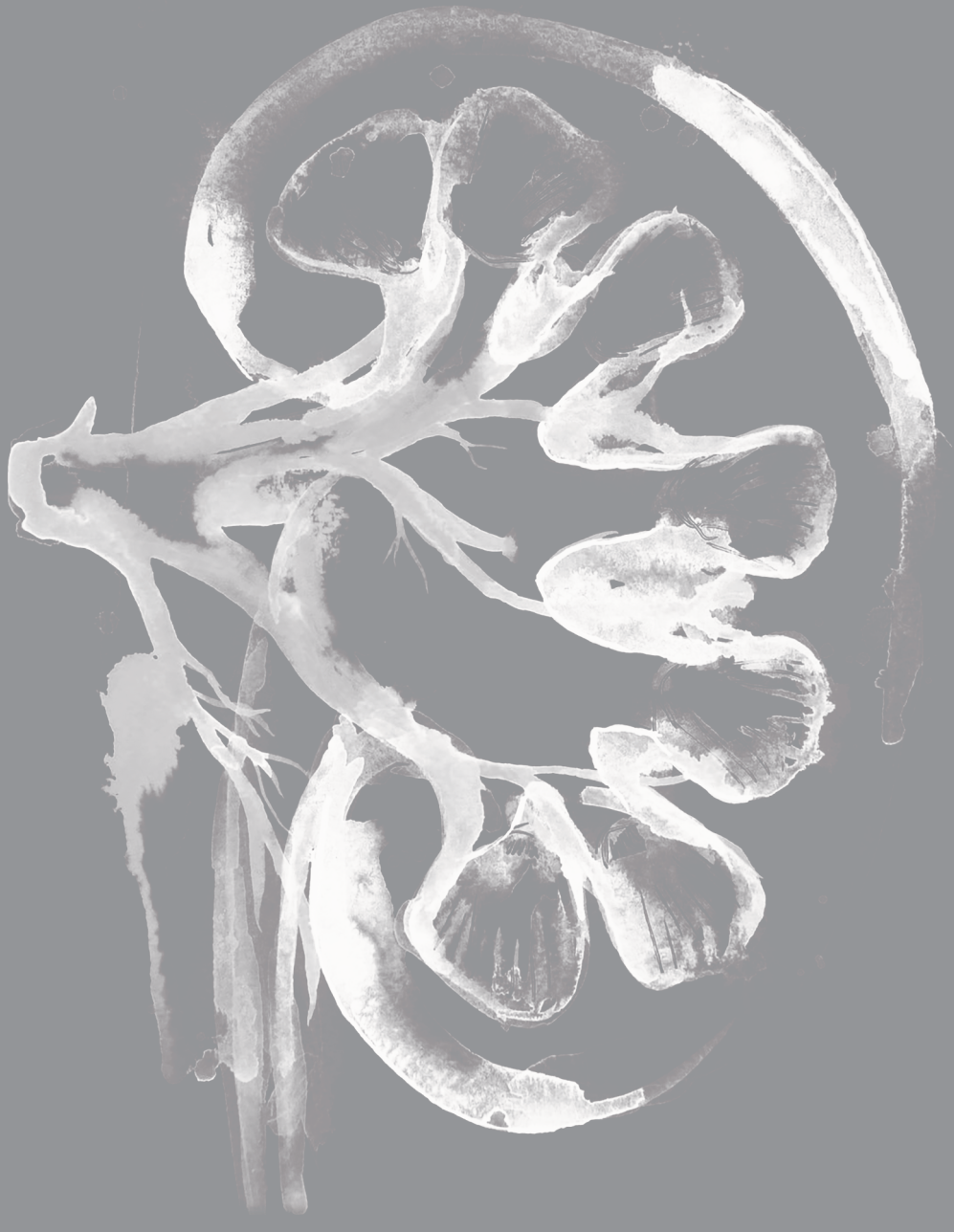

Chapter 3

Ciprofloxacin for 7 days versus 14 days in febrile urinary tract infection: a randomized, double-blind, placebo-controlled non-inferiority trial in men and women

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Abstract

Background

In adults with febrile urinary tract infections (fUTIs), data on optimal treatment duration are limited, especially in men, the elderly and patients with comorbidities.

Methods

A randomized placebo-controlled double-blind multicenter non-inferiority trial among 35 primary care centers and 7 emergency departments of regional hospitals in the Netherlands. Consecutive women and men aged ≥18 years with a presumptive diagnosis of community-acquired fUTI were randomly assigned to receive ciprofloxacin 500 mg orally twice daily for 7 days or for 14 days.

The primary endpoint was the clinical cure rate through the 10- to 18-day post-treatment visit.

