National Patterns in the Treatment of Urinary Tract Infections in Women by Ambulatory Care Physicians

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Background: Trimethoprim-sulfamethoxazole has consistently been the recommended drug for uncomplicated urinary tract infections in women. Which antibiotics physicians use has implications for patient outcomes, antimicrobial resistance, and costs.

Methods: This study was based on a sample survey of practicing physicians participating in the National Ambulatory Medical Care Survey from 1989 through 1998. Eligible visits were limited to those by women aged 18 to 75 years diagnosed with uncomplicated acute cystitis or urinary tract infection (N=1478). We evaluated trends in the proportions of visits at which physicians prescribed (1) trimethoprim-sulfamethoxazole, (2) recommended fluoroquinolones, (3) nitrofurantoin, and (4) nonrecommended antibiotics (neither trimethoprim-sulfamethoxazole nor recommended fluoroquinolones). We also identified predictors of specific antibiotic prescribing among visits to primary care physicians.

Results: The most frequently prescribed antibiotics were trimethoprim-sulfamethoxazole, recommended fluoroquinolones, and nitrofurantoin. We found that the proportion of trimethoprim-sulfamethoxazole prescriptions declined from 48% in 1989-1990 to 24% in 1997-1998 (adjusted odds ratio [OR], 0.33; 95% confidence interval [CI], 0.21-0.52 per decade). Conversely, fluoroquinolone use increased (19% to 29%) (OR, 2.28; 95% CI, 1.35-3.83) as did nitrofurantoin prescribing (14% to 30%) (OR, 2.44; 95% CI, 1.44-4.13). Among primary care physicians, internists were the most likely to prescribe fluoroquinolones while obstetricians were the most likely to use nitrofurantoin.

Conclusions: Ambulatory care physicians are increasing their use of fluoroquinolones and nitrofurantoin, even though they are not highly recommended and not the most cost-effective. Antibiotic prescribing in urinary tract infections may be influenced by clinical factors such as pregnancy and drug allergies but may also be shaped by nonclinical factors such as subspecialty culture.

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URINARY TRACT infections (UTIs) account for at least 7 million outpatient visits and 1 million hospital admissions in the United States annually.1 Recent reports have raised concerns about increasing bacterial resistance to antibiotics commonly used for UTI such as trimethoprim-sulfamethoxazole and fluoroquinolones.2-4 Given the prevalence of this infection and the unique spectrum of organisms involved, the question of how physicians treat UTIs has significance for patient well-being, antimicrobial resistance, and health care costs. Recommendations for the treatment of common infections are unique in their requirement to consider both individual and environmental concerns.

The recommendations for the treatment of UTIs have not changed significantly over the past decade. In their 1993 review article, Stamm and Hooton1 recommended trimethoprim-sulfamethoxazole or selected fluoroquinolones to treat UTIs. The authors of the 1999 Infectious Disease Society of America guideline selected trimethoprim-sulfamethoxazole as standard therapy with specific fluoroquinolones as second-line choices.5 Although both drug classes are effective in treating UTIs, trimethoprim-sulfamethoxazole has always been the preferred choice because of concerns about resistance and costs. Guideline authors have wanted to discourage the immediate adoption of fluoroquinolones to slow the development of high rates of resistance seen in other nations.6 Stark differences in cost have also influenced recommendations: in 1999, a 10-day course of trimethoprim-sulfamethoxazole cost $1.79, while a course of ciprofloxacin cost $70.98.7 To promote these recommendations, the guideline committee devised a measure of prescribing quality, which is the percentage of patients with uncomplicated acute cystitis treated with trimethoprim-sulfamethoxazole (in communities where resistance rates are lower than 20%).

