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MAJOR ARTICLE

Fosfomycin Vs Ciprofloxacin as Oral Step-Down Treatment for *Escherichia coli* Febrile Urinary Tract Infections in Women: A Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial

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Background. We aimed to determine the noninferiority of fosfomycin compared to ciprofloxacin as an oral step-down treatment for *Escherichia coli* febrile urinary tract infections (fUTIs) in women.

Methods. This was a double-blind, randomized, controlled trial in 15 Dutch hospitals. Adult women who were receiving 2–5 days of empirical intravenous antimicrobials for *E. coli* fUTI were assigned to step-down treatment with once-daily 3 g fosfomycin or twice-daily 0.5 g ciprofloxacin for 10 days of total antibiotic treatment. For the primary end point, clinical cure at days 6–10 post-end of treatment (PET), a noninferiority margin of 10% was chosen. The trial was registered on Trialregister.nl (NTR6449).

Results. After enrollment of 97 patients between 2017 and 2020, the trial ended prematurely because of the coronavirus disease 2019 pandemic. The primary end point was met in 36 of 48 patients (75.0%) assigned to fosfomycin and 30 of 46 patients (65.2%) assigned to ciprofloxacin (risk difference [RD], 9.6%; 95% confidence interval [CI]: −8.8% to 28.0%). In patients assigned to fosfomycin and ciprofloxacin, microbiological cure at days 6–10 PET occurred in 29 of 37 (78.4%) and 33 of 35 (94.3%; RD, −16.2%; 95% CI: −32.7 to −0.0%). Any gastrointestinal adverse event was reported in 25 of 48 (52.1%) and 14 of 46 (30.4%) patients (RD, 20.8%; 95% CI: 1.6% to 40.0%), respectively.

Conclusions. Fosfomycin is noninferior to ciprofloxacin as oral step-down treatment for fUTI caused by *E. coli* in women. Fosfomycin use is associated with more gastrointestinal events.

Clinical Trial Registration. Trial NL6275 (NTR6449).

Keywords. urinary tract infection; fosfomycin; *Escherichia coli*; antimicrobial resistance.

Febrile urinary tract infections (fUTIs), defined as UTIs with systemic symptoms, frequently occur in women and are predominantly caused by *Escherichia coli* [1]. Guidelines recommend treating fUTIs that require hospitalization with a 7- to 14-day course of antibiotics that usually consists of empiric intravenous (IV) treatment preferably followed by an oral step-down treatment targeted to the susceptibility pattern of the causal uropathogen [2, 3]. Optimal treatment of fUTIs is hampered by the increase in multiresistant gram-negative bacteria [1]. While new antibiotics are being developed for the IV treatment of fUTIs, the arsenal of oral antibiotics has remained stable for decades [4]. Based on antimicrobial resistance, 2%–5% of patients hospitalized for community-acquired fUTIs in the Netherlands cannot be treated with oral antibiotics [5, 6], with even higher rates of antimicrobial resistance in other parts of the world [7, 8], implying the need for prolonged IV antibiotic therapy and extended hospitalization [9–11].

Fosfomycin is a phosphoenolpyruvate analogue that is orally available as fosfomycin–trometamol. It is licensed for the treatment of uncomplicated cystitis in women, has a good safety

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[a]The FOsfomycin Randomised controlled trial for *E. coli* Complicated urinary tract infections as Alternative Stepdown Treatment (FORECAST) Study Team members are listed in the Notes section.

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profile [12], and has in vitro activity against *E. coli*. Despite its increased use, persisting low resistance rates are observed against fosfomycin, up to 2% [13]. In retrospective studies, fosfomycin appeared effective as a step-down treatment for fUTIs [14, 15]. Our objective in this randomized, controlled trial was to determine if fosfomycin is noninferior to ciprofloxacin for the oral step-down treatment of fUTIs caused by *E. coli* in women.

METHODS

Study Design

A randomized, controlled, double-blind, double-dummy, investigator-initiated trial was conducted to determine whether oral fosfomycin is noninferior to oral ciprofloxacin for achieving clinical cure in the step-down treatment of *E. coli* fUTIs in women. The protocol was published [16]. The University Medical Center Utrecht Institutional Review Board provided ethical approval. The study was performed in 15 Dutch hospitals: 4 academic centers and 11 large teaching hospitals. All respective institutional review boards approved the study. The manuscript was written according to the CONSORT checklist [17].

