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ORIGINAL ARTICLE

Oral fosfomycin for the treatment of lower urinary tract infections among kidney transplant recipients—Results of a Spanish multicenter cohort

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Abbreviations: AB, asymptomatic bacteriuria; CI, confidence interval; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ESBL, extended-spectrum β-lactamase; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; GESITRA-IC, Spanish Group for the Study of Infection in Transplantation and the Immunocompromised Host; IDSA, Infectious Diseases Society of America; IQR, interquartile range; KTR, kidney transplant recipient; MDR, multidrug resistant; OR, odds ratio; REIPI, Spanish Network for Research in Infectious Diseases; REDINREN, Spanish Network for Research in Renal Diseases; SD, standard deviation; SEIMC, Spanish Society of Clinical Microbiology and Infectious Diseases; UTI, urinary tract infection; VRE, vancomycin-resistant *Enterococcus faecium*.

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Oral fosfomycin may constitute an alternative for the treatment of lower urinary tract infections (UTIs) in kidney transplant recipients (KTRs), particularly in view of recent safety concerns with fluroquinolones. Specific data on the efficacy and safety of fosfomycin in KTR are scarce. We performed a retrospective study in 14 Spanish hospitals including KTRs treated with oral fosfomycin (calcium and trometamol salts) for posttransplant cystitis between January 2005 and December 2017. A total of 133 KTRs developed 143 episodes of cystitis. Most episodes (131 [91.6%]) were produced by gram-negative bacilli (GNB), and 78 (54.5%) were categorized as multidrug resistant (including extended-spectrum β-lactamase-producing *Enterobacteriaceae* [14%] or carbapenem-resistant GNB [3.5%]). A median daily dose of 1.5 g of fosfomycin (interquartile range [IQR]: 1.5-2) was administered for a median of 7 days (IQR: 3-10). Clinical cure (remission of UTI-attributable symptoms at the end of therapy) was achieved in 83.9% (120/143) episodes. Among those episodes with follow-up urine culture, microbiological cure at month 1 was achieved in 70.2% (59/84) episodes. Percutaneous nephrostomy was associated with a lower probability of clinical cure (adjusted odds ratio: 10.50; 95% confidence interval: 0.98-112.29; $P = 0.052$). In conclusion, fosfomycin is an effective orally available alternative for treating cystitis among KTRs.

KEYWORDS
antibiotic, clinical research/practice, infection and infectious agents - bacterial, infectious disease, kidney transplantation/nephrology

1 | INTRODUCTION

Kidney transplant recipients (KTRs) constitute a high-risk group for the development of urinary tract infections (UTIs), as they present a combination of immunosuppression with structural modifications of the urinary tract, such as the presence of urethral catheters, double-J stents, or ureteral anastomosis.[1] Moreover, this combination of risk factors is present in a context of higher susceptibility to healthcare-associated infection by multidrug-resistant (MDR) bacteria in the early posttransplant period. A progressive increase in the incidence of UTI due to MDR has been demonstrated among KTRs over the last decade.[2] Such a trend might compromise the feasibility of programs of kidney transplantation and other solid organs in the following years. The recent US Food and Drug Administration (FDA) warning on the risk of severe adverse events associated with the use of fluoroquinolones (including aortic aneurysm development, aortic dissection, and rhegmatogenous retinal detachment) and the subsequent restriction in certain patient populations, limits even more the available armamentarium for the treatment of this frequent infection.[3-5] In addition, the overuse of fluoroquinolones among KTRs contributes to the emergence of *Clostridioides difficile* infection due to the nonselective impact on the gut microbiome exerted by this drug class. Unfortunately, the use of nitrofurantoin—a uroselective bacteriostatic agent—is associated with pulmonary toxicity and should be avoided in patients with creatinine clearance (CrCl) below 40 mL/min.[6]

Fosfomycin is a phosphonic acid derivative first isolated from diverse species of *Streptomyces* at the end of the 1960s.[7] This agent exerts a bactericidal activity due to a unique manner of action based in the irreversible inhibition of MurA. This enzyme is responsible for the first step in the peptidoglycan biosynthesis pathway by the production of UDP-*N*-acetylmuramic acid. This site of action differs completely from those of other antibiotics that also inhibit the synthesis of the bacterial cell wall as β-lactams or glycopeptides.[8,9]

This difference explains the minimal cross-resistance between fosfomycin and other types of antibiotics. Fosfomycin has a favorable safety profile, with usually transient and nonsevere adverse events. Furthermore, it shows no potential for drug-to-drug interactions with immunosuppressive agents. Two oral formulations have been developed, calcium salt and trometamol (or tromethamine) salt, which differ in their pharmacokinetic properties. Oral bioavailability and area under concentration-time curve are greater for the trometamol formulation, whereas the apparent volume of distribution and total body clearance are higher for the calcium salt.[10] Therefore, dosing regimens are not equivalent for both formulations. Following oral administration, 54%-65% of the absorbed dose of fosfomycin is recovered unaltered in the urine. No dose adjustment is needed in case of hepatic impairment, and it can be safely used in elderly and pregnant populations.[9] No dose adjustment is necessary in patients with renal impairment and CrCl above 10 mL/min when a single 3 g dose of fosfomycin trometamol is used for the treatment of cystitis.[11] There are no current recommendations for renal dose adjustment for multiple dose oral fosfomycin trometamol treatment, or recommendations for renal dosing adjustment for the calcium salt formulation.

