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Clinical Appraisal of Fosfomycin in the Era of Antimicrobial Resistance

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Fosfomycin is recommended as one of the first-line agents for treatment of urinary tract infections (UTIs) in the latest guidelines endorsed by the Infectious Diseases Society of America (IDSA) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID). We evaluated the use of fosfomycin among inpatients at a tertiary care hospital between 2009 and 2013. UTI cases were defined using physician diagnosis and the National Healthcare Safety Network (NHSN) surveillance definitions. The number of patients treated with fosfomycin increased from none in 2009 to 391 in 2013. Among 537 patients who received fosfomycin for any indication during this period, UTI was the most common indication (74%), followed by asymptomatic bacteriuria (10%). All except 19 patients received a single dose of fosfomycin. *Escherichia coli* was the most common organism involved (52%). For 119 patients with UTIs, after exclusion of those with negative urine culture results, negative urinalysis results, receipt of additional agents, or indeterminate clinical outcomes, the clinical success rate at 48 h was 74.8%. Of 89 patients who met the criteria for NHSN-defined UTIs, 89.9% had successful outcomes. Recurrent infections occurred in 4.3% of cases, and mild adverse events were observed in 2.0%. All 100 randomly selected extended-spectrum β-lactamase (ESBL)-producing *E. coli* clinical isolates from this period were susceptible to fosfomycin. In conclusion, the use of fosfomycin has increased substantially since implementation of the updated guidelines at this hospital. Fosfomycin was used mainly for the treatment of physician-diagnosed UTIs, and the clinical outcomes were generally favorable. Fosfomycin maintained activity against *E. coli* despite the increased use of the agent.

One of every three women experience at least one episode of urinary tract infection (UTI) requiring the use of an antimicrobial agent by early adulthood, with most of the UTIs being caused by *Escherichia coli* (1, 2). U.S. surveillance data indicate the rapid emergence of *E. coli* resistance to oral antimicrobial agents commonly used to treat UTIs (3). Hence, there is an increasing need to identify new treatment options or to reevaluate existing agents for the treatment of UTIs. In this context, there has been renewed interest in fosfomycin, an agent that was first discovered in 1969 (4). Its activity against *E. coli* and some other *Enterobacteriaceae* species, including multidrug-resistant (MDR) strains, has been maintained despite more than four decades of use (5–7). Although there are reports of emerging fosfomycin resistance in *E. coli* (8), recent surveillance studies from North America have demonstrated rates of *in vitro* fosfomycin activity against *E. coli* exceeding 95% (5, 9).

Due to its unique broad-spectrum activity, fosfomycin has been widely used as both oral and intravenous formulations for various indications outside the United States, whereas it has been approved only as an oral formulation (fosfomycin tromethamine) for the treatment of uncomplicated UTIs in the United States. Fosfomycin is typically prescribed as a one sachet-one time only medication. In 2011, the Infectious Diseases Society of America (IDSA) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) updated their guidelines for the treatment of acute uncomplicated UTIs and pyelonephritis in women, recommending fosfomycin as one of the first-line agents for the treatment of uncomplicated UTIs (10). In that document, the use of fosfomycin was endorsed primarily on the basis of historic *in vitro* and clinical data. However, how this recommendation has affected clinical practice and patient outcomes has not been well documented. Therefore, we sought to elucidate recent trends in the use of fosfomycin, its indications, and the clinical outcomes of hospitalized patients treated with this agent at a large teaching hospital in the United States.

MATERIALS AND METHODS

Study design and patients. We conducted a retrospective cohort study of hospitalized patients who received fosfomycin at the University of Pittsburgh Medical Center Presbyterian (Pittsburgh, PA) between January 2009 and December 2013. The hospital has more than 750 medical and surgical beds (including approximately 150 critical care beds), with an average of 32,000 inpatient admissions per year. The study period was selected to capture the use of this agent before and after the release of the IDSA/ESCMID guidelines in March 2011. Initial screening was conducted by querying the electronic medical records of patients who were prescribed fosfomycin tromethamine and actually received at least one dose during their hospitalization. Only patients who were admitted to acute care units were included. Therefore, patients who received fosfomycin in the emergency department, in-hospital rehabilitation units, and skilled nursing facilities were excluded. The medical records of patients who met the aforementioned inclusion criteria were then reviewed to identify baseline demographics, underlying comorbid conditions (with Charlson co-

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morbidity index scores), indications for treatment, type of infection (if present), dosing of fosfomycin, concurrent antimicrobial use, microbiological data, clinical outcomes at 48 h, and adverse events related to the use of fosfomycin. The types of infections were determined according to the standard definitions set forth by the National Healthcare Safety Network (NHSN) (11). Causative organisms were classified as multidrug resistant (MDR) if resistance to three or more classes of agents was documented (12). The inpatient and outpatient electronic medical record systems were then screened for follow-up visits, to identify recurrent infections that occurred within 30 days after the receipt of fosfomycin. If a patient received fosfomycin during more than one hospital admission and the second infection occurred within 30 days after receipt of the first dose of this agent, then the patient was deemed to have a recurrent infection. If the patient was given fosfomycin again after the 30-day window, then that episode was considered unique. Data were collected and managed using REDCap electronic data capture tools hosted at the University of Pittsburgh (13). The study was approved by the institutional review board at the University of Pittsburgh (protocol PRO14060634).

