Contemporary Clinical Trials Communications 21 (2021) 100714

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: http://www.elsevier.com/locate/conctc

Study Protocol: Seven vs. 14 days treatment for afebrile men with urinary tract infection

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ARTICLE INFO

Keywords:
Urinary tract infection
Clinical trial
Antibiotics

ABSTRACT

The optimal treatment duration for men with urinary tract infection (UTI) is poorly defined. Observational data suggests that shorter-duration therapy may perform as well as longer-duration therapy, but trial data are lacking. We present the protocol and methods for a Department of Veterans Affairs-funded trial of seven vs. 14 days of antimicrobial therapy for afebrile men with UTI, with the primary outcome of symptom resolution 14 days after completing active antimicrobial treatment. An optional sub-study will investigate the effect of treatment duration on the intestinal carriage of antimicrobial-resistant microorganisms. Subjects are enrolled after their UTI is diagnosed and treatment initiated, using a combination of in-person and mail enrollment to maximize participation and minimize resource utilization. This trial will provide high-quality evidence to guide the management of a common infectious disease and potentially limit unnecessary antimicrobial use.

1. Introduction

Urinary tract infection (UTI) is a common outpatient diagnosis resulting in antibiotic use, with an estimate of 7 million outpatient encounters and more than 100,000 hospitalizations annually in the United States [1]. Management of UTI in women is well-studied, with multiple antibiotic options available for specific durations of therapy. These range from single-dose fosfomycin to five days of nitrofurantoin, both of which are endorsed by guidelines from the Infectious Diseases Society of America and both of which give comparable results to three days of trimethoprim-sulfamethoxazole (TMP-SMZ) or ciprofloxacin [2]. Among men, management is not as well-defined, and in particular, treatment duration is uncertain. Prior studies of men with febrile UTI suggested that 14 days performed as well as 28 days, but that seven was slightly inferior to 14 days [3,4]. Trial data for men with UTI without fever are lacking, leaving clinicians with only observational studies and expert opinion to guide them.

Observational data from the Veterans Affairs (VA) system suggests that treatment for longer than seven days confers no benefit for men with UTI, a finding that is contrary to the trial evidence for men with febrile UTI [5]. To help preserve the activity of antibiotics in the face of increasing antimicrobial resistance and decreasing development of new antimicrobials, antibiotics should be given for as short a time as needed for clinical efficacy. To determine the optimal treatment duration for afebrile men with UTI, we are conducting a pragmatic multi-site randomized, double-blind, placebo-controlled trial of seven vs. 14 days treatment duration in the VA health care system. An optional sub-study will address whether the additional seven days of antibiotic exposure leads to an increase in the intestinal carriage of antimicrobial-resistant organisms.

2. Methods

A randomized, double-blind, placebo-controlled trial of seven vs 14 days treatment duration for men with UTI without fever is conducted to determine whether shorter-duration of treatment is non-inferior to longer-duration therapy. Patients clinically diagnosed with UTI and treated largely in the ambulatory setting (no more than 24 h hospitalization allowed) with ciprofloxacin or TMP-SMZ are reviewed for eligibility by study coordinators and contacted and offered participation if they meet eligibility criteria. Only patients treated with TMP-SMZ or ciprofloxacin are considered because prior data shows these drugs account for approximately 90% of UTI prescriptions at our facility and be-

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https://doi.org/10.1016/j.conctc.2021.100714
Received 7 July 2020; Received in revised form 20 November 2020; Accepted 12 January 2021
Available online 16 January 2021

cause this allows effective blinding using different formulations of the same medications or placebo on days eight through 14 of therapy.

2.1. Identification of potential UTI subjects

The study coordinators identify potential patients mainly through a report using VISTA, the system architecture behind the VA's Computerized Patient Record System (CPRS). A template was created to run the report for specific dates to identify male patients with specific ICD 9 (later ICD 10) codes that related to UTI or UTI symptoms that were study inclusion criteria. The study coordinators enter the names of all identified patients into a screening log, then use CPRS to determine which inclusion and exclusion criteria were met.

Subjects need to meet all of the following inclusion criteria: 1) male gender, 2) new-onset (within 7 days) of at least one of the following symptoms: dysuria, urinary frequency, urgency, hematuria, perineal pain, supra-pubic pain, costovertebral angle tenderness, or flank pain, 3) treated as outpatient (Primary Care Center or Emergency Department) with <24 h observation in the hospital or Emergency Department following the initial diagnosis, and 4) prescribed treatment with at least seven but not more than 14 days of either TMP-SMZ or ciprofloxacin.

