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Short versus prolonged antibiotic treatment for complicated urinary tract infection after kidney transplantation

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SUMMARY

There is no consensus regarding the optimal duration of antibiotic therapy for urinary tract infection (UTI) following kidney transplantation (KT). We performed a retrospective study comparing short (6–10 days) versus prolonged (11–21 days) antibiotic therapy for complicated UTI among KT recipients. Univariate and inverse probability treatment weighted (IPTW) adjusted multivariate analysis for composite primary outcome of all-cause mortality or readmissions within 30 days and relapsed UTI 180 days were performed. Overall, 214 KT recipients with complicated UTI were included; 115 short-course treatment (median 8, interquartile range [IQR] 6–9 days), 99 prolonged course (median 14, IQR 12–21 days). The composite outcome occurred in 33 (28.6%) in the short-course group and 30 (30%) in the prolonged-course group; relapsed UTI occurred in 19 (16.5%) vs. 21 (21%), respectively. Duration of antibiotic treatment was not associated with any of these outcomes. The only risk factor for mortality/readmissions in multivariate analysis was deceased donor. No differences between groups were demonstrated for length of hospital stay, rates of bacteraemia, resistance development, and serum creatinine at 30 and 90 days. In conclusion, we found no difference in clinical outcomes between KT recipients treated for complicated UTI with short-course antibiotic (6–10 days) versus longer course (11–21 days).

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Key words
antibiotic stewardship, kidney transplantation, mortality, readmission, urinary tract infection

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Introduction

Urinary tract infection (UTI) is the most common infection after kidney transplantation (KT). The reported prevalence varies widely across studies, with rates as high as 75% [1–8]. The highest incidence has been reported in the first 3–6 months after transplantation [1,4,7,9]. These infections carry increased risk for mortality and UTI recurrence [10].

There is no consensus regarding the optimal duration of treatment of UTI in kidney transplant recipients. The Kidney disease improving global outcome (KDIGO) guidelines recommend that all KT recipients with kidney allograft pyelonephritis should be hospitalized and

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treated with intravenous antibiotics, at least initially, and be treated for 14 days in the absence of kidney abscess [11]. These recommendation is based on expert opinion. Two major guidelines dedicated for the diagnosis and treatment of UTI in solid organ transplant (SOT) recipients were published recently [10,12]. The Group for the Study of Infection in Transplant Recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Network for Research in Infectious Diseases (REIPI), as well as the American Society of Transplantation Infectious Diseases Community of Practice guidelines, recommends that kidney transplant recipients with allograft pyelonephritis should undergo a 14–21 days course of antibiotics, depending on the time elapsed from transplantation. They state that no data are available on short courses (7 days) of antibiotic therapy for pyelonephritis in SOT recipients; therefore, short-term treatment is not recommended in SOT [10].

Rates of resistant bacteria, especially of *Enterobacterales* producing extended-spectrum β-lactamases (ESBLs) species are increasing and represent a growing threat to kidney transplant recipients [13–15]. The emergence of resistance has raised awareness to the importance of antibiotic stewardship intervention [16]. An important stewardship measure is to treat infections for the shortest duration of therapy. The majority of studies that evaluated duration of antibiotic courses for complicated UTI/pyelonephritis, including bloodstream infections (BSI), in adults, have demonstrated no significant difference in clinical outcomes in favour of the prolonged courses over the short course [17,18]. Shorter duration of antibiotics may provide an advantage of reducing duration of hospital stay; cost; adverse events; and superinfections, including *Clostridioides difficile*, a common infection among SOTs. Therefore, we sought to examine whether short-course antibiotic therapy for complicated UTI/ pyelonephritis in hospitalized KT recipients is applicable.

Methods

This is a retrospective cohort study. All consecutive adult (age >18 years) KT recipients who were admitted with complicated UTI (as defined below) between 1/2011 and 7/2019 were included. All were transplanted at Rabin Medical Center and were followed in the outpatient clinic, hence all data related to transplantation were available. For each patient, only the first episode of hospitalized symptomatic UTI was recorded, at any time following transplantation. Our policy is not to treat asymptomatic bacteriuria, except during the first month. These patients were not included in the cohort. Participants were identified from the computerized database of the transplantation department and microbiology laboratory at Rabin Medical Center. The retrieved data were crossed-referenced with the electronic medical chart looking for: (i) diagnoses in the discharge document of pyelonephritis or UTI (ICD9 code) or the presence of leukocytosis of more than 15.000 K/micrl or fever >38 on admission or during hospital stay and (ii) positive urine culture for a uropathogen. Computerized medical records of identified patients were reviewed to include patients fulfilling complicated UTI criteria, as defined below. Recipients of multiple organ transplantation (e.g., kidney–pancreas); recipients with undrained kidney abscess (as they require prolonged treatment); recipients with no access to their medical record and recipients who had allograft failure for other reasons before developing UTI were excluded.

