LESS IS MORE

Urinary Tract Infection in Male Veterans

Treatment Patterns and Outcomes

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Background: Lengthier antimicrobial therapy is associated with increased costs, antimicrobial resistance, and adverse drug events. Therefore, establishing minimum effective antimicrobial treatment durations is an important public health goal. The optimal treatment duration and current treatment patterns for urinary tract infection (UTI) in men are unknown. We used Veterans Affairs administrative data to study male UTI treatment and outcomes.

Methods: Male UTI episodes in the Veterans Affairs system (fiscal year 2009) were identified by combining *International Classification of Diseases, Ninth Revision* codes with UTI-relevant antimicrobial prescriptions. Episodes were categorized as index, early recurrence (<30 days), or late recurrence (≥30 days) cases. Drug name, treatment duration, and outcomes (recurrence and *Clostridium difficile* infection during 12 months) were recorded for index cases. Demographic, clinical, and treatment characteristics were assessed for associations with outcomes in univariate and multivariate analyses.

Results: Among 4 854 765 outpatient male veterans, 39 149 UTI episodes involving 33 336 unique patients were identified, including 33 336 index cases (85.2%), 1772 early recurrences (4.5%), and 4041 late recurrences (10.3%). Highest-use antimicrobial agents were ciprofloxacin (62.7%) and trimethoprim-sulfamethoxazole (26.8%); 35.0% of patients received shorter-duration treatment (≤7 days), and 65.0% of patients received longer-duration treatment (>7 days). Of the index cases, 4.1% were followed by early recurrence and 9.9% by late recurrence. Longer-duration treatment was not associated with a reduction in early or late recurrence but was associated with increased late recurrence compared with shorter-duration treatment (10.8% vs 8.4%, $P<.001$), including in multivariate analysis (odds ratio, 1.20; 95% CI, 1.10-1.30). In addition, *C difficile* infection risk was significantly higher with longer-duration vs shorter-duration treatment (0.5% vs 0.3%, $P=.02$) and exhibited a similar suggestive trend in multivariate analysis (odds ratio, 1.42; 95% CI, 0.97-2.07).

Conclusion: Longer-duration treatment (>7 days) for male UTI in the outpatient setting was associated with no reduction in early or late recurrence.

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DURATION OF ANTIMICROBIAL therapy is critically important because insufficient treatment can lead to therapeutic failure or recurrent disease,[1,2] whereas prolonged treatment can increase costs, promote antimicrobial resistance, and increase the risk for *Clostridium difficile* infection (CDI).[3,4] The optimal treatment duration for urinary tract infection (UTI) in ambulatory, noncatheterized women is well defined.[5] In contrast, the optimal treatment duration for UTI in men (hereafter, male UTI) is unknown.

See Invited Commentary at end of article

Current expert recommendations are to treat male UTI for 7 to 14 days.[6-8] The recommendation to treat no longer than 14 days is supported by a study[9] of men with febrile UTI (a severe subset of male UTI) that showed equivalent efficacy between 14 and 28 days of treatment. Likewise, the recommendation to treat longer than 3 days is supported by a study[10] of patients with spinal cord injury (70% male) with UTI, among whom recurrence was more likely after 3 days vs 14 days of treatment. However, no study to date has specifically assessed the adequacy of 7-day therapy for male UTI or has compared 7 with 14 days to determine whether 7 days of treatment is as effective or less toxic.

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In other infectious diseases, including cellulitis,[11] ventilator-associated pneumonia,[4] and ventilator-associated tracheitis,[3] shorter-duration treatment seems to be as effective as longer-duration treatment and yields less colonization and infection with

antimicrobial-resistant microorganisms. Whether this is true also for UTI therapy is unknown. Antimicrobial resistance is of particular concern with UTI because the causative microorganisms are mainly gram-negative bacilli, for which few reliably active oral antimicrobial agents are available.[12]

Although the use of minimum effective antimicrobial treatment durations may retard the emergence of antimicrobial resistance, the potential usefulness of this strategy with male UTI is uncertain because current treatment patterns are unknown. That is, if most episodes already receive the minimum effective treatment duration, little improvement is possible. However, if many episodes are overtreated, then the potential benefit from converting all male UTI therapy to shorter-duration therapy could be substantial. Conversely, if longer-duration treatment improves efficacy but many male UTI episodes are undertreated, outcomes could be improved by routinely using longer-duration therapy.

