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Daily fosfomycin versus levofloxacin for complicated urinary tract infections

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ABSTRACT Fosfomycin, approved in the United States only for cystitis, is an attractive alternative for oral treatment of outpatient complicated urinary tract infections (cUTIs) as it has antimicrobial activity against most common uropathogens. The study was a multicenter, randomized, open-label pragmatic superiority clinical trial evaluating the efficacy of oral fosfomycin versus oral levofloxacin strategies in cUTIs (FOCUS study). The trial compared two strategies for initial or step-down oral therapy of cUTI without bacteremia after 0–48 hours of parenteral antibiotic therapy. Subjects were assigned to 3 g of fosfomycin or 750 mg (or dose adjusted for kidney function) of levofloxacin daily for 5–7 days. Clinical and microbiological cures were assessed at the end of therapy (EOT) and test of cure (TOC) (approximately 21 days from the start of antibiotics). The trial did not meet accrual goals; thus, the results were descriptive. Only 51 subjects were included in the microbiological intention-to-treat population. The subjects were mainly females (76%), with a mean age of 46.7 years (standard deviation [SD] = 20.8) and acute pyelonephritis (88%). At the end of therapy, clinical cure remained similar (69% and 68% for fosfomycin and levofloxacin strategies, respectively), and microbiological success was 100% for both strategies. At the test of cure, clinical cure was similar (84% and 86% in the fosfomycin and levofloxacin strategies, respectively); however, a numerically lower microbiological success was observed for fosfomycin (69% compared to 84% for levofloxacin). These limited data suggest that fosfomycin could be an oral alternative as a step-down therapy for the treatment of cUTIs (registry number NCT 03697993).

IMPORTANCE Concerns over resistance and safety have been identified in the current treatment regimen for complicated urinary tract infections. Fosfomycin is a drug that is routinely used for the treatment of uncomplicated cystitis. This study shows that fosfomycin could be an oral alternative as step-down therapy for the treatment of complicated urinary tract infections, with a clinical cure rate comparable to levofloxacin but a lower microbiological success rate 3 weeks from start of antibiotics.

KEYWORDS complicated UTI, fosfomycin, oral antibiotic

Complicated urinary tract infections (cUTIs) are a widespread clinical problem associated with substantial burden to the healthcare system (1, 2) and high morbidity (3) and mortality (4), all exacerbated when cUTIs are caused by multidrug-resistant (MDR) organisms.

Quinolones tend to be the most commonly used antibiotics in the treatment of cUTI (5); however, their use is limited by antimicrobial resistance and potential side effects. *Escherichia coli*, the most common uropathogen, currently shows resistance rates of 5%–32% to quinolones in developed countries and 55%–85% in developing countries (6). More than half of quinolone-resistant strains also express extended-spectrum

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beta-lactamases (ESBLs) (7), making them resistant to most beta-lactam antibiotics except carbapenems. Furthermore, in European countries, 15%–60% of uropathogenic *E. coli* isolates are resistant to trimethoprim-sulfamethoxazole (6), eliminating most available oral antibiotics for cUTI. In addition, the U.S. Food and Drug Administration (FDA) has warned against many potential severe side effects of quinolones such as tendinitis/tendon rupture, worsening myasthenia gravis, potentially irreversible peripheral neuropathy, psychiatric effects, hypoglycemic risks, and increased risks of ruptures or tears of the aorta (8–10). Thus, based on current resistance patterns and safety concerns, there is a critical need for alternative oral therapeutic strategies to treat cUTIs.

In the United States, a tromethamine salt of fosfomycin has been FDA-approved since 1996 as a single oral sachet for the treatment of uncomplicated urinary tract infections (UTIs) (e.g., cystitis [11]). Fosfomycin has broad *in vitro* antibacterial activity against many clinically significant multidrug-resistant uropathogens (12) and excellent penetration into the urinary tract (13). For more serious infections, oral administration may provide inadequate concentrations due to its limited systemic bioavailability (37%) and dose-limiting gastrointestinal tolerability (e.g., predominately diarrhea) (11). While prior studies on the use of more than one dose of fosfomycin for the treatment of cUTIs were promising, the findings were limited by their retrospective design (14–16).

The current trial assessed the safety and efficacy of a strategy of fosfomycin compared to a strategy of levofloxacin as initial or step-down oral therapy in patients with cUTI including pyelonephritis. The study utilized a unique pragmatic design, comparing personalized antibiotic strategies (COMPASS) (17). Recent pharmacokinetic data support the use of daily 3-g oral dose of fosfomycin (18). Furthermore, randomized clinical trials have shown that 750-mg levofloxacin once daily for 5 days is non-inferior to 10 days of ciprofloxacin in adults (19) with 7 days of quinolones non-inferior to 14 days of treatment for acute pyelonephritis (20). We therefore elected to compare two strategies in terms of safety and efficacy: 3 g of fosfomycin (Strategy 1) or 750 mg of levofloxacin (Strategy 2) for 5–7 days to ensure clinically relevant and potentially highly effective oral comparator arms.