Results

Of 357 patients included, 200 were eligible for randomization; 97 patients were randomly assigned to 7 days of ciprofloxacin and 103 patients to 14 days of ciprofloxacin. Overall, in an intention to treat analysis, clinical cure occurred in 85 (90%) patients treated for 7 days and in 94 (95%) of those treated 14 days (difference 4.5%; 90% CI -1.7 to 10.7; p=0.114, non-inferiority confirmed). In women, clinical cure was 94% and 93% in those treated for 7 and 14 days, respectively (47 of 50 vs 54 of 58; p=0.426). In men, however, clinical cure was 86% after 7 days treatment and 98% in those treated 14 days (38 of 44 vs 40 of 41; p=0.031).

Conclusions

In women including postmenopausal women and those with comorbidities, fUTI can be treated successfully with oral ciprofloxacin for 7 days. In men, 7 days of antibiotic treatment for fUTI is inferior to a 14-day course of oral ciprofloxacin.

Introduction

In the last decade, treatment of urinary tract infection (UTI) has become more complicated by rising antimicrobial resistance of Enterobacteriaceae, the most common uropathogens.[1] With a scarcity of new antimicrobial classes in the development pipe-line, it is essential to develop strategies to maintain effectiveness of available antimicrobials.[2] Therefore, among strategies to control resistance, the determination of an optimal duration of treatment is essential in addition to optimization of diagnostics to target treatment and antibiotic stewardship concerning antibiotic choice and dose. Shortening of antimicrobial therapy will lead to less selection pressure on the gut microbiome with benefits to both the individual patient as well as ecological environment including reduction of antibiotic resistance development.[3] Even in a common infection like UTI, there is a scarcity of controlled randomized studies that address minimal yet optimally efficacious duration of UTI treatment. With respect to febrile UTI (fUTI) or acute pyelonephritis, trials have usually focused on young women with uncomplicated UTI and have addressed optimal treatment duration by comparing the same drug for different durations of therapy, or compared various treatment durations of different antimicrobial agents. Recently, a randomized placebo-controlled trial showed that community-acquired acute uncomplicated pyelonephritis in women of all ages can be safely and efficaciously treated with oral ciprofloxacin for 7 days.[4] Clearly, such findings need to be extended to men and patients with significant comorbidities. In the present investigator-initiated randomized trial of treatment duration, we use fUTI as the clinical syndrome of interest because this is a broadly recognized specific clinical presentation of patients. Consecutive patients with fUTI were included, including men and women with comorbidities, and treated with ciprofloxacin for 7 days or 14 days. The aims of the study were to compare clinical and bacteriological cure both at short term and long term.

Methods

Study design and patients

We conducted a randomized placebo-controlled double-blind multicenter non-inferiority trial; the protocol has been published previously.[5]
Consecutive women and men aged 18 years or older with a presumptive diagnosis of community-acquired fUTI established by primary care physician

or on presentation at hospital's emergency department (ED) were recruited. Eligible patients had all of the following criteria: fever of ≥ 38.2°C and/or a history of feeling feverish with shivering or rigors in the past 24 hours, one or more symptoms suggestive of UTI (i.e. dysuria, frequency, urgency, perineal or suprapubic pain, costovertebral tenderness or flank pain) and positive urine nitrate test and/or pyuria (positive leucocyte esterase test or >5 leucocytes per high-power field in a centrifuged sediment). Patients enrolled were competent to provide written informed consent. Exclusion criteria for study entry were: known allergy to fluoroquinolones, pregnancy or lactation, polycystic kidney disease, permanent renal replacement therapy, kidney transplantation, residence outside The Netherlands and inability to speak or read Dutch.

Contra-indications for randomization were: isolation of ciprofloxacin-resistant causal uropathogen, presence of renal abscess, metastatic infectious foci or underlying chronic bacterial prostatitis as defined by recurrent UTI with the same uropathogen. Patients enrolled with fUTI but not randomized to trial medication, remained in the observational part of the study to assess outcome.

The independent medical ethics committees of the participating centers approved the study protocol. The trial was registered at ClinicalTrials.gov [NCT00809913] and trialregister.nl [NTR1583].

Randomization and antimicrobial treatment

Patients were randomized in a 1:1 ratio stratified per center and sex, to receive either a 7-day or a 14-day regimen of antimicrobial treatment. In the second week, treatment was continued double-blinded, with either ciprofloxacin 500 mg or placebo orally twice daily, according to randomization code. In inpatients, the treating physician could administer discretionary empirical intravenous antibiotics at the start of treatment according to local guidelines (in all hospitals participating: a β-lactam antibiotic ± aminoglycoside). These patients were switched as soon as deemed possible to open label oral ciprofloxacin (non-blinded) up to the 7th day after inclusion. The decision whether to treat as outpatient or inpatient, was made by the attending physician based on clinical judgment.