Some studies have suggested that fosfomycin may play a role in the treatment of MDR bacteria including MDR *Pseudomonas aeruginosa*, extended-spectrum β-lactamase (ESBL)–producing *Enterobacteriaceae*, carbapenem-resistant *Klebsiella pneumoniae*, vancomycin-resistant *Enterococcus faecium* (VRE), and methicillin-resistant *Staphylococcus aureus*.[12-14] Nevertheless, and despite the above-mentioned advantages, available experience on the usefulness and safety of oral fosfomycin for the treatment of symptomatic UTI (mainly in the form of cystitis) or asymptomatic bacteriuria (AB) among KTRs are based on single-center series with a small number of cases [15-17] and poor representation of MDR strains. Thus the aim of the study was to assess the efficacy and safety of oral fosfomycin for the treatment of lower UTI in a large contemporary multicenter cohort of KTRs in Spain.

2 | PATIENTS AND METHODS

2.1 | Study design and setting

The present retrospective cohort study was developed in 14 Spanish hospitals with a dedicated program for kidney transplantation. The study was supported by the Spanish Network for Research in Infectious Diseases (REIPI), the Spanish Network for Research in Renal Diseases (REDinREN), and the Group for the Study of Infection in Transplantation and the Immunocompromised Host (GESITRA-IC) of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC). The study protocol was approved by the Ethics Committee for Clinical Research of the University Hospital "12 de Octubre" (Madrid, Spain) and by the local Ethics Committees of the other participating centers, as needed.

We included episodes of symptomatic lower UTI (cystitis) occurring in KTRs that were treated with oral fosfomycin between January 1, 2005 and December 31, 2017. Episodes of AB were excluded in accordance with the more recent recommendations endorsed by the Infectious Diseases Society of America (IDSA)[18] and the Infectious Diseases Community of Practice of the American Society of Transplantation.[6] Both clinical guidelines recommend against screening for or treating AB beyond the first [18] or second [6] month after kidney transplantation. Cystitis was defined by the presence of symptoms of lower UTI (dysuria, urgency, frequency) with simultaneous monomicrobial significant bacteriuria. Episodes in which an additional active agent (ie, showing in vitro activity against the isolated uropathogen and achieving adequate urine concentrations) was simultaneously administered or due to strains with in vitro nonsusceptibility to fosfomycin were excluded. We also excluded those episodes in which the patient had signs or symptoms suggestive of invasive UTI syndromes, including pyelonephritis (eg, fever, flank pain, abdominal pain, or swelling over the kidney graft), prostatitis in male patients, or UTI-associated bloodstream infection.[19] Susceptibility testing was performed at each participating center by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) method, and minimum inhibitory concentration values were interpreted according to the proposed clinical breakpoints,[20] or alternatively extrapolated for those microorganisms for which no interpretative categories have been established (ie, *Pseudomonas* spp).

Two different formulations of oral fosfomycin are currently available in Spain and other European countries: hard gelatin capsules containing 500 mg of calcium fosfomycin (marketed as "Fosfocina," "Fosfocin," or other trade names) or sachets containing 5631 mg of fosfomycin trometamol or tromethamine (equivalent to 3 g of fosfomycin) as water dispersible granules ("Monurol" or "Monural"). As previously stated, dosing regimens differ for both formulations. Calcium fosfomycin is usually given at 500-1000 mg every 8 hours for at least 5 days. Although the approved regimen in Spain and other European countries for the treatment of uncomplicated cystitis in women with the trometamol formulation is a 3 g single dose, multiple dose regimens for 2-3 days are often used in routine practice, despite the absence of specific dosing recommendations in the setting of renal dysfunction.[21] Both formulations were used in the present study according to individual preferences of physicians and patients.

Different search strategies were applied, according to the participating center, to identify oral fosfomycin prescriptions among eligible patients throughout the study period: (a) review of institutional database of KTRs, (b) data from prescription registers provided by the departments of pharmacy, and (c) automated search in electronic health records (EHRs). We used a standardized data collection form that included demographic and clinical characteristics as well as pre- and posttransplant variables. For each lower UTI episode, details on the presence of attributable symptoms and signs, microbiological data about the isolated uropathogen and in vitro susceptibility pattern, kidney graft function, type of immunosuppression, presence of urinary tract instrumentation, and clinical and microbiological outcomes were also recorded. Data were collected by local investigators

in an anonymized manner and introduced in a protected electronic database for analysis. All the episodes were reviewed individually by one of the coordinating investigators of the study to verify the fulfillment of inclusion and exclusion criteria. Cases with missing or incomplete data were excluded.