Duration of treatment was dichotomized into short (6–10 days) and prolonged (11–21 days) courses. This dichotomy is based on the most common clinical practice in our institute and was used as well in other studies of antibiotic duration for similar indications [18–20]. In our hospital, there is no written protocol to guide the duration of therapy for UTI, and the accepted duration is between the ranges of 6–21, on the discretion of treating physician. Patients who received less than 5 days or longer than 21 days of antibiotic therapy were excluded from the analyses, as this probably indicate inadequate treatment or reflecting an uncontrolled source of infection such as an abscess that was not documented, respectively. The first day of treatment was counted as the first day of appropriate antibiotic treatment. Completion of the course was either during admission or after discharge.

The primary outcomes were as follows: (i) A composite of all-cause mortality or readmission for any cause within 30 days from index culture and (ii) relapse of UTI within 180 days. Secondary outcomes were individual components of the primary outcome; readmission for any cause within 90 days; overall hospital stay; documentation of bacteraemia within 30 days; serum creatinine within 30 and 90 days; the emergence of multidrug resistant (MDR) bacteria in any clinical or surveillance cultures in 180 days after the index UTI and the development of *C. difficile* infection. The outcomes of this study were reported according to STROBE guidelines [21].

This study was approved by the local institutional review board and conducted in accordance with the declaration of Helsinki and the declaration of Istanbul.

Definitions and microbiological methods

For complicated UTI, we used the definition used by Goldman *et al.* [12]: Complicated UTI (pyelonephritis or upper tract UTI) includes significant (>10^4 CFU/ml) growth of a uropathogen and at least one of the following: fever, chills, malaise, hemodynamic instability, leukocytosis (>15 000/ml), and bacteraemia with same organism as in the urine or pain over the allograft or the costovertebral angles for allograft or native kidney involvement. All infections were microbiologically documented.

Relapse of UTI was defined as a recurrent UTI within 180 days with the same pathogen as the index UTI [12].

Multidrug resistance (MDR) organisms were defined as those micro-organisms that were resistant to at least one agent in three or more antimicrobial categories [22].

Urine cultures were analysed for bacterial infection using the Diaslide method. Cultures are transferred to the microbiology laboratory already inoculated on dip slides. Colony forming units (CFU) per ml is determined using NOVAMED Colony Density Chart. Cultures are considered positive if CFU/ml ≥10 000 for midstream urine collection or ≥1000 for catheter urine collection, for a single pathogen. Bacterial identification is performed using Bruker MALDI-TOF MS system. Resistance is determined using the Clinical and Laboratory Standards Institute breakpoints.

Immunosuppression regimen

The standard maintenance calcineurin inhibitors (CNIs) for the majority of KT recipients in our institute is tacrolimus (Prograf, Astellas Pharma, Ireland or Tacrocel, Sandoz, Switzerland) with a target 12-h trough level of 8–12 ng/ml during the first three months after transplantation, and 5–8 ng/ml thereafter. Minority of KT recipients receive cyclosporine (Sandimmune Neoral, Novartis Pharmaceutical, Basel, Switzerland) with a target 12-h trough level of 150–300 ng/ml during the first three months and 100–200 ng/ml thereafter. Mammalian target of rapamycin (mTOR) inhibitors are less frequently used without any CNI. Immunosuppressant therapy also includes an antimetabolite (usually mycophenolate mofetil) and corticosteroids. Induction is given with one of the following: anti-IL-2 receptor antagonist basiliximab (Simulect, Novartis Pharma, East Hanover, NJ, USA) or daclizumab (Zenapax, Roche Pharmaceuticals); for the low-risk group (1st transplant without DSA); rabbit anti-thymocyte globulin (ATG) (Thymoglobulin; Genzyme Corp, Cambridge, MA, USA) for any re-transplantation and for the high risk patients who are highly-sensitized with positive DSA and negative serological crossmatch; rituximab, IVIG, and plasmapheresis.

