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Assessment of Fosfomycin for Complicated or Multidrug-Resistant Urinary Tract Infections: Patient Characteristics and Outcomes

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Urinary tract infection · Uropathogen · Vancomycin-resistant enterococci · Carbapenemase · Extended-spectrum beta-lactamase

Abstract
Background: Bacterial resistance among uropathogens is on the rise and has led to a decreased effectiveness of oral therapies. Fosfomycin tromethamine (fosfomycin) is indicated for uncomplicated urinary tract infections (UTIs) and displays in vitro activity against multidrug-resistant (MDR) isolates; however, clinical data assessing fosfomycin for the treatment of complicated or MDR UTIs are limited. ***Methods:*** We conducted a retrospective evaluation of patients who received ≥1 dose of fosfomycin between January 2009 and September 2015 for treatment of a UTI. Patients were included if they had a positive urine culture and documented signs/symptoms of a UTI. ***Results:*** Fifty-seven patients were included; 44 (77.2%) had complicated UTIs, 36 (63.2%) had MDR UTIs, and a total of 23 (40.4%) patients had a UTI that was both complicated and MDR. The majority of patients were female (66.7%) and elderly (median age, 79 years). Overall, the most common pathogens isolated were *Escherichia coli* (n = 28), *Enterococcus* spp. (n = 22), and *Pseudomonas aeruginosa* (n = 8). Twenty-eight patients (49.1%) were clinically evaluable; the preponderance achieved clinical success (96.4%). Fifteen out of 20 (75%) patients with repeat urine cultures had a microbiological cure. ***Conclusions:*** This retrospective study adds to the limited literature exploring alternative therapies for complicated and MDR UTIs with results providing additional evidence that fosfomycin may be an effective oral option.

Introduction

Antibiotic resistance among urinary tract infection (UTI) pathogens, notably *Escherichia coli*, is rising [1, 2] and resistance to oral agents like trimethoprim-sulfamethoxazole and fluoroquinolones is particularly problematic [2–4]. Treatment options are further limited in patients with drug allergies. Therefore, assessment of alternative oral drugs for UTIs caused by multidrug-resistant (MDR) pathogens is needed.

Fosfomycin tromethamine is indicated for the treatment of acute uncomplicated UTIs caused by *E. coli* and *Enterococcus faecalis* [5]. It has broad-spectrum activity, including MDR pathogens such as extended-spectrum

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beta-lactamase (ESBL) producers, carbapenem-resistant *Enterobacteriaceae* (CRE), and vancomycin-resistant enterococci (VRE) [6–8]. Fosfomycin is recommended as the first-line treatment for uncomplicated UTIs; however, published experience with fosfomycin in the USA is limited, which may lead to clinician reluctance regarding its use in comparison to alternative agents [3]. Additionally, there are few published clinical studies on its use for MDR or complicated UTIs [9–12]. The objectives of this study were to describe patient characteristics and clinical and microbiological outcomes following fosfomycin treatment with a focus on those with complicated or MDR UTIs.

Materials and Methods

This retrospective evaluation was conducted at a 672-bed teaching hospital affiliated with Harvard Medical School. Hospitalized adult patients (≥18 years) who received ≥1 dose of fosfomycin between January 2009 and September 2015 were included. All patients had a positive urine culture and signs/symptoms (polyuria, dysuria, hematuria, urinary frequency or urgency, fever, flank pain, altered mental status) of a UTI, regardless of their urinary catheter status. Of note, fosfomycin orders require approval by Infectious Diseases or Antimicrobial Stewardship (ID/AS) staff. This study was approved by the institutional review board.

Data were collected from electronic records. Pathogens were considered MDR if nonsusceptible to ≥1 agent in ≥3 antimicrobial classes as per the Clinical and Laboratory Standards Institute M100-S24 susceptibility criteria [13, 14]. Infections in men or in patients with a urinary Foley catheter, suprapubic catheter, or other anatomical or functional abnormality, such as a neurogenic bladder or ureteral stent, were considered to be complicated [3, 9, 12]. Patients were deemed clinically evaluable if UTI signs/symptoms were present prior to fosfomycin treatment and they were hospitalized for ≥24 h following treatment with fosfomycin. Clinical cure was defined as the resolution of UTI signs/symptoms during or at completion of fosfomycin treatment as per the documentation in progress notes. Clinical failure included an incomplete resolution of UTI signs/symptoms at completion of treatment as per the documentation in progress notes, or treatment reinitiated within 30 days of treatment completion. Patients with repeat urine cultures were considered microbiologically evaluable; microbiological cure was defined as a negative culture during or at completion of therapy and/or the absence of relapse or reinfection [9]. Relapse occurred when the same organism was recultured from the urine, while reinfection was the occurrence of a UTI with a different organism within 30 days [9].

