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Fosfomycin for treatment of multidrug-resistant pathogens causing urinary tract infection: A real-world perspective and review of the literature

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ABSTRACT

Among 47 patients with urinary tract infections (UTIs) due to multidrug-resistant (MDR) bacteria, treatment with fosfomycin resulted in clinical cure rates of 87% and 94% at 48 hours and 14 days, respectively. Response rates did not vary across pathogens. Our retrospective, observational findings support fosfomycin treatment against MDR pathogens causing UTIs.

Urinary tract infections (UTI) are the most common health care-associated infection in the United States. Over the past decade there has been a notable increase in the rate of UTIs due to multidrug-resistant (MDR) pathogens (Zilberberg and Shorr 2013). Compared to non-MDR pathogens, UTIs caused by MDR bacteria are associated with prolonged hospital lengths of stay, higher rates of secondary bacteremia, and worse patient outcomes (van Duin et al. 2013). Treatment options for MDR pathogens are often limited to intravenous (IV) antibiotics associated with substantial toxicity, suboptimal urinary concentrations, or high costs (DiazGranados et al. 2005; van Duin et al. 2013). Fosfomycin is a phosphonic acid derivative (*cis*-1,2-eposypropyl-phosphonic acid) that exerts bactericidal antimicrobial activity by blocking the early stage of peptidoglycan synthesis. Fosfomycin has a broad range of *in vitro* activity against both Gram-positive and Gram-negative pathogens and is well-tolerated as a single oral dose (Sastry et al. 2015). Consensus guidelines recommend fosfomycin as one of the first line treatment options for uncomplicated cystitis (Gupta et al. 2011). Data to support fosfomycin treatment of MDR pathogens causing UTI, however, are limited (Neuner et al. 2012; Seroy et al. 2016; Giancola et al. 2017). Our objectives were to assess the clinical outcomes of hospitalized patients treated with fosfomycin for UTIs due to MDR pathogens and to compare our clinical experience to the reported literature.

We conducted a retrospective cohort study of patients with UTIs caused by MDR pathogens, including carbapenem-resistant Enterobacteriaceae (CRE), extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (ESBL-E), and vancomycin-resistant enterococci (Violi et al. 1995). Patients who received at least one dose of fosfomycin between 2011 and 2018 for treatment of these 3 MDR pathogens were included in the study. Fosfomycin was prescribed at the discretion of the treating physician. Patients who received fosfomycin and combination therapy with another *in vitro* active antibiotic were excluded. UTI was defined as a positive urine culture (growing ≥50,000 CFU/ml of bacteria) and at least one of the following symptoms: dysuria, increased urinary frequency, flank pain or tenderness, fevers, and/or altered mental status without an alternative etiology, or as a positive urine culture growing ≥5,000 CFU/ml of bacteria with aforementioned symptoms and a clinical diagnosis confirmed by an Infectious Diseases consultant. Routine bacterial identification and antimicrobial susceptibility testing was performed with Microscan WalkAway™ (Siemens Healthcare Diagnostics). Fosfomycin susceptibility testing was not performed. The primary outcome of our analysis was 14-day clinical cure, which was defined as resolution of UTI signs and symptoms, or discharge from the hospital in

Abbreviations: BPH, Benign prostatic hyperplasia; BMT, Bone marrow transplant; CRE, Carbapenem-resistant Enterobacteriaceae; ESBL-E, Extended-spectrum β-lactamase-producing Enterobacteriaceae; ID, Infectious diseases; PCR, Polymerase chain reaction; MDR, Multidrug-resistant; UPJ, Uteropelvic junction; VRE, Vancomycin-resistant enterococci.

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stable condition without further antibiotic therapy. Secondary outcomes included clinical cure at 48 hours, as defined previously by the same criteria (Sastry et al. 2015), microbiologic failure at 14 days, and relapsing UTI within 30 days of treatment completion. The study was approved by the institutional review board at the University of Pittsburgh. Statistical analyses were performed with GraphPad Prism version 7 (GraphPad Software, San Diego, CA). Categorical variables were evaluated by using the χ^2 test or Fisher's exact test, as appropriate.

