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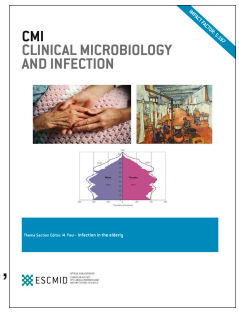

Antibiotics versus no therapy in kidney transplant recipients with asymptomatic bacteriuria (BiRT): a pragmatic, multicentre, randomised controlled trial

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Antibiotics versus no therapy in kidney transplant recipients with asymptomatic bacteriuria (BiRT): a pragmatic, multicentre, randomised controlled trial

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Keywords: urinary tract infection, bacteriuria, kidney transplantation, asymptomatic bacteriuria, pyelonephritis

ABSTRACT

Objectives

Many transplant physicians screen for and treat asymptomatic bacteriuria (ASB) during post-kidney transplant surveillance. We investigated whether antibiotics are effective in reducing the occurrence of symptomatic urinary tract infection (UTI) in kidney transplant recipients with ASB.

Methods

We performed this multicentre, randomised, open-label trial in kidney transplant recipients who had ASB and were ≥2 months post-transplantation. We randomly assigned participants to receive antibiotics or no therapy. The primary outcome was the incidence of symptomatic UTI over the subsequent 12 months.

Results

199 kidney transplant recipients with ASB were randomly assigned to antibiotics (100 participants) or no therapy (99 participants). There was no significant difference in the occurrence of symptomatic UTI between the antibiotic and no-therapy groups (27% [27/100] versus 31% [31/99], univariate Cox model: hazard ratio 0.83 [95% CI: 0.50-1.40], log-rank test: p=0.49). Over the one-year study period, antibiotic use was five times higher in the antibiotic group than in the no-therapy group (30 antibiotic days/participant [interquartile range, 20-41] versus 6 [interquartile range, 0-15], p<0.001). Overall, 155/199 participants (78%) had at least one further episode of bacteriuria during the follow-up. Compared with the participant's baseline episode of ASB, the second episode of bacteriuria was more frequently caused by a bacteria resistant to clinically relevant antibiotics (ciprofloxacin, cotrimoxazole, 3rd-generation cephalosporin) in the antibiotic group than in the no-therapy group (18% [13/72] versus 4% [3/83], p=0.003).

Conclusions

Applying a screen-and-treat strategy for ASB does not reduce the occurrence of symptomatic UTI in kidney transplant recipients who are more than two months post-transplantation. Furthermore, this strategy increases antibiotic use and promotes the emergence of resistant organisms.

INTRODUCTION

Symptomatic urinary tract infection (UTI) is the commonest infection after kidney transplantation [1]. Given the frequency of symptomatic UTI and its associated morbidity [2], it has been suggested that bacteriuria should be screened for, and treated if present, with the intent to eradicate bacteriuria and reduce the incidence of symptomatic UTI [3-6]. There is also concern that post-transplant pyelonephritis may present asymptomatically, due to graft denervation and immunosuppression [5, 7]. As observed in a recent European survey, more than 70% of transplant physicians always screen for asymptomatic bacteriuria (ASB) during post-kidney transplant surveillance, and ASB is often treated [8].

The historical practice of screening for and treating ASB after kidney transplantation potentially results in significant antibiotic exposure because the cumulative incidence of ASB is high when urine cultures are systematically repeated during post-transplant surveillance (e.g., 51% of patients in the first three years post-transplant [3]). Furthermore, the use of fluoroquinolones (which are the most commonly prescribed antibiotics to treat post-transplant ASB) significantly promotes the selection and amplification of resistant organisms, which is a major issue in solid organ transplantation [3, 8-11].

To date, two randomised controlled trials (RCTs)[10, 12] and one quasi-RCT [13] have compared antibiotics versus no therapy in kidney transplant recipients with ASB. An updated meta-analysis of these studies found no significant effect of antibiotics on the incidence of symptomatic UTI (see **appendix p 3**: data for 287 participants, risk ratio [RR] 1.02, 95% confidence interval [CI] 0.66-1.59)[14]. However, all three studies had significant limitations. In particular, sample sizes were relatively small and there was limited compliance to the intervention in both RCTs (29% to 51% of the participants allocated to antibiotics did not receive antibiotics exactly as planned). Additionally, in both RCTs, the primary endpoint of pyelonephritis occurred much less frequently than expected (in ≤5 participants/group). As a consequence, the certainty of evidence was low for important outcomes such as symptomatic UTI [15, 16].

We therefore conducted the Bacteriuria in Renal Transplantation (BiRT) study to determine whether antibiotics reduce the risk of symptomatic UTI in kidney transplant recipients with ASB.