Definitions. A case was defined as a physician-diagnosed UTI if the patient received fosfomycin for a presumed or confirmed UTI, as determined by the treating physician (14). A fosfomycin-treated UTI was defined as a physician-diagnosed UTI without negative urine culture results, negative urinalysis results, or receipt of additional antimicrobial agents after the UTI diagnosis. In addition, among the patients with positive urine culture results, defined as the presence of $\geq 10^5$ CFU/ml of one or two UTI-causing organisms, with the exclusion of *Candida albicans*, criteria specified by the NHSN were used to define those with NHSN-defined UTIs. For this purpose, we used the NHSN definitions for symptomatic UTIs (SUTIs) and catheter-associated UTIs (CAUTIs) that were in effect before the definition change in January 2013 and required the lack of an alternative source of fever to improve the specificity of the diagnosis (http://www.cdc.gov/nhsn/PDFs/Newsletters/January-2013-PSC-Updates.pdf). Positive urinalysis results were defined as white blood cell counts of >5 cells per high-power field. Complicated UTIs were defined as UTI cases meeting any of the following criteria: hospital-acquired infection, presence of diabetes mellitus, moderate or severe renal disease, or urinary tract obstruction, presence of an indwelling catheter, stent, or nephrostomy, history of recent urological procedures, renal transplantation, or presence of immunosuppression.

The primary outcome was defined as a clinical response after 48 h of treatment. Patients were deemed to be cured if they had resolution of clinical symptoms (dysuria, frequency, and urgency) and signs (temperature between 36.0°C and 38.0°C, white blood cell count between $3{,}000 \times 10^6$ and $10{,}900 \times 10^6$ cells/ml, and systolic blood pressure of ≥90 mm Hg with the patient not receiving vasopressors), with or without negative urine culture results, after 48 h of treatment. The outcome was considered indeterminate if any of the aforementioned parameters were missing but the patient did well overall and was discharged from the hospital with a general feeling of well-being, as determined by the treating physician. These patients were then included in the final analysis as having clinical success. Failure to show improvement in the aforementioned clinical symptoms and signs, with or without the presence of persistent growth of the same organism in culture after 48 h of treatment, was defined as clinical failure.

The secondary outcomes were defined as recurrence of the same infection within 30 days after the date of receipt of fosfomycin, adverse events attributed to treatment with fosfomycin, and 30-day in-hospital mortality rates after treatment with fosfomycin. These outcomes were defined prior to data collection.

Susceptibility testing. Since fosfomycin susceptibility is not routinely tested, we randomly selected a total of 100 representative extended-spectrum β-lactamase (ESBL)-producing *E. coli* isolates (20 from each year of the study period) and tested them for fosfomycin susceptibility by the agar dilution method, using cation-adjusted Mueller-Hinton agar supplemented with 25 μg/ml of glucose-6-phosphate. The sources were urine (64 isolates), respiratory tract (18 isolates), wounds (14 isolates), and blood (4 isolates). The results were interpreted according to the breakpoints endorsed by the Clinical and Laboratory Standards Institute (CLSI) (15).

Statistical analyses. All statistical analyses were performed using SAS 9.3 software. Univariate logistic regression analysis was used to test for predictors of failure at 48 h. Variables that had univariate *P* values of ≤0.2 were eligible for inclusion in the multivariate model. Multivariate analysis was conducted using stepwise logistic regression and evaluation for confounding. Two-tailed *P* values of ≤0.05 were considered statistically significant.

RESULTS

Identification of fosfomycin-treated inpatients. A total of 760 unique patients had pharmacy orders for fosfomycin during the 5-year period between January 2009 and December 2013. Among them, 611 were admitted to acute care units, and actual administration of fosfomycin was documented for 548 patients. Among those 548 patients, 537 patients had adequate documentation of the hospital admissions available for this retrospective review (Fig. 1).

Trend in fosfomycin use. There was no fosfomycin use in 2009. However, there was a steady but substantial increase in the use of fosfomycin after the release of the IDSA/ESCMID guidelines. There were 3, 21, 180, and 563 patients for whom fosfomycin was ordered in the years 2010, 2011, 2012, and 2013, respectively, and receipt of at least one dose of fosfomycin was documented for 0, 16, 130, and 391 patients in those 4 years. This trend suggested robust uptake of the new IDSA/ESCMID guidelines at the hospital.