Additionally, subjects must fulfil none of the following exclusionary criteria: 1) admission to hospital for >24 h at the time of diagnosis, 2) documented temperature of $\geq$38.0 Celsius at time of initial evaluation, 3) previous enrollment in the study, 4) treatment for UTI in the 14 days before the current UTI diagnosis, 5) unable to give informed consent, 6) unwilling to enroll in the study via in-person enrollment at the Minneapolis or Houston VA Medical Center, or in-person at the participant's home, or via mail enrollment, 7) symptoms thought more likely to be caused by a non-UTI diagnosis, 8) other antimicrobial therapy, new or ongoing, prescribed for a non-UTI diagnosis, 9) treatment initiated with an empiric antimicrobial to which the urine culture isolate is non-susceptible based on standard laboratory criteria, and 10) treatment initiated with an empiric antimicrobial regimen that is underdosed based on current guidelines [2] and reviews [6,7].

Patients meeting all inclusion and no exclusion criteria are contacted by phone and informed of the study and asked if they are interested in participating. Those interested are given the option to enroll through one of three methods: 1) in-person enrollment at the Minneapolis or Houston VA Medical Centers, 2) in-person enrollment at the patient's home (patients with a behavior flag in CPRS, a history of inappropriate behavior, or any possible safety issues are not eligible for home enrollment), or 3) mail enrollment. Patients who cannot be contacted about the study are mailed out the enrollment packet, which contains an eligibility letter, a cover letter explaining how to enroll in the study by mail, a consent form, and a HIPAA waiver form. This is done because of the time-sensitive nature of the study, with all participants needing to start study medication on day 8 of their current treatment course. This allows potentially interested patients who cannot be reached by phone to decide whether they want to participate in the trial. Enrolling after the time of UTI diagnosis and treatment initiation is possible because the intervention (7 vs. 14 days of treatment) only impacts therapy after day 7, and also allows study staff to enroll from multiple clinics and shifts, which otherwise would require significantly higher levels of staffing.

2.2. Setting

The study was initially planned to be conducted as a single-site trial at the Minneapolis VA Health Care System (MVAHCS), a tertiary VA medical center serving Minnesota and parts of Wisconsin, North and South Dakota, Iowa, and Nebraska. Enrollment at this site began in April 2014. To address slower than expected enrollment, a second site (the Michael E. DeBakey VA Medical Center in Houston Texas) was approved midway through the study and began enrolling patients in January of 2018. At both sites enrollment focuses on outpatient primary care clinics and emergency departments, including Community Based Outpatient Clinics operated by the Minneapolis and Houston VA Health Care Systems.

2.3. Study medications

All participants are randomized to receive, for days eight through 14, either the antibiotic they were originally prescribed (resulting in 7 days of total antibiotic duration) or placebo (resulting in 7 days of total antibiotic duration). Patients are told that regardless of whether they were randomized to active antibiotic or placebo, they will receive medication that was different in appearance from their clinically prescribed medication for the second week of treatment. This medication is either the active antibiotic (but from an alternate manufacturer and different in appearance than their original medication) or a placebo tablet. The placebo and all antibiotic tablets were similar in size (approximately 1 g). Placebo tablets were purchased through an agreement with the VA Cooperative Study Program Clinical Pharmacy in Albuquerque, New Mexico, while the ciprofloxacin and TMP-SMZ were purchased using study funds by the research pharmacist at the MVAHCS.

2.4. Data collection

Data from the visit where the UTI was initially diagnosed and treated are recorded by study coordinators, including clinical symptoms of UTI, presence of factors known to complicate UTI treatment (stones, strictures, prostate hypertrophy, etc), Charlson comorbidity index, details of the treating provider, information about the prescribed treatment (medication, dose, and duration), and laboratory values on or about the day of the visit. Laboratory data recorded include peripheral white blood cell count, serum creatinine, urinalysis results, and urine culture results. However, laboratory data are not required for study participation; if clinicians opt to diagnose and treat UTI without such data, patients can enroll if they otherwise meet study eligibility criteria.

Study follow-up occurs via telephone on the day study medication stops, and then days seven, 14, and 28 after stopping (Table 1). During each call study coordinators ask subjects about adverse effects of antibiotics, the status of their presenting UTI symptoms, whether they have had any new UTI symptoms, and whether they sought treatment for a UTI since completing study medication. Subjects are given the office number of study staff to call with any questions or issues regarding the study. Subjects are encouraged to follow up with their primary care provider if they have recurrent UTI symptoms, adverse events that are bothersome, or any other concerns about their medical condition.

Table 1
Timing of study tasks and assessments.

