

Antibiotic Treatment Versus No Treatment for Asymptomatic Bacteriuria in Kidney Transplant Recipients: A Multicenter Randomized Trial

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Background. Whether antibiotic treatment of asymptomatic bacteriuria (AB) can prevent acute graft pyelonephritis (AGP) in kidney transplant (KT) recipients has not been elucidated.

Methods. In this multicenter, open-label, nonblinded, prospective, noninferiority, randomized controlled trial, we compared antibiotic treatment with no treatment for AB in KT recipients in the first year after transplantation when urinary catheters had been removed. The primary endpoint was the occurrence of AGP. Secondary endpoints included bacteremic AGP, cystitis, susceptibility of urine isolates, graft rejection, graft function, graft loss, opportunistic infections, need for hospitalization, and mortality.

Results. We enrolled 205 KT recipients between 2013 and 2015. AB occurred in 41 (42.3%) and 46 (50.5%) patients in the treatment and no treatment groups, respectively. There were no differences in the primary endpoint in the intention-to-treat population (12.2% [5 of 41] in the treatment group vs 8.7% [4 of 46] in the no treatment group; risk ratio, 1.40; 95% confidence interval, 0.40–4.87) or the per-protocol population (13.8% [4 of 29] in the treatment group vs 6.7% [3 of 45] in the no treatment group; risk ratio, 2.07, 95% confidence interval, 0.50–8.58). No differences were found in secondary endpoints, except for antibiotic susceptibility. Fosfomycin ($P = .030$), amoxicillin-clavulanic ($P < .001$) resistance, and extended-spectrum β -lactamase production ($P = .044$) were more common in KT recipients receiving antibiotic treatment for AB.

Conclusions. Antibiotic treatment of AB was not useful to prevent AGP in KT recipients and may increase antibiotic resistance. However, our findings should be regarded with caution, due to the small sample size analyzed.

Key words. asymptomatic bacteriuria; kidney transplantation; pyelonephritis.

INTRODUCTION

Urinary tract infection is the most common complication in kidney transplant (KT) recipients, notably in the first months after KT, with an incidence that varies from 6% to 83% depending on whether symptomatic or asymptomatic infections are considered [1–5]. The most serious manifestation is acute graft pyelonephritis (AGP), which is the leading cause of bacteremia in this

population and is often complicated by acute graft dysfunction requiring hospitalization [6, 7]. Cytomegalovirus (CMV) infection, rejection, chronic allograft dysfunction, and mortality have also been associated with AGP in some studies [4, 5, 8–11].

Infections due to multidrug-resistant (MDR) organisms have become a serious problem in KT recipients [12] because of their association with higher complication and recurrences rates [13, 14]. Moreover, MDR infections require treatment with last resort antibiotics that are usually associated with more adverse events, including nephrotoxicity, which may be increased by the concomitant use of calcineurin inhibitors [15]. Given this worrisome scenario, effective strategies of antibiotic stewardship are urgently needed to reduce resistance rates while maintaining patient safety. When considering this, however, it is important that we acknowledge the key role of antibiotic pressure as the major driver for the selection of MDR bacteria.

Measures are needed to prevent AGP after KT, and the potential preventive role of antibiotic treatment for asymptomatic

Received 20 March 2019; editorial decision 15 May 2019; accepted 20 May 2019.

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DOI: 10.1093/ofid/ofz243

bacteriuria (AB) remains controversial [16, 17]. At present, the management of AB in KT recipients varies between transplant centers [18] and due to a lack of solid evidence [19–22]. However, recently published guidelines provide recommendations against screening and treating AB episodes after KT, especially within the first month following KT [23, 24]. Moreover, a randomized trial found no apparent benefit from screening and treating AB in 112 KT recipients beyond the second month after transplantation [25].

In this multicenter, randomized controlled trial (RCT), we aimed to test the hypothesis that no treatment for AB in KT recipients would be noninferior to antibiotic treatment in the prevention of AGP.

METHODS

Design and Study Endpoints

This prospective, multicenter, open-label, nonblinded, noninferiority RCT was conducted from January 2013 to September 2015. We compared the efficacies of antibiotic treatment and no treatment of AB to prevent AGP in KT recipients during the first year posttransplantation and after urinary catheters removal. The primary study endpoint was the incidence of the first episode of AGP. Secondary endpoints included AGP-related bacteremia, cystitis, acute graft rejection, opportunistic infections, hospitalization due to any cause, graft function, graft loss, mortality, and antimicrobial susceptibility of microorganisms isolated in urine cultures.

Setting and Study Population

The study was performed centrally in 2 university hospitals with active renal transplant programs in Barcelona. Patients were identified at each participating hospital by checking daily if a KT had been performed. Consecutive KT recipients were eligible for enrolment if they were aged 18 years or older, had received a KT in the previous month, and if they or their legal surrogate provided written informed consent. Patients were excluded from inclusion if they were already included in another clinical trial in which the treatment of AB was recommended or if they did not provide informed consent.