Surgical stent policy

All transplants were done in the regular fashion using mostly Leich-Gregoir Technique ureterocystostomy leaving a double J stent for 4–6 weeks after transplant. Stents were removed earlier in patients with complicated UTI unresponsive to antibiotic therapy within the first 24 h. In any patient with a complicated UTI associated with increased creatinine levels, an ultrasound Doppler of the allograft was performed to exclude other causes for allograft dysfunction and to assure prior stent extraction.

Antimicrobial prophylaxis

Recipients routinely received prophylactic anti-CMV treatment with valganciclovir (Valcyte) for three to six months (according to donor/recipient IgG status) and prophylactic antibiotic against *Pneumocystis jirovecii* (PCP) with trimethoprim-sulfamethoxazole (TMP/SMX) at a dose of 160/800 mg three times a week for 1 year. No additional antibacterial prophylaxis is routinely provided in our centre.

Statistical analysis

Data were expressed as means with SD or medians with interquartile range (IQR) as appropriate for continuous variables and as numbers (percentages) for categorical variables.

Comparisons between continuous variables were made using parametric tests for normally distributed, or nonparametric tests for non-normally distributed variables. Comparisons between categorical variables were conducted using Chi-square test or Fisher's exact test, when appropriate. Baseline characteristics of patients receiving short versus long treatment were compared and Inverse probability of treatment weighting (IPTW) using propensity score was performed to adjust for confounders affecting the choice of treatment duration. We examined whether balance between the measured covariates was achieved in the weighted population by comparing standardized mean differences. Variables statistically significant ($P < 0.05$) or clinically plausible were inserted into the propensity score model. The

weighted score was introduced into the multivariate analysis of the primary outcome. Risk factors for the composite outcome were evaluated in a univariate and multivariate, IPTW adjusted, logistic regression.

Results

Overall, 646 adult KT recipients were hospitalized with complicated UTI during the study period, and 214 were included in the study (see Fig. 1 for study flow chart describing reasons for exclusion); 115 received short-course treatment [median 8, interquartile range (IQR) 6–9 days] and 99 received prolonged-course treatment (median 14, IQR 12–21 days). Patients' characteristics are described in Table 1. Mean age was 51.1 (±15.2) years, females were ~50% of the cohort (109/214). There were similar rates of transplantation from deceased donor; 52 (45.2%) vs. 51 (51.5%). Other donor characteristics were also similar between the groups (Table 1). *Enterobacterales* were the most common bacteria isolated, in 185 (86.4%), with *Escherichia coli* the dominant bacteria; 125/184 (68%) microbiologically documented *Enterobacterales* infections were resistant to TMP/SMX, 89/98 (91%) of them were documented during the first year post-transplantation. A third of the *Enterobacterales* infections (61/182, 33%) were ESBL; 1/16 (6%) of the *pseudomonas* infections was MDR. There were no vancomycin-resistant enterococcus (VRE) infections. Only six patients (2.8%) were admitted to intensive care unit. Patients who received prolonged course were more likely to be hospitalized during the first 6 months after transplantation, to have BSI accompanying UTI and higher mean serum creatinine level on admission (Table 1).

Eleven of the patients who had UTI during the first 6 months after transplantation (five in the short-course and six in the prolonged-course group) had postoperative urological complications; six required a collection drainage, one had wound dehiscence, all others had urinary leak. Nephrostomy during the UTI episode was present in eight patients (five in the short-course and three in the prolonged-course group). Time of double J (DJ) removal was available for 60 patients who had UTI during the first 6 months after transplantation; 23 in the short course and 37 in the prolonged course; mean 24.6 ± 13.6 days from transplantation (21.2 ± 12.3 vs. 26.1 ± 15.2, respectively).

Baseline characteristics of study populations with standardized mean difference of the original and weighted cohorts are presented in Table S1. Baseline differences were 0.1 or less standardized differences after weighting.

