

Urinary Tract Infections in Male Veterans With Human Immunodeficiency Virus

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Treatment duration for men with urinary tract infection (UTI) and human immunodeficiency virus (HIV) infection is unknown. Fiscal year 2009 Veterans Affairs administrative data were used to compare men with HIV and UTI with non-HIV men with UTI. Antimicrobial selection and duration were similar. Shorter treatment (≤ 7 days) did not affect recurrence, suggesting that treatment beyond 7 days may be unnecessary.

Keywords. *Clostridium difficile*; HIV; human immunodeficiency virus; urinary tract infection; UTI.

Opportunistic infections are well described in patients infected with human immunodeficiency virus (HIV), but routine infections in this population are relatively understudied. Urinary tract infections (UTIs) in particular have received scant attention. Although a high rate of UTIs has been described in patients with advanced HIV [1, 2], data to guide UTI treatment in patients with HIV are lacking.

A recently described cohort of approximately 33 000 male veterans [3] provided an opportunity to assess the treatment of UTI in men with HIV. We hypothesized that men with HIV would be treated for a longer duration than their HIV-negative comparators due to concerns regarding immune suppression, and that this might result in an increase in *Clostridium difficile* infections (CDIs). Among all men in this cohort, treating UTIs for >7 days did not reduce early recurrences, but it did result in an increase in late recurrences and CDI [3]; however, it is unknown whether this result applies to men with HIV.

With increasing antimicrobial resistance [4] and CDIs [5], optimizing treatment duration is an increasingly important strategy to preserve antimicrobial efficacy and limit CDI morbidity. Accordingly, we utilized fiscal year 2009 Veterans Affairs (VA) administrative data to compare treatment duration and outcomes for men with UTI with and without HIV infection.

METHODS

We utilized a previously described cohort of 33 336 male veterans with UTI, all with both a UTI-relevant International Classification of Diseases-9th revision (ICD-9) code and an associated prescription for an antimicrobial typically used to treat UTI. This combination was used to exclude follow-up visits, which are also often coded as UTI [3]. To capture the maximal number of UTI episodes, a total of 13 ICD-9 codes were included; however, 3 codes (599.0, urinary tract infection, site not specified; 595.9, cystitis, unspecified; and 595.0, acute cystitis) comprised 97.6% of all included episodes, making this a study largely of lower-urinary tract infections [3].

From this cohort, we identified subjects with HIV infection, defined as having a diagnosis of HIV infection documented in the 2 years prior to the qualifying UTI episode. We compared demographic information, underlying medical conditions, treatment factors, and outcomes between the patients with and without HIV, including comorbid conditions that could potentially predispose for UTIs. Treatment of ≤ 7 days was classified as shorter-duration, whereas >7 days was classified as longer-duration. Descriptive statistics were used to compare treatment patterns and outcomes. Continuous variables were compared using *t* tests, whereas categorical variables were compared using χ^2 tests. Because trimethoprim-sulfamethoxazole (TMP-SMZ) is commonly used both to treat UTIs and as prophylaxis for patients with advanced HIV, we assessed for any interaction between TMP-SMZ use and HIV infection with regard to treatment duration.

Clostridium difficile infection episodes were determined by ICD-9-coded CDI diagnoses during the 2 years before and 90 days after the index UTI episode. Because our source data do not include microbiology results, we were unable to verify CDI diagnoses with a positive test result. The Minneapolis Veterans Affairs Institutional Review Board approved this research.

RESULTS

Among the 33 336 male veterans with UTI, 234 (0.7%) were diagnosed with HIV. The patients with HIV were significantly

Received 3 August 2014; accepted 13 October 2014.

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Open Forum Infectious Diseases

Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2014. This work is written by (a) US Government employee(s) and is in the public domain in the US. DOI: 10.1093/ofid/ofu100

younger than those without HIV (56.5 vs 68.0 years; $P < .001$). A majority (133 of 234; 56.8%) of patients with HIV were African American compared with only 20.4% (67/66 of 33 102) in the non-HIV group ($P < .001$). Among the assessed comorbidities known or hypothesized to be associated with UTI, several differences between patients with HIV vs patients without HIV were observed, with most being less common in patients with HIV (Table 1). In particular, diabetes (23.1% vs 34.7%; $P < .001$), benign prostatic hypertrophy (19.2% vs 33.1%; $P < .001$), other prostate issues (0.4% vs 2.4%; $P = .046$), and urethral stricture (4.3% vs 7.8%; $P = .047$) were less common in patients with HIV. In contrast, prostatitis was the only comorbidity significantly more common in patients with HIV (5.1% vs 2.6%; $P = .02$).