2.2 | Study definitions

"Significant bacteriuria" was defined by the isolation of a single bacteria strain in a spontaneously voided clean-catch urine specimen with quantitative counts ≥10^5 colony-forming units per milliliter.[22] "Clinical cure" was defined as the remission of UTI-attributable symptoms at the end of treatment. "Microbiological cure" was defined by the absence of the bacteria initially isolated (ie, same strain and similar susceptibility pattern or acquired resistance phenotype) in a urine culture obtained after the end of the treatment and within the first 30 days from lower UTI diagnosis. The uropathogen was categorized as MDR in the presence of nonsusceptibility to at least one agent in 3 or more antimicrobial categories according to the classification proposed by the European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention; intrinsic resistance was not taken into account.[23] The composite outcome "therapeutic failure" was created to capture the lack of clinical cure at the end of treatment and/or microbiological cure in the first month in episodes with follow-up urine culture performed within the appropriate time frame. Episodes were analyzed only once (ie, none of the episodes fulfilling the definition of "therapeutic failure" were newly entered into the study database). "Failure of previous antibiotic therapy" applied only to those episodes in which the isolated pathogen exhibited in vitro susceptibility to the agent administered prior to initiating the oral fosfomycin regimen. An adverse effect was defined as severe when it promoted fosfomycin to be stopped before scheduled, if it produced a permanent renal failure, or if the patient required hospital admission and/or intravenous drugs for its treatment. The graft function was assessed by estimated glomerular filtration rate (eGFR) using the abbreviated Modification of Diet in Renal Disease (MDRD-4) equation.

2.3 | Statistical analysis

Quantitative variables are shown as the mean ± standard deviation (SD) or the median with interquartile range (IQR). Qualitative data are expressed as absolute and relative frequencies. The chi-square test or Fisher's exact test was used to compare categorical variables, as appropriate. The Student's *t* test or Mann-Whitney *U* test was applied for continuous variables. Multivariate logistic regression models were used to identify factors predicting lack of clinical cure (for the overall number of episodes included) and therapeutic failure (for evaluable episodes only [ie, those with follow-up urine culture performed within the appropriate time frame from the completion of therapy]). To this aim, those variables that had been found to be significant at the univariate level were included into the multivariate models in a backward stepwise fashion. Associations are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The Hosmer-Lemeshow test was used to evaluate the goodness of fit of the models. All tests were two-tailed. A $P < .05$ was considered significant. SPSS version 22.0 (IBM Corporation, Armonk, NY) was used for statistical analysis.

3 | RESULTS

3.1 | Clinical and microbiological features

We included in the present study 133 KTRs that developed 143 episodes of cystitis treated with oral fosfomycin in the participating centers during the study period. The clinical characteristics of the study population are detailed in Table 1. About 64% of the participants were female. Mean age at transplantation and diagnosis of UTI were 52.5 ± 15.4 years and 56.7 ± 13.9 years, respectively. The majority of patients had undergone a single kidney transplantation (97.0% [129/133]). Most common underlying end-stage renal diseases included chronic interstitial nephropathy (24.1% [32/133]), glomerulonephritis (21.8% [29/133]), and polycystic kidney disease (17.3% [23/133]).

As detailed in Table 2, most of the patients were receiving an immunosuppression regimen based on steroids (86.7% [124/143]) (median daily dose of 7.5 mg of prednisone), tacrolimus (87.4% [125/143]), and mycophenolate mofetil or mycophenolic acid (79.7% [114/143]) at

TABLE 1 Demographics and clinical characteristics of the study population (n = 133)

Variable	
Age at transplantation, years, mean ± SD	52.5 ± 15.4
Gender (female), n (%)	85 (63.9)
Type of kidney transplantation, n (%)	
Single kidney	129 (97.0)
Pancreas-kidney	2 (1.5)
Liver-kidney	1 (0.8)
Previous kidney transplantation, n (%)	19 (14.3)
Two previous transplants, n (%)	4 (3.0)
Living donor, n (%)	1 (0.8)
Underlying end-stage renal disease, n (%)	
Chronic interstitial nephropathy	32 (24.1)
Glomerulonephritis	29 (21.8)
Polycystic kidney disease	23 (17.3)
Diabetic nephropathy	15 (11.3)
Nephroangiosclerosis	10 (7.5)
Lupus nephropathy	2 (1.5)
Congenital nephropathy	1 (0.8)
Obstructive uropathy	1 (0.8)
Unknown	15 (11.3)
Other	5 (3.8)

IQR, interquartile range; SD, standard deviation.

TABLE 2 Predisposing factors at the time of diagnosis of episodes of posttransplant cystitis included (n = 143)

Variable	
Immunosuppression at diagnosis, n (%)	
Corticosteroids	124 (86.7)
Daily dose, mg, median (IQR)[a]	5 (5-10)
Tacrolimus	125 (87.4)
Cyclosporine	9 (6.3)
MMF or MPA	114 (79.7)
mTOR inhibitor	13 (9.1)
Azathioprine	2 (1.4)
Previous acute graft rejection, n (%)[b]	5 (3.5)
Previous UTI, n (%)[b]	62 (43.4)
Number of prior episodes, median (IQR)	1 (1-2)
Anatomic abnormality of the urinary tract, n (%)	36 (25.2)
Neurogenic bladder, n (%)	9 (6.3)
Urinary tract instrumentation, n (%)	33 (23.1)
Double-J ureteral stent	19 (13.3)
Indwelling urinary catheter	20 (14.0)
Percutaneous nephrostomy	4 (2.8)
Suprapubic urinary catheter	0 (0.0)

IQR, interquartile range; SD, standard deviation; UTI, urinary tract infection.
[a]Prednisone dose or equivalent.
[b]Within the previous 3 mo.