Outcomes

The composite outcome of all-cause mortality, or readmission for any cause within 30 days of from index culture occurred in 30 (30%) patients in the prolonged-course group and 33 (28.6%) in the short-course group (Table 2). Only two patients died during the study

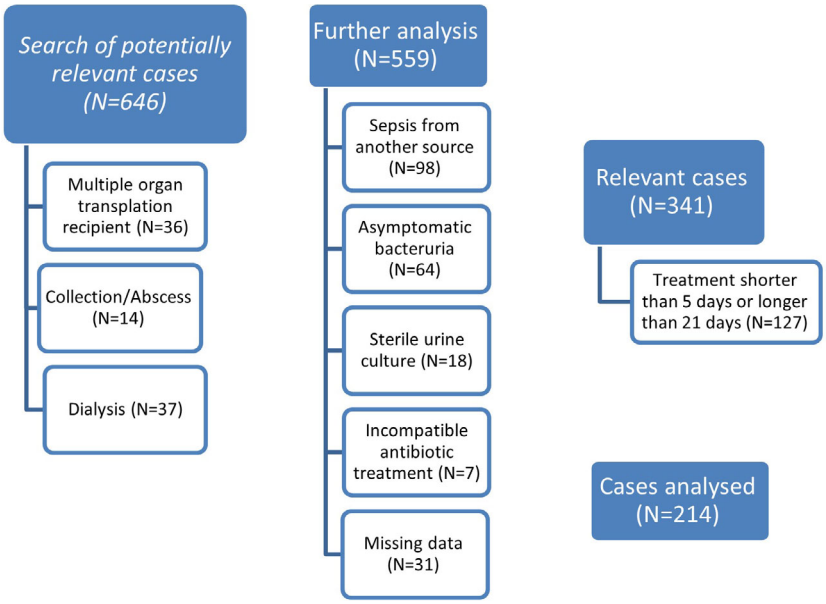

Figure 1 Exclusion flow chart.

Table 1. Patient Characteristics by length of treatment.

	Short treatment $N = 115$	Prolonged treatment $N = 99$	All cohort $N = 214$	*P*-value
Age at infection (mean± SD)	50.8 ± 15.1	51.7 ± 14.9	51.1 ± 15.2	0.696
Weight (kg), $N = 187$ (median, 25–75%)	75 (59.7–87.2)	71 (60.2–82.9)	73.2 (59–85)	0.352
Height (m), $N = 161$ (median, 25–75%)	165 (158.5–173)	164 (160–171.5)	165 (159–172)	0.597
Gender (female)	62 (53.9%)	47 (47.5%)	109 (50.9%)	0.348
Time from transplant to admission (median, 25–75%), months, $N = 207$	17.9 (2.6–70.9)	5 (0.6–73.4)	11.7 (1.2–72.2)	0.039
Time from transplant to admission (<half a year)	43/113 (38.1%)	50/94 (53.2%)	93/207 (44.9%)	0.029
Dialysis vintage before transplantation (months), $N = 187$ (median, 25–75%)	37 (19–66)	37 (14–69)	37 (15.7–69)	0.375
CMV serology prior to transplantation (positive)	92 (80%)	82 (82.8%)	174 (81.3%)	0.597
Immunosuppression				
Tacrolimus	103/114 (90.4%)	84/97 (86.6%)	187/211 (88.6%)	0.392
Cyclosporine A	5/114 (4.4%)	9/97 (9.3%)	14/211 (6.6%)	0.155
Sirolimus	2/114 (1.8%)	1/97 (1%)	3/211 (1.4%)	1
Renal failure aetiology				
Diabetic nephropathy	21 (18.3%)	14 (14.1%)	35 (16.4%)	0.824
Hypertension	9 (7.8%)	5 (5.1%)	14 (6.5%)	
Polycystic kidney disease	14 (12.2%)	14 (14.1%)	28 (13.1%)	
Congenital anomaly of kidney/urinary tract	12 (10.4%)	8 (8.1%)	20 (9.3%)	
Glomerulonephritis	33 (28.7%)	33 (33.3%)	66 (30.8%)	
Other (including nephrolithiasis)	26 (22.6%)	25 (25.3%)	51 (23.8%)	
Functional capacity				
Independent	89 (77.4%)	81 (37.9%)	170 (79.4%)	0.647
Instrumental ADL dependent	3 (2.6%)	3 (3%)	6 (2.8%)	
Basic ADL dependent	23 (20%)	15 (15.2%)	38 (17.8%)	
Functional capacity (2 + 3)	26 (22.6%)	18 (18.2%)	44 (20.6%)	0.424
Nephrostomy	5 (4.3%)	3 (3%)	8 (3.7%)	0.728
Charlson score (during UTI episode)				
CHF	4 (3.5%)	3 (3%)	7 (3.3%)	1
Hemiplegia/hemiparesis	2 (1.7%)	1 (1%)	3 (1.4%)	1
DM	37 (32.2%)	31 (31.3%)	68 (31.8%)	0.893
Dementia	–	–	–	–
Chronic pulmonary disease	4 (3.5%)	2 (2%)	6 (2.8%)	0.688
Chronic liver disease	2 (1.7%)	3 (3%)	5 (2.3%)	0.664
Mod-severe renal disease	–	–	–	–
Cancer	5 (4.3%)	8 (8.1%)	13 (6.1%)	0.254
Charlson score (median, 25–75%)	1 (1–2)	1 (1–2)	1 (1–2)	0.990
Donor details				
Donor (deceased)	52 (45.2%)	51 (51.5%)	103 (48.1%)	0.358
Transplant number (>1)	21 (18.3%)	27 (27.3%)	48 (22.4%)	0.115
Age	45.1 ± 16.4	46.1 ± 17.05	45.2 ± 16.8	0.635
Gender (female)	38 (33%)	35 (35.4%)	73 (34.1%)	0.722
Creatinine peak	0.8 (0–1.1)	0.65 (0–0.93)	0.75 (0.0–1.04)	0.386
Creatinine last (median, 25–75%)	0.76 (0.54–0.95)	0.73 (0.55–0.89)	0.75 (0.54–0.92)	0.386
CMV	71 (73.2%)	73 (84.9%)	144 (78.7%)	0.054
Hospitalization presentation				
Blood stream infection (BSI)	28 (24.3%)	46 (46.5%)	74 (34.6%)	0.001
Temperature 48 h, $N = 211$ (median, 25–75%)	37.5 (36.9–38.3)	37.7 (36.9–38.8)	37.5 (36.9–38.5)	0.335
Systolic blood pressure 48 h, $N = 212$ (mean ± SD)	116.3 ± 18.6	114.5 ± 20.9	115.6 ± 19.7	0.519
Diastolic blood pressure 48 h, $N = 212$ (median, 25–75%)	60 (53–69.5)	60 (52–69)	61 (53–70)	0.928
Creatinine admission, $N = 177$ (median, 25–75%)	1.52 (1.06–2.12)	2.02 (1.5–3.01)	1.71 (1.17–2.49)	0.001
WBC admission, N = 176 (median, 25–75%)	11.2 (7.6–15.4)	10.0 (6.5–15.3)	10.8 (7.24–15.2)	0.261
Bilirubin at admission, $N = 206$ (median, 25–75%)	0.48 (0.31–0.7)	0.51 (0.33–0.79)	0.49 (0.32–0.79)	0.311
Platelets at admission, $N = 213$ (median, 25–75%)	195 (142.7–250)	184 (140–235)	189.5 (143–244)	0.345