Participants

Eligible patients were competent women aged ≥18 years, hospitalized with a diagnosis of fUTI, with at least 1 urinary tract symptom and systemic symptoms or signs. Urine (≥10^4 colony-forming units [CFU]/mL) and/or blood cultures had to reveal *E. coli* susceptible to both ciprofloxacin (minimal inhibitory concentration [MIC] ≤0.25 mg/L) and fosfomycin (MIC ≤32 mg/L) according to European Committee on Antimicrobial Susceptibility (EUCAST) criteria [18], as measured with automated panel tests (PHOENIX or VITEK), disc diffusion, or Etest. If blood and urine cultures both revealed *E. coli*, local symptoms were not required. Patients should have received appropriate empirical IV antibiotics for 2–5 days, consisting of second- or third-generation cephalosporin, amoxicillin ± clavulanic acid, an aminoglycoside, carbapenem, fluoroquinolones, trimethoprim–sulfamethoxazole, or a combination of these with in vitro susceptibility of the causative *E. coli*, according to EUCAST criteria, to at least 1 of the agents used [18]. Patients were judged to be eligible for an IV–oral switch on clinical judgment, according to the Dutch guideline that recommends switching therapy after 48–72 hours of intravenous antibiotic therapy [19]. A patient was excluded if urine culture (≥10^3 CFU/mL) or blood culture yielded non–*E. coli* pathogens. Patients with urinary catheters, placed ≥24 hours before admission, were excluded. Other eligibility criteria are listed in the protocol (Supplementary Material, Protocol S1).

Randomization and Masking

Because empirical antimicrobial treatment for fUTIs differed between hospitals, randomization was performed with stratification per hospital so that each hospital contained a blinded allocation list. Patients, physicians, local dispensing pharmacists, and investigators were blinded for treatment allocation.

Procedures

Baseline variables at admission and randomization were collected using participant questionnaires and from the electronic patient file (Supplemental Material, Protocol S1). Patients were assigned (1:1) to an IV–oral switch to fosfomycin–trometamol every 24 hours as a powder for solution, equivalent to 3 g fosfomycin, or ciprofloxacin 0.5 g every 12 hours as capsules. Patients received an identical placebo for both active substances to ensure blinding (double-dummy). The duration of antimicrobial treatment was set at 10 days that consisted of 2–5 days empirical IV treatment and the remaining 5–8 days oral study treatment.

Patients were asked to register the intake of study medication and the occurrence of adverse events (AEs) in a paper diary. A physical appointment was planned 6–10 days after study treatment was finished to assess early end points and to collect urine; a telephone appointment at 30–35 days was set to assess late end points. At inclusion and during both follow-up meetings, structured questionnaires were obtained regarding urinary tract and systemic symptoms, antimicrobial use, health status, and healthcare consumption.

Outcomes

The primary end point was clinical cure at days 6–10 post-end of treatment (PET). Clinical cure was defined as being alive with reduction of all initial local and systemic fUTI-related symptoms, without the requirement of additional antibiotic therapy for UTI (except for antibiotic prophylaxis). In case of an indwelling catheter, local symptoms were not counted. According to this definition, patients who did not meet the criteria for early clinical cure could do so for late clinical cure and vice versa. Secondary end points included microbiological cure at days 6–10 PET and clinical cure, relapse, reinfection, no additional antibiotic therapy for presumed UTI, and AEs at days 30–35 PET. Microbiological cure was defined as a negative urine culture for *E. coli* (<10^3 CFU/mL) with an identical antibiotic resistance profile as the initially cultured *E. coli*. Microbiological cure was only established in patients who did not use additional antibiotic treatment. Definitions and criteria of all secondary end points are specified in the protocol (Supplementary Material, Protocol S1).

Statistical Analyses

The planned sample size of 240 patients, including 10% loss to follow-up, was based on an assumed cure rate of 92.5% and using a noninferiority margin of 10% difference in clinical cure, with a power of 80% and a 2-sided 95% confidence interval (CI). All end points were analyzed according to the intention-to-treat

principle with inclusion of patients who received at least 1 dose of the oral study drug. A per-protocol analysis was planned for the primary end point and the secondary end point "microbiological cure" for patients who completed at least 80% of the study medication. Risk differences between study arms ($P < .05$) were calculated with a 2-sided z score for proportions. A Mann-Whitney U test was used to compare means. Two interim analyses were planned by the Data and Safety Monitoring Board (DSMB) to assess the safety after inclusion of 50 patients and to assess the safety and futility of the study after inclusion of 100 patients. Due to the limited final sample size, we decided to not perform exploratory multivariable analyses of associations between certain populations and the outcome.

RESULTS

The trial was halted on 1 July 2020 as a consequence of low enrollment during the coronavirus disease 2019 pandemic and discontinued on 26 October 2020 because of expiration of study medication and exhaustion of personnel and financial capacity. Based on the results of the DSMB interim analyses on 13 October 2020 with 97 randomized patients, there was no reason to stop the study prematurely for safety reasons or futility.