Randomization and Allocation Concealment

Randomization was performed by computer-generated random code allocation with a block size of ten. The program randomly assigned participants on a 1:1 basis to 2 parallel groups in 2 treatment arms, stratified by hospital site. A biostatistician held the random code centrally. One investigator in each hospital opened the sealed and sequentially numbered opaque envelopes for the randomly assigned patients who had provided written informed consent and met the study criteria. No attempt was made to conceal study arm intervention from patients or treating clinicians.

Intervention

Patients fulfilling the inclusion requirements were randomly assigned to receive antibiotic treatment or no treatment when

AB was documented. If AB occurred during follow-up, antibiotic treatment was prescribed for 5–7 days according to the susceptibility of the microorganism isolated in urine culture. If fosfomycin was used, a shorter antibiotic course of 1–3 days was considered appropriate. To avoid the interference of foreign bodies, study interventions only began when urethral and ureteral catheters had been removed. From KT to removal of urinary catheters, the decision whether to treat AB with antibiotics was made by the attending physician.

Follow-up and Outcomes Assessments

Clinical follow-up was performed by transplant physicians in outpatient settings at the following posttransplantation intervals: weekly in the first month, every 2 weeks from the second to third month, once monthly from the third to sixth month, and every 3 months from the sixth to the twelfth month. It was ensured that essential data about outcomes were registered and that all necessary urinary and blood samples were collected and analyzed. If the patients required other medical visits or needed hospitalization, the investigators evaluated them and relevant data were collected.

Urine cultures and blood analysis of graft function were done at every follow-up visit, plus when the attending physician considered testing necessary. Quantitative urine cultures were analyzed in cystine lactose electrolyte deficient agar with a 0.001 mL calibrated loop. Antibiotic susceptibility of isolated microorganisms was assessed by the disk-diffusion method, and the minimum inhibitory concentration was determined. If urine cultures were contaminated, they were considered negative and not repeated. Urine cultures were performed if symptoms of urinary infection were present, and blood cultures were performed if AGP was suspected clinically.

To evaluate the primary endpoint, all episodes of AGP during follow-up were carefully evaluated and recorded. Secondary endpoints also were registered. For all episodes of AB, isolated organisms and antibiotic susceptibilities were recorded. All antibiotics prescribed in patients assigned to the antibiotic group were recorded.

Definitions

AB was considered present if a patient without symptoms provided a single, clean-catch voided urine specimen with 1 bacterial isolate present at $\geq 10^5$ colony-forming units/mL. Cystitis was diagnosed if bacteriuria was present with symptoms of dysuria, frequency, and urinary urgency, without meeting the criteria for AGP. Acute graft pyelonephritis was defined by the simultaneous presence of fever with bacteriuria or bacteremia, or both, and 1 or more of the following: renal allograft tenderness, chills, or criteria for cystitis [21]. Contaminated urine culture was defined as a culture of urinary sample that grows 3 or more different types of bacteria. Allograft rejection was diagnosed based on impaired renal function with suggestive findings on renal biopsy. Graft loss was defined as loss of kidney

function necessitating chronic dialysis. Opportunistic infection was considered when any infection due to an opportunistic pathogen occurred during study follow-up (ie, CMV, BK virus). Hospitalization was defined as any hospital admission due to causes other than AGP. Mortality was defined as death due to any cause during study follow-up.

Exclusion Criteria Before Trial Intervention

We excluded patients with graft loss or who were lost to follow-up before urinary catheters were removed, as well as patients with surgical complications that prolonged the need for urinary catheters. KT recipients without documented AB during follow-up also were excluded.

Statistical Analysis

The sample size was estimated based on the hypothesis that no treatment would be noninferior to antibiotic treatment at affecting the incidence of AGP in KT recipients with AB. The required sample size was estimated for a noninferiority of 15% between the 2 management strategies and a probability that AGP would occur in 20%. This indicated that 100 patients would be necessary per group to achieve an estimated power of 65.8%, allowing for the likelihood that 40% of randomized patients would be excluded for not presenting with AB or for other reasons.

Data were collected and anonymously entered in a dedicated database that was reviewed periodically by descriptive analysis to detect illogical data. The baseline characteristics and outcome measures were compared by the χ^2 test for categorical variables and t test or nonparametric Mann-Whitney test for continuous variables, as appropriate. Noninferiority was defined as the upper limit of the 1-sided, 97.5% confidence interval (CI) of the difference in the incidence of AGP in KT recipients between study groups being $<15\%$. All statistical analyses were performed with R (version 3.4.1 for Windows).

The intention-to-treat (ITT) population was defined as KT recipients who developed AB within 12 months of follow-up after urethral and ureteral catheter removal. The per-protocol (PP) population comprised the ITT population that received antibiotic treatment or no treatment for AB according to randomization.

Ethical Issues

This trial is registered with the US National Library of Medicine at <https://clinicaltrials.gov/> as study number NCT01771432 and was conducted according to the principles of the Declaration of Helsinki (2008) and current Spanish legislation (Real decreto 223/2004). The principal investigator or collaborator at each site obtained written informed consent from all patients (or legal representatives if they lacked capacity) before enrollment. The study data were identified by a code, maintaining patient confidentiality in accordance with current legislation. The trial protocol, the informed consent form, and information sheet received research ethics committee approval. Clinical trial authorization was granted by the Spanish Agency for

Medicines and Health Products. In accordance with Spanish legislation governing clinical trials (RD 223/2004), this study had liability insurance covering possible damages to patients during their participation in the study (HDI Hannover International, Spanish branch, policy number 130/002/001691).

