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Efficacy and Safety of Oral Fosfomycin for Asymptomatic Bacteriuria in Kidney Transplant Recipients: Results from a Spanish Multicenter Cohort

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ABSTRACT Current guidelines recommend against systematic screening for or treating asymptomatic bacteriuria (AB) among kidney transplant (KT) recipients, although the evidence regarding episodes occurring early after transplantation or in

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the presence of anatomical abnormalities is inconclusive. Oral fosfomycin may constitute a good option for the treatment of posttransplant AB, particularly due to the emergence of multidrug-resistant (MDR) uropathogens. Available clinical evidence supporting its use in this specific setting, however, remains scarce. We performed a retrospective study in 14 Spanish institutions from January 2005 to December 2017. Overall, 137 episodes of AB diagnosed in 133 KT recipients treated with oral fosfomycin (calcium and trometamol salts) with a test-of-cure urine culture within the first 30 days were included. Median time from transplantation to diagnosis was 3.1 months (interquartile range [IQR], 1.1 to 10.5). Most episodes (96.4% [132/137]) were caused by Gram-negative bacteria (GNB), and 56.9% (78/137) were categorized as MDR (extended-spectrum β-lactamase-producing *Enterobacterales* [20.4%] and carbapenem-resistant GNB [2.9%]). Rate of microbiological failure at month 1 was 40.1% (95% confidence interval [CI], 31.9% to 48.9%) for the whole cohort and 42.3% (95% CI, 31.2% to 54.0%) for episodes due to MDR pathogens. Previous urinary tract infection (odds ratio [OR], 2.42; 95% CI, 1.11 to 5.29; *P* value = 0.027) and use of fosfomycin as salvage therapy (OR, 8.31; 95% CI, 1.67 to 41.35; *P* value = 0.010) were predictors of microbiological failure. No severe treatment-related adverse events were detected. Oral fosfomycin appears to be a suitable and safe alternative for the treatment (if indicated) of AB after KT, including those episodes due to MDR uropathogens.

KEYWORDS asymptomatic bacteriuria, fosfomycin, kidney transplant

Asymptomatic bacteriuria (AB) and symptomatic urinary tract infection (UTI) are the most common infectious complications after kidney transplantation (KT) (1, 2). On the basis of the results derived from various prospective studies, including randomized clinical trials (3–5), current guidelines recommend against systematic screening for and treatment of AB in KT recipients following the first posttransplant months. However, patients are exposed to higher levels of immunosuppression and are more likely to undergo urinary tract instrumentation during the first 1 or 2 months after transplantation. At the present time, there is insufficient evidence to recommend for or against screening and treating episodes of AB that occur during this early period (6–8).

The emergence of multidrug-resistant (MDR) uropathogens, such as extended-spectrum β-lactamase (ESBL)-producing or carbapenem-resistant isolates, has become a major concern in clinical practice in the KT population (8–12). Indeed, the therapeutic management of MDR bacteria is increasingly challenging, since available options are often associated with adverse events, such as nephrotoxicity, which may be increased by the concomitant use of immunosuppressive agents, particularly calcineurin inhibitors (11). In addition, posttransplant UTIs due to MDR bacteria have been associated with higher risk of complications and recurrence (4, 9, 13, 14). Fosfomycin has been proposed as an effective and safe alternative for the treatment of MDR pathogens causing UTI in different patient populations (15–18). Of note, we have recently demonstrated the efficacy and safety of oral fosfomycin for the treatment of cystitis in a large multicenter cohort of KT recipients (18).

Fosfomycin exerts bactericidal action through the inhibition of the early phases of the peptidoglycan synthesis pathway. Further actions of this agent include its capacity to reduce bacterial adherence to the urinary epithelium (19) and an alleged immunomodulatory effect (20). Fosfomycin has a broad range of *in vitro* activity against MDR Gram-positive and Gram-negative pathogens. Other advantages include its good oral bioavailability, minimal potential for drug-drug interactions, lack of requirement for dose adjustment for hepatic impairment, and low risk of adverse events (20). Although there is limited information on the pharmacokinetics of oral fosfomycin in the presence of impaired renal function, no dose adjustment is necessary in patients with creatinine clearance greater than 10 ml/min when a single 3-g dose of fosfomycin trometamol is used for the treatment of cystitis (21).