Susceptibility testing was conducted in the clinical microbiology laboratory. With the exception of fosfomycin, Vitek 2 (bioMerieux Inc., Durham, N.C., USA) was used to determine antimicrobial susceptibility. Fosfomycin was tested upon request using disk diffusion and the results for all species were interpreted according to criteria for *E. faecalis* and *E. coli* (zone diameter ≥16 mm as susceptible) [2, 14, 15].

Table 1. Clinical characteristics of the study patients (n = 57)

Male	19 (33.3)
Age, years	79 (24–100)
Hospital length of stay, days	6 (1–378)
Comorbidities	
Recurrent UTI	28 (49.1)
Diabetes mellitus	20 (35.1)
Hematology/oncology disorder	16 (28.1)
Chronic kidney disease	15 (26.3)
Solid organ transplant	9 (15.8)
Immunosuppression[1]	6 (10.5)
Positive urinalysis[2]	57 (100)
Functional or anatomic urinary tract abnormality	
Foley or suprapubic catheter	27 (47.4)
Documentation of catheter change/removal	19 (70.4)
Neurogenic bladder	4 (7.0)
Renal stents	3 (5.3)
Receipt of active antimicrobial combination therapy[3]	16 (28.1)

Data are presented as n (%) or median (range).

[1] Defined as receipt of prednisone ≥10 mg daily (or equivalent) for at least 1 month, or receipt of other immunosuppressive agents.

[2] Positive urinalysis was defined as >5 white blood cells/high-powered field or the presence of leukocyte esterase.

[3] Antibiotic therapy with ≥1 agent with in vitro activity against urinary pathogen initiated concomitantly or following fosfomycin.

Results

A total of 57 patients were included; all patients had either complicated (n = 44; 77.2%) or MDR (n = 36; 63.2%) UTIs. Twenty-three patients (40.4%) had a UTI that was both complicated and MDR. Most patients were female (n = 38; 66.7%) with a median age of 79 years (range 24–100). The clinical characteristics of the patients are presented in table 1.

The distribution of uropathogens is shown in table 2. Thirty-six patients (63.2%) had at least 1 MDR organism isolated, and of these 36 patients 3 had 2 MDR organisms isolated. Fosfomycin susceptibility testing was performed for 31 isolates in 28 patients; 30 (96.8%) were susceptible (zone of inhibition ≥16 mm). Twenty-three tested isolates were MDR: 15 *E. coli*, 3 *P. aeruginosa*, 3 VRE, 1 *K. pneumoniae*, and 1 *Proteus* spp. Eight isolates were non-MDR: 3 *Enterococcus* spp., 3 *E. coli*, and 2 *P. aeruginosa*. The isolate that was resistant to fosfomycin was an otherwise pan-susceptible *P. aeruginosa*.

Table 2. Pathogens isolated from urine and fosfomycin susceptibility data

Organism/susceptibility	All patients (n = 57)	Complicated cases (n = 44)	MDR cases (n = 36)
>1 organism	10 (17.5)	8 (18.2)	6 (16.7)
E. coli	28 (49.1)	16 (36.4)	22 (61.1)
NS to at least one 3GC	16 (57.1)	6 (37.5)	16 (72.7)
Enterococcus spp.	22 (38.6)	20 (45.5)	10 (27.8)
VRE	8 (36.4)	7 (35)	8 (80)
P. aeruginosa	8 (14.0)	8 (18.2)	6 (16.7)
NS to carbapenem	6 (75)	6 (75)	6 (100)
Klebsiella spp.	3 (5.3)	3 (6.8)	1 (2.8)
NS to at least one 3GC	1 (33.3)	1 (33.3)	1 (100)
Proteus spp.	3 (5.3)	2 (4.5)	2 (5.6)
Alpha-hemolytic *Streptococcus*	2 (3.5)	2 (4.5)	0 (0)
Morganella spp.	1 (1.8)	1 (2.3)	1 (2.8)
NS to at least one 3GC	1 (100)	1 (100)	1 (100)
Fosfomycin susceptibility tested	28 (49.1)	21 (47.7)	22 (61.1)
Susceptible to fosfomycin	27 (96.4)	20 (95.2)	22 (100)

Data are presented as n (%). NS = Nonsusceptible; 3GC = third-generation cephalosporin.

