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Epidemiology and outcomes of carbapenem-resistant *Klebsiella pneumoniae* bacteriuria in kidney transplant recipients

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Abstract

Background—Little is known about the epidemiology of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) bacteriuria following kidney transplantation. We determined the incidence of post-transplant CRKP bacteriuria in adults who underwent kidney transplant from 2007 to 2010 at two New York City centers.

Methods—We conducted a case-control study to identify factors associated with CRKP bacteriuria compared to of carbapenem-susceptible *K. pneumoniae* (CSKP) bacteriuria, assessed whether CRKP bacteriuria was associated with mortality or graft failure, and compared outcomes of treated episodes of CRKP and CSKP bacteriuria.

Results—Of 1852 transplants, 20 (1.1%) patients developed CRKP bacteriuria. Factors associated with CRKP bacteriuria included receipt of multiple organs (odds ratio [OR] 4.7, 95% confidence interval [CI] = 1.1–20.4), deceased donor allograft (OR 5.9, 95% CI 1.3–26.8), transplant admission length of stay (OR 1.1 per day, 95% CI 1.0–1.1), pre-transplant CRKP infection or colonization (OR 18.3, 95% CI 2.0–170.5), diabetes mellitus (OR 2.8, 95% CI 1.0–7.8), and receipt of antimicrobials other than trimethoprim-sulfamethoxazole (OR 4.3, 95% CI 1.6–11.2).

Conclusion—Compared to CSKP bacteriuria, CRKP bacteriuria was associated with increased mortality (30% vs. 10%, $P = 0.03$) but not graft failure. Treated episodes of CRKP bacteriuria were less likely to achieve microbiologic clearance (83% vs. 97%; $P = 0.05$) and more likely to recur within 3 months (50% vs. 22%, $P = 0.02$) than CSKP episodes. CRKP bacteriuria after kidney transplant is associated with mortality and antimicrobial failure after treatment.

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Keywords

carbapenem-resistant *Klebsiella pneumoniae*; carbapenem-resistant Enterobacteriaceae; multidrug resistance; bacteriuria; kidney transplantation

The incidence of infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has increased dramatically over the past decade (1). CRKP initially became endemic in the New York City metropolitan area in the early 2000s; however, it is no longer limited to this area and is now being encountered globally (2–7). This rapid increase in CRKP has been driven by the spread of plasmid-mediated carbapenemases that hydrolyze nearly all beta-lactam antimicrobial agents and severely limit treatment options. Mortality rates among hospitalized adults with CRKP infection range between 40% and 50% (8, 9).

Solid organ transplant recipients may be at high risk for CRKP infection because of poor functional status, frequent need for antimicrobial therapy, intensive care unit admissions, mechanical ventilation, and prolonged hospitalizations (8–12). The management of CRKP infections in transplant recipients is complicated because of their immunocompromised status and the frequent need to use nephrotoxic antimicrobials for therapy, including polymyxins and aminoglycosides, which may further exacerbate the renal toxicity of concomitantly used calcineurin inhibitors (13, 14).

The use of these nephrotoxic antimicrobials may be particularly problematic in kidney transplant (KT) recipients, whose allografts are highly susceptible to injury. KT recipients are also highly vulnerable to urinary tract infections (UTIs). However, little is known about the impact of CRKP infections, and CRKP bacteriuria in particular, on this population. We therefore conducted this study to (i) assess the incidence of and factors associated with developing CRKP bacteriuria in KT recipients, (ii) determine whether post-transplant CRKP bacteriuria is associated with increased mortality and renal allograft failure compared to those who develop carbapenem-susceptible *K. pneumoniae* (CSKP) bacteriuria, and (iii) assess treatment outcomes of CRKP bacteriuria in this population.

Materials and methods

Setting and study population

This nested case-control study was performed at the Columbia University Medical Center (CUMC) and Weill Cornell Medical Center (WCMC) campuses of New York-Presbyterian Hospital, 2 large academic medical centers in New York City. Institutional Review Board approval was obtained at both centers. All adult (age ≥ 18 years at the time of transplant) patients who underwent KT at CUMC or WCMC between January 2007 and December 2010 were included in this study. Patients' medical records were reviewed through December 2011 or until death or loss to follow up.