Over the study period, 47 patients with MDR UTIs were included (Table 1). The median age was 65 years (range, 20–95), 81% (38/47) were women, and the median Charlson Comorbidity index was 5 (range, 0–19). Twenty-three percent (11/47) of patients were immunocompromised. At the onset of infection, the most common symptoms included fever (28%, 13/47), increased urinary frequency (28%, 13/47), and altered mental status (26%, 12/47). Seventy-eight percent (37/47) of cases were classified as complicated UTIs (Sastry et al. 2015). Sixty-four percent (30/47) of cases met current CDC/NHSN definitions of UTI (Horan et al. 2008), and 51% were considered healthcare-associated. Ninety-one percent (43/47) of patients had urine cultures with ≥50,000 CFU/ml; the remaining 4 patients were seen by Infectious Diseases consultants who ruled out other causes of symptoms and confirmed the diagnosis of UTI. Two patients were diagnosed with pyelonephritis. Fifty-two percent (24/47) of patients had blood cultures collected within 7 days of UTI, and none had concomitant bacteremia.

Fosfomycin was prescribed as empiric therapy in 34% (16/47) of patients according to local guidelines. Among the remaining patients who received definitive therapy, fosfomycin was prescribed due to documented resistance against alternative agents (n = 20), dosing convenience (n = 7), or hypersensitivity to alternative agents (n = 4). Seventeen percent (8/47) of patients received more than one dose of fosfomycin at the discretion of the treating physician. Thirty-eight percent (18/47), 32% (15/47), and 30% (14/47) of patients were infected by VRE, CRE, and ESBL-E, respectively. Clinical cure at 48 hours occurred in 87% (41/47) of patients as follow-up was available. The 14-day clinical cure rate was 94% (44/47). Improvement in signs and symptoms of infection was documented within 48 hours of therapy for 52% (23/44), and presumed following hospital discharge in the remaining 48% (21/44) of patients. Microbiologic failures with the same organisms occurred within 14 days of fosfomycin treatment in 15% (7/47); 57% (4/7) of patients with microbiologic failures were asymptomatic. Rates of clinical and microbiologic outcomes at 14 days did not vary across MDR pathogens or by the number of fosfomycin doses received (Table 1). Eleven percent (5/44) of patients with clinical cure had recurrent UTIs caused by the same pathogen within 30 days. The in-hospital mortality rate was 8.5% (4/47); one death was attributed to CRE bacteremia and pneumonia 12 days after fosfomycin treatment of CRE UTI. One patient experienced nausea without diarrhea following fosfomycin treatment, but tolerated repeat dosing.

Next, we identified all published articles describing fosfomycin treatment outcomes of MDR UTIs through September 2018 on PubMed using the following MeSH terms: carbapenem-resistant Enterobacteriaceae, CRE, extended-spectrum β-lactamase-producing Enterobacteriaceae, ESBL, vancomycin-resistant Enterococcus, VRE, multidrug-resistant, MDR, fosfomycin, and urinary tract infection. Additional articles were reviewed following ancestry and bibliography reviews of identified articles. Articles with only clinical efficacy data for fosfomycin against UTIs caused by ESBL-E were excluded given a prior review on this topic (Falagas et al. 2010). Our search identified 5 retrospective cases series and one nested cohort study (Neuner et al. 2012; Reid et al. 2013; Brizendine et al. 2015; van Duin et al. 2015; Seroy et al. 2016; Giancola et al. 2017), which are summarized in Table 2. The median age of patients treated with fosfomycin ranged across studies from 56 to 79 years; 58% of subjects were female. Two studies included only solid organ transplant (SOT) recipients and one did not report on percentage of SOT patients; the percentage of SOT recipients across three other studies was 38% (60/158). Thirty-four percent (41/120) of patients received fosfomycin in combination with another antibiotic. By individual study definition, reported rates of clinical cure ranged from

Table 1
Patient demographics, underlying diseases, and clinical outcomes.