the time of diagnosis of cystitis. In 43.4% (62/143) of episodes, the KTR had been diagnosed with a previous episode of UTI within the preceding 3 months, whereas the occurrence of acute rejection had been documented in 3.5% (5/143) of them. An anatomic abnormality of the urinary tract was present in 25.2% (36/143) of the episodes, whereas the presence of urinary tract instrumentation was documented in 23.1% (33/143) cases, mainly double-J ureteral stent and indwelling urinary catheter. The median interval from transplantation to the occurrence of cystitis was 15.7 months (IQR: 3.4-75.9). *Escherichia coli* was the most frequently isolated agent (67.8% [97/143] of the episodes), gram-positive cocci were implicated in 8.4% (12/143) of them, and *Pseudomonas* spp. in 3.5% (5/143). About half of the episodes (54.5% [78/143]) were due to MDR microorganisms, mainly ESBL-producing *Enterobacteriaceae* (Table 3).

3.2 | Characteristics of fosfomycin therapy

Fosfomycin was used as salvage therapy (ie, following clinical and/or microbiological failure with another antibiotic agent) in 16.8% (24/143) of the episodes. These cases were more likely to have been preceded by one or more UTI episodes within the prior 3 months (66.7% [16/24] vs 38.7% [46/119]; $P = .012$) or to be due to a MDR pathogen (81.0% [17/21] vs 55.5% [61/110]; $P = .029$), as compared to those in which oral fosfomycin has been used as first-line therapy (Table S1 in Supporting Material).

Overall, fosfomycin was prescribed at a median daily dose of 1.5 g (IQR: 1.5-2) during a median of 7 days (IQR: 3-10). In detail, episodes treated with fosfomycin trometamol (16.8% [24/143]) received either one single 3 g dose (45.8% [11/24]) or extended courses during two (16.7% [4/24]), three (33.3% [8/24]), or eight (4.2% [1/24]) consecutive days, resulting in a median cumulative dose of 6 g (IQR: 3-6). The remaining episodes (83.2% [119/143]) were treated with 500 mg capsules of calcium fosfomycin every 8 or 12 hours for a median of 8 days (IQR: 6-10), resulting in a median cumulative dose of 10.5 g (IQR: 6.4-15). A urine culture was performed at some point during follow-up in 92.3% (132/143) of episodes (within the first week and first month after completion of therapy in 26.9% [35/143] and 64.6% [84/143] of cases, respectively). None of the patients experienced severe adverse effects.

3.3 | Therapeutic outcomes

Clinical cure was achieved in 83.9% (120/143) of the episodes of cystitis. Microbiological cure at the first week from the completion of therapy was achieved in 74.3% (26/35) of evaluable episodes (ie, those with appropriate follow-up urine culture), whereas the corresponding rate for the first month was 70.2% (59/84).

Factors predicting lack of clinical cure were analyzed (Table 4). Male gender (56.6% [13/23] vs 30.0% [36/120]; $P = .015$) and the presence of percutaneous nephrostomy (13.0% [3/23] vs 0.8% [1/120]; $P = .014$) were more frequently observed in those episodes not achieving clinical cure. The later condition was almost statistically significant in the multivariate analysis (OR: 10.50; 95% CI: 0.98-112.29; $P = .052$).

We also assessed the clinical and microbiological factors predicting therapeutic failure (as defined above) in the 84 evaluable episodes of cystitis with follow-up urine culture in the first month (Table 5). Again, both male gender (53.3% [16/30] vs 29.6% [16/54]; $P = .032$) and the presence of a percutaneous nephrostomy (13.3% [4/30] vs 0.0% [0/54]; $P = .014$) were significantly more common in the group of therapeutic failure. None of them, however, remained as an independent risk factor in the multivariate model.

3.4 | Sensitivity analyses

We performed a set of sensitivity analyses to better characterize the efficacy of oral fosfomycin as a therapeutic option of cystitis among KTRs. First, we compared the use as first-line or salvage therapy following the failure of a previous antibiotic, with no significant differences in the rates of clinical cure (85.6% [101/118] vs 75.0% [18/24]; $P = .199$, respectively) or microbiological cure at the first week (74.1% [20/27] vs 75.0% [6/8]; $P = 1.000$) or the first month (70.6% [20/68] vs 69.8% [11/16]; $P = 1.000$). There were no significant differences according to the period elapsed between transplantation and the occurrence of UTI either (Table S2). Similar rates of clinical and microbiological cure were observed across decreasing categories of eGFR at diagnosis (Table S3). Finally, we found no significant differences in the odds of achieving clinical

TABLE 3 Clinical and microbiological characteristics, variables related to fosfomycin therapy, and outcome of episodes of posttransplant cystitis included (n = 143)