Because Veterans Affairs (VA) medical facilities treat predominantly male patients and share a comprehensive electronic medical record, the Veterans Health Administration is an ideal system within which to study male UTI treatment patterns. Accordingly, we used administrative data extracted from the VA Computerized Patient Record System to document treatment patterns for male UTI among outpatients and to specifically assess the effect of the treatment duration on associated outcomes, including recurrence and CDI.

METHODS

PATIENT IDENTIFICATION

We identified male veterans with a UTI diagnosis by searching for specific *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes (eTable 1; http://www.jamainternalmed.com) within the Outpatient Events file for fiscal year (FY) 2009. The Outpatient Events file contains outpatient information from all Veterans Health Administration facilities, derived from the VA electronic medical record. Each outpatient encounter is associated with up to 10 *ICD-9* codes for the diagnoses and symptoms addressed during the encounter; no primary or secondary codes are designated in the Outpatient Events file. We used past user flags from the VA Enrollment Data files to restrict our cohort to patients identified as VA users in FY 2007 or FY 2008, which permitted assessment of comorbid conditions (including history of prior UTI) using diagnosis codes from previous encounters.

To include only those UTI diagnoses that likely reflected an acute UTI episode, we focused on relevant providers and clinics. Specifically, we included only physicians and mid-level providers, excluding dietitians, respiratory therapists, nurses, and others, and included only those clinics likely to be staffed by physicians and mid-level providers.

DEFINITION OF UTI

A UTI episode was defined as a clinical encounter with an associated *ICD-9* code for UTI, plus (within 72 hours of that encounter) a filled prescription for an antimicrobial typically used to treat UTI (hereafter, UTI-relevant antimicrobial) (eTable 2). Patients meeting these criteria were the study participants. All the UTI episodes were classified as an index case, an early recurrence, or a late recurrence. An index case was the first UTI episode during FY 2009, an early recurrence was any UTI episode less than 30 days after a prior UTI episode, and a late recurrence was any UTI episode 30 days or longer after a prior UTI episode. Cases in the first month of FY 2009 were excluded if a prior UTI episode in FY 2008 had occurred within 30 days of the FY 2009 episode. The study was restricted to outpatients because (1) few patients with UTI require hospitalization[13] and (2) hospitalized patients commonly have multiple antimicrobial regimen changes or multiple documented or suspected infections, confounding assessment of therapy. All the patients were assessed for recurrence for 12 months following their index UTI episode, counting from the date of diagnosis.

Table 1. Clinical Characteristics (Categorical Variables) of 33 336 Outpatient Male Veterans Treated for Urinary Tract Infection in Fiscal Year 2009

Characteristic	No. (%) (n = 33 336)
Diabetes mellitus	11 549 (34.6)
Prostate hypertrophy	10 996 (33.0)
History of prior urinary tract infection	10 275 (30.8)
Incontinence	5438 (16.3)
Prostate cancer	3690 (11.1)
Chronic renal disease	3608 (10.8)
Urethral stricture	2579 (7.7)
Urinary calculi	2338 (7.0)
Spinal cord injury	1564 (4.7)
Prostatitis	866 (2.6)
Prostate disease, other	808 (2.4)
Stroke	482 (1.4)
Dementia	405 (1.2)
Multiple sclerosis	381 (1.1)
Human immunodeficiency virus infection	234 (0.7)
Vesicoureteral reflux	33 (0.1)

