**Original Investigation**

Current Antibiotic Therapy for Isolated Urinary Tract Infections in Women

Alexander J. Kallen, MD; H. Gilbert Welch, MD, MPH; Brenda E. Sirovich, MD, MS

**Background:** Sulfa antibiotics, such as a combination product of trimethoprim and sulfamethoxazole, have traditionally been the drugs of choice for urinary tract infections (UTIs) and remained the most common treatment as recently as a decade ago. However, increasing sulfua resistance among *Escherichia coli* may have led to changes in prescribing practices.

**Methods:** We used the 2000-2002 National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey to obtain nationally representative data on antibiotics prescribed for women with isolated outpatient UTIs following visits to physicians’ offices, hospital clinics, and emergency departments (n=2638). Logistic regression was used to determine predictors of quinolone use.

**Results:** Quinolones were more commonly prescribed than sulfa antibiotics in each year evaluated. In the most recent year of data, quinolones were prescribed in 48% and sulfas in 33% of UTI visits (*P*<.04). Quinolones were significantly more likely to be prescribed to older patients and in visits occurring in the Northeast; however, no difference in quinolone prescribing was seen when evaluating insurance status, setting, race, ethnicity, health care provider type, and year. Approximately one third of the quinolones used were broader-spectrum agents.

**Conclusions:** Quinolones have surpassed sulfas as the most common class of antibiotic prescribed for isolated outpatient UTI in women. Few significant predictors of quinolone use exist, suggesting that the increase is not confined to a certain subset of patients. This pervasive growth in quinolone use raises concerns about increases in resistance to this important class of antibiotics.

Arch Intern Med. 2006;166:635-639

---

**Data Source**

We combined data from the 3 most recent years (2000-2002) of the National Ambulatory Medi-
cal Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS). These surveys, administered by the National Center for Health Statistics of the Centers for Disease Control and Prevention, gather data on a nationally representative sample of outpatient visits to nonfederally funded office-based physicians (NAMCS), nonfederal short-stay hospital emergency departments (NHAMCS-ED), and hospital outpatient departments (NHAMCS-OPD) in the United States. Using multistage probability sampling, these surveys are designed to give national estimates of the characteristics of outpatient visits in each of these 3 settings. In each survey a randomly selected health care provider is asked to complete data collection forms on a random sample of patient visits during a prespecified period, supplying data such as reason for visit, diagnoses, and medications prescribed.11-13

IDENTIFICATION OF UTI VISITS

Figure 1 shows our method for identifying visits for isolated outpatient UTIs in women (subsequently referred to as a UTI visit). We included visits in our analysis if they involved adult (18 years or older) women who had any of 3 International Classification of Diseases, Ninth Revision (ICD-9) codes for UTI listed as a diagnosis: acute cystitis (595.0), unspecified cystitis (595.9), or site-unspecified UTI (599.0). To best capture uncomplicated isolated outpatient UTIs, we started by excluding patients whose disposition was hospital admission. We then excluded those who had a coexisting infection (eg, upper respiratory tract infections, ICD-9 codes 460-466 and 473; pneumonia, ICD-9 codes 480-487; otitis media, ICD-9 code 382; or cellulitis and abscess, ICD-9 codes 680-686). Last, patients who had an upper UTI (ICD-9 code 590) were also excluded. This yielded 2638 sample visits, the denominator used for our analyses of antibiotic use. Each visit had an upper UTI (ICD-9 code 590) were also excluded. This yielded 2638 sample visits, the denominator used for our analyses of antibiotic use.

UTI VISIT CHARACTERISTICS

For each eligible visit, we determined patient age and race and visit payer, practice setting, region, and health care provider type. If more than one health care provider type was listed (eg, nurse practitioner and attending physician or house staff and attending physician), visits were assigned to the midlevel health care provider (nurse practitioner, physician assistant, or nurse midwife) or house staff (information on house staff available only from NHAMCS, not from NAMCS). We also determined whether a urinalysis or urine culture was performed. Data for urine cultures were available only for the years 2001 and 2002.

ANTIBIOTICS

Data on antibiotics were included in 1914 of the UTI visits (the denominator used for our analyses of antibiotic use). Each visit was associated with up to 6 medications and their corresponding drug classes. We determined antibiotic class using a variable included in the data set that is based on the 1995 National Drug Code Directory Drug Classes, except in the case of nitrofurantoin, which was identified using the actual medication code rather than the class. This was because nitrofurantoin was categorized in a class that included drugs not used for UTI treatment (urinary tract antiseptics, class 0394), such as phenazopyridine. Specific quinolones were identified by name using their brand and generic name codes. These antibiotics were further categorized into narrower-spectrum (norfloxacin, ofloxacin, ciprofloxacin) and broader-spectrum groups (levofloxacin, gatifloxacin, trovafloxacin).14-15

DATA ANALYSIS

Descriptive analyses were performed on the general characteristics of UTI visits and the type of antibiotic used in each visit. Multiple logistic regression was performed to determine predictors of quinolone use. Because this was a common outcome, all odds ratios were converted to relative risks using the method of Zhang and Yu.16 All analysis incorporated appropriate sampling weights and accounted for a multistage clustered sampling strategy using the survey commands in STATA 8.2 (StataCorp, College Station, Tex). Our weighted data represent approximately 27 million visits.