Variable	
Age at diagnosis, years, mean ± SD	56.7 ± 13.9
Time interval from transplantation to diagnosis, months, median (IQR)	15.7 (3.4-75.9)
Isolated microorganisms, n (%)	
Enterobacteriaceae	126 (88.1)
Escherichia coli	97 (67.8)
Klebsiella pneumoniae	19 (13.3)
Klebsiella oxytoca	1 (0.7)
Proteus mirabilis	6 (4.2)
Proteus vulgaris	0 (0.0)
Citrobacter spp.	0 (0.0)
Enterobacter spp.	2 (1.4)
Serratia spp.	1 (0.7)
Nonfermenting gram-negative bacilli	5 (3.5)
Pseudomonas aeruginosa	4 (2.8)
Pseudomonas fluorescens	1 (0.7)
Gram-positive cocci	12 (8.4)
Enterococcus faecalis	5 (3.5)
Enterococcus faecium	3 (2.1)
Staphylococcus epidermidis	3 (2.1)
Viridans group streptococci	1 (0.7)
Antibiotic susceptibility testing, n (%)	
Multidrug resistance	78 (54.5)
ESBL production	20 (14.0)
Carbapenem resistance	5 (3.5)
eGFR at diagnosis, mL/min, mean ± SD	44.1 ± 31.7
eGFR < 30 mL/min, n (%)	46 (32.2)
Failure of previous antibiotic therapy, n (%)[a]	24 (16.8)
Fosfomycin formulation, n (%)	
Calcium salt	119 (83.2)
Daily dose, g, median (IQR)	1.5 (1.5-1.69)
Duration of therapy, days, median (IQR)	8 (6-10)
Trometamol (or tromethamine) salt	24 (16.8)
Daily dose, g, median (IQR)	3 (3-3)
Duration of therapy, days, median (IQR)	2 (1-3)
Severe adverse effects, n (%)	0 (0.0)
Performance of follow-up urine culture, n (%)	132 (92.3)
Time interval from completion of therapy to urine culture, days, median (IQR)	13 (4.8-34)
Urine culture within the first week, n (%)	35/132 (26.9)
Urine culture within the first month, n (%)	84/132 (64.6)
Clinical cure, n (%)	120 (83.9)
Microbiological cure at first week, n (%)[b]	26/35 (74.3)
Microbiological cure at first month, n (%)[b]	59/84 (70.2)
Clinical and microbiological cure at first week, n (%)[b]	24/35 (68.6)
Clinical and microbiological cure at first month, n (%)[b]	54/84 (64.3)

eGFR, estimated glomerular filtration rate according to MDRD-4 variable equation; ESBL, extended-spectrum β-lactamase; IQR, interquartile range; NA, not applicable; SD, standard deviation; UTI, urinary tract infection.

[a]Refers to failure of previous antibiotic regimens (other than fosfomycin) used for the incident episode of UTI.

[b]Percentages calculated on the number of episodes with follow-up urine culture performed within each period.

cure according to the formulation of oral fosfomycin used (trometamol or calcium salt) (Table S4), or in episodes treated with repeated daily doses of fosfomycin trometamol as compared to those that received a single 3 g dose (100.0% [13/13] vs 81.8% [9/11], respectively; P = .119) (Table S5). However, it should be noted that the numbers in these subanalyses were small.

4 | DISCUSSION

In this collaborative multicenter cohort study, we included a large number of episodes of symptomatic lower UTI (cystitis) treated with oral fosfomycin in different Spanish kidney transplant programs. Clinicians have to deal on a daily basis with posttransplant UTI in the KTR population, often due to MDR uropathogens. Orally available alternatives for treating this complication have been drastically reduced in the last decades, since many of such strains are in vitro resistant to β-lactams, quinolones, and cotrimoxazole. Recent warnings issued by the FDA and other regulatory agencies about the unfavorable safety profile and the risk of severe adverse effects associated with fluoroquinolones in some populations, including elderly individuals,[3-5] have contributed to limit even more alternatives for the treatment of UTI. In the present study, oral fosfomycin demonstrated to be effective in achieving clinical cure in 84% of the episodes of cystitis, whereas the overall rate of microbiological cure among evaluable episodes was over 70%. These results overlap with those obtained with fosfomycin for the treatment of this type of infection in other patient populations.[8] In a review by Falagas et al, which included studies performed in nonimmunocompromised hosts, clinical and microbiological cure was achieved in more than 80% of the patients and 60% of the episodes of uncomplicated UTI, respectively, treated with oral fosfomycin.[8]

The present experience adds to previous studies that have also analyzed the use of fosfomycin for the treatment of cystitis among KTRa, as summarized in Table 6. Of note, most of them were based in small single-center cohorts, or alternatively covered larger populations in which KTRs were relatively underrepresented. Three of them offer relevant information. First, a previous study in the transplant setting that included 36 episodes of cystitis treated with oral fosfomycin. The rate of clinical success was 85%.[24] Second, in a short series of KTRs with UTIs treated with oral fosfomycin, 6 of

TABLE 4 Univariate and multivariate analysis of factors predicting lack of clinical cure