ANTIMICROBIAL USE

Orders for UTI-relevant antimicrobials were regarded as associated with the UTI diagnosis if dispensed within 72 hours of the relevant encounter. If multiple antimicrobials were dispensed within 72 hours of the encounter, we inferred their role in UTI therapy based on the number and sequence of prescriptions. That is, if 2 UTI-relevant antimicrobials were dispensed on the same day, we assumed that both were for the UTI (and taken concurrently), whereas if they were dispensed on different days, we assumed that the later-prescribed antimicrobial replaced the initial one. Patients who received 3 or more UTI-relevant antimicrobials on the same day were excluded as having an excessively complex situation. The number of days of medication dispensed was considered the treatment duration. When UTI-relevant antimicrobials were used sequentially, we calculated duration by assuming that the later-prescribed antimicrobial replaced any earlier-dispensed antimicrobials. We categorized treatment as shorter duration ($\leq$7 days) or longer duration ($>$7 days) and grouped antimicrobials by drug class, except for moxifloxacin hydrochloride (a fluoroquinolone not approved or recommended for UTI treatment).

COMORBID CONDITIONS

We assessed comorbid conditions by calculating a Charlson Comorbidity Index based on diagnoses from encounters during the 2 years preceding the index UTI episode.[14,15] In addition, during the same 2-year period, we assessed for conditions known or hypothesized to predispose to UTI (**Table 1**). We did not

assess urinary catheter use because our group had observed a high incidence of discordance in *ICD-9* codes indicating urinary catheter use vs documented use in a prior medical record review,[16] such that we opted to exclude this variable.

C difficile INFECTION

We recorded *ICD-9*–coded CDI diagnoses during the 2 years before and 90 days after the index UTI episode. We did not assess other known complications of antimicrobial use, including allergy, nausea, vomiting, and non-CDI diarrhea, because they lack condition-specific *ICD-9* codes and some (nausea and diarrhea) are common and nonspecific.

STATISTICAL ANALYSIS

We assessed each demographic, clinical, and treatment characteristic for an association with recurrent UTI using a *t* test or Wilcoxon rank sum test for continuous variables or a χ^2 test for categorical variables. We then used logistic regression to simultaneously test all variables for independent associations, separately, with recurrent UTI and CDI. The multivariate models included age, putative UTI risk factors, Charlson Comorbidity Index, and antimicrobial used for UTI treatment and the treatment duration, as well as (for the CDI model) history of prior CDI. We used a separate multivariate model to assess for clinical variables associated with the treatment duration. Analyses were performed using commercially available software (STATA, version 10.1; StataCorp LP). This study was approved by the Minneapolis Veterans Affairs Health Care System Institutional Review Board.

RESULTS

The Outpatient Events file contained 4 854 765 unique male users of VA outpatient services in FY 2009. After excluding encounters involving noneligible providers and clinics and individuals with no outpatient encounters in the prior 2 years, we searched for outpatient encounters associated with UTI-related *ICD-9* codes.

Of 105 025 such encounters, 65 674 (62.5%) had no concurrent prescription for a UTI-relevant antimicrobial and were excluded. Of the remaining 39 351 presumed UTI-associated encounters, 202 were excluded for other reasons (primarily because ≥3 antimicrobials were ordered on the same day), leaving 39 149 encounters for analysis.

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

The 39 149 analyzed UTI-related encounters included 33 336 index cases (85.2% of all encounters), 1772 early recurrences (4.5% of all encounters), and 4041 late recurrences (10.3% of all encounters) and involved 33 336 unique patients (Table 1). Patients had a mean age of 67.9 years and a mean Charlson Comorbidity Index of 1.76. The most common UTI-predisposing conditions identified were diabetes mellitus (34.6%), prostate hypertrophy (33.0%), and history of prior UTI (30.8%).

