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MAJOR ARTICLE

Multiple-Dose Oral Fosfomycin for Treatment of Complicated Urinary Tract Infections in the Outpatient Setting

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Background. Few published studies exist to describe the off-label use of multiple-dose fosfomycin for outpatient treatment of complicated urinary tract infections (UTI). The purpose of this study was to characterize the patients, infections, drug susceptibilities, and outcomes of multiple-dose fosfomycin episodes for outpatient UTI treatment.

Methods. This retrospective study evaluated patients who received an outpatient prescription for multiple-dose fosfomycin between July 1999 and June 2018. Multiple-dose fosfomycin prescriptions dispensed for UTI prophylaxis were excluded. The primary outcome was clinical resolution (complete resolution of signs and symptoms) of infection within 30 days. Secondary outcomes included descriptions of antibiotics and cultures before and after treatment, 30-day bacteriologic resolution (posttreatment urine culture $<10^3$ colony-forming units of the original pathogen), and 90-day healthcare utilizations for UTI or pyelonephritis. Data were analyzed using descriptive statistics.

Results. Of 171 multiple-dose fosfomycin treatment episodes, the most common regimen was 1 dose every 3 days, mean duration of 6.1 days. Clinical resolution occurred in 115 of 171 (67.3%) episodes, and bacteriologic resolution occurred in 37 of 76 (48.7%) episodes with posttreatment cultures. Most patients used antibiotics or had urine cultures before treatment (81.9% and 97.7%, respectively). Additional antibiotic use, urine cultures, and healthcare utilizations within 90 days posttreatment occurred in 51.5%, 66.1%, and 24.6% of patients, respectively.

Conclusions. For treating complicated UTI with multiple-dose fosfomycin, clinical resolution occurred in 2 of 3 treatment episodes and bacteriologic resolution occurred in one-half of treatment episodes. Future research is necessary to determine the relative efficacy and safety and optimal dosing regimen, duration, and population for UTI treatment with multiple-dose fosfomycin.

Keywords. antibacterial agents; anti-infective agents/urinary; fosfomycin; multiple dose; urinary tract infections.

More than 10 million office visits and 2 million emergency room visits occur annually in the US due to urinary tract infections (UTI), costing approximately $3.5 billion [1, 2]. In 1996, the US Food and Drug Administration (FDA) approved fosfomycin tromethamine, a broad-spectrum oral antibiotic, for single-dose treatment of acute uncomplicated cystitis caused by *Escherichia coli* or *Enterococcus faecalis* in women. Fosfomycin is bactericidal against Gram-negative and Gram-positive bacteria, including extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* [3–6]. Based on its efficacy and safety, the 2011 Infectious Diseases Society of America (IDSA) clinical practice guidelines endorsed single-dose fosfomycin as a first-line treatment for uncomplicated UTI [7–10].

Fosfomycin has been used off-label in multiple-dose regimens for treatment of both uncomplicated and complicated UTI caused by multidrug-resistant organisms (MDROs) [11–18]. The MDRO infections are resistant to many oral antibiotics, often necessitating parenteral antibiotic treatment. Parenteral antibiotics can contribute to increased healthcare costs, risk of complications, and patient discomfort [19]. Antimicrobial stewardship principles discourage the use of antibiotics that may promote resistance or increase risk of adverse events, particularly in populations at risk for infections with MDRO (eg, elderly, frequent antibiotic use) [20–22]. Fosfomycin presents an acceptable treatment alternative because it is oral, well tolerated, has low resistance rates, and rarely interacts with other drugs [23].

Fosfomycin has been previously studied as multiple-dose regimens in both inpatient and outpatient settings [11–18]. However, these studies were small, confined to narrow populations, used varying dosing regimens, and evaluated different outcomes with variable results. Given the inconsistency of data

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assessing the utility of multiple-dose fosfomycin (MDF) for outpatient treatment of complicated UTI, the purpose of this descriptive study was to characterize the patients, infections, drug susceptibilities, and outcomes of MDF treatment for outpatient UTIs.

METHODS

Study Design and Population

This retrospective cohort study evaluated adult patients who were dispensed a prescription for MDF (ie, more than 1 sachet) between July 1, 1999 and June 30, 2018, at Kaiser Permanente Colorado (KPCO). KPCO cares for >650 000 members in Colorado's urban and rural areas through a network of medical offices, pharmacies, and contracted facilities. Coded and free-text data on diagnoses, procedures, laboratory tests, medications, hospitalizations, and membership are maintained in KPCO's administrative and claims databases. At the time of this study, no internal protocols directed the use of MDF for UTI treatment, although fosfomycin was maintained on the formulary and infrequently recommended in multiple-dose regimens for recurrent and/or MDRO infections. This study was approved by the KPCO Institutional Review Board with a waiver of informed consent.