	Clinical cure (n = 120)	No clinical cure (n = 23)	*P*	Univariate		Multivariate		*P*
				OR	95% CI	OR	95% CI	
Age at diagnosis, years, mean ± SD	56.9 ± 13.7	56.0 ± 15.3	0.778					
Male gender, n (%)	36 (30.0)	13 (56.5)	0.015	2.99	1.20-7.46	2.37	0.91-6.20	.078
Time interval from transplantation to diagnosis, months, median (IQR)	16.5 (4-77.9)	11.6 (2.2-44.3)	0.364					
Previous kidney transplantation, n (%)	16 (13.6)	4 (17.4)	0.630					
Previous acute graft rejection, n (%)	4 (3.4)	1 (4.3)	1.000					
Previous UTI, n (%)	48 (40.3)	13 (56.5)	0.151					
Anatomic abnormality of the urinary tract, n (%)	28 (23.5)	8 (34.8)	0.256					
Neurogenic bladder, n (%)	7 (5.9)	2 (8.7)	0.612					
Urinary tract instrumentation, n (%)	26 (21.8)	7 (30.4)	0.372					
Double-J ureteral stent, n (%)	16 (13.4)	3 (13.0)	0.959					
Indwelling urinary catheter, n (%)	15 (12.6)	5 (21.7)	0.249					
Percutaneous nephrostomy, n (%)	1 (0.8)	3 (13.0)	0.014	17.70	1.75-178.73	10.50	0.98-112.29	.052
Daily corticosteroid dose, mg, median (IQR)	5 (5-10)	7.5 (5-16.5)	0.160					
eGFR at diagnosis, mL/min, mean ± SD	44.9 ± 33.6	40.7 ± 19.0	0.560					
Failure of previous antibiotic therapy, n (%)	18 (15.1)	6 (26.1)	0.199					
Nonfermenting gram-negative bacilli, n (%)	5 (4.2)	0 (0.0)	1.000					
Multidrug-resistant isolate, n (%)	62 (56.9)	16 (76.2)	0.098					
ESBL-producing isolate, n (%)	17 (16.0)	3 (16.7)	0.947					
Carbapenem-resistant isolate, n (%)	5 (4.6)	0 (0.0)	0.591					
Daily fosfomycin dose, g, median (IQR)	1.5 (1.5-2)	1.5 (1.5-2)	0.727					
Duration of therapy, days, median (IQR)	7 (3-10)	8 (6-10)	0.124					

CI, confidence interval; eGFR, estimated glomerular filtration rate; ESBL, extended-spectrum β-lactamase; IQR, interquartile range; OR, odds ratio SD, standard deviation; UTI, urinary tract infection.

the 9 patients were initially cured, albeit microbiological clearance at 3 months was demonstrated in only 31% of cases. The authors attributed this high failure rate to patients' clinical characteristics (ie, anatomical abnormalities or immunosuppression) rather than to the intrinsic antibacterial activity of fosfomycin.[15] Finally, a Dutch study included 33 episodes of cystitis and 15 of AB after kidney transplantation, with rated clinical and microbiological cure of 67% and 25%, respectively.[17] These rates are slightly lower than those presented in our study. The main reason for this discrepancy could be that in the Dutch experience fosfomycin was used mainly as a last-resort oral therapy for recurrent UTI. Notably, no patient developed severe adverse events.

In comparison with these previous experiences, our study benefits from inclusion restricted to monomicrobial episodes of symptomatic lower UTI and large sample size, which allowed us to perform a multivariate analysis to assess the factors predicting clinical and therapeutic failure following oral fosfomycin. As clinically relevant findings, the presence of percutaneous nephrostomy (but not of double-J ureteral stent or indwelling urinary catheter) exhibited a borderline association with lack of clinical cure, whereas male gender remained in the models for both outcomes, although not achieving statistical significance. Despite the low number of episodes (n = 4), the deleterious impact observed for percutaneous nephrostomy is not surprising, and supports the recommendation of considering early stent removal while balancing the risk of urologic complications.[6] It must be highlighted that fosfomycin achieved clinical and microbiological cure in the five cases of cystitis produced by carbapenem-resistant strains. Overall, fosfomycin achieved microbiological cure within the first month in 71.4% (35 of 49) of the evaluable episodes due to MDR pathogens. A previous study including different patient populations demonstrated a cure rate of 55% for UTI produced by MDR bacteria.[25] Various European surveillance studies have reported susceptibility rates for *E. coli* isolates exceeding 96%, which have remained stable over the previous 10 years.[26,27] A recent German study found that 78% of carbapenem-nonsusceptible *Enterobacteriaceae* isolates (including KPC, VIM, NDM, and OXA-48 carbapenemases producers) remained susceptible to fosfomycin.[28]

TABLE 5 Univariate and multivariate analysis of factors predicting therapeutic failure (ie, lack of clinical response at end of treatment and/or microbiological response at first month) in evaluable episodes (ie, those with follow-up urine culture performed within the appropriate time frame) (n = 84)