MATERIALS AND METHODS

Trial design, oversight, and procedures

The FOCUS study was a multicenter, randomized, open-label pragmatic superiority clinical trial evaluating the efficacy of oral fosfomycin versus oral levofloxacin strategies in complicated urinary tract infections. The trial compared two strategies for initial or step-down oral therapy of cUTI without bacteremia after 0–48 hours of parenteral antibiotic therapy. Strategy 1 was 3 g of fosfomycin daily, and Strategy 2 was 750 mg of levofloxacin daily (or the equivalent dosing based on kidney function [21]). Assessment of compliance was performed at each of the three follow-up visits and by observing the first dose. The trial was designed in accordance with FDA guidelines (22) using a dynamic treatment strategy (17) allowing for investigator-directed adjustment. The adjustment to another adequate oral therapy was allowed (i) if the causative pathogen was not susceptible *in vitro* to quinolone initial or step-down therapy in a subject randomized to the levofloxacin strategy; (ii) if the subject developed intolerance or allergy to the initial or step-down oral therapy, at the investigator's discretion; or (iii) if the subject had an underlying condition posing increased risk of adverse events from quinolone therapy (Fig. 1). The duration of oral study therapy (initial + investigator-directed adjustment if indicated) in each strategy was 5–7 days of any per protocol antibiotic to which the pathogen was susceptible, such that the total duration of effective antibacterial therapy (including pre-study administration of oral therapy escalated to parenteral therapy or parenteral therapy alone) was 7 days. All microbiology laboratories used matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) to identify uropathogens and the automated broth microdilution (VITEK 2) for quinolone susceptibility testing. Fosfomycin

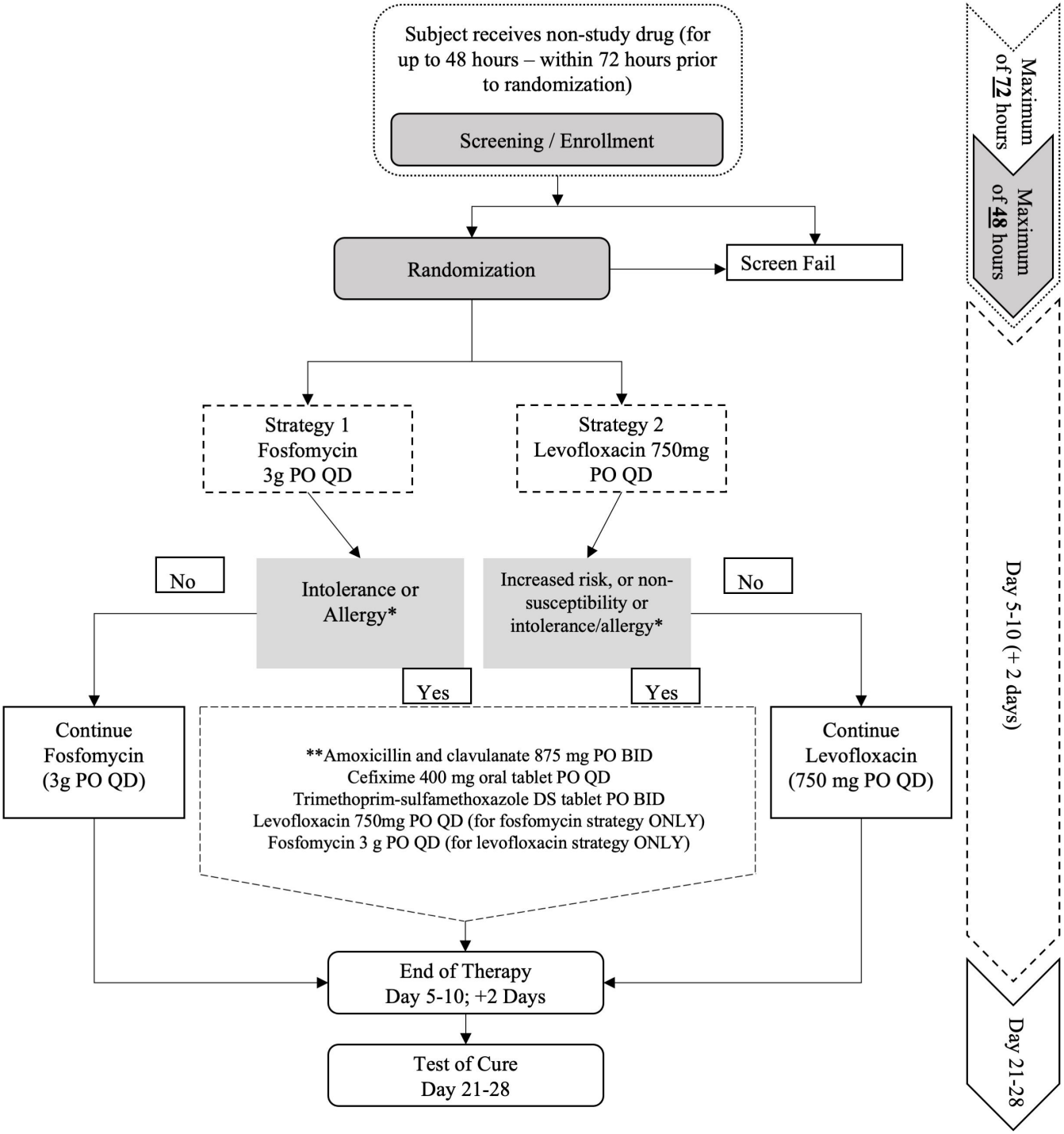

FIG 1 Schematic of the study design. QD, once daily; PO, orally; BID, twice a day; DS, double strength.