Table 1. Continued.

	Short treatment $N = 115$	Prolonged treatment $N = 99$	All cohort $N = 214$	*P*-value
Albumin at admission, $N = 206$ (median, 25–75%)	3.8 (3.5–4.2)	3.7 (3.4–4.1)	3.8 (3.4–4.1)	0.165
Duration of treatment (median, 25–75%)	8 (6–9)	14 (12–15)	10 (7–14)	0.000
ICU	2 (1.7%)	4 (4%)	6 (2.8%)	0.419
Bacteria isolated				
Enterobacterales	97 (84.3%)	88 (88.9%)	185 (86.4%)	0.315
Pseudomonas aeruginosa	9 (7.8%)	8 (8.1%)	17 (7.9%)	
Enterococcus spp.	9 (7.8%)	3 (3%)	12 (5.6%)	

ADL, activities of daily living; CHF, congestive heart failure; CMV, cytomegalovirus; DM, diabetes mellitus; ICU, intensive care unit.

Table 2. Outcomes.

	Short treatment $N = 115$	Long treatment $N = 99$	All cohort $N = 214$	*P*-value
Primary outcomes				
Composite outcome	33 (28.7%)	30 (30.3%)	63 (29.4%)	0.797
Relapse of UTI	19 (16.5%)	21 (21.2%)	40 (18.7%)	0.38
Secondary outcomes				
30-day mortality	2 (1.7%)	0	2 (0.9%)	0.500
Readmission 30 days	31 (27%)	30 (30.3%)	61 (28.5%)	0.589
Readmission 90 days	42 (36.5%)	44 (44.4%)	86 (40.2%)	0.239
Days of hospital stay- all cohort, (median, 25–75%)	9 (7–15)	10 (8–18)	10 (8–16)	0.103
Days of hospital stay (alive at day 30), (median, 25–75%)	9 (7–15)	10 (8–18)	10 (8–16)	0.114
Bacteraemia within 30 days	20 (17.4%)	24 (24.2%)	44 (20.6%)	0.216
MDR development within 180 days	26/113 (23%)	23/98 (23.5%)	49/211 (23.2%)	0.937
Creatinine 30 days, $N = 153$ (median, 25–75%)	1.5 (1.01–2.01)	1.47 (1.11–2.12)	1.49 (1.09–2.05)	0.630
Creatinine 90 days, $N = 147$ (median, 25–75%)	1.41 (0.95–2.04)	1.34 (1.01–1.81)	1.41 (0.99–1.87)	0.779