We compared antibiotics commonly prescribed for UTI between patients with HIV vs those without HIV. Assessed antibiotics included TMP-SMZ, fluoroquinolones (specifically, ciprofloxacin and levofloxacin), β -lactams (specifically, cefixime, cefpodoxime, ceftioxin, cefuroxime, cephalexin, amoxicillin, and amoxicillin-clavulanic acid), and others (nitrofurantoin, fosfomycin). Overall, most patients were prescribed fluoroquinolones (66.2%) and TMP-SMZ (26.8%), followed by β -lactams (6.7%) and others (6.2%), with the total percentage exceeding 100% due to some patients being prescribed multiple agents. The proportion of patients prescribed each drug between patients with HIV vs patients without HIV was not significantly different, although there was a trend towards an increase in fluoroquinolones prescribed to patients with HIV (72.2% vs 66.2%; $P = .052$).

Table 1. Comorbidities Known or Hypothesized to Be Associated With Urinary Tract Infection (UTI) Among Patients With and Without Human Immunodeficiency Virus (HIV) Infection

Comorbidity	HIV-Negative, No. (%) With Condition	HIV-Positive, No. (%) With Condition	<i>P</i> Value
Diabetes Mellitus	11 495 (34.7%)	54 (23.1%)	<.001
Benign Prostatic Hypertrophy	10 951 (33.1%)	45 (19.2%)	<.001
Prior UTI	10 211 (30.9%)	64 (27.3%)	.25
Incontinence	5407 (16.3%)	31 (13.2%)	.20
Chronic Kidney Disease	3581 (10.8%)	27 (11.5%)	.72
Prostate Cancer	3672 (11.1%)	18 (7.7%)	.10
Urethral Stricture	2569 (7.8%)	10 (4.3%)	.047
Urinary Calculi	2317 (7.0%)	21 (9.0%)	.24
Spinal Cord Injury	1556 (4.7%)	8 (3.4%)	.36
Prostatitis	854 (2.6%)	12 (5.1%)	.02
Other Prostate Issues	807 (2.4%)	1 (0.4%)	.046
Stroke	482 (1.5%)	0 (0.0%)	.06
Multiple Sclerosis	381 (1.1%)	0 (0.0%)	.10
Dementia	405 (1.2%)	0 (0.0%)	.09
Vesicoureteral Reflux	33 (0.1%)	0 (0.0%)	.63

Among the patients with HIV, 74 (31.6%) were treated for shorter-duration, whereas 160 (68.4%) were treated for longer-duration. Similar ratios were seen for the patients without HIV, with 35.0% treated for shorter-duration and 65.0% for longer-duration ($P = .28$). Looking more closely at the patients with HIV, the overall mean duration of treatment was 7.4 days (standard deviation, 2.9). Among the 74 receiving shorter-duration therapy, 56 received 7 days, 11 received 5 days, 6 received 3 days, and 1 received a single day of therapy. Among the 160 receiving longer-duration therapy, 83 received 10 days, 39 received 14 days, and 6 received 30 days. There were 24 other durations, ranging from 8 to 91 days, which were prescribed for ≤ 3 patients each.

Because TMP-SMZ is prescribed prophylactically in patients with low CD4 counts, some of the prescriptions for TMP-SMZ categorized as being UTI-related may have been for prophylaxis, thereby artificially lengthening therapy duration. To assess this hypothesis, we examined prescriptions for 30, 60, or 90 days (± 1 day) and identified 9 such prescriptions. Of these, 5 were for ciprofloxacin, and 4 were for TMP-SMZ. Accordingly, in these 4 cases, it is possible that the TMP-SMZ was being provided for prophylaxis, rather than for an acute UTI, and may have slightly increased the mean duration of therapy.