antimicrobial susceptibility testing results were generally not available in real time. Centralized testing for fosfomycin was adapted to assist in the interpretation of the trial data as the agar dilution method recommended for minimum inhibitory concentration (MIC) testing is not routinely performed in clinical microbiology laboratories.

The study was conducted both in the outpatient and inpatient settings from November 2018 to October 2019 when it was halted due to slow enrollment. Subjects

were enrolled at five sites in different states in the United States (Georgia, Illinois, New York, and Iowa).

Eligibility criteria

Eligible subjects were adults (aged ≥18 years) who (i) had documented or suspected microbial pathogen isolated on urine culture, (ii) had not received fosfomycin in the past year or any oral antibiotic prior to presentation, (iii) were anticipated to be able to be stepped down or initially started on study oral antibiotic therapy within 48 hours of enrollment, (iv) had a creatinine clearance of more than 20 mL/min, (v) had pyuria, (vi) had absence of bacteremia/sepsis, and (vii) presented with clinical symptoms of cUTI. cUTI was indicated by at least two signs or symptoms (chills, rigors, fever, or hypothermia; dysuria or urinary frequency or urgency; lower abdominal or pelvic pain or tenderness; nausea or vomiting; new onset of foul smell of urine or increased cloudiness of urine per subject or their caregiver); and at least one complicating factor (indwelling urinary catheter, current obstructive uropathy, or any functional or anatomical abnormality with voiding disturbance). Acute pyelonephritis was indicated by at least two of the following signs or symptoms: chills, rigors, or fever; flank pain; tenderness in the costovertebral angle; dysuria or urinary frequency or urgency; and nausea or vomiting. Subjects were excluded if they had a complete, permanent obstruction of the urinary tract, perinephric or intrarenal abscess, suspected prostatitis, or an ileal loop or known vesicoureteral reflux.

Randomization

Subjects were randomly assigned in a 1:1 ratio to receive oral therapy from Strategy 1 (initial or step-down to oral fosfomycin) or Strategy 2 (initial or step-down to oral levofloxacin). Randomization was performed by statisticians at the Data Coordinating Center (the Emmes Corporation) using an interactive web system and was stratified according to site location and baseline diagnosis (acute pyelonephritis or other cUTIs). There were no masking procedures as the trial was open label.

Analysis populations, assessments, and end points

The intention-to-treat (ITT) or safety population included all randomly assigned subjects who received at least one dose of study drug. The analyses on the safety population were performed per treatment actually received. The microbiological intention-to-treat (mITT) population included all subjects in the ITT population who had a positive baseline urine culture.

Study procedures included assessment of study outcomes, collection of urine for urinalysis and cultures, and blood for creatinine (renal function), complete blood count and bacterial culture, as well as pregnancy testing (if not already collected through standard of care) and optional pharmacokinetic analyses. Assessments of adverse events, vital signs (including body temperature), and physical examinations were also conducted. Investigator assessment was also supported by an iterative structured subject questionnaire and subjects' memory aid. Therapeutic drug monitoring was not implemented. Identification and susceptibility testing were conducted as part of standard of care at local laboratories (using the Clinical and Laboratory Standards Institute [CLSI] methods [23]). Levofloxacin susceptibility was tested at the participating site as per routine clinical care. Fosfomycin susceptibility was centrally tested in duplicate by the agar dilution method in Mueller-Hinton agar supplemented with 25 mg/L of glucose-6-phosphate as stipulated by the CLSI. If there was more than a twofold difference between the two results, a third round was performed, and those runs in agreement were accepted. Thus, the result of fosfomycin susceptibility testing was not available at the time of treatment. Positive baseline culture was defined as a culture grown from a urine sample collected prior to treatment that had $\geq 10^5$ colony-forming units (CFU)/mL (50,000 and above was an allowed cut-off, provided it was a causative

uropathogen) for non-catheter specimens or ≥10^4 CFU/mL for catheter specimens of a single species of bacteria that causes cUTI. Up to two isolated pathogens were allowed per urine culture. Urine cultures with three or more bacterial organisms were considered contaminated unless there was a causative uropathogen that was growing at ≥50,000 CFU/mL and the contaminant was growing at ≤40,000 CFU/mL.

Clinical cure was defined as resolution of core symptoms from presentation with no new UTI symptoms with avoidance of parenteral antibiotic therapy, in or out of hospital, or oral antibiotic therapy different from per protocol at any time after randomization. Microbiological success was defined as reduction of the baseline uropathogen to <10^4 CFU/mL for non-catheter specimens or <10^3 CFU/mL for catheter specimens on urine culture (22). Clinical cure and microbiological success were assessed at end of therapy (EOT) and test of cure (TOC) (approximately 21 days from start of antibiotics).