METHODS

Study design

We conducted a prospective, randomised, parallel-group, multicentre, open-label, superiority trial in France (seven sites) and Belgium (six sites) to compare antibiotics with no therapy in kidney transplant recipients with ASB. The protocol was developed in accordance with SPIRIT guidelines [17], with support from the Centre for Evidence in Transplantation (Oxford, UK), and was published in *The Lancet* (www.thelancet.com/protocol-reviews/14PRT-5447). The study was designed to be pragmatic (see **appendix p 11**). The trial was approved by ethics committees and authorities in France and Belgium, and registered with the European Clinical Trials Database, 2012-003857-26, and ClinicalTrials.gov, NCT01871753.

Participants

Adult kidney transplant recipients (≥18 years) were eligible if they had ASB, and were ≥2 months post-transplantation. Participants were recruited through usual follow-up clinics, using the fact that we routinely perform life-long screening for bacteriuria after kidney transplantation. ASB was defined as isolation of a single bacterial species at $\geq 10^5$ CFU/mL in a urine specimen from a patient without symptoms of UTI. Following routine practice in our centres [8], a second positive culture was not necessary before enrolment. A second specimen was however sent for culture before randomisation when possible for the patient. Patients developing ASB while on cotrimoxazole prophylaxis were eligible for inclusion; cotrimoxazole was routinely used as *Pneumocystis jirovecii* prophylaxis for a duration ranging from three months post-transplant to life-long. Patients who had an indwelling urinary (bladder and/or ureteral) catheter were excluded. Other exclusion criteria are listed in the **appendix p 4**. All participants provided written informed consent.

Randomisation and masking

Patients were centrally assigned (1:1) to either antibiotics or no therapy using an internet-based randomisation service. Randomisation was stratified by sex and age (<50 versus ≥50 years). The randomisation sequence was computer-generated and used blocks of four. Investigators were masked to the randomisation sequence. Participants and clinicians were not blinded to allocation.

Procedures

In the antibiotic group, antibiotics were administered for 10 days. The antibiotic was selected by the treating physician, but had to be active *in vitro* against the causative bacteria. In the control group, no antibiotics were prescribed for ASB.

In both groups, participants were followed for 12 months post-randomisation, with study visits scheduled at 1, 2, 4, 6, 8, 10 and 12 months. For each follow-up visit, a urine culture was performed to screen for bacteriuria. All seven visits used a pre-established questionnaire, and also included history taking, temperature measurement, and blood analysis. If ASB occurred again at a study follow-up visit, antibiotics were re-administered in the antibiotic group but not in the control group (see **appendix p 5** for details regarding the screen-and-treat strategy). Participants were asked to contact the local staff if they developed symptoms of infection. Data were collected prospectively using an electronic case report form.

To ensure data quality, we monitored all participant data using central reviewing (i.e., monthly online monitoring of study data) and on-site visits with the help of an independent monitoring team (Clinical Research Centre, Lille University Hospital, France).

Outcomes

The primary outcome was the incidence of symptomatic UTI during the one-year follow-up, defined as the association of (1) ≥1 symptom/sign from a prespecified list (of cystitis, pyelonephritis, prostatitis, or bloodstream infection due to UTI – see **appendix p 6**), and (2) a positive urine culture (i.e., isolation of a bacterial organism at $\geq 10^4$ CFU/mL). To limit the risk of bias associated with the open-label design of this trial, primary outcomes were adjudicated before analysis with the help of three co-investigators blinded to allocation and not involved in patient care. All secondary outcomes are listed in the **appendix p 6**. All outcomes were prespecified.

Sample size calculation

We estimated that the one-year cumulative incidence of symptomatic UTI would be 20% among untreated patients [1, 3, 13]. We considered a reduction in the incidence of symptomatic UTI from 20% to 6% to

represent the minimal clinically important difference (taking into account the impact of antibiotics on the spread of antibiotic resistance, and the fact that many symptomatic UTIs occurring after kidney transplantation are cystitis which has a limited impact on the patient and his/her graft) [1]. This 70% decrease was consistent with the effect of antibiotics reported in pregnant women with ASB [18]. A sample size of 198 participants was needed to have an 80% chance of detecting a reduction in the incidence of symptomatic UTI from 20% to 6% as significant at the 5% level, considering a potential 10% loss to follow-up.

Statistical analysis

Baseline participant characteristics are expressed as proportions for categorical variables, means and standard deviations (SDs) for normally distributed continuous variables, and median and interquartile ranges (IQRs) for non-normally distributed continuous variables. Primary analysis was by intention-to-treat. For the primary outcome, we used Kaplan-Meier survival curves to estimate the cumulative incidence of symptomatic UTI. The curves were compared using the log-rank test. The hazard ratios (HR) and their 95% CIs were derived from a univariate Cox model, with p-values corresponding to the Wald's test. To investigate the consistency of the study conclusions among different subpopulations, an analysis of the primary endpoint was undertaken in three pre-specified subgroups: (1) time between transplantation and study inclusion <6 vs. ≥6 months; (2) baseline estimated glomerular filtration rate <40 vs. ≥40 ml/min/1.73 m^2; and (3) resistant organism at baseline vs. other organism (details in **appendix p 12**). A per-protocol analysis was also conducted, excluding participants with a protocol deviation (see **appendix p 13**). For secondary outcomes, we compared categorical variables between study groups using Pearson's chi-square test or Fisher's exact test (as appropriate), and continuous variables using Student's t test or Mann-Whitney-Wilcoxon test (as appropriate). Change in serum creatinine throughout the follow-up period was compared using a two-way repeated measures ANOVA. A two-sided p value of <0.05 was considered as statistically significant. Additional details related to the statistical analysis are provided in the **appendix p 8**.