Further details upon randomization, trial medication, microbiological methods and study procedures are previously published.[11]

Main outcome measures

The primary endpoint was the clinical cure rate through the 10- to 18-day post-treatment visit (short-term clinical cure). Clinical cure was defined as being alive with absence of fever and resolution of UTI symptoms (either absence of symptoms or at least 2 points improvement on a 0 through 5 points severity score), without additional antimicrobial therapy (for relapse of UTI). Secondary outcome measures were bacteriological cure through the 10- to 18-day post-treatment visit, clinical cure rate through the 70- tot 84-day post-treatment visit (cumulative clinical cure), all-cause mortality, adverse event rate determined 10-18 days and 70-84 days post-treatment, and rate of UTI relapses. In addition, outcome measures were analyzed as stratified by specific subgroups (i.e., men, patients with complicated UTI, postmenopausal women, patients with any comorbidity and bacteremic UTI). Bacteriologic cure was defined as eradication of the study entry uropathogen with no recurrence of bacteriuria (pathogen growth $<10^4$ cfu/mL in women or $<10^3$ cfu/mL in men of a midstream urine culture combined with disappearance of leucocyturia).[6]

Statistical analysis

The primary endpoint was analyzed on the intention-to-treat (ITT) population, including all randomized patients who received at least one dose of the study drug, and on the per-protocol (PP) population, including all randomized patients who had been given the study drug for a minimum of 24 hours (in case of treatment failure) or who had been taken at least 80% of the study drug (in case of clinical cure).

The study sample size was calculated on the basis of a clinical cure rate of 10 percentage points lower at short-term follow-up in the 7-day treatment arm with the assumption of a 90% clinical cure rate in patients treated for 14 days.[7, 8] We adopted 10% as the margin of non-inferiority as suggested previously.[9] As we are only interested in non-inferiority and not in equivalence, the sample size calculation was based on a one-tailed alpha of 0.05. Assuming a non-inferiority margin of 0.10, 1-tailed alpha of 0.05 and a power of 0.90, the required sample size per group was 200. This implies that the 90% confidence interval of a two-tailed Chi-square test should not cross the predefined risk difference of 10% lower clinical cure rate, or equivalently, the one-sided p-value is less than the 0.05 significance level.[10] Interim analyses were done after randomization of 100 and 200 patients. After the second interim analysis, the principal investigators, who obviously were still blinded with respect to treatment allocation, noted that the overall cure rate

was 92% implying that the trial already had reached sufficient power (e.g. comparable with the power in a recently published similar trial).[4] Besides this, the overall cure rate was remarkably different for women and men (94% versus 91%). For men the principal investigators estimated and concluded the trial would likely end in futility, since the high overall cure rate in men was considered to be unlikely unless very large differences in cure rate between

Table 1. Baseline characteristics of 357 patients with febrile urinary tract infection

	Randomized (n=200)			
	Ciprofloxacin for 7 days (n=97)	Ciprofloxacin for 14 days (n=103)	Not randomized (n=157)	p-value"
Age (years)	60 (48-72)	61 (40-73)	63 (49-75)	0.277
Male sex	44 (45%)	42 (41%)	58 (37%)	0.247
Urologic history				
Indwelling urinary catheter	3 (3%)	2 (2%)	12 (8%)	0.024
Urinary tract disorder*	28 (29%)	28 (27%)	52 (33%)	0.296
Recurrent UTI^	19 (20%)	19/100 (19%)	47/147 (32%)	0.007
Comorbidity				
Diabetes	12 (12%)	17 (17%)	25 (16%)	0.709
Malignancy	3 (3%)	5 (5%)	17 (11%)	0.012
Heart failure	12 (12%)	6 (6%)	19 (12%)	0.340
Cerebrovascular disease	5 (5%)	5 (5%)	13 (8%)	0.210
Chronic renal insufficiency	3 (3%)	2 (2%)	10 (6%)	0.070
COPD	10 (10%)	11 (11%)	23 (15%)	0.236
Immunocompromised	3 (3%)	8 (8%)	14 (9%)	0.209
Presentation				
At emergency department	59 (61%)	68 (66%)	145 (92%)	<0.001
Antibiotic pretreatment	23 (24%)	29 (28%)	56 (36%)	0.048
Fever duration, hours	30 (15-48)	36 (20-60)	48 (19-96)	0.081
Dysuria	82/95 (86%)	78/102 (77%)	102/145 (70%)	0.019
Flank pain	57/96 (59%)	67/102 (66%)	91/144 (63%)	0.914
Suprapubic pain	51/96 (53%)	48/100 (48%)	72/145 (50%)	0.876
Perineal pain	4/96 (4%)	7/98 (7%)	8/140 (6%)	0.986
Outpatient treatment	45 (46%)	45 (44%)	23 (15%)	<0.001
Positive urine culture	69 (71%)	68 (66%)	107 (68%)	0.944
Positive blood culture	20/88 (23%)	15/98 (15%)	45/153 (29%)	0.012
Positive urine and/or blood culture	75 (77%)	70 (68%)	118 (75%)	0.571
Initial intravenous dose(s) of antibiotics	48 (50%)	55 (53%)	133 (85%)	<0.001

Data presented as number (%) or median (IQR)

* any functional or anatomical abnormality of urinary tract except urinary catheter

