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MAJOR ARTICLE

Fosfomycin vs Ertapenem for Outpatient Treatment of Complicated Urinary Tract Infections: A Multicenter, Retrospective Cohort Study

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Background. We sought to determine the comparative efficacy of fosfomycin vs ertapenem for outpatient treatment of complicated urinary tract infections (cUTIs).

Methods. We conducted a multicenter, retrospective cohort study involving patients with cUTI treated with outpatient oral fosfomycin vs intravenous ertapenem at 3 public hospitals in Los Angeles County between January 2018 and September 2020. The primary outcome was resolution of clinical symptoms 30 days after diagnosis.

Results. We identified 322 patients with cUTI treated with fosfomycin (n = 110) or ertapenem (n = 212) meeting study criteria. The study arms had similar demographics, although patients treated with ertapenem more frequently had pyelonephritis or bacteremia while fosfomycin-treated patients had more retained catheters, nephrolithiasis, or urinary obstruction. Most infections were due to extended-spectrum β-lactamase–producing *E. coli* and *Klebsiella pneumoniae*, 80%–90% of which were resistant to other oral options. Adjusted odds ratios for clinical success at 30 days, clinical success at last follow-up, and relapse were 1.21 (95% CI, 0.68–2.16), 0.84 (95% CI, 0.46–1.52), and 0.94 (95% CI, 0.52–1.70) for fosfomycin vs ertapenem, respectively. Patients treated with fosfomycin had significant reductions in length of hospital stay and length of antimicrobial therapy and fewer adverse events (1 vs 10). Fosfomycin outcomes were similar irrespective of duration of lead-in intravenous (IV) therapy or fosfomycin dosing interval (daily, every other day, every third day).

Conclusions. These results would support the conduct of a randomized controlled trial to verify efficacy. In the meantime, they suggest that fosfomycin may be a reasonable stepdown from IV antibiotics for cUTI.

Keywords. complicated urinary tract infections; ertapenem; fosfomycin.

Rising rates of community-acquired resistance to the fluoroquinolones, as well as the spread of extended-spectrum beta-lactamases (ESBLs), have resulted in increasing difficulty in treating urinary tract infections with oral agents [1–4]. In some centers, up to 90% of ESBL-producing *Enterobacterales* are fluoroquinolone-resistant, and half or more are resistant to trimethoprim-sulfamethoxazole (TMP-SMX) [5]. No other Food and Drug Administration–approved oral options remain for the indication of complicated urinary tract infections (cUTIs) caused by such pathogens. Patients with these infections therefore typically receive intravenous (IV) antibiotics even if clinically stable and tolerating oral intake.

Fosfomycin has been used for many decades in Europe for a variety of infections. In the United States, it is only approved for single-dose oral administration for uncomplicated cystitis. However, given the complexity and inherent safety concerns associated with prolonged IV therapy, there is renewed interest in using multiple-dose oral fosfomycin regimens off-label to treat cUTI. Pharmacokinetic data support every 24–48-hour dosing to maintain fosfomycin levels above target minimum inhibitory concentrations (MICs) in urine [6]. Furthermore, recent case series describe 65%–80% cure rates for oral fosfomycin for the treatment of cUTI [7, 8], and case reports highlight successfully treated prostatitis with prolonged oral fosfomycin [9]. We sought to define the relative efficacy of fosfomycin vs intravenous therapy by conducting a multicenter, retrospective cohort study to compare outcomes of patients with cUTIs treated with oral fosfomycin or IV ertapenem.

METHODS

Data Collection

We searched the common, Cerner-based electronic medical record (EMR) for relevant patients cared for at the 3 Los

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Angeles County Department of Health Services acute care safety net hospitals: Los Angeles County + University of Southern California Medical Center, Harbor-University of California Los Angeles (UCLA) Medical Center, and Olive View-UCLA Medical Center. The EMR query was generated for patients with positive urine cultures who also received discharge prescriptions for ertapenem or fosfomycin between January 2018 and September 2020. Antimicrobial susceptibility testing and ESBL detection were performed using VITEK AST-GN73 cards (bioMérieux, Marcy-l'Étoile, France). Fosfomycin susceptibility testing (by disk diffusion) was performed only on ESBL-positive *E. coli* urine isolates. Ertapenem susceptibility testing (gradient diffusion, E-test) was performed on physician request. Urine cultures included specimens obtained from in- and out-catheterization, indwelling catheters, and clean catch specimens. Charts were manually abstracted to confirm diagnoses and receipt of intended antibiotics, as well demographics, cUTI risk factors, and outcomes. The study was approved with waiver of informed consent by the University of Southern California Biomedical Research Institutional Review Board.