	No therapeutic failure (n = 54)	Therapeutic failure (n = 30)	*P*	Univariate		Multivariate		*P*
				OR	95% CI	OR	95% CI	
Age at diagnosis, years, mean ± SD	58.7 ± 13.0	56.9 ± 14.5	.574					
Male gender, n (%)	16 (29.6)	16 (53.3)	.032	2.71	1.08-6.85	2.34	0.90-6.07	.081
Time interval from transplantation to diagnosis, months, median (IQR)	11.4 (1.8-71.4)	11.6 (4.3-58.5)	.723					
Previous kidney transplantation, n (%)	6 (11.1)	5 (16.7)	.470					
Previous acute graft rejection, n (%)	1 (1.9)	1 (3.3)	1.000					
Previous UTI, n (%)	23 (42.6)	16 (53.3)	.344					
Anatomic abnormality of the urinary tract, n (%)	15 (27.8)	10 (33.3)	.594					
Neurogenic bladder, n (%)	3 (5.6)	2 (6.7)	1.000					
Urinary tract instrumentation, n (%)	13 (24.1)	9 (30.0)	.554					
Double-J ureteral stent, n (%)	10 (18.5)	4 (13.3)	.541					
Indwelling urinary catheter, n (%)	7 (13.0)	4 (13.3)	1.000					
Percutaneous nephrostomy, n (%)	0 (0.0)	4 (13.3)	.014	18.51	0.97-356.64	-	-	-
Daily corticosteroid dose, mg, median (IQR)	5 (5-10)	7.5 (5-10)	.835					
eGFR at diagnosis, mL/min, mean ± SD	48.3 ± 44.6	45.2 ± 23.2	.721					
Failure of previous antibiotic therapy, n (%)	9 (16.7)	7 (23.2)	.456					
Nonfermenting gram-negative bacilli, n (%)	4 (7.4)	0 (0.0)	.292					
Multidrug-resistant isolate, n (%)	31 (59.6)	18 (66.7)	.540					
ESBL-producing isolate, n (%)	6 (11.1)	7 (23.3)	.138					
Carbapenem-resistant isolate, n (%)	3 (5.6)	0 (0.0)	.549					
Daily fosfomycin dose, g, median (IQR)	1.5 (1.5-2)	1.5 (1.5-2)	.902					
Duration of therapy, days, median (IQR)	7 (3-10)	7 (6.8-10)	.277					

CI, confidence interval; eGFR, estimated glomerular filtration rate; ESBL, extended-spectrum β-lactamase; IQR, interquartile range; OR, odds ratio SD, standard deviation; UTI, urinary tract infection.

Daily dose and duration of treatment with the different oral formulations of fosfomycin were not under control, and no firm conclusions can be drawn from the present study regarding the optimal therapeutic regimen in the specific setting of posttransplant UTI. Albeit a single 3 g dose of fosfomycin trometamol is currently approved by the FDA for the treatment of uncomplicated cystitis in women, more than half of the KTR included in our cohort received daily doses for two (16.7% [4/24]) or more consecutive days (37.5% [9/24]). It is likely that, due to the underlying immunosuppression, prescribing physicians could have felt more comfortable by prolonging treatment courses. A subgroup analysis suggested that clinical cure would be numerically, albeit not statistically, more frequent with repeated doses of fosfomycin trometamol. Nevertheless, this finding must be taken with extreme caution due to the low number of episodes and the potential for confounding by indication bias. In addition, off-label multiple-dosing regimens frequently used in clinical practice are not supported by modern robust pharmacokinetic or safety data, particularly in patients with impaired renal function.

Some limitations in our study deserve consideration. The multicenter retrospective design implied that various methodological approaches were used for case identification, and some degree of selection bias cannot be ruled out. However, it comprises a large sample that allegedly reflects the clinical spectrum of uncomplicated UTIs among KTRs in Spain, reinforcing the representativeness of our findings. In addition, misclassification bias seems to be unlikely because rigorous inclusion and exclusion criteria were applied. Due to this observational design, a follow-up urine culture performed as test-of-cure was available for only two-thirds of episodes, and

TABLE 6 Summary of studies assessing the use of fosfomycin for the treatment of UTI in KTRs

Author and year	Study design/type of UTI included	Number of cases treated with fosfomycin	Fosfomycin dose	Outcomes	Comments
Neuner EA, 2012[14]	Retrospective single center cohort of hospitalized adults from the general population/lower and upper UTI	10 episodes of posttransplant UTI due to MDR pathogens	Average of 3.3 ± 1.9 doses per episode	2/8 episodes with microbiological cure	No distinction between lower and upper UTI At least 2/8 episodes with microbiological failure were in KTR with upper UTI
Reid GE, 2013[15]	Single center retrospective cohort of KTR/lower and upper UTI	14 episodes of posttransplant UTI in 9 KTR (6/14 as first-line therapy)	1 to 7 doses of 3 g of oral fosfomycin trometamol (57% received 3 doses)	Overall clearance rate at three months of 31% (4/13 evaluable episodes)	No distinction between lower and upper UTI Fosfomycin was considered "optimal" for UTI treatment among KTR. Recurrence was attributed "to host factors such as immunosuppression and comorbid conditions (eg, upper UTI, diabetes, and genitourinary abnormalities) more than to poor efficacy of fosfomycin"
Mathews PC, 2016[41]	Single center retrospective cohort of adults from the general population/lower and upper UTI	11 episodes of posttransplant UTI	71% of the episodes treated with a single 3 g oral dose of fosfomycin trometamol	Clinical cure observed in 8/11 episodes	No distinction between lower and upper UTI Most of infections in the global cohort were due to *E coli* (69%), 59% of which were ESBL-producers The authors found "an important role for oral fosfomycin for MDR UTI treatment"
Kerstenetzky L, 2017[24]	Single center retrospective cohort of SOT recipients/AB, lower and upper UTI	76 episodes (36 in KTR) of posttransplant UTI (in 64 SOT recipients)	1 or "multiple doses" of 3 g of oral fosfomycin trometamol	85.5% of "fosfomycin success" for the global cohort of SOT recipients	No distinction made between AB and symptomatic UTI No significant difference in treatment success was noted between CrCl < 40 mL/min and CrCl ≥ 40 mL/min for the global cohort of SOT recipients No data on outcome provided for the subgroup of KTR Fosfomycin is considered "an effective agent even in the setting of renal dysfunction in a diverse population of SOT recipients"
Loethen AA, 2017[16]	Same cohort than Kerstenetzky, 2017/AB and cystitis	Same cohort than Kerstenetzky et al	Same cohort than Kerstenetzky et al	Same cohort than Kerstenetzky et al	No separate outcome assessment for AB and cystitis No significant difference in treatment success was noted between single or multiple doses of 3 g oral fosfomycin trometamol No data on outcome provided for the subgroup of KTR Fosfomycin "appears to be successful in the treatment of cystitis in abdominal solid organ transplant recipients"
Ten Doesschate T, 2019[17]	Retrospective cohort from two Dutch hospitals/AB, lower and upper UTI	33 episodes of posttransplant cystitis	1 or multiple doses of 3 g of oral fosfomycin trometamol given in 2 or 3-day intervals for as long as 15 days	Cinical cure in 67% of episodes	Fosfomycin trometamol was prescribed for known or presumed resistance to first-line oral antibiotics in all episodes Fosfomycin trometamol was considered to present "a reasonable effectiveness as last-resort oral treatment for lower-UTI"