The index date for study inclusion was the dispense date of the MDF regimen according to prescription dispensing records. Individual patients could contribute more than 1 episode to the study whether the MDF prescriptions were dispensed >90 days apart. Only the first episode was counted as a unique episode if a second MDF prescription was dispensed <90 days after the index date. Each episode underwent review of electronic health records (EHRs) to assess the purpose of MDF treatment (categorized as UTI treatment, UTI prophylaxis, or other/unknown) and evaluate outcomes. During EHR review, the abstractor reviewed all clinical documentation at the index date (eg, office notes, telephone notes) to evaluate patient symptomatology, laboratory values, and documented clinician differential diagnosis. In the absence of symptoms, the purpose of fosfomycin was categorized as UTI treatment if the prescribing clinician documented that the patient presented with known or suspected UTI. An episode was excluded from analysis if EHR review determined 1 or more of the following: (1) MDF was dispensed for a purpose other than UTI treatment (ie, UTI prophylaxis or other/unknown); (2) the MDF index date was <90 days after another MDF dispense for the same patient; (3) only 1 dose was dispensed by the pharmacy; (4) there was clinical documentation (eg, office visit, telephone, or e-mail encounter) that the patient took ≤1 dose; or (5) information regarding the UTI episode was unavailable in the EHR. When assessing antibiotic susceptibilities from urine cultures, cultures were excluded from analysis if the culture had no/insufficient bacterial growth, grew normal/mixed flora, or were otherwise classified by the microbiology laboratory as a clinically insignificant or unreliable culture on final report.

Outcomes

This study described patient demographics, prescription characteristics, pre- and postfosfomycin antibiotic use, and organisms observed on urine cultures in the 90 days pre- and post-MDF index date. The primary outcome was clinical resolution of UTI within 30 days postindex date, defined as complete resolution of signs and symptoms of infection (ie, dysuria, urinary frequency and urgency, suprapubic pain, hematuria, and/or subjective fever) as determined by EHR review. Secondary outcomes included bacteriologic resolution within 30 days and healthcare utilization within 90 days postindex date (ie, urgent care visit, emergency room visit, or hospitalization for UTI or pyelonephritis). Bacteriologic resolution was defined as a postindex date urine culture demonstrating $<10^3$ colony-forming units of the pathogen originally found in the preindex date culture. When analyzing bacteriologic resolution outcomes, only patients with urine cultures within 30-days pre- and postindex date were included in the analysis. Preindex date cultures could include cultures collected on the index date in the event that patients had submitted a urine sample for culture before picking up the prescription from the pharmacy. Susceptibility to antibiotics was evaluated using urine culture reports available in the EHR. During the study period, KPCO used MicroScan technology (Siemens Medical Solutions Diagnostics, Munich, Germany) to determine antibiotic susceptibilities until 2003, at which time Vitek 2 (bioMérieux, Durham, NC) became the antibiotic susceptibility technology. Interpretive criteria used by the microbiology laboratory were based on Clinical and Laboratory Standards Institute document M100 [24], which was in effect during the time of the study.

Data Collection and Analysis

In addition to EHR review, patient characteristics and data regarding healthcare utilizations within 180 days before, and 90 days after the index date were retrieved from healthcare encounters stored in administrative databases. Patient characteristics were determined or calculated at the time of the index date. The Chronic Disease Score, a measure of chronic illness burden determined by medication dispenses, and Charlson Comorbidity Index were calculated using medication dispensing records and *International Classification of Diseases, 9th Revision* and *10th Revision* diagnosis codes in the EHR, respectively, during the 180 days before the index date [25, 26]. Data were analyzed descriptively (eg, means and percentages), analyses of categorical data were done by χ^2 or Fisher's exact tests where appropriate, and the Wilson Score method was used to calculate 95% confidence intervals (CIs) [27]. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient and Prescription Characteristics

During the 19-year study period, 398 MDF episodes were identified and reviewed; 227 episodes were subsequently excluded (Figure 1). The final analysis included 171 MDF treatment episodes, representing 147 unique patients. The study population was primarily non-Hispanic white, female patients with a mean ± standard deviation (SD) age of 72 ± 13.4 years (Table 1). Most episodes occurred in patients with at least 1 UTI within the 180 days before the index date (72.1%), and the most common comorbidities included hypertension (57.8%), chronic kidney disease (41.5%), and diabetes (32.0%). All included patients were being treated for complicated and/or recurrent lower tract UTI; MDF was not used for pyelonephritis treatment.

At the time of dispensing, the most common signs and symptoms of infection were dysuria (38.0%) and urinary frequency (28.7%). Unspecified symptoms were present in 9.9% of episodes. The most common dosing regimen was 1 sachet every 3 days (n = 124, 72.5%), followed by 1 sachet every other day (n = 34, 19.9%) or daily (n = 11, 6.4%). The mean ± SD quantity of sachets dispensed was 2.9 ± 0.6 for a mean ± SD duration of 6.1 ± 2.1 days.