Demographics and indications for fosfomycin use. Of the 537 patients who received a dose of fosfomycin for any indication, 456 (85%) were female, 81 (15%) were male, and 451 (84%) were ≥50 years of age. The majority (402 patients [76%]) were on a regular ward, whereas 101 (19%) were in an intensive care unit and 29 (5%) were in a stepdown unit. Also, 162 patients (30%) had urinary catheters in place for >48 h prior to the administration of fosfomycin, 111 (21%) had central intravenous catheters in place, 99 (18%) were receiving immunosuppressive agents, 25 (5%) had received solid-organ transplants, and 93 (18%) had undergone surgery within the prior 30 days. The range of patients with comorbid conditions included 305 patients (57%) with Charlson comorbidity index scores between 0 and 5, 215 patients (40%) with scores between 5 and 10, and 15 patients (3%) with scores of ≥11. In terms of the acquisition location, using the criteria of Friedman et al. (16), 130 cases (24%) were community associated, 152 (28%) were health care associated, and 214 (40%) were hospital acquired. Among cases with positive urine culture results, the causative organism was *E. coli* in 52%, and 23% of all causative organisms met the definition of being MDR. The reported susceptibilities are shown in Table S1 in the supplemental material. For the group of patients with NHSN-defined UTIs, the causative organisms were found to be primarily *E. coli* (50/89 cases; 20 were MDR, including 7 ESBL producers), with the rest being *Klebsiella pneumoniae* (2 MDR and 1 possible extensively drug resistant [XDR], which was also an ESBL producer), *Proteus mirabilis* (2 MDR), *Enterobacter* spp. (4 MDR), *Enterococcus* spp. (5 MDR), *Citrobacter freundii* (1 MDR), *Morganella morganii* (1 MDR), *Pseudomonas aeruginosa* (1 non-MDR), and *Serratia marcescens* (1 non-MDR).

Among the 537 patients in the study group, 396 (74%) received fosfomycin for an indication of UTI determined by the treating

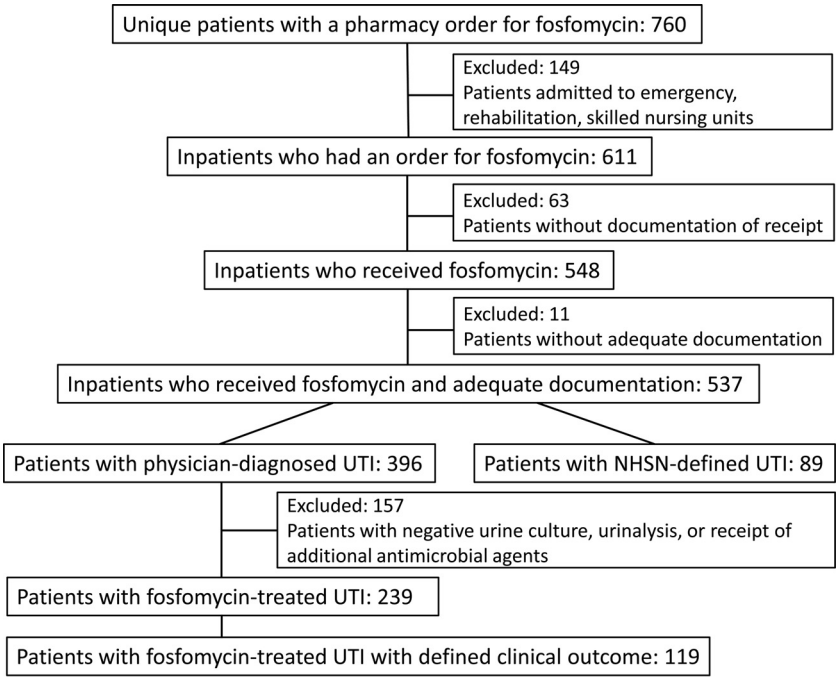

FIG 1 Flowchart of patients included in the study.

physician (physician-diagnosed UTI), 56 (10%) for asymptomatic bacteriuria, and 46 (9%) for an indication other than the aforementioned indications, such as fever, leukocytosis, or sepsis of uncertain etiology. Thirty-nine patients (7%) did not have a documented indication for treatment.

While fosfomycin is approved for use as a single dose, a total of 19 patients received more than one dose (12 with two doses and 7 with three doses). Three of the patients were dosed every 24 h, with one successful and two indeterminate clinical outcomes. Six of the patients were dosed every 48 h, with three successful and three indeterminate clinical outcomes. Ten of the patients were dosed every 72 h, with five successful and four indeterminate outcomes but with one clinical failure.

