Survey; UTI, urinary tract infection.

[a] Data available for NAMCS only. Accordingly, odds ratios are from a separate model that includes only data from NAMCS.

* χ^2 test.

discouraged its use [31]. The rating system was revised and now discourages long-term nitrofurantoin use (>90 days) rather than short-term use [32]. The reasons for higher fluoroquinolone prescription among internal medicine providers may be due to differences in the patient population, such as higher prevalence of comorbidities or medication allergies that would preclude the use of antibiotics other than fluoroquinolones, although the reasons are unclear. At the same time, this finding suggests an opportunity to include internists in future outpatient antibiotic stewardship initiatives aimed at improving appropriate antibiotic use for the management of uncomplicated UTI. Additional studies are needed to understand determinants of fluoroquinolone prescribing for uncomplicated UTI in order to optimize its use.

The importance of antibiotic stewardship efforts has been increasingly recognized. In a policy statement developed jointly by the Society of Healthcare Epidemiology of America, the Pediatric Infectious Diseases Society, and IDSA, antibiotic stewardship is defined as "coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration" [33]. Studies among general practitioners have shown that interventions such as audit and feedback [34, 35] and academic detailing [36, 37] have resulted in more appropriate use of antibiotics for UTI in the intervention group. Increased awareness of the importance of antibiotic stewardship has led to initiatives at the national level. For example, in September 2014, President Obama signed an executive order prioritizing federal efforts to combat the rise in antibiotic-resistant bacteria [38]. The following March, the White House issued the National Action Plan for Combating Antibiotic Resistant Bacteria, which calls for a 50% reduction in inappropriate antibiotic use among monitored conditions in outpatient settings by 2020.

Our study has several limitations. First, NAMCS and NHAMCS do not capture all outpatient antibiotic prescriptions. For example, we likely underestimated antibiotic prescribing for UTI because telephone consultations and prescribing were not

included. Urinary tract infection is one of the most common conditions associated with such prescribing [39]. In addition, visits to retail clinics and urgent care centers, which have been expanding over the years [39], are also not captured by the 2 surveys. Second, we are not able to fully assess the appropriateness of antibiotic selection, because NAMCS and NHAMCS do not contain all information on factors that could influence providers' antibiotic selection, such as patients' medication allergy or antibiotic resistance in the region. Third, although we attempted to restrict the included visits to those linked with acute or new-onset UTIs, follow-up visits still might have been included, given that 20% of the visits were not associated with any antibiotic prescription. Finally, the study period ends in 2011, which may not allow enough time to assess the impact of the new IDSA guidelines on antibiotic prescribing patterns. However, fluoroquinolones have consistently been the most frequently selected antibiotic class despite the observed changes in trimethoprim-sulfamethoxazole and nitrofurantoin use, which suggests that fluoroquinolone overuse for uncomplicated UTI is likely to continue.

CONCLUSIONS

In conclusion, an additional decade of information showed that fluoroquinolones remain the most frequently prescribed antibiotics for uncomplicated UTI in women. Additional studies are needed to determine the most effective drivers to optimize prescribing for UTI in ambulatory care settings. Providers and practices should consider assessing antibiotic selection for UTI as potential target for antibiotic stewardship implementation.

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