As previously noted, the recommendation for treating posttransplant AB would still apply to those episodes occurring within the first 2 months after KT (6, 8). Despite the

TABLE 1 Clinical characteristics of the KT recipients with ≥1 episode of AB (*n* = 133)

Variable[a]	Value
Age at transplantation (yrs) (mean ± SD)	54.8 ± 13.6
Female gender (*n* [%])	76 (57.1)
Type of kidney transplantation (*n* [%])	
Single kidney	125 (93.9)
Double kidney	1 (0.8)
Pancreas-kidney	7 (5.3)
Previous kidney transplantation (*n* [%])	22 (16.5)
Two previous transplants (*n* [%])	5 (3.8)
Living donor (*n* [%])	4 (3.0)
Underlying end-stage renal disease (*n* [%])	
Glomerulonephritis	36 (27.1)
Diabetic nephropathy	24 (18.0)
Polycystic kidney disease	22 (16.5)
Chronic interstitial nephropathy	12 (9.0)
Nephroangiosclerosis	8 (6.0)
Lupus nephropathy	5 (3.8)
Congenital nephropathy	2 (1.5)
Obstructive uropathy	1 (0.8)
Other	3 (2.3)
Unknown	20 (15.0)
Immunosuppression at diagnosis of AB (*n* [%])	
Corticosteroids	119 (89.5)
Daily dose (mg) (median [IQR])	10 (5–15)
Tacrolimus	123 (92.5)
Cyclosporine	5 (3.8)
MMF or MPA	121 (91.0)
Sirolimus	6 (4.5)
Azathioprine	3 (2.3)
Previous acute graft rejection (*n* [%])[b]	2 (1.5)
Previous UTI (*n* [%])[c]	59 (44.4)
Anatomical abnormality of the urinary tract (*n* [%])	31 (23.3)
Urinary tract instrumentation (*n* [%])	30 (22.6)
Double-J ureteral stent	26 (19.5)
Indwelling urinary catheter	8 (6.0)
Percutaneous nephrostomy	6 (4.5)

[a]AB, asymptomatic bacteriuria; IQR, interquartile range; MMF, mycophenolate mofetil; MPA, mycophenolic acid; SD, standard deviation; UTI, urinary tract infection.
[b]Within the previous month.
[c]Within the previous 3 months.

appealing profile of fosfomycin, the available clinical evidence supporting its use in this specific clinical scenario remains scarce. The present study was aimed at investigating the rate of microbiological eradication and factors predicting microbiological failure in episodes of AB treated with oral fosfomycin in a large multicenter cohort of KT recipients.

RESULTS

Characteristics of KT recipients. We identified 137 episodes of AB diagnosed in 133 KT recipients that were treated with oral fosfomycin monotherapy during the study period. Demographics and clinical characteristics of KT recipients are detailed in Table 1. Mean age at transplantation was 54.8 ± 13.6 years, and most patients (57.1% [76/133]) were female. Glomerulonephritis was the most common underlying end-stage renal disease (27.1% [36/133]), followed by diabetic nephropathy (18.0% [24/133]). Twenty-two patients (16.5%) had undergone a previous transplantation. The

TABLE 2 Clinical and microbiological characteristics, variables related to fosfomycin therapy, and outcome of episodes of posttransplant AB (n = 137)