RESULTS

Study population

199 kidney transplant recipients with ASB were enrolled and randomly assigned to receive antibiotics (100 participants) or no therapy (99 participants). These 199 participants constituted the intention-to-treat population (**Figure 1**). Baseline characteristics are shown in **Table 1**. At study inclusion, 27.1% of the patients were in the first post-transplant year (54/199). The most common organism responsible for the inclusion episode of ASB was *Escherichia coli* (63.3%, 126/199). Overall, 98% of the participants (195/199) completed (188/199) or died before (7/199) the 12-month follow-up.

Interventions and protocol compliance

At baseline, 198/199 participants (99.5%) received the planned intervention (i.e., antibiotics vs. no therapy). In the antibiotic group, fluoroquinolones were the most commonly prescribed agents at baseline (27%, 27/100), followed by 2^{nd}/3^{rd}-generation cephalosporins (26%, 26/100), amoxicillin (18%, 18/100), amoxicillin-clavulanic acid (17%, 17/100), nitrofurantoin (5%, 5/100), cotrimoxazole (4%, 4/100), and fosfomycin-trometamol (3%, 3/100). During the one-year follow-up period, more than 90% of the scheduled urine cultures were performed (1272/1393, 91.3%) and 19 participants (9.5%) had a protocol deviation (details in **appendix p 13**). Therefore, the per-protocol analysis included 92 participants in the no-therapy group and 87 participants in the antibiotic group (**Figure 1**).

Outcomes

Overall, 58/199 participants (29.1%) developed at least one symptomatic UTI during the follow-up period. On an intention-to-treat basis, the risk of symptomatic UTI did not differ significantly between participants in the antibiotic group and those in the no-therapy group (27/100 [27%] vs. 31/99 [31%], univariate Cox model: HR 0.83 [95% CI: 0.50-1.40], p=0.49; log-rank test: p=0.49, **Figure 2**). The characteristics of these 58 symptomatic UTI episodes are summarised in **Table 2**. The per-protocol analysis confirmed these findings (incidence of symptomatic UTI: 23/87 [26%] in the antibiotic group vs. 30/92 [33%] in the no-therapy group, univariate Cox model: HR 0.78 [95% CI: 0.45-1.34], p=0.36; log-rank test: p=0.36). Antibiotics did not significantly reduce the cumulative incidence of symptomatic UTI in any of the pre-specified subgroups (**appendix p 12**).

Antibiotics had no significant impact on any secondary clinical outcome (**Table 3**). Specifically, the incidence of pyelonephritis did not differ significantly between study groups (17/100 [17%] in the antibiotic group vs. 16/99 [16%] in the no-therapy group, RR 1.05 [95% CI 0.56-1.96], p=0.87). Treating ASB did not significantly improve kidney function (**Table 3**).

One month after randomisation, 93% of the participants (186/199) had a urine specimen sent for culture. Among them, the prevalence of ASB was significantly lower in the antibiotic group than in the no-therapy group (29% [27/92] vs. 66% [62/94], p<0.001). Compared with untreated participants, those in the antibiotic group also had a significantly lower total number of ASB episodes during the complete follow-up period, and were significantly less likely to have ASB at end-of-study (**Table 3**).

Antibiotic use varied significantly between groups (**Table 3** and **appendix p 15**). Especially, the median number of days receiving antibiotics for any cause was five times higher in the antibiotic group than in the no-therapy group (30 days per patient throughout the one-year study period [IQR, 20-41] vs. 6 days [IQR, 0-15], respectively, p<0.001, excluding antibiotic prophylaxis, e.g., cotrimoxazole used to prevent *Pneumocystis* pneumonia).

To determine the impact of antibiotics on antibiotic resistance, we focused on the 155/199 participants (77.9%) who had at least one further episode of bacteriuria during the follow-up. Compared with the participant's baseline episode of ASB, this second episode of bacteriuria was more frequently caused by a bacteria resistant to clinically relevant antibiotics (i.e., ciprofloxacin, cotrimoxazole, or 3rd-generation cephalosporin) in the antibiotic group than in the no-therapy group (18% [13/72 participants] vs. 4% [3/83 participants], p=0.003, details in **appendix p 16**). Overall, 93 serious adverse events (SAEs) were reported: 50 SAEs among 28/100 participants (28%) in the antibiotic group versus 43 SAEs among 23/99 participants (23%) in the no-therapy group (p=0.44, details in **appendix p 18**).