Table 3. Patient outcomes following fosfomycin treatment

	All patients (n = 57)	Complicated (n = 44)	MDR (n = 36)	Combination therapy[1] (n = 16)	3 g by mouth ×1 dose (n = 26)
Clinically evaluable	28 (49.1)	24 (54.5)	18 (50)	6 (37.5)	11 (42.3)
Clinical success[2]	27 (96.4)	23 (95.8)	17 (94.4)	5 (83.3)	11 (100)
Microbiologically evaluable	20 (35.1)	16 (36.4)	13 (36.1)	7 (43.8)	10 (38.5)
Microbiological cure[3]	15 (75)	12 (75)	9 (69.2)	4 (57.1)	8 (80)
UTI relapse[3]	2 (10)	1 (6.3)	2 (15.4)	1 (14.3)	0 (0)
UTI reinfection[3]	3 (15)	3 (18.8)	2 (15.4)	2 (28.6)	2 (20)

Data are presented as n (%).
[1] Antibiotic therapy with ≥1 agent with in vitro activity against urinary pathogen initiated concomitantly or following fosfomycin.
[2] Of clinically evaluable patients.
[3] Of microbiologically evaluable patients.

The reasons for fosfomycin use varied and were multifactorial. When documented, the most common reasons included: MDR organism with limited options (n = 27; 47.3%), multiple allergies (n = 11; 19.3%), avoidance of intravenous antibiotics (n = 5; 8.8%), and per ID recommendation (n = 5; 8.8%). The most common fosfomycin regimens were 3 g by mouth (p.o.) once (n = 26; 45.6%; 20 complicated and 16 MDR) and 3 g p.o. for 3 doses (n = 20; 35.1%; 16 complicated and 13 MDR). Other regimens prescribed included 3 g p.o. for 2, 4, or 5 doses, and 3 g p.o. once per week. Doses were generally given every 48–72 h. Patients received an average of 1.4 doses while in the hospital. Combination therapy (i.e. initiated concomitantly or following fosfomycin) with antibiotics having in vitro activity against the urinary pathogen was used in 16 patients (28.1%; 13 complicated and 9 MDR) and included gentamicin, ceftriaxone, ceftazidime, cefepime, meropenem, piperacillin-tazobactam, and vancomycin.

Descriptive statistics of patient outcomes are presented in table 3. Twenty-eight patients (49.1%) were clinically evaluable. All but 1 patient (96.4%) had documented

clinical success. The patient who experienced clinical failure had a complicated UTI caused by MDR *P. aeruginosa* and received combination therapy with cefepime. He was a male with a Foley catheter and a history of recurrent UTIs. Follow-up cultures were collected on days 4 and 27 after the index culture (3 and 26 days after fosfomycin treatment), and the culture collected on day 27 revealed reinfection with *K. pneumoniae*. Twenty of the 29 patients (69%) who were not clinically evaluable received fosfomycin on the day of discharge and were therefore lost to follow-up. Resolution or persistence of urinary symptoms was undocumented for the remaining 9 patients and therefore were not included in the clinically evaluable group.

Since repeat urine cultures for test of cure was not standard practice, only 20 patients (35.1%) were microbiologically evaluable. Overall, microbiological cure was achieved in 75% (15 of 20 patients), while 2 patients had a relapse (1 *P. aeruginosa* and 1 VRE). The 3 patients with reinfection had UTIs caused by *P. aeruginosa* (n = 2) and VRE (n = 1). One of the patients with *P. aeruginosa* was the patient described above with clinical failure; the other was a male who suffered a reinfection with $>10^5$ organisms/ml of Gram-positive bacteria (alpha hemolytic colonies) 23 days after treatment with fosfomycin. The patient with VRE was a male who had reinfection with *K. pneumoniae* and *E. coli* 11 days after treatment with fosfomycin.