RESULTS

CHARACTERISTICS OF UTI VISITS

The UTI visits were most likely to take place in physicians’ offices (75%) rather than the emergency department (18%) or hospital clinics (8%) (Table). The typical patient was a white woman approximately 50 years old with private insurance. Although urinalysis was commonly part of the workup (76%), an order for urine culture was relatively rare (23%).

ANTIBIOTIC USE

Throughout the study period (2000-2002), quinolones were the most common antibiotic class prescribed (44% of visits), followed by sulfa antibiotics (30%) and nitrofurantoin (18%). An apparent nonsignificant trend occurred toward increasing quinolone use with each successive year of data: 38% in 2000, 46% in 2001, and 48% in 2002 (P = .11). As shown in Figure 2, in the most recent year of data (2002), quinolones were prescribed in 48% of UTI visits, and antibiotics and sulfas were prescribed in 33% (P for difference <.04).

PREDICTORS OF QUINOLONE USE

Figure 3 shows that age and region were the only significant predictors of quinolone use. Quinolones were sig-
nificantly more likely to be used if the patient was older than 30 years. Women 30 to 49 years old (45%) and 50 years or older (49%) were significantly more likely to receive a quinolone than those younger than 30 years (31%). Quinolones were significantly less likely to be prescribed in visits occurring in the Midwest (41%) or West (35%) compared with the Northeast (55%). The prescribing of quinolones did not vary significantly by race, ethnicity, health care provider type, setting type, or year of visit.

We performed additional subanalyses on 2 variables that were not consistently available in our data: physician specialty and whether an encounter was an initial visit or a follow-up visit. When specialty was included in a model, obstetrician-gynecologist (n=357) was a significant negative predictor of quinolone use (relative risk, 0.31; 95% confidence interval, 0.11-0.73). When initial and follow-up visit were included in a model (n=1358), the variable had little impact (relative risk for follow-up, 0.96; 95% confidence interval, 0.67-1.18).

**SPECTRUM OF QUINOLONE USE**

Ciprofloxacin (61%) and levofloxacin (32%) were the most commonly used quinolones in 2002. Narrower-spectrum quinolones were more commonly used than broader-spectrum quinolones. Nevertheless, broader-spectrum quinolones were used in approximately one third of UTI visits in 2002 (37%).

**COMMENT**

Quinolones have become the dominant treatment for UTI. Their use has steadily increased; between 1989-1990 and 1997-1998, reported use of quinolones for the treatment of UTIs increased from 19% to 29% in one study.4 Our analysis demonstrates that this trend has continued through 2002, with quinolones now firmly established as the most common class of antibiotics used for treatment of UTI. Few patient and visit characteristics predicted quinolone use, suggesting that the increase in the use of quinolones is not limited to a few subgroups of patients or to certain settings. Finally, when quinolones are prescribed, broader-spectrum agents from this class are too often used.

Although it is tempting to ascribe increased quinolone use to rising sulfa resistance, patterns of resistance across both geography and time do not support the observed quinolone use. Sulfa resistance rates vary greatly by area.17 If the increasing use of quinolones was solely a response to increasing resistance, one would expect higher rates of quinolone use in areas of higher resistance. However, although at the time these data were collected rates of sulfa-resistant *E coli* were lowest in the Northeast,17,18 we found that these were the areas where quinolones were most likely to be prescribed. Additionally, the West, which had among the highest sulfa resistance,17,18 was the area with the lowest proportion of quinolone use. Further, patterns of quinolone use do not track with sulfa resistance rates over time. Overall nationwide resistance rates remained at approximately 16% between 2 national studies performed in 1998 and 2001, leading to speculation that rates of trimethoprim-sulfamethoxazole resistance are plateauing.17,19 Despite stable resistance patterns, we found that use of quino-
tempting to choose appropriate antibiotics. Many institutions, may therefore mislead clinicians at different types of studies, such as the antibiograms produced by hospitals, to estimate resistant organisms that are obtained from these institutions. Prevalence estimates of resistant organisms, especially in studies that base their estimates on cultures obtained in clinical practice. Preventing estimates of antibiotic resistance may overestimate the true prevalence of resistant organisms in cases where resistant organisms are more likely. This would overestimate the true prevalence of resistant organisms, especially in studies that base their estimates on cultures obtained in clinical practice. Prevalence estimates of resistant organisms that are obtained from these types of studies, such as the antibiograms produced by many institutions, may therefore mislead clinicians attempting to choose appropriate antibiotics.