Clinical outcomes of patients with UTIs treated with fosfomycin. Among the 239 patients with fosfomycin-treated UTIs (i.e., physician-diagnosed UTIs after exclusion of those with negative urine culture results, negative urinalysis results, or receipt of additional antimicrobial agents), 89 had successful clinical outcomes, 120 had indeterminate outcomes (symptoms after treatment not documented or lost to follow-up monitoring), and 30 had clinical failures. Therefore, the overall clinical success rate was 74.8% when only those with known outcomes were considered (Table 1) and 87.5% when indeterminate outcomes were considered successes (see Table S2 in the supplemental material). The univariate risk factors associated with clinical failure included for both of these groups the presence of a central intravenous catheter for ≥48 h prior to the receipt of fosfomycin ($P = 0.07$ and $P = 0.02$, respectively) and a history of surgery within 30 days before the receipt of fosfomycin ($P = 0.002$ for both groups) and for the second group not being on a regular ward ($P = 0.08$). By stepwise multivariate logistic regression, a history of surgery within 30 days before the receipt of fosfomycin was independently associated with clinical failure in the fosfomycin-treated UTI group that included indeterminate clinical outcomes as success (odds ratio [OR], 3.68 [95% confidence interval [CI], 1.58 to 8.55]; $P = 0.002$) (see Table S2 in the supplemental material).

Eighty-nine subjects met the NHSN definition of symptomatic UTIs and/or catheter-associated UTIs (CAUTIs), which offered a more attributable cohort than physician-diagnosed UTIs. The clinical outcomes of these patients were found to be generally favorable also and comparable to the outcomes of patients who received fosfomycin for physician-diagnosed UTIs (Table 2). Eighty (89.9%) of 89 patients had successful clinical outcomes and only 9/89 patients (10.1%) met the criteria for clinical failure. All patients with clinical failures had complicated UTIs, and the outcomes were defined as failure mostly on the basis of persistent fever or leukocytosis (see Table S3 in the supplemental material). The univariate risk factors for clinical failure in this group of patients were similar to those in the physician-diagnosed UTI cohorts and included a history of surgery within 30 days before the receipt of fosfomycin ($P = 0.005$). Additionally, the presence of a urinary catheter for ≥48 h prior to the receipt of fosfomycin ($P = 0.04$) and use of a second agent along with fosfomycin for treatment of the UTI ($P = 0.02$) were identified as univariate risk factors for clinical failure in this group. Multivariate analysis was not performed for this NHSN-defined UTI group, due to the small number of patients who failed treatment.

Secondary outcomes. Secondary outcomes were evaluated for all study patients. The recurrence of infection occurred within 30 days for 4.3% of the patients (23/537 patients). The rate of adverse events attributed to fosfomycin treatment was 2.0% (11/537 patients). All cases of adverse events were mild and involved gastrointestinal symptoms. Of the 11 patients, 2 had nausea, 6 had diarrhea, 2 had both nausea and diarrhea, and 1 had abdominal cramping. These adverse events all occurred within 24 h after the receipt of fosfomycin, were mild, and resolved spontaneously

TABLE 1 Univariate analysis of clinical failure at 48 h for patients with fosfomycin-treated UTIs[a]

Variable	No. (%)		OR (95% CI)	*P*
	Failure ($n = 30$)	Success ($n = 89$)		
Male	4 (13.3)	8 (9.0)	1.56 (0.43–5.60)	0.50
Transfer from another hospital	14 (48.3)	31 (36.5)	1.63 (0.69–3.81)	0.26
Central intravenous catheter	11 (36.7)	18 (20.2)	2.28 (0.92–5.64)	0.07
Urinary catheter	9 (30.0)	25 (28.1)	1.10 (0.44–2.72)	0.84
Transplant recipient	1 (3.3)	3 (3.4)	0.99 (0.10–9.88)	0.99
Recent surgery	11 (36.7)	9 (10.2)	5.08 (1.84–14.00)	0.002
Immunosuppressants	5 (16.7)	18 (20.2)	0.79 (0.27–2.35)	0.67
Recent antimicrobial use	10 (33.3)	26 (29.2)	1.21 (0.50–2.94)	0.67
ESBL producer	2 (9.1)	5 (7.1)	1.30 (0.23–7.22)	0.76
E. coli	11 (50.0)	38 (52.8)	0.89 (0.34–2.33)	0.82
Complicated UTI	25 (83.3)	67 (75.3)	1.64 (0.56–4.81)	0.37
Race				0.66
White	25 (83.3)	66 (74.2)	Baseline	
Black	3 (10.0)	16 (18.0)	0.55 (0.16–1.97)	
Other/unknown	2 (6.7)	7 (7.9)	0.87 (0.18–4.21)	
Age				0.50
18–34 y	4 (13.3)	5 (5.6)	Baseline	
35–49 y	2 (6.7)	8 (9.0)	0.36 (0.05–2.60)	
50–74 y	14 (46.7)	37 (41.6)	0.47 (0.11–2.01)	
≥75 y	10 (33.3)	39 (43.8)	0.33 (0.07–1.43)	
Floor				0.21
Ward	20 (66.7)	65 (73.0)	Baseline	
Intensive care unit	5 (16.7)	19 (21.3)	0.90 (0.30–2.67)	
Stepdown	5 (16.7)	5 (5.6)	3.19 (0.84–12.15)	
Charlson comorbidity index				0.28
0–5	20 (66.7)	43 (49.4)	Baseline	
6–10	10 (33.3)	38 (43.7)	0.58 (0.24–1.38)	
≥11	0 (0.0)	6 (6.9)	0.16 (<0.01–3.82)	
Type of infection				0.16
Community associated	5 (16.7)	30 (33.7)	Baseline	
Health care associated	6 (20.0)	22 (24.7)	1.60 (0.45–5.76)	
Hospital acquired	19 (63.3)	34 (38.2)	3.13 (1.07–9.21)	
Unknown	0 (0.0)	3 (3.4)	0.79 (0.02–27.40)	
MDR	6 (20.0)	18 (20.2)	1.03 (0.37–2.85)	0.96