Statistical analysis

While originally designed and powered to evaluate superiority of Strategy 1 over Strategy 2 (sample size of 634), study enrollment was terminated prematurely due to slow recruitment, yielding a sample size with low power for hypothesis testing. All resulting analyses on the mITT population are thus considered descriptive in nature.

RESULTS

A total of 79 subjects were screened, and 62 were randomized. Fifty-one subjects were included in the mITT population (with a positive baseline bacterial urine culture) and 58 in the safety population (Fig. 2), and 3 subjects were lost to follow-up. Demographics and baseline characteristics are described in Table 1. The subjects were mostly females (39 of

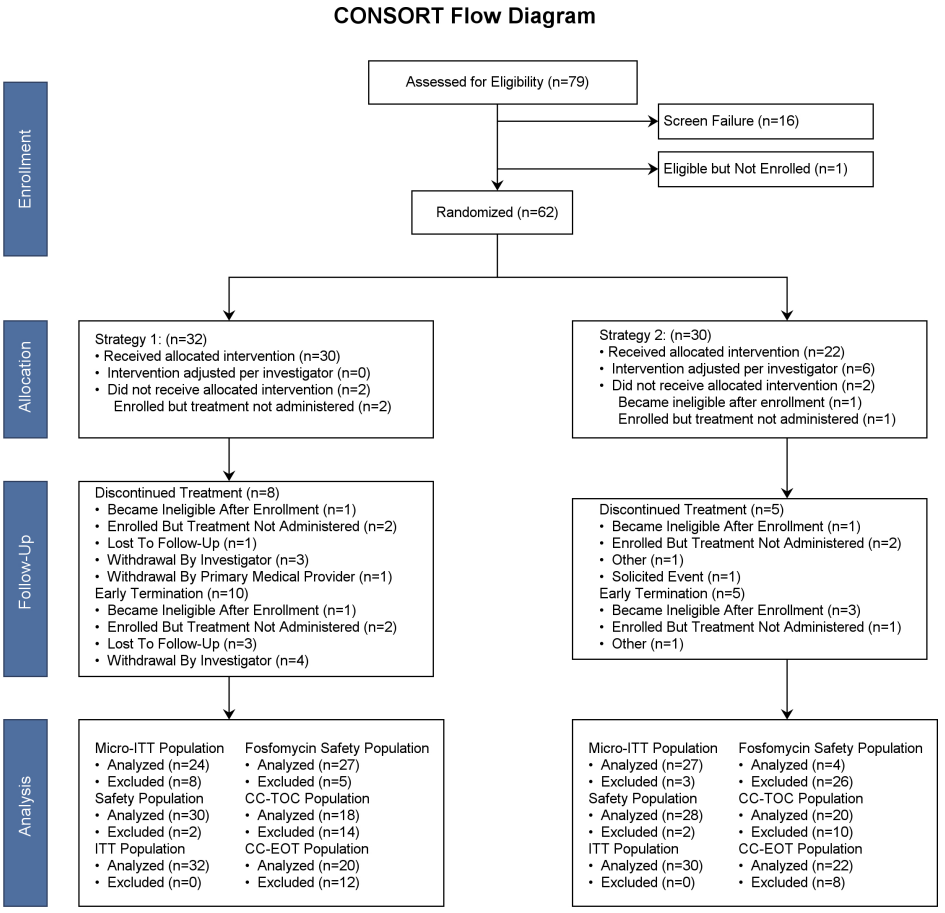

FIG 2 Consolidated standards of reporting trials (CONSORT) diagram. CC, complete cases.

TABLE 1 Summary of demographic and baseline characteristics by treatment group-mITT population[e]