First, resistance rates are typically measured in vitro (eg, on a plate, and likely overestimates clinically relevant resistance. Clinical cure rates with trimethoprim-sulfamethoxazole are estimated to be close to 85% even when sulfa resistance rates among E. coli are 30% (well above those currently seen in the United States). This finding reflects both the activity of the drug on sensitive species and spontaneous resolution of a subset of resistant infections.2

Second, current methods of measuring in vitro sulfa resistance may overestimate resistance rates at the population level. Our finding that most visits for UTI (77%) do not result in a urine culture is in keeping with recommendations by experts that patients with typical symptoms and without risk factors for complicated UTIs may be treated empirically.20,21 However, the unintended effect of selectively performing urine cultures may be to inflate estimates of antibiotic resistance by oversampling cases where resistant organisms are more likely. This would overestimate the true prevalence of resistant organisms, especially in studies that base their estimates on cultures obtained in clinical practice. Prevalence estimates of resistant organisms that are obtained from these types of studies, such as the antibiograms produced by many institutions, may therefore mislead clinicians attempting to choose appropriate antibiotics.

Second, current methods of measuring in vitro sulfa resistance may overestimate resistance rates at the population level. Our finding that most visits for UTI (77%) do not result in a urine culture is in keeping with recommendations by experts that patients with typical symptoms and without risk factors for complicated UTIs may be treated empirically.20,21 However, the unintended effect of selectively performing urine cultures may be to inflate estimates of antibiotic resistance by oversampling cases where resistant organisms are more likely. This would overestimate the true prevalence of resistant organisms, especially in studies that base their estimates on cultures obtained in clinical practice. Prevalence estimates of resistant organisms that are obtained from these types of studies, such as the antibiograms produced by many institutions, may therefore mislead clinicians attempting to choose appropriate antibiotics.

Finally, it is not clear why 27% of those visits with a diagnosis of UTI did not involve the prescription of an-
tibiotics. Similar results have been reported in another NAMCS-based study. At least 3 possible explanations exist for this observation. First, some of these UTI visits may represent follow-up visits and therefore not result in a new antibiotic prescription. Second, some visits may reflect physician visits where antibiotics are withheld pending results of a culture or other tests. Third, incorrect diagnosis codes or drug class codes could have been used for some of these visits. Regardless of the explanation, exclusion of these patients from our analysis of antibiotic use is unlikely to have systematically biased our estimates of quinolone use.

In conclusion, quinolones have now replaced sulfon antibiotics as the most common antibiotic prescribed during visits for uncomplicated UTIs. The increase in quinolone use may be a reaction to potentially inflated measures of sulfon resistance among E coli or exaggerated perceptions of resistance among physicians or it may be due to other factors, including clinicians’ increasing familiarity and comfort with quinolones. Regardless, much of this increased use is likely unnecessary and may be associated with increased cost and the further development of resistance to this important class of antimicrobials.

Given these concerns, we believe it is time to reassess antibiotic treatment strategies for UTIs. In particular, it is important to persuade clinicians that narrower-spectrum agents are preferable to broader-spectrum agents to reduce the selective pressure for resistance to the latter. Using sulfas (or nitrofurantoin) instead of a quinolone or using a narrower-spectrum quinolone rather than a broader-spectrum quinolone will help preserve the clinical activity of these important antimicrobials. Additionally, to better inform treatment decisions, researchers need to develop better methods to measure clinically relevant (in vivo) rates of sulfon resistance in representative populations of patients treated (not just those cultured) for UTIs, as well as specific clinical predictors of such resistance.

Accepted for Publication: October 30, 2005.

Correspondence: Alexander J. Kallen, MD, VA Outcomes Group, 111B, 215 N Main St, VA Medical Center, White River Junction, VT 05009 (alexander.j.kallen@dartmouth.edu).

Author Contributions: Dr Kallen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: During the period 2000-2002 (before the initiation of this project), Dr Kallen served as a member of the Speakers’ Bureau for Johnson & Johnson (makers of levofloxacin, a drug included in this analysis). He received several (3) honoraria for lectures he gave during this time. All these lectures were on general infectious disease topics (not drug specific). In this article, levofloxacin is not singled out specifically with respect to other members of its class. Furthermore, the article argues against increased use of this class of drugs.

Funding/Support: Dr Kallen is supported by a Veterans Administration MD Ambulatory Care Postdoctoral Fellowship. Dr Sirovich is supported by a Veterans Affairs Career Development Award in Health Services Research & Development. This study was supported by Research Enhancement Award 03-098 from the Department of Veterans Affairs to investigate the harms from excessive medical care.

Disclaimer: The views expressed herein do not necessarily represent the views of the Department of Veterans Affairs or the US government.

Previous Presentation: This study was presented as a poster at the 28th Annual Meeting of the Society of General Internal Medicine; May 14, 2005; New Orleans, La.

Acknowledgment: We thank the members of the VA Outcomes Group and Jennifer Shu, MD, for their thoughtful review of this project.

REFERENCES