While an understanding of antibiotic prescribing for UTI would have value for measuring health care quality and predicting future bacterial resistance, studies of current UTI treatment patterns are limited and varied. A recent interventional study by Saint et al8 reported that

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METHODOLOGICAL

THE NAMES

Data for this study came from the NAMCS, 1989 to 1998. Conducted by the National Center for Health Statistics, Hyattsville, Md, the survey uses a multistage probability sample design. The sampling process makes use of the American Medical Association and American Osteopathic Association master lists of all US physicians. Each year a sample of patient care physicians from these lists is selected by random, stratified sampling by geographic area and specialty. Among identified physicians, annual participation ranged from 74% in 1989 to 68% in 1998. For participating physicians, patient visits during a randomly selected week are sampled systematically.

For each selected patient visit, the physician completes an encounter form detailing the specific clinical services provided during the visit, as well as patient demographics, reasons for the visit, and diagnoses. The first listed diagnosis represents the principal diagnosis most closely associated with the patient’s visit. Physicians also are instructed to record, using brand or generic names, all new and continued medications.

DATA EXTRACTION

We identified all female patients, ages 18 to 75 years, who had an International Classification of Diseases, Ninth Revision (ICD-9) code for either acute cystitis (595.0) or UTI, site unspecified (599.0) listed as a diagnosis. Patients were excluded if they had an additional code for urologic procedures, pregnancy, diabetes mellitus, cancer, human immunodeficiency syndrome and/or acquired immunodeficiency syndrome, or other infection (skin infections, vaginitis, cervicitis, and sexually transmitted disease). In addition, we excluded patients who were admitted to a hospital following their visit. These criteria allowed us to define a set of 1478 visits for investigation.

Among these patients, we identified those receiving antibiotic therapy by the coding of generic or proprietary names for all antibiotics in the following classes: trimethoprim, trimethoprim-sulfamethoxazole, sulfamethoxazole, fluoroquinolones, penicillins, cephalosporins, aminoglycosides, nitrofurantoin, fosfomycin, antianaerobic agents (metronidazole and clindamycin), and tetracyclines. Recommended fluoroquinolones were identified as ciprofloxacin, ofloxacin, lomefoxacin, enoxacin, and fleroxacin. Newer fluoroquinolones such as levofloxacin and trovafloxacin were coded as nonrecommended. If a patient received more than one antibiotic, we coded the patient as having received the more optimal antibiotic (trimethoprim-sulfamethoxazole or recommended fluoroquinolones).

Along with the prescribing of antibiotics, we further identified patients who had a symptom or diagnostic code suggesting a complicated UTI (flank pain, low back pain, pyelonephritis, or urethral stricture secondary to infection). We performed a subset analysis of predictors of antibiotic prescribing that excluded patients with complicated UTI.

STATISTICAL ANALYSIS

All analyses were conducted with SAS statistical software (Release 8.1; SAS Institute Inc, Cary, NC). The national estimate of the number of UTI visits under study was obtained using the patient visit weights. Each visit is assigned a weight derived from the probability of being sampled, to account for regional and specialty sampling bias.

STUDY POPULATION

The initial study population was 1478, which corresponds to a national estimate of 3.60 million annual visits. About half (55%) of the women were younger than 45 years, and most were white (84%) (Table 1). Nearly one third (32%) of patients had a documented prior UTI, and 15% of patients had a reason or diagnostic code suggestive of a complicated UTI. Most of the women visited primary care physicians (81%) and most had seen the physician previously (85%). The South was the most heavily represented region in this sample (38%). The most common form of health insurance was private (47%). The demographic and visit characteristics were similar for visits by women found in the overall NAMCS population from 1989 to 1998.

VISIT CHARACTERISTIC TRENDS

All trend analysis results are presented as the impact of a decade on the odds of a patient or visit characteristic occurring. We found that the odds of women younger than 45 years visiting physicians for UTIs did not change significantly over time (OR, 0.79; 95% CI, 0.55-1.13 per decade).
as well as nonresponse. We carried out all subsequent analyses using modified sample weights.

