Title

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Journal

Transplantation, 96(8)

ISSN

0041-1337

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Publication Date

2013-10-27

DOI

10.1097/tp.0b013e3182a04997

Peer reviewed

Published in final edited form as:
Transplantation. 2013 October 27; 96(8): . doi:10.1097/TP.0b013e3182a04997.

Independent Risk Factors for Urinary Tract Infection and for Subsequent Bacteremia or Acute Cellular Rejection: A Single Center Report of 1166 Kidney Allograft Recipients

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Abstract

Background—Urinary tract infection (UTI) is a frequent, serious complication in kidney allograft recipients.

Methods—We reviewed the records of 1166 kidney allograft recipients who received their allografts at our institution between January 2005 to December 2010 and determined the incidence of UTI during the first three months after transplantation (early UTI). We utilized Cox proportional hazard models to determine the risk factors for early UTI and whether early UTI was an independent risk factor for subsequent bacteremia or acute cellular rejection (ACR).

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Author Contributions:
JL: Research design, data analyses, and writing of the manuscript. No conflict of interest.
HB: Data analyses and writing of the manuscript. No conflict of interest.
DD: Research design. No conflict of interest.
CH: Research design. No conflict of interest.
MA: Research design. No conflict of interest.
MS: Research design and writing of the manuscript. No conflict of interest.
PA: Research design and writing of the manuscript. No conflict of interest.
MS: Research design, data analyses, and writing of the manuscript. No conflict of interest.
TM: Research design, data analyses, and writing of the manuscript. No conflict of interest.

Results—UTI, defined as ≥10^5 bacterial colony forming units per milliliter of urine, developed in 247 (21%) of the 1166 recipients. Independent risk factors for the first episode of UTI were: female gender (hazard ratio [HR]: 2.9, 95% Confidence Intervals (CI): 2.2–3.7, P<0.001), prolonged use of Foley catheter (HR: 3.9, 95% CI: 2.8–5.4, P<0.001), ureteral stent (HR 1.4, 95% CI: 1.1–1.8, P=0.01), age (HR: 1.1, 95% CI: 1.0–1.2, P=0.03), and delayed graft function (HR:1.4, 95% CI: 1.0–1.9, P=0.06). Trimethoprim/sulfamethoxazole prophylaxis was associated with a reduced risk of UTI (HR: 0.6, 95% CI: 0.3–0.9, P=0.02). UTI was an independent risk factor for subsequent bacteremia (HR: 2.4, 95% CI: 1.2–4.8, P=0.01). Untreated, but not treated, UTI was associated with an increased risk of ACR (HR: 2.8, 95% CI: 1.3–6.2, P=0.01).

Conclusions—Female gender, prolonged use of Foley catheter, ureteral stent, age, and delayed graft function are independent risk factors for early UTI. UTI is independently associated with the development of bacteremia, and untreated UTI is associated with subsequent ACR.

Keywords

Urinary Tract Infection; Bacteremia; Acute Rejection; Kidney Transplantation

INTRODUCTION

Urinary tract infection (UTI) is a common, serious infection following kidney transplantation and a number of studies have examined risk factors for UTI in kidney graft recipients (reviewed in (1)). Bacteria are the most frequent causes of UTI, and UTI has been attributed as a cause for septicemia in kidney allograft recipients (2,3). Despite its high prevalence and potential for serious complications, strategies for prophylaxis, screening, and treatment of post-transplant UTI are not standardized. Questions also remain regarding diagnostic criteria, duration of antimicrobial therapy, and the appropriateness of screening for and treating asymptomatic UTI. The relationship between UTI and acute rejection has also not been well characterized.

We therefore conducted a retrospective cohort study comprised of 1166 adult kidney graft recipients to determine the incidence of UTI early after transplantation, to identify independent risk factors for UTI, and to examine the relationship between UTI and subsequent development of bacteremia or acute rejection.

RESULTS

Study Cohort

Between January 2005 and December 2010, 1213 adult patients received a kidney allograft at our institution. Forty-seven of these patients were excluded because of insufficient clinical and laboratory data, leaving a study cohort of 1166 patients. Table 1 lists the baseline clinical and transplantation characteristics of the study cohort. As part of our outpatient clinical protocol, urine analysis and cultures were obtained at every post-transplant clinic visit in the first 3 months of transplantation.