^ ≥3 UTIs in past 12 months or ≥2 UTIs in past 6 months

" randomized (both 7 and 14 days ciprofloxacin) vs not-randomized patients

the treatment arms were assumed. As this was considered either not-realistic or the justification to halt trial inclusion because then non-inferiority was evidently rejected, we decided to stop the trial at this point.
Descriptive statistics were used to describe the baseline characteristics in each arm with Chi-square tests for binomial and categorical data and Mann-Whitney tests for continuous data. All analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Between November 2008 and May 2013, 357 patients with a diagnosis of fUTI were enrolled into the study. Of these, 200 were randomly assigned to receive ciprofloxacin for 7 days (n=97) or 14 days (n=103). Reasons for exclusion from randomization, ITT and PP analyses are listed in Figure 1.
Of the 157 non-randomized patients, 119 (76%) were evaluable for short-term efficacy and 116 (74%) for cumulative efficacy.
Baseline characteristics of the study population are summarized in Table 1. Randomized, evaluable subjects in the two treatment arms were well matched with respect to demographic characteristics and presentation on study entry. The 157 patients who were not randomized, generally had more comorbidities and were more ill as more were referred to the ED. Additional details are listed in the Supplement. Baseline urine cultures were performed in 341 patients (96%) (Table 2). In 99 (28%) patients, urine culture showed either no significant bacteriuria or a mixed flora; in over half of these cases (58%), patients were pre-treated with antibiotics (in the group randomized to 7 days of ciprofloxacin: 13 (59%), and to 14 days of ciprofloxacin: 20 (63%)); a similar percentage pertained to those not randomized: 23 (51%), Blood cultures were obtained in 339 patients of which 80 (24%) had bacteremia with growth of *E. coli* in the majority of the cases (n=67, 84%).
Both treatment regimens resulted in a high clinical cure rate at short-term follow-up in ITT population: 90% vs 95% in patients treated with ciprofloxacin for 7 or 14 days, respectively (Table 3). The difference in short-term clinical cure rate between both treatment arms was 4.5% (90% CI -1.7 to 10.7, p-value non-inferiority test 0.114), thus the confidence interval surpassed the predefined non-inferiority margin of 10%. The median time to defervescence did not differ between the two groups: 2 (IQR 1-2) days in 7-day ciprofloxacin, 2 (IQR 1-3) days in 14-day ciprofloxacin. Short-term

clinical cure was 85% in non-randomized patients, whereas median time to defervescence amounted to 2 (IQR 1-3) days.
Short-term clinical cure rates were analyzed in preset subgroups of patients. In women, short-term clinical cures for 7- and 14-day arm were 47 of 50 (94%) vs 54 of 58 (93%), respectively. In men, clinical cure rates differed significantly between those treated for 7 or 14 days (38 of 44 [86%] vs 40 of 41 [98%], p=0.031) (Figure 2A and 2B). Clinical cure rates in patients with stepdown treatment were 41 of 47 (87%) and 48 of 52 (92%), in 7- and 14-day arm, respectively. Clinical cure rates were somewhat higher in patients treated with oral ciprofloxacin right from enrollment (44 of 47 [94%] vs 46 of 47 [98%], respectively for 7- and 14-day arm). Patients with positive blood cultures had higher clinical cure rates when treated with ciprofloxacin for 14 days compared to 7 days (15 of 15 [100%] vs 18 of 20 [90%]).
No differences were noted in cure rates between women with a complicated fUTI treated for 7 or for 14 days (33 of 35 [94%] vs 34 of 37 [92%]). Moreover, clinical cure rates did not differ in postmenopausal women treated for 7 or 14 days (28 of 30 [93%] vs 31 of 33 [94%]. Detailed information on subgroup analyses among men and women are listed in Figure 2A and 2B, respectively. Both treatment regimens post-randomization were well tolerated with no differences in side effects.
Post treatment urine cultures (at day 28-32) were obtained in 93 of 94 (99%) patients assigned to 7 days of ciprofloxacin, in 92 of 99 (93%) patients assigned to 14 days of ciprofloxacin, and in 109 of 119 (92%) non-randomized patients, with the short-term follow-up visit. Bacteriologic cure was 91% in the 7-day treatment arm, 97% in patients treated with ciprofloxacin for 14 days, and 86% in non-randomized patients (Table 3). More details upon clinical and microbiological outcomes are listed in the Supplement.

