American Journal of Transplantation 2016; 16: 2943–2953
Wiley Periodicals Inc.

doi: 10.1111/ajt.13829

Should Asymptomatic Bacteriuria Be Systematically Treated in Kidney Transplant Recipients? Results From a Randomized Controlled Trial

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This study was partially presented at the 25th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Copenhagen, Denmark (April 25–28, 2015).

The indication for antimicrobial treatment of asymptomatic bacteriuria (AB) after kidney transplantation (KT) remains controversial. Between January 2011 and December 2013, 112 KT recipients that developed one episode or more of AB beyond the second month after transplantation were included in this open-label trial. Participants were randomized (1:1 ratio) to the treatment group (systematic antimicrobial therapy for all episodes of AB occurring ≤24 mo after transplantation [53 patients]) or control group (no antimicrobial therapy [59 patients]). Systematic screening for AB was performed similarly in both groups. The primary outcome was the occurrence of acute pyelonephritis at 24-mo follow-up. Secondary outcomes included lower urinary tract infection, acute rejection, *Clostridium difficile* infection, colonization or infection by multidrug-resistant bacteria, graft function and all-cause mortality. There were no differences in the primary outcome in the intention-to-treat population (7.5% [4 of 53] in the treatment group vs. 8.4% [5 of 59] in the control group; odds ratio [OR] 0.88, 95% confidence interval [CI] 0.22–3.47) or the per-protocol population (3.8% [1 of 26] in the treatment group vs. 8.0% [4 of 50] in the control group; OR 0.46, 95% CI 0.05–4.34). Moreover, we found no differences in any of the secondary outcomes. In conclusion, systematic screening and treatment of AB beyond the second month after transplantation provided no apparent benefit among KT recipients (NCT02373085).

Abbreviations: AB, asymptomatic bacteriuria; ATG, antithymocyte globulin; CI, confidence interval; CMV, cytomegalovirus; eGFR, estimated GFR; ESRD, end-stage renal disease; ITT, intention-to-treat; KT, kidney transplantation; MDR, multidrug-resistant; mPP, modified per-protocol; OR, odds ratio; PP, per-protocol; SD, standard deviation; TMP-SMX, trimethoprim/sulfamethoxazole; UC, urine culture; UTI, urinary tract infection

Received 03 November 2015, revised 04 April 2016 and accepted for publication 08 April 2016

Introduction

Urinary tract infections (UTIs) are the most common infectious complications in kidney transplant (KT) recipients (1–3). Asymptomatic bacteriuria (AB) occurs frequently during the first year after transplantation, with reported incidence of up to 50% (4). The benefit of screening for and treating AB had been proven only during pregnancy and in patients undergoing urological procedures with anticipated mucosal disruption (5). Nevertheless, and despite recommendations supported for decades, a recent trial questioned the utility of this strategy in pregnant women (6). Studies performed in other populations (i.e. diabetic or elderly women or patients with long-term catheterization) failed to demonstrate any effect from this intervention (7–13).

Controversy has been ongoing about the common practice of administrating antimicrobial therapy in KT recipients with AB, taking into account the potential risk of progression to symptomatic UTI and, alternatively, the consequences of antimicrobial overuse in terms of emergence of multidrug-resistant (MDR) bacteria, incidence of *Clostridium difficile* infection and increased economic cost (14–16).

The latest Infectious Diseases Society of America guidelines concluded that no recommendation can be made on this subject (grade of evidence CIII) (5), whereas other guidelines do not make any specific recommendations (17,18). Our group and others have found higher rates of symptomatic UTI among KT recipients with recurrent AB compared with those without this event (4,19,20). It remains unclear whether treatment of posttransplant AB can reduce subsequent episodes of symptomatic UTI or provide any other benefit.

To our knowledge, the present study is the first randomized clinical trial evaluating an approach based on the systematic screening for and antimicrobial treatment of posttransplant AB among KT recipients, with the ultimate aim of decreasing the subsequent risk of symptomatic UTI and the detrimental impact of this complication on graft and patient outcomes.

Materials and Methods

Study population and setting

The present open-label, parallel-group, randomized trial was performed between January 2011 and December 2013 at the University Hospital "12 de Octubre" (Madrid, Spain). Adult KT recipients (aged ≥18 years) who developed at least one episode of AB beyond the second month after transplantation were deemed potentially eligible. This set point was chosen to enroll patients as soon as possible after transplantation because most urological complications should have resolved by the second month. Exclusion criteria included pregnancy, kidney–pancreas transplantation and the presence of a double-J ureteral stent or indwelling urethral catheter at randomization. Potentially eligible patients that had already developed one episode or more of AB beyond the second month (regardless of whether or not they received antibiotic therapy) at the time of randomization were also excluded, as were those suffering from graft loss within the first 2 mo after transplantation.

The local ethics committee approved the study protocol, and written informed consent was obtained from each patient, in accordance with the Declaration of Helsinki. This trial was performed in adherence to the Declaration of Istanbul and is registered at ClinicalTrials.gov (NCT02373085).

Randomization and masking

Participants were randomized (1:1 ratio) using a predetermined computer-generated sequence (generated with an online randomization service [Sealed Envelope Ltd., London, UK]) and consecutively numbered sealed envelopes. Each participant was assigned to either the treatment group (systematic antimicrobial therapy for AB [experimental arm]) or the control group (no antimicrobial treatment [control arm]). Because of its design, the tested intervention could not be blinded for patients, attending physicians or investigators.

