Multiple-dose oral fosfomycin for treatment of complicated urinary tract infections in the outpatient setting

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Key points:
In this retrospective cohort study assessing 171 multiple-dose fosfomycin treatment episodes for complicated UTI, the most common regimen was one dose every three days for three doses. Thirty-day clinical and bacteriological resolution rates were 66.1% and 47.8%, respectively.
ABSTRACT

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 (post-treatment urine culture <10³ 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 one dose every three days, mean duration of 6.1 days. Clinical resolution occurred in 115/171 (67.3%) episodes and bacteriologic resolution occurred in 37/76 (48.7%) episodes with post-treatment cultures. Most patients utilized antibiotics or had urine cultures before treatment (81.9% and 97.7%, respectively). Additional antibiotic use, urine cultures, and healthcare utilizations within 90 days post-treatment 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 two of three treatment episodes and bacteriologic resolution 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.

Key words: Urinary tract infections, anti-infective agents/urinary, fosfomycin, anti-bacterial agents, multiple dose
INTRODUCTION

Over 10 million office visits and 2 million emergency room visits occur annually in America due to urinary tract infections (UTI), costing approximately $3.5 billion [1,2]. In 1996, the 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 multi-drug resistant organisms (MDRO) [11–18]. 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 (e.g., 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 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 (i.e., more than one 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 one episode to the study if 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 record (EHR) 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 (e.g., 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 one or more of the following: 1) MDF was dispensed for a purpose other than UTI treatment (i.e., UTI prophylaxis or other/unknown); 2) the MDF index date was <90 days after another MDF dispense for the same patient; 3) only one dose was dispensed by the pharmacy; 4) there was clinical documentation (e.g., 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 was otherwise classified by the microbiology laboratory as a clinically insignificant or unreliable culture on final report.

Outcomes

The purpose of this study was to describe patient demographics, prescription characteristics, pre- and post-fosfomycin 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 post-index date, defined as complete resolution of signs and symptoms of infection (i.e., 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 post-index date (i.e., urgent care visit, emergency room visit, or hospitalization for UTI or pyelonephritis). Bacteriologic resolution was defined as a post-index date urine culture demonstrating <10^3 colony-forming units (CFUs) of the pathogen originally found in the pre-index date culture.

When analyzing bacteriologic resolution outcomes, only patients with urine cultures within 30-days pre- and post-index date were included in the analysis. Pre-index date cultures could include cultures collected on the index date in the event that patients had submitted a urine sample for culture prior to 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 primary antibiotic susceptibility technology. Interpretive criteria used by the microbiology laboratory were based on the CLSI document M100, Performance Standards for Antimicrobial Susceptibility Testing (Clinical and Laboratory Standards Institute, Wayne, PA) that were in effect during the time of the study [24].

Data Collection and Analysis

In addition to EHR review, patient characteristics and data regarding health care utilizations within 180 days prior to, 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* (ICD-9) and *10th revision* (ICD-10) diagnosis codes in the EHR during the 180 days prior to the index date [25,26]. Data were analyzed descriptively (e.g., means and percentages), analyses of categorical data were done by chi square or Fisher’s exact tests where appropriate, and the Wilson Score method was used to calculate 95% confidence intervals (CI) [27]. All analyses were conducted using SAS v.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 mostly 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 one UTI within the 180 days prior to 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 one sachet every three days (n=124, 72.5%), followed by one 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.

**Pre-index date antibiotic use and urine cultures**

Pre-index date antibiotic use occurred in 140 episodes (81.9%), with a mean±SD of 2.3±1.4 antibiotic courses administered in each episode prior to 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 prior to the index date (n=167, 97.7%), and 112 (65.5%) episodes had both pre- and post-treatment urinary cultures. Seven of the 167 pre-treatment cultures were polymicrobial (one three-organism culture and six two-organism cultures). Fourteen cultures grew normal flora or had insufficient growth and were excluded from the antibiotic susceptibility descriptions. From 167 pre-treatment cultures, 165 organisms with reported susceptibilities were isolated (Table 3). The most common organism isolated was *Escherichia 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 one 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 113/171 episodes (66.1%, 95% CI 59.7%-74.2%) (Table 4). Clinical resolution varied greatly according to the pathogens isolated in pre-index date cultures, ranging from 20.0% with *Citrobacter* spp. to 83.3% with *Pseudomonas* spp. Clinical resolution occurred in 87/131 episodes in females (66.4%; 95% CI 57.6%-74.4%) and 28/40 episodes in males (70.0%; 95% CI 53.5%-83.4%) with no statistically significant difference (P=0.70). Clinical resolution occurred in 92/140 episodes with antibiotic use in the previous 90 days (65.7%; 95% CI 57.2%-73.5%) and 23/31 episodes without antibiotic use in the previous 90 days (74.2%; 95% CI 55.4%-88.1%) with no statistically significant difference (P=0.36).