Definitions

cUTI was defined as a positive urine culture with (1) documented symptoms including dysuria, urinary frequency, or suprapubic pain with an indwelling catheter, renal stone, urinary obstruction, ureteral stent, or renal transplant or (2) the presence of flank pain or tenderness, with fever or leukocytosis.

Patients were assigned to the fosfomycin arm if they received oral fosfomycin at hospital discharge, regardless of initial IV therapy. Repeat fosfomycin- or ertapenem-treated cUTI episodes were considered separate events, so the same patient may have been included multiple times, including in either arm (depending on which drug the individual cUTI episodes were treated with). Relapse was defined as recurrence of urinary tract infection (UTI) symptoms within 3 months of initial diagnosis with urine culture demonstrating the same organism as the initial episode.

Inclusion and Exclusion Criteria

We included all adult patients meeting the above cUTI diagnostic criteria who received ertapenem or fosfomycin, either as monotherapy or in sequence, following upfront alternative IV therapy. Children under 18 years old were excluded. Both women and men were included, although men with clinical diagnosis or symptoms of prostatitis were excluded. Additionally, we excluded patients clinically diagnosed with asymptomatic bacteriuria, uncomplicated cystitis, epididymo-orchitis, and non-UTI infections.

Outcomes

The primary end point was clinical treatment success, defined as resolution of signs and symptoms of infection without relapse, at 30 days after cUTI diagnosis (eg, date of the index urine culture for that episode of infection). Additional predefined secondary outcomes included resolution of symptoms at last documented follow-up (with lack of documented follow-up imputed as success) and microbiologically confirmed 3-month UTI relapse rates. Relapse required re-presentation for symptoms of cUTI with a repeat urine culture growing an isolate identical to the prior isolate. We also compared length of hospital stay and adverse event frequency between groups, as well as treatment outcomes, by fosfomycin dosing interval and length of IV lead-in therapy.

Statistical Analysis

Data were checked for normality of distributions. Continuous variables were compared using the Student *t* test and dichotomous variables with the chi-square (χ^2) or Fisher exact test, with $\alpha = .05$ for significance.

Using STATA 16.1 (STATACorp, College Station, TX, USA), we conducted multivariable logistic regression for the outcomes of 30-day clinical success, resolution of symptoms at last follow-up, and absence of relapse at 3 months. Multivariable analysis was chosen given the multiple, recorded, clinically relevant predictors we believed a priori to be important potential covariates for treatment failure, including age, biologic sex, diabetes mellitus, type of infection, presence of bacteremia, presence of a Foley catheter at discharge, kidney stones, *E. coli* as the predominant organism, duration of treatment before hospital discharge, and duration of postdischarge treatment. Adjusted odds ratios were estimated with 95% CIs (Table 4).

RESULTS

A total of 386 episodes of outpatient fosfomycin- or ertapenem-treated cUTIs were identified in patients with a positive urine culture. Sixty-four episodes were excluded due to failure to meet study inclusion criteria (Figure 1), leaving 322 eligible cUTI episodes for analysis during the study period: 110 in the fosfomycin arm and 212 in the ertapenem control arm. One hundred thirteen episodes (68 in the ertapenem arm and 45 in

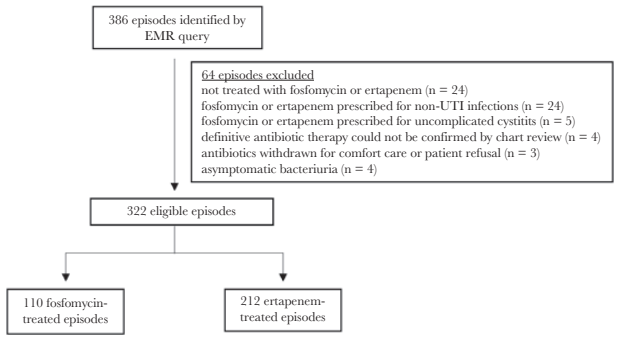

Figure 1. Patient selection flowchart. Abbreviation: EMR, electronic medical record; UTI, urinary tract infection.

the fosfomycin arm) happened in patients with multiple cUTI occurrences.