Preindex Date Antibiotic Use and Urine Cultures

Preindex date antibiotic use occurred in 140 episodes (81.9%), with a mean ± SD of 2.3 ± 1.4 antibiotic courses administered in each episode before MDF (Table 2). The most common antibiotics prescribed pre-MDF included oral cefuroxime (58.6%), ciprofloxacin (48.6%), and nitrofurantoin (40.7%).

Most episodes had a urinary culture within 90 days before the index date (n = 167, 97.7%), and 112 (65.5%) episodes had both pre- and posttreatment urinary cultures. Seven of the 167 pretreatment cultures were polymicrobial (one 3-organism culture and six 2-organism cultures). Fourteen cultures grew normal flora or had insufficient growth and were excluded from the antibiotic susceptibility descriptions. From 167 pretreatment cultures, 165 organisms with reported susceptibilities were isolated (Table 3). The most common organism isolated was *E coli* (n = 104, 63.0%); other species occurred with <10% frequency each. Organisms generally demonstrated a high degree of antibiotic nonsusceptibility. Fosfomycin susceptibility was available for 69 organisms (41.8%); the majority were susceptible (n = 67, 97.1%). One isolate of *E coli* was intermediately susceptible to fosfomycin, and 1 additional *E coli* isolate was resistant.

Clinical and Bacteriologic Outcomes

The primary outcome, clinical resolution of signs and symptoms of infection within 30 days of the index date, occurred in 113 of 171 episodes (66.1%; 95% CI, 59.7%–74.2%) (Table 4). Clinical resolution varied greatly according to the pathogens isolated in preindex date cultures, ranging from 20.0% with *Citrobacter* spp to 83.3% with *Pseudomonas* spp. Clinical resolution occurred in 87 of 131 episodes in females (66.4%; 95% CI, 57.6%–74.4%) and 28 of 40 episodes in males (70.0%; 95% CI, 53.5%–83.4%) with no statistically significant difference ($P = .70$). Clinical resolution occurred in 92 of 140 episodes with antibiotic use in the previous 90 days (65.7%; 95% CI, 57.2%–73.5%) and 23 of 31 episodes without antibiotic use in the previous 90 days (74.2%; 95% CI, 55.4%–88.1%) with no statistically significant difference ($P = .36$).

Only 76 episodes had a pre- and postindex date urinary culture within 30 days to assess the secondary outcome of bacteriologic resolution. Of these, bacteriologic resolution occurred in 37 episodes (48.7%; 95% CI, 37.0%–67.4%). Bacteriologic resolution was also highly variable according to the isolated

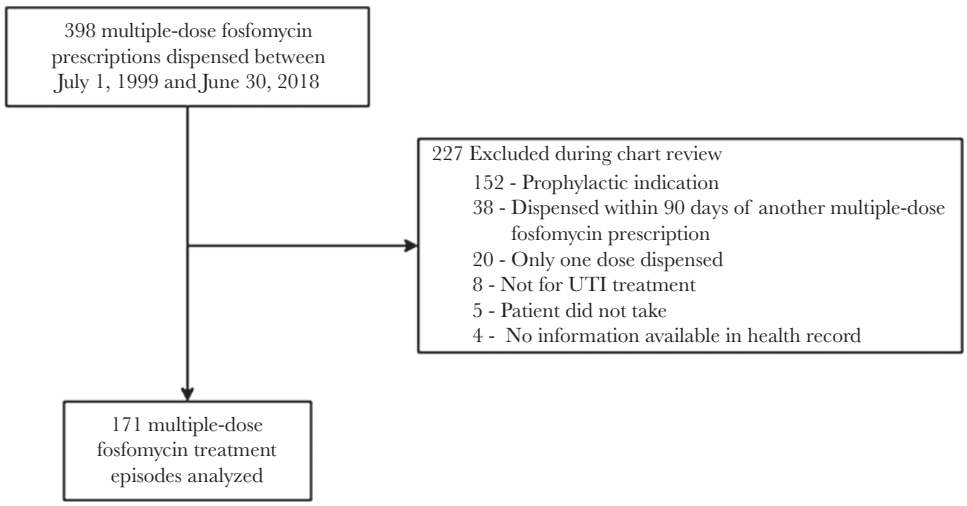

Figure 1. Patient Dispositions. UTI, urinary tract infection.

pathogen and ranged from 0% with *Proteus* or *Pseudomonas* spp to 100% with *Enterococcus* spp. Bacteriologic resolution occurred in 41 of 74 episodes in females (55.4%; 95% CI, 43.4%–67.0%) and 9 of 27 episodes in males (33.3%; 95% CI, 16.5%–54.0%), with an insignificant trend toward lower rates in men ($P = .07$). Bacteriologic resolution occurred in 33 of 69 episodes with antibiotic use in the previous 90 days (47.8%; 95% CI, 35.7%–60.2%) and 9 of 15 episodes without antibiotic use in the previous 90 days (60.0%; 95% CI, 32.3%–83.7%), with no statistically significant difference ($P = .39$).