Study design and intervention

The posttransplant follow-up schedule was identical for both cohorts. The monitoring plan was intended to be as close as possible in an attempt to minimize the risk of misdiagnosis of AB. Patients were seen at the outpatient clinic at least every other week during the first 3 mo, monthly until the first year, and every 1–3 mo thereafter. They were asked about symptoms of UTI at each of these contacts. A midstream urine specimen was systematically obtained for culture at each visit and, whenever necessary, in the presence of symptoms suggestive of UTI. Dedicated nurses instructed the patients in the proper collection of urinary samples to minimize the risk of contamination. In case of contamination of the culture, a repeated sample was to be obtained within the following month or as soon as possible in the presence of urinary tract symptoms. Episodes of symptomatic UTI diagnosed throughout the study period received empirical antimicrobial therapy with subsequent adjustment, if necessary, according to the antimicrobial susceptibility testing results. Episodes of AB diagnosed within the first 2 mo were treated systematically in both study groups. Beyond that point, patients allocated to the treatment group received therapy for subsequent episodes of AB occurring up to 24 mo after KT with an appropriate antibiotic according to antimicrobial susceptibility testing. The first episode of AB was treated for 3–7 days, and the first relapse (as defined below) was treated for 14 days. In the presence of two or more relapses, a urinary tract ultrasound examination was ordered to rule out obstruction, and a 6-week antibiotic course was prescribed. If a further relapse was detected, long-term suppressive therapy with low doses of antibiotic was set up for 6 mo (21). Reinfections (as defined in the "Study definitions" section) were treated like the first episode (for 3–7 days). A follow-up urine culture (UC) for test of cure was ordered 2 weeks after completion of therapy in every episode of UTI or treated AB in both study groups. If this UC was contaminated, a repeated sample was to be collected within the next 2 weeks. If this second culture was also contaminated, and provided that the patient remained asymptomatic, a bacteriological cure was clinically assumed.

Patients allocated to the control group were also systematically screened for AB throughout this period, but episodes of AB remained untreated. Episodes of AB were considered treated if the patient received concurrent antimicrobial treatment for another cause and the agent used was active against the isolated uropathogen. Prophylaxis with trimethoprim/sulfamethoxazole was not taken into account because it was similarly administered to both study groups (160/800 mg three times weekly during the first 9 mo), and the resistance rate to this agent among uropathogens isolated from KT recipients in our center exceeded 80% at the beginning of the recruitment period (22). The follow-up period extended to the first 24 mo after transplantation unless acute pyelonephritis, graft loss, or death occurred sooner.

Data were analyzed on intention-to-treat (ITT) and per-protocol (PP) bases. The ITT population consisted of all randomized participants, whereas the PP population included only those who adhered strictly to the study protocol (i.e. receipt of antibiotic treatment for every episode of AB in the treatment group and for none in the control group). Because the number of patients in the treatment group in which the planned intervention was strictly fulfilled turned out to be lower than expected, an additional modified PP (mPP) analysis was created *post hoc*. For this analysis, we selected those patients allocated to the treatment group who received an appropriate course of antimicrobial therapy (i.e. effective antibiotic according to antimicrobial susceptibility testing in adequate doses for an appropriate duration) for all episodes of AB (if the overall number of episodes was one or two) or for at least two thirds of the episodes, if the overall number of episodes of AB was three or more. Details of immunosuppression and prophylaxis regimens, as well as surgical procedures, are provided in the Supplementary Methods in the Supporting Information.

Study outcomes and follow-up

The primary study outcome was the cumulative incidence of the first episode of acute pyelonephritis at the end of follow-up. Although most previous studies evaluated the occurrence of all forms of symptomatic UTI (23–25), we decided to limit the primary outcome to acute pyelonephritis because the diagnosis of this entity is well defined and consistent among different physicians. In contrast, it is more likely that lower UTI may be

overdiagnosed and that antimicrobial treatment may be initiated solely on the presence of vague voiding symptoms. Secondary outcomes included long-term graft function estimated at months 12 and 24 after transplantation; all-cause mortality; and cumulative incidences of lower UTI, acute graft rejection, *Clostridium difficile* infection, colonization or infection due to MDR bacteria, and graft loss at the end of the follow-up period.

Study definitions

Significant bacteriuria in women was defined as two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts $\geq 10^5$ colony-forming units per milliliter, whereas a single clean-catch voided urine specimen was sufficient for diagnosis in male patients (5). The diagnosis of AB required the presence of significant bacteriuria in a patient without any signs or symptoms of UTI (5). The term *UTI* was restricted to symptomatic episodes of monomicrobial invasion of the urinary tract and comprised both lower UTI and acute pyelonephritis. Lower UTI was defined by the presence of bacteriuria and irritative voiding symptoms (dysuria, frequency, or urgency) in the absence of diagnostic criteria for pyelonephritis. Acute pyelonephritis was defined by the simultaneous presence of fever and bacteriuria and/or bloodstream infection along with at least one of the following: lumbar pain, graft pain, chills and/or irritative voiding symptoms (5). Bacteriological cure was defined as the absence of the pathogen isolated in the pretreatment UC (the same species with an identical antimicrobial susceptibility profile) at 2 weeks from completion of the antibiotic course or as the spontaneous resolution of AB. Relapse was defined by the isolation of the same pathogen found in the pretreatment isolate within the first 2 weeks after completion of the antibiotic therapy. Minor differences in antimicrobial susceptibility profiles that could be attributable to the intra-assay variability of the broth microdilution method were allowed.

Reinfection was defined by the isolation of either a different microorganism or the same species with a different antimicrobial-susceptibility profile within the first 2 weeks after the completion of the antibiotic course or by the isolation of any microorganism once the prior UC obtained for test of cure was negative. *C. difficile* infection was defined as the passage of three or more unformed stools in 24 h in the presence of a positive stool test for toxigenic *C. difficile* (26). Multidrug resistance was defined as nonsusceptibility to at least one agent in three or more antimicrobial categories (27). Acute graft rejection was suspected in cases with elevation of the serum creatinine levels and diagnosed by histological examination if possible (28). If renal biopsy was not technically possible, episodes responding to empirical antirejection therapy were also taken into account. Graft loss included permanent return to dialysis or retransplantation. Estimated GFR was assessed by means of the MDRD equation (29). Delayed graft function denoted the need for dialysis within the first week after transplantation.