Discussion

As antibiotic resistance among uropathogens increases, fewer oral drugs retain their activity [1, 9, 11], creating the need for outcome data following treatment with agents effective against MDR pathogens. Limited clinical data examining the use of fosfomycin for complicated or MDR UTI treatment are available [9, 10, 12].

Of the 57 fosfomycin-treated patients in this study, 36 (63.2%) had an MDR UTI. Forty-four (77.2%) were male or had complicating factors; 23 of those had an MDR pathogen isolated. It is also important to note that 54 patients were >45 years of age and 42 patients were >65 years of age. Although not included in our definition, many clinicians may consider postmenopausal women to have a complicated UTI, as the IDSA guidelines for uncomplicated UTI include only premenopausal women [3].

Clinical success and microbiological cure were common in patients with complicated UTIs and MDR pathogens isolated. The rate of microbiological cure in patients with an MDR pathogen was comparable to that observed by Neuner et al. [9] (59%; 24% relapse and 17% reinfection) in a retrospective study of 41 patients treated with fosfomycin for MDR UTIs. These success rates were similar to an observational, prospective study that found no difference between fosfomycin (3 g every 48 h for 3 doses) and carbapenems (meropenem 1 g every 8 h or imipenem-cilastatin 500 mg every 6 h for 14 days) for ESBL-producing *E. coli*-complicated UTIs [12]. Clinical (77.8 vs. 95%; $p > 0.05$) and microbiological (59.2 vs. 80%; $p > 0.05$) response rates were similar for the fosfomycin and carbapenem groups, respectively.

A recent retrospective study by Sastry et al. [16] also reported clinical characteristics and outcomes of hospitalized patients treated with fosfomycin for physician-diagnosed UTIs (n = 239) and National Healthcare Safety Network (NHSN)-defined UTIs (n = 89). Our clinical success rates were similar to those with NHSN-defined UTIs (89.9%), of which most were considered complicated. Another study retrospectively evaluated fosfomycin use in 71 hospitalized patients with UTIs; 31% were male and 38% had an invasive urinary device. They defined UTI cure based on both clinical and microbiological outcomes and found comparable success rates (83%) [17].

Susceptibility to fosfomycin was only tested in a minority of isolates since testing is done by clinician request; however, 30 of 31 (96.8%) tested isolates were susceptible, including all of the MDR tested isolates (n = 23). No quantitative MICs were available as disk diffusion was utilized by the clinical microbiology laboratory. A recent fosfomycin susceptibility study conducted by our group of 323 prospectively collected urine isolates from hospitalized or emergency department patients demonstrated that nonsusceptibility to fosfomycin (MIC >64 mg/l) using agar dilution was uncommon (<6%) [18]. Fosfomycin has also demonstrated consistent activity against MDR and ESBL-producing isolates collected from our institution using agar dilution testing [19].

The FDA-approved dose of fosfomycin for uncomplicated UTIs due to *E. coli* and *E. faecalis* is 3 g p.o. once [5]. This was the most common dosing regimen utilized during this study (n = 26; 45.6%). A consensus on the appropriate regimen for complicated UTIs is lacking; however, the common alternative regimens prescribed here have been utilized previously with some success [10, 20].

This study has several limitations. First, as a small, retrospective, single-center study that included mostly el-

derly and female patients, our findings may not be generalizable. Fosfomycin regimens were not standardized as dosing was at the discretion of the treating physicians. The documentation of urinary symptoms may have been unreliable and could have underestimated symptomatic UTI patients. Lastly, only a small number of patients were clinically or microbiologically evaluable due to the receipt of fosfomycin just prior to discharge, or lack of follow-up urine cultures, respectively.

In conclusion, these real-world data add to the limited clinical literature exploring alternative oral therapies for complicated and MDR UTIs. Larger studies are needed to validate these results, but our study indicates that fosfomycin may be effective for patients with complicated or MDR UTIs.

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Statement of Ethics

This study was approved by the Institutional Review Board at Beth Israel Deaconess Medical Center (BIDMC; Boston, Mass., USA). Owing to the retrospective nature of the study, informed consent from patients was waived.

Disclosure Statement

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