Patient and Infection-Related Characteristics

Demographic features were similar between groups (Table 1). The ertapenem group had significantly more bacteremia and pyelonephritis without PCNTs (but not PCNTs), while the fosfomycin group had more indwelling catheters, nephrolithiasis, and other urinary obstructions (eg, benign prostatic hypertrophy, chronic obstruction requiring in- and out-catheterization, or penile edema).

E. coli was the predominant pathogen in both groups, followed by *Klebsiella pneumoniae*; combined, these 2 pathogens accounted for 115/130 (88.4%) and 208/322 (64.6%) of all isolates in the fosfomycin and ertapenem arms, respectively (Supplementary Table 1). High percentages of urine cultures included at least 1 ESBL-producing organism: 99/117 (84.6%) and 194/213 (91.0%) in the fosfomycin and ertapenem arms, respectively. High rates of resistance to TMP/SMX and ciprofloxacin were also encountered, with rates of resistance to TMP/SMX significantly higher in the fosfomycin arm (Supplementary Table 2).

Clinical Outcomes

Patients treated with fosfomycin and ertapenem had similar 30-day clinical success rates overall (72/110 [65.4%] vs 157/212 [74.1%]; $P = .1$) and across all comorbidity subgroups (Table 2). There were no significant differences in symptom resolution at last follow-up or in relapse rates, either overall or in any comorbidity subgroup (Table 2). However, the lowest success rates were seen in patients with persistent indwelling catheters (whether bladder or PCNTs) at hospital discharge. While the failure rates among these patients did not differ whether treated with fosfomycin or ertapenem, there were more patients with retained catheters at discharge in the fosfomycin cohort. Of note, in-hospital catheter exchange was not recorded among those patients discharged with urinary catheters given a lack of reliable clinical documentation.

Therapy Before Fosfomycin Stepdown

There was significant heterogeneity in duration of initial antibiotic therapy before definitive therapy with either fosfomycin stepdown or IV ertapenem. We sought to determine whether variations in upfront IV lead-in therapy duration

Table 1. Demographics by Treatment Arm

		Fosfomycin (n = 110)	Ertapenem (n = 212)	*P* Value
Race				.5
Asian		2 (2)	8 (4)	
Black		3 (3)	14 (7)	
White		11 (10)	21 (10)	
Hispanic		92 (84)	163 (77)	
Other		2 (2)	6 (3)	
Gender	Female	63 (57)	125 (59)	.8
	Male	47 (43)	87 (41)	
Age, mean ± SD, y		52.9 ± 15.9	55.2 ± 16.8	.2
cUTI type				
Bladder catheter at diagnosis		27 (24)	31 (15)	.03
Pyelonephritis, no PCNT		48 (44)	139 (66)	<.001
PCNT		15 (14)	32 (15)	.7
Cystitis with nephrolithiasis		5 (5)	1 (<1)	.02
Other urinary obstruction[a]		11 (10)	5 (2)	.004
Other cUTI[b]		4 (4)	4 (2)	.3
Comorbidities				
Diabetes mellitus		48 (43.6)	99 (46.7)	.6
Urinary obstruction		55 (50.0)	93 (44)	.3
Renal abscess		2 (1.8)	7 (3.3)	.4
Nephrolithiasis (all cUTI types)		25 (22.7)	35 (16.5)	.1
Bacteremia		7 (6.4)	82 (38.7)	<.0001
Bladder catheter at discharge		31 (28.2)	40 (18.9)	.06
Renal transplant		0 (0)	7 (3.3)	.05
Mean time to last follow-up (range; IQR), d		297.0 (0–982; 26–552)	334.2 (0–1016; 26–617)	.5

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CHF, ; cUTI, complicated urinary tract infection; IQR, interquartile range; PCNT, percutaneous nephrostomy tube.

[a]Other urinary obstruction includes intermittent catheterization, benign prostatic hypertrophy without catheter, or penile edema due to CHF.

[b]Other cUTI includes indwelling ureteral stent (n = 1 for fosfomyin), multiple rapid recurrences failing prior nonfosfomycin therapy (n = 3 for fosfomycin), ongoing ureteral fistula without catheter in place (n = 1 for ertapenem), or cystitis with bacteremia without obstruction, catheters, or clinical evidence of pyelonephritis (n = 3 for ertapenem).