Bacterial identification and susceptibility testing

Urine samples were obtained and processed in accordance with current recommendations (30) and cultivated using calibrated loop 1/100 and the automatic inoculation system WASP (Walk Away Specimen Processor Instrument; Copan Diagnostics Inc, Murrieta, CA) on blood and MacConkey agars at 36°C for 18–24 h. Bacterial identification and antimicrobial susceptibility testing were performed by the automatic system MicroScan Walkaway (Siemens, Sacramento, CA) and interpreted according to the Clinical and Laboratory Standard Institute guidelines until 2012 and by the European Committee for Antimicrobial Susceptibility Testing guidelines afterward.

Sample size calculation

The required sample size was estimated for the hypothesis that the application of a strategy based on the systematic screening for and treatment of AB would decrease the risk of developing the primary study outcome compared with usual care. Based on our previous experience (4,19) in which this strategy was associated with lower incidence of acute pyelonephritis than that reported in previous studies, we designed a superiority rather than a noninferiority clinical trial. We expected 23% cumulative incidence of acute pyelonephritis in the control group (20,23,24). Using a two-tailed χ^2 test and assuming a type I error (α) of 5%, a sample size of 110 patients (55 per arm) ensured statistical power ($1-\beta$) of 90% to detect an absolute risk reduction of 20% between study groups.

Statistical analysis

Qualitative variables were expressed as absolute and relative frequencies. Quantitative data were shown as the mean plus or minus standard deviation or the median with range. Categorical variables were compared using the χ^2 test or Fisher exact test, whereas the Student t-test or Mann–Whitney *U* test was applied for continuous variables, as appropriate. The effect of the tested intervention on the study outcomes was expressed as odds ratios with 95% confidence intervals. Only the first episode of each outcome was considered to estimate cumulative incidence at the end of follow-up. All tests were two-tailed, and a p-value <0.05 was deemed significant. Statistical analysis was performed using SPSS version 22.0 (IBM Corp, Armonk, NY).

Results

Patient disposition and baseline characteristics

Overall, 392 of 444 patients that underwent KT during the study period were potentially eligible. At least one episode of AB beyond the second month after transplantation was detected in 154 patients (39.3%). Three patients refused to participate, nine were excluded because of the presence of an indwelling urinary catheter, and 30 were excluded because they had already been diagnosed with AB beyond the second month once they were screened for eligibility and prior to randomization. Basal characteristics of these patients did not differ significantly from the rest of the cohort. Finally, 112 patients underwent randomization, 53 in the treatment group (systematic antimicrobial therapy for all episodes of AB [experimental arm]) and 59 in the control group (no antimicrobial therapy [control arm]), and constituted the ITT population (Figure 1). Both groups were well balanced in their demographics and clinical characteristics (Table 1). Details of the UTI episodes that occurred within the first 2 mo after transplantation (i.e. prior to study inclusion) are available in the Supporting Information (Table S1). Overall, 27 episodes of graft rejection were diagnosed in 22 patients throughout the study period (Table S2).

Inclusion and follow-up

The first and last participants were included April 17, 2011, and February 28, 2014, respectively. The median interval from transplantation to study inclusion was 83 days (range 57–606 days). Only nine patients (8.0%) were included beyond the first year after transplantation. The 12- and 24-mo follow-up periods were completed for 98 (86.6%) and 61 (54.4%) patients, respectively. Fourteen patients were