DISCUSSION

The present study was designed to determine whether antibiotics are beneficial in kidney transplant recipients who have ASB beyond the first two months post-transplant. Although antibiotic use was associated with fewer subsequent cases of bacteriuria, this microbiological effect did not translate into significant clinical benefit over the one-year study period, including in our primary outcome of symptomatic UTI. Furthermore, antibiotic consumption was five times higher among participants from the antibiotic group than among those from the no-therapy group, and treating ASB significantly promoted the emergence of more resistant organisms in the urine.

While symptomatic UTIs represent a heterogeneous group of events ranging from mild episodes of cystitis to more severe episodes of graft pyelonephritis, it is remarkable that treating ASB did not reduce the incidence of pyelonephritis or improve any of the other graft-related outcomes (i.e., kidney function, graft rejection, and graft loss). These results argue against the hypothesis that ASB may represent "silent pyelonephritis" among kidney transplant recipients, as a consequence of both transplant denervation and immunosuppression [5, 7].

This study has several strengths, including its randomised design. Compared with previously published trials focusing on kidney transplant recipients with ASB, we had double the number of participants assigned to antibiotics (100 participants in the current study vs. 41-53 participants/study in previous trials)[10, 12, 13]. The high level of compliance with study protocol and the clear microbiological effect of antibiotics support our conclusions that antibiotics are not clinically beneficial in this situation. Also, benefits and harms of antibiotics were rigorously examined, using comprehensive data monitoring for all patients.

This study also has several limitations. Firstly, participants and physicians were not blinded to treatment allocation, and this may have biased our results for the primary outcome because symptoms of UTI are partly subjective. However, the open-label design was selected to reflect usual care. To minimise the risk of bias, primary outcomes were adjudicated with the help of assessors blinded to treatment allocation.

Secondly, our trial was powered to detect a large effect, and hence we cannot rule out a small to moderate effect of antibiotics on the risk of symptomatic UTI. This is illustrated by the relatively wide confidence interval surrounding the hazard ratio for the primary outcome (HR 0.83, 95% CI: 0.50-1.40). However, our results confirm those of three previous trials, which also did not demonstrate a significant clinical benefit associated with the use of a screen-and-treat strategy for ASB after kidney transplantation [10, 12, 13]. We updated our meta-analysis with the data from the current trial and, again, found no significant effect of antibiotics on the prevention of symptomatic UTI (4 studies, data for 486 participants, RR 0.94, 95% CI 0.69-1.28, see **appendix p 22**).

A third potential limitation is that we are unable to determine what proportion of patients assessed for eligibility were enrolled, because we did not keep a log of subjects screened but not included. To assess the external validity of our trial findings, we instead performed an observational co-study in some of the trial sites [19]. This co-study showed that the characteristics of the BiRT study participants resembled those of kidney transplant recipients who have ASB in usual care, in terms of sex, age, kidney function, and time post-transplant [19].

Fourthly, trial participants were relatively late after transplant as illustrated by the fact that only 13% of the participants were included in the first six months after transplantation. In particular, we cannot extrapolate our conclusions to the first two months post-transplant, as such patients were not eligible for our trial. Similarly, patients developing ASB in the first weeks/months after transplant were excluded from the previously published trials comparing antibiotics versus no therapy [10, 12, 13].

Lastly, the 10-day antibiotic duration used in the current trial to treat ASB was relatively long. While this duration was selected to be of sufficient length to be potentially effective (especially because, as described above, there is concern that post-transplant pyelonephritis may present asymptomatically), this choice may also have impacted our estimates for the outcomes of antimicrobial resistance and antibiotic consumption.

Our findings support the recent recommendation made by the Infectious Diseases Society of America (IDSA), the American Society of Transplantation, and the European Association of Urology against systematic antibiotic

use in kidney transplant recipients with ASB [20-22]. However, as acknowledged by the IDSA [15], this recommendation was made despite a low certainty of evidence for important outcomes such as symptomatic UTI. Although our trial results reinforce the existing body of evidence against a systematic screen-and-treat strategy for ASB, effectively reducing antibiotic prescribing may be challenging. Importantly, treatment of ASB persists in various settings despite publication of negative trials and guidelines advocating the contrary [23]. Because antibiotic prescribing for ASB typically occurs in response to the positive result of a urine culture, efforts should be made to stop the routine use of urine cultures in kidney transplant recipients who are asymptomatic and more than two months post-transplant.

In summary, using a screen-and-treat strategy for ASB did not significantly improve clinical outcomes of kidney transplant recipients who were more than two months post-transplant. By contrast, this strategy drastically increased antibiotic use and promoted the emergence of more resistant organisms in the urine. More research is needed to determine the effects of screening for and treating ASB in the first two months post-transplant. While we agree with the recent suggestion by the IDSA that the efficacy of this strategy needs to be studied early after transplant [20], it is also important to consider the potential risks of leaving ASB untreated in these patients who are heavily immunocompromised and often have a ureteral catheter, which may facilitate the ascent of pathogens from the bladder to the graft.