	All MDR pathogens n = 47	VRE n = 18	CRE[1] n = 15	ESBL-E[1] n = 14
Demographics				
Median age, years (range)	65 (20–95)	70 (20–89)	59 (38–86)	71.5 (23–95)
Male gender, n (%)	9 (19.1)	3 (16.7)	3 (20.0)	3 (21.4)
Underlying diseases				
Diabetes mellitus, n (%)	21 (44.7)	7 (38.9)	10 (66.7)	4 (28.6)
Chronic kidney disease, n (%)	13 (27.7)	5 (27.7)	4 (26.7)	4 (28.6)
Solid organ transplant, n (%)	4 (8.5)	1 (5.6)	2 (13.3)	1 (7.1)
Genitourinary tract abnormality, n(%)[2]	11 (23.4)	4 (22.2)	5 (33.3)	2 (14.3)
Immunosuppressed, n (%)[3]	11 (23.4)	7 (38.9)	2 (13.3)	2 (14.3)
Median Charlson comorbidity index (range)	5 (0–19)	5.5 (0–10)	4 (1–9)	4 (0–19)
Treatment characteristics				
Complicated UTI	37 (78.7)	14 (77.8)	14 (93.3)	9 (64.3)
Prior infection with MDR organism, n (%)	18 (38.3)	3 (16.7)	8 (53)	6 (42.8)
Concomitant infection, n (%)[4]	7 (14.9)	1 (5.6)	3 (20)	3 (21.4)
Empiric therapy, n (%)	16 (34.0)	4 (22.2)	6 (40.0)	6 (42.9)
Received >1 dose of fosfomycin, n (%)[5]	8 (17.0)	3 (16.7)	4 (26.7)	1 (7.1)
ID consulted, n (%)	23 (48.9)	9 (50.0)	10 (66.7)	4 (28.6)
Outcomes				
48-h clinical success, n (%)	41 (87.2)	17 (94.4)	12 (80)	12 (85.7)
14-day clinical cure, n (%)	44 (94.0)	18 (100)	14 (93.3)	12 (85.7)
14-day microbiological failure, n (%)	7 (14.9)	3 (16.7)	3 (20)	1 (7.1)
Documented 30-day relapse, n (%)	5 (10.6)	1 (5.5)	1 (6.7)	3 (21.4)
In hospital mortality/hospice, n (%)	4 (8.5)	2 (11.1)	1 (6.7)	1 (7.1)

1 = All CRE were due to *Klebsiella pneumoniae;* all ESBL-E were due to *Escherichia coli.*
2 = Genitourinary abnormality n (%) included: nephrostomy tube 2 (4.3), BPH 2 (4.3), ureteral stent 3 (6.4), urological procedure within the past 180 days 3 (6.4), recurrent/persistent renal calculi 4 (8.5), neurogenic bladder 4 (8.5).
3 = Immunosuppression: solid-organ transplantation, bone marrow transplantation, neutropenia, hematological malignancy, chronic steroid therapy, autoimmune suppressive therapy, chemotherapy.
4 = 2 patients had concomitant *Staphylococcus aureus* bacteremia. 2 patients had PCR confirmed *Clostridioides difficile.* 1 patient had a *Staphylococcus aureus* septic arthritis, 1 patient had *Serratia marcescens* bacteremia.
5 = 3 patients received 3 doses and 5 patients received 2 doses.

Table 2
Studies examining fosfomycin for the treatment CRE and MDR UTIs.