Bacterial UTI, defined as the growth of ≥10^5 colony forming units per milliliter of urine (cfu/ml), was observed in 247 (21%) of the 1166 patients within the first 3 months of transplantation. Only the first episode of UTI was evaluated, and the median time from transplantation to identification of the first UTI episode was 19 days (interquartile range: 9 to 40 days). The presence of fever, urgency, or dysuria was documented in 79 (32%) of the 247 patients with UTI. Pyuria, defined as >5 white blood cells per high power field in urinanalysis, occurred in 165 (67%) of the 247 patients. Nine out of the 247 patients with UTI had recorded technical/anatomical issues: 4 had undergone pre-transplant bladder

surgeries, 3 had obstruction requiring percutaneous nephrostomy, and 2 had repair of urinary leak.

Bacterial Species and Antimicrobial Sensitivities of Urinary Isolates

Among the 247 UTIs, the three most commonly isolated bacteria were: *Escherichia coli*, *Enterococcus* species, and *Klebsiella* species. Antimicrobial susceptibilities of identified bacteria are presented in Table 2. Among the transplant recipients receiving trimethoprim/sulfamethoxazole prophylaxis (TMP/SMX) (N=1112), TMP/SMX resistance was common in: (i) *Escherichia coli* (resistant, N=53 vs. sensitive, N=8) and (ii) *Klebsiella* spp. (resistant, N=25 vs. sensitive, N=5). There were no differences (P>0.05) with respect to age, female gender, African-American race, diabetes mellitus, prior transplantation, deceased donor transplantation, ureteral stent placement, use of vancomycin as preoperative prophylaxis, anti-thymocyte induction, corticosteroid maintenance, delayed graft function, and prolonged use of Foley catheter between patients infected with resistant strains and those infected with sensitive strains for each of these two bacteria. *Enterococcus* spp. is inherently resistant to TMP/SMX.

Treatment Status of UTI

Among the 247 patients with UTI, 100 patients (40%) were not treated with antibiotics. Although the retrospective nature of our study prevents definitive reasons for the lack of treatment in each instance, the following three reasons, not necessarily mutually exclusive, appeared to be responsible for the managing physician electing not to treat an episode of UTI: (i) lack of symptoms in 89 patients (89%); (ii) a subsequent urine culture obtained after 4 days (median, interquartile range: 3 to 7 days) being negative in 67 patients (67%); and (iii) mixed bacterial flora in 24 patients (24%).

Risk Factors for UTI

Baseline patient and transplant-related variables that were significantly associated with UTI by univariate Cox regression analysis (P<0.10) were: female gender, intraoperative ureteral stent placement, delayed graft function, prolonged use of Foley catheter, the use of vancomycin as preoperative prophylaxis, age, African American race, and deceased donor transplantation. The use of TMP/SMX prophylaxis was associated with a reduced risk of UTI (Table 3).

In the multivariable Cox regression analysis, age, female gender, intraoperative ureteral stent placement, prolonged use of Foley catheter, and delayed graft function were independently associated with an increased risk of UTI. The use of TMP/SMX prophylaxis was associated with a reduced risk of UTI (Table 3). The multivariable Cox regression analysis was also restricted to those only on TMP/SMX prophylaxis (N=1112). Female gender, intraoperative ureteral stent placement, prolonged use of Foley catheter, and delayed graft function, but not age, were associated with UTI in this analysis.

UTI and Bacteremia

Bacteremia occurred in 53 (4.5%) of the 1166 transplant recipients within the first three months of transplantation. Bacteremia was more common in patients with UTI, occurring in 30 (12.1%) of the 247 patients with UTI and 23 (2.5%) of the 919 patients without UTI (P<0.001, Fisher's exact test). Among the 30 episodes of bacteremia in patients with UTI, 7 preceded UTI, 9 occurred at the time of the first UTI episode, and 14 occurred at a median of 15 days subsequent to the UTI episode. In the 14 bacteremia events that occurred after the UTI episode, 6 out of the 14 UTI were asymptomatic. The organism isolated in the first UTI

episode was the same bacteria in 14 (61%) of the 23 bacteremias that occurred at the time or subsequent to the UTI event.

To examine whether UTI is a risk factor for subsequent bacteremia, we controlled for the bacteremia events occurring prior to a UTI by using UTI as a time dependent covariate in a Cox regression analysis. UTI was associated with bacteremia by univariate analysis. Age, intraoperative ureteral stent placement, delayed graft function, and prolonged use of Foley catheter were also identified as risk factors for bacteremia by univariate analysis ($P<0.10$). After adjustment for demographic and relevant clinical characteristics, UTI remained significantly associated with bacteremia by multivariable Cox proportional hazards regression analysis. Age, prolonged use of Foley catheter, and ureteral stent placement were also independent risk factors for bacteremia in multivariable analysis (Table 4).