Figure 1. Trial profile
* concurrent medical conditions (n=16), logistic reasons (n=5), abroad during treatment with trial medication (n=3)

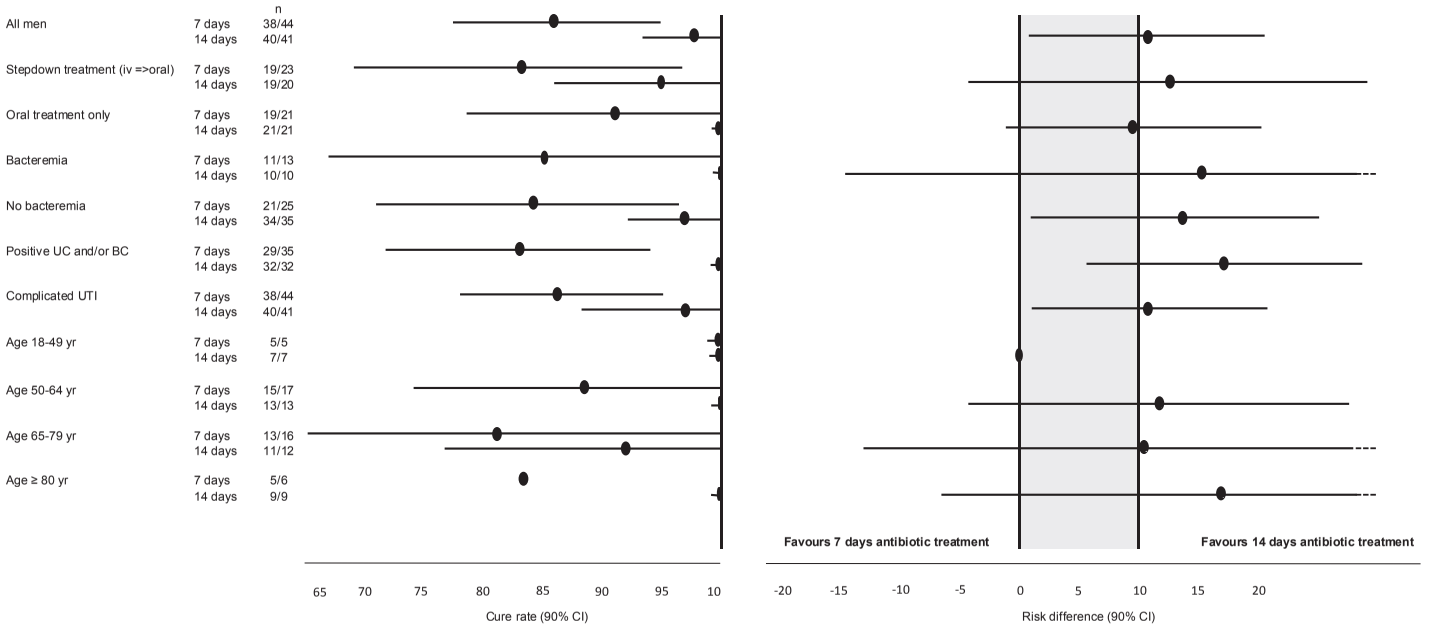

Figure 2a. Cure rate of febrile UTI in men and specific male subgroups
UC: urine culture, BC: blood culture, CI: confidence interval