Only 76 episodes had a pre- and post-index 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 pathogen and ranged from 0% with *Proteus* or *Pseudomonas* spp. to 100% with *Enterococcus* spp. Bacteriologic resolution occurred in 41/74 episodes in females (55.4%; 95% CI
43.4%-67.0%) and 9/27 episodes in males (33.3%; 95% CI 16.5%-54.0%), with an insignificant trend toward lower rates in men (P=0.07). Bacteriologic resolution occurred in 33/69 episodes with antibiotic use in the previous 90 days (47.8%; 95% CI 35.7%-60.2%) and 9/15 episodes without antibiotic use in the previous 90 days (60.0%; 95% CI 32.3%-83.7%), with no statistically significant difference (P=0.39).

Four of 113 episodes with post-index date cultures were polymicrobial with two 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=17/18, 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 one course each of 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 one 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 one fosfomycin sachet every three days for a total of three doses. Despite the complicated nature of 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 post-treatment and over one-half (51.5%) of MDF episodes were associated with the need for additional antibiotic therapy.

Our study demonstrated 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 and ranged from 63–78% and 31–84%, respectively, after an average of three doses of fosfomycin [11,13,15,18]. The clinical and bacteriologic resolution rates demonstrated in our study are thus consistent with those previously reported in similarly complex patients including those with complicated infections, multiple comorbidities, and MDRO pathogens. 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 one 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 (i.e., daily vs. every-other-day vs. every three days) may have also contributed to the observed clinical and bacteriologic resolution rates compared to 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, while those who are clinically improved are less likely to have a need for repeat cultures purely for purposes of demonstrating bacteriologic eradication. It is thus 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 (3/87 pre- and post-treatment 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 which includes many resistant uropathogens (e.g. 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 to 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 (e.g., phlebitis) [30,31]. As demonstrated in the current study, patients commonly receive several courses of antibiotics and experience consecutive treatment failures prior to receiving MDF. If MDF were to be prescribed as initial therapy, the medication costs and other healthcare expenses (e.g. office visits) associated with unsuccessful treatment involving multiple courses of alternative antibiotics and healthcare utilizations could potentially be reduced. Further, although not statistically significant, we
observed a numerically higher trend in clinical and bacteriologic resolution rates among those with no antibiotic use in the prior 90 days, which should be investigated with a larger sample size. Fosfomycin is well tolerated, can be used in unique patient populations (i.e., pregnancy, elderly, renal dysfunction, liver dysfunction), and has a low incidence of allergic, hypersensitivity, and adverse reactions compared to 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. However, 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 twelve episodes in which Pseudomonas spp. were identified in a pre-treatment 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 nine had post-treatment 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. While 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. Unfortunately, neither the IDSA nor European Urology Association offer 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 (NCT03697993).

This study also identified opportunities to optimize the dispensing of MDF for UTI treatment within our institution. Because the unique dose (three grams) is numerically the same as the most common number of doses (three), there is potential for medication dispensing errors, as pharmacists may mis-interpret the intended number of doses (three) and dispense only one packet (three grams). This error could explain why, during medical record review, we observed several instances where clinical documentation described that the patient took only one dose, although dispensing data suggested that the patient was dispensed more than one dose. We are unaware of formal evaluations of fosfomycin dispensing errors, although this would be important for institutions to internally assess prior to 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 to other UTI treatments. However, 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 non-adherence may have affected our findings. Given our study’s relatively small sample size with wide confidence intervals 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 which may predict clinical or bacteriologic resolution with MDF treatment.

CONCLUSION

This retrospective study found that in patients with complicated infections and multiple prior UTI treatment episodes, MDF treatment was associated with clinical resolution in two of three treatment episodes and bacteriologic resolution in one-half of treatment episodes. Infections due to Escherichia 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 post-treatment cultures in order 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.
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### Table 1: Patient and Prescription Characteristics of Multiple-dose Fosfomycin Episodes

| Characteristic                      | UTI Treatment Episodes (N=171)* |
|-------------------------------------|---------------------------------|
| **Patient Characteristics**         |                                 |
| Mean Ageb (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/1.73 m²)               | 59.5 (129, 23.7)                |
| Chronic Disease Scorec              | 4.1 (3.0)                       |
| Charlson Comorbidity Indexc         | 2.9 (2.7)                       |
| **Comorbidities**                   |                                 |
| 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 UTId**                      |                                 |
| Median count [IQR]f                  | 1 [0,2]                         |
| At Least One Prior UTIc              | 106, 72.1%                      |
| Kidney stone d                      | 10, 5.9%                        |
| Ureteral stent or other urogenital implant<sup>c</sup> | 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<sup>e</sup>: 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<sup>f</sup>**
- Before: 167, 97.7%
- After: 113, 66.1%
- Before and After: 112, 65.5%

<sup>a</sup> For 147 unique patients

<sup>b</sup> Based on patient’s first fosfomycin dispensing during the study period

<sup>c</sup> Calculated within 180 days prior to the index date

<sup>d</sup> Diagnosed within 180 days prior to each episode fosfomycin dispensing

<sup>e</sup> For example, twice weekly

<sup>f</sup> Within 90 days of fosfomycin dispensing

COPD – chronic obstructive pulmonary disease; eGFR - estimated glomerular filtration rate; IQR – interquartile range; SD - standard deviation; UTI - urinary tract infection
Table 2: Antibiotics used within 90 days before multiple-dose fosfomycin treatment episodes (N = 171)

| Medication class | Antibiotics courses (n=140) |
|------------------|-----------------------------|
| **Antibiotics prescribed prior to 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% |