UTI and Acute Rejection

Biopsy confirmed acute cellular rejection (ACR) developed in 58 (5.0%) of 1166 transplant patients during the first year of transplantation. ACR was not more common in patients with UTI, occurring in 15 (6.1%) of the 247 patients with UTI and 43 (4.7%) of the 919 patients without UTI ($P=0.41$). Among the 15 ACR episodes in patients with UTI, 3 ACRs occurred prior to the first UTI episode and 12 occurred at a median of 86.5 days after the first episode of UTI.

To examine whether UTI is a risk factor for subsequent ACR, we controlled for the ACR events occurring prior to a UTI event by using UTI as a time dependent covariate in Cox regression analysis. UTI was not significantly associated with ACR (HR: 1.35, 95% CI: 0.71–2.57, $P=0.36$) by univariate analysis.

We next investigated whether treatment status for UTI was associated with the development of ACR. Among the 247 patients with UTI, 147 received antibiotic therapy and the remaining 100 patients did not receive antibiotic therapy in proximity to a positive urine culture. In the univariate analysis with no UTI group as the reference (i.e. HR=1), untreated UTI was significantly associated with ACR whereas treated UTI was not associated with ACR. We also found in univariate analyses that the use of preoperative prophylaxis with vancomycin and delayed graft function were positively associated with ACR whereas female gender and antithymocyte globulin induction therapy were associated with a reduced risk of ACR (Table 5).

In the multivariable Cox proportional hazards regression analysis, untreated UTI remained associated with ACR and treated UTI was not. The use of preoperative prophylaxis with vancomycin and delayed graft function continued to be associated with an increased risk of ACR; antithymocyte globulin induction therapy and female gender were associated with a reduced risk of ACR (Table 5).

DISCUSSION

We examined a large cohort of kidney graft recipients managed at a single center who were screened by protocol for UTI and found that 21% of kidney graft recipients developed UTI within the first 3 months after kidney transplantation. *Escherichia coli*, *Enterococcus* species, and *Klebsiella* species accounted for the vast majority of UTI. Not surprisingly, UTI was an independent risk factor for the subsequent development of bacteremia. An intriguing and novel finding that has emerged from the current investigation is that untreated UTI, but not treated UTI, is associated with development of biopsy confirmed ACR.

Multivariable analysis for determining independent risk factors for UTI

A number of features related to our elucidation of risk factors for UTI in our study are worthy of emphasis. First, our study cohort was comprised of 1166 kidney transplant recipients, all from a single center and managed with a standardized protocol that included systematic screening of urine during the first 3 months of transplantation. Second, we only included patients with complete clinical and laboratory information. Third, and very importantly, we utilized a multivariable Cox regression analysis to elucidate the relative contributions of different variables (risk factors) to a single outcome (incident UTI). It is very likely that multiple factors, both biologic as well as iatrogenic, contribute to the high incidence of UTI in kidney graft recipients, and multivariable Cox regression analysis, unlike univariate analysis, adjusts for the contribution of different risk factors (e.g., female gender, prolonged use of Foley catheter) and allows for the identification of the independent contribution of each factor to the development of UTI in kidney graft recipients (Table 3).

Female gender, age, and prolonged use of Foley catheter have been reported as risk factors in the general population (4) and in the kidney transplant population (5–9). Our study supports the independent effects of these 3 factors. In terms of transplant specific factors, ureteral stent placement has been associated with UTI in prior studies (10, 11). Our study also identifies the independent risk of ureteral stent placement on UTI.

Both deceased donor transplantation and delayed graft function have been previously reported as risk factors for UTI (5, 9) and it is unclear whether one or both are associated with UTI. In our univariate analyses, both of these factors were associated with UTI but interestingly in our multivariable analysis, only delayed graft function was associated with UTI. Our findings thus support UTI as another potential complication from delayed graft function.

Antibiotic prophylaxes for preoperative surgical management and for PCP prophylaxis are now routinely used in clinical transplantation but have not been well studied in terms of UTI risk. In our study, preoperative surgical prophylaxis was mostly given as cefazolin and vancomycin, which have differing antimicrobial profiles. While vancomycin prophylaxis increased the risk for UTI in a univariate analysis, it was not significantly associated with UTI in the multivariable analysis. TMP/SMX (960 mg/day) prophylaxis was introduced in clinical renal transplantation to prevent *Pneumocystis jiroveci* (PCP) pneumonia (12). Early studies showed an added benefit from low-dose TMP/SMX prophylaxis (480 mg/day) for reducing UTI incidence when compared to placebo (13, 14). Our study supports that low dose TMP/SMX PCP prophylaxis has an additional benefit of independently reducing the risk of early UTI in kidney transplant recipients.