Four of 113 episodes with postindex date cultures were polymicrobial with 2 isolated organisms. After removing 47 cultures due to normal flora or insufficient growth (Supplemental Table 1), 74 organisms with reported susceptibilities were isolated from urine cultures after treatment with MDF. The most common organism was *E coli* (n = 31, 45.9%). The majority of organisms for which fosfomycin susceptibility was tested were still susceptible to the drug (n = 17 of 18, 94.4%).

Post Fosfomycin Antibiotic Use and Healthcare Utilization

Half of the episodes (n = 88, 51.5%) required further post-MDF treatment antibiotic use for UTI. A mean ± SD of 2.0 ± 1.1 additional antibiotic courses per patient were administered. Single-dose fosfomycin was most common (43.2%), followed by ciprofloxacin (33.0%) and cefuroxime (29.5%). Parenteral treatment was administered in 26 courses (29.5%) and included ertapenem (n = 17), ceftriaxone (n = 3), piperacillin-tazobactam (n = 2), and 1 course each of cefepime, ceftazidime, gentamicin, and tigecycline. Patients with documented clinical or bacteriologic failure (n = 32 and n = 38, respectively) most commonly used single-dose fosfomycin (44.8%) and ciprofloxacin (41.4%) after MDF treatment.

Hospitalizations, emergency room visits, and urgent care visits for UTI or pyelonephritis in the 90 days after the 171 index-date fosfomycin treatment episodes occurred in 11.7%, 8.2%, and 4.7% of episodes, respectively. Among the 28 episodes with clinical failure, 14.3%, 14.3%, and 10.7% were associated with a subsequent hospitalization, emergency room visit, and urgent care visit, respectively, for UTI or pyelonephritis in the 90 days after fosfomycin treatment.

DISCUSSION

This retrospective cohort study found that patients treated with MDF were most often older females with at least 1 previous UTI, several comorbidities, and a history of repeated antibiotic exposure within the previous 90 days. The most common pathogens treated with MDF were *E coli*, *Klebsiella* spp, *Enterococcus* spp, and *Pseudomonas* spp; these pathogens were associated with high rates of nonsusceptibility to common antibiotics and multidrug resistance was common. Most commonly, patients were instructed to administer 1 fosfomycin sachet every 3 days for a total of 3 doses. Despite the complicated nature of

Table 1. Patient and Prescription Characteristics of Multiple-Dose Fosfomycin Episodes

Characteristic	UTI Treatment Episodes
n, % or Mean (SD)	(N = 171)[a]
Patient Characteristics	
Mean Age[b] (years)	72.0 (13.4)
Female	114, 77.6%
Race	
White	116, 78.9%
Other	12, 8.2%
Undeclared/unknown	19, 12.9%
Ethnicity	
Hispanic	21, 14.3%
Non-Hispanic	121, 82.3%
Undeclared/unknown	5, 3.4%
Serum creatinine (mg/dL)	1.2 (135, 0.8)
eGFR (mL/min per 1.73 m^2)	59.5 (129, 23.7)
Chronic Disease Score[c]	4.1 (3.0)
Charlson Comorbidity Index[c]	2.9 (2.7)
Comorbidities[d]	
Hypertension	85, 57.8%
Chronic kidney disease	61, 41.5%
Diabetes	47, 32.0%
COPD	41, 27.9%
Peripheral vascular disease	36, 24.5%
Heart failure	25, 17.0%
Cerebrovascular disease	17, 11.6%
Previous myocardial infarction	9, 6.1%
Liver disease	11, 7.5%
Prior UTI[d]	
Median count [IQR][c]	1 [0–2]
At least one prior UTI[c]	106, 72.1%
Kidney stone[d]	10, 5.9%
Ureteral stent or other urogenital implant[c]	1, 0.6%
Fosfomycin Prescription Characteristics	
Frequency	
Daily	11, 6.4%
Every other day	34, 19.9%
Every 3 days	124, 72.5%
Every 7 days	0, 0.0%
Other[e]	2, 1.2%
Mean duration (days)	6.1 (2.1)
Mean quantity dispensed (sachets)	2.9 (0.6)
Infection Characteristics	
Signs and Symptoms Present	
Dysuria	65, 38.0%
Fever	3, 1.8%
Hematuria	12, 7.0%
Nocturia	5, 2.9%
Present but unspecified	17, 9.9%
Suprapubic, pelvic, or perineal pain	8, 4.7%
Urinary retention	11, 6.4%
Urinary frequency	49, 28.7%
Urinary Cultures[f]	
Before	167, 97.7%
After	113, 66.1%
Before and After	112, 65.5%

Abbreviations: COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation; UTI, urinary tract infection.

[a]For 147 unique patients.

[b]Based on patient's first fosfomycin dispensing during the study period.

[c]Calculated within 180 days before the index date.

[d]Diagnosed within 180 days before each episode fosfomycin dispensing.

[e]For example, twice weekly.

[f]Within 90 days of fosfomycin dispensing.