[a] Physician-diagnosed UTIs were considered after exclusion of cases with negative urine culture results, negative urinalysis results, or concurrent use of agents other than fosfomycin. Indeterminate clinical outcomes also were excluded.

within 24 to 48 h after the onset of symptoms. None of the patients experienced adverse events related to anaphylaxis, skin rash, or *Clostridium difficile* infection. The rate of in-hospital deaths at 30 days was 1.9% (10/537 patients), but all deaths were due to underlying medical conditions and none was associated with the conditions for which fosfomycin was administered.

Susceptibility of ESBL-producing *E. coli* isolates. The ESBL-producing *E. coli* isolates that were randomly selected from the years 2009, 2010, 2011, 2012, and 2013 (20 isolates from each year) had MICs of ≤2, ≤4, ≤16, ≤4, and ≤2 μg/ml, respectively. The MIC_{50} and MIC_{90} were 1 μg/ml and 2 μg/ml, respectively, across the years. Using the CLSI susceptibility breakpoint of 64 μg/ml, all 100 isolates thus were susceptible to fosfomycin.

DISCUSSION

Fosfomycin represents a potentially reliable treatment option for uncomplicated UTIs, both as empirical therapy and as definitive therapy for most organisms, particularly the drug-resistant variety, given the emerging reports on the observed efficacy of fosfomycin against MDR/XDR organisms (17, 18). Historically, randomized controlled trials demonstrated no difference in clinical outcomes when UTIs were treated with fosfomycin or a comparator (19). However, contemporary data on the use and efficacy of fosfomycin are scarce, especially for fosfomycin tromethamine, which is the only formulation approved for use in the United States. Our study was initiated on the basis of anecdotal observations that an increasing number of inpatients were being treated for UTIs with fosfomycin.

We found that the use of fosfomycin at this center increased substantially over the past 5 years and this was temporally associated with the release by the IDSA and the ESCMID of the updated guidelines for the treatment of uncomplicated UTIs. The indications for fosfomycin use were mostly treatment of uncompli-

TABLE 2 Univariate analysis of clinical failure at 48 h for subjects with NHSN-defined UTIs