TRANSPARENCY DECLARATION

CONFLICT OF INTERESTS

All authors have completed the ICMJE uniform disclosure form. Julien COUSSEMENT reports research grants from « Fonds Erasme pour la Recherche Médicale », « Fonds David et Alive VAN BUUREN », and « Fonds Carine VYGHEN » (during the conduct of the study), and personal fees from Sanofi (outside the submitted work). Magali GIRAL reports grants from Novartis and Sanofi (outside the submitted work), and travel funding and/or honoraria from Astellas, Chiesi, Novartis, Sandoz and Sanofi (also outside the submitted work). Nassim KAMAR reports personal fees from Abbvie, Amgen, Astellas, Biotest, CSL Behring, Chiesi, Gilead, Fresenius Medical care, Merck Sharp and Dohme, Neovii, Novartis Pharma, Sanofi, Sandoz, and Shire (outside the submitted work). Anne SCEMLA reports non-financial support from Bristol-Myers Squibb (outside the submitted work). Other authors declare no competing interests.

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ACCESS TO DATA

Data collected for the study, including de-identified individual participant data and a data dictionary defining each field in the set, will be made available to researchers who provide a methodologically sound proposal to the corresponding author with a signed data access agreement, at any point.

CONTRIBUTION

JC was the chief investigator. JC, LW, AS, JR, KMW, MH, OD and DA contributed to the design of the study. JC, NK, MM, LW, AS, MG, EA, LM, MK, LG, ENB, KMW, MH and DA were the site principle investigators, responsible for participant recruitment and data collection. JC and DA were responsible for the day-to-day running of the trial. JC, JR, KMW, MH and DA did the data analysis. JC wrote the first draft of the manuscript; all authors revised this draft. All authors read and approved the final version. JC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figures and tables.