Table 2. Antibiotics Used Within 90 Days Before Multiple-Dose Fosfomycin Treatment Episodes (N = 171)

Medication Class	Antibiotics Courses
n, % or mean (SD)	(n = 140)
Antibiotics prescribed before fosfomycin	140/171, 81.9%
Previous antibiotic courses per patient, mean (SD)	2.3 (1.4)
Penicillin	
Amoxicillin	2, 1.4%
Ampicillin	2, 1.4%
Beta-lactam/beta-lactamase inhibitor combination	
Amoxicillin-Clavulanate	30, 21.4%
Cephalosporin	97, 69.3%
Cefepime	1, 0.7%
Cefixime	5, 3.6%
Ceftriaxone	2, 1.4%
Cefuroxime	82, 58.6%
Cephalexin	7, 5.0%
Carbapenem	
Ertapenem	16, 11.4%
Fluoroquinolone	78, 55.7%
Ciprofloxacin	68, 48.6%
Levofloxacin	10, 7.1%
Macrolide/ketolide	
Doxycycline	1, 0.7%
Other, Miscellaneous	
Daptomycin	1, 0.7%
Fosfomycin	15, 10.7%
Linezolid	2, 1.4%
Nitrofurantoin	57, 40.7%
TMP-SMX	26, 18.6%
Trimethoprim	11, 7.9%

Abbreviations: SD, standard deviation; TMP-SMX, trimethoprim-sulfamethoxazole.

the patients and infections described in this study, MDF was associated with a clinical response rate of 66%. Subsequent urgent care visits, emergency room visits, or hospitalizations for UTI or pyelonephritis within the 180 days after fosfomycin treatment did occur with some frequency but were comparable to previously published national estimates [28]. However, even these multiple-dose regimens of fosfomycin were associated with a relatively low bacteriologic response (49%) within 30 days posttreatment, and more than one half (51.5%) of MDF episodes were associated with the need for additional antibiotic therapy.

Our study identified a clinical response rate of 66% and bacteriologic response rate of 49% after MDF treatment. Lower bacteriologic response rates have been observed after single-dose fosfomycin treatment of uncomplicated UTI [7, 8]. Previous studies of MDF (range 2–6 doses) for outpatient treatment of uncomplicated UTI reported clinical and microbiologic success rates of 78%–95% and 62%–98%, respectively [12, 14, 18]. However, in more complicated infections including MDROs, more similar to those in the current study, clinical and microbiologic response rates were lower numerically and ranged from 63%–78% to 31–84%, respectively, after a mean of 3 doses of fosfomycin [11, 13, 15, 18]. The clinical and bacteriologic resolution rates reported in our study are, thus, consistent with those previously reported in similarly complex patients including those with complicated infections, multiple comorbidities, and MDRO pathogens. More importantly, although the majority of patients in these previous studies received MDF, analyses also sometimes included patients who received only a single dose. Our analyses were restricted to only those patients taking more than 1 dose of fosfomycin, and we included both MDRO and non-MDRO infections, which could help explain our results. Both clinical and bacteriologic resolution rates in the current study are similar to previous studies that restricted analyses to MDRO infections (~60%–70%), and the presumed recurrence rate of 51% (based on need for additional antibiotics) is also similar to the recurrence rate of 54% reported in a previous study [15]. The unstandardized multiple-dose regimens in the current study (ie, daily vs every-other-day vs every 3 days) may have also contributed to the observed clinical and bacteriologic resolution rates compared with previous reports.

It is also possible that the low bacteriologic response rates observed in this retrospective study are a result of selection bias at the time of the original clinical management of the patients. Patients who are most likely to have follow-up urine cultures are those who have had an inadequate clinical response to treatment, whereas those who are clinically improved are less likely to have a need for repeat cultures purely for purposes of demonstrating bacteriologic eradication. It is feasible that the high bacteriological failure rates in this study are artificially elevated; however, the results of the present study are consistent with previous investigations and may accurately reflect the challenging patient populations and difficult infections selected for treatment with MDF. Although lack of susceptibility to fosfomycin was unusual in the present study (3 of 87 pre- and posttreatment isolates, 3.4%), fosfomycin susceptibility was not determined for all isolates and cannot be ruled out as a cause of reduced clinical and bacteriologic response to treatment.

As an oral antibiotic with few serious adverse effects, low risk for allergic reactions, and a broad spectrum of antibacterial activity that includes many resistant uropathogens (eg, ESBL-producers), fosfomycin tromethamine has the potential to improve patients' quality of life while minimizing healthcare costs related to outpatient UTI treatment. Despite the higher cost of fosfomycin compared with other oral antibiotic options (approximately US $100/3-gram dose [29]), fosfomycin is significantly less expensive than parenteral antibiotic therapies, which reduce quality of life and patient satisfaction while increasing the risk for complications from intravenous therapy (eg, phlebitis) [30, 31]. As demonstrated in the current study, patients commonly receive several courses of antibiotics and experience consecutive treatment failures before receiving MDF. If MDF were to be prescribed as initial therapy, the medication costs