Between 11 November 2017 and 24 June 2020, 543 patients were screened for participation, of whom 177 were eligible and 97 provided informed consent. Of these, 48 patients were assigned to fosfomycin and 49 to ciprofloxacin (Figure 1). Three were not evaluable for early end points as they were withdrawn

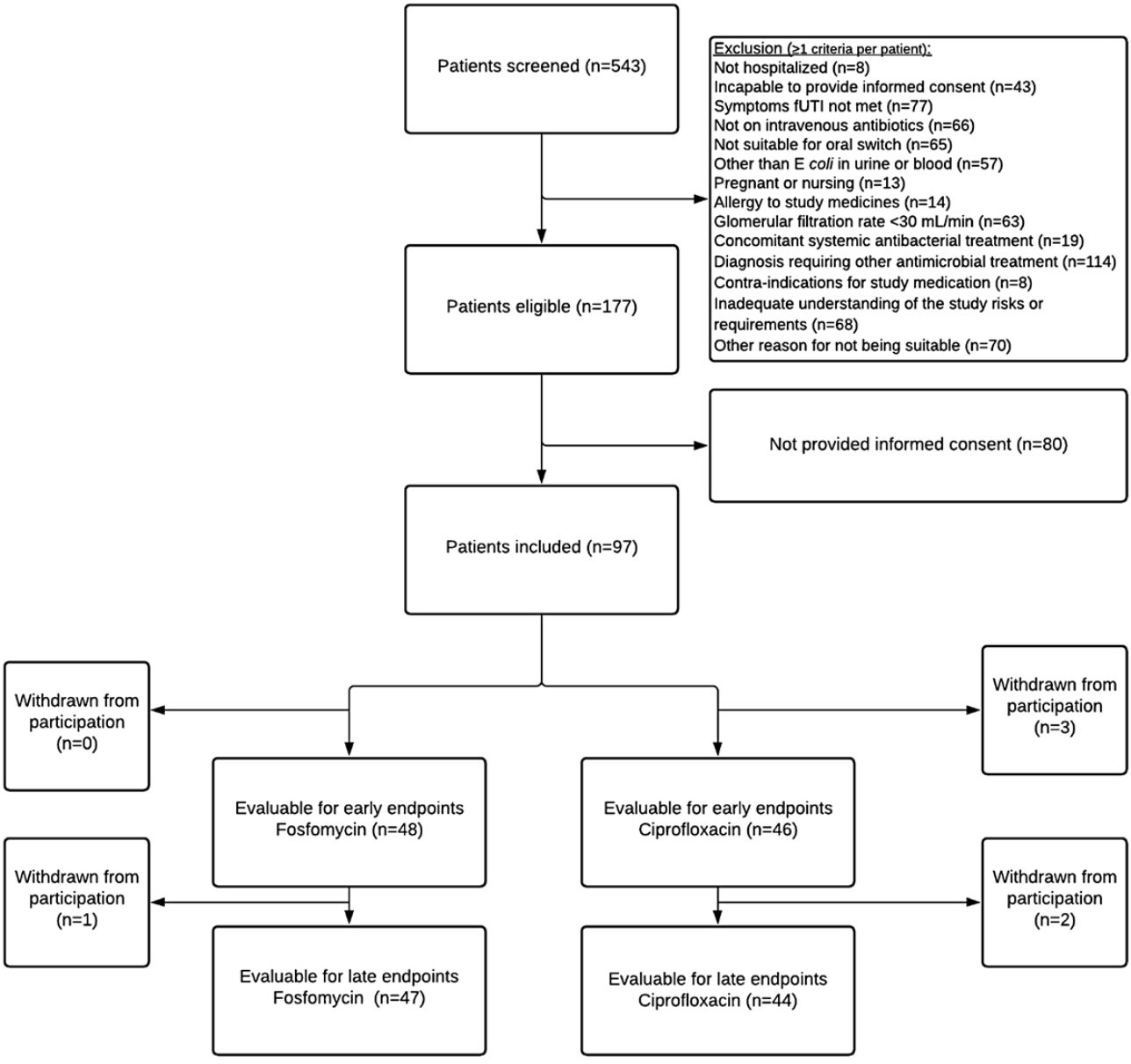

Figure 1. Trial profile for the FORECAST randomized, controlled trial. Abbreviations: FORECAST, FOsfomycin Randomised controlled trial for *E. coli* Complicated urinary tract infections as Alternative Stepdown Treatment; fUTI, febrile urinary tract infection.

from the study directly on the day of initiation because of a renal abscess that required IV antibiotic therapy (n = 1), failure to perform study procedures in a nursing home (n = 1), and withdrawal of consent (n = 1). Three patients were not evaluable for late end points due to loss to follow-up. Yet, the safety of these 6 patients could be assessed; at discontinuation of the study, all were alive without hospital readmissions.