RESULTS

Study Population

The flow chart for study inclusion is shown in Figure 1. In total, 402 KTs were performed in the participating hospitals during the study period. Among these, 205 KT recipients were enrolled in the study and underwent randomization, wherein 102 were assigned to the antibiotic treatment group and 103 were assigned to the no treatment group. The median time from KT to study inclusion was 4 days (interquartile range [IQR] 3–7). Before protocol intervention, a further 17 KT recipients were excluded for different reasons. All of these patients were excluded early after KT and before urinary catheters were removed. Among the remaining 188 KT recipients, AB did not occur in 101 during follow-up (53.7%), so these were also excluded.

ITT and PP Populations

During the 12 month follow-up period, AB was documented in 41 patients in the antibiotic treatment group and in 46 patients in the no treatment group. The median follow-up from the first episode of AB in the ITT population was 302 days (IQR 244–321.5) in antibiotic treatment group and 277 days (IQR 226.5–329) in no treatment group, while in the PP population it was 308 days (IQR 223–323) in antibiotic treatment group and 281 days (IQR 226–330) in no treatment group. The median time between KT and the first episode of AB was 58 days (IQR 46–121) in antibiotic treatment group and 68 days (IQR 44.75–117.25) in no treatment group. In the PP population, the mean days between KT and the first episode of AB was 53 days (IQR 44.5–117.5) in antibiotic treatment group and 68 days (IQR 44.5–113) in the no treatment group of AB. The baseline characteristics of the ITT populations were comparable and are detailed in Table 1. In 12 KT recipients assigned to receive antibiotic treatment, no antibiotic was prescribed despite AB being identified; also, a single KT recipient assigned to the no treatment group received antibiotic therapy when AB was present. Consequently, the PP population included 29 KT recipients in the antibiotic treatment group and 45 KT recipients in the no treatment group. No differences were found in baseline characteristics of the PP population.

Urine Cultures

In the ITT population, the mean number of urine cultures obtained per KT recipient with AB was 7.5 and 7.8 in the antibiotic treatment and no treatment groups, respectively. The mean number of positive urine cultures was comparable in each group with AB (2.7 in the antibiotic treatment group and 2.8 in the no treatment group). More than 70% of KT recipients in