Variable, statistic	Characteristics	Strategy 1 (*n* = 24)	Strategy 2 (*n* = 27)	All subjects (*n* = 51)
Age (years), mean (SD)	–	46.7 (20.4)	46.7 (21.6)	46.7 (20.8)
Sex, *n* (%)	Male	4 (17)	8 (30)	12 (24)
	Female	20 (83)	19 (70)	39 (76)
Race, *n* (%)	American Indian or Alaska Native	–	–	–
	Asian	–	–	–
	Native Hawaiian or other Pacific Islander	–	–	–
	Black or African American	11 (46)	13 (48)	24 (47)
	White	10 (42)	11 (41)	21 (41)
	Multiracial	–	–	–
	Unknown	3 (13)	3 (11)	6 (12)
BMI (kg/m^2), mean (SD)	–	26.20 (7.19)	28.94 (8.49)	27.65 (7.95)
cUTI type, *n* (%)	Acute pyelonephritis	23 (96)	22 (81)	45 (88)
	Other cUTI	1 (4)	5 (19)	6 (12)
Calculated creatinine clearance, n (%)	≥90 mL/min	11 (46)	17 (63)	28 (55)
	60–89 mL/min	5 (21)	5 (19)	10 (20)
	30–59 mL/min	8 (33)	3 (11)	11 (22)
	≤29 mL/min	–	2 (7)	2 (4)
Medical history, n (%)	With recurrent UTIs	9 (38)	8 (30)	17 (33)
	With obstructive uropathy	1 (4)	–	1 (2)
	With indwelling urinary catheter	1 (4)	3 (11)	4 (8)
	Diabetes mellitus	8 (33)	6 (22)	14 (27)
All uropathogens, n (%)	–	24 (100)	27 (100)	51 (100)
Enterobacteriaceae uropathogens,[a] n (%)	Not susceptible to quinolones[b]	1 (4)	2 (7)	3 (6)
	Not susceptible to fosfomycin	–	–	–
	Not susceptible to carbapenems	–	–	–
	ESBL[c]	1 (4)	1 (4)	2 (4)
	Multidrug resistant[d]	5 (21)	3 (11)	8 (16)
Any prior use of antibiotics, n (%)	Yes	18 (75)	17 (63)	35 (69)
	No	6 (25)	10 (37)	16 (31)
Prior use of antibiotics, n (%)	Sulfamethoxazole and trimethoprim	–	1 (4)	1 (2)
	Ceftriaxone	18 (75)	13 (48)	31 (61)
	Levofloxacin	–	1 (4)	1 (2)
	Meropenem	–	2 (7)	2 (4)

[a]*Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterobacter cloacae.*
[b]Levofloxacin and ciprofloxacin.
[c]Resistance to either ceftazidime, aztreonam, or ceftriaxone.
[d]Resistance to at least one antibiotic from at least three different classes.
[e]mITT, microbiologic intention-to-treat population, denotes all randomized patients who have a positive baseline bacterial culture of urine; *n*, number of subjects in the mITT population; BMI, body mass index, weight (kg)/height (m)^2.

52 or 76%); the mean age was 46.7 years (SD = 20.8); almost half (24 of 51 or 47%) were African American; and the most common presentation was acute pyelonephritis (45 of 51 or 88%). The mean body mass index was 27.7 kg/m^2 (SD = 8). The majority (38 of 51 or 75%) had preserved kidney function (calculated creatinine clearance above 60 mL/min) with some having a history of recurrent UTIs (17 of 51 or 33%) or diabetes (14 of 51 or 27%). The majority of the uropathogens were *E. coli* (63%), *Klebsiella pneumoniae* (9.3%), and *Staphylococcus saprophyticus* (5.6%) (Fig. 3). All *E. coli* isolates tested were susceptible to fosfomycin. Six subjects had a uropathogen that was resistant to at least one antibiotic from at least three different antimicrobial categories (multidrug-resistant) or resistant to quinolones (*Enterobacter cloacae*, *E. coli*, and *Proteus mirabilis*).

The maximum duration of antimicrobial therapy was 7 days (median 5–6 days for Strategies 1 and 2, respectively). Six subjects had adjustment in therapy in Strategy 2 based on having a medical condition for which quinolones are contraindicated (*n* = 3) or having urine culture result showing resistance (*n* = 3) (Fig. 2). One subject, after being switched from Strategy 2 to Strategy 1, could not tolerate fosfomycin because of diarrhea