TREATMENT DETAILS

The 33 336 index cases received 1 day to 173 days of antimicrobial therapy (median, 10; interquartile range, 7-10), with 11 666 patients (35.0%) receiving shorter-duration treatment (≤7 days) and 21 670 patients (65.0%) receiving longer-duration treatment (>7 days). Of 11 666 patients with shorter-duration treatment, most received 7 days of treatment (77.2%), followed by 5 days (14.2%) and 3 days (6.6%); the other 2.0% received treatment ranging from 1 to 6 days. Of 21 670 patients with longer-duration treatment, most received 10 days of treatment (66.2%), followed by 14 days (18.7%) and 30 days (3.5%); the other 11.6% received treatment ranging from 8 to 173 days. The treatment duration fell within the recommended 7 to 14 days for 28 132 index cases (84.4%).

Overall, most index cases were treated with ciprofloxacin (62.7%) or trimethoprim-sulfamethoxazole (26.8%), followed by nitrofurantoin (6.1%), amoxicillin or amoxicillin–clavulanic acid (5.6%), and levofloxacin (3.9%), with other antimicrobials (eTable 2) being used in less than 3% of cases each. In total, 30 937 index cases (92.8%) received a single antimicrobial, whereas 2264 index cases (6.8%) received 2 antimicrobials, and 135 index cases (0.4%) received 3 or more antimicrobials.

RECURRENCE

Of 33 336 index cases, 1373 (4.1%) had a single early recurrence episode (3.9%) or multiple early recurrence episodes (0.2%). The median time to early recurrence was 14 days (range, 1-30 days). Similarly, 3313 index cases (9.9%) had a single late recurrence episode (8.2%) or multiple late recurrence episodes (1.7%). The median time to late recurrence was 107 days (range, 31-364 days). Combining early and late recurrences, 4449 index cases (13.3%) had any recurrence; 237 index cases experienced both early and late recurrences.

FACTORS ASSOCIATED WITH EARLY UTI RECURRENCE

In univariate analysis, shorter-duration and longer-duration treatment exhibited similar rates of early recurrence whether assessed for all the antimicrobials combined (3.9% for ≤7 days vs 4.2% for >7 days, $P = .16$) or for individual drugs (data not shown). When we limited this comparison to 91.4% of patients who received 3 to 7 days of treatment or 8 to 14 days of treatment to exclude possible bias from those receiving short treatment (1-2 days [78 patients]) or long treatment (>14 days [2771 patients]), early recurrence rates remained similar to those of shorter-duration vs longer-duration therapy (3.9% vs 4.1%, $P = .55$).

Several demographic and putative UTI risk factors were associated with early recurrence, including age, incontinence, and history of prior UTI (**Table 2**). However, most such factors, including diabetes, prostatitis, and chronic renal disease, were not associated with early recurrence. Treatment-related factors significantly associated with early recurrence included fluoroquinolone use (ciprofloxacin or levofloxacin decreased risk) and trimethoprim-sulfamethoxazole and β-lactam treatment (increased risk).

In multivariate logistic regression analysis, the treatment duration was not associated with early recurrence

Table 2. Univariate Associations of Demographic, Clinical, and Treatment Characteristics With Risk of Early Recurrence (<30 Days) of Urinary Tract Infection Among Outpatient Male Veterans in Fiscal Year 2009[a]

Characteristic[b]	No./Total No. (%)		*P* Value
	Characteristic Present	Characteristic Absent	
Prostate hypertrophy	546/10 996 (5.0)	827/22 340 (3.7)	<.001
History of prior urinary tract infection	590/10 275 (5.7)	783/23 061 (3.4)	<.001
Incontinence	323/5438 (5.9)	1050/27 898 (3.8)	<.001
Urethral stricture	150/2579 (5.8)	1223/30 757 (4.0)	<.001
Urinary calculi	116/2338 (5.0)	1257/30 998 (4.1)	.03
Spinal cord injury	99/1564 (6.3)	1274/31 772 (4.0)	<.001
Multiple sclerosis	29/381 (7.6)	1344/32 955 (4.1)	.001
Fluoroquinolone treatment	870/22 080 (3.9)	503/11 256 (4.5)	<.001
Trimethoprim-sulfamethoxazole treatment	504/8920 (5.7)	869/24 416 (3.6)	<.001
β-Lactam treatment	161/2218 (7.3)	1212/31 118 (3.9)	<.001

[a] Only those variables that yielded $P \leq .10$ are included in the table.
[b] Assessed characteristics with $P > .10$ included age, stroke, dementia, prostatitis, prostate cancer, diabetes mellitus, treatment duration, vesicoureteral reflux, chronic renal disease, prostate disease (other), Charlson Comorbidity Index, and human immunodeficiency virus infection.