MDR, multidrug resistance.

follow up, both in the short-course group. Relapse of UTI within 180 days occurred in 21 (21.2%) in the prolonged-course and 16 (16.5%) in the short-course group ($P = 0.38$; Table 2).

No significant difference between groups was found for all other outcomes evaluated, including readmissions, length of stay, rates of bacteraemia, and MDR development. Only two episodes of *C. difficile* infection occurred in the entire cohort (both in the short-course group). Median serum creatinine within 30 and 90 days of admission was similar for both groups (see Table 2 for details). Univariate analysis for risk factors for the primary outcomes is presented in Table 3 (and Tables S2 and S3). Risk factors that were found to be significantly associated with the composite outcome of all-cause mortality or readmission for any cause were male gender, obesity, admission for UTI during the first 6 months after transplantation, longer dialysis vintage before transplantation, congestive heart failure (CHF), history of cancer and transplantation from deceased donor and higher creatinine level on admission. Risk factors that were found to be significantly associated with relapse UTI were admission for index UTI during the first 6 months after transplantation and higher creatinine level on admission. Duration of treatment was not associated with either outcome, even when examining separately those in the prolonged-duration group who received up to 14 days or more than 14 days treatment. Using multivariate logistic regression analysis adjusted by inverse propensity score weighting, the only

Table 3. Risk factors for primary outcomes – univariate analysis.

	Composite outcome (No) $N = 151$	Composite outcome (Yes) $N = 63$	*P*-value
Age at infection (mean ± SD)	50.4 ± 14.9	53.2 ± 15.1	0.218
Gender (female)	84 (55.6%)	25 (39.7%)	0.033
Time from transplant to admission (median, 25–75%), $N = 207$	15.9 (1.6–88.7)	4.2 (0.8–43.8)	0.035
Time from transplant to admission (<180 days)	58/146 (39.7%)	35/61 (57.4%)	0.02
Dialysis vintage before transplantation (months), $N = 187$ (median, 25–75%)	34 (14–65.5)	48.5 (28.2–78.2)	0.018
Nephrostomy	3 (2%)	5 (7.9%)	0.050
Congestive heart failure	2 (1.3%)	5 (7.9%)	0.024
Cancer	6 (4%)	7 (11.1%)	0.046
Charlson score during UTI episode (median, 25–75%)	1 (1–2)	1 (1–2)	0.120
Donor (deceased)	65 (43%)	38 (60.3%)	0.021
Transplant number (>1)	34 (22.5%)	14 (22.2%)	0.962
Hospitalization presentation			
Blood stream infection (BSI)	55 (36.4%)	19 (30.2%)	0.380
Creatinine on admission mg/dl, $N = 177$ (median, 25–75%)	1.67 (1.15–2.34)	2.03 (1.33–3.03)	0.057
Albumin at admission, g/dl $N = 206$ (median, 25–75%)	3.8 (3.4–4.1)	3.7 (3.4–4)	0.245
Intensive care unit	4 (2.6%)	2 (3.2%)	1
Treatment duration			
Long (11–21)	69 (45.7%)	30 (47.6%)	0.797
Long (11–14)	47/129 (36.4%)	17/50 (34%)	0.760
Long (15–21)	41/123 (33.3%)	22/55 (40%)	0.390
	Relapse UTI (No) $N = 174$	**Relapse UTI (Yes) $N = 40$**	***P*-value**
Age at infection (mean ± SD)	51.4 ± 14.9	50.6 ± 15.6	0.759
Gender (female)	90 (51.7%)	19 (47.5%)	0.630
Time from transplant to admission (<180 days)	70/160 (43.8%)	23/36 (63.9%)	0.029
Dialysis vintage before transplantation (months), (median, 25–75%), $N = 187$	37 (16.5–66)	44.5 (18.7–89.2)	0.207
Donor (deceased)	86 (50%)	19 (48.7%)	0.885
Transplant number (>1)	37 (21.5%)	9 (23.1%)	0.831
CMV serology prior to transplantation (positive)	137 (78.7%)	37 (92.5%)	0.045
DM	60 (34.5%)	8 (20%)	0.076
Functional capacity (2 + 3)	40 (23%)	4 (10%)	0.083
Nephrostomy	7 (4%)	1 (2.5%)	1
Charlson score during UTI (median, 25–75%)	1 (1–2)	1 (1–2)	0.145
Hospitalization presentation			
Blood stream infection (BSI)	59 (33.9%)	15 (37.5%)	0.667
Creatinine on admission, $N = 177$ (median, 25–75%)	1.63 (1.15–2.4)	2.33 (1.69–2.79)	0.021
ICU	5 (2.9%)	1 (2.5%)	1
Treatment duration			
Long (11–21)	78 (44.8%)	21 (52.5%)	0.380
Long (11–14)	52 (35.1%)	12 (38.7%)	0.706
Long (15–21)	49 (33.8%)	14 (42.4%)	0.349