Variable	No. (%)		OR (95% CI)	*P*
	Failure ($n = 9$)	Success ($n = 80$)		
Male	2 (22.2)	14 (17.5)	1.35 (0.25–7.18)	0.73
Transfer from another hospital	5 (55.6)	27 (35.5)	2.27 (0.56–9.16)	0.25
Transfer from long-term-care facility	0 (0.0)	15 (28.3)	1.45[a] (0.21 to infinity)	0.77
Hospitalization in past 90 days	2 (22.2)	31 (38.8)	0.45 (0.09–2.32)	0.34
Hospital clinic visit in past 90 days	2 (22.2)	26 (33.8)	0.56 (0.11–2.89)	0.49
Central intravenous catheter	5 (55.6)	21 (26.6)	3.45 (0.85–14.09)	0.08
Urinary catheter	6 (66.7)	24 (30.0)	4.67 (1.08–20.22)	0.04
Transplant recipient	1 (11.1)	4 (5.1)	2.34 (0.23–23.60)	0.48
Recent surgery	6 (66.7)	15 (19.0)	8.53 (1.91–38.08)	0.005
Immunosuppressants	1 (11.1)	14 (17.5)	0.59 (0.07–5.10)	0.63
Concurrent antimicrobial therapy	5 (55.6)	15 (18.8)	5.42 (1.30–22.63)	0.02
Recent antimicrobial use	2 (22.2)	30 (37.5)	0.48 (0.09–2.44)	0.37
Complicated UTI	9 (100.0)	63 (78.8)	0.31[a] (0.0–1.62)	0.27
ESBL producer	0 (0.0)	8 (10.0)	1.31[a] (0.24 to infinity)	0.82
Species				0.41
E. coli	5 (55.6)	45 (56.3)	Baseline	
K. pneumoniae	0 (0.0)	12 (15.0)	0.33 (0.02–7.16)	
P. mirabilis	0 (0.0)	8 (10.0)	0.49 (0.02–11.41)	
Enterobacter spp.	2 (22.2)	2 (2.5)	8.27 (0.96–71.31)	
Enterococcus spp. (non-VRE)[b]	0 (0.0)	6 (7.5)	0.64 (0.03–16.13)	
Enterococcus spp. (VRE)	1 (11.1)	1 (1.3)	8.27 (0.45–152.21)	
P. aeruginosa	0 (0.0)	1 (1.3)	2.80 (0.03–277.72)	
Other	1 (11.1)	5 (6.3)	2.26 (0.26–19.27)	
Positive urinalysis results	9 (100.0)	68 (88.3)	0.64[a] (0.0–3.51)	0.70
Race				0.21
White	6 (66.7)	68 (85.0)	Baseline	
Black	1 (11.1)	7 (8.8)	2.11 (0.28–16.02)	
Other/unknown	2 (22.2)	5 (6.3)	4.79 (0.80–28.75)	
Age				0.84
18–34 y	1 (11.1)	9 (11.3)	Baseline	
35–49 y	2 (22.2)	10 (12.5)	1.51 (0.15–15.15)	
50–74 y	4 (44.4)	38 (47.5)	0.74 (0.09–5.80)	
≥75 y	2 (22.2)	23 (28.8)	0.67 (0.07–6.35)	
Floor				0.73
Ward	6 (66.7)	59 (74.7)	Baseline	
ICU	2 (22.2)	13 (16.5)	1.70 (0.34–8.52)	
Stepdown	1 (11.1)	7 (8.9)	1.83 (0.24–13.95)	
Estimated glomerular filtration rate				0.59
≥90 ml/min	4 (50.0)	30 (42.9)	Baseline	
60–89 ml/min	2 (25.0)	10 (14.3)	1.61 (0.28–9.30)	
30–59 ml/min	1 (12.5)	23 (32.9)	0.43 (0.06–3.08)	
15–29 ml/min	1 (12.5)	2 (2.9)	4.07 (0.32–51.75)	
<15 ml/min	0 (0)	5 (7.1)	0.62 (0.02–17.16)	
Charlson comorbidity index				0.80
0–5	7 (77.8)	50 (63.3)	Baseline	
6–10	2 (22.2)	27 (34.2)	0.61 (0.13–2.82)	
≥11	0 (0.0)	2 (2.5)	1.35 (0.03–60.11)	
Type of infection				0.19
Community associated	1 (11.1)	20 (25.0)	Baseline	
Health care associated	0 (0.0)	22 (27.5)	0.30 (0.01–8.49)	
Hospital acquired	8 (88.9)	38 (47.5)	3.02 (0.47–19.30)	
Drug resistance profile				0.77
Non-MDR	5 (55.6)	48 (60.0)	Baseline	
MDR	4 (44.4)	32 (40.0)	1.22 (0.32–4.65)	
Dosing of fosfomycin				0.89
Single dose	9 (100.0)	77 (96.3)	Baseline	
Every other day	0 (0.0)	1 (1.3)	2.70 (0.03–264.59)	
Every third day	0 (0.0)	2 (2.5)	1.63 (0.04–71.49)	

[a] Median unbiased estimate.
[b] VRE, vancomycin-resistant enterococci.

cated UTIs, but there was some off-label use of the agent for complicated UTIs (patients with indwelling catheters, obstructive uropathy, pyelonephritis, renal insufficiency, history of renal transplantation, diabetes mellitus, immunodeficiency, or fever, leukocytosis, or sepsis of undetermined origin).

The majority of the patients in this study who received fosfomycin for the treatment of UTIs were female, similar to the general population at risk for developing UTIs. The causative organism was identified as *E. coli* in the majority of cases, which also reflected the etiology of UTIs in the general adult population (2). There were equal mixtures of patients with and without comorbidities and also equal representation of community-associated, health care-associated, and hospital-acquired infections in the two cohorts investigated. Most of the study patients were being treated with fosfomycin for uncomplicated or complicated UTIs, making the findings applicable to clinical practice.

The overall clinical outcomes of the patients were favorable, with success rates of 75 to 90% for the various UTI cohorts examined. The nine patients in the NHSN-defined UTI group who experienced clinical failure were at increased risk for this outcome, with complicated UTIs and multiple serious comorbidities, but failure was defined mostly on the basis of the presence of persistent leukocytosis of unknown origin, which is a clinical scenario commonly encountered among hospitalized patients and may or may not be associated with UTIs; this possibly resulted in underestimation of the clinical success rate for this group.