At admission, the mean age of enrolled women was 59.4 years (standard deviation [SD], 20.2), the mean Charlson comorbidity index (CCI) was 7.3 (SD, 4.6), 9 patients (9.3%) had a nonresuscitative policy, and 50 (51.6%) had *E. coli* bacteremia. More patients assigned to fosfomycin had a history of diabetes mellitus, and more patients in the ciprofloxacin had a history of nephrolithiasis (Table 1). Patients who declined participation (n = 80) had a mean age of 60.3 years (SD, 22.2), a mean CCI of 5.9 (SD, 5.5), a nonresuscitative policy in 2 (of 58 with nonmissing data, 3.4%), and 30 (37.5%) had *E. coli* bacteremia. Empirical antimicrobial treatment was given for a mean duration of 3.3 days (SD, 1.1), consisting of a second-generation cephalosporin (n = 35), a third-generation cephalosporin (n = 33), a second-generation cephalosporin with an aminoglycoside (n = 15), a carbapenem (n = 2), or another regimen (n = 12), leaving a mean of 6.7 days (SD, 1.1) of oral study medication.

At randomization, the presumptive diagnosis according to the treating physician was urosepsis in 48 patients (49.5%), acute pyelonephritis in 35 (36.1%), and unspecified fUTI in 14 (14.4%). In 27 (27.8%) patients, an indwelling catheter was placed at some point during admission. At the moment oral study medication started, patients were afebrile for a median of 2 days (interquartile range, 1–3).

The causative *E. coli* isolate was resistant against amoxicillin–clavulanic acid in 28 of 97 patients (28.9%), against sulfamethoxazole–trimethoprim in 21 of 97 patients (21.6%), and was extended-spectrum beta-lactamase–producing Enterobacteriaceae–producing in 6 of 97 patients (6.2%).

Sixty-six patients (70.2%) met the criteria for clinical cure, 36 of 48 (75.0%) assigned to fosfomycin and 30 of 46 (65.2%) assigned to ciprofloxacin, yielding a risk difference for clinical cure of 9.6% in favor of fosfomycin (95% CI:–8.8% to 28.0%). The lower bound of –8.8% is within the predefined noninferiority margin of 10% (Figure 2). In the per-protocol analysis, 64 of 81 (79.0%) met the criteria for clinical cure, 28 of 38 (73.7%) in the ciprofloxacin arm and 36 of 43 (83.7%) in the fosfomycin arm (risk difference [RD], 10.2%; 95% CI: –8.0 to 28.4). In a post hoc analysis of patients with *E. coli* bacteremia, clinical cure was found in 18 of 25 (72.0%) patients assigned to fosfomycin and 15 of 22 (68.2%) patients assigned to ciprofloxacin (RD, 3.9%; 95% CI: –22.2 to 30.0).

Microbiological cure was met in 62 of 72 (86.1%) patients, 29 of 37 (78.4%) assigned to fosfomycin and 33 of 35 (94.3%) assigned to ciprofloxacin (RD, –16.2%; 95% CI: –32.7% to –0.0%; Table 2). In the per-protocol analysis, microbiological cure was met in 29 of 37 (78.4%) and 32 of 34 (94.1%) patients (RD –15.9%, 95% CI: –32.5% to –0.7%), respectively. Four patients with microbiological failure had diabetes mellitus, all of them were assigned to fosfomycin. Three patients had an indwelling catheter, 2 in the fosfomycin arm and 1 in the ciprofloxacin arm; none of them met the criteria for microbiological failure. The detected isolates are listed in Supplementary Table 2. Additional antibiotic therapy for presumed UTIs was prescribed in 6 of 47 patients (12.8%) using fosfomycin and 7 of 44 patients (15.9%) using ciprofloxacin (RD, –3.4%; 95% CI: –18.6% to 11.9%). Other secondary end points are listed in Table 2.

Sixty-seven of 94 (71.3%) patients reported 1 or more AEs, 35 of 48 patients (72.9%) assigned to fosfomycin and 32 of 46 (69.6%) assigned to ciprofloxacin (RD, 3.3%; 95% CI: –15.0% to 21.6%). Probably-related AEs occurred in 25 of 48 (52.1%) patients assigned to fosfomycin and 20 of 46 (43.5%) assigned to ciprofloxacin (RD, 8.3%; 95% CI: –11.6% to 28.1%). The nature, relatedness, duration, and severity of AEs are listed in Table 3. Most notably, gastrointestinal AEs were reported by 25 of 48 (52.1%) patients assigned to fosfomycin and 14 of 46 (30.4%) assigned to ciprofloxacin (RD, 20.8%; 95% CI: 1.6% to 40.0%). Seven patients discontinued the study medication prematurely as a consequence of AEs, 3 of 48 (6.3%) assigned to fosfomycin and 4 of 46 (8.7%) assigned to ciprofloxacin (RD, –2.8%; 95% CI: –15.1% to 9.5%).