Variable[a]	Value
Age at diagnosis (yrs) (mean ± SD)	57.7 ± 13.0
Time interval from transplantation to diagnosis of AB (mo) (median [IQR])	3.1 (1.1–10.5)
AB within the first 2 posttransplant mo (*n* [%])	53 (38.7)
Isolated microorganisms (*n* [%])	
Enterobacterales	129 (94.2)
Escherichia coli	95 (69.3)
Klebsiella pneumoniae	21 (15.3)
Klebsiella oxytoca	5 (3.6)
Proteus mirabilis	5 (3.6)
Citrobacter freundii	1 (0.7)
Enterobacter spp.	2 (1.5)
Nonfermenting Gram-negative bacilli	3 (2.2)
Pseudomonas aeruginosa	3 (2.2)
Gram-positive cocci	5 (3.6)
Staphylococcus epidermidis	2 (1.5)
Enterococcus faecalis	1 (0.7)
Enterococcus faecium	1 (0.7)
Staphylococcus aureus	1 (0.7)
Antibiotic susceptibility testing (*n* [%])	
Multidrug resistance	78 (56.9)
ESBL production	28 (20.4)
Carbapenem resistance	4 (2.9)
eGFR at diagnosis of AB (ml/min) (mean ± SD)[b]	42.8 ± 20.5
eGFR <30 ml/min (*n* [%])	37 (28.2)
eGFR <10 ml/min (*n* [%])	3 (2.3)
Salvage therapy (*n* [%])	15 (10.9)
Daily fosfomycin dose (g) (median [IQR])	3 (1.5–3)
Duration of fosfomycin therapy (days) (median [IQR])	3 (2–9)
Fosfomycin formulation (*n* [%])	
Trometamol fosfomycin	72 (52.6)
Calcium fosfomycin	65 (47.4)
Interval from initiation of therapy to test-of-cure culture (days) (median [IQR])	13 (8–21)
Interval from end of therapy to test-of-cure culture (days) (median [IQR])	9 (3–15.5)
Urine culture within the first wk (*n* [%])	31 (22.6)
Urine culture within the first mo (*n* [%])	133 (100.0)
Microbiological failure at first wk (*n* [%])	13/31 (41.9)
Microbiological failure at first mo (*n* [%])	55/137 (40.1)

[a]AB, asymptomatic bacteriuria; eGFR, estimated glomerular filtration rate according to MDRD-4 variable equation; ESBL, extended-spectrum β-lactamase; IQR, interquartile range; SD, standard deviation.
[b]eGFR at the time of diagnosis was not available for 6 episodes.

immunosuppression regimen was mainly based on corticosteroids (89.5% [119/133]), tacrolimus (92.5% [123/133]), and mycophenolate mofetil or mycophenolic acid (91.0% [121/133]). Some anatomical abnormality of the urinary tract was present in 23.3% (31/133) of patients, whereas the presence of urinary tract instrumentation was reported for 22.6% (30/133) of patients, mainly double-J ureteral stenting (19.5% [26/133]).

Characteristics of AB episodes. The clinical and microbiological characteristics of 137 episodes of AB included are detailed in Table 2. Median time from transplantation to diagnosis was 3.1 months (interquartile range [IQR], 1.1 to 10.5 months), with 38.7% (53/137) of episodes occurring in the first 2 months after transplantation. Anatomical abnormality was present in 47.2% (25/53) of these early-onset AB episodes. *Escherichia coli* was the most frequently isolated microorganism (69.3% [95/137]); Gram-positive

TABLE 3 Univariate and multivariate analysis of factors predicting microbiological failure at month 1 from the initiation of therapy with oral fosfomycin ($n = 137$)