Table 3. Prefosfomycin Treatment Cultures Within 90 Days of Fosfomycin Dispensing

		Organisms						
	Total Isolated Organisms With Reported Susceptibilities[a]	*Escherichia coli*	*Klebsiella* spp[b]	*Enterococcus* spp	*Pseudomonas* spp[c]	ESBL-Producing *E coli*	*Citrobacter* spp[d]	*Proteus mirabilis*
Antibiotic	(N = 165)	(n = 104)	(n = 15)	(n = 13)	(n = 12)	(n = 8)	(n = 5)	(n = 4)
Amoxicillin-clavulanate	113	94	13	0	5	0	0	1
Susceptible	28 (24.8)	25 (26.6)	2 (13.3)	NA	0 (0.0)	NA	NA	1 (100.0)
Intermediate	50 (44.2)	42 (44.7)	8 (53.4)	NA	0 (0.0)	NA	NA	0 (0.0)
Resistant	35 (31.0)	27 (28.7)	3 (20.0)	NA	5 (100.0)	NA	NA	0 (0.0)
Ampicillin	144	104	15	13	0	7	1	4
Susceptible	22 (15.2)	8 (7.7)	1 (6.7)	11 (84.6)	NA	0 (0.0)	0 (0.0)	2 (50.0)
Intermediate	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	1 (25.0)
Resistant	121 (84.0)	96 (92.3)	14 (93.3)	2 (15.4)	NA	7 (100.0)	1 (100.0)	1 (25.0)
Cefazolin	136	104	15	0	0	7	5	4
Susceptible	24 (17.6)	17 (16.3)	4 (26.7)	NA	NA	0 (0.0)	1 (20.0)	2 (50.0)
Intermediate	1 (0.7)	1 (1.0)	0 (0.0)	NA	NA	0 (0.0)	0 (0.0)	0 (0.0)
Resistant	111 (81.6)	86 (82.7)	11 (73.3)	NA	NA	7 (100.0)	4 (80.0)	2 (50.0)
Ceftriaxone	131	101	13	1	0	7	4	4
Susceptible	28 (21.4)	20 (19.8)	3 (20.0)	0 (0.0)	NA	0 (0.0)	2 (50.0)	3 (75.0)
Intermediate	1 (0.7)	1 (1.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)
Resistant	102 (77.9)	80 (79.2)	10 (66.7)	1 (100.0)	NA	7 (100.0)	2 (50.0)	1 (25.0)
Ciprofloxacin	150	104	15	0	12	8	5	4
Susceptible	25 (16.7)	9 (8.7)	6 (40.0)	NA	7 (53.8)	0 (0.0)	1 (20.0)	1 (25.0)
Intermediate	6 (4.0)	2 (1.9)	2 (13.3)	NA	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)
Resistant	119 (79.3)	93 (89.4)	7 (46.7)	NA	5 (46.2)	8 (100.0)	4 (80.0)	1 (25.0)
Ertapenem	103	83	7	0	0	8	4	1
Susceptible	102 (99.0)	82 (98.8)	7 (100.0)	NA	NA	8 (100.0)	4 (100.0)	1 (100.0)
Intermediate	1 (1.0)	1 (1.2)	0 (0.0)	NA	NA	0 (0.0)	0 (0.0)	0 (0.0)
Resistant	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	0 (0.0)	0 (0.0)	0 (0.0)
Fosfomycin	69	67	1	0	0	1	0	0
Susceptible	67 (97.1)	65 (62.5)	1 (100.0)	NA	NA	1 (100.0)	NA	NA
Intermediate	1 (1.4)	1 (1.0)	0 (0.0)	NA	NA	0 (0.0)	NA	NA
Resistant	1 (1.4)	1 (1.0)	0 (0.0)	NA	NA	0 (0.0)	NA	NA
Gentamicin	147	101	13	2	12	8	5	4
Susceptible	83 (56.5)	57 (56.4)	6 (40.0)	2 (100.0)	9 (69.2)	2 (25.0)	3 (60.0)	3 (75.0)
Intermediate	3 (2.0)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Resistant	61 (41.5)	42 (41.6)	7 (46.7)	0 (0.0)	3 (23.1)	6 (75.0)	2 (40.0)	1 (25.0)
Nitrofurantoin	151	104	15	13	0	8	5	4
Susceptible	90 (59.6)	65 (62.5)	6 (40.0)	10 (76.9)	NA	5 (62.5)	3 (60.0)	0 (0.0)
Intermediate	35 (23.2)	24 (23.1)	5 (33.3)	1 (7.7)	NA	3 (37.5)	1 (20.0)	0 (0.0)
Resistant	26 (17.2)	15 (14.4)	4 (26.7)	2 (15.4)	NA	0 (0.0)	1 (20.0)	4 (100.0)
TMP-SMX	136	104	15	0	0	8	3	4
Susceptible	33 (24.3)	21 (20.2)	6 (40.0)	NA	NA	1 (12.5)	1 (33.3)	3 (75.0)
Intermediate	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	0 (0.0)	0 (0.0)	0 (0.0)
Resistant	103 (75.7)	83 (79.8)	9 (60.0)	NA	NA	7 (87.5)	2 (66.7)	1 (25.0)

Abbreviations: ESBL, extended-spectrum beta-lactamase; NA, not available; TMP-SMX, trimethoprim-sulfamethoxazole.