**TREND ANALYSES**

We evaluated the initial study population (N=1478) for demographic and practice trends over time using logistic regression. In all logistic regression analyses, we used year as a linear predictor. These results are reported as the impact of a decade on the odds of a visit characteristic occurring. Because premenopausal and postmenopausal women may have different propensities for experiencing acute or chronic UTIs, which are managed with different antibiotics, we adjusted for age younger than 45 years. Similarly, we adjusted all trend analyses for history of UTIs. We examined trends in the age and racial makeup of patients, visits by patients with a history of UTIs, visits by individuals with complicated UTIs, and the relative frequency of visits to primary care physicians or urologists. Primary care physicians were defined as family or general practitioners, internists, and obstetricians/gynecologists.

In addition, we sought to identify trends in physician practices such as the frequency of ordering urinalyses or antibiotic selection. Among patients who received antibiotics (n=989), we examined trends in the prescribing of (1) trimethoprim or trimethoprim-sulfamethoxazole, (2) recommended fluoroquinolones, (3) nitrofurantoin, and (4) overall nonrecommended antibiotics (antibiotics other than trimethoprim, trimethoprim-sulfamethoxazole, and recommended fluoroquinolones).

**PREDICTORS OF ANTIBIOTIC CHOICE**

We conducted a subset analysis of antibiotic choice among those patients who had no symptoms suggesting a complicated UTI, visited primary care physicians, and received antibiotics (n=361). The unit of analysis was the patient visit. The outcome variables were the previously defined antibiotic classes. Independent variables were patient demographics (age younger than 45 years and nonwhite race), complaint of dysuria, history of prior UTI, established patient status (patient seen previously by physician), visit duration, geographic region of the country, primary care physician specialty, expected payment source (private, HMO, government insurance, self-pay), and survey year. Geographic region and primary care specialty were coded as dummy variables. Because many patients had more than one type of insurance, each form of insurance was coded as an individual dichotomous variable.

We tested unadjusted associations between predictors and outcomes with univariable logistic regression. These results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Adjusted associations were assessed using weighted multivariable logistic regression for the years 1989 through 1998 (n=361). In our models we adjusted for all independent variables. Because of our concerns about the influence of drug allergies or the development of chronic UTI, the analyses were repeated for the subpopulation of patients who had no documented history of UTIs (n=391). We did not adjust for clustering effect because physician identifiers were not available until 1991. However, for the years 1991 through 1998, we carried out selected analyses with both logistic regression and the general estimating equation and found no differences in results.

We also created interaction terms between selected predictors to test for effect modification. To test for the strength of an association over time, we created interaction terms between the selected predictors and visit year.
received antibiotics (n = 561) (Table 1). In our univariable analysis of trimethoprim or trimethoprim-sulfamethoxazole prescribing, younger women (younger than 45 years) were more likely to receive this antibiotic than older women (41% vs 28%). Conversely, patients who had a history of UTIs were less likely to receive the antibiotic than those who had no history (23% vs 41%). Patients with an established relationship with their physicians were also less likely to receive trimethoprim-sulfamethoxazole than were new patients (34% vs 51%). In multivariable logistic regression, age younger than 45 years and history of UTI remained significant predictors (Table 3).

In the full model, the physician specialty of obstetrician/gynecologist emerged as a predictor of less frequent prescribing of trimethoprim-sulfamethoxazole than the general/family practitioner specialty (27% vs 37%). As seen in trend analyses for the whole study population, the use of this drug class declined over time in adjusted and unadjusted analyses.

When limiting the analysis to patients who had no history of UTI (n = 391) (Table 1), age younger than 45 years continued to be a predictor of trimethoprim-sulfamethoxazole use while visits to obstetricians/gynecologists lost significance as a predictor of nonuse. We tested several interaction terms between obstetricians/gynecologists, patient age, and prior UTI for entry into the model, and none was statistically significant. Similarly, interaction terms with the variable visit year did not enter the model, suggesting no changes in these associations over time.