KT recipients provided routine clean catch or straight-catheterized urine specimens for microscopic examination and culture prior to stent removal and/or when presenting with signs or symptoms consistent with a UTI. In addition, at WCMC, urine cultures were collected at each patient visit during the first 3 months after transplantation, regardless of

whether UTI signs or symptoms were present. Microbiology reports were reviewed to identify all cases of bacteriuria (10^4 colony-forming units/mL of urine) caused by *K. pneumoniae* that occurred in the study population. All concomitant microscopic urinalyses were reviewed, and pyuria was defined as >10 white blood cells/high-power field. For each case-patient who developed CRKP bacteriuria (see “Microbiologic Testing”) after transplantation, 4 control patients who developed CSKP bacteriuria were randomly selected, using a random number generator and matched by study center.

The surgical procedure for KT did not change during the study period. Perioperative antimicrobials included intravenous cefazolin (or vancomycin in penicillin-allergic patients) and gentamicin bladder irrigation. A urinary catheter was placed during surgery and removed by 1 week after transplantation. Intraoperative placement of a ureteral stent was performed at the surgeon’s discretion; if placed, stents were typically removed within 6 weeks after KT. Prophylactic oral cefpodoxime was given at the time of stent removal (or levofloxacin in penicillin-allergic patients). Prophylactic trimethoprim-sulfamethoxazole (TMP-SMX) was routinely given for 1 year after the transplant. Either anti-thymocyte globulin or an interleukin-2 receptor antagonist was used for induction immunosuppression. Maintenance immunosuppression typically consisted of a calcineurin inhibitor (tacrolimus or cyclosporine) and an anti-metabolite (mycophenolate mofetil or azathioprine). Alternative agents were used if additional immunosuppression was required or in patients intolerant of standard maintenance immunosuppressives.

Clinical data and definitions

The following variables were collected for each patient and were evaluated as potential risk factors for CRKP bacteriuria: age at the time of transplantation; time from transplant to first episode of *K. pneumoniae* bacteriuria; gender; race/ethnicity; etiology of underlying kidney disease; type of renal replacement therapy required before transplantation; retransplantation status; solid organ concomitantly transplanted at the time of KT; transplant type (deceased or living donor); placement of ureteral stent at the time of transplant and duration of stent; presence of delayed graft function (need for renal replacement therapy within 7 days of KT); length of stay during the transplant admission; need for reoperation within 30 days of KT; induction and maintenance immunosuppressive medications; number of hospitalizations for any indication within 1 year of KT; CRKP colonization or infection before transplantation; receipt of prednisone, TMP-SMX, and/or any other antibacterial agent within 30 days of the post-KT bacteriuria; and the development of biopsy-proven rejection. Graft failure was defined as the requirement for renal replacement therapy following KT.

Episodes of *K. pneumoniae* bacteriuria were considered treated if at least 3 days of antimicrobials active against the respective CRKP or CSKP isolate were administered. Clearance of bacteriuria was defined as a negative urine culture within 30 days of initiation of therapy, or the absence of symptoms at the next clinic appointment, provided that the patient was symptomatic at diagnosis and repeat urine culture was not obtained within the same time period. Bacteriuria was considered recurrent if the same phenotypic *K. pneumoniae* isolate was cultured from urine within 90 days of clearance. Serum creatinine values were collected for each patient at the time of antimicrobial initiation, during therapy,

and 2 weeks after antimicrobial discontinuation. Nephrotoxicity during therapy was defined according to RIFLE criteria (15). Recovery of renal function was defined as return to pre-treatment serum creatinine level 2 weeks after completion of antimicrobial therapy.

Microbiologic testing

The clinical microbiology laboratories primarily used Vitek 2 (bioMérieux Inc., Durham, North Carolina USA) for bacterial identification and antimicrobial susceptibility testing of *K. pneumoniae* isolates, and applied the 2009 Clinical and Laboratory Standards Institute (CLSI) interpretive breakpoints (16). Etest (bioMérieux) was performed upon clinician request. At WCMC, isolates resistant to ertapenem by Vitek 2, but not to meropenem or imipenem, underwent modified Hodge testing (MHT) to evaluate for carbapenemase activity. In this study, carbapenem resistance was defined by imipenem, or meropenem resistance by Vitek 2 or carbapenemase detection by MHT.

Statistical analysis

Continuous variables were expressed as medians with interquartile ranges (IQRs) and were compared using the Mann–Whitney test. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. Univariable conditional logistic regression models were used to identify risk factors for CRKP bacteriuria. Variables with $P \leq 0.05$ in univariable analysis were then entered into a multivariable conditional logistic regression model to identify factors independently associated with CRKP bacteriuria. Kaplan–Meier survival analysis was performed, and differences between survival curves for overall mortality and graft failure were assessed using the log-rank test. Multivariable Cox proportional hazard modeling was performed for overall mortality utilizing CRKP vs. CSKP bacteriuria, as well as clinically and statistically significant risk factors identified in univariable risk factor analysis. All statistical tests were 2-tailed, and the threshold for statistical significance was $P < 0.05$. All statistical analysis was performed using SAS software, Version 9.3 (SAS Institute Inc., Cary, North Carolina USA).