Immunosuppressive therapy is considered to be a risk factor for infectious complications. Induction therapy, specifically rabbit antithymocyte globulin, has been associated with UTI in some studies in a univariate analysis (15). In our current investigation, neither the type of induction immunosuppression therapy (antithymocyte globulin vs. interleukin receptor-2 antibodies) nor corticosteroid maintenance vs. corticosteroid early withdrawal was identified as an independent risk factor for UTI similar to the study by Vidal et al (9). Our observations, however, must be interpreted with due caution as there may be additional unmeasured confounders that led to an under appreciation of the impact of immunosuppression therapy.

Identification of UTI as an independent risk factor for bacteremia

Bacteremia affects approximately 4% of kidney transplant recipients (3) and causes significant morbidity and mortality in this immunocompromised population. Our study precisely delineates the impact of UTI on this important post-transplant complication. Prior

studies of bacteremia in kidney graft recipients (2,3) have not controlled for the timing of the UTI event in relationship to the detection of bacteremia. In contrast, our study with the use of a time-dependent covariate Cox regression analysis identified UTI as an independent risk factor for the development of bacteremia. Our statistical analysis controlled for the temporal relationship between UTI and bacteremia (that is including only UTI that preceded the incident bacteremia and excluding UTI that occurred simultaneously with or after the incident bacteremia event). We also found that, in the bacteremia episodes subsequent to UTI, not only symptomatic UTI but also asymptomatic UTI preceded the bacteremia event, suggesting that kidney transplant recipients may be yet another population in whom asymptomatic UTI must be treated. Our finding may help fill the existing gap in KDIGO guidelines regarding management of asymptomatic UTI in kidney graft recipients (16).

Unmasking the novel association between untreated UTI and ACR

Among the 247 patients with UTI, 40% did not receive treatment with antibiotics. The availability of two distinct groups within the UTI cohort, one group treated with an antibiotic therapy and the other untreated, provided a unique opportunity to examine the potential impact of untreated UTI on the development of ACR. Using a time dependent covariate Cox regression analysis, our study uniquely identified an independent association between untreated UTI, but not treated UTI, and ACR. This novel finding brings in to sharp focus the therapeutic question of whether any UTI in kidney graft recipients should be treated irrespective of the presence or absence of symptoms. Our findings advance knowledge since earlier publications have not examined the association between untreated UTI and development of ACR nor the temporal relationship between UTI and ACR.

Limitations

Our study has a number of limitations. We used a retrospective cohort study design to identify independent risk factors for UTI and subsequent bacteremia and biopsy confirmed ACR. Although our analysis included several known risk factors for UTI, data regarding pre-transplant urine volume, post void residual volume, and prostate volume were not available in all instances for inclusion in our data analyses. More extensive bacteriologic data, e.g. presence of β-lactamase-producing *E. coli*, was not obtained, which may have had an impact on the outcomes of bacteremia and ACR. Adherence to treatment was not assessed in the patients treated with antibiotics. Our study was also designed to analyze the risk factors associated with development of the first UTI event and its relationship with bacteremia and ACR but does not take into account the effects of multiple UTI events.

Implications

We found a 21% incidence of UTI within the first 3 months after transplantation, indicating a need for improved methods to prevent UTI. Our finding that bacteremia is clearly more frequent following a UTI further suggests that current management strategies are also inadequate to prevent this serious complication. Whether additional antibiotic prophylaxis targeting a selected group at high risk for UTI may prevent UTI and bacteremia is unknown and worth consideration. The following were the published guidelines from the Infectious Disease Society of America in 2005: “No recommendation can be made for screening for or treatment of asymptomatic bacteriuria in renal transplant or other solid organ transplant recipients (C-III)” (17). Because untreated UTI is associated with development of ACR in this study, better parameters to treat or not to treat a positive urine culture need to be developed for kidney graft recipients.

MATERIALS AND METHODS

Study Cohort

We reviewed the records of 1213 adult patients who received a kidney transplant at the New York Presbyterian – Weill Cornell Medical Center between January 2005 and December 2010 for the development of early UTI. Forty seven were excluded from data analysis because of incomplete clinical or laboratory information and the remaining 1166 transplant recipients were included in this study. Demographic characteristics, clinical and laboratory data, and follow up information were obtained from these patients. This study was approved by our Institutional Review Board.

Transplant Protocols

All kidney graft recipients had a Foley catheter inserted during transplant surgery that was removed within 7 days of transplantation. Prolonged use of Foley catheter was defined as the use of a Foley catheter beyond day 7 after transplantation or the use of intermittent self-catheterization post-transplantation.