There were 8 serious AEs (SAEs) reported, 6 in patients assigned to fosfomycin and 2 in patients assigned to ciprofloxacin. Of these, 4 were considered to probably be related to the study medication, 3 after use of fosfomycin and 1 after use of ciprofloxacin. Two patients assigned to fosfomycin redeveloped fever under fosfomycin use that resolved after a switch to intravenous cefuroxime and amoxicillin, respectively. Two patients assigned to fosfomycin died during follow-up; the deaths were considered consequences of underlying diseases, not related to (failure of) study medication. Supplementary Table 3 provides a description of all SAEs.

DISCUSSION

In this randomized, controlled, double-blind trial, oral step-down treatment with fosfomycin after initial IV antibiotic treatment in women with *E. coli* fUTIs was noninferior to ciprofloxacin in achieving clinical cure 6–10 days after the end of treatment. The risk difference for clinical cure was 9.6% in favor of fosfomycin with a lower 95% confidence interval boundary of –8.8%, within the predefined 10% noninferiority margin. These results indicate that fosfomycin can be used for the step-down treatment of *E. coli* fUTIs in women, reducing the need for prolonged IV antibiotic regimens and hospitalizations for patients with *E. coli* that is resistant to other oral antibiotic options [9–11].

The clinical cure rate of 65.2% with ciprofloxacin was considerably lower than in previous studies, for which we provide the

Table 1. Characteristics of Enrolled Patients

Characteristic		Fosfomycin (n = 48)	Ciprofloxacin (n = 49)
General			
Age, mean (SD), years		58.9 (18.8)	59.9 (21.7)
Charlson comorbidity index (age adjusted), mean (SD)		7.4 (4.7)	7.2 (4.5)
History of diabetes mellitus (%)		17 (35.4)	7 (14.3)
History of anatomic abnormalities of the urinary tract (%)		1 (2.1)	1 (2.0)
History of nephrolithiasis (%)		2 (4.2)	6 (12.2)
At admission			
Days of urinary tract infection symptoms/signs, median (interquartile range)		3.0 (1.0 to 5.3)	3.00 (1.0 to 5.0)
Urinary tract infection symptoms/signs	Fever[a] (%)	33 (68.8)	40 (81.6)
	Rigors (%)	39 (81.3)	32 (65.3)
	Confusion (%)	16 (33.3)	18 (36.7)
	Hallucinations (%)	9 (18.8)	7 (14.3)
	Flank pain (%)	26 (54.2)	32 (65.3)
Vital signs[b]	Temperature, mean (SD), °C	39.0 (1.0)	39.1 (1.0)
	Pulse, mean (SD)	105.7 (17.1)	104.7 (19.1)
	Mean arterial pressure,[c] mean (SD), mm Hg	79.4 (15.3)	82.0 (15.8)
Hemodynamic instability requiring intravenous fluids[d]		13 (27.7)	13 (26.5)
Laboratory values[b]	C-reactive protein, mean (SD), mg/L	167.7 (137.4)	169.2 (111.8)
	White blood count 10^9/mL, mean (SD)	14.2 (6.7)	13.8 (5.3)
	Estimated glomerular filtration rate, mean (SD), mL/min	83.2 (29.0)	77.5 (35.2)
	Leucocyte esterase in urine (>25 µL) (%)	46 (95.8)	43 (87.8)
Blood culture positive for *Escherichia coli* (%)		25 (52.1)	25 (51.0)
Urine culture positive for *E. coli* (%)		44 (91.7)	47 (95.9)
Hospital urology department (%)		10 (20.8)	14 (28.6)
	Internal medicine (%)	34 (70.8)	32 (65.3)
	Other (%)	4 (8.3)	3 (6.1)
Of empirical treatment			
Antibiotic class	Second-generation cephalosporin (%)	18 (37.5)	17 (34.7)
	Third-generation cephalosporin (%)	16 (33.3)	17 (34.7)
	Second-generation cephalosporin with aminoglycoside (%)	6 (12.5)	9 (18.4)
	Carbapenem (%)	1 (2.1)	1 (2.0)
	Other (%)	6 (12.5)	5 (10.2)
Hours from presentation until antibiotic injection, mean (SD)		3.0 (4.8)	2.8 (4.4)
Days of intravenous therapy, mean (SD, range)		3.4 (1.1, 2.0 to 5.0)	3.2 (1.1, 2.0 to 5.0)
At randomization			
Presumptive diagnosis	Urosepsis (%)	24 (50.0)	24 (49.0)
	Acute pyelonephritis (%)	18 (37.5)	17 (34.7)
	Unspecified (%)	6 (12.5)	8 (16.3)
Do not resuscitation policy		5 (10.4)	4 (8.2)
Intensive care requirement[e] (%)		2 (4.2)	0
Indwelling catheter[e] (%)		12 (25.0)	15 (30.6)
Vital signs[f]	Temperature, mean (SD), °C	37.2 (0.6)	37.0 (0.5)
	Pulse, mean (SD)	79.1 (12.3)	78.1 (14.2)
	Mean arterial pressure,[c] mean (SD), mm Hg	94.6 (12.2)	98.0 (15.4)
Laboratory values[f]	C-reactive protein in mg/L, mean (SD)	121.7 (86.0)	118.3 (66.0)
	White blood count 10^9/mL, mean (SD)	11.1 (4.8)	10.4 (5.9)
	Creatinine, mean (SD), µmol/L	95.6 (22.9)	90.9 (27.2)