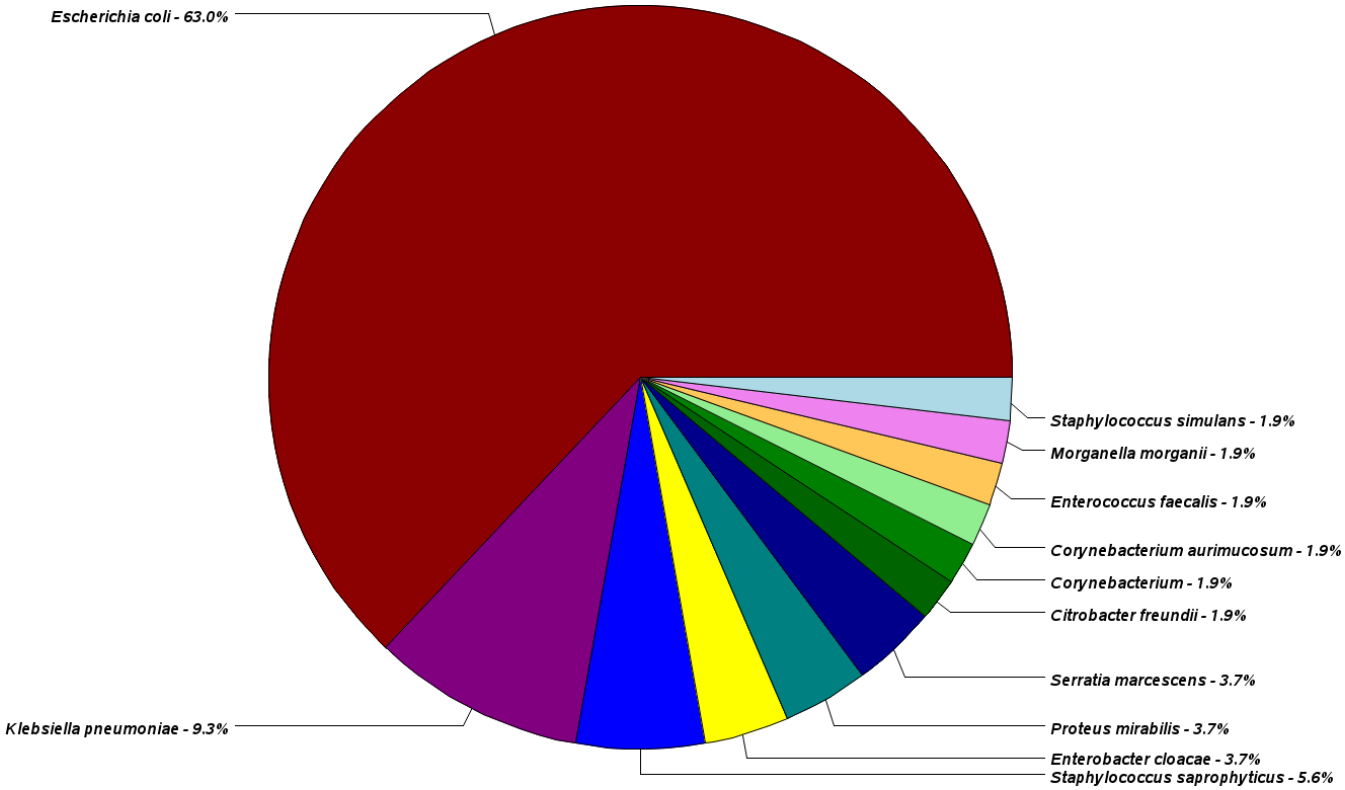

FIG 3 Distribution of uropathogens at baseline in the microbiological intention-to-treat population.

and required a different antibiotic (sulfamethoxazole-trimethoprim). All other subjects had some moderate to severe side effects while on antibiotics; however, these side effects did not result in adjustment in therapy. In Strategy 1 (fosfomycin group), 67% (20 of 30) had moderate to severe adverse events with more than half experiencing diarrhea (53% or 16 of 30). The only severe side effects in Strategy 1 were gastrointestinal symptoms. Similar rates of moderate to severe adverse events were seen in Strategy 2 (levofloxacin group and other adjustment therapies); however, symptoms were mainly insomnia and back pain (28% or 8 of 28) (though may not necessarily be differentiated from costovertebral angle pain). The majority of side effects seen in Strategy 2 were related to central nervous system symptoms (insomnia, dizziness, and headache) (Fig. 4). No allergic reactions were observed in either strategy. At the end of therapy, the clinical cure rates were similar in Strategy 1 (69%) compared to Strategy 2 (68%), and the microbiological success rate was 100% for both strategies. At the test of cure, the clinical cure rates were similar in both strategies (84% in Strategy 1 and 86% in Strategy 2); however, lower microbiological success rates were observed for Strategy 1 at 69% compared to 84% in Strategy 2, with a composite cure in Strategy 1 of 55% compared to 73% in Strategy 2 (Table 2). Among subjects with microbiological failure, one subject in Strategy 2 had both recurrent UTI and an indwelling urinary catheter, while two subjects in Strategy 1 had a recurrent UTI. No subject required readmission for intravenous antibiotics.

DISCUSSION

Each year in the United States alone, UTIs result in more than 10 million office visits, 2 million emergency department visits, and half a million hospitalizations costing approximately $3.5 billion (24, 25). The rise in antimicrobial resistance frequently limits oral treatment options and requires the use of parental therapy, further increasing healthcare costs and leading to risk of complications and patient discomfort (26).