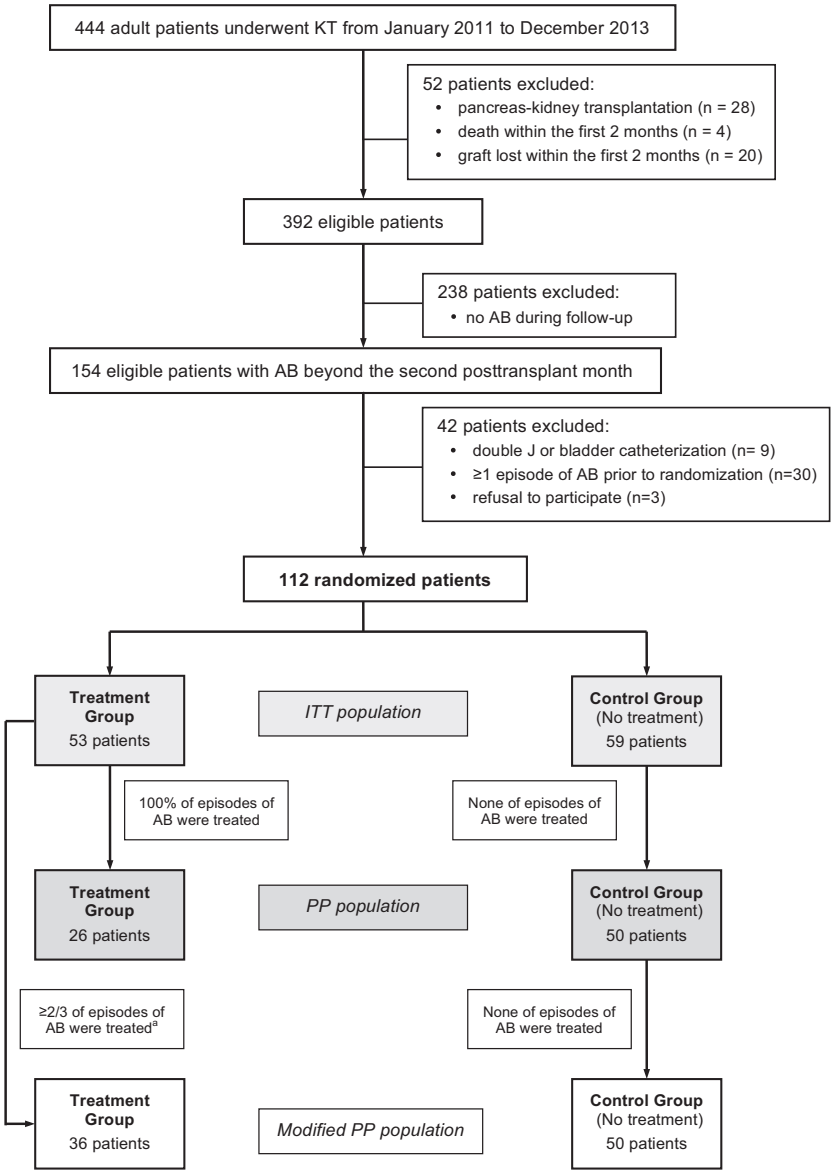

Figure 1: Patient flow diagram. [a]The modified PP population comprised those patients that received an appropriate course of antimicrobial therapy for all episodes of AB (if the overall number of episodes was one or two) or for at least two thirds of the episodes, if the overall number of episodes of AB was three or more. AB, asymptomatic bacteriuria; ITT, intention-to-treat; KT, kidney transplantation; PP, per-protocol.

withdrawn from the study because of the development of the primary study outcome (nine patients), death (three patients) or graft loss (two patients).

Median posttransplant follow-up period for the overall cohort was 24 mo (range 2.73–24 mo). This follow-up was <12 mo in nine patients, as per study protocol (eight developed the primary study outcome and one had graft loss). Another five patients were followed for <12 mo (but >9 mo) after transplantation. Median postenrollment follow-up period for the overall cohort was 16.9 mo (range 0.43–22 mo). This follow-up was <12 mo in 19 patients, as per study protocol (nine developed the primary outcome, one died, one had graft loss and eight reached month 24 after transplantation). Another 14 patients were followed for <12 mo (but >6 mo) after enrollment.

Study protocol compliance

Given the high number of UCs ordered throughout the study period (18.15 ± 6.2 per patient), occasional protocol violations were unavoidable. Consequently, only 49.1% (26 of 53) and 84.7% (50 of 59) of patients in the treatment and control groups, respectively, strictly fulfilled the study protocol and constituted the PP

Table 1: Demographics and baseline clinical characteristics (intention-to-treat population)[1]

	Treatment group (n = 53)	Control group (n = 59)
Age of recipient, years, mean ± SD	55.4 ± 14.5	53.04 ± 15.8
Male sex, n (%)	28 (52.8)	31 (52.5)
Pretransplant diabetes mellitus, n (%)	18 (34)	13 (22)
Previous KT, n (%)	7 (13.2)	9 (15.3)
Double KT, n (%)	2 (3.8)	0 (0.0)
Etiology of underlying ESRD, n (%)		
Glomerulonephritis	10 (18.9)	14 (23.7)
Diabetic nephropathy	15 (28.3)	11 (18.6)
Nephroangiosclerosis	3 (5.7)	8 (13.6)
Polycystosis	11 (20.8)	5 (8.5)
Other	14 (26.4)	21 (35.6)
Pretransplant dialysis, n (%)	47 (88.7)	53 (89.8)
Dialysis vintage, mo, median (range)	12.96 (0–98)	18.6 (0–198)
Age of donor, years, mean ± SD	56.2 ± 15.5	54.2 ± 15.2
Type of donor, n (%)		
Donor after brain death	26 (49.1)	37 (62.7)
Donor after circulatory death	21 (39.6)	16 (27.1)
Living donor	6 (11.3)	6 (10.2)
CMV serostatus, donor-positive/recipient-negative, n (%)	4 (7.5)	5 (8.5)
Cold ischemia time, h, mean ± SD	16.5 ± 8.1	16.3 ± 7
Number of HLA mismatches, mean ± SD	4 (0–6)	5 (0–6)
Induction therapy with ATG, n (%)	26 (49.1)	21 (35.6)
Anti-CMV prophylaxis, n (%)	26 (49.1)	28 (47.5)
Double-J urinary stent in place, n (%)	32 (60.4)	31 (52.5)
Length of catheterization, days, mean ± SD	28.5 ± 9.6	30.8 ± 12
Bladder catheterization >15 days, n (%)	16 (30.2)	18 (30.5)
Bladder catheterization >30 days, n (%)	2 (3.7)	3 (5.1)
Total length of hospitalization, days, median (range)	14 (7–44)	16 (8–67)
Prophylaxis for *Pneumocystis jirovecii* (TMP-SMX for 9 mo)[2]	52 (98.1)	57 (96.6)
Early posttransplant complications, n (%)		
Transfusion requirement[3]	9 (16.9)	18 (30.5)
Reintervention within the first 7 days after transplant	2 (3.8)	4 (6.8)
Reintervention within the first 30 days after transplant	5 (9.4)	6 (10.2)
Delayed graft function	28 (52.8)	35 (59.3)
Urinary tract infection[4]	7 (13.2)	9 (15.2)
Acute pyelonephritis[4]	5 (9.4)	4 (6.8)
Postoperative seroma/lymphocele[4]	6 (11.3)	13 (22)
Urinary fistula[4]	3 (5.7)	4 (6.8)
Surgical site infection[4]	4 (7.5)	9 (15.3)
Acute graft rejection[4]	4 (7.5)	6 (10.1)
Colonization/infection by MDR bacteria, n (%)[4,5]	9 (16.9)	9 (15.2)
Interval from transplantation to enrollment, days, median (range)	81 (60–606)	91 (57–500)
Posttransplant follow-up, mo, median (range)	21.7 (3.6–24)	24 (2.73–24)
Postenrollment follow-up, mo, median (range)	16.8 (1.4–22)	17 (0.43–22)
eGFR at enrollment, mL/min/1.73 m^2, mean ± SD	41.2 ± 20.4	41.8 ± 21.5
Obstructive uropathy after enrollment, n (%)	2 (3.7)	2 (3.4)

ATG, antithymocyte globulin; CMV, cytomegalovirus; eGFR, estimated GFR; ESRD, end-stage renal disease; KT, kidney transplantation; MDR, multidrug-resistant; SD, standard deviation; TMP-SMX, trimethoprim/sulfamethoxazole.