Abbreviation: SD, standard deviation.

[a]Reported by the patient.

[b]Measured at admission.

[c]Mean arterial pressure = (systolic blood pressure + 2 (diastolic blood pressure))/3.

[d]Within 24 hours before or after admission.

[e]At any moment during admission.

[f]If measured within 24 hours before or after randomization.

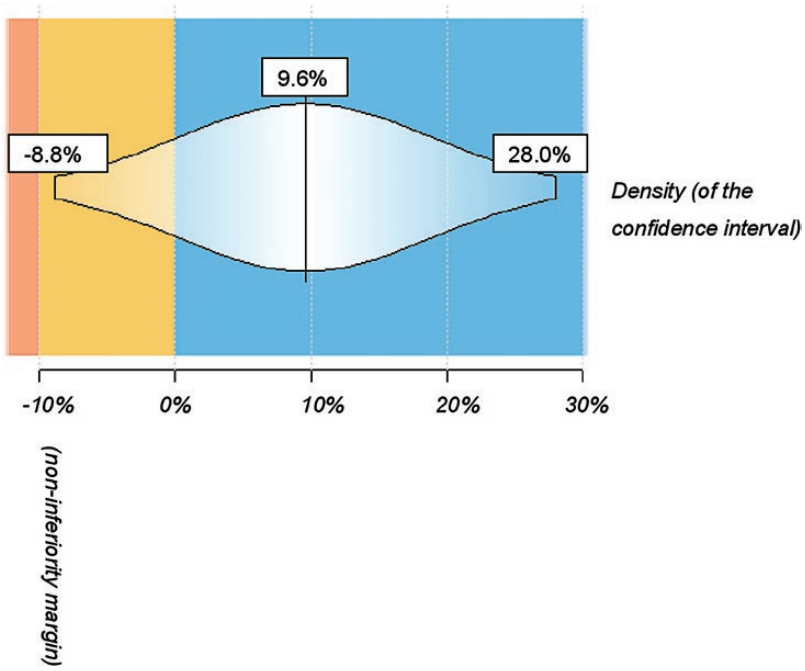

Figure 2. Noninferiority margin for the risk difference on early clinical cure between fosfomycin and ciprofloxacin. In the blue area, the risk difference is in favor of fosfomycin. In the yellow area, the risk difference is in favor of ciprofloxacin with a margin up to 10%. In the red area, the risk difference is in favor of ciprofloxacin with a margin beyond 10%. The 95% confidence interval remains within the blue and yellow area, indicating that fosfomycin is noninferior to ciprofloxacin with a margin of 10%.

following explanations. First, we used a stringent definition for the primary end point to reflect the clinical goal of step-down treatment, that is, the reduction of initial urinary tract and systemic symptoms without additional systemic antibiotic therapy for UTIs. Previous studies used more pragmatic end points that mimic our secondary end point "no additional antibiotic therapy for presumed UTI" at days 30–35, which was met in 84.1% in the ciprofloxacin arm. Second, the population in our trial was sicker, as evidenced by the high bacteremia rate of 51% vs 8%–27% in previous trials [20–22].