NOTE: All values are no. (%) unless noted otherwise.

[a]Included 1 isolate of *Aerococcus urinae*, 1 isolate of *Enterobacter aerogenes*, and 1 isolate of *Staphylococcus epidermidis* in addition to isolates represented in table. Excluded 9 normal or mixed flora and 5 no or insignificant growth. Seven cultures included were polymicrobial in nature (1 with 3 isolated organisms, 6 with 2 isolated organisms).

[b]Included 3 isolates of *Klebsiella oxytoca* and 12 isolates of *Klebsiella pneumoniae*.

[c]Included 1 isolates of *Pseudomonas fluorescens* and 11 isolates of *Pseudomonas aeruginosa*.

[d]Included 4 isolates of *Citrobacter freundii* and 1 isolate of *Citrobacter koseri*.

and other healthcare expenses (eg, office visits) associated with unsuccessful treatment involving multiple courses of alternative antibiotics and healthcare utilizations could potentially be reduced. Furthermore, although not statistically significant, we observed a numerically higher trend in clinical and bacteriologic resolution rates among those with no antibiotic use in the

Table 4. Clinical and Bacteriological Outcomes Overall and by Culture Organism

Outcome n, %, 95% Confidence Interval	All Treatment Episodes[a]	Cultured Organisms[a,b]						
		Citrobacter spp	*Escherichia coli*	ESBL *E coli*	*Enterococcus* spp	*Klebsiella* spp	*Proteus* spp	*Pseudomonas* spp
	(N = 171)	(n = 5)	(n = 101)	(n = 8)	(n = 13)	(n = 15)	(n = 4)	(n = 12)
Clinical Resolution[c]	113, 66.1% (59.7%, 74.2%)	1, 20.0% (0.5%, 71.6%)	76, 75.2% (65.7%, 83.3%)	5, 62.5% (24.5%, 91.5%)	8, 61.5% (31.6%, 86.1%)	11, 73.3% (44.9%, 92.2%)	1, 25.0% (0.6%, 80.6%)	10, 83.3% (51.6%, 97.9%)
Bacteriologic	37/76, 48.7%	2/4, 50.0%	20/38, 52.6%	1/3, 33.3%	4/4, 100.0%	7/11, 63.6%	0/1, 0.0%	0/9, 0.0%
Resolution[d]	(37.0%, 67.4%)	(6.8%, 93.2%)	(35.8%, 69.0%)	(0.8%, 90.6%)	(39.7%, 100%)	(30.8%, 89.1%)	(0%, 97.5%)	(0%, 33.6%)

Abbreviations: ESBL, extended-spectrum beta lactamase; SD, standard deviation.

[a]Patients could contribute to data multiple times if they had multiple bacterial isolates (n = 7 episodes).

[b]Only includes patients who had at least 1 organism identified with a pretreatment culture. Not all identified cultures included.

[c]Within 30 days of fosfomycin dispensing. Defined as complete resolution of signs and symptoms of infection including dysuria, urinary frequency and urgency, suprapubic pain, hematuria, and fever.

[d]Defined as offending organism colony-forming units $<10^3$ on posttreatment culture within 30 days of fosfomycin dispensing. Ninety-five treatment episodes did not have follow-up cultures within 30 days to include in the analysis.

prior 90 days, which should be investigated with a larger sample size. Fosfomycin is well tolerated, can be used in unique patient populations (ie, pregnancy, elderly, renal dysfunction, liver dysfunction), and has a low incidence of allergic, hypersensitivity, and adverse reactions compared with other first-line options for treatment of complicated UTI such as trimethoprim-sulfamethoxazole, cephalosporins, fluoroquinolones, and nitrofurantoin. For example, a recent FDA Safety Communication required manufacturers to alter the prescribing information for fluoroquinolones to include warnings regarding blood sugar alterations and mental health side effects [32]. Given the relative risks with other antibiotics and the relative benefits with fosfomycin treatment, it is possible that utilizing MDF for complicated UTI earlier in the treatment cascade could optimize quality of life while minimizing cost. Nevertheless, further research is needed to assess these specific outcomes, potential benefits, and cost-effectiveness of fosfomycin in the setting of complicated UTI and those caused by MDRO.