Factor[a]	Value			Univariate[b]		Multivariate[c]		
	Microbiological cure ($n = 82$)	Microbiological failure ($n = 55$)	*P* value	OR	95% CI	OR	95% CI	*P* value
Age at diagnosis of AB (yrs) (mean ± SD)	55.3 ± 12.9	56.6 ± 14.6	0.362					
Female gender (*n* [%])	44 (53.7)	35 (66.0)	0.154					
Time interval from transplantation to diagnosis of AB (mo) (median [IQR])	3.9 (1.2–16.9)	3.2 (1.3–11.1)	0.986					
Previous kidney transplantation (*n* [%])	13 (15.9)	9 (16.4)	0.936					
Diabetic nephropathy (*n* [%])	15 (18.3)	9 (16.4)	0.771					
Polycystic kidney disease [(*n* [%])	14 (17.1)	9 (16.4)	0.913					
Previous UTI (*n* [%])[d]	30 (36.6)	32 (58.2)	0.013	2.92	1.39–6.12	2.42	1.11–5.29	0.027
Anatomical abnormality of the urinary tract (*n* [%])	19 (23.2)	12 (21.8)	0.853					
Double-J ureteral stenting (*n* [%])	15 (18.3)	11 (20.0)	0.803					
Indwelling urinary catheter (*n* [%])	6 (7.3)	2 (3.6)	0.475					
Percutaneous nephrostomy (*n* [%])	5 (6.1)	1 (1.8)	0.401					
Daily corticosteroid dose (mg) (median [IQR])	10 (5–20)	8.8 (5–10)	0.130					
eGFR at diagnosis (ml/min) (mean ± SD)	42.9 ± 19.3	42.7 ± 22.5	0.956					
Trometamol fosfomycin (*n* [%])	46 (56.1)	26 (47.3)	0.311					
Salvage therapy (*n* [%])	2 (2.4)	13 (23.6)	0.000	10.92	2.33–51.31	8.31	1.67–41.35	0.010
Multidrug-resistant isolate (*n* [%])	45 (58.4)	33 (61.1)	0.759					
ESBL-producing isolate (*n* [%])	12 (14.6)	16 (29.1)	0.040	2.12	0.89–5.02			
Carbapenem-resistant isolate (*n* [%])	4 (4.9)	0 (0.0)	0.149					
Daily fosfomycin dose (g) (median [IQR])	3 (1.5–3)	3 (1.5–3)	0.494					
Duration of therapy (days) (median [IQR])	3 (2–7)	3 (2–10)	0.636					

[a]AB, asymptomatic bacteriuria; eGFR, estimated glomerular filtration rate; ESBL, extended-spectrum β-lactamase; IQR, interquartile range; UTI, urinary tract infection.
[b]OR, odds ratio; CI, confidence interval.
[c]Hosmer-Lemeshow *P* value = 0.781.
[d]Within the previous 3 months.

cocci were involved in 3.6% (5/137) of the episodes and *Pseudomonas aeruginosa* in 2.2% (3/137). Half of the episodes (56.9% [78/137]) were produced by pathogens fulfilling the definition for MDR.

Fosfomycin was prescribed at a median daily dose of 3 g (IQR, 1.5 to 3 g), for a median duration of 3 days (IQR, 2 to 9 days). Fosfomycin was used as a salvage therapy in 10.9% (15/137) of the episodes. None of the patients developed severe treatment-related adverse events (AEs).

Microbiological failure. The median interval from the initiation of therapy to the test-of-cure urine culture was 13 days (IQR, 8 to 21 days). Persistence of the same uropathogen was observed in 55 episodes, accounting for a rate of microbiological failure at month 1 of 40.1% (95% confidence interval [CI], 31.9% to 48.9%) for the whole cohort and 42.3% (95% CI, 31.2% to 54.0%) in the subgroup of MDR pathogens.

We next investigated factors predicting microbiological failure (Table 3). Diagnosis of UTI in the preceding 3 months, use of fosfomycin as salvage therapy, and infection due to an ESBL-producing strain were more common in episodes experiencing this outcome. In the multivariate analysis, previous UTI (odds ratio [OR], 2.42; 95% CI, 1.11 to 5.29; *P* value = 0.027) and use of fosfomycin as salvage therapy (OR, 8.31; 95% CI, 1.67 to 41.35; *P* value = 0.010) were identified as independent risk factors for microbiological failure.

DISCUSSION

Asymptomatic bacteriuria is a common event among KT recipients, particularly during the first months following the procedure. Various recent clinical trials have failed to demonstrate any benefit in terms of incidence of symptomatic UTI or graft rejection for KT recipients in which AB episodes occurring beyond the second posttransplant month (3, 5) or when urethral and ureteral catheters had been removed (4) were systematically screened and treated. Thus, a paradigm shift toward a more conservative

approach has occurred in the management of posttransplant AB. Indeed, the more recent guidelines issued by the Infectious Diseases Society of America (IDSA) explicitly recommend against screening for or treating AB beyond the first posttransplant month (6). However, available evidence concerning AB occurring earlier is still scarce, since these episodes were excluded in previous clinical trials (3, 5). Both the amount of immunosuppression and the rate of urologic interventions usually peak during the first months after KT and decrease thereafter, and the common presence of indwelling urinary catheters and double-J stents during this period would increase the risk of progression from AB to symptomatic UTI, including acute graft pyelonephritis. Therefore, the recommendation for screening for and treating AB in current guidelines would still apply to the first months after KT (6, 7). More than one third (37.8%) of AB episodes in our cohort occurred within the early posttransplant period.