risk factor that remained significantly associated with the composite outcome of all-cause mortality or readmission for any cause for the entire cohort was transplant from deceased donor (OR 2.04, 95% CI 1.02–4.1, $P = 0.044$; Table 4).

A separate analysis was performed for the patients who were admitted with early UTI (during the first 6 months after transplantation). There were overall 93 patients; 43 received short-course treatment and 50 received prolonged-course treatment. No significant differences in baseline characteristics were demonstrated between patients receiving short versus prolonged course in this group of patients, excluding baseline serum creatinine, which was higher in the long duration

Table 4. Risk factors for the primary outcomes – multivariate analysis.

Risk factor	Multivariate analysis OR (95% CI)	*P*-value
All-cause mortality/readmission		
Gender (female)	0.68 (0.34–1.35)	0.271
Time from transplant to admission (<180 days)	1.71 (0.86–3.42)	0.127
Creatinine admission	1.002 (0.84–1.2)	0.981
Dialysis duration	1 (0.99–1.001)	0.500
Treatment duration (long)	1.01 (0.52–1.96)	0.983
Donor (deceased)	2.04 (1.02–4.1)	0.044
Cancer	2.52 (0.87–7.36)	0.089
Relapse UTI		
Treatment duration (long)	1.15 (0.55–2.42)	0.702
Time from transplant to admission (<180 days)	1.9 (0.86–4.23)	0.113
Diabetes mellitus	0.41 (0.16–2.66)	0.078
Creatinine admission	1.04 (0.87–1.23)	0.674

CI, confidence interval; OR, odds ration.

arm (data not shown). Severity of UTI, defined by septic shock, BSI or the need for ICU, was not different between those who had early or late UTI. The composite outcome of all-cause mortality or readmission occurred more frequently in this population compared to those with late UTI, with 35/93 (38%) having this outcome. No difference in the primary outcome was observed in this population between short-term and long-term groups.

Discussion

In this retrospective cohort of KT recipients hospitalized with complicated UTI, we found no significant difference in clinical outcomes between patients who were treated with a short course of antibiotics (6–10 days) versus prolonged course (11–21 days). Duration of therapy was not associated with significant difference in either mortality, readmission or relapse of UTI, as well as subsequent bacteraemia, length of stay, resistance development or graft function after 30 and 90 days. Among patients with early UTI (during the first 6 months), the composite outcome occurred more frequently compared with patients who had late UTI, with no difference between patients who received short course or prolonged course. The presence of DJ or nephrostomy tube was also not associated with any of the outcomes.

Previous studies evaluating duration of antibiotic therapy for complicated UTI or Gram-negative bacteraemia in general population demonstrate noninferiority of short (≤7 days) versus longer treatment (>7 days) [18,20,23]. A recent retrospective observational study examining treatment duration in pyelonephritis in children, showed no difference in odds of treatment failure for patients prescribed a short course (6–9 days) versus a prolonged course (≥10 days) of antibiotics (11.2% vs. 9.4%; odds ratio, 1.22; 95% CI, 0.75–1.98) [24].