Author, year	Inclusion criteria	Outcome definitions	Patients/organism	Patient demographics	Treatment [11]	Outcomes	Ref No.
Neuner et al. 2012	Abnormal urinalysis[1] and positive MDR[2] urine culture	Microbiological cure: negative urine culture at completion of therapy and/or the absence of relapse or reinfection Microbiological failure: development relapse or reinfection Relapse: UTI with the same pathogen within 30 days Reinfection: UTI with a different organism within 30 days	41 patients (44 MDR organisms) 16 *K. pneumoniae* (13: CRE, 3 ESBL) 9: *E.coli* (4 ESBL) 8: *P. aeruginosa* 7: VRE 1: *A. baumannii* 1: *E. cloacae* 1: *E. faecalis* 1: *P. mirabili*	Mean Age: 62 Male: 45% Median Charlson comorbidity index: 4 DM: 58.5% CKD: 46.3% SOT: 36.6% IS: 51% GU abnormality[3]: 36.6%	Microbiological cure: 3.3 doses of ±1.9 Microbiological failure: 2.4 ± 1.5 Combination therapy: 27% (n = 11) Tigecycline: 12% (n = 5), Aminoglycosides: 5% (n = 2) Colistin: 2% (n = 1), piperacillin-tazobacta: 2% (n = 1) Imipenem: 2% (n = 1) Daptomycin: 2% (n = 1).	Microbiological cure: 59% Microbiological failure: 41% CR-Kp Microbiological cure: 46% SOT Microbiological cure rate: 33.3% Development of fosfomycin resistance: 3 patients with CR-Kp (23%) Hospital mortality: 10% (n = 4)	8
Reid et al. 2013	MDR (not defined) urine culture with positive urine analysis (not defined) or symptoms	Recurrence: infection with same organism within 3 months Persistence: infection with same organism within 1 week of treatment completion Clearance: no persistence or recurrence within 3 months	9 patients 14 UTI episodes 7: *E.coli* (6: ESBL) 5: CR-Kp 2: *P. aeruginosa*	Mean age: 78 Male: 22% SOT (kidney): 100% DM: 33.3% GU abnormality: 88.9%	3 doses: 57% Range: 1–7 doses Combination therapy: 14.29% (n = 1) Colistin/Azteronam:11% (n = 1)	Overall clearance: 31% Recurrence rate: 54% Persistence: 21% No adverse reactions	12
Brizendine et al. 2015	UTI as per CDC/NHSN definition [4]	Clinical failure: symptoms ≥72 h after therapy Microbiological failure: positive urine culture of same organism ≥72 h after therapy	22 patients CR-Kp Fosfomycin treated cases: 10 (45%)	Mean Age[5]: 56 73% male[5] SOT: 100%	Mean duration: 9.3 days Monotherapy: 20% (n = 2) Combination therapy 80% (n = 8): Tigecycline and colistin (n = 3) Tigecycline (n = 3) Aminoglycoside (n = 2)	Fosfomycin treated cases combined clinical response and microbiological response: 50% Fosfomycin treated cases clinical failure: 20% Fosfomycin treated cases microbiological failure: 50%	11
van Duin et al. 2015	Physician diagnosed CR-Kp UTI: patients who received directed treatment for CR-Kp bacteriuria CDC/NHSN defined UTIs [6]	Treatment success: negative urine culture after index culture and did not meet any of the criteria for treatment failure. Treatment failure: recurrent CR-Kp in urine culture ≥7 days after index culture, death or discharge to hospice Indeterminate: patients who did not meet criteria for success or failure.	157 CR-Kp physician defined UTI. CDC/NHSN defined UTI: 53 (34%) Fosfomycin treated cases: 19 (12%)	Median age: 72 Male: 41%[7] Median Charlson comorbidity index: 3 [7] GU abnormality 27% [7] AKI (Scr > 2): 22% [7]	Monotherapy: 42% (n = 8) Combination therapy 58% (n = 11): Aminoglycosides (n = 7) Tigecycline (n = 3) Colistin (n = 1)	Overall treatment success 15% Overall treatment failure: 34% Overall Indeterminate outcome: 51% Fosfomycin treated UTIs treatment success: 10.5% Fosfomycin treated UTIs treatment failure: 47% Fosfomycin treated UTIs Indeterminate:42.1%	13
Seroy et al. 2016	Positive urine analysis[1] and culture with MDR[2] organism with symptoms	Cure: absence of persistent or recurrent infection Persistent infection: isolation same organism from a urine culture ≥7 days after treatment completion	69 Patients 33: *E.coli* (20 ESBL) 23 *K. pneumoniae* (13 CRE, 8 ESBL) 3: *P. aeruginosa* 2: VRE 2. *P. mirabilis* 1: *E. cloacae*	Average age: 62.2 Male: 27% Charlson comorbidity index average: 3.3 DM: 38% CKD: 33%	3 doses: 43% (n = 30) 1 dose: 32% (n = 22) Combination therapy not reported	Overall cure rate 55% Recurrent infection: 21% CRE cure rate 38% SOT cure rate: 71.4% Mortality: 3% (n = 2)	7

(continued on next page)

Table 2 *(continued)*

Author, year	Inclusion criteria	Outcome definitions	Patients/organism	Patient demographics	Treatment [11]	Outcomes	Ref No.
		Recurrent infection: same organism from urine culture within 3 months of treatment completion	1: *P. vulgaris*	ESRD: 2% SOT: 12% GU abnormality[3]: 20%			
Giancola et al. 2017	Positive urine culture with MDR[2] with signs/symptoms	Clinical cure: resolution of UTI symptoms/signs. Clinical failure: incomplete resolution of UTI symptoms/signs and/or treatment reinitiated within 30 days Microbiological cure: negative culture by completion of therapy and/or the absence of relapse	36 patients (42 MDR organisms) 22: *E.coli* 10: *Enterococcus sp.* 6: *Pseudomonas* 1: *Klebsiella* 1: *Proteus* 1: *Morganella*	Median age: 79 Male: 33.3% Comorbid conditions[8] DM: 35.1% Heme/onc condition: 16% CKD: 15% SOT: 9% IS: 6% GU abnormality[3]: 12%	1 dose: 44% (n = 16) 3 doses: 36% (n = 13) Combination therapy: 25% (n = 9) Combination therapy included gentamicin, ceftriaxone, ceftazidime, cefepime, meropenem, piperacillin-tazobactam, and vancomycin	MDR Clinical cure: 94.4% (17/18) Microbiological cure: 69.2% (9/13) Relapse: 14.3% Reinfection: 15.4%	6