In the present collaborative multicenter study, oral fosfomycin monotherapy was demonstrated to be effective in achieving microbiological cure in 59.8% of episodes of posttransplant AB. These results are in line with those reported for nontransplant patient populations (20, 22–24). Even if uncertainties remain on the clinical benefit to be expected from treating AB during the first months after KT (6, 25), the present experience still serves as a reliable measure of the efficacy of oral fosfomycin in the transplant setting.

The emergence and spread of MDR bacteria, particularly Gram-negative bacilli, constitutes a major concern in clinical practice. Due to increased selection pressure resulting from frequent antibiotic use and prolonged hospital and intensive care unit stays, KT recipients are at a particular risk of colonization and infection with MDR bacteria (11). In a single-center study that analyzed changes in antimicrobial susceptibility patterns in 1,052 urine culture isolates obtained in two different cohorts of KT recipients (2002 to 2004 and 2011 to 2013), significant increases over time were reported in the rates of MDR (43.9% versus 67.8%, respectively), ESBL-producing (6.6% versus 26.1%), and carbapenem-resistant *Enterobacterales* (0.0% versus 5.0%) (26). These trends in resistance patterns among uropathogens recovered from KT recipients have led to unintended consequences, such as the use of antibiotics with unfavorable safety profiles in terms of nephrotoxicity (e.g., aminoglycosides or polymyxins), higher rates of inappropriate empirical therapy, prolonged hospitalizations, and poorer patient and graft outcomes (8, 9).

More than half (56.9%) of the episodes of AB included in the present study were due to MDR Gram-negative bacilli. This figure is sensibly higher than that reported in other studies on posttransplant UTI also performed in our setting (4, 27), likely reflecting the propensity of clinicians to reserve fosfomycin for infections in which other therapeutic options were limited. Indeed, oral fosfomycin was used as salvage therapy following failure of other agents in 10.9% of cases. No differences in the rate of microbiological failure were observed between MDR and non-MDR strains (39.6% versus 42.3%, respectively), and eradication in the test-of-cure culture was achieved in all 4 episodes due to carbapenem-resistant *Enterobacterales*. Not surprisingly, the occurrence of UTI in the previous months and the use of fosfomycin as salvage therapy were identified in the multivariate model as predictors of microbiological failure. It could be hypothesized that both factors act as surrogate markers of clinical complexity and identify more difficult-to-treat infections occurring in patients with persistent or repeated instrumentation of the urinary tract or colonized by uropathogens that express virulence factors (such as adhesin production or biofilm formation) (14). In line with previous experiences in transplant (18) and nontransplant populations (15, 17, 22, 24), no severe treatment-related AEs were identified, thus confirming the well-established safety of oral fosfomycin.

Some limitations in our study merit consideration. First, its retrospective and multicenter design, in which systematic case capture was not attempted, may have introduced some degree of selection bias. Nevertheless, we included a large number of cases from different institutions to reflect the microbiological spectrum of

uropathogens among KT recipients in our setting, and only episodes with an appropriate test-of-cure assessment were considered. This cohort represents current resistance patterns in KT units in Spain, although our findings may not be extensible to other countries with different epidemiology. Beyond ESBL production or carbapenem resistance, phenotypic or molecular characterization was not available for MDR uropathogens, although the high nonsusceptibility rates observed in Spain for amoxicillin-clavulanate, ciprofloxacin, or co-trimoxazole could likely account for most of the isolates (26, 28). Finally, since we lacked a control group, we were not able to investigate the relative contribution of oral fosfomycin in microbiological cure compared with that for other agents.

We acknowledge that most of the AB episodes included were diagnosed beyond the second posttransplant month; therefore, the administration of antibiotic therapy would not have been indicated according to current guidelines (6–8). Notwithstanding this, our findings regarding the rate and risk factors for microbiological failure can be extrapolated to episodes occurring early after transplantation. In conclusion, oral fosfomycin appears to be a suitable and safe alternative for the treatment (if indicated) of AB after KT, including those episodes due to MDR uropathogens. This approach would contribute to reduce the widespread use of broad-spectrum antibiotics with higher potential for AEs and resistance induction.