Most interventional studies excluded solid organ transplant recipients. Yahav *et al.* [18] conducted a randomized-controlled trial including 604 patients with Gram-negative bacteraemia, mostly *Enterobacterales* from a urinary source, and found noninferiority of 7 vs. 14 days of antibiotic therapy. Fifty-one KT recipients were included in this study, and no significant difference in the composite primary outcome of mortality, relapse, complications, and readmissions was demonstrated between 25 KT recipients receiving 7 days and 26 receiving 14 days of antibiotics. Even in retrospective studies on duration of therapy for UTI or Gram-negative bacteraemia, KT recipients are poorly represented. Sousa *et al.* [25] included 85 immunocompromised patients (out of 395 patients) in a study comparing short (7–10 days) versus long (>10 days) antibiotic therapy for Gram-negative bacteraemia, and demonstrated no difference in mortality between arms among immunocompromised patients.

Limited data from these studies suggest higher relapse rates among immunocompromised patients treated with a short antibiotic course. Gianella *et al.* [26] retrospectively compared short (≤10 days) versus long (>10 days) antibiotic treatment for *E. coli* bacteraemia. Among 51 solid organ transplant recipients included, higher risk of relapse was demonstrated in the short duration arm. Nelson *et al.* [27] included 45 immunocompromised patients in a retrospective study comparing short (7–10 days) versus long courses (>10 days) of antibiotics for uncomplicated Gram-negative bacteraemia. Immunocompromise was a statistically significant risk factor for mortality or recurrent infection. In our cohort, we did not find differences between treatment duration groups in relapse of UTI or readmission rates. Since the above studies evaluated relapsed bacteraemia (rather than UTI), and addressed various immunocompromised populations, further studies are needed to confirm our findings.

Transplant from deceased donor was found to be associated with the primary composite outcome. Previous studies have similarly demonstrated an association between deceased donor and re-hospitalization. Several

explanations were suggested, including that these recipients tend to spend longer time on waiting lists and longer time on dialysis; receive more immunosuppression, and experience worse graft and patient survival [28].

More than 50% of patients receiving prolonged course in our cohort were transplanted less than 6 months before hospitalization. An association between early time from transplantation and the composite outcome was demonstrated in univariate, but not multivariate analysis, probably reflecting the higher immunosuppression level and postoperative complications in these patients. Antibiotic duration did not affect the primary outcome among this group. In the guidelines for the treatment of UTI in SOT, the authors recommend that patients with allograft pyelonephritis in the early post-transplant period presenting with sepsis should be treated for at least 14–21 days [10]. Our results warrant further discussion as to those recommendations.

There are increasing evidence that the use of antibiotics may be harmful for kidney transplant recipients. Solid organ transplant recipients are at increased risk for *C. difficile* infection and are prone to have complicated infection [29]. Infections with multidrug resistant bacteria in organ recipients are associated with limited therapeutic options and worse outcomes. Hence, antibiotic policies and strategies to limit these infections are considered essential in the management transplanted patients [30]. Programs for antibiotic stewardship are being implemented for SOT patienty [16]. Shortening antibiotic courses is considered an important component of antibiotic stewardship.

Our study has several limitations. It is an observational study, thus although we used a propensity score analysis, residual confounding factors that might influence the physicians' decision on antibiotic duration cannot be ruled out. While there was no difference in the hospital presentation between the groups, there is clinical heterogeneity among the patients in terms of underlying cause for ESKD or the time elapsed from transplantation. This, however, reflects real life heterogeneity of the KT population.

In conclusion, in our cohort, we found that short-course antibiotic of 6–10 days was as effective as longer course of 11–21 days in KT recipients hospitalized with UTI without collection or abscesses. Further randomized-controlled studies are needed in order to confirm the safety and efficacy of short-course antibiotics in KT recipients with UTI and/or BSIs, and define optimal duration.

Authorship

SA-N: data collection, performance of the research, paper writing and final approve. DY: research design, performance of the research, data analysis, paper writing and final approve. EN: data collection, paper revising and final approves. BR-Z: data analysis, paper revising and final approve. RR: paper writing and final approve. EM: paper writing and final approve. HB-Z: data collection, performance of the research, final approve. YM: data collection, performance of the research, final approve. AA: performance of the research, paper writing and final approve. HG: research design, performance of the research, data analysis, paper writing and final approve.

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Conflict of interest

The authors declare no conflict of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Covariates before and after weighting*.

Table S2. Risk factors for composite outcome – univariate analysis (all variables).

Table S3. Risk factors for relapse UTI – univariate analysis (all variables).

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