[1]There were no significant differences between study groups for any of the variables.

[2]The remaining three patients received intravenous pentamidine.

[3]During the transplant procedure or within the first week.

[4]Within the first 2 mo after transplant (i.e. prior to study inclusion).

[5]Isolates included extended spectrum β-lactamase–producing *Escherichia coli* (n = 7), extended spectrum β-lactamase–producing *Klebsiella pneumoniae* (n = 3), carbapenemase-producing *Enterobacter cloacae* (n = 2), carbapenemase-producing *K. pneumoniae* (n = 2), and MDR *Pseudomonas aeruginosa* (n = 2).

population. As detailed in the "Materials and Methods" section, we performed an additional mPP analysis in which 67.9% of patients allocated to the treatment group (36 of 53) were taken into account (Figure 1). Test of cure was performed at the scheduled time (i.e. 2 weeks after completion of therapy) in 90% of

episodes. In the remaining cases, the median interval between the initial positive UC and the test of cure was 35 days (range 20–120 days).

Analysis of AB episodes

The 112 patients included in the study developed 439 episodes of AB (204 in the treatment group and 235 in the control group). There were no differences in number of episodes per patient between groups (3.74 ± 2.8 in the treatment group vs. 4.08 ± 3.3 in the control group; p = 0.55). Antimicrobial treatment was administered for 143 (32.6%) episodes (131 [64.2%] in the treatment group and 12 [5.1%] in the control group). The most common uropathogen was *Escherichia coli* (43.3% of episodes), followed by *Klebsiella pneumoniae* (17.9%), *Enterococcus faecalis* (11.4%), and *Pseudomonas aeruginosa* (7.3%). Details about the episodes of AB that received antibiotic therapy in patients allocated into the control group are provided in Table S3.

Data on the microbiological features, antibiotic courses and rates of bacteriological cure for the 131 episodes of AB diagnosed in patients within the treatment group are available in Tables S4 and S5. In 46 of these episodes (35.1%), the test-of-cure UC demonstrated the persistence of the same microorganism (i.e. the same species with identical antimicrobial-susceptibility profile) despite therapy, whereas 18 episodes (13.7%) yielded a different uropathogen; therefore, sterilization in follow-up UC was achieved in only 51.1% (67 of 131) of those episodes of AB that were intentionally treated within the tested intervention.

Of the 296 episodes of AB that remained untreated, 175 (59.1%) showed persistence of the same uropathogen, 24 (8.1%) had a follow-up UC yielding a different microorganism, and 97 (32.7%) experienced spontaneous clearance. As expected, the probability of persistence of the same uropathogen in the follow-up cultures was lower in treated episodes (35.1% [46 of 131] vs. 59.1% [175 of 296]; p < 0.0001). In contrast, the probability of developing AB by a different microorganism in the control UC was higher if the episode was treated (13.7% [18 of 131] vs. 8.1% [24 of 296]; p = 0.07).

The probability of bacterial clearance, either spontaneously or with antimicrobial therapy, was lower in episodes of AB caused by *K. pneumoniae* (rate of persistence of the uropathogen in the follow-up UC: 70.8% [56 of 79] for *K. pneumoniae* vs. 47.2% [170 of 360] for the remaining microorganisms; p < 0.0001). This difference remained in episodes that were treated (58.3% vs. 31.1%; p = 0.01) and untreated (76.3% vs. 55.2%; p = 0.004). The persistence of the same microorganism in the follow-up culture was also more frequent if the initial episode of AB was caused by MDR bacteria (72.9% [78 of 107] vs. 44.5% [148 of 332]; p < 0.0001).

The cumulative incidence of acute pyelonephritis and lower UTI were 8.0% (9 of 112) and 15.2% (17 of 112), respectively. Of all 439 episodes of AB occurring in both groups, only 16 (3.6%) were followed by UTI caused by the same microorganism. Six of these UTIs were acute pyelonephritis, with a median interval between the detection of AB and symptom onset of 8.5 days (range 3.8–42.0 days). The remaining 10 episodes were categorized as lower UTI (median interval between the detection of AB and symptoms onset: 34.0 days [range 13.0–52.0 days]). Of these 16 episodes of AB preceding UTI, five were treated and 11 were left untreated. Of note, three episodes of pyelonephritis and 12 episodes of lower UTI occurred in the absence of previous AB caused by the same microorganism.

Study outcomes

There were no differences in the incidence of acute pyelonephritis in the ITT population (7.5% [4 of 53] in the treatment group vs. 8.4% [5 of 59] in the control group; p = 1.00) (Table 2). There were also no differences when the analyses were restricted to the PP population (3.8% [1 of 26] vs. 8.0% [4 of 50]; p = 0.65) or the mPP population (5.5% [2 of 36] vs. 8.0% [4 of 50]; p = 1.00) (Tables 3 and 4). Finally, we found no significant differences in any of the secondary outcomes regardless of the type of population analyzed (Tables 2–4). Detailed clinical and microbiological characteristics of the nine episodes of acute pyelonephritis and the 22 episodes of lower UTI are provided in the Supporting Information (Tables S6 and S7). In addition, the temporal relationships between acute pyelonephritis and rejection in the four patients with both complications are detailed in Table S8.