The higher early clinical cure rate in the fosfomycin arm may be a consequence of the long half-life of fosfomycin in urine compared with ciprofloxacin, which could suppress local symptoms [23]. Microbiological cure 6–10 days after the end of treatment was lower for patients assigned to fosfomycin. Possibly, fosfomycin is less able to eliminate

Table 2. Secondary End Points of the Intention-to-Treat Population

Secondary End Point	Fosfomycin (n = 48)	Ciprofloxacin (n = 49)	Risk Difference (95% Confidence Interval/*P* Value)
6–10 days post-end of therapy			
Microbiological cure	29/37 (78.4%)	33/35 (94.3%)	–16.2% (–32.7% to –0.0%)
30–35 days post-end of therapy			
Clinical cure	35/47 (74.5%)	33/44 (75.0%)	0.4% (–18.4% to 17.6%)
Reinfection	4/47 (8.5%)	7/44 (15.9%)	–7.8% (–22.3% to 6.6%)
Relapse	2/47 (4.3%)	0/44	5.2% (–4.0% to 14.3%)
Additional antibiotic therapy for presumed urinary tract infection	6/47 (12.8%)	7/44 (15.9%)	–3.4% (–18.6% to 11.9%)
Length of hospital stay, mean (SD), days	4.4 (1.2)	5.4 (2.5)	*P* = .9156[a]
Hospital readmission (any cause)	3/48 (6.3%)	1/49 (2.0%)	5.0% (–5.3% to 15.2%)
Absenteeism days[b] mean (SD)	3.0 (6.7)	2.5 (7.0)	*P* = .5508[c]
Intensive care unit admission[a]	1/48 (2.1%)	0/49	2.9% (–5.3% to 11.0%)
Mortality (any cause)	2/48 (4.2%)	0/49	5.4% (–3.3% to 14.0%)
Mortality (probably related)	0/48	0/49	NA

Abbreviation: SD, standard deviation.

[a]After randomization.

[b]Number of days absent from paid or voluntary work.

[c]Calculated using a Mann-Whitney test.

Table 3. List of Adverse Events

Adverse Event		Fosfomycin (n = 48)	Ciprofloxacin (n = 46)
Total number of adverse events		83	79
Mild symptoms[a] (score 1–5)		33	35
Severe symptoms[a] (score 6–10)		27	20
Duration, median (interquartile range), days		3 (1–6)	2 (1–4)
Related		44	39
Gastrointestinal		42	19
	Diarrhea	22	4
	Nausea	9	6
	Abdominal cramping	7	2
Skin		1	5
Increased vaginal discharge		1	4
Neurological/mental		11	8
Thoracic		0	2
Other		13	20
	Change in smell or taste	0	5
Patients without adverse events		13 (27.1%)	14 (30.4%)

[a]Severity is scored by the patient on a scale of 1 to 10 (not to be confused with a serious adverse event).

bacteria from the urinary tract. In a previous trial evaluating a single dose of 3 g fosfomycin for *E. coli* uncomplicated cystitis in women, a microbiological cure rate of only 58% was observed [24]. Microbiological failures may have been a consequence of diabetes mellitus, which is associated with a 2- to 3-fold higher prevalence of asymptomatic bacteriuria [25]. Four of 10 patients with microbiological failure had diabetes mellitus, all of them assigned to fosfomycin. Only 2 of 10 patients with microbiological failure, both assigned to fosfomycin, had symptoms that required antimicrobial treatment.

Two patients redeveloped fever under the use of fosfomycin, which resolved after the switch to intravenous cefuroxime and amoxicillin, respectively. These failures may be attributable to the relatively low fosfomycin plasma levels that are reached after the oral use of 3 g fosfomycin. It is unclear to what extent plasma and/or urine levels are decisive for efficacy in the step-down treatment of fUTIs. Higher oral doses up to 6–12 g per day are expected to be needed for the empiric treatment of systemic infections [26, 27]. We decided to dose fosfomycin at 3 g every 24 hours because we anticipated that higher doses would not be tolerated [27]. We considered this dose to be safe, bearing in mind that fosfomycin is prescribed intravenously in doses up to 24 g per day [28]. Noninferiority of fosfomycin to ciprofloxacin suggests that either the achievement of high concentrations in urine is sufficient or that the added value of step-down treatment for fUTIs is questionable. However, according to current standards, the 3.3 days of intravenous antibiotic treatment in our trial is too short for treatment of fUTIs, justifying an oral step-down treatment [2, 3].

Fosfomycin was more frequently associated with gastrointestinal AEs than ciprofloxacin, most notably diarrhea. Yet, this did not result in more frequent discontinuation of fosfomycin. In another study, healthy patients less frequently experienced diarrhea when fosfomycin (3 g) was dosed every 48 hours instead of every 24 hours [27]. It remains to be determined if fosfomycin every 48 hours is also efficacious for this indication [29].

