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%), 1,772 early recurrences (4.5%), and 4,041 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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In other infectious diseases, including cellulitis, ventilator-associated pneumonia, and ventilator-associated tracheitis, 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 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.

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 (≤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;\textsuperscript{46} such that we opted to exclude this variable.

\textbf{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.

\section*{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 \( \chi^2 \) 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 categorical 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.

\section*{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 \( \geq 3 \) antimicrobials were ordered on the same day), leaving 39,149 encounters for analysis.

\section*{DEMOGRAPHICS AND CLINICAL CHARACTERISTICS}

The 39,149 analyzed UTI-related encounters included 33,336 index cases (85.2\% of all encounters), 17,722 early recurrences (4.5\% of all encounters), and 4,041 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\%).

\section*{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 (\( \leq 7 \) 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 (Table 2) being used in less than 3\% of cases each. In total, 30,937 index cases (92.8\%) received a single antimicrobial, whereas 2,264 index cases (6.8\%) received 2 antimicrobials, and 135 index cases (0.4\%) received 3 or more antimicrobials.

\section*{RECURRENTNESS}

Of 33,336 index cases, 1,373 (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, 3,313 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, 4,449 index cases (13.3\%) had any recurrence; 237 index cases experienced both early and late recurrences.

\section*{FACTORS ASSOCIATED WITH EARLY UTI RECURRENTNESS}

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 \( \leq 7 \) 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 [2,771 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 \( \beta \)-lactam treatment (increased risk).

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

\section*{REFERENCES}

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

\section*{APPENDIX}

\section*{SUPPLEMENTAL MATERIAL}

\subsection*{Tables and Figures}

\begin{itemize}
  \item Table 1: Characteristics of index cases.
  \item Figure 1: Kaplan-Meier survival curves for recurrent UTIs.
\end{itemize}
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 Charlson Comorbidity Index, human immunodeficiency virus infection, and trimethoprim-sulfamethoxazole treatment.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Lactam treatment</td>
<td>1.81 (1.52-2.17)</td>
</tr>
<tr>
<td>History of prior urinary tract infection</td>
<td>1.49 (1.32-1.68)</td>
</tr>
<tr>
<td>Incontinence</td>
<td>1.18 (1.00-1.36)</td>
</tr>
<tr>
<td>Prostate hypertrophy</td>
<td>1.22 (1.08-1.38)</td>
</tr>
<tr>
<td>History of prior urinary tract infection</td>
<td>2.05 (1.27-3.30)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>2.58 (1.42-4.68)</td>
</tr>
<tr>
<td>Dementia</td>
<td>3.40 (1.82-6.35)</td>
</tr>
<tr>
<td>History of prior C difficile infection</td>
<td>8.82 (5.45-14.27)</td>
</tr>
</tbody>
</table>

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

Table 4. 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

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

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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).

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 and as demonstrated experimentally in primates.

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. 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. 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 and population level and with increased drug costs. Therefore, trials directly comparing shorter-duration vs longer-duration treatment for male UTI, similar to those performed for cellulitis and ventilator-associated respiratory tract infections, 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 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, 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. 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.

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.

Accepted for Publication: July 22, 2012.
Published Online: December 3, 2012. doi:10.1001/2013.jamainternmed.829
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Author Contributions: Dr Drekonja 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. Study concept and design: Drekonja and Johnson. Acquisition of data: Cutting. Analysis and interpretation of data: Drekonja, Rector, and Johnson. Drafting of the manuscript: Drekonja. Critical revision of the manuscript for important intellectual content: Drekonja, Rector, Cutting, and Johnson. Statistical analysis: Rector. Obtained funding: Drekonja. Administrative, technical, and material support: Cutting and Rector. Study supervision: Drekonja, Rector, and Johnson.

Conflict of Interest Disclosures: Dr Johnson has research grants from or contracts with Merck, Rochester Medical, and Syntiron.

Funding/Support: This study was supported by the resources of the Minneapolis Veterans Affairs Health Care System, including the Center for Epidemiological and Clinical Research and the Center for Chronic Disease Outcomes Research.


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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 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. Against this background, 2 studies by Drekonja et al3,4 in this issue of the journal stand out in welcome relief. Both studies are from the same research group in Minneapolis, Minnesota. Both studies address questions about the field of UTI in which the existing literature is sparse. The studies by Drekonja et al3,4 in this issue of the journal stand out in welcome relief. Both studies are from the same research group in Minneapolis, Minnesota. Both studies address questions about the field of UTI in which the existing literature is sparse.