Patients were assessed for both early (within 30 days from the index episode) and late (>30 days from the index episode) recurrence. Among patients with HIV, only 7 (3.0%) had an early recurrence and 27 (11.5%) had a late recurrence. No differences were observed when compared with patients without HIV (4.1% early recurrence, 9.9% late recurrence; $P =$ not significant for both comparisons).

Of the 7 patients with HIV who had an early recurrence of UTI (3.0%), all received longer-duration treatment ($P = .10$). Of the 27 patients who had a late recurrence (11.5%), 6 of 27 (22%) received shorter-duration treatment for their initial episode, and 21 of 27 (78%) received longer-duration treatment ($P = .28$). Evaluating all recurrences of UTI, whether early or late, 6 patients receiving shorter-duration and 28 patients receiving longer-duration experienced any episode of recurrence ($P = .07$).

The one significant difference observed between patients with and without HIV was the proportion of subjects experiencing CDI. Among patients with HIV, 3 (1.3%) developed CDI, compared with 141 (0.4%) in the non-HIV group ($P = .047$). After examining the effect of treatment duration on the 234 patients with HIV, we noted that among the 74 patients who received shorter-duration therapy, there were no episodes of CDI, whereas in the 160 patients receiving longer-duration therapy, there were 3 episodes (0% vs 2%; $P = .55$).

DISCUSSION

In this study of male veterans with UTI in fiscal year 2009, we assessed various factors between men with and without HIV, including medical comorbidities, antibiotic selected for treatment,

duration of treatment, recurrence of UTI, and CDI. Contrary to our expectation that patients with UTI and HIV would be treated with antimicrobials for a longer duration, we found that treatment was similar to that provided to men without HIV. A majority of patients, both with and without HIV, were treated with fluoroquinolones or TMP-SMZ. There was also no significant difference in the duration of treatment between the 2 groups, suggesting that practitioners treat patients with HIV and UTI similar to the general male VA population with UTIs.

Although we observed differences in comorbidities between patients with and without HIV, it is not clear whether these differences are related to the significant age difference between the 2 groups, or possibly associated with some other confounding variable. A multivariate analysis to explore these associations was considered, but given the limited number of patients with HIV it was thought that any detected associations would be of questionable validity and with large confidence intervals. Accordingly, we limited ourselves to descriptive statistics of the various comorbid conditions present in our cohort.

Regarding recurrence of UTI in patients with and without HIV, we found that there was no difference in either early or late recurrence by HIV status and that treatment duration also had no effect on recurrence. After evaluating recurrence by treatment duration in the 234 patients with HIV, we noted that there was a trend towards increased recurrence among those who received longer-duration treatment. Although this observation likely represents unmeasured confounders, it is notable that there was no suggestion of an increase in recurrence with the shorter-duration treatment.

The 1 major between-group difference was the proportion of subjects who experienced CDI. Patients with HIV had a 3-fold risk of CDI compared with the patients without HIV. Possible explanations for this increase may be related to varying degrees of immunosuppression in patients with HIV or the increased use of antibiotics for prophylaxis in high-risk patients.

Study limitations include the small sample size, its observational nature, and the reliance on administrative data. In addition, although we hypothesized that lower CD4 cell counts and associated antibiotic prophylaxis might be contributing to the increased rate of CDI in patients with HIV, CD4 status is not available through our source data file. However, because

TMP-SMZ use between patients with and without HIV was not significantly different, and there were few TMP-SMZ prescriptions for 30, 60, or 90 days, it seems unlikely that increased prophylactic antimicrobials were causing this difference. Microbiology results, recent urologic surgery, and catheter use are other relevant data points which would be of clinical interest but which are also not available.

In this study of male veterans with UTI, we found that patients with and without HIV were treated similarly with regard to treatment duration and antimicrobial selection. Longer-duration treatment in patients with HIV did not affect recurrence. Rates of CDI, which were elevated in patients with HIV relative to non-HIV patients, were not significantly affected by treatment duration. These findings suggest that longer-duration treatment for UTI may not be beneficial, even in men with HIV. Further studies in this population are needed.

Acknowledgments

Author contributions. All authors had access to the data and a role in writing the manuscript.

Financial support. This work 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.

Potential conflicts of interest. D. M. D. has served as a consultant (medical monitor) for a phase 2 clinical trial of recurrent *Clostridium difficile* infection conducted by Rebiotix.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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