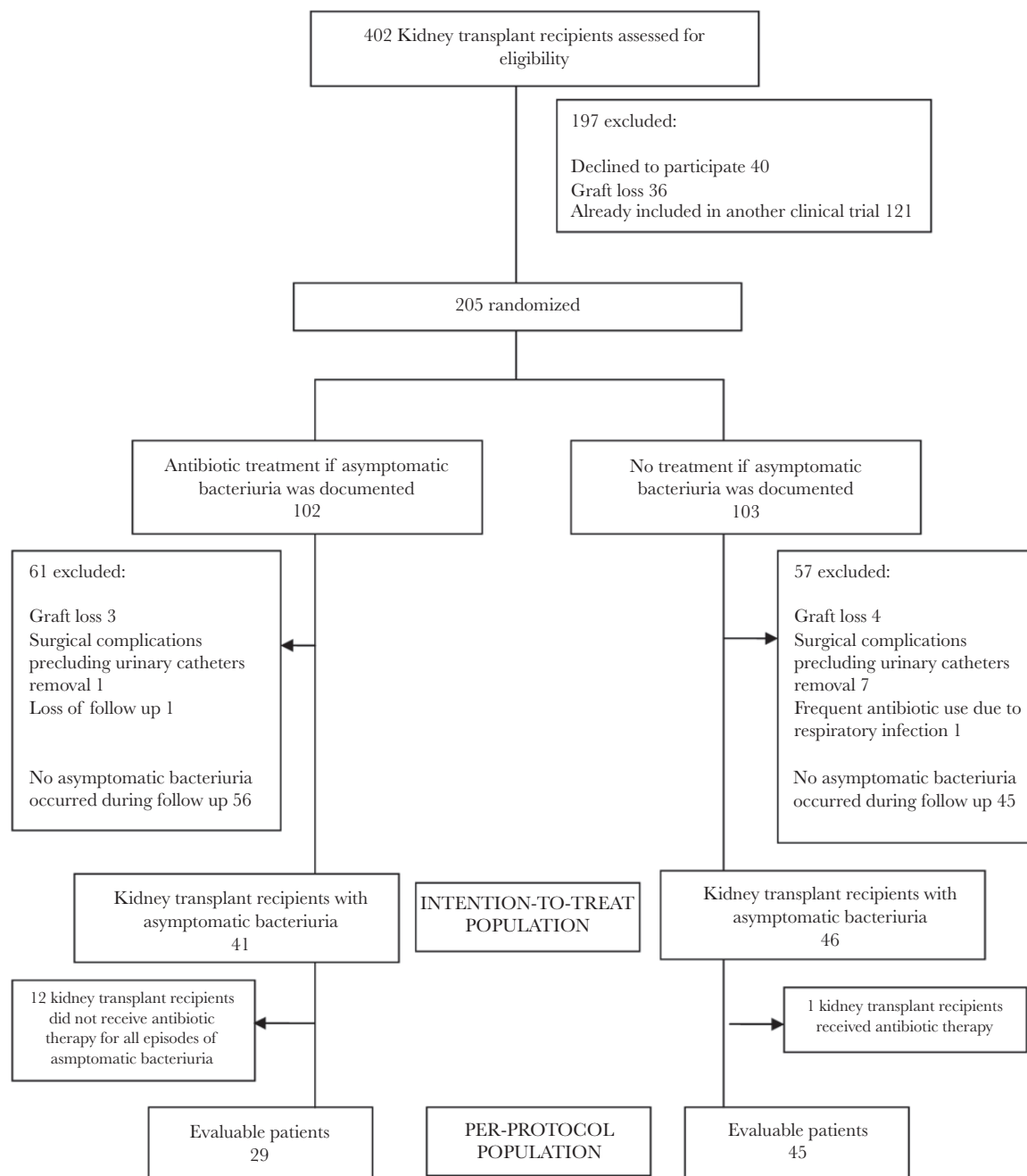


Figure 1. Flow Diagram of the Study

each group had 2 or more episodes of AB during follow-up. The mean number of contaminated urine cultures obtained per KT recipient in the ITT population was 1.1 in the antibiotic treatment group and 1.5 in the no treatment group. In the ITT population, 114 episodes of AB were documented in the treatment group and 77 (67.5%) were treated with antibiotics. In the no treatment group, 129 episodes of AB occurred and 4 (3.1%) of them were treated with antibiotics.

In the PP population, the success rate in clearing AB in antibiotic treatment group was 36.2% (25 of 69 episodes) and 45.7%

(38 of 83 episodes) in no treatment group, excluding urine cultures performed in the twelfth month after KT as no screening urine cultures were performed thereafter. Considering all AB episodes, independently of the group assigned, the success rate in clearing AB was 34.2 % (25 of 73 episodes) in AB episodes treated with antibiotics and 46.9% (54 of 115 episodes) in those without antibiotic treatment.

In the ITT population prior to ureteral catheter removal, 25 KT recipients in the treatment group had 40 episodes of AB and 24 KT recipients in the no treatment group had 38

Table 1. Baseline Characteristics in Intention-to-Treat Population

	Antibiotic Treatment of Asymptomatic Bacteriuria n = 41		No Treatment of Asymptomatic Bacteriuria n = 46	
	n	%	n	%
Male sex	15	36.6	21	45.7
Age, years, mean ± SD	61.048 ± 11.582		60.194 ± 11.412	
Type of donor				
Living donor	10	24.4	6	13.0
Decreased donor	31	75.6	40	87.0
Etiology of renal impairment				
Unknown	7	17.1	12	26.1
Diabetic nephropathy	9	22.0	8	17.4
Kidney polycystic disease	5	12.2	9	16.9
Glomerulonephritis	6	14.6	7	15.2
Nephroangiosclerosis	4	9.8	2	4.3
Other	10	24.4	8	17.4
Previous kidney transplant	11	26.8	7	15.2
Diabetes mellitus				
Before kidney transplant	10	24.4	13	28.3
After kidney transplant	7	17.1	5	10.9
Preemptive transplant	8	19.5	6	13.0
Previous hemodialysis	30	73.0	34	73.9
Previous peritoneal dialysis	3	7.3	6	13.0
Months in dialysis, mean ± SD	31.900 ± 36.848		24.181 ± 30.801	
Donor positive/recipient negative CMV serostatus	1	2.4	5	10.9
Complications during admission after kidney transplant	22	53.7	24	52.2
Delayed graft function	7	17.9	12	29.3
Reintervention	1	2.6	3	7.3
ICU admission	7	18.4	3	7.3
Acute rejection ^a	3	7.3	2	4.3
Days of admission for kidney transplant, mean ± SD	14.926 ± 7.705		12.434 ± 7.960	
Immunosuppressive treatment				
Monoclonal antibodies	15	55.6	23	50.0
Antithymocyte globulin	15	36.6	21	45.7
Plasmapheresis	4	9.8	2	4.3
Intravenous immunoglobulin	8	19.5	6	13.0
Corticosteroids	40	97.5	46	100
Corticosteroids at discharge	40	97.5	43	93.5
Calcineurin inhibitors	40	97.6	45	97.8
Mycophenolate	39	95.1	45	97.8
TMP-SMX prophylaxis	41	100	45	97.8
Days of TMP-SMX prophylaxis, mean ± SD	117.289 ± 54.343		100.069 ± 37.750	
CMV prophylaxis with valganciclovir	22	53.7	25	54.3
Days of bladder catheterization, mean ± SD	8.125 ± 4.303		8.577 ± 4.648	
Days of double-J catheterization, mean ± SD	35.124 ± 7.467		35.065 ± 5.405	

Abbreviations: CMV, cytomegalovirus; ICU, intensive care unit; SD, standard deviation; TMP-SMX, trimethoprim-sulfamethoxazole.

^a Only rejection episodes occurring before trial intervention was initiated were considered in this variable.

episodes of AB. Antibiotic treatment was prescribed in 45% (18 of 40) episodes of AB in the treatment group and in 47% (18 of 38) episodes of AB in the no treatment group before urinary catheters were removed.