Study task	Days after start of urinary tract infection treatment					
	0	7	14	21	28	42
Patient screening & outreach	X					
Informed consent and enrollment		X				
Study medication initiated		X				
Study medication completed			X	X	X	X
UTI symptom assessment			X	X	X	X
Adverse event assessment			X	X	X	X
Subject completes study						X

2.5. Randomization

The study is designed as a double-blind randomized controlled trial, with participants randomized to study medication on day 8 of UTI treatment. Randomization is stratified by study site and by the presence or absence of urinary catheter use (including indwelling catheters and intermittent catheterization), to ensure similar numbers of catheterized patients in each treatment arm. Randomization lists using permuted blocks of four were prepared before study launch and were provided to the research pharmacist at each site. Randomization occurs when the research pharmacist receives the subject's signed informed consent form, at which time the assigned study medication is delivered to the subject, either in person or by mail.

2.6. Logistics of enrollment

Subjects enrolling in person at the VA Medical Center have their eligibility verified, review the informed consent form with a study coordinator, and then receive their study medication in a seven-day pill box. Subjects enrolling at home first review study materials and an informed consent form that are mailed to them via an overnight service, then discuss the forms over the telephone, and sign and return the forms if they consent to enroll. Study coordinators take the signed forms to the research pharmacist, who dispenses the study medication which the coordinator delivers to the patient. Subjects enrolling by mail follow a similar procedure, receiving the informed consent form and other forms via overnight delivery, reviewing them with the coordinator over the phone, and then signing and returning the forms by overnight delivery. However, instead of the coordinator delivering the study medications, the medications are sent directly to the subject, again via overnight delivery. For each enrollment option (in person at the VA Medical Center, in person at home, and by mail) study coordinators are in frequent contact to answer questions, ensure forms are completed, ensure no treatment gaps, and otherwise verify that enrollment is complete.

2.7. Resistance sub-study

To investigate potential harms of longer-duration antibiotic use, aside from the readily apparent costs and inconvenience to patients, a resistance sub-study is to assess the effect of treatment duration on the intestinal carriage of antimicrobial-resistant Gram-negative bacilli. Subjects in the main study are offered participation in the resistance sub-study, which consists of submitting two swabs with fecal material to a research laboratory at the MVAHCS. Fecal material is collected either by a rectal swab performed by the study coordinator or by patient self-collection. Received swabs are plated onto selective media to encourage growth of Gram-negative bacilli, including tergitol-7 plates with added ciprofloxacin and TMP-SMZ to select for resistant strains. From plates yielding growth of Gram-negative bacilli, one representative each of up to three of the most-numerous colony morphologies per plate is identified to the species level using the API-20E system (BioMerieux, Durham, NC). Susceptibility to 22 antimicrobial agents is determined by disk diffusion, using methods, control strains, and interpretive criteria as specific by the Clinical and Laboratory Standards Institute.

2.8. Endpoints

The primary endpoint for this pragmatic trial is resolution of UTI symptoms 14 days after completing active antibiotic treatment. To assess this uniformly, patients are asked if they have UTI symptoms on days seven and 14 after completing study medication. After the study is complete and treatment allocation is unblinded, the assessment corresponding to 14 days after completing active antibiotic therapy will be used for the primary outcome (seven days after completing study medication for those randomized to shorter-duration therapy, 14 days after completing study medication for those randomized to longer-duration therapy). If patients are equivocal about resolution of symptoms, they are asked if they sought treatment for a UTI. If yes, this is considered a treatment failure; if no, this is considered a clinical success.

Secondary endpoints include recurrence rates at 28 days after completing study medication, incidence of any adverse drug event in the 28 days after completing study medication, and intestinal carriage of antimicrobial-resistant Gram-negative bacilli after completing study medication, as compared to a baseline sample taken early in treatment.

2.9. Ethical considerations

Written informed consent is obtained from all subjects; surrogate consent is not used. The study was reviewed and approved by the Institutional Review Boards at the Minneapolis and Houston VA Medical Centers. Subjects are compensated for their time and effort with a $40 payment at the time of enrollment, and a payment for each stool swab they submitted for the optional sub-study ($20 for the first swab, $40 for the second).

2.10. Sample size

A sample size of 290 subjects (145/group) was calculated, using a one-sided alpha level of 0.025 and power of 85%, to allow detection of a minimum clinically significant absolute difference of 10% (e.g., 90% for 14-day treatment, vs. 80% for 7-day treatment).

2.11. Statistical analysis

The primary outcome (resolution of UTI symptoms 14 days after completing active antimicrobial therapy) will be assessed in a binary manner: subjects with persistent UTI symptoms or having received further antimicrobials because of UTI symptoms will be considered to have not met the primary outcome, whereas those without persistent UTI symptoms and not having received further antimicrobials will be considered to have met the primary outcome. The proportion of subjects meeting the primary outcome will be compared between the two treatment groups using a per-protocol analysis, with subjects analyzed according to which treatment they received. An intention-to-treat analysis will be performed as a secondary analysis. Subjects reporting taking seven or fewer days of study medication will be analyzed as having received shorter-duration therapy, whereas subjects reporting taking eight or more days of study medication will be analyzed as having received longer-duration therapy. Non-inferiority testing of the differences in the group proportions of symptom resolution will be done using a z-statistic derived by the adaptive percentage non-inferiority margin approach [8,9]. Exploratory sub-group analysis using multiple logistic regression will be performed to assess outcomes stratified by the following putatively clinically relevant characteristics: catheter-associated UTI, functional or mechanical urinary tract obstruction, and diabetes. We anticipate that the proposed study will be under-powered for these analyses, and thus they will primarily be used as pilot data to identify potential specialized populations for future study.