MATERIALS AND METHODS

Study population and setting. We performed a retrospective cohort study that was developed in 14 Spanish institutions with a dedicated KT program. 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 of the Spanish Society of Clinical Microbiology and Infectious Diseases (GESITRA-IC/SEIMC). The study protocol was approved by the ethics committee for clinical research of the University Hospital 12 de Octubre and by the local ethics committees of the other centers, as required.

Study design. Evaluable episodes of AB in KT recipients treated with oral fosfomycin monotherapy from 1 January 2005 to 31 December 2017 were included. Episodes in which a further active agent was simultaneously administered were excluded as well as those due to strains with *in vitro* nonsusceptibility to fosfomycin. Local investigators in participating centers identified eligible patients by means of different data searching and extraction strategies (i.e., institutional databases of KT recipients, prescription registers from pharmacy departments, or electronical medical records). A standardized data collection form including demographic, clinical, and transplant-related variables was used. In detail, microbiological information on the isolated uropathogen and results of *in vitro* susceptibility testing, immunosuppression regimen and graft function at diagnosis, presence of urinary tract instrumentation, and microbiological outcomes were recorded for each AB episode in an anonymized fashion and entered into a protected electronic database.

Study outcome. The study outcome was the rate of microbiological failure, defined by the presence of the same bacteria initially isolated (i.e., identical species and *in vitro* susceptibility pattern) in a urine culture obtained within the first 30 days from the initiation of therapy with oral fosfomycin (test-of-cure urine culture). Episodes in which the test-of-cure culture was not obtained within the appropriate time frame were excluded.

Fosfomycin formulations. The two oral formulations of fosfomycin currently available in Spain (calcium fosfomycin and fosfomycin trometamol or tromethamine) were used in the present study. Dosing regimens differ for both formulations. Calcium fosfomycin is usually given at 500 to 1,000 mg every 8 h for at least 5 days (28). A single dose of the trometamol formulation is the regimen approved in Spain and other European countries for the treatment of uncomplicated cystitis in women. However, although there are no specific dosing recommendations for patients with renal dysfunction, multiple-dose regimens are commonly used in clinical practice.

Microbiological methods. Antimicrobial susceptibility testing was performed at each participating center by the methodology established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), and MIC values were interpreted according to the proposed clinical breakpoints or extrapolated for those microorganisms for which no interpretative categories have yet been established (i.e., *Pseudomonas aeruginosa*) (29).

Study definitions. Asymptomatic bacteriuria (AB) was defined as the presence of $>10^5$ bacterial CFU/ml in quantitative culture performed in a single clean-catch voided urine specimen in the absence of signs or symptoms attributable to UTI (6). Multidrug resistance (MDR) was defined by the demonstration of acquired resistance to at least one agent in $\geq$3 different categories of antibiotics (30). Salvage therapy was defined by the use of oral fosfomycin following documented microbiological failure with another antibiotic agent. A treatment-related adverse event (AE) was graded as severe if it promoted fosfomycin to be discontinued before the scheduled end of therapy, led to acute kidney injury (defined according to the RIFLE criteria [31]) within the first 72 h from the first dose, or required hospitalization and/or administration of intravenous therapy.

Statistical analysis. Quantitative variables are shown as the means ± standard deviations (SDs) or the medians with interquartile ranges (IQRs). Qualitative data are expressed as absolute and relative frequencies. The χ^2 test or Fisher's exact test were used to compare categorical variables, as appropriate. The Student's *t* test or Mann-Whitney U test was applied for continuous variables. A multivariate logistic regression model was constructed to identify independent risk factors predicting microbiological failure after adjusting for confounding variables. Those factors that were found to be significant at the univariate level were included as explanatory variables in a backward stepwise fashion. Associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The Hosmer-Lemeshow test was used to evaluate the goodness of fit of the model. All tests were two tailed. A *P* value of <0.05 was set for statistical significance. Statistical analysis was performed with SPSS version 22.0 (IBM Corporation, Armonk, NY).

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