Figure 1. Trial profile

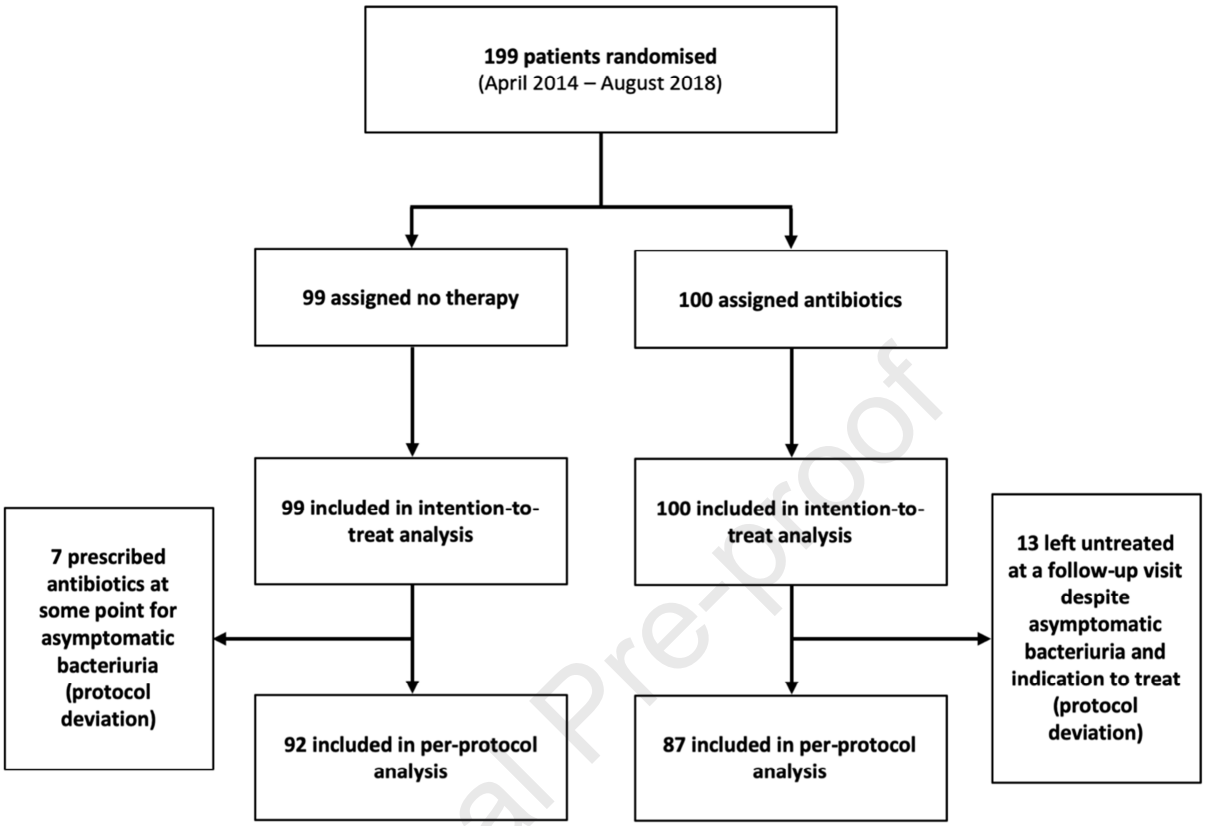
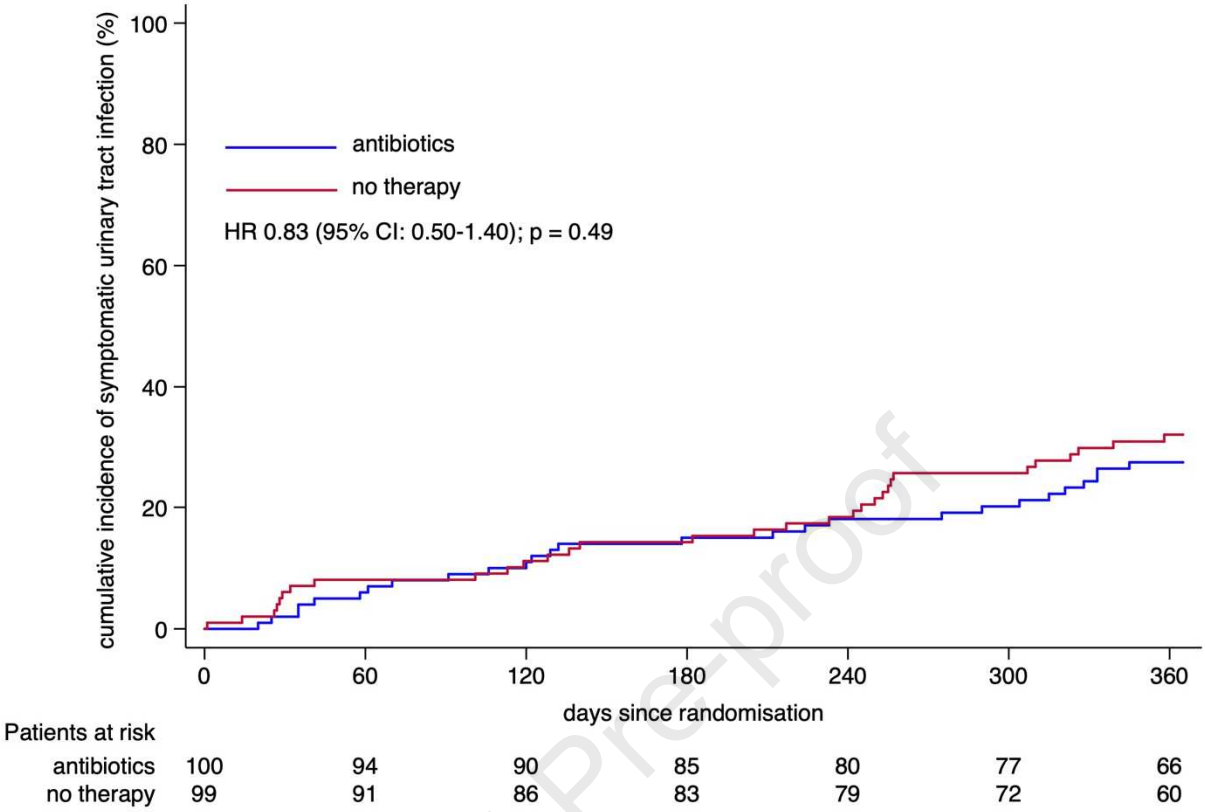


Figure 2. Cumulative incidence of symptomatic urinary tract infection (intention-to-treat analysis)



CI: confidence interval, HR: hazard ratio; p-value refers to log-rank test

Table 1. Baseline characteristics (intention-to-treat analysis)

	No therapy (n=99)	Antibiotics (n=100)
Female, n (%)	74 (75)	77 (77)
Age (years), mean ± SD	60.1 ± 11.6	60.2 ± 11.5
Primary kidney disease diagnosis		
Glomerular disease (other than diabetes)	26 (26)	24 (24)
Polycystic kidney disease	16 (16)	17 (17)
Diabetes	11 (11)	13 (13)
Tubulo-interstitial nephritis	8 (8)	17 (17)
Vascular nephropathy	13 (13)	8 (8)
Uropathy	11 (11)	5 (5)
Unknown	14 (14)	16 (16)
Dialysis before transplantation	85 (86)	90 (90)
Duration (months), median (IQR)	28 (16 - 43)	33 (18 - 52)
Oliguria/anuria at time of transplant (≤ 500 mL/day), n (%), n=168	37 (46)	48 (55)
Haemodialysis (vs. peritoneal dialysis), n (%)	71 (84)	77 (86)
Time from transplantation to study inclusion (months), median (IQR)	49 (18 - 109)	26 (10 - 77)
Study inclusion in the first 12 months post-transplant, n (%)	21 (21)	33 (33)
1st transplant (vs. 2nd or 3rd transplant), n (%)	85 (86)	77 (77)
Single (vs. dual) kidney transplant, n (%)	98 (99)	97 (97)
Urinary catheterisation in the month prior to inclusion, n (%)	1 (1)	0 (0)
Diabetes, n (%)	29 (29)	39 (39)
Deceased donor (vs. living), n (%)	90 (91)	93 (93)
Donor age (years), mean ± SD, n=198	52 ± 19	54 ± 17
History of biopsy-proven acute rejection since transplantation, n (%)	11 (11)	13 (13)
Induction immunosuppressive therapy at transplantation, n (%), n=198		
Anti-CD25	50 (51)	45 (45)
Thymoglobulin	29 (30)	35 (35)
Other induction regimen	7 (7)	11 (11)
None	12 (12)	9 (9)
Number of antirejection drugs at time of study inclusion, n (%)		
Three-drug immunosuppressive therapy	65 (66)	72 (72)
Two-drug immunosuppressive therapy	33 (33)	27 (27)
Single drug immunosuppressive therapy	1 (1)	1 (1)