(odds ratio, 1.01; 95% CI, 0.90-1.14). Factors significantly associated with early recurrence included incontinence, β-lactam treatment, history of prior UTI, and prostate hypertrophy (all positive associations) (**Table 3**).

FACTORS ASSOCIATED WITH LATE UTI RECURRENCE

Likewise, longer-duration treatment was not associated with a decrease in late recurrence compared with shorter-duration treatment, but rather was associated with an increase in late recurrence (10.8% for >7 days vs 8.4% for ≤7 days, $P < .001$). Significant associations with late UTI recurrence were observed for all the factors associated with early recurrence, plus several additional factors (**Table 4**).

The association between longer-duration treatment and late recurrence remained significant in multivariate analysis (odds ratio, 1.20; 95% CI, 1.10-1.30) (**Table 5**). Of the other variables that were significantly associated with late recurrence in multivariate analysis, history of prior UTI exhibited the highest odds ratio (2.74; 95% CI, 2.52-2.97).

C difficile INFECTION

Of 33 336 index cases, 144 (0.4%) were diagnosed as having CDI within 90 days after the index case. The interval between the UTI and CDI diagnoses ranged from 1 day to 89 days (mean [SD], 38.7 [26.9] days).

FACTORS ASSOCIATED WITH CDI

In univariate analysis, longer-duration treatment was associated with an increase in CDI compared with shorter-duration treatment (0.5% vs 0.3%, $P = .02$). Other factors significantly associated with CDI (all positive associations) included β-lactam treatment, spinal cord injury, history of prior UTI, history of prior CDI, and human immunodeficiency virus infection (data not shown). In addition, the risk for CDI increased progressively with higher Charlson Comorbidity Index, with 0.2%, 0.3%, 0.5%, and 0.7% of patients with Carlson Comorbidity Indexes of 0, 1, 2, and 3, respectively, experiencing CDI ($P < .001$).

In multivariate analysis, the associations of β-lactam treatment, history of prior CDI, and Charlson Comorbidity Index with CDI remained significant (Table 3). However, the association of the treatment duration with CDI lost statistical significance in multivariate analysis (odds ratio, 1.42; 95% CI, 0.97-2.07).

Table 3. Multivariate Associations of Demographic, Clinical, and Treatment Characteristics Among Outpatient Male Veterans in Fiscal Year 2009

Characteristic	Odds Ratio (95% CI)
Association With Risk of Early Recurrence (<30 Days) of Urinary Tract Infection[a]	
β-Lactam treatment[b]	1.81 (1.52-2.17)
History of prior urinary tract infection	1.49 (1.32-1.68)
Incontinence	1.18 (1.00-1.36)
Prostate hypertrophy	1.22 (1.08-1.38)
Association With Risk of *Clostridium difficile* Infection Within 90 Days of the Index Urinary Tract Infection Episode[c]	
β-Lactam treatment[b]	2.05 (1.27-3.30)
Charlson Comorbidity Index[d]	
2	2.58 (1.42-4.68)
≥3	3.40 (1.82-6.35)
History of prior *C difficile* infection	8.82 (5.45-14.27)
Association With Longer-Duration Treatment (>7 Days) for the Index Urinary Tract Infection Episode[e]	
Dementia	0.79 (0.64-0.97)
History of prior urinary tract infection	1.16 (1.10-1.22)
Human immunodeficiency virus infection	1.35 (1.01-1.81)
Incontinence	1.08 (1.00-1.17)
Prostate disease, other	1.25 (1.06-1.46)
Prostate hypertrophy	1.08 (1.03-1.14)
Prostatitis	1.35 (1.15-1.57)
Spinal cord injury	1.53 (1.34-1.75)
Stroke	0.79 (0.65-0.95)