The rates of adverse events related to oral fosfomycin treatment that have been reported in the literature vary between 3 and 6%, with the higher rate being observed for patients treated with more than one dose of fosfomycin (20, 21). Our study found a lower rate of adverse events, all of which were mild and transient; this was expected, given the single-dose regimen, but was reassuring. However, the convenient dosing schedule and favorable safety profile may have disadvantages as well as advantages. In our study, 396 patients were given fosfomycin for treatment of physician-diagnosed UTIs, and only 89 patients met the NHSN criteria for symptomatic UTIs and/or CAUTIs. The potential for overtreatment of possible UTIs may become an issue for antimicrobial stewardship in hospitals, as we have fewer and fewer oral options for the treatment of UTIs that are reliable. It is reassuring that our survey of fosfomycin susceptibility during the same period did not identify fosfomycin-resistant isolates, but resistance to fosfomycin by means of MurA substitution or overexpression, loss of the transporters UhpT and GlpT, and production of Fos group-inactivating enzymes has been well described (22). In particular, plasmid-borne *fosA3* is being increasingly observed in East Asia (23, 24) and may eventually make its way to the United States. The absence of routine susceptibility testing for this agent increases the risk that the emergence of such resistant isolates may not be identified in a timely manner.

Our study has several limitations. It was a retrospective single-center study; therefore, the findings may not be directly applicable to other centers. In addition, the single-arm study design precluded comparisons of efficacies. However, given the very high clinical success rates of 75 to 90% with fosfomycin, which were comparable to the historic clinical success rates for antimicrobial treatment of UTIs (20, 25), the additional value of having a comparator arm would have been modest. We also limited our analysis to inpatients, since the general lack of follow-up data made it difficult to study outpatients retrospectively; this would require a prospective approach. In addition, we were not able to assess microbiological cures systematically, since testing of cure cultures for UTIs is not generally recommended and therefore data were not available for the majority of the subjects. Finally, we were not able to collect and to test the susceptibility of the actual isolates that were treated with fosfomycin or to test for microbiological cures, which also would require a prospective study design.

In conclusion, the use of fosfomycin has increased substantially since implementation of the updated IDSA treatment guidelines at this hospital. Despite this surge in use, fosfomycin was used primarily for the treatment of uncomplicated UTIs, which is the approved indication. Whether physician-diagnosed UTI or NHSN-defined UTI was used for case definition, the clinical outcomes were favorable. Fosfomycin maintained excellent activity against *E. coli* despite the increased use of the agent. However, mechanisms for prudent use and monitoring of susceptibility are needed if we are to preserve this agent in the future.

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REFERENCES

1. **Foxman B.** 2002. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med **113**(Suppl 1A)**:**5S–13S.
2. **Foxman B.** 2010. The epidemiology of urinary tract infection. Nat Rev Urol **7:**653–660. http://dx.doi.org/10.1038/nrurol.2010.190.
3. **Sanchez GV, Master RN, Karlowsky JA, Bordon JM.** 2012. In vitro antimicrobial resistance of urinary *Escherichia coli* isolates among U.S. outpatients from 2000 to 2010. Antimicrob Agents Chemother **56:**2181–2183. http://dx.doi.org/10.1128/AAC.06060-11.
4. **Michalopoulos AS, Livaditis IG, Gougoutas V.** 2011. The revival of fosfomycin. Int J Infect Dis **15:**e732–e739. http://dx.doi.org/10.1016/j.ijid.2011.07.007.
5. **Johnson JR, Drawz SM, Porter S, Kuskowski MA.** 2013. Susceptibility to alternative oral antimicrobial agents in relation to sequence type ST131 status and coresistance phenotype among recent *Escherichia coli* isolates from U.S. veterans. Antimicrob Agents Chemother **57:**4856–4860. http://dx.doi.org/10.1128/AAC.00650-13.
6. **Sorlozano A, Jimenez-Pacheco A, de Dios Luna Del Castillo J, Sampedro A, Martinez-Brocal A, Miranda-Casas C, Navarro-Mari JM, Gutierrez-Fernandez J.** 2014. Evolution of the resistance to antibiotics of bacteria involved in urinary tract infections: a 7-year surveillance study. Am J Infect Control **42:**1033–1038. http://dx.doi.org/10.1016/j.ajic.2014.06.013.
7. **Endimiani A, Patel G, Hujer KM, Swaminathan M, Perez F, Rice LB, Jacobs MR, Bonomo RA.** 2010. *In vitro* activity of fosfomycin against bla_{KPC}-containing *Klebsiella pneumoniae* isolates, including those nonsusceptible to tigecycline and/or colistin. Antimicrob Agents Chemother **54:**526–529. http://dx.doi.org/10.1128/AAC.01235-09.
8. **Karageorgopoulos DE, Wang R, Yu XH, Falagas ME.** 2012. Fosfomycin: evaluation of the published evidence on the emergence of antimicrobial resistance in Gram-negative pathogens. J Antimicrob Chemother **67:**255–268. http://dx.doi.org/10.1093/jac/dkr466.
9. **Karlowsky JA, Denisuik AJ, Lagace-Wiens PR, Adam HJ, Baxter MR, Hoban DJ, Zhanel GG.** 2014. *In vitro* activity of fosfomycin against *Escherichia coli* isolated from patients with urinary tract infections in Canada as part of the CANWARD surveillance study. Antimicrob Agents Chemother **58:**1252–1256. http://dx.doi.org/10.1128/AAC.02399-13.
10. **Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE.** 2011. International

clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis **52:**e103–e120. http://dx.doi.org/10.1093/cid/ciq257.