Induction immunosuppressive therapy consisted primarily of antithymocyte globulin and interleukin-2 receptor antibody and maintenance immunosuppression included a calcineurin inhibitor and mycophenolate mofetil with or without corticosteroids (18).

All patients received a dose of preoperative antibiotics prior to surgery. Post-transplant infection prophylaxis included clotrimazole for the first 3 months, valganciclovir or acyclovir for 6 months for cytomegalovirus prophylaxis, and prophylaxis for *Pneumocystis jiroveci* for 12 months with trimethoprim/sulfamethoxazole. Patients with a history of sulfa allergy received dapsone, pentamidine, or no prophylaxis.

Our post-transplant standard of care during the first 3 months of transplantation included collection of urine specimens for urine analysis and culture during each visit to the transplant clinic. Transplant recipients were seen twice weekly in the first month, once weekly in the second month, and once every other week in the third month. The decision on whether to treat a positive urine culture with antimicrobial therapy was made by the clinical transplant team. Bacterial identification and susceptibility testing were performed by Vitek 2 (Biomérieux Inc., Durham, NC) in accordance with Clinical and Laboratory Standards Institute guidelines.

Study Definitions

We defined UTI as the growth of $\geq 10^5$ bacterial cfu/ml. Only the first episode of UTI was included in data analyses. Symptomatic UTI was defined as a positive urine culture and the presence of one of the following symptoms: subjective fever or documented fever > 38.0°C, dysuria, or urgency. Pyuria was defined as >5 white blood cells per high power field in urinanalysis.

Bacteremia was defined as a positive blood culture. If blood cultures were negative or if there was no indication for obtaining a blood culture, the patient was considered to be negative for bacteremia.

Acute cellular rejection was defined as a biopsy proven diagnosis based on Banff classification schema (19). If the allograft biopsy did not meet the criteria for acute cellular rejection or if the patient did not have a diagnostic biopsy in the first year of transplantation, the patient was considered to be negative for acute cellular rejection.

Statistical Analysis

The association between UTI and bacteremia or ACR was assessed using Fisher's exact test. We used multivariable Cox-proportional hazard model to identify risk factors for UTI, bacteremia, and biopsy confirmed acute cellular rejection. The hazard rate is the probability of instantaneous occurrence of an event that has not already occurred. Cox proportional hazard analyses models the logarithm of the relative hazard. In this model, $e^{z\beta}$ is the multiplicative contribution of each variable on the hazard function, where β is the regression coefficient and z is the observed variable. Absences or presence of a variable that is studied is usually coded 0 and 1, respectively. In that case, e^{β} is the risk induced by the studied variable on the hazard rate without this factor. To control for confounders, we built a multivariable model that included variables with a P value of <0.1 in the univariate analyses.

To analyze the relationship between UTI and bacteremia or acute cellular rejection, we used UTI as a time-dependent covariate. As compared to fixed- covariates (e.g., female gender), the use of a time-dependent covariate allows for modeling a variable that changes over time.

In cases where bacteremia or acute cellular rejection was recorded simultaneously with UTI, we assumed, as a conservative estimate, that the UTI happened after the event and was not associated with the outcome. All statistical analyses were performed using STATA 12.0 I/C (Statacorp, College Station, TX) and we used 2-sided tests and confidence intervals with type I error of 5%.

Acknowledgments

We thank all our patients and our colleagues at the Division of Transplant Surgery, New York Presbyterian Hospital – Weill Cornell Medical Center, and The Rogosin Institute for their kind help in conducting this study.

Parts of the information reported in this article were presented as an abstract at the American Society of Nephrology Kidney Week 2012. J.L. is a recipient of a KL2 Scholars Award from the Weill Cornell Clinical and Translational Science Center. This publication has been supported in part by the National Center for Advancing Translational Sciences at the National Institutes of Health, through the Weill Cornell CTSC grant KL2-TR-000458.