Primary Endpoint

In the PP analysis, the number of patients with AGP was 4 of 29 in the treated group and 3 of 45 in the untreated group. The difference in the AGP incidence was 7.13% (97.5% CI,

-7.39%–21.64%). In intention to treat analysis results were similar with a difference in the AGP incidence of 3.50% (97.5% CI, -9.40%–16.41%) (Tables 2 and 3). Prior AB due to the microorganism that caused AGP occurred in 7 episodes in the ITT population (4 of 6 in the antibiotic treatment group and 3 of 6 in the no treatment group) and 5 episodes in the PP population (3 of 5 in the treatment group and 2 of 4 in the no treatment group). Characteristics of AGP episodes are detailed in Table 4.

Table 2. Study Outcomes in Intention-to-Treat Population

	Antibiotic Treatment if Asymptomatic Bacteriuria n = 41		No Treatment if Asymptomatic Bacteriuria n = 46		P value	RR	95% CI
	n	%	n	%			
Primary endpoint							
KT recipients with acute graft pyelonephritis ^a	5	12.2	4	8.7	.59	1.40	0.40–4.87
Secondary endpoints							
Bacteremic pyelonephritis	1	2.4	3	6.5	.36	0.37	0.036–3.588
Cystitis ^b	6	14.6	3	6.5	.215	2.24	0.60–8.40
Opportunistic infections	9	22.0	10	21.7	.98	1.01	0.46–2.24
Cytomegalovirus infection ^c	9	22.0	10	21.7	.98	1.01	0.46–2.24
BK virus infection	2	4.9	0		.13		
Rejection episodes ^d	1	2.4	2	4.3	.63	0.56	0.05–5.96
Need for hospital admission ^e	22	53.7	26	56.5	.83	0.95	0.65–1.39

Abbreviations: CI, confidence interval; KT, kidney transplant; RR, risk ratio.

^aOne KT recipient in the antibiotic treatment group and 2 KT recipients in the nontreatment group had 2 episodes of acute graft pyelonephritis (AGP). The median days from transplantation to the first episode of AGP were 61 days in the antibiotic treatment group and 121.5 days in the nontreatment group.

^bTwo KT recipients in the antibiotic treatment group and 1 recipient in the nontreatment group had 2 episodes of cystitis.

^cTwo KT recipients in the treatment group and 3 patients in the nontreatment group had 2 episodes of cytomegalovirus (CMV) infection. Antibiotic group (no.): viremia (11) and viral syndrome (1); nontreatment group (no.): viremia (10), viral syndrome (1), and digestive disease (1).

^dOnly rejection episodes occurring after trial intervention was initiated were considered in this variable.

^eAdmission due to AGP is not considered in this variable. Twelve (26.1%) KT recipients in the treatment group and 8 (19.5%) patients in the nontreatment group needed 2 or more hospital admissions for events other than episodes of AGP. Antibiotic group (no.): renal biopsy per protocol (19), congestive heart failure (2), renal impairment (4), CMV disease (1), lymphocele (1), pneumonia (2), and diarrhea (1); nontreatment group (no.): renal biopsy per protocol (22), congestive heart failure (5), renal impairment (1), CMV disease (2), lymphocele (2), pneumonia (1), diarrhea (1), and *Clostridium difficile* colitis (1).

Secondary Endpoints

Secondary study endpoints in the ITT and PP populations are detailed in Tables 2, 3, and Figure 2. During follow-up, no differences were found between the 2 populations in the incidence rates of bacteremic AGP or cystitis, in the estimated glomerular filtration rates, in the hospital admission rates for

causes other than AGP, or in the rates of opportunistic infections or acute graft rejection. There were no graft losses or deaths.

The incidence of a first episode of symptomatic urinary tract infection in treatment versus no treatment group of AB in the ITT population was 10 of 41 (24.3%) versus 7 of 46 (15.2%) ($P = .280$; RR, 1.60; 95% CI, 0.67–3.82) and in the PP population it was 7

Table 3. Study Outcomes in Per-Protocol Population

	Antibiotic Treatment if Asymptomatic Bacteriuria n = 29		No Treatment if Asymptomatic Bacteriuria n = 45		P value	RR	95% CI
	n	%	n	%			
Primary endpoint							
KT recipients with acute graft pyelonephritis ^a	4	13.8	3	6.7	.31	2.07	0.50–8.58
Secondary endpoints							
Bacteremic pyelonephritis	0		2	4.4	.25		
Cystitis ^b	4	13.8	3	6.7	.31	2.07	0.50–8.58
Opportunistic infections	5	17.2	10	22.2	.77	0.78	0.30–2.04
Cytomegalovirus infection ^c	5	17.2	10	22.2	.77	0.78	0.30–2.04
BK virus infection	2	6.9	0		.07		
Rejection episodes ^d	1	3.4	2	4.4	.83	0.78	0.07–8.17
Need for hospital admission ^e	16	55.8	26	57.8	1	0.95	0.63–1.44

Abbreviations: CI, confidence interval; KT, kidney transplant; RR, risk ratio.