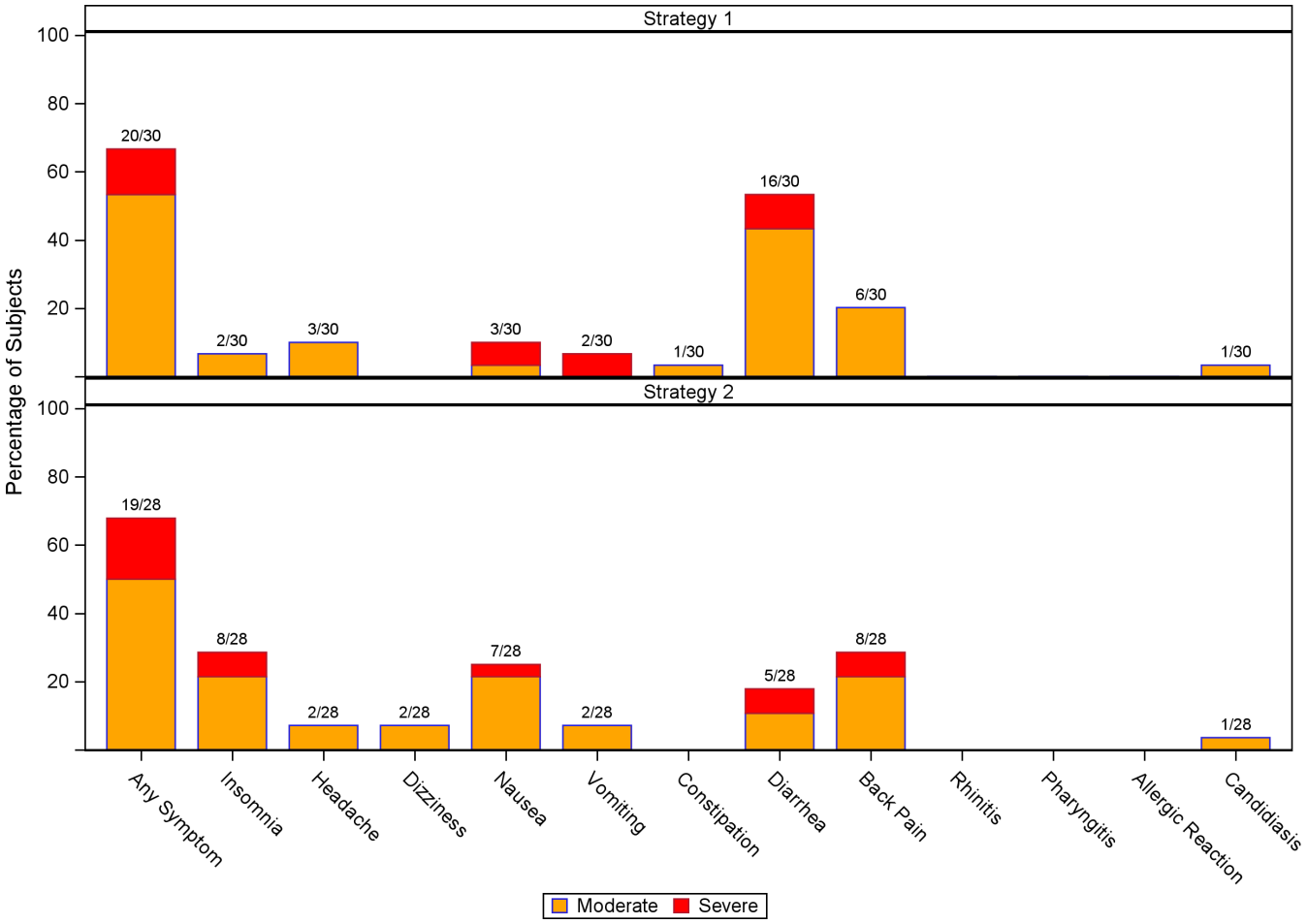

FIG 4 Solicited grade 2 and 3 adverse events in subjects who received at least one dose of study drug by maximum severity and by strategy (Strategy 1: initial or step-down to oral fosfomycin; Strategy 2: initial or step-down to oral levofloxacin).

TABLE 2 Comparison of composite cure, clinical cure, and microbiological cure rates at TOC and EOT between treatment group and mITT population[c]

	Strategy 1			Strategy 2			Difference (95% CI)[b]
End point	*n*[a]	No. missing	%[b]	*n*[a]	No. missing	%[b]	%
Test of cure							
Composite cure	24	5	55	27	5	73	−18 (−43.4 to 8.7)
Clinical cure	24	5	84	27	4	86	−2 (−21.1 to 17.9)
Microbiological cure	24	5	69	27	5	84	−15 (−37.5 to 8.7)
End of therapy							
Composite cure	24	3	67	27	4	67	0 (−26.3 to 25.3)
Clinical cure	24	3	69	27	4	68	1 (−24.4 to 26.8)
Microbiological cure	24	3	100	27	4	100	0 (NE)

[a]*n*, number of subjects in the mITT population at that end point. Multiple imputations are used to impute missing values.
[b]Composite, clinical, or microbiological cure rates will be estimated from the multiple imputation model and 95% Wald CI without continuity correction will be provided. Clinical cure is defined as (i) resolution of UTI symptoms from presentation, (ii) no new UTI symptoms, and (iii) avoidance of parenteral antibiotic therapy, in or out of hospital, at any time after randomization or oral antibiotic therapy different from per protocol. Microbiological cure is defined as a reduction of the pathogen found at presentation to $<10^4$ CFU/mL for non-catheter specimens or $<10^3$ for catheter specimens on urine culture. Treatment success (composite cure) is defined as a combination of clinical cure and microbiological success. Strategy 1 is the initial or step-down to oral fosfomycin; strategy 2 is the initial or step-down to oral levofloxacin.
[c]Notes: NE, not estimated. Confidence interval (CI) and *P* values were not estimated since the microbiological cure rates were 100% for both treatment strategies. Missing values were ignored for this result.

Fosfomycin is considered an acceptable alternative to quinolones for the treatment of cUTIs as it is given orally, is well tolerated, and has low resistance rates against uropathogens (0%–7%) (27). However, its utility as a multiple dose regimen for treatment of cUTIs is not well described.