Seven of the 50 patients (14.0%) allocated into the control group that remained free of UTI during the entire follow-up period despite not receiving treatment for any episode of AB showed persistent AB due to the same microorganism for a median of 7 mo (range 6–14 mo).

Adverse events

No severe adverse events attributable to the tested intervention were reported. Two patients experienced mild diarrhea in relation with a course of amoxicillin/clavulanate. One patient had nausea and refused to receive additional antibiotic therapy.

The cumulative incidence of *C. difficile* infection in the ITT population was 5.7% (3 of 53) in the treatment group and 8.5% (5 of 59) in the control group (p = 0.72). A single patient, allocated to the treatment group, developed *C. difficile* infection after being treated with ertapenem for an episode of AB; therefore, the complication could be directly attributable to the intervention. Three patients had not previously received antibiotic therapy for AB at the time of diagnosis of *C. difficile* infection, whereas the remaining four were treated for AB within the first 2 mo after transplantation or for symptomatic UTI.

Table 2: Occurrence of study outcomes in the study groups (intention-to-treat population)

	Treatment group (n = 53)	Control group (n = 59)	OR (95% CI)	p-value
Primary study outcome				
Acute pyelonephritis, n (%)	4 (7.5)	5 (8.4)	0.88 (0.22–3.47)	1.00
Secondary study outcomes				
Lower UTI, n (%)	7 (13.2)	8 (13.5)	0.97 (0.32–2.88)	0.95
Overall UTI, n (%)	11 (20.7)	11 (18.6)	1.14 (0.45–2.90)	0.78
Hospital admission for UTI, n (%)	2 (3.7)	3 (5.1)	0.73 (0.11–4.55)	0.73
Clostridium difficile infection, n (%)	3 (5.7)	5 (8.5)	0.65 (0.14–2.85)	0.72
Infection or colonization caused by MDR bacteria, n (%)	13 (24.5)	12 (20.3)	1.27 (0.50–3.10)	0.65
Acute graft rejection, n (%)	10 (18.9)	12 (20.3)	0.91 (0.35–2.32)	0.84
Graft loss, n (%)	1 (1.9)	1 (1.7)	1.11 (0.06–18.30)	1.00
All-cause mortality, n (%)	2 (3.8)	1 (1.7)	2.30 (0.20–25.80)	0.60
eGFR, mL/min/1.73 m^2, mean ± SD				
At month 12	46.3 ± 17.6	48.7 ± 18.5		0.50
At month 24	44.3 ± 14.4	47.9 ± 14.8		0.34
Number of UCs performed after enrollment, mean ± SD	17.5 ± 6.5	18.7 ± 6		0.32
Number of episodes of AB	204	235		
Isolated microorganisms, n (%)				
Escherichia coli	105 (51.5)	85 (36.2)		0.001
Klebsiella pneumoniae	33 (16.2)	46 (19.6)		0.38
Enterococcus faecalis	30 (14.7)	20 (8.5)		0.05
Pseudomonas aeruginosa	9 (4.4)	23 (9.8)		0.04
Klebsiella oxytoca	2 (0.9)	15 (6.4)		0.005
Enterobacter cloacae	3 (1.5)	12 (5.1)		0.06
Others	22 (10.7)	34 (14.4)		0.25

AB, asymptomatic bacteriuria; CI, confidence interval; eGFR, estimated GFR; MDR, multidrug-resistant; OR, odds ratio; SD, standard deviation; UC, urine culture; UTI, urinary tract infection.

MDR bacteria were isolated at some point during follow-up in 38.4% of the patients. After randomization, 25 patients developed colonization or infection, with no differences between groups in the ITT population (24.5% [13 of 53] in the treatment group vs. 20.3% [12 of 59] in the control group; p = 0.65). Antibiotic therapy for AB was previously administered in nine patients in the treatment group and in two patients in the control group. No antibiotic therapy was administered prior to the first isolation of MDR bacteria in the remaining patients.

Discussion

Identification of potentially modifiable risk factors for posttransplant UTI is of foremost importance in view of the morbidity burden posed by this complication. Almost 40% of the recipients initially deemed eligible for the present trial experienced at least one episode of AB beyond the second month after transplantation, in keeping with previously observed rates (4). It is plausible that AB would favor the development of pyelonephritis through ascendant bacterial progression in the setting of immunosuppression, prior manipulation and nonanatomical urinary tract reconstruction. Based on this rationale and on the facts that immunosuppressive therapies can mask clinical signs of UTI and that pain may be absent in the denervated graft, physicians have historically tended to treat posttransplant AB, especially during the first year following transplantation. Nevertheless, in line with other high-risk populations in which the results from randomized trials have advocated changes in previous clinical practice (i.e. diabetic patients or pregnant women (6–13)), our study provides novel evidence against the implementation of systematic screening and treatment of AB among KT recipients with no current urinary tract instrumentation.

Several reasons may account for the negative results emerging from our trial. Only a minority (3.6%) of AB episodes were followed by a symptomatic UTI in which the same species with an identical antimicrobial susceptibility profile could be isolated. Of note, a third of the episodes of pyelonephritis were not preceded by AB caused by the same uropathogen and thus turned out not to be preventable by applying the tested strategy. In the remaining cases, the time interval elapsed between the detection of AB and symptom onset was markedly variable. In three of these episodes, the interval was so short that the initiation of targeted antimicrobial treatment was not possible because the antimicrobial susceptibility testing results were still pending. In contrast, the long time frame observed in two of the remaining episodes (>40 days) prevented the establishment of a causal link between the events.