In addition to favorable patient tolerability and acceptability, fosfomycin has a broad spectrum of bacteriologic activity against common uropathogens, including MDRO. Fosfomycin has excellent in vitro activity against ESBL-producing bacteria, vancomycin-resistant enterococci, and carbapenemase-producing *Klebsiella pneumoniae* [3, 33, 34]. In vivo, 90%–100% of Enterobacteriaceae, including those that produce ESBL, are susceptible to fosfomycin [35, 36]. In the 12 episodes in which *Pseudomonas* spp were identified in a pretreatment urinary culture, we observed an 83% clinical response rate and 0% bacteriologic response rate. None of these *Pseudomonas* isolates had fosfomycin susceptibility testing performed and only 9 had posttreatment cultures; it is therefore difficult to speculate whether the low bacteriologic resolution rate is due to poor demonstrated in vivo activity or baseline resistance to fosfomycin, or potentially due to other patient-specific factors. Although antimicrobial resistance continues to grow as a global public health threat in conjunction with safety concerns for common antibiotics [37, 38], fosfomycin—whether used in single or multiple-dose regimens—offers a viable treatment option for outpatient UTI given its currently overall low reported resistance rates in clinical isolates (0% to 6.7%). Whether increased use of fosfomycin, or longer treatment durations as described in this study, will lead to clinically important changes in fosfomycin resistance among uropathogens is currently unknown but remains of concern and should be monitored [39].

Based on the descriptive design and findings from this and other studies, it is unclear which patient populations are the most appropriate to receive MDF for initial treatment of UTI or when it should be considered in relation other more traditional antibiotic options. It is also not clear how the clinical and bacteriologic efficacy of MDF compares to the FDA-labeled single-dose regimens. It is unfortunate that neither the IDSA nor European Urology Association offers guidance for use of

MDF for treatment of UTI [7, 40]. Formal comparative assessments of standardized, MDF regimens for outpatient treatment of UTI is warranted to determine with certainty the relative risks, benefits, and cost-effectiveness of this dosing strategy. The ongoing FOCUS study is randomizing patients to receive either fosfomycin once daily for 5–7 days or levofloxacin once daily for 5–7 days to treat complicated UTI and may further inform clinical decisions in this area (ClinicalTrials.gov NCT03697993).

This study also identified opportunities to optimize the dispensing of MDF for UTI treatment within our institution. Because the unique dose (3 grams) is numerically the same as the most common number of doses (3), there is potential for medication dispensing errors, because pharmacists may misinterpret the intended number of doses (3) and dispense only 1 packet (3 grams). This error could explain why, during medical record review, we observed several instances in which clinical documentation described that the patient took only 1 dose, although dispensing data suggested that the patient was dispensed more than 1 dose. We are unaware of formal evaluations of fosfomycin dispensing errors, although this would be important for institutions to internally assess before implementing MDF protocols. Furthermore, to avoid administration errors, explicit patient education is crucial to ensure optimal administration of fosfomycin, which is uniquely dispensed as a sachet to dissolve in water and drink, unlike other oral antibiotic products.

To our knowledge, this study is the largest to date assessing the utility and outcomes related to MDF regimens in complicated UTI in the outpatient setting. The integrated healthcare delivery system setting allowed us to assess patient characteristics, verify prescription pick up, evaluate response to therapy, and track healthcare utilization. However, the results should be interpreted within the context of known and potential limitations. The retrospective cohort study design cannot determine causality but justifies a future prospective study evaluating MDF treatment and outcomes. In addition, this was a single-arm cohort study, and MDF regimens were not compared with other UTI treatments. Nonetheless, it was demonstrated that most patients who received MDF had used an antibiotic for UTI treatment in the prior 90 days. The choice of therapy, duration of treatment, and subsequent monitoring were at the discretion of the prescriber, which reflects local clinical practice patterns; this potentially allows generalizability in the interpretation of our findings to other practice settings. Patients who did not interact with the health system after the index date were assumed to have a clinical resolution; therefore, we may be overestimating true clinical resolution rates. In addition, patients were not directly observed for administration of fosfomycin, and outpatient nonadherence may have affected our findings. Given our study's relatively small sample size with wide CIs for some isolates, findings from future studies with larger sample sizes may vary from those in the present study. Finally, UTI occurring within the follow-up periods were not specifically characterized as bacteriologic relapse or reinfection, which may affect the rate of bacteriologic resolution. Future research may choose to build upon these findings by prospectively assessing the efficacy and safety of MDF or determining factors that may predict clinical or bacteriologic resolution with MDF treatment.

CONCLUSIONS

This retrospective study identified that in patients with complicated infections and multiple prior UTI treatment episodes, MDF treatment was associated with clinical resolution in 2 of 3 treatment episodes and bacteriologic resolution in one half of treatment episodes. Infections due to *E coli*, *Pseudomonas* spp, and *Klebsiella* spp were most likely to respond to multiple-dose treatment. When considering MDF for treatment of complicated UTI, clinicians should consider obtaining posttreatment cultures to verify successful treatment and guide the need for subsequent additional management. Future prospective research with MDF is necessary to determine the relative efficacy and safety, optimal dosing regimen and duration, and ideal population for use.

Supplementary Data

Supplementary materials are available at *Open Forum 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.
Supplementary Table 1. Postfosfomycin Treatment Cultures Within 90 Days of Fosfomycin Dispensing

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