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Table 1

Baseline and Transplant Characteristics of the 1166 Kidney Graft Recipients

Characteristics	N (%)
Recipient	
Median Age	53
Female Gender	452 (38.8%)
African American Race	320 (27.4%)
Diabetes Mellitus	364 (31.2%)
Transplant Characteristics	
Prior Kidney Transplantation	125 (10.7%)
Deceased Donor Transplantation	607 (52.1%)
Ureteral Stent Placement	532 (45.6%)
Preoperative Antibiotic Therapy[a]	
Cefazolin	991 (85.0%)
Vancomycin	136 (11.7%)
Other Cephalosporin Agent	10 (0.8%)
Other Antibiotic	29 (2.5%)
Induction Therapy	
Antithymocyte Globulin	1008 (86.4%)
Basiliximab	142 (12.1%)
Dacluzimab	5 (0.4%)
Other/None	11 (0.9%)
Corticosteroid Maintenance Group[b]	217 (18.6%)
Delayed Graft Function (DGF)[c]	249 (21.4%)
Prolonged Use of Foley Catheter[d]	89 (7.6%)
Pneumocystis Jiroveci Prophylaxis Agent	
Trimethoprim/Sulfamethoxazole	1112 (95.4%)
Dapsone	40 (3.4%)
Pentamidine	11 (0.9%)
None	3 (0.3%)

[a] Prophylactic antibiotics given prior to the transplant surgery.

[b] Kidney transplant recipients maintained on corticosteroid immunosuppression.

[c] Defined as the need for hemodialysis within seven days of kidney transplantation. DGF occurred in 237 (39.0%) out of 607 deceased donor transplants and in 12 (2.2%) out of 559 living donor transplants

[d] Continued use of Foley catheter or intermittent self catheterization beyond 7 days after transplantation.

Table 2

Bacterial Pathogens Isolated During the First Urinary Tract Infection Episode and Antimicrobial Susceptibilities

Bacterial Species	Number of Isolates	Antibiotic Sensitivities					
	N=247 (100%)	Ampicillin	Cefazolin	Levofloxacin	Piperacillin/ Tazobactam	Trimethoprim/ Sulfamethoxazole	Vancomycin
Escherichia coli	67 (27.1%)	25.4%	76.3%	64.2%	96.7%	19.4%	R
Enterococcus species	54 (21.9%)	84.6%	R	61.5%	NT	R	88.5%
Klebsiella species	32 (13.0%)	R	76.0%	78.1%	87.1%	21.9%	R
Mixed bacterial flora	30 (12.1%)	NT	NT	NT	NT	NT	NT
Coagulase-negative *Staphylococcus*	13 (5.3%)	NT	NT	NT	NT	NT	100.0%
Pseudomonas species	11 (4.5%)	R	R	90.9%	88.9%	R	R
Enterobacter species	10 (4.0%)	R	R	100.0%	90.0%	60.0%	R
Citerobacter species	9 (3.6%)	R	R	100.0%	60.0%	0.0%	R
Other[a]	21 (8.5%)	NT	NT	NT	NT	NT	NT

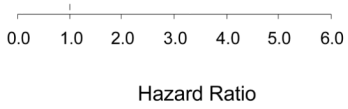
R, bacteria inherently resistant to selected antimicrobial. NT, not tested

[a]Other includes: *Lactobacillus* species (N=5), *Stenotrophomonas maltophilia* (N=5), *Proteus* species (N=3), viridans group streptococci (N=3), *Morganella* species (N=2), *Staphylococcus saprophyticus* (N=1), *Streptococcus agalactiae* (N=1), and *Corynebacterium* species (N=1).

Table 3

Risk Factors For Early UTI

Variable	N (%)	Univariate Analysis HR (95% CI)	Univariate Analysis P Value	Multivariable Analysis HR (95% CI)	Multivariable Analysis P Value
Age (per decade increase)	1166 (100.0%)	**1.09 (0.99-1.20)**	**0.06**	**1.11 (1.01-1.23)**	**0.03**
Female	452 (38.8%)	**2.66 (2.06-3.43)**	**<0.001**	**2.87 (2.21-3.73)**	**<0.001**
African American	320 (27.4%)	**1.28 (0.98-1.67)**	**0.07**	1.01 (0.75-1.35)	0.96
Diabetes Mellitus	364 (31.2%)	1.03 (0.79-1.35)	0.81		
Prior Kidney Transplant	125 (10.7%)	1.14 (0.78-1.69)	0.50		
Deceased Donor Transplant	607 (52.1%)	**1.25 (0.97-1.60)**	**0.09**	0.97 (0.72-1.32)	0.86
Ureteral Stent	523 (45.6%)	**1.64 (1.28-2.11)**	**<0.001**	**1.40 (1.07-1.82)**	**0.01**
Vancomycin Prophylaxis[a]	136 (11.7%)	**1.45 (1.03-2.04)**	**0.03**	1.19 (0.84-1.69)	0.33
Antithymocyte Globulin Induction	1008 (86.4%)	1.04 (0.72-1.50)	0.83		
Corticosteroid Maintenance[b]	217 (18.6%)	1.11 (0.81-1.52)	0.51		
Delayed Graft Function[c]	249 (21.4%)	**1.64 (1.25-2.15)**	**<0.001**	**1.38 (0.99-1.92)**	**0.06**
Prolonged Use of Foley Catheter[d]	89 (7.6%)	**4.10 (3.00-5.60)**	**<0.001**	**3.92 (2.83-5.43)**	**<0.001**
TMP/SMZ Prophylaxis[e]	1112 (95.4%)	**0.45 (0.28-0.71)**	**0.001**	**0.55 (0.34-0.89)**	**0.02**