Though our study did not reach its accrual goal, the strategies appeared to be equally well tolerated, and only one subject could not tolerate fosfomycin due to diarrhea, resulting in change in antibiotic regimen. The only severe side effects seen in Strategy 1 were related to gastrointestinal symptoms, while insomnia and back pain were mostly noted in Strategy 2. The clinical cure rates 3 weeks after starting oral step-down therapy were similar in the fosfomycin strategy (84%) compared to the levofloxacin strategy (86%). However, the microbiological success rates were numerically lower in the fosfomycin strategy (69%) compared with the levofloxacin strategy (84%) at test of cure (although not at end of therapy), consistent with data on cUTI from retrospective studies on fosfomycin (31%–84%) (27). The microbiological success rates were within range of those observed in contemporary prospective cUTI clinical trials with other agents (28, 29). Interestingly, discordant outcomes with respect to microbiological failure and clinical cure were also reported for other agents tested in cUTI clinical trials at TOC (doripenem at 14.8% versus levofloxacin 6.3% [30]). In our study, microbiological failure was observed mainly in subjects with non-identifiable risk factors for microbiological relapse. No resistance to fosfomycin nor quinolones in the microbiological failures was reported in the study. Though the follow-up was limited to 3–4 weeks, we were aware of only four subjects who required additional oral antibiotics outside the study, suggesting that microbiological failure does not necessarily translate into clinical failure. Test of cure cultures are discouraged in clinical settings when clinical cure is achieved, and therefore the long-term clinical significance of microbiological failure is unclear in the setting of clinical cure.

Eighty-seven percent of uropathogens were gram-negative bacteria, mostly *E. coli* as expected for cUTIs, but a surprisingly low number (n = 6) of uropathogens were MDR, given the study was conducted at tertiary academic centers. The susceptibility characteristics of the causative uropathogens could reflect a selection bias where some sicker subjects with MDR organisms were not eligible for de-escalation within 48 hours. Additionally, many of these subjects had acute pyelonephritis rather than known structural abnormalities.

Single-dose oral fosfomycin is approved for uncomplicated UTIs. Multidose regimens (e.g., 3 g once every 2–3 days for three doses) have been described, particularly for MDR UTIs (31) and prostatitis (32). In our cUTI study, fosfomycin was given daily for 5–7 days and only resulted in one therapy adjustment due to gastrointestinal side effects, suggesting that repeated dosing of fosfomycin could be a safe alternative to quinolones for UTIs.

The study utilized a unique pragmatic design, COMPASS (17), valuable in the setting of antibiotic resistance. Management of patients with cUTI is not based on a single decision point. It is dynamic and based on a sequence of decisions, with personalized therapeutic adjustments, tailored to individual patients as new information becomes available. The most important question for informing patient management is how strategies, decision rules that guide empirical and definitive therapy, compare with respect to ultimate outcome. Traditional trial designs comparing drugs rather than strategies are unable to address this most important question. COMPASS was used to compare two strategies mirroring clinical practice: (i) empirical fosfomycin with therapeutic adjustments for intolerance or allergy and (ii) empirical levofloxacin with therapeutic adjustments for non-susceptibility, increased risks for adverse events, or intolerance/allergy.

The study has many limitations. Our trial did not meet the originally planned target enrollment, making our results strictly descriptive. Of note, more than 15% of interventional adult cUTI trials registered in clinicaltrials.gov do not meet enrollment goals. Though this was a multicenter study, 71% of patients were enrolled from one

site. The duration of follow up was short, though typical of cUTI studies, and not long enough to detect resistance development nor relapse. In addition, imbalances between the treatment groups could have affected our results, though none were statistically significant. Though no documented fosfomycin resistance was noted in our population, established CLSI breakpoints are applicable only for *E. coli* isolates, and there were several non-*E. coli* uropathogens that demonstrated MICs greater than 64 mg/L, thereby exceeding the current susceptibility breakpoint for *E. coli*. In addition, while the majority of pathogens were *E. coli* as typically seen in UTIs, we cannot conclude whether fosfomycin is effective against other pathogens such as *Klebsiella* spp. with concerns for suboptimal response to fosfomyin (33). Certain patient groups were excluded from the study, including patients with end-stage renal disease as well as pregnant women and the study mainly enrolled females, making the results less generalizable. The study allowed the inclusion of immunocompromised patients, including those with renal transplantation, to enrich the population at risk of MDR infection, though our MDR rates were low. The study mostly included patients with pyelonephritis who typically have better cure rates than patients with cUTIs other than pyelonephritis. "Foul-smelling" or "cloudy urine" was part of the inclusion criteria as many patients and caregivers seek testing and treatment solely based on these reasons. Of the 29 patients with these symptoms, 28 already had two or more other qualifying symptoms; in addition, all patients included in the analysis had a positive urine culture, making the inclusion of the subjective findings less relevant.

Conclusion

These limited data suggest that fosfomycin could be an oral alternative as step-down therapy for treatment of cUTIs, though the study included less than 10% of the planned sample and was underpowered to draw formal conclusions. Further clinical studies are warranted to evaluate the efficacy and safety of repeated dosing regimens of oral fosfomycin in patients with urogenital infections in order to establish an appropriate benefit/risk ratio.

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