Table 2. Clinical Outcomes

	Fosfomycin (n = 110), No. (%)	Ertapenem (n = 212), No. (%)	*P* Value
Clinical success at 30 d by cUTI type (primary end point)[a]	72 (65.4)	157 (74.1)	.1
Bladder catheter at diagnosis	16 (59.3)	21 (67.7)	.1
Pyelonephritis, no PCNT	33 (68.8)	110 (79.1)	.1
PCNT	8 (53.3)	19 (57.6)	.8
Other cUTI	15 (75)	7 (70)	.9
Clinical success at 30 d by comorbidity[a]			
Diabetes mellitus	35 (72.9)	68 (68.7)	.6
Urinary obstruction	37 (67.3)	61 (66.3)	.8
Renal abscess	2 (100.0)	6 (85.7)	.8
Nephrolithiasis (all cUTI types)	18 (72.0)	19 (54.3)	.2
Bacteremia	5 (71.4)	65 (79.3)	.8
Bladder catheter at discharge	19 (61.2)	27 (67.5)	.6
Renal transplant	0 (0.0)	4 (57.1)	***
Resolution of symptoms at last follow-up by cUTI type	68 (61.8)	135 (63.7)	.7
Indwelling bladder catheter at diagnosis	13 (48.1)	19 (61.3)	.3
Pyelonephritis, no PCNT	36 (75.0)	93 (66.9)	.3
PCNT	7 (46.7)	17 (51.5)	.8
Other cUTI	12 (60)	6 (60)	.7
Resolution of symptoms at last follow-up by comorbidity[a]			
Diabetes mellitus	35 (72.9)	67 (67.7)	.5
Urinary obstruction	32 (68.5)	48 (51.6)	.4
Renal abscess	2 (100.0)	6 (85.7)	.8
Nephrolithiasis	18 (72.0)	17 (48.6)	.07
Bacteremia	6 (85.7)	59 (80.0)	.4
Foley catheter at discharge	17 (54.8)	25 (62.5)	.5
Renal transplant	0 (0.0)	5 (71.4)	***
Absence of relapse at 3 mo by cUTI type	72 (65.5)	155 (73.1)	.2
Bladder catheter at diagnosis	16 (59.3)	20 (64.5)	.6
Pyelonephritis (no PCNT)	35 (73)	105 (75.5)	.7
PCNT	7 (46.7)	22 (67.7)	.2
Other cUTI	14 (70)	7 (70)	.7
Absence of relapse at 3 mo by comorbidity[a]			
Diabetes mellitus	33 (68.8)	72 (72.7)	.6
Urinary obstruction	35 (64.8)	54 (58.1)	.5
Renal abscess	2 (100.0)	5 (71.4)	.6
Nephrolithiasis	18 (72.0)	17 (48.6)	.07
Bacteremia	6 (85.7)	64 (78.0)	.6
Foley catheter at discharge	18 (58.1)	24 (60.0)	.9
Renal transplant	0 (0.0)	7 (100.0)	***

Abbreviations: cUTI, complicated urinary tract infection; PCNT, percutaneous nephrostomy tube.

[a]Numbers of patients with each cUTI type are listed in Table 1; a patient may have >1 comorbidity.

***P value incalculable.

affected fosfomycin treatment outcomes. Thus, we compared 4 fosfomycin-treated subgroups: fosfomycin without upfront IV lead-in (n = 15), those treated with IV therapy for 1–3 days (n = 38), 4–5 days (n = 44), or ≥6 days (n = 13) before oral fosfomycin stepdown. Clinical success at 30 days, resolution at last follow-up, and relapse did not significantly differ irrespective of IV therapy lead-in duration (Table 3).

Fosfomycin Dosing Intervals

Three different fosfomycin dosing regimens were used, with fosfomycin administered daily (n = 29), every other day (n = 59), or every third day (n = 22). Thirty-day clinical response, resolution at last follow-up, and relapse did not significantly differ across the 3 dosing regimens (Table 3).