Antirejection drugs used at time of study inclusion, n (%)		
Calcineurin inhibitor (tacrolimus or cyclosporin)	86 (87)	92 (92)
Antiproliferative drug (mycophenolic acid or azathioprine)	84 (85)	88 (88)
Steroids	78 (79)	78 (78)
Belatacept	8 (8)	7 (7)
mTOR inhibitors	6 (6)	7 (7)
Use of cotrimoxazole prophylaxis after transplantation, n (%), n=198	91 (93)	87 (87)
Ongoing cotrimoxazole prophylaxis at time of study inclusion, n (%)	12 (12)	27 (27)
Major events in the year before study enrolment, n (%)		
UTI requiring hospital admission, n=197	13 (13)	8 (8)
Antibiotics for symptomatic UTI or asymptomatic bacteriuria, n=198	51 (52)	42 (42)
Antibiotics for infection other than UTI, n=197	16 (16)	23 (23)
Infection or colonisation by an ESBL-producing organism, n=197	9 (9)	4 (4)
Urine test results at study entry, n (%)		
Pyuria (i.e., ≥ 25 leucocytes/mm3 of urine)	81 (82)	78 (78)
Bacterial species		
Enterobacteriaceae	86 (87)	87 (87)
Escherichia coli	62 (63)	64 (64)
***Klebsiella* spp.**	12 (12)	16 (16)
***Enterobacter* spp.**	5 (5)	1 (1)
Proteus mirabilis	2 (2)	2 (2)
Other	5 (5)	4 (4)
Pseudomonas aeruginosa	2 (2)	1 (1)
Enterococcus spp.	9 (9)	10 (10)
Others	2 (2)	2 (2)
Second urine specimen sent for culture before randomisation, n (%)	66 (67)	73 (73)
Same organism identified, n=139	61 (92)	71 (97)
Same organism identified, at ≥ 100,000 CFU/mL, n=138	54 (83)	66 (90)
Numbers of baseline urinary samples with antimicrobial resistant isolates, n (%)		
Ciprofloxacin-resistant Gram-negative bacteria, n=178	26 (29)	23 (26)
Cotrimoxazole-resistant Gram-negative bacteria, n=178	39 (43)	51 (58)
3rd generation cephalosporin-resistant Gram-negative bacteria, n=168	18 (21)	7 (9)
Blood analysis at time of study inclusion		
White blood cell count (/mm^3), mean ± SD	7239 ± 2567	7462 ± 2842
Neutrophil count (/mm^3), mean ± SD, n=177	5102 ± 2364	5248 ± 2338

CRP (mg/L), median (IQR), n=195	3 (1 - 6)	3 (1 – 9)
Serum creatinine level (mg/dL), mean ± SD	1.5 ± 0.6	1.4 ± 0.5
Estimated glomerular filtration rate (ml/min/1.73 m^2)*, mean ± SD	44 ± 19	45 ± 15

CRP: C-reactive protein; ESBL: extended spectrum beta-lactamase; IQR: interquartile range; mTOR: mammalian target of rapamycin; SD: standard deviation; UTI: urinary tract infection; n=: number of participants analysed (if < 199); *according to Modification of Diet in Renal Disease formula

Table 2. Characteristics of first episode of symptomatic UTI (primary endpoint; intention-to-treat analysis)