In the unadjusted analysis of recommended fluoroquinolone use, patients complaining of dysuria were prescribed these antibiotics more frequently than those who did not have this complaint (31% vs 20%). On the other
hand, younger women were less likely to receive these antibiotics than older women (19% vs 30%); nonwhite patients were also less likely to be given these antibiotics than their white counterparts (11% vs 26%). Among practitioners, obstetricians/gynecologists were much less likely to prescribe fluoroquinolones than general practitioners (10% vs 23%). In the model including all variables, we found that each of these predictors remained statistically significant (Table 3). In addition, visits to internal medicine physicians emerged as a predictor of fluoroquinolone use (31% vs 26%).

When excluding patients who had prior UTIs, younger and nonwhite patients continued to be less likely to receive fluoroquinolones, and internists remained heavier prescribers of fluoroquinolones. Obstetricians/gynecologists lost significance as predictors of nonuse. As seen in trend analyses for the whole study population, the use of this drug class increased over time in adjusted and unadjusted analyses. Again, none of our interaction terms was found to be statistically significant.

With regard to the prescribing of nitrofurantoin for UTI, several predictors were associated with their use in univariable analyses. Patients who had been seen earlier by the same physician were more likely to receive these drugs than new patients (33% vs 15%). Obstetricians/gynecologists prescribed these antibiotics more frequently than general/family practitioners (46% vs 22%). Younger women were also more likely to receive nitrofurantoin than patients with non-managed care insurance (32% vs 21%). In the multivariable logistic model, a visit to an obstetrician/gynecologist and HMO membership remained significant predictors (Table 3). In a comparison with generalists, internists emerged as significant nonprescribers of nitrofurantoin in the full model.

Because a number of these patients receiving nitrofurantoin may have actually had chronic UTIs, we repeated this analysis excluding patients with a history of UTIs. In this model, nonwhite racial status, presence of dysuria, and a visit to an obstetrician/gynecologist were associated with the increased use of nitrofurantoin, but HMO membership lost significance as a predictor. A visit to an internist continued to be associated with nonuse of nitrofurantoin. No interaction terms were found to be significant in either model.

Finally, we performed subset analysis on all patients who did not receive either one of the recommended first-line antibiotics, trimethoprim-sulfamethoxazole or an appropriate fluoroquinolone. Nonwhites were more likely to receive nonrecommended antibiotics than their white counterparts (49% vs 38%). Patients with prior UTIs were prescribed these antibiotics more frequently than patients with no history of the infection (50% vs 37%). Similarly, established patients were more likely to receive nonrecommended antibiotics than new patients (42% vs 27%). Obstetricians/gynecologists were much more likely to prescribe these antibiotics than general practitioners (61% vs 39%). Patients with dysuria and patients with short visits were less likely to receive nonrecommended antibiotics than those without dysuria and those with short visits (33% vs 43% and 37% vs 49%, respectively). When we adjusted for all variables, nonwhites, those with a history of UTI, and patients visiting obstetricians/gynecologists continued to be more likely to receive nonrecommended antibiotics (Table 3). Only patients who had short visits or saw internists were