2.12. Secondary outcomes

The proportion of subjects reporting recurrence of symptomatic UTI in each group will be calculated, along with corresponding 95% confidence intervals. Between-group comparisons will be made using the Chi-square test. Incidence of adverse drug events of varying severity in each treatment group will be assessed and compared, first categorically by the Chi-square test and then by the number of days subjects experienced adverse drug events (Mann-Whitney *U* test). Finally, intestinal carriage of antimicrobial-resistant Gram-negative bacilli in each group

will be assessed. This analysis includes (1) examining the proportion of subjects who develop newly detected intestinal carriage of antimicrobial-resistant Gram-negative bacilli between the baseline sample obtained during treatment and the sample obtained 7 days after completing study medication (Chi-square test), (2) the density of antimicrobial-resistant Gram-negative bacilli among samples with any growth (*t*-test or Mann-Whitney *U* test, depending on the frequency distributions), and (3) the overall resistance score, defined as the total number of antimicrobials to which at least one of the isolated Gram-negative bacilli is resistant (*t*-test or Mann-Whitney *U* test).

3. Discussion

This randomized controlled trial of treatment duration for men with UTI will provide guidance for managing a common disease and will lead to improved clinical outcomes by defining the optimal duration of antibiotics. If shorter-duration therapy leads to more patients having persistent symptoms, then this will be useful information to inform future practice guidelines and help avoid unnecessary morbidity and repeat office visits. Alternatively, if shorter-duration therapy is non-inferior to longer-duration therapy, then the potential reduction of unnecessary antimicrobial use could lead to decreased antimicrobial resistance, lower costs, fewer adverse events, and increased patient satisfaction. In addition to answering a clinically relevant question, a unique aspect of this trial is enrollment and randomization after UTI therapy has been initiated. This reduces time pressures for the study coordinator, since recruitment can occur during normal business hours. It also avoids conducting lengthy discussion regarding the trial and the informed consent process in busy emergency departments and clinics, where room space and turnover are closely watched metrics.

Limitations of this study include that it assesses only afebrile men with UTI, and treatment only with ciprofloxacin and TMP-SMZ. However, since men with febrile UTI are relatively uncommon and have been the subject of prior study, and these agents are used for 90% of men with UTI in the VA system, this study will be relevant for a large proportion of men seen in and out of the VA system.

In conclusion, our trial will provide high-quality data to inform the management of a common infection. This should improve outcomes, help preserve the activity of antimicrobials, and minimize harms from unnecessary antimicrobial use.

Funding

This work was supported by VA Clinical Science Research and Development, Merit Review Program, grant number 1I01CX000830-01A2.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the clinicians and patients of the Minneapolis and Houston VA Medical Centers for their help in making this trial possible.

References

[1] B. Foxman, Epidemiology of urinary tract infections: incidence, morbidity, and economic costs, Am. J. Med. 113 (Suppl 1A) (2002) 5S–13S.
[2] K. Gupta, T.M. Hooton, K.G. Naber, et al., International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, Clin. Infect. Dis. 52 (5) (2011) e103-120.
[3] C. van Nieuwkoop, W.E. van der Starre, J.E. Stalenhoef, et al., Treatment duration of febrile urinary tract infection: a pragmatic randomized, double-blind, placebo-controlled non-inferiority trial in men and women, BMC Med. 15 (1) (2017) 70.
[4] P. Ulleryd, Febrile urinary tract infection in men, Int. J. Antimicrob. Agents 22 (Suppl 2) (2003) 89–93.
[5] D.M. Drekonja, T.S. Rector, A. Cutting, J.R. Johnson, Urinary tract infection in male Veterans: treatment patterns and outcomes, Arch. Intern. Med. (2012) 1–7.
[6] D.M. Drekonja, J.R. Johnson, Urinary tract infections, Prim Care 35 (2) (2008) 345–367 (vii).
[7] T.M. Hooton, The current management strategies for community-acquired urinary tract infection, Infect. Dis. Clin. 17 (2) (2003) 303–332.
[8] L.L. Laster, M.F. Johnson, M.L. Kotler, Non-inferiority trials: the 'at least as good as' criterion with dichotomous data, Stat. Med. 25 (7) (2006) 1115–1130.