[a] Variables included in the model but not significantly associated with early recurrence were age, stroke, dementia, prostatitis, prostate cancer, diabetes mellitus, spinal cord injury, treatment duration, multiple sclerosis, chronic renal disease, vesicoureteral reflux, prostate disease (other), Charlson Comorbidity Index, human immunodeficiency virus infection, and trimethoprim-sulfamethoxazole treatment,
[b] Fluoroquinolone treatment was used as the reference group.
[c] Variables included in the model but not significantly associated with *C difficile* infection were age, stroke, dementia, prostatitis, incontinence, urinary calculi, prostate cancer, urethral stricture, diabetes mellitus, spinal cord injury, multiple sclerosis, treatment duration, prostate hypertrophy, chronic renal disease, vesicoureteral reflux, prostate disease (other), trimethoprim-sulfamethoxazole treatment, and human immunodeficiency virus infection.
[d] Charlson Comorbidity Index of 0 used as the reference group.
[e] Variables included in the model but not significantly associated with longer-duration treatment were age, urinary calculi, prostate cancer, urethral stricture, diabetes mellitus, multiple sclerosis, vesicoureteral reflux, chronic renal disease, and Charlson Comorbidity Index.

Table 4. Univariate Associations of Demographic, Clinical, and Treatment Characteristics With Risk of Late Recurrence (≥30 Days) of Urinary Tract Infection Among Outpatient Male Veterans in Fiscal Year 2009[a]

Characteristic[b]	No./Total No. (%)		*P* Value
	Characteristic Present	Characteristic Absent	
Charlson Comorbidity Index			
0	657/8982 (7.3)	2652/24 354 (10.9)	<.001
1	908/8974 (10.1)	2401/24 362 (9.9)	
2	712/6450 (11.0)	2597/26 886 (9.7)	
≥3	1032/8930 (11.6)	2277/24 406 (9.3)	
Prostate hypertrophy	1386/10 996 (12.6)	1923/22 340 (8.6)	<.001
History of prior urinary tract infection	1897/10 275 (18.5)	1412/23 061 (6.1)	<.001
Incontinence	1025/5438 (18.8)	2284/27 898 (8.2)	<.001
Prostate cancer	442/3690 (12.0)	2867/29 646 (9.7)	<.001
Chronic renal disease	426/3608 (11.8)	2883/29 728 (9.7)	<.001
Urethral stricture	447/2579 (17.3)	2862/30 757 (9.3)	<.001
Urinary calculi	329/2338 (14.1)	2980/30 998 (9.6)	<.001
Spinal cord injury	344/1564 (22.0)	2965/31 772 (9.3)	<.001
Prostatitis	137/866 (15.8)	3172/32 470 (9.8)	<.001
Prostate disease, other	123/808 (15.2)	3186/32 528 (9.8)	<.001
Multiple sclerosis	62/381 (16.3)	3247/32 955 (9.9)	.001
Treatment duration >7 d	2332/21 670 (10.8)	977/11 666 (8.4)	<.001
Fluoroquinolone treatment	2104/22 080 (9.5)	1205/11 256 (10.7)	.001
β-Lactam treatment	283/2218 (12.8)	3026/31 118 (9.7)	<.001

[a] Only those variables that yielded $P \leq .10$ are included in the table.
[b] Assessed characteristics with $P > .10$ included age, stroke, dementia, diabetes mellitus, vesicoureteral reflux, human immunodeficiency virus infection, and trimethoprim-sulfamethoxazole treatment.