	No therapy (31 episodes)	Antibiotics (27 episodes)	p
Need for hospital admission, n (%)	10 (32)	6 (22)	0.39
If hospital admission: length of stay (days), median (IQR)	7 (5-13)	5 (3-36)	0.66
Symptoms of cystitis, n (%) *	22 (71)	22 (81)	0.35
Symptoms of pyelonephritis (i.e., fever and/or chills and/or kidney pain), n (%) *	14 (45)	16 (59)	0.28
Blood test results **:			
White blood cell count (/mm^3), mean ± SD	9252 ± 3489	10022 ± 5030	0.53
Neutrophil count (/mm^3), mean ± SD, n=43	7322 ± 3658	7873 ± 5239	0.69
CRP (mg/L), median (IQR)	24 (3-68)	52 (4-65)	0.60
Serum creatinine level (mg/dL), mean ± SD, n=49	1.8 ± 0.7	1.7 ± 0.6	0.85
Acute kidney injury †, n (%), n=49	10 (36)	6 (29)	0.60
Bloodstream infection, n (%), n=17	6 (60)	3 (43)	0.64
Microbiological findings:			
Pyuria (i.e., ≥ 25 leucocytes/mm3 of urine), n (%)	30 (97)	26 (96)	1
Pathogen causing symptomatic UTI, n (%):			0.21
Escherichia coli	19 (61)	19 (70)	
Klebsiella spp.	4 (13)	1 (4)	
Enterococcus faecalis	3 (10)	0 (0)	
Other pathogens ***	5 (16)	7 (26)	
Same species present without symptoms at study visit immediately preceding the symptomatic UTI, n (%)	18 (58)	6 (22)	**0.006**

IQR: interquartile range; SD: standard deviation; n=: number of participants analysed (if < 58); * some patients had symptoms of cystitis and of pyelonephritis; ** blood analysis performed in 50/58 participants; † acute kidney injury was defined as an increase in serum creatinine of ≥ 0.3 mg/dL from previous value (i.e., previous study visit); *** UTIs due to *Proteus mirabilis* (n=2), *Enterobacter* spp. (n=1), *Serratia spp.* (n=1), *Citrobacter* spp. (n=1), *Pseudomonas aeruginosa* (n=1), *Staphylococcus saprophyticus* (n=1), or *Staphylococcus epidermidis* (n=1), or mixed UTIs associating *Escherichia coli* and another pathogen (*Proteus mirabilis* [n=1], *Enterobacter* spp. [n=1], *Citrobacter* spp. [n=1], *Streptococcus agalactiae* [n=1]).

Table 3. Secondary outcomes during the one-year follow-up (intention-to-treat analysis)

	No therapy (n=99)	Antibiotics (n=100)	p
Death, n (%)	3 (3)	4 (4)	1
Graft loss (death-censored), n (%)	3 (3)	2 (2)	0.68
Biopsy-proven graft rejection, n (%)	2 (2)	3 (3)	1
Increase in serum creatinine level (mg/dL) from baseline to end-of-study, n=196, mean ± SD	0.09 ± 0.50	0.19 ± 0.61	0.2
Pyelonephritis, n (%)	16 (16)	17 (17)	0.87
Bloodstream infection due to UTI, n (%)	6 (6)	4 (4)	0.51
Hospital admission due to symptomatic UTI, n (%)	12 (12)	8 (8)	0.33
Number of symptomatic UTI episodes per participant:			0.76
no episode, n (%):	68 (69)	73 (73)	
1 episode, n (%):	23 (23)	21 (21)	
≥ 2 episodes, n (%):	8 (8)	6 (6)	
***Clostridioides difficile*-associated diarrhoea, n (%)**	0 (0)	0 (0)	NA
Asymptomatic bacteriuria at 1 month post-study inclusion, n=186*, n (%)	62 (66)	27 (29)	**< 0.001**
Asymptomatic bacteriuria at 12 months post-study inclusion (end-of-study), n=186*, n (%)	49 (53)	31 (33)	**0.008**
Total number of asymptomatic bacteriuria episodes per participant during the one-year follow-up, median (IQR)	3 (1-6)	1 (0-3)	**< 0.001**
Number of participants in whom second episode of bacteriuria (asymptomatic or symptomatic) was caused by a more resistant bacteria than was their baseline episode of asymptomatic bacteriuria **, n=155 †	3 (4)	13 (18)	**0.003**
Number of participants in whom first episode of symptomatic UTI was caused by a more resistant bacteria than was their baseline episode of asymptomatic bacteriuria **, n=53	4 (15)	4 (15)	1
Antibiotic consumption during the one-year study period:			
Median (IQR) number of antibiotic days per patient, for any cause	6 (0-15)	30 (20-41)	**< 0.001**
Median (IQR) number of antibiotic days per patient, for asymptomatic bacteriuria only	0 (0-0)	20 (10-30)	**< 0.001**
Median (IQR) number of antibiotic days per patient, for symptomatic UTI only	0 (0-8)	0 (0-7)	0.54

IQR: interquartile range; SD: standard deviation; UTI: urinary tract infection; n= : number of variables included (if < 199); NA: not available; * 186/199 participants performed a urine culture at this follow-up visit (other participants either did not do a urine test at this visit, or had died); ** defined as isolation of a Gram-negative bacteria resistant to ≥ 1 clinically relevant antibiotic (i.e., ciprofloxacin, cotrimoxazole, or 3rd generation

cephalosporin), if not already present at baseline; † 155/199 participants had ≥ 1 further episode of bacteriuria during the one-year study follow-up (and were therefore included in this analysis)