(Continues)

TABLE 6 (Continued)

Author and year	Study design/type of UTI included	Number of cases treated with fosfomycin	Fosfomycin dose	Outcomes	Comments
Bielen L, 2019[42]	Single center retrospective cohort of adults from the general population/lower UTI due to ESBL-producing *Enterobacteriaceae*	Four cases of posttransplant UTI	"Multiple doses" of 3 g of oral fosfomycin trometamol with an average of 5 doses per patient	Clinical cure in 4/4 episodes, microbiological cure in 3/4 episodes	The authors concluded that "fosfomycin may be a valid option for oral treatment of lower UTI caused by ESBL-producing pathogens for which very few antibiotic options remain"
Present study, 2019	Retrospective cohort of KTR from 14 Spanish hospitals/cystitis	143 episodes of posttransplant cystitis (in 133 KTRs)	1 or more doses of 3 g of fosfomycin trometamol, 1 or 2 500 mg capsules of calcium fosfomycin every 8 h for a median of 7 d	Clinical cure in 120/143 (89.3%) episodes	54.5% of episodes due to MDR strains The use of fosfomycin as a first-line therapy for cystitis among KTR is suggested

AB, asymptomatic bacteriuria; CrCl, creatinine clearance; ESBL, extended-spectrum β-lactamase; KTR, kidney transplant recipient; MDR, multidrug resistant; SOT, solid organ transplantation; UTI, urinary tract infection.

therefore we were not able to assess whether microbiological failure was associated with the emergence of fosfomycin resistance. The present cohort represents the reality of resistance pattern found in uropathogens in Spain, which might not be exportable to other countries. Because we lacked a control group, we could not analyze the relative contribution of oral fosfomycin as compared with other agents. Previous studies have shown a cure rate for UTI with a single dose of oral fosfomycin similar to that obtained after a 5-day course oral ciprofloxacin.[29] Nevertheless, the objective of our study was to appraise the usefulness of oral fosfomycin in terms of both clinical and microbiological outcomes to spare the indiscriminate use of broad-spectrum antibiotics for the treatment of a frequent and usually benign condition.

Recent guidelines issued by the Infectious Diseases Community of Practice of the American Society of Transplantation[6] propose to reserve fosfomycin for the treatment of noncomplicated UTI produced by drug-resistant pathogens. Nevertheless, and in view of the encouraging experience reported herein, we would suggest that oral fosfomycin may be considered as a first-line option for cystitis and other forms of lower UTI among KTRs on the basis of three arguments: clinical efficacy, potential for adverse events, and ecological impact. First, the present and previous studies (Table 6) demonstrate a rate of therapeutic success similar to that reported for nontransplant populations. Second, the safety of oral fosfomycin compares favorably to other alternatives, such as fluoroquinolones or nitrofurantoin in terms of collagen-associated serious adverse events[3-5] and pulmonary toxicity,[30] respectively. This advantage would be particularly relevant in patients with decreased CrCl. Third, oral fosfomycin combines broad spectrum and uroselective action, minimizing the risk of resistance selection and the lower impact on gut microbiota as compared to β-lactams[31,32] or fluoroquinolones.[33] Indeed, no selection of *C. difficile* has been demonstrated when healthy volunteers receive high intravenous doses of fosfomycin.[34] The emergence of acquired resistance to fosfomycin is less likely in the presence of high drug concentrations (as those reached in the urinary tract),[35] and the pooled probability for development of resistance during treatment for UTIs and other types of infection has been estimated as low as 3.4%.[36] Therefore, fosfomycin is being positioned as a carbapenem-sparing drug for the treatment of infections due to MDR gram-negative bacteria,[37,38] and offers a valid alternative to tigecycline, linezolid, or daptomycin for MDR gram-positive cocci such as VRE.[39] This approach may result in a further advantage within the current politics of widespread implementation of antimicrobial stewardship programs.[40]

In conclusion, in the current scenario of high prevalence of infections due to MDR bacteria in the solid organ transplant population, oral fosfomycin should be added to the antibiotic armamentarium as a safe, affordable, and effective alternative for the treatment of cystitis among KTRs.

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DISCLOSURE

The authors have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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