Variables associated with UTI in the univariate Cox regression (P<0.10) were included in the multivariable Cox regression for the identification of independent risk factors for UTI within the first 3 months of kidney transplantation. Hazard ratios (HR) with 95% confidence interval (CI) and P value are reported. The black square represents the hazard ratio and the lines on either side represent the 95% CI. Highlighted in bold are the variables associated with UTI with a P value of less than 0.10.

[a]Preoperative antibiotic therapy with vancomycin vs. other antibiotics.

[b]Kidney transplant recipients maintained on corticosteroid immunosuppression.

[c]Defined as the need for hemodialysis within seven days of kidney transplantation.

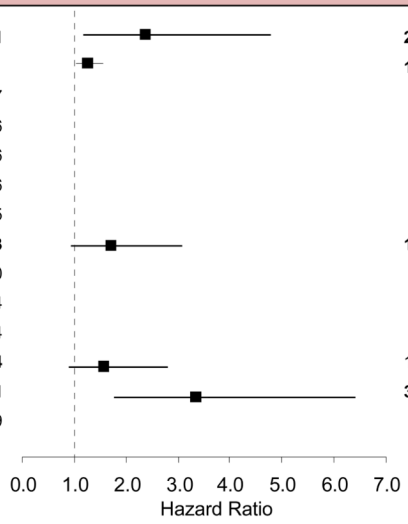
[d]Continued use of Foley catheter or intermittent self catheterization beyond 7 days after kidney transplantation.

[e]Trimethoprim/Sulfamethoxazole (TMP/SMX) for the prevention of *Pneumocystis Jiroveci* pneumonia vs. other prophylaxes (dapsone, pentamidine, or none).

Table 4

Multivariable Cox Regression Analysis for the Risk Factors for Bacteremia

Variable	N (%)	Univariate Analysis HR (95% CI)	Univariate Analysis P Value	Multivariable Analysis HR (95% CI)	Multivariable Analysis P Value
UTI (Time Dependent)	247 (21.2%)	**3.68 (1.92-7.06)**	**<0.001**	**2.38 (1.19-4.77)**	**0.01**
Age (per decade increase)	1166 (100.0%)	**1.32 (1.07-1.63)**	**0.01**	**1.27 (1.03-1.57)**	**0.03**
Female	452 (38.8%)	0.81 (0.46-1.43)	0.47		
African American	320 (27.4%)	1.49 (0.85-2.62)	0.16		
Diabetes Mellitus	364 (31.2%)	1.23 (0.70-2.16)	0.46		
Prior Kidney Transplant	125 (10.7%)	0.68 (0.25-1.89)	0.46		
Deceased Donor Transplant	607 (52.1%)	1.30 (0.75-2.24)	0.35		
Ureteral Stent	532 (45.6%)	**2.36 (1.34-4.17)**	**0.003**	**1.72 (0.95-3.10)**	**0.07**
Vancomycin Prophylaxis[a]	136 (11.7%)	0.78 (0.31-1.97)	0.60		
Antithymocyte Globulin Induction	1008 (86.4%)	0.88 (0.42-1.87)	0.74		
Corticosteroid Maintenance[b]	217 (18.6%)	1.29 (0.68-2.46)	0.44		
Delayed Graft Function[c]	249 (21.4%)	**2.28 (1.31-3.97)**	**0.004**	1.58 (0.89-2.80)	0.12
Prolonged Use of Foley Catheter[d]	89 (7.6%)	**5.13 (2.82-9.34)**	**<0.001**	**3.37 (1.78-6.40)**	**<0.001**
TMP/SMZ Prophylaxis[e]	1112 (95.4%)	0.58 (0.21-1.60)	0.29		



Multivariable Cox regression analysis was used to determine whether UTI, modeled as a time-dependent covariate, is an independent risk factor for bacteremia within the first three months of transplantation. Variables associated with bacteremia in the univariate analysis (P<0.10) were included in the multivariable Cox regression analysis. Hazard ratios (HR) with 95% confidence interval (CI) and P value are reported. The black square represents the hazard ratio and the lines on either side represent the 95% CI. Highlighted in bold are the variables associated with bacteremia with a P value of less than 0.10.