^aOne KT recipient in the antibiotic treatment group and 1 recipient in the nontreatment group had 2 episodes of acute graft pyelonephritis (AGP). The median days from transplantation to the first episode of AGP were 63 days in the antibiotic treatment group and 169 days in the nontreatment group.

^bTwo KT recipients in the antibiotic treatment group and 1 recipient in the nontreatment group had 2 episodes of cystitis.

^cTwo KT recipients in the treatment group and 3 patients in the nontreatment group had 2 episodes of cytomegalovirus (CMV) infection. Antibiotic group (no.): viremia (7) and viral syndrome (1); nontreatment group (no.): viremia (10), viral syndrome (1), and digestive disease (1).

^dOnly rejection episodes occurring after trial intervention was initiated were considered in this variable.

^eAdmission due to AGP is not considered in this variable. Twelve (26.7%) KT recipients in the treatment group and 7 (24.1%) patients in the nontreatment group need 2 or more hospital admissions different from episodes of AGP. Antibiotic group (no.): renal biopsy per protocol (13), congestive heart failure (1), renal impairment (4), CMV disease (1), and pneumonia (2). Nontreatment group (no.): renal biopsy per protocol (22), congestive heart failure (4), renal impairment (1), CMV disease (1), lymphocele (2), pneumonia (1), and *Clostridium difficile* colitis (1).

Table 4. Characteristics of Acute Graft Pyelonephritis Episodes in Patients Included in the Study

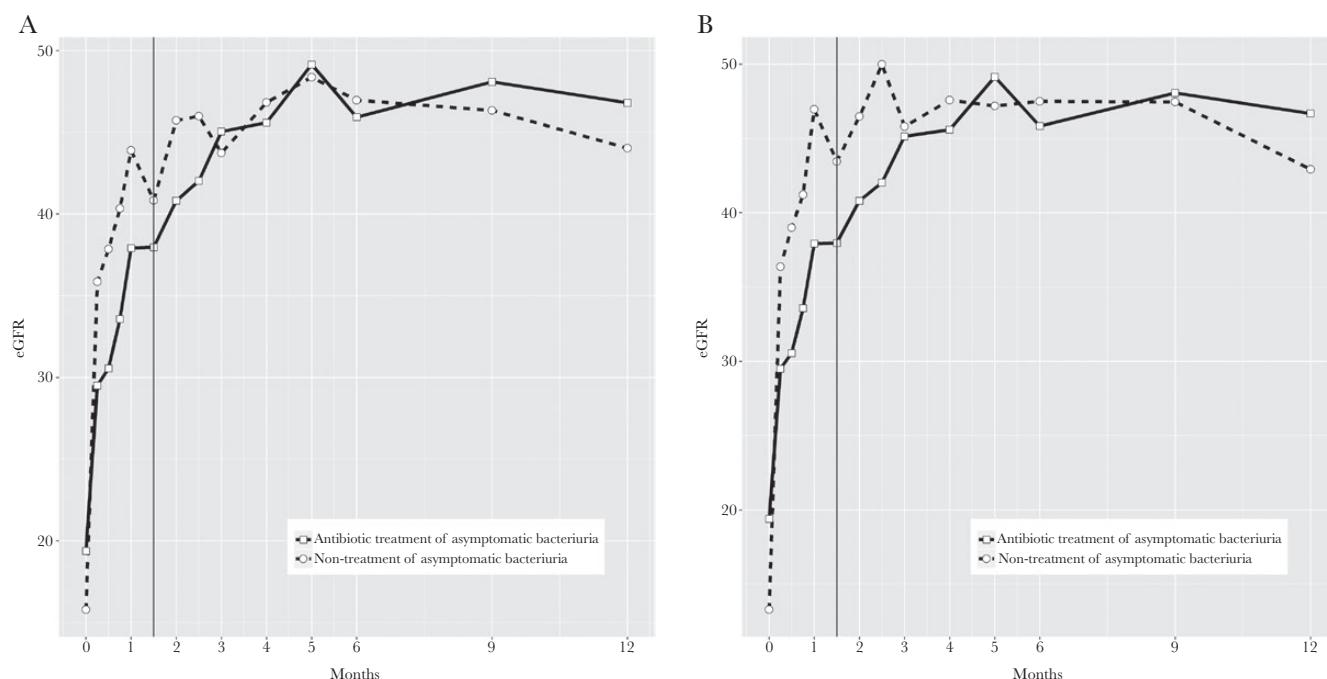
Patient	Study Group	AGP due to the Previous Microorganism Isolated in AB Urine Cultures	Antibiotic Treatment for AB	Days Since Kidney Transplant	Bacteremic AGP	Complications Related to AGP Episode
1	Antibiotic treatment	Yes	Yes	284	No	Renal insufficiency
2	Antibiotic treatment	Yes	Yes	61	No	Renal insufficiency
2	Antibiotic treatment	Yes	Yes	344	No	Renal insufficiency
3	Antibiotic treatment	No		65	No	No
4	Antibiotic treatment	No		98	No	Renal insufficiency
5 ^a	Antibiotic treatment	Yes	No	72	Yes	No
6	No treatment	No		303	No	No
6	No treatment	No		326	No	Renal insufficiency
7	No treatment	Yes	No	219	Yes	Renal insufficiency
8	No treatment	Yes	No	169	Yes	No
9 ^a	No treatment	No		74	Yes	Renal insufficiency
9 ^a	No treatment	Yes	Yes	330	No	Renal insufficiency

Abbreviations: AB, asymptomatic bacteriuria; AGP, acute graft pyelonephritis.