SD = standard deviation; UTI = urinary tract infection; TMP-SMX = trimethoprim-sulfamethoxazole
Table 3: Pre-fosfomycin treatment cultures within 90 days of fosfomycin dispensing

| Antibiotic                  | Total Isolated Organisms (N = 165) | Organisms                        |
|-----------------------------|-------------------------------------|----------------------------------|
|                             | Total Isolated Organisms (N = 165) | Escherichia coli (n=104) | Klebsiella spp. (n=15) | Enterococcus spp. (n=13) | Pseudomonas spp. (n=12) | ESBL-producing E. coli (n=8) | Citrobacter spp. (n=5) | Proteus mirabilis (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 | Resistant |
|----------------|--------------|-----------|
| Intermediate   | 6 (4.0)      | 119 (79.3)|
| Resistant      | 1 (1.0)      | 0 (0.0)   |

|                | Ertapenem    |
|----------------|--------------|
| Susceptible    | 102 (99.0)   |
| Intermediate   | 1 (1.0)      |
| Resistant      | 0 (0.0)      |

|                | Fosfomycin   |
|----------------|--------------|
| Susceptible    | 67 (97.1)    |
| Intermediate   | 1 (1.4)      |
| Resistant      | 1 (1.4)      |

|                | Gentamicin   |
|----------------|--------------|
| Susceptible    | 83 (56.5)    |
| Intermediate   | 3 (2.0)      |
| Resistant      | 61 (41.5)    |

|                | Nitrofurantoin|
|----------------|--------------|
| Susceptible    | 90 (59.6)    |
| Intermediate   | 35 (23.2)    |
| Resistant      | 26 (17.2)    |

|                | TMP-SMX      |
|----------------|--------------|
| Susceptible    | 33 (24.3)    |
| Intermediate   | 0 (0.0)      |
| Resistant      | 103 (75.7)   |

*All values are no. (%) unless noted otherwise. ESBL = extended-spectrum beta-lactamase; NA = not available; TMP-SMX = trimethoprim-sulfamethoxazole

*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. 7 cultures included were poly-microbial in nature (1 with 3 isolated organisms, 6 with 2 isolated organisms).
| Included          | Bacterial strain          |
|-------------------|---------------------------|
| 3 isolates of     | Klebsiella oxytoca and 12|
|                   | isolates of Klebsiella    |
|                   | pneumoniae                |
| 1 isolates of     | Pseudomonas fluorescens   |
|                   | and 11 isolates of        |
|                   | Pseudomonas aeruginosa    |
| 4 isolates of     | Citrobacter freundii and  |
|                   | 1 isolate of Citrobacter  |
|                   | koseri                    |

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

| Outcome                  | Treatment | All | Cultured Organisms<sup>a,b</sup> |
|--------------------------|-----------|-----|----------------------------------|
|                          |           | Treatment | Citrobacter spp. | E. coli (n=5) | ESBL E. coli (n=8) | Enterococcus spp. (n=13) | Klebsiella spp. (n=15) | Proteus spp. (n=4) | Pseudomonas spp. (n=12) |
| n, %, 95% confidence     |           | Episodes<sup>a</sup> (N=171) | (n=5) | (n=101) | (n=8) | (n=13) | (n=15) | (n=4) | (n=12) |
| Clinical Resolution<sup>c</sup> | | 113, 66.1% | 20.0% | 76, 75.2% | 5, 62.5% | 8, 61.5% | 11, 73.3% | 1, 25.0% | 10, 83.3% |
|                          | | (59.7%, 74.2%) | (0.5%, 65.7%) | (24.5%, 83.3%) | (24.5%, 81.5%) | (31.6%, 86.1%) | (44.9%, 92.2%) | (0.6%, 80.6%) | (51.6%, 97.9%) |
| Bacteriologic Resolution<sup>d</sup> | | 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% |
|                          | | (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%) |

<sup>a</sup> Patients could contribute to data multiple times if they had multiple bacterial isolates (n=7 episodes)

<sup>b</sup> Only includes patients who had at least one organism identified with a pre-treatment culture. Not all identified cultures included.

<sup>c</sup> 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, fever.
Defined as offending organism CFU < $10^3$ on post-treatment culture within 30 days of fosfomycin dispensing. 95 treatment episodes did not have follow-up cultures within 30 days to include in the analysis.

ESBL – extended-spectrum beta lactamase; SD - standard deviation
FIGURE LEGENDS

Figure 1: Patient Dispositions

UTI=urinary tract infection
Figure 1

Figure: Patient Dispositions

398 multiple-dose fosfomycin prescriptions dispensed between July 1, 1999 and June 30, 2018

227 Excluded during chart review
152 - Prophylactic indication
38 - Dispensed within 90 days of another multiple-dose fosfomycin prescription
20 - Only one dose dispensed
8 - Not for UTI treatment
5 - Patient did not take
4 - No information available in health record

171 multiple-dose fosfomycin treatment episodes analyzed