Table 3: Occurrence of study outcomes in the study groups (per-protocol population)

	Treatment group (n = 26)	Control group (n = 50)	OR (95% CI)	p-value
Primary study outcome				
Acute pyelonephritis, n (%)	1 (3.8)	4 (8.0)	0.46 (0.05–4.34)	0.65
Secondary study outcomes				
Lower UTI, n (%)	2 (7.7)	6 (12.0)	0.61 (0.11–3.26)	0.71
Overall UTI, n (%)	3 (11.5)	8 (16.0)	0.68 (0.16–2.83)	0.74
Hospital admission for UTI, n (%)	0 (0.0)	2 (4.0)	0.65 (0.55–0.76)	0.54
Clostridium difficile infection, n (%)	2 (7.7)	3 (6.0)	1.30 (0.20–8.35)	1.00
Infection or colonization caused by MDR bacteria, n (%)	2 (7.7)	9 (18.0)	0.38 (0.07–1.90)	0.31
Acute graft rejection, n (%)	6 (23.1)	9 (18.0)	1.36 (0.43–4.37)	0.60
Graft loss, n (%)	1 (3.8)	1 (2.0)	1.96 (0.12–32.66)	1.00
All-cause mortality, n (%)	1 (3.8)	1 (2.0)	1.96 (0.12–32.66)	1.00
eGFR, mL/min/1.73 m^2, mean ± SD				
At month 12	45.9 ± 16.5	47.34 ± 15.3		0.72
At month 24	46.3 ± 16.3	47.1 ± 15.2		0.88
Number of UCs performed after enrollment, mean ± SD	17.6 ± 6.8	18.4 ± 5.9		0.61
Number of episodes of AB	57	153		
Isolated microorganisms, n (%)				
Escherichia coli	29 (50.9)	60 (39.2)		0.15
Klebsiella pneumoniae	5 (8.8)	12 (7.8)		0.78
Enterococcus faecalis	9 (15.8)	19 (12.4)		0.5
Pseudomonas aeruginosa	5 (8.8)	23 (15.0)		0.26
Klebsiella oxytoca	1 (1.8)	0 (0.0)		0.27
Enterobacter cloacae	0 (0.0)	10 (6.5)		0.06
Others	8 (14)	29 (18.9)		0.54

AB, asymptomatic bacteriuria; CI, confidence interval; eGFR, estimated GFR; MDR, multidrug-resistant; OR, odds ratio; SD, standard deviation; UC, urine culture; UTI, urinary tract infection.

We found a low rate of urine sterilization after the administration of susceptibility testing–guided antimicrobial therapy (51.1%) that was not so different from the rate observed for spontaneous clearance of AB (32.7%). The rate of bacteriological cure was even lower in episodes caused by *K. pneumoniae* or MDR bacteria, in line with a recent study on risk factors for recurrent UTI after KT (25). It is predictable that even if we were able to detect and treat every episode of AB in the usual clinical practice setting, urine sterilization would be achieved in fewer than half of the occasions. Of note, 14.0% of the patients allocated to the control group had persistent AB caused by the same uropathogen for >6 mo without developing symptoms. Consequently, detection of AB beyond the second month after transplantation seems to be a poor predictor of progression to symptomatic UTI.

There is no consensus currently on whether AB should be treated in KT recipients or, if deciding to treat, on the optimal posttransplant period during which this strategy should be applied. Two retrospective studies assessed the risk of progression to symptomatic UTI 1 month after a given episode of AB in KT recipients. El Amari et al found no differences between treated and untreated episodes of AB caused by *E. coli* or *E. faecalis* (31). Green et al were also unable to demonstrate differences in the primary end point, and they even reported worse outcomes among treated patients (32). Because the decision to treat or not treat the episodes of AB was not randomized in these studies, confounding by indication bias may be present.

The only quasirandomized prospective study that compared 43 recipients with treated AB and 45 recipients that did not receive therapy found no differences in the incidence of symptomatic UTI during 12-mo follow-up (33). This study, however, had certain limitations such as an unclear definition of study outcome and a lack of details of the chronological or microbiological link between asymptomatic and symptomatic episodes. Finally, because the authors did not include patients in the first year after transplantation, their results may not be applicable to the immediate posttransplant period.

Our study has the strength of being the first clinical trial focused on the potential impact of systematic screening and treatment of posttransplant AB on patient and graft outcome. Nevertheless, some limitations should be noted. Because the observed cumulative incidence of acute pyelonephritis in the control group was lower than expected, our sample size might have been underpowered, and a potential type 2 statistical error cannot be excluded. The clinical diagnosis of pyelonephritis was not confirmed histologically.

The major limitation of this study lies in the fact that compliance with the study protocol was lower than

Table 4: Occurrence of study outcomes in the study groups (modified per-protocol population)