^aPatients 5 and 9 were included in the ITT population but not in the PP population.

of 29 (24.1%) versus 6 of 45 (13.3%) ($P = .233$; RR, 1.81; 95% CI, 0.68–4.85). We counted 4 episodes of bacteremic AGP in patients with previous same-microorganism AB in the ITT population (1 of 1 in the antibiotic treatment group and 2 of 3 in the no treatment group) and 2 episodes in the PP population (0 of 0 in the treatment

group and 2 of 2 in the no treatment group). As cystitis in patients with previous same-microorganism AB, we observed 7 episodes in the ITT population (7 of 8 in the antibiotic treatment group and 0 of 4 in the no treatment group) and 6 episodes in the PP population (6 of 7 in the treatment group and 0 of 4 in the no treatment group).

**Figure 2.** Evolution of Estimated Glomerular Filtration Rate During 12-Month Follow-up in Intention-to-Treat and in Per-Protocol Populations. Abbreviation: eGFR, estimated glomerular filtration rate mL/min/1.73m².

The identification and antibiotic susceptibility of microorganisms isolated in urine cultures of patients with AB are detailed in Table 5 for the ITT and PP populations. The most frequent microorganism in each group was *Escherichia coli*, followed by *Klebsiella pneumoniae* and *Enterococcus faecalis*. The number of KT recipients who experienced an extended-spectrum beta-lactamase (ESBL)-producing bacteria at some point during the study follow-up was 8 (19.5%) in treatment group versus 7 (15.2%) in no treatment group of AB in the ITT population and 5 (17.2%) in treatment group versus 6 (13.3%) in no treatment group of AB in the PP population. When all isolates of AB episodes were considered, fosfomycin-resistant isolates (22.7% vs 12.4% in the ITT population; $P = .030$, and 23.4% vs 10.2% in the PP population; $P = .007$), ESBL-producing Enterobacteriaceae (24.5% vs 13.3% in the ITT population; $P = .044$, and 21.1% vs 11.0% in the PP population; $P = .067$), and amoxicillin-clavulanate resistant Enterobacteriaceae (52.1% vs 26.7% in the ITT population; $P < .001$, and 51.3% vs 22.0% in the PP population; $P < .001$) were more common

in the antibiotic treatment groups in both the ITT and the PP populations. (Table 5)

Antibiotic Treatment for Asymptomatic Bacteriuria

The antibiotics prescribed by isolate susceptibility in urine cultures are detailed in Table 5 for the ITT and the PP populations. No serious adverse reactions were associated with any antibiotic prescriptions in patients with AB.

DISCUSSION

In this noninferiority, multicenter RCT of KT recipients with AB, we found no significant differences in the incidence of AGP in the first year after transplantation between a group receiving antibiotic treatment and a group receiving no treatment. However, antibiotic susceptibility testing suggests that this approach may increase antibiotic resistance rates. However, our findings should be regarded with caution due to the small sample size analyzed that confers low level of statistical power.

Table 5. Isolated Microorganisms, Susceptibility Patterns, and Antibiotics Administered in Asymptomatic Bacteriuria Episodes in Intention-to-Treat and in Per-Protocol Population

	Intention-to-Treat Population		Per-Protocol Population	
	Antibiotic Treatment of AB	No Treatment of AB	Antibiotic Treatment of AB	No Treatment of AB
	119 Isolates n (%)	137 Isolates n (%)	92 Isolates n (%)	128 Isolates n (%)
Isolated microorganisms in urine samples of AB episodes				
Gram negative	102	113	81	107
<i>Escherichia coli</i>	43 (36.1)	74 (54.0)	40 (43.5)	71 (55.4)
<i>Klebsiella pneumoniae</i>	37 (31.1)	24 (17.5)	26 (28.2)	24 (18.7)
<i>Enterobacter aerogenes</i>	6 (5.0)	2 (1.5)	5 (5.4)	2 (1.6)
<i>Morganella morganii</i>	4 (3.3)	2 (1.5)	2 (2.2)	0
<i>Proteus mirabilis</i>	3 (2.5)	2 (1.5)	2 (2.2)	2 (1.6)
Other enterobacteriaceae	1 (0.8)	1 (0.7)	1 (1.1)	1 (0.7)
<i>Pseudomonas aeruginosa</i>	8 (6.7)	8 (5.8)	5 (5.4)	7 (5.5)
Gram positive	17	24	11	21
<i>Enterococcus faecalis</i>	13 (10.9)	19 (13.8)	8 (8.7)	17 (13.3)
<i>Enterococcus faecium</i>	1 (0.8)	1 (0.7)	1 (1.1)	1 (0.7)
Other Gram-positive microorganisms	3 (2.5)	4 (2.9)	2 (2.2)	3 (2.3)
Antibiotic susceptibility of isolated microorganisms in urine samples of AB episodes				
Ciprofloxacin resistant Gram-negative bacilli	61/102 (59.8)	73/113 (64.6)	48/81 (59.2)	62/107 (57.9)
Fosfomycin-resistant microorganisms	27/119 (22.7)	17/137 (12.4)	22/94 (23.4)	13/128 (10.2)
TMP-SMX-resistant enterobacteriaceae	78/94 (82.9)	77/105 (73.3)	62/76 (81.6)	67/100 (67.0)
Amoxicillin-clavulanate-resistant enterobacteriaceae	49/94 (52.1)	28/105 (26.7)	39/76 (51.3)	22/100 (22.0)
ESBL-producing enterobacteriaceae	23/94 (24.5)	14/105 (13.3)	16/76 (21.0)	11/100 (11.0)
MDR <i>Pseudomonas aeruginosa</i>	4/8 (50.0)	5/8 (62.5)	3/5 (60.0)	4/7 (57.1)
Antibiotics administered for asymptomatic bacteriuria episodes				
Cefuroxime	17	1	16	0
Amoxicillin-clavulanate	8	0	8	0
Ciprofloxacin	20	0	18	0
Fosfomycin	32	4	30	0