Table 5. Multivariate Associations of Demographic, Clinical, and Treatment Characteristics With Risk of Late Recurrence (≥30 Days) of Urinary Tract Infection Among Outpatient Male Veterans in Fiscal Year 2009

Characteristic[a]	Odds Ratio (95% CI)
Age	1.01 (1.00-1.01)
Charlson Comorbidity Index[b]	
1	1.13 (1.01-1.27)
2	1.22 (1.07-1.40)
≥3	1.16 (1.01-1.34)
History of prior urinary tract infection	2.74 (2.52-2.97)
Incontinence	1.44 (1.30-1.59)
Prostate hypertrophy	1.15 (1.05-1.25)
Prostatitis	1.37 (1.12-1.67)
Spinal cord injury	1.68 (1.43-1.96)
Treatment duration >7 d	1.20 (1.10-1.30)
Urethral stricture	1.23 (1.09-1.39)
Urinary calculi	1.21 (1.06-1.38)

[a] Variables included in the model but not significantly associated with late recurrence were stroke, dementia, β-lactam treatment, prostate cancer, diabetes mellitus, multiple sclerosis, vesicoureteral reflux, chronic renal disease, prostate disease (other), fluoroquinolone treatment, human immunodeficiency virus infection, and trimethoprim-sulfamethoxazole treatment.
[b] Charlson Comorbidity Index of 0 was used as the reference group.

FACTORS ASSOCIATED WITH THE TREATMENT DURATION

Associations with the treatment duration were assessed to identify possible underlying factors influencing providers' choice of length of therapy for their patients. In univariate analysis, multiple demographic and clinical characteristics were associated with longer-duration treatment (data not shown), some of which remained significant in multivariate analysis (Table 3).

COMMENT

In this study of 33 336 outpatient male veterans treated for UTI in FY 2009, we assessed current treatment patterns, along with demographic and clinical variables, in relation to recurrent UTI and subsequent CDI. We found that 2 drugs (ciprofloxacin and trimethoprim-sulfamethoxazole) were used to treat most male UTI episodes and that the treatment duration varied substantially within the recommended 7 to 14 days (84.4% of patients) and outside of this range (15.6% of patients). Most important, compared with shorter-duration treatment (≤7 days), longer-duration treatment (>7 days) exhibited no association with a reduced risk for early or late recurrence.

Our finding that shorter-duration treatment was not associated with increased early recurrence contrasts with the increase in recurrence observed in a trial of 3 days vs 14 days of treatment for UTI.[10] Notably, our study was observational, and residual confounding could explain why longer-duration treatment was not associated with clinical benefit. For instance, patients at increased risk for recurrence because of some unmeasured factor (eg, catheter use) may have been overrepresented in the group that received longer-duration treatment. In addition, most patients in our shorter-duration treatment group received more than the 3 days of therapy, which previously had been associated with increased recurrence.[10]

The finding that longer-duration treatment was associated with an increased late recurrence risk in univariate and multivariate analyses was unexpected. Although we anticipated that late recurrence risk would be greater in association with predisposing host factors, we did not expect it to be influenced by the duration of

therapy used for the index UTI episode. This association may be confounded by other factors (measured or unmeasured) that lead clinicians to prescribe longer-duration treatment. Alternatively, the increased risk for late recurrence among recipients of longer-duration treatment may be related to the resultant more profound disruption of the endogenous microbiota, as documented in young women with cystitis[17] and as demonstrated experimentally in primates.[18,19]

The other assessed outcome, CDI, is a known and occasionally severe complication of antimicrobial use, for which specific *ICD-9* codes are readily available. Although no investigations to date have validated *ICD-9* codes as a case-finding method for outpatients, the codes have been successfully used among hospitalized patients.[20,21] Longer-duration treatment was significantly associated with CDI in univariate analysis, although in multivariate analysis this association lost statistical significance. Our analysis was limited to the outpatient setting; accordingly, our estimate of CDI may be an underestimate. Increased antimicrobial use is known to increase the risk for CDI, probably through more profound perturbation of the normally protective endogenous colonic microbiota.[22,23] In addition, β-lactam treatment was associated with subsequent CDI and with early recurrence, suggesting that these antimicrobials should be second-line agents for the treatment of male UTI.