	Treatment group (n = 36)	Control group (n = 50)	OR (95% CI)	p-value
Primary study outcome				
Acute pyelonephritis, n (%)	2 (5.5)	4 (8.0)	0.67 (0.11–3.91)	1.00
Secondary study outcomes				
Lower UTI, n (%)	3 (8.3)	6 (12.0)	0.66 (0.15–2.86)	0.73
Overall UTI, n (%)	5 (13.9)	8 (16.0)	0.84 (0.25–2.84)	0.78
Hospital admission for UTI, n (%)	1 (2.7)	2 (4.0)	0.68 (0.06–7.86)	1.00
Clostridium difficile infection, n (%)	2 (5.5)	3 (6.0)	0.92 (0.14–5.82)	1.00
Infection or colonization caused by MDR bacteria, n (%)	8 (22.2)	9 (18.0)	1.30 (0.45–3.78)	0.78
Acute graft rejection, n (%)	8 (22.2)	9 (18.0)	1.30 (0.45–3.78)	0.78
Graft loss, n (%)	1 (2.7)	1 (2.0)	1.40 (0.08–23.15)	1.00
All-cause mortality, n (%)	1 (2.7)	1 (2.0)	1.40 (0.08–23.15)	1.00
eGFR, mL/min/1.73 m^2, mean ± SD				
At month 12	46.36 ± 16.4	47.34 ± 15.3		0.79
At month 24	46.3 ± 15.2	47.1 ± 15.2		0.85
Number of UCs performed after enrollment, mean ± SD	17.7 ± 6.7	18.4 ± 5.9		0.64
Number of episodes of AB	112	153		
Isolated microorganisms, n (%)				
Escherichia coli	62 (55.4)	60 (39.2)		0.01
Klebsiella pneumoniae	11 (9.8)	12 (7.8)		0.66
Enterococcus faecalis	20 (17.9)	19 (12.4)		0.22
Pseudomonas aeruginosa	6 (5.4)	23 (15.0)		0.02
Klebsiella oxytoca	2 (1.8)	0 (0.0)		0.17
Enterobacter cloacae	0 (0.0)	10 (6.5)		0.06
Others	11 (9.8)	29 (18.9)		0.05

AB, asymptomatic bacteriuria; CI, confidence interval; eGFR, estimated GFR; MDR, multidrug-resistant; OR, odds ratio; SD, standard deviation; UC, urine culture; UTI, urinary tract infection.

expected because only half of the patients assigned to the treatment group strictly fulfilled the planned rigorous treatment protocol for every episode of AB occurring in the first 2 years after transplant. Although reflecting real-world clinical scenarios, this drawback implies that our results should be interpreted with caution.

A relatively high proportion of AB episodes were unnoticed or deliberately untreated in patients allocated to the experimental arm. A main reason for poor compliance with the preestablished protocol in these patients may have been the limited oral alternatives in case of AB caused by MDR bacteria. Most of the MDR strains were extended spectrum β-lactamase–producing *E. coli* and *Klebsiella* spp and carbapenemase-producing *Enterobacteriaceae*, which were mostly treated with oral courses of fosfomycin and amoxicillin/clavulanate. The failure to achieve bacteriological cure after several courses of antibiotic therapy, however, could have raised concerns among attending physicians regarding the emergence of higher resistance or drug-related toxicity and prompted them to decide not to treat subsequent episodes. Although two patients received outpatient intravenous treatment with ertapenem after failure of multiple oral courses and another six episodes of AB were treated with intravenous antibiotics during hospitalization for other reasons, it is difficult to assume that the routine administration of parenteral therapy for asymptomatic patients would become a feasible strategy in the clinical practice. Finally, 15% of patients in the control group were treated at some point during follow-up for different infectious syndromes with antimicrobial agents that also had *in vitro* activity against the uropathogens isolated in concurrent AB or had an episode of AB treated per the decision of the attending physician. These cases had also to be excluded from the PP and mPP analyses. Despite this limited protocol compliance, it should be noted that we found no apparent effect of the tested intervention, even in additional analyses restricted to PP or mPP populations.

In our opinion, poor protocol compliance might be considered a relevant result because it exemplifies the low feasibility of the tested strategy, even in the well-controlled setting of a clinical trial. Given the considerable prevalence of AB in this population, the high risk of recurrence —even after correct antimicrobial treatment—and the increasing resistance rates of uropathogens, the systematic treatment of all episodes of AB throughout the first years after transplantation appears to be an objective unlikely to be achieved.

In conclusion, according to the results of the present trial, the implementation of a strategy based on the systematic screening and treatment of episodes of AB occurring beyond the second month after transplantation,

in the absence of ureteral stents or urinary catheters, does not provide any apparent benefit. Although limited by small sample size and poor protocol compliance, our findings constitute preliminary evidence that might eventually lead to revision of the current recommendations for this controversial issue. Our research also may serve as a basis for further studies, which are urgently needed in light of the increasing threat posed by the emergence of MDR bacteria in the transplant setting.

Acknowledgments

This work was partially supported by the Fundación Mutua Madrileña de Investigación Médica (FMM Grant 2010/0015), by the Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III (Fondo de Investigaciones Sanitarias [FIS] 12/02269 and Proyecto Integrado de Excelencia [PIE] 13/00045), and by the European Development Regional Fund (EDRF) *"A way to achieve Europe"*. J.O. holds a research-training contract "Rio Hortega" (CM13/00180) from the Spanish Ministry of Economy and Competitiveness (Instituto de Salud Carlos III). M.F.R. holds a clinical research contract "Juan Rodés" (JR14/00036) from the Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III.

Disclosure

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

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary Methods.

Table S1: Clinical and microbiological characteristics of the episodes of urinary tract infection occurring within the first 2 mo after transplantation (prior to study inclusion).

Table S2: Characteristics of the episodes of graft rejection in both study groups.

Table S3: Clinical and microbiological characteristics of the episodes of asymptomatic bacteriuria in patients allocated into the control group that received antibiotic therapy.

Table S4: Details of the 131 courses of antibiotic therapy administered for episodes of asymptomatic bacteriuria in patients allocated into the treatment group.

Table S5: Microbiological data of the 131 episodes of asymptomatic bacteriuria that received antibiotic therapy in patients allocated into the treatment group.

Table S6: Detailed clinical and microbiological characteristics of the nine episodes of acute pyelonephritis occurring in both study groups.

Table S7: Clinical and microbiological characteristics of the episodes of lower urinary tract infection occurring during the study period.

Table S8: Clinical characteristics of the episodes of graft rejection diagnosed in patients that developed the primary study outcome.