Multivariable Adjustment

Given heterogeneity across disease types—for example, more pyelonephritis and bacteremia in the ertapenem cohort and more catheter-associated infections and retained catheters at discharge in the fosfomycin arm—we ran an adjusted analysis. After multivariable adjustment, infection in the setting of PCNT relative to pyelonephritis predicted decreased clinical success, with an odds ratio at 30 days of 0.5 (95% CI, 0.3–0.9) and at last

Table 3. Outcomes for Fosfomycin Subgroups by IV Lead-in Duration and Dosing Interval

Duration of IV Therapy Lead-in	None (n = 15), No. (%)	1–3 Days (n = 38), No. (%)	4–5 Days (n = 44), No. (%)	≥6 Days (n = 13), No. (%)	*P* Value
Clinical success at 30 d	10 (66.7)	22 (57.9)	27 (61.4)	10 (76.9)	.6
Resolution at last follow-up	7 (46.7)	23 (67.3)	30 (68.2)	11 (84.6)	.2
Absence of relapse	9 (60.0)	24 (63.2)	31 (70.5)	8 (61.5)	.8
Fosfomycin dosing interval	Every 24 h (n = 29)	Every 48 h (n = 59)	Every 72 h (n = 22)		
Clinical success at 30 d	18 (62.1)	40 (67.8)	14 (63.4)		.9
Resolution at last follow-up	18 (62.1)	35 (59.3)	15 (68.1)		.8
Absence of relapse	19 (65.5)	37 (62.7)	16 (72.3)		.7

Abbreviation: IV, intravenous.

follow-up of 0.4 (95% CI, 0.20–0.81) (Table 4). Nephrolithiasis also predicted decreased clinical success at last follow-up and relapse, with an odds ratio of clinical success of 0.5 (95% CI, 0.3–1.0) and of relapse of 0.43 (95% CI, 0.23–0.80). In contrast, increasing age predicted increased clinical success at 30 days, with an odds ratio of 1.02 (95% CI, 1.01–0.03). No other variables were significantly associated with outcome.

In the multivariate model, accounting for the above variables, adjusted odds ratios for 30-day clinical success, symptom resolution at last follow-up, and relapse were 1.21 (95% CI, 0.68–2.16), 0.84 (95% CI, 0.46–1.52), and 0.94 (95% CI, 0.52–1.70) for fosfomycin vs ertapenem, respectively (Table 3).

Durations of Hospitalization and Therapy

Fosfomycin-treated patients had significant reductions in length of hospitalization (average 1.4 days shorter), IV therapy (average inpatient IV 1.4 days shorter, total inpatient plus outpatient IV therapy 9.1 days shorter), postdischarge therapy (average 2.5 days shorter), and duration of total therapy (average 3.8 days shorter) compared with ertapenem-treated patients (Table 5).

Adverse Events

Numerically fewer adverse events occurred in the fosfomycin arm than in the ertapenem arm, including drug- and IV catheter–related events (1 vs 10; $P = .06$). Adverse events in the ertapenem group included new hospitalization for vancomycin-resistant IV catheter–related enterococcal bacteremia (n = 1); hospital return for IV-line malfunction or accidental removal (n = 3); failure to establish home IV access (n = 1); and bleeding at the site of peripherally inserted central catheter (PICC) line insertion (n = 2). No line-related adverse events were encountered in the fosfomycin arm. Drug-related adverse events were mild in both arms, including 2 patients in the ertapenem arm and 1 in the fosfomycin arm who developed diarrhea, nausea, or abdominal pain and 1 patient in the ertapenem arm who manifested an oral problem described as "gum receding." No patients developed *C. difficile* colitis in either arm.

DISCUSSION

Traditionally, patients with cUTIs caused by bacteria resistant to fluoroquinolones, β-lactams, and TMP-SMX have been treated with alternative IV agents. However, prolonged IV therapy is associated with numerous adverse effects and longer hospitalizations for many infections, including osteomyelitis [10], bacteremia [11], and infective endocarditis [12]. While oral fosfomycin is of interest in treating UTIs, there are no comparative data to enable assessment of its relative efficacy compared with IV therapy for cUTIs. Our results are reassuring that patients treated with fosfomycin, either as initial or subsequent stepdown therapy, had similar outcomes compared with those receiving definitive therapy with ertapenem. Furthermore, patients treated with fosfomycin had significantly reduced hospitalizations and overall antimicrobial treatment durations, less exposure to indwelling catheters, and numerically fewer adverse events.