| Table 3. Factors Associated With Antibiotic Prescribing for Uncomplicated Urinary Tract Infections (UTIs) Among Primary Care Physicians (n = 561)* |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Patient and Visit Characteristics** | **Trimethoprim- Sulfamethoxazole Model** | **Recommended Fluoroquinolones Model†** | **Nitrofurantoin Model** | **Nonrecommended Antibiotics Model‡** |
| Age < 45 y | 2.10 (1.38-3.20) | 0.64 (0.41-0.99) | 0.83 (0.52-1.32) | 0.77 (0.52-1.14) |
| Nonwhite | 1.01 (0.61-1.68) | 0.38 (0.19-0.77) | 1.45 (0.83-2.52) | 1.81 (1.10-2.97) |
| Complaint of dysuria | 0.97 (0.63-1.48) | 1.72 (1.10-2.70) | 1.30 (0.82-2.07) | 0.68 (0.45-1.03) |
| History of UTI | 0.37 (0.23-0.59) | 1.45 (0.90-2.33) | 1.37 (0.86-2.18) | 1.82 (1.20-2.75) |
| Established patient | 0.76 (0.44-1.31) | 0.84 (0.43-1.62) | 2.11 (0.97-4.59) | 1.63 (0.90-2.95) |
| Visit shorter than 15 min | 1.47 (0.96-2.27) | 1.21 (0.75-1.96) | 0.74 (0.47-1.17) | 0.60 (0.40-0.91) |
| Region | | | | |
| South | Referent | Referent | Referent | Referent |
| Northeast | 1.19 (0.67-2.12) | 1.48 (0.77-2.86) | 0.98 (0.50-1.90) | 0.59 (0.33-1.06) |
| Midwest | 0.87 (0.51-1.48) | 1.42 (0.77-2.61) | 1.05 (0.57-1.93) | 0.87 (0.52-1.47) |
| West | 0.89 (0.42-1.12) | 1.11 (0.62-1.97) | 0.99 (0.57-1.72) | 1.17 (0.73-1.87) |
| Primary care physician specialty | | | | |
| General/family practice | Referent | Referent | Referent | Referent |
| Internal medicine | 1.05 (0.68-1.62) | 1.67 (1.05-2.66) | 0.53 (0.31-0.91) | 0.62 (0.40-0.96) |
| Obstetrics/gynecology | 0.52 (0.29-0.91) | 0.47 (0.22-0.99) | 3.19 (1.85-5.53) | 2.37 (1.41-3.99) |
| Insurance | | | | |
| Private | 0.78 (0.49-1.25) | 1.14 (0.68-1.91) | 1.01 (0.60-1.69) | 1.15 (0.74-1.80) |
| Government (Medicare/Medicaid) | 1.30 (0.83-2.22) | 0.78 (0.45-1.35) | 0.96 (0.56-1.70) | 0.96 (0.60-1.55) |
| Managed care | 0.87 (0.52-1.46) | 0.87 (0.50-1.53) | 1.92 (1.12-3.29) | 1.24 (0.76-2.01) |
| Self-pay | 0.78 (0.44-1.41) | 0.98 (0.50-1.91) | 0.89 (0.45-1.76) | 1.39 (0.78-2.49) |
| Year (per decade) | 0.21 (0.10-0.41) | 3.12 (1.46-6.68) | 2.21 (1.01-4.88) | 1.85 (0.95-3.59) |

*Data are odds ratios (95% confidence intervals).
†Recommended fluoroquinolones were defined as ciprofloxacin, ofloxacin, lomefloxacin, enoxacin, and fleroxacin.
‡Nonrecommended antibiotics were defined as all antibiotics other than trimethoprim or trimethoprim-sulfamethoxazole or recommended fluoroquinolones.
less likely to receive nonrecommended antibiotics. When we evaluated patients with no history of UTI, nonwhite race and visits to obstetricians/gynecologists continued to be significant predictors. No interaction terms entered the model.

ASSOCIATION BETWEEN PREDICTORS

We evaluated associations between specific predictors: age younger than 45 years, nonwhite status, history of UTI, and visit to an obstetrician/gynecologist. Younger and nonwhite patients were more likely to visit obstetricians/gynecologists than the other primary care physicians (OR, 4.18; 95% CI, 2.37-7.37, and OR, 1.71; 95% CI, 1.02-2.88, respectively). Nonwhites were younger than their white counterparts (OR, 1.83; 95% CI, 1.14-2.93). We found no other significant relationships. In particular, obstetricians/gynecologists did not see patients with a history of UTI more frequently.

Urinary tract infections in women account for a substantial number of ambulatory care visits each year, and the manner in which UTIs are managed has implications for patients and clinical microbiology. The intent of our study was to provide a national and longitudinal description of patients, physicians, and treatment choices for ambulatory UTI visits. In our analysis of demographic and clinical trends, we found no evidence to suggest substantial changes in the characteristics of women presenting with UTIs, despite our perception that an increasing number of uncomplicated infections are managed outside of physicians’ offices. In particular, there were no trends in complaints suggesting increasingly complex or recurrent UTIs and no increase in visits to urologists.