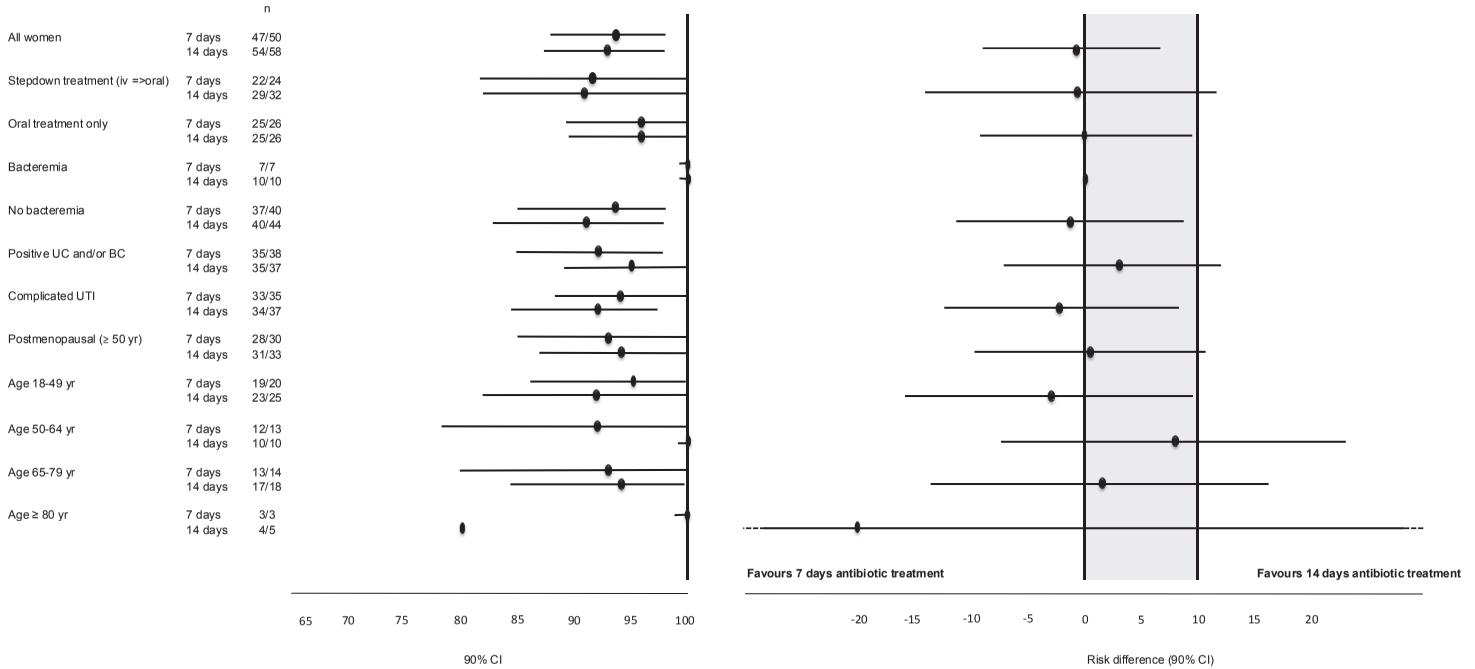

Figure 2b. Cure rate of febrile UTI in women and specific female subgroups
UC: urine culture, BC: blood culture, CI: confidence interval

Table 2. Urine culture results at entry*

	Randomized		Not randomized
	Ciprofloxacin for 7 days	Ciprofloxacin for 14 days	
Escherichia coli	65 (68%)	65 (59%)	85 (51%)
Klebsiella spp.	2 (2%)	4 (4%)	13 (8%)
Proteus spp.	1 (1%)	6 (5%)	6 (4%)
Pseudomonas aeruginosa	–	–	2 (1%)
Enterococcus spp.	1 (1%)	–	8 (5%)
Staphylococcus spp.	–	–	1 (1%)
Other^	3 (3%)	3 (3%)	8 (5%)
None or contaminated culture	22 (23%)	32 (29%)	45 (27%)

Data presented as number (%). Urine culture performed in: 7 days ciprofloxacin: 91 (94%), 14 days ciprofloxacin: 100 (97%), non-randomized: 150 (96%)

* some patients had multiple isolates; ciprofloxacin 7 days: n=6, ciprofloxacin 14 days: n=10, not randomized n=17

^ ciprofloxacin 7 days: *Proteus mirabilis* (1), *Citrobacter sedlakii* (1), *Citrobacter koseri* (1), *Candida* spp. (2)
ciprofloxacin 14 days: *Morganella morganii* (1), β-hemolytische streptokok group B *S. agalactiae* (2)
not randomized: *Serratia marcescens* (1), β-hemolytic streptococci group B (1), *Enterobacter cloacae* (1), *Streptococcus bovis* (1), *Citrobacter koseri (1), Morganella morganii (1), Proteus mirabilis (1), β-hemolytische streptokok group A (1)*

Table 3. Clinical and bacteriologic outcomes in the intention-to-treat and per-protocol population

	Randomized				
	Ciprofloxacin for 7 days	Ciprofloxacin for 14 days	Difference (90% CI)	Non-inferiority test p-value	Not randomized population
Intention-to-treat population	(n=94)	(n=100)			
Short-term efficacy	(n=94)	(n=99)			(n=119)
Clinical cure	85 (90%)	94 (95%)	4.5% (-1.7 to 10.7)	0.114	101 (85%)
Bacteriologic cure	86/93 (91%)	89/92 (97%)	4.3% (-1.2 to 9.8)	0.101	94/109 (86%)
Cumulative efficacy	(n=94)	(n=94)			(n=116)
Clinical cure	87 (93%)	86 (91%)	-1.1% (-7.6 to 5.5)	0.394	88 (76%)
Per-protocol population	(n=92)	(n=93)			
Short-term efficacy	(n=92)	(n=92)			NA
Clinical cure	83 (90%)	87 (95%)	4.3% (-2.1 to 10.8)	0.135	
Bacteriologic cure	84/91 (92%)	83/86 (97%)	4.2% (-1.5 to 10.0)	0.114	
Cumulative efficacy	(n=92)	(n=87)			
Clinical cure	85 (92%)	79 (91%)	-1.6% (-8.5 to 5.3)	0.352	

Data presented as number (%), unless otherwise indicated. NA: not applicable.
Short-term efficacy: endpoints assessed at 10- to 18-days post-treatment visit.
Clinical cure: being alive with absence of fever and resolution of UTI symptoms through post-treatment visit with no additional antimicrobial therapy for a relapse of UTI prescribed.
Bacteriologic cure: elimination of study entry uropathogen or pathogen growth <10^4 colony forming units/mL (women) or <10^3 colony forming units/mL (men) combined with disappearance of leucocyturia.
Cumulative efficacy: endpoint assessed at 70- to 84-days post-treatment visit.

Discussion

Our findings show that community-acquired febrile urinary tract infection can be safely and efficaciously treated with oral ciprofloxacin for 7 days in women, including the elderly with significant comorbidity, and irrespective of severity of disease at presentation. However in men, the 7-day treatment was significantly inferior to 14 days of treatment.