Together, our findings suggest that longer-duration treatment for male UTI in the outpatient setting is not associated with a reduction in early or late recurrence and may be associated with an increase in subsequent CDI. Moreover, although not assessed herein, increased antimicrobial use has known associations with antimicrobial resistance at the individual level[3,4,24] and population level[25,26] and with increased drug costs. Therefore, trials directly comparing shorter-duration vs longer-duration treatment for male UTI, similar to those performed for cellulitis[11] and ventilator-associated respiratory tract infections,[3,4] are needed to guide optimal management for this common condition.

Strengths of our study include the large sample size and the inclusion of patients from the entire United States. The chief limitation, inherent to all studies based on administrative data, is clinical uncertainty, resulting herein from our inability to verify that encounters coded as UTI represented patients actually being treated for symptomatic UTI. Conceivably, a visit coded as a UTI could represent a follow-up examination for a history of prior UTI, asymptomatic bacteriuria, or an acute symptomatic UTI. We attempted to optimize the validity of the data by requiring study UTI episodes to have both a UTI-related *ICD-9* code and a UTI-relevant antimicrobial prescription and by excluding nonrelevant providers and clinics. In contrast to prior work that used only *ICD-9* codes,[13] this approach eliminated more than 65 000 potential patients and resulted in a study population consisting of less than 1% of all male VA users within the study period. However, this approach allowed us to analyze more than 33 000 patients, while improving our confidence that the individuals truly were treated for UTI. We are unaware of literature describing the sensitivity and specificity of *ICD-9* codes for UTI, although for several chronic conditions their sensitivity and specificity ranged from 24% to 78% and from 88% to 100%, respectively, compared with patient self-report.[27] Finally, we did not capture UTI episodes occurring outside of the Veterans Health Administration. Although this would lead to an underestimate of recurrence, no reason exists to suspect that the frequency of non-VA care would differ by the treatment duration, and such care has been shown to be minimal among VA patients.[28]

In summary, in this study of more than 33 000 outpatient male veterans treated for UTI during FY 2009, the range of antimicrobial agents used was limited, but the treatment duration was variable. Longer-duration treatment (>7 days) was not associated with reduced risk for early or late recurrence risk but may have been associated with subsequent CDI. These findings question the role of longer-duration treatment for male UTI in the outpatient setting. A randomized trial is needed to directly assess the benefits and harms of shorter-duration vs longer-duration treatment for male UTI.

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INVITED COMMENTARY

New Perspectives on Urinary Tract Infection in Men

Most studies on the treatment of acute urinary tract infection (UTI) in outpatients have been performed in women, usually premenopausal women. The most recent treatment guidelines for acute, uncomplicated cystitis issued by the Infectious Diseases Society of America[1] specifically exclude men from their recommendations, presumably for a lack of evidence to guide recommendations. The extensive literature on UTI in women recognizes that the pathogenesis, risk factors, and optimal management of UTI may differ by age and by menopausal status. We would expect similar distinctions in male UTI, particularly given the role of age-associated prostatic enlargement in urinary retention, but the available literature neither refutes nor supports this point. Recommendations for the treatment of male UTI generally state that 7 to 14 days of antibiotic therapy are required, without clear evidence to guide this statement.[2]

Against this background, 2 studies by Drekonja et al[3,4] in this issue of the journal stand out in welcome relief. Both studies are from the same research group and patient population, namely, older male veterans at the Minneapolis Veterans Affairs Health Care System, Minneapolis, Minnesota. Both studies address questions about the field of UTI in which the existing literature is insufficient to guide clinical management. The full article,[3] entitled "Urinary Tract Infection in Male Veterans: Treatment Patterns and Outcomes," focuses on the appropriate duration of antibiotic therapy for outpatient male veterans with UTI. This retrospective study used administrative data and *International Classification of Diseases, Ninth Revision* codes to examine outpatient male UTI, with attention to whether shorter duration ($\leq$7 days) or longer duration ($>$7 days) of antibiotic therapy was prescribed. Clinical outcomes studied