AKI = Acute kidney injury; CKD = Chronic kidney diseases; CR = creatinine; CR-Kp = Carbapenem resistant *Klebsiella pneumoniae*; CRE = Carbapenem resistant Enterobacteriaceae, diabetes mellitus; ESBL = Extended spectrum β-Lactamase producing Enterobacteriaceae; ERSD = End stage renal diseases; IS = immunosuppression; GU = genitourinary; Heam/Onc = hematological /oncological; MDR = Multidrug resistant; SOT = Solid organ transplant; UTI = Urinary tract infection; VRE = Vancomycin resistant *Enterococcus*.
1 = Positive urine analysis defined as: a urinalysis with more than five leucocytes per high-powered field or positive leucocyte esterase.
2 = MDR defined as non-susceptible to ≥1 agent in ≥3 antimicrobial classes.
3 = GU abnormality included: urological surgery, GU tract stents, neurogenic bladder, percutaneous nephrostomy tube, suprapubic catheter. Presence of Foley catheter not included as a GU abnormality.
4 = Centers for Disease Control and Prevention. 2014. CDC/NHSN surveillance definitions for specific types of infections. Centers for Disease Control and Prevention, Atlanta, GA: http://www.cdc.gov/nhsn/PDFs/pscManual/17pscNosInfDef_current.pdf.
5 = Characteristics of all CR-Kp patients, not only ones treated with Fosfomycin.
6 = CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting (Horan et al. 2008; Gupta et al. 2011).
7 = Characteristics of all CR-Kp patients, not only ones treated with Fosfomycin.
8 = Percentage of all 57 patients included in study.

44 to 94%. Clinical cure rates were lower for patients infected by CRE compared to non-CRE pathogens (33% [18/55] *vs.* 52% [54/103]; $P = 0.02$). Specifically, patients infected by ESBL-E (56% [23/41]; $P = 0.09$) or VRE (78% [7/9]; $P = 0.02$) demonstrated higher rates of clinical success (Neuner et al. 2012; Reid et al. 2013; Seroy et al. 2016). Cure rates were lower for SOT recipients compare to non-transplant patients (36% [16/45] *vs.* 65% [49/77]; $P = 0.003$) (Neuner et al. 2012; Reid et al. 2013; Brizendine et al. 2015; Seroy et al. 2016). Following fosfomycin treatment, UTI relapse rates occurred in 14–21% of patients.

The most notable finding of our study is the high rates of clinical and microbiologic cure we encountered among patients with MDR UTIs treated with fosfomycin monotherapy. Response rates did not vary by MDR pathogen or fosfomycin dosing regimen, and are consistent with the overall success rates among patients with UTIs due to susceptible pathogens (Sastry et al. 2015). Our findings are noteworthy considering the vulnerable patient population we studied, which included hospitalized patients with complicated UTIs caused by MDR pathogens. These data corroborate studies reporting high rates of clinical cure following fosfomycin treatment of UTIs caused by ESBL-E (Falagas et al. 2010; Matthews et al. 2016), and extend the limited literature available for fosfomycin treatment of UTIs due to CRE and VRE (Table 2) (Heintz et al. 2010; Neuner et al. 2012; Seroy et al. 2016). Contrary to previous reports (Neuner et al. 2012; Reid et al. 2013; Brizendine et al. 2015; van Duin et al. 2015; Seroy et al. 2016), we did not identify lower rates of clinical cure among SOT recipients or patients infected by CRE, although our ability to draw conclusions is limited by our sample size. Other factors associated with higher rates of treatment failure in prior studies have included genitourinary anatomic abnormalities and chronic kidney disease (Seroy et al. 2016), which did not correlate with failure in our study. Finally, we have provided new insights into the potential role of fosfomyin for treatment of UTIs caused by VRE, which was the most common MDR pathogen treated with fosfomycin in our study. Until now, treatment outcomes have only been reported in 9 cases (Table 2). Among 18 additional patients included in our study, clinical cures were achieved in 100% and 83% of patients at 14 and 30 days, respectively. Taken together, the available clinical data demonstrate favorable clinical responses following fosfomycin treatment of UTIs due to MDR pathogens.