The main strength of this trial is its pragmatic nature reflecting daily clinical practice with the inclusion of consecutive patients with fUTI, both men and women, irrespective of age and underlying medical conditions, with the notable exception of those with severe kidney disease, antibiotic allergy and pregnancy. Several hospitals were involved, including a referral university hospital, and general practitioners who enrolled about one fourth of our patients. Therefore, patients recruited into the study are considered representative of individuals with acute community-acquired fUTI, encompassing acute pyelonephritis and prostatitis. Of note, the findings hold for both the intention-to-treat and the per protocol analysis, underlying the high compliance by patients randomized with respect to the treatment protocol and precluding that poor study procedures may have concealed differences in patient management.

In contrast, the group of patients who were not randomized (because of the isolation of ciprofloxacin-resistant causal uropathogen, renal abscess or underlying chronic bacterial prostatitis) had a significantly higher treatment failure rate.

Our study lacks statistical power to draw confident conclusions on the various subgroups because of the limited number of patients enrolled. However, further enrollment was precluded by the already significant difference in outcome between 7 and 14 days of treatment in the male subgroup.

Our findings extend recent findings of a highly similar controlled randomized study done in women with acute pyelonephritis in Sweden, showing non-inferiority of 7 and 14 days of antimicrobial treatment.[4] Although that study did not exclude the elderly or those severely ill, their patient group was younger with less comorbidity and complicated UTI than that enrolled in our study.

In men, our results indicate an increase in rate of clinical and bacteriological treatment failure after the 7-day treatment as compared to 14 days. Of note, this lack of efficacy could not be attributed upfront to a propensity of prostatitis in men, as the difference was especially clear in those men presenting with clinically evident costovertebral tenderness, although the number of

cases constrained a purposeful exploration of subgroups. Given the identical efficacy of the 7-day and 14 -day treatment in women, and the absence of a relation with manifest or possible prostatitis as reason for the inferiority of 7-day treatment in men, our findings cannot reliably explain this outcome. There is a lack of studies on optimal treatment duration of fUTI in men. One study directly compared different treatment duration in an open, prospective and randomized trial in 72 men with community-acquired fUTI showing similar bacteriological cure rates with ciprofloxacin 500 mg orally twice daily for either 2 or 4 weeks.[11] Similarly, a randomized, double-blind trial in Sweden lent support for the efficacy of 14 day treatment with fluoroquinolones in men.[12] Taken together, the studies confirm that at present, a 14-day treatment regimen of fluoroquinolones is the minimum period necessary for optimal therapy of fUTI in men. Recently however, a retrospective analysis of a large database of male veterans indicated that more than 7 days of antibiotic treatment (the vast majority being treated with ciprofloxacin) was not associated with a reduction of UTI recurrence.[13] In addition, this study showed that treatment with β-lactams was associated with a higher risk of recurrence as compared to fluoroquinolone treatment. Furthermore, they showed that UTI recurrence was independently associated with comorbidities and age. As in our study about half of the patients were initially treated with a β-lactam intravenously, implying less penetration into the prostrate,[14] this may have influenced our results and possibly this may explain the larger difference in cure rates within the subgroup of men with stepdown treatment. Interestingly, in line with this we found no significant difference in men who were solely treated with ciprofloxacin whereas in men aged less than 50 years, there was a similar cure rate with antibiotic treatment for 7 or 14 days. Future studies should address whether in men less than 50 years, fUTI can be efficaciously treated with 7 days of ciprofloxacin.

Given the consistency of our findings and those of the recent study in Sweden[4], we conclude that women can be treated orally with 7 days of adequately dosed fluoroquinolones, unless the urinary isolate is proven not susceptible to this antibiotic. Ciprofloxacin was chosen as treatment because of its reliable intestinal resorption and bioavailability, and excellent antimicrobial activity against a broad spectrum of susceptible gram-negative microorganisms, the most common etiologic microbiological agents in UTI, making it a drug of choice in both outpatient as well as hospital setting. As a surplus, activity against perineum and vagina colonizing Enterobacteriaceae may help prevent early recurrences.[15] Current results obtained with ciprofloxacin may likely be extrapolated to the other fluoroquinolones with

gram-negative activity but not to other antibiotic classes. An important concern has been the rise of ciprofloxacin resistance in the community, i.e., up to 15% of Enterobacteriaceae currently being resistant in The Netherlands, that, if it continues at the current rate, may prelude the use of fluoroquinolones as first-choice empiric oral treatment of fUTI. Of great concern, in other countries this figure has been reported as high as 40 to 50%.[16, 17] In countries with concurrent high rates of co-trimoxazole resistance in Enterobacteriaceae, there may be no oral antibiotic option left for general practitioners to treat fUTI at home, raising health care costs. These findings underscore the importance of controlling antimicrobial resistance, through antibiotic stewardship including the administration of antibiotics with optimal duration.