Our study supports findings from other publications [8, 13–15] and, by including an active control group of IV therapy, expands on the scope of prior work by suggesting oral fosfomycin as a potentially viable treatment option for cUTI treatment.

There were subtle differences in clinician therapy choice, with a preference for IV ertapenem among conventionally "sicker" patients, such as those with bacteremia, suggesting greater clinician comfort with IV agents in these settings. However, outcomes were favorable even in the presence of bacteremia or other complicated clinical situations for which fosfomycin is typically avoided, including pyelonephritis and the presence of urinary tract tubes and catheters. Of note, irrespective of drug treatment, patients with bacteremia and pyelonephritis had higher clinical cure rates and were more common in the ertapenem cohort, while patients with indwelling catheters had lower clinical cure rates and were more common in the fosfomycin cohort. As bacteremia did not independently correlate with worse outcomes, while retained catheters did, the imbalances in underlying risk factors between the cohorts tended to disadvantage fosfomycin therapy. Nevertheless, overall unadjusted outcomes were not significantly different between

Table 4. Multivariable Adjustment for Outcomes

Clinical success at 30 d (primary end point)	Odds Ratio	95% CI
Fosfomycin treatment	1.21	0.68–2.16
Age	1.02	1.01–1.03
Male	0.76	0.45–1.27
Diabetes mellitus	1.34	0.81–2.23
Bacteremia	1.40	0.75–2.58
Bladder catheter at discharge	0.97	0.43–2.19
Nephrolithiasis	0.73	0.40–1.35
E. coli vs other pathogens	1.36	0.74–2.49
Duration of IV pretreatment	1.00	0.91–1.1
Duration of postdischarge treatment	1.01	0.98–1.04
Duration of total therapy	0.41	0.13–1.33
cUTI type (relative to pyelonephritis)		
PCNT	0.50	0.25–0.98
Catheter associated	0.68	0.27–1.67
Other cUTI	0.71	0.29–1.75
Resolution of symptoms at last follow-up		
Fosfomycin treatment	0.84	0.46–1.52
Age	1.01	0.99–1.03
Male	1.29	0.74–2.26
Diabetes mellitus	1.06	0.61–1.82
Bacteremia	1.13	0.59–2.20
Bladder catheter at discharge	0.69	0.30–1.60
Nephrolithiasis	0.53	0.28–0.99
E. coli vs other pathogens	1.30	0.69–2.48
Duration of IV pretreatment	1.06	0.96–1.17
Duration of postdischarge treatment	1.01	0.97–1.05
Duration of total therapy	1.14	0.33–3.96
cUTI type (relative to pyelonephritis)		
PCNT	0.40	0.20–0.81
Catheter associated	0.66	0.26–1.68
Other cUTI	1.01	0.37–2.76
Absence of relapse at 3 mo		
Fosfomycin treatment	0.94	0.52–1.70
Age	1.00	0.98–1.02
Male	0.91	0.53–1.56
Diabetes mellitus	1.01	0.59–1.73
Bacteremia	1.44	0.74–2.77
Bladder catheter at discharge	0.57	0.25–1.3
Nephrolithiasis	0.43	0.23–0.80
E. coli vs other pathogens	1.07	0.57–2.03
Duration of IV pretreatment	1.01	0.92–1.11
Duration of postdischarge treatment	1.02	0.98–1.06
Duration of total therapy	2.88	0.82–10.10
cUTI type (relative to pyelonephritis)		
PCNT	0.50	0.25–1.01
Catheter associated	0.83	0.33–2.08
Other cUTI	1.05	0.40–2.76

Abbreviations: cUTI, complicated urinary tract infection; IV, intravenous; PCNT, percutaneous nephrostomy tube.

Table 5. Lengths of Therapy and Hospitalization

	Fosfomycin (n = 110)	Ertapenem (n = 212)	*P* Value
Average lengths of treatment and hospitalization			
Length of inpatient stay	4.3 ± 3.8	5.7 ± 3.9	.002
Duration of inpatient IV therapy	3.3 ± 2.1	4.7 ± 3.3	<.0001
Duration of therapy postdischarge	5.3 ± 4.1	7.8 ± 8.3	.003
Total duration of IV therapy	3.3 ± 2.1	12.4 ± 8.9	<.0001
Total duration of antibiotic therapy	8.6 ± 4.4	12.4 ± 9.8	<.0001

Durations are reported as mean ± SD in days.