11. **Centers for Disease Control and Prevention.** 2015. Urinary tract infection (catheter-associated urinary tract infection [CAUTI] and non-catheter-associated urinary tract infection [UTI]) and (other urinary system infection [USI]) events. Centers for Disease Control and Prevention, Atlanta, GA. http://www.cdc.gov/nhsn/PDFs/pscManual/7pscCAUTIcurrent.pdf.
12. **Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL.** 2012. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect **18:**268–281. http://dx.doi.org/10.1111/j.1469-0691.2011.03570.x.
13. **Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG.** 2009. Research electronic data capture (REDCap): a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform **42:**377–381. http://dx.doi.org/10.1016/j.jbi.2008.08.010.
14. **van Duin D, Cober E, Richter SS, Perez F, Kalayjian RC, Salata RA, Evans S, Fowler VG, Jr, Kaye KS, Bonomo RA.** 2015. Impact of therapy and strain type on outcomes in urinary tract infections caused by carbapenem-resistant *Klebsiella pneumoniae*. J Antimicrob Chemother **70:**1203–1211.
15. **Clinical and Laboratory Standards Institute.** 2014. Performance standards for antimicrobial susceptibility testing; twenty-fourth informational supplement. Clinical and Laboratory Standards Institute, Wayne, PA.
16. **Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, Briggs JP, Lamm W, Clark C, MacFarquhar J, Walton AL, Reller LB, Sexton DJ.** 2002. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med **137:**791–797. http://dx.doi.org/10.7326/0003-4819-137-10-200211190-00007.
17. **Pontikis K, Karaiskos I, Bastani S, Dimopoulos G, Kalogirou M, Katsiari M, Oikonomou A, Poulakou G, Roilides E, Giamarellou H.** 2014. Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria. Int J Antimicrob Agents **43:**52–59. http://dx.doi.org/10.1016/j.ijantimicag.2013.09.010.
18. **Neuner EA, Sekeres J, Hall GS, van Duin D.** 2012. Experience with fosfomycin for treatment of urinary tract infections due to multidrug-resistant organisms. Antimicrob Agents Chemother **56:**5744–5748. http://dx.doi.org/10.1128/AAC.00402-12.
19. **Falagas ME, Vouloumanou EK, Togias AG, Karadima M, Kapaskelis AM, Rafailidis PI, Athanasiou S.** 2010. Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials. J Antimicrob Chemother **65:**1862–1877. http://dx.doi.org/10.1093/jac/dkq237.
20. **Moroni M.** 1987. Monuril in lower uncomplicated urinary tract infections in adults. Eur Urol **13**(Suppl 1)**:**S101–S104.
21. **Qiao LD, Zheng B, Chen S, Yang Y, Zhang K, Guo HF, Yang B, Niu YJ, Wang Y, Shi BK, Yang WM, Zhao XK, Gao XF, Chen M.** 2013. Evaluation of three-dose fosfomycin tromethamine in the treatment of patients with urinary tract infections: an uncontrolled, open-label, multicentre study. BMJ Open **3:**e004157. http://dx.doi.org/10.1136/bmjopen-2013-004157.
22. **Castañeda-García A, Blázquez J, Rodríguez-Rojas A.** 2013. Molecular mechanisms and clinical impact of acquired and intrinsic fosfomycin resistance. Antibiotics **2:**217–236. http://dx.doi.org/10.3390/antibiotics2020217.
23. **Ho PL, Chan J, Lo WU, Lai EL, Cheung YY, Lau TC, Chow KH.** 2013. Prevalence and molecular epidemiology of plasmid-mediated fosfomycin resistance genes among blood and urinary *Escherichia coli* isolates. J Med Microbiol **62:**1707–1713. http://dx.doi.org/10.1099/jmm.0.062653-0.
24. **Wachino J, Yamane K, Suzuki S, Kimura K, Arakawa Y.** 2010. Prevalence of fosfomycin resistance among CTX-M-producing *Escherichia coli* clinical isolates in Japan and identification of novel plasmid-mediated fosfomycin-modifying enzymes. Antimicrob Agents Chemother **54:**3061–3064. http://dx.doi.org/10.1128/AAC.01834-09.
25. **Rodriguez A, Gallego A, Olay T, Mata JM.** 1977. Bacteriological evaluation of fosfomycin in clinical studies. Chemotherapy **23**(Suppl 1)**:**247–258.