The strengths of this study are the double-blind design with the use of a double-dummy placebo, which diminishes the risk of information bias. Second, the high percentage of patients with bacteremia illustrates that patients were seriously ill with an evident indication for IV and oral step-down antimicrobial treatment. Third, AEs were queried with a diary, which provided a complete picture of the safety and tolerability of multidose fosfomycin. Last, the research was conducted in hospitals of various sizes, both academic and regional hospitals, and the variety of patients and empirical antibiotic regimens was large, which benefits the generalizability.

This study has some limitations. First, the study was terminated before the planned sample size was reached. Yet, noninferiority of fosfomycin for the primary end point was demonstrated so that the results support the use of fosfomycin for this indication. Continuation of the trial until the planned sample size would have provided more precision for the secondary end points. Second, the current study was performed in settings with low levels of antibiotic resistance, and practices in other countries may differ in the broadness of empirical antibiotic treatment, duration on IV treatment, and IV–oral switch. Nevertheless, eligibility was conditional on susceptibility to both fosfomycin and ciprofloxacin. Therefore, we consider our findings, that is, noninferiority of fosfomycin to ciprofloxacin as oral step-down treatment, valid in such settings for fosfomycin-susceptible isolates. Third, for feasibility and safety reasons, we used a treatment duration of 10 days for all patients, even though

7 days of ciprofloxacin has been demonstrated to be sufficient for treatment of acute pyelonephritis and gram-negative bacteremia [22, 30, 31]. Last, implementation of fosfomycin use for step-down treatment requires reliable susceptibility testing. The MIC of *E. coli* to fosfomycin, as measured with automated panel tests, seems to correlate poorly with clinical and microbiological efficacy of fosfomycin for the empirical treatment of cystitis [24]. Future improvements in routine fosfomycin susceptibility testing possibly affect the targeted use of fosfomycin, although theoretically it would lead to a higher of fosfomycin efficacy.

In conclusion, this trial demonstrates that fosfomycin 3 g every 24 hours as targeted step-down treatment for *E. coli* fUTIs in women is noninferior to ciprofloxacin with regard to clinical cure. Fosfomycin is an additional oral antibiotic option for this indication, especially in cases of resistance, intolerance, or allergies to existing options.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

The FOsfomycin Randomised controlled trial for *E .coli* Complicated urinary tract infections as Alternative Stepdown Treatment (FORECAST) study team consists of Thijs ten Doesschate[1 2], Andy. I.M. Hoepelman[1], Cornelis. H. van Werkhoven[2], Marc J.M. Bonten[2], Cees van Nieuwkoop[3], Sander Kuiper[3 5], Marleen M. van Dijk[4], Janneke E. Stalenhoef[5], Linda Smid[5] Robert-Jan Hassing[6], Tom Ketels[6], Yvonne den Ouden-van der Thiel[7], Elisabeth H. Gisolf[6], Suzan P. van Mens[8], Wouter van den Bijllaardt[9 10], Akke K. van der Bij[11], Tanja Voogt-Vrijhoef[11], Suzanne E. Geerlings[12], Thomas W. van der Vaart[12], Ad Koster[13], Evert L. Koldewijn[14], Mandy Hobijn[14], Maartje Van 't Hof[14], Judith Branger[15], Aafke S. Cents-Bosma[15], Arend-Jan Meinders[16], Steven van Lelyveld[17], Kelly D. Hendriks[18]

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Author contributions. T. D., C. N., M. B., S. G., S. M., and A. H. constructed the design of the study. H. W. and T. D. performed the statistical analysis. T. D. wrote the first draft of the report with input from M. B. and S. K. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. T. D. and H. W. have accessed and verified the data.

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Data sharing. The study protocol was published before the execution of the study in the Supplement. The questionnaire (in Dutch) providing demographic data, comorbidity, urinary tract symptoms and signs at baseline, and follow-up is available in the Supplementary Material. The statistical analyses plan is available on request to the corresponding author. Deidentified individual patient data will remain available exclusively for study team members.

Others. Ethics approval and consent to participate was provided by the medical ethics committee of the University Medical Centre Utrecht approved the study protocol, followed by the Institutional Scientific Boards of the following Dutch participating centers:

- Academic Medical Centre, Amsterdam
- Amphia hospital, Breda
- St. Antonius hospital, Nieuwegein
- Diakonessenhuis hospital, Utrecht
- St. Catharina hospital, Eindhoven
- Flevohospital, Almere
- Haaglanden Medical Centre, The Hague
- Haga Teaching Hospital, The Hague
- Leiden University Medical Centre, Leiden
- Maastricht University Medical Centre, Maastricht
- Rijnstate hospital, Arnhem
- Spaarne Gasthuis, Harlem
- Tergooi hospital, Hilversum
- University Medical Centre, Utrecht
- Viecuri Medical Centre, North-Limburg

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