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Supplement

Baseline characteristics

In the 7-day treatment arm, 23 (24%) patients had been pretreated for presumptive UTI with: norfloxacin (n=1, 4%), none with ciprofloxacin, nitrofurantoin (n=5, 22%), trimethoprim ± sulfamethoxazole (n=3, 13%), amoxicillin ± clavulanic acid (n=12, 52%), phosphomycin (n=1, 4%) and others (n=1, 4%). Of those randomized to 14 days ciprofloxacin, 29 (28%) had been pretreated with ciprofloxacin (n=3, 10%), norfloxacin (n=1, 3%), nitrofurantoin (n=6, 21%), trimethoprim ± sulfamethoxazole (n=7, 24%), amoxicillin ± clavulanic acid (n=8, 28%), others (n=3, 10%) and unknown (n=1, 3%). In the non-randomized group, 56 (36%) had been pretreated with ciprofloxacin (n=8, 14%), norfloxacin (n=2, 6%), nitrofurantoin (n=8, 14%), trimethoprim ± sulfamethoxazole (n=7, 13%), amoxicillin ± clavulanic acid (n=21, 38%), phosphomycin (n=1, 2%), others (n=4, 7%) and unknown (n=5, 9%).

About half of the patients were initially treated with intravenous antibiotics, and this did not differ between treatment arms: in the 7 days of ciprofloxacin, 48 (50%) patients (cefuroxime n=21, 44%; cefuroxime + gentamicin n=22, 46%; other n=5, 10%) and in the 14 day, 55 (53%) patients (cefuroxime (n=32, 58%), cefuroxime ± gentamicin (n=20, 36%), ciprofloxacin i.v. (n=1, 2%) and other antibiotics (n=2, 4%)). In the non-randomized group, 133 (85%) patients had initial dose(s) of intravenous antibiotics, i.e., cefuroxime (n=61, 46%), cefuroxime ± gentamicin (n=49, 37%), ciprofloxacin (n=4, 3%) and other (n=18, 14%). Of note, the median time till switch from intravenous to oral antibiotics was 3 days (IQR 2-4), and did not differ between the groups.

Clinical outcome

During short-term follow-up, nine patients assigned to ciprofloxacin for 7 days had a clinical recurrence. Three patients had an episode of (afebrile) acute cystitis at day 17, 18 and 20, whereas six patients had an additional episode of fUTI at day 9, 14, 15, 17, 20 and 26 after treatment. Among patients assigned to 14 days of ciprofloxacin, one patient had an acute cystitis at day 30 and four patients had recurrent fUTI at day 8, 9, 19 and 20.

For cumulative clinical cure rate, 94 patients were evaluable in each treatment arms. Clinical cure rates were high: 93% vs 91% in patients treated with ciprofloxacin for 7 of 14 days (Table 3). During late follow-up, seven patients assigned to 7 days had a clinical recurrence. Six patients had an

episode of (afebrile) acute cystitis at day 38, 40, 56, 63, 64 and 83 and one patient had an additional episode of fUTI. Among patients assigned to 14 days, seven patients had an (afebrile) acute cystitis at day 40, 44, 71 and 77 (n=3 day unknown) and one patients had recurrent signs of fUTI at day 90. One patient assigned to ciprofloxacin for 7 days was readmitted at day 9 because of treatment failure, and was treated intravenously with cefuroxime followed by oral ciprofloxacin for 14 days, now with good clinical response. None of the patients assigned to the 14-days treatment arm were readmitted because of treatment failure.

During the study period, no patients given 7 days of ciprofloxacin died. One patient, an 84-year old man assigned to 14 days of ciprofloxacin, died on day 92 due to pneumonia and sepsis. Five non-randomized patients died during follow-up due to concurrent medical problems.

With respect to side effects, one patient who received placebo, discontinued trial drug because of mucosal candida infection (day 2 after start placebo). Five patients on ciprofloxacin discontinued trial drug because of itching exanthema (n=2, both on day 3, i.e., day 10 of treatment) or feeling tired (n=3; day 1,3 and 5). During trial drug period, patients reported the following adverse events in 7- and 14 days treatment arm: nausea (7% vs 4%), vomiting (2% vs 1%), diarrhea (3% vs 2%), headache (16% vs 4%), dizziness (10% vs 9%), itching exanthema or rash (4% vs 4%) and myalgia (10% vs 12%).

Microbiological outcome

In the group assigned to 7 days of ciprofloxacin, seven patients had asymptomatic bacteriuria at short-term follow-up (five with *E. coli*, one with *Klebsiella oxytoca* and one with *Enterococcus faecalis*). Three patients treated with ciprofloxacin for 14 days had asymptomatic bacteriuria at short-term follow-up (one with *E. coli*, one with *E. faecalis* and one with coculture of *E. faecalis* and *S. aureus*). Fifteen non-randomized patients had asymptomatic bacteriuria at short-term visit: seven with *E. coli*, one with *E. coli* and *E. faecalis*, one with *Klebsiella* spp and *S. saprophyticus*, one with *Proteus* spp, two with *E. faecalis*, one with *E. faecalis* and *P. aeruginosa*, one with *P. aeruginosa* and one with *Enterobacter cloacae*.