Abbreviation: IV, intravenous.

cohorts, and multivariate adjustment further elucidated similar outcomes in patients treated with fosfomycin vs ertapenem.

Consistent with our results, a recent pharmacokinetic analysis found favorable urine levels of fosfomycin after daily or every-other-day oral dosing [6]. Fortuitously, most ESBL-producing *E. coli* isolates have low fosfomycin MICs, below achievable urine levels [16]. While CLSI breakpoints for fosfomycin susceptibility are not available for non–*E. coli* bacteria, our study showed encouraging clinical success with fosfomycin in UTIs caused by other bacterial species alone or as co-pathogens in *E. coli*– and *Klebsiella pneumoniae*–predominant polymicrobial infections. Consistent with these pharmacologic data, and similar to a prior observational study of fosfomycin for pyelonephritis and cUTI [8], we found no difference in clinical success related to fosfomycin dosing variations. However, this finding should be interpreted with caution given low numbers when evaluating subgroups of patients by fosfomycin dosing intervals.

Our study has several important limitations, including its retrospective nature. However, unlike prior fosfomycin observational-only investigations, our study is strengthened by inclusion of a direct standard-of-care ertapenem comparator. Given limited numbers, extrapolation and applicability of our results to immunocompromised patients should be done with caution and warrants further randomized, prospective studies. We were also limited to data recorded in our EMR and cannot exclude the possibility of missed follow-up for cUTI recurrence outside our system. However, average length of documented follow-up was >10 months in both groups, allowing identification of relapse and complications, and in a safety net health care system like ours, patients are less likely to receive care at outside institutions given limited insurance. Additionally, given our health system's single EMR, capturing all urine cultures and subsequent hospitalizations and emergency department and clinic visits, we were less likely to miss future relapses during the study period. Our analysis was also strengthened by 100% confirmation of reported outcomes by manual chart review with no missing data elements, rather than relying on administrative data.

Finally, comparably favorable fosfomycin success rates may represent possible confounding by indication due to preselected cUTI populations at low risk of failure: primarily postdischarge,

outpatients on stepdown therapy after initial IV therapy. However, all included patients had complex disease, with high proportions of urinary obstruction, indwelling catheters, and recurrence. Fosfomycin was the only antibiotic received in 5.7% of patients, and in patients with initial IV therapy, fosfomycin constituted on average 56% of the total treatment duration. Additionally, there were no significant differences in outcomes among the 15 fosfomycin recipients who received no IV lead-in therapy compared with those who received 1 or more days of an upfront IV agent. Thus, despite heterogeneity in initial choice of upfront IV therapy, our study suggests fosfomycin stepdown efficacy that cannot be attributed solely to initial IV therapy alone, as seen in our analysis of treatment outcomes stratified by length of upfront parenteral therapy. Finally, inpatients who are being prepared for oral stepdown therapy are generally those for whom concerns for high systemic oral bioavailability may be less important.

It would not be rational to administer oral therapy of any kind to a patient too unstable to be transitioned to outpatient care.

And last, it is important to note variations in overall length of therapy, with ertapenem recipients receiving on average >4 more days of total antibiotic therapy than fosfomycin recipients. Two years before our study period, all study sites adopted an Expected Practice (EP) [17] on antibiotic duration that included a recommendation for 5–7 total days for cUTI. And despite mean antibiotic days of therapy for UTIs of all types significantly decreasing after EP implementation in the largest of the 3 study sites [18], total duration still remained >12 days. Our study suggests the safety of shorter courses for cUTI and further opportunities for improvements in antimicrobial stewardship.

In summary, we found that patients receiving off-label oral fosfomycin for UTIs—including those with pyelonephritis, bacteremia, and bladder catheters or nephrostomy tubes—have comparably favorable outcomes compared with those receiving ertapenem. Our findings support a basis for future randomized controlled trials of fosfomycin vs IV comparators as stepdown for cUTI. Meanwhile, oral fosfomycin appears worthy of broader consideration as UTI therapy outside its current narrow indication, enabling shorter lengths of IV catheter exposure and hospital stays, with similar clinical outcomes.

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Patient consent. Given its retrospective nature, this work does not include factors necessitating patient consent. The study was approved with waiver of informed consent by the University of Southern California Biomedical Research Institutional Review Board.

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