Despite the growing body of observational clinical data, a number of unanswered questions remain. First, the emergence of fosfomycin resistance following systemic treatment has been well-documented (Karageorgopoulos et al. 2012); however, rates of resistance among MDR pathogens following fosfomycin treatment of UTIs are largely unknown. Neuner and colleagues reported the emergence of fosfomycin resistance in 3 patients (23%), but other observational studies have not reported such outcomes. Of primary concern is that supratherapeutic exposures of fosfomycin do not prevent the emergence of resistance against MDR pathogens, including ESBL-E or CRE, during dynamic *in vitro* experiments (Docobo-Perez et al. 2015). Secondly, it is unclear how fosfomycin pharmacokinetics influences patient outcomes. Following a single 3-g oral administration, considerable inter-patient variability has been demonstrated among healthy female volunteers (Wijma et al. 2018). Similarly, patients with augmented renal clearance may not achieve therapeutic fosfomycin exposures following a single dose (Parker et al. 2013). For such patients, it is possible that repeated doses of fosfomycin may be required to achieve pharmacokinetic-pharmacodynamic targets, which is the focus of an ongoing randomized clinical trial (clinicaltrials.gov, NCT02570074). Finally, it remains to be seen how increasing usage of fosfomycin will influence overall resistance rates against the agent (Sastry and Doi 2016). In the United States there has been renewed interest in the development of intravenous fosfomycin for systemic infections. A phase III randomized trial of fosfomycin compared to piperacillin-tazobactam for UTIs has been completed (Kaye et al., n.d.). Regional prescription patterns likely drive local fosfomycin susceptibility rates (Jiang et al. 2015), which may be facilitated by the spread of plasmid-mediated modifying

enzymes, including FosA and FosB (Jiang et al. 2015). This calls for the need for routine surveillance of fosfomycin resistance among UTI pathogens including isolates recovered while on therapy, as it is currently not routinely included in standard susceptibility testing panels.

Each of these unanswered questions could have deleterious effects on patient outcomes. In a recent randomized clinical trial, fosfomycin was found to be inferior to nitrofurantoin for the treatment of uncomplicated UTIs (Huttner et al. 2018). This result was in contrast to two historical double-blind, placebo-controlled studies that showed similar clinical and microbiological cure rates for the two agents (Van Pienbroek et al. 1993; Stein 1999). A key difference between studies was the use of thrice daily nitrofurantoin dosing in the most recent study, which has spurred further inquiries into the oral dosing regimen of fosfomycin.

In conclusion, our study adds new insights to the growing body of evidence to support the use of fosfomycin for treatment of MDR pathogens causing UTIs among patients who can be treated with oral agents. Importantly, these data extend beyond the FDA approved fosfomycin indication for treatment of uncomplicated cystitis due to *E. coli* and *E. faecalis,* and should be interpreted as exploratory until confirmatory studies have been completed. Indeed, fosfomycin treatment was largely effective across pathogens and well-tolerated among patients. It should be noted that our results reflect institutional practices and local epidemiology, and thus, may not be applicable to other patient settings or populations. To this end, we included patients who did not meet current CDC/NHSN criteria for UTI, but exhibited clinically relevant symptoms, a positive urine culture, and a confirmatory diagnosis by Infectious Diseases physicians. We excluded patients who received fosfomycin combination therapy, and therefore patients may have been more likely to experience a favorable outcome. As with other observational studies, our ability to identify microbiologic failures and concomitant bacteremia was contingent upon a clinical indication to obtain cultures and favorable outcome was presumed in a proportion of cases. Rates of microbiologic success have been reported to be lower when systematic surveillance is completed, as is the case in randomized-controlled trials (Huttner et al. 2018). Fosfomycin susceptibility testing was not routinely performed, and therefore we were unable to evaluate for the emergence of fosfomycin resistance. While these data, taken together with those reported in the literature, are encouraging for treatment of UTIs caused by MDR pathogens, further well-designed, prospective studies are needed to confirm these findings and to compare fosfomycin with alternative oral treatments. Such studies will be particularly useful for identifying new indications for intravenous fosfomycin should it become available in the United States.

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