[a]Preoperative antibiotic therapy with vancomycin vs. other antibiotics.

[b]Kidney transplant recipients maintained on corticosteroid immunosuppression.

[c]Defined as the need for hemodialysis within seven days of kidney transplantation.

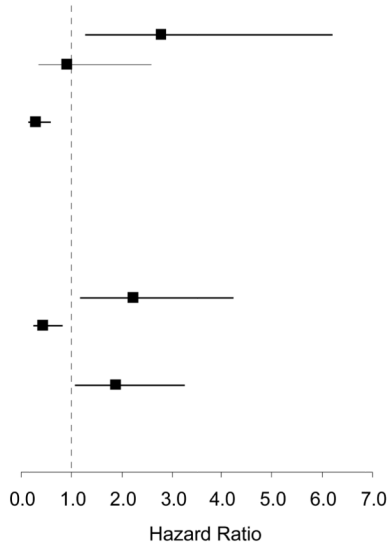
[d]Continued use of Foley catheter or intermittent self catheterization beyond 7 days after kidney transplantation.

[e]Trimethoprim/Sulfamethoxazole (TMP/SMX) for the prevention of *Pneumocystis Jiroveci* pneumonia vs. other prophylaxes (dapsone, pentamidine, or none).

Table 5

Multivariable Cox Regression Analysis for the Risk Factors for Biopsy Confirmed ACR

Variable	N (%)	Univariate Analysis HR (95% CI)	Univariate Analysis P Value	Multivariable Analysis HR (95% CI)	Multivariable Analysis P Value
UTI Status					
Untreated UTI (Time Dependent)	100 (8.6%)	**2.31 (1.08-4.94)**	**0.03**	**2.80 (1.27-6.20)**	**0.01**
Treated UTI (Time Dependent)	147 (12.6%)	0.74 (0.26-2.07)	0.57	0.92 (0.33-2.61)	0.88
Age (per decade increase)	1166 (100.0%)	0.89 (0.74-1.07)	0.21		
Female	452 (38.8%)	**0.32 (0.16-0.63)**	**0.001**	**0.30 (0.15-0.60)**	**0.001**
African American	320 (27.4%)	1.31 (0.76-2.27)	0.34		
Diabetes Mellitus	364 (31.2%)	1.27 (0.74-2.17)	0.38		
Prior Kidney Transplant	125 (10.7%)	1.40 (0.66-2.95)	0.38		
Deceased Donor Transplant	607 (52.1%)	1.54 (0.91-2.62)	0.11		
Ureteral Stent	532 (45.6%)	1.23 (0.73-2.05)	0.44		
Vancomycin Prophylaxis[a]	136 (11.7%)	**2.00 (1.06-3.78)**	**0.03**	**2.24 (1.18-4.24)**	**0.01**
Antithymocyte Globulin Induction	1008 (86.4%)	**0.43 (0.24-0.78)**	**0.005**	**0.46 (0.25-0.83)**	**0.01**
Corticosteroid Maintenance[b]	217 (18.6%)	1.27 (0.69-2.36)	0.45		
Delayed Graft Function[c]	249 (21.4%)	**2.25 (1.32-3.84)**	**0.003**	**1.89 (1.09-3.27)**	**0.02**
Prolonged Use of Foley Catheter[d]	89 (7.6%)	1.84 (0.83-4.05)	0.13		
TMP/SMX Prophylaxis[e]	1112 (95.4%)	2.71 (0.37-19.5)	0.32		



Multivariable Cox regression analysis was used to determine whether treatment status of UTI is an independent risk factor for biopsy confirmed ACR within the first twelve months of transplantation. With no UTI as a reference (HR 1), untreated UTI and treated UTI were both modeled as time dependent covariates. Variables associated with bacteremia in the univariate analysis (P<0.10) were included in the multivariable Cox regression analysis. Hazard ratios (HR) with 95% confidence interval (CI) and P value are reported. The black square represents the hazard ratio and the lines on either side represent the 95% CI. Highlighted in bold are the variables associated with ACR with a P value of less than 0.10.

[a]Preoperative antibiotic therapy with vancomycin vs. other antibiotics.

[b]Kidney transplant recipients maintained on corticosteroid immunosuppression.

[c]Defined as the need for hemodialysis within seven days of kidney transplantation.

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[e]Trimethoprim/Sulfamethoxazole (TMP/SMX) for the prevention of *Pneumocystis Jiroveci* pneumonia vs. other prophylaxes (dapsone, pentamidine, or none).