Abbreviations: AB, asymptomatic bacteriuria; ESBL, extended-spectrum beta-lactamase; MDR, multidrug resistant; TMP-SMX, trimethoprim-sulfamethoxazole.

Some retrospective studies have shown a higher incidence of subsequent AGP in KT recipients with AB, even though antibiotic treatment was given at the asymptomatic stage [26, 27]. Increased urine cytokines have also been documented in KT recipients with AB, suggesting that it may reflect an occult inflammatory process in the renal allograft [28, 29]. Given that AB in KT recipients has therefore been associated with the development of symptomatic infection, other retrospective studies have assessed the usefulness of giving antibiotics to KT recipients with AB. However, results have been conflicting. Although some authors have shown that antibiotic therapy may prevent symptomatic urinary infections [30], others have shown no differences in the progression toward symptomatic infection between treated and untreated AB episodes [31, 32]. Moreover, other research has observed a higher risk of symptomatic infections in KT recipients receiving antibiotic therapy for AB [33]. In a recent RCT comparing antibiotic treatment with no treatment for AB in 112 KT recipients beyond the second month after transplantation, no differences were seen in the incidence of AGP or lower urinary tract infections [25].

It has been suggested that rejection and allograft dysfunction may be associated with urinary infections [4, 5, 8–11]. Nevertheless, antibiotic treatment of AB had no benefit in the incidence of rejection or allograft function within the first year after transplantation in our trial. Our findings concur with those encountered by other investigators [25, 31–33].

The selection of MDR organisms by the widespread use of antibiotics is of increasing concern. Given the high prevalence of AB in KT recipients, antibiotic treatment in these cases could significantly affect antimicrobial resistance rates in this vulnerable population. We observed higher antibiotic resistance rates in the urine isolates of KT recipients who received treatment for AB more often than in those who did not receive treatment and this difference was not observed in the first episode of AB. However, this finding does not allow for firm assertions due to the small number of patients included. Moreover, this conflict with data from a previous study [25], in which higher antibiotic resistance rates were not seen in the isolates from KT recipients treated for AB.

Our study had some limitations that should be acknowledged. A percentage of KT during the study period were not eligible due to inclusion in other trials, mainly related to immunosuppressive therapies. The planned study sample size was not achieved, in part, because the expected incidence of AGP was overestimated during study design. The low incidence of AGP in KT recipients documented in the study could be explained as only patients without urinary catheters were included and, in addition, KT recipients with urological complications were excluded. We know the small sample size limits any categorical conclusion about the results. Second, there was poor protocol compliance for KT recipients with AB assigned to the antibiotic treatment group, reflecting the inconvenience for attending

physicians of considering and treating positive urine culture results in asymptomatic patients, especially when the utility of this practice is not clearly established. Protocol deviations were due to failure in revising urine culture results in some cases by the attending physician and, in a few cases, isolation of microorganisms without oral antibiotic treatment options.

In conclusion, our results suggest that antibiotic treatment of AB has no use in the prevention of AGP among KT recipients after urinary catheters are removed in the first year after transplantation. In addition, antibiotic treatment of AB may increase antibiotic resistance in urine isolates. However, the study limitations regarding sample size require further randomized studies to corroborate our findings.

Acknowledgments

N.S., J.M.C., and J.C. participated in the performance of the research, research design, writing the article, and data analysis. I.O., E.M., O.L., and F.M. participated in performance of the research, writing the article, and data analysis. I.L.A., M.P., L.L.R., and A.M. participated in performance of the research and data analysis. C.P. participated in performance of the research and research design; D.G. participated in performance of the research; and C.T. participated in data analysis.

Financial support. This study was supported by a grant from Fondo de Investigaciones Sanitarias (FIS PI11 1540) and by the Plan Nacional de I+D+i and the Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Economía y Competitividad, and the Spanish Network for Research in Infectious Diseases (REIPI RD12/0015; REIPI RD16/0016), which is co-financed by European Development Regional Fund's "A Way to Achieve Europe." I.O. also received a research grant from the University of Barcelona.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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