In the analysis of diagnostic and treatment choices, we found that the frequency of urinalysis ordering declined over time. The most commonly selected antibiotics for UTI were trimethoprim-sulfamethoxazole, fluoroquinolones, and nitrofurantoin. Over the course of the 10 years of observation, trimethoprim-sulfamethoxazole use declined while the use of the other 2 agents rose. Even when adjusting for all patient and visit characteristics available to us, these trends continued to be statistically significant. In the 1998 data, we noted a small proportion of UTI visits where broad-spectrum fluoroquinolones such as levofloxacin were used. When considering these trends as a whole, prescribing for UTI in most recent years seems to be almost evenly distributed among the top 3 antibiotics. Outside of these antibiotics, there seems to be continued use of penicillins and cephalosporins, despite the fact that β-lactam resistance has been relatively high for at least a decade.

We found several themes in our analysis of antibiotic prescribing predictors. Younger patients, presumably premenopausal, were more likely to receive trimethoprim-sulfamethoxazole but were less likely to receive fluoroquinolones. Patient age seemed to have no relationship with resistance patterns and the prescribing trends we observed. While patient and physician characteristics were associated with distinct prescribing patterns, we consistently found no regional differences in antibiotic use. For the purposes of assessing antibiotic prescribing quality, we would like to have seen how these prescribing patterns corresponded to regional resistance trends. Unfortunately, we do not know of any national studies of uropathogen resistance in women with cystitis. In a recent trial of pyelonephritis treatment in women, investigators found that Escherichia coli resistance to trimethoprim-sulfamethoxazole varied regionally from 7% in the East to 32% in the West. Because these data came from patients with pyelonephritis, we cannot draw firm conclusions regarding the relationship between these resistance patterns and the prescribing trends we observed.

Because the NAMCS data are based on self-reported practice patterns, we are unable to fully evalu-
ate the appropriateness of antibiotic prescribing. For example, we could not assess the presence of allergies, diagnostic accuracy of reported UTIs, or the success of treatments. Another related limitation of our study is that the NAMCS did not regularly collect data on urine culture ordering or the duration of therapy. However, we assume that patients who were coded as having a UTI and given an antibiotic have a high likelihood of actually having a UTI. While we could not account for the presence of allergies or recurrent UTI, we were able to conduct subset analyses on patients who had no history of UTI.

Despite these limitations, we can report that physicians are managing UTIs in a fashion that raises concerns about antimicrobial resistance and costs. The ordering of urinalysis is declining. This most likely corresponds with a decline in urine culture and susceptibility testing. While the ordering of urine cultures may have little clinical consequence, the decline will have the unintended effect of decreasing available information for assessment of local resistance trends. In addition, current prescribing patterns suggest that, on a national level, we are providing selective pressure for future antimicrobial resistance to 3 drug classes simultaneously. Fluoroquinolone resistance may increase not only because of increased use for UTI, but because of broader use of newer fluoroquinolones (eg, levofloxacin).

Current prescribing patterns have implications for costs as well. While a 10-day course of trimethoprim-sulfamethoxazole in 1999 cost $1.79, ciprofloxacin cost $70.98, and generic nitrofurantoin cost $20.34.

Using the national estimate of annual UTI visits where an antibiotic is given (2.45 million), spending differences on antibiotic is given (2.45 million), spending differences on antibiotic prescribing for UTI that run counter to formal recommendations as physicians begin to use new broad-spectrum fluoroquinolones, despite their overly broad coverage and increased costs. A fraction of antibiotic choices may be explained by clinical factors such as pregnancy, drug allergies, or local resistance patterns. However, given the durability of our findings in multivariable and subgroup analyses, we suspect that the trends also are the result of nonclinical forces such as pharmaceutical promotions and subspecialty culture. Further exploration of the reasons for subspecialty variation in UTI therapy may be a crucial first step to improving antibiotic prescribing practices.

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