Results

Between January 2007 and December 2010, 1852 adult KT were performed at the study sites (1003 at Site 1 and 849 at Site 2). Twenty patients developed CRKP bacteriuria following transplant (15 at Site 1 and 5 at Site 2) and 252 patients developed CSKP bacteriuria following transplant (72 at Site 1 and 180 at Site 2). The incidence of CRKP bacteriuria and CSKP bacteriuria during the study period was 1.1% and 13.6%, respectively. The final study population consisted of 100 patients (20 with CRKP bacteriuria and 80 matched controls with CSKP bacteriuria).

Eighteen of the 20 initial CRKP urinary isolates had meropenem or imipenem minimum inhibitory concentrations of $\geq 16 \mu\text{g/mL}$. Two isolates had meropenem minimum inhibitory concentrations of $\geq 4 \mu\text{g/mL}$, but tested positive for carbapenemase production by MHT.

The median time from KT to the first episode of *K. pneumoniae* bacteriuria was 47 days (IQR 8–340 days) for patients with CRKP bacteriuria and 126 days (IQR 43–417 days) for patients with CSKP bacteriuria ($P = 0.09$), suggesting a trend towards CRKP bacteriuria

presenting earlier than CSKP bacteriuria after transplantation. Demographic characteristics, transplant-related variables, and medication use within the 30 days before *K. pneumoniae* bacteriuria are summarized in Table 1. Although we were not able to obtain complete information on donor cultures for all patients, we did not identify any donor cultures that were positive for CRKP.

Predictors of post-transplant CRKP bacteriuria

In univariable analysis, risk factors for the development of CRKP bacteriuria following KT included concomitant receipt of another solid organ at the time of KT (odds ratio [OR] 4.7, 95% confidence interval [CI] 1.1–20.4), use of deceased donor allograft (OR 5.9, 95% CI 1.3–26.8), increased transplant admission length of stay (OR 1.1 per day increase, 95% CI 1.0–1.1), history of CRKP infection or colonization prior to transplant (OR 18.3, 95% CI 2.0–170.5), diabetes mellitus (OR 2.8, 95% CI 1.0–7.8), and receipt of an antimicrobial other than TMP-SMX within 30 days of bacteriuria (4.3, 95% CI 1.6–12.0; Table 1). Of these variables, diabetes (adjusted OR [aOR] 5.5, 95% CI 1.4–21.6), increased transplant admission length of stay (aOR 1.1 per day, 95% CI 1.0–1.1), and recent receipt of an antimicrobial other than TMP-SMX (aOR 4.9, 95% CI 1.1–20.9) remained independently associated with CRKP bacteriuria in multivariable analysis (Table 2).

Patient outcomes

The development of secondary *K. pneumoniae* bacteremia, defined as bacteremia within 14 days of bacteriuria onset, was more common among those with CRKP than CSKP bacteriuria (15% vs. 3%, $P = 0.02$). While overall mortality for the 100 study subjects with post-transplant *K. pneumoniae* bacteriuria was 14%, mortality from any cause was higher among subjects with CRKP bacteriuria than among those with CSKP bacteriuria (30% vs. 10% respectively, $P = 0.03$). Of the 6 patients with CRKP bacteriuria who died, 2 deaths were caused by subsequent CRKP sepsis, occurring 29 and 80 days after the initial bacteriuria episode, respectively. None of the 8 deaths among those with CSKP bacteriuria was related to CSKP sepsis. Kaplan–Meier analysis comparing time from *K. pneumoniae* bacteriuria until death revealed a significant increase in overall mortality among those with CRKP bacteriuria compared to those with CSKP bacteriuria ($P = 0.007$; Fig. 1). In univariable analysis, concomitant receipt of another solid organ at the time of KT (hazard ratio [HR] 5.6, 95% CI 1.7–18.3), kidney allograft rejection at any time after the transplant (HR 3.1, 95% CI 1.0–9.2), and post-transplant CRKP bacteriuria (HR 4.0, 95% CI 1.4–11.8) were associated with mortality following KT. Compared to CSKP bacteriuria, CRKP bacteriuria remained a risk factor for mortality following KT, when adjusted for rejection and receipt of another solid organ at the time of KT (adjusted HR 3.0, 95% CI 1.0–9.0; $P = 0.04$).

Graft failure occurred in 17% of the 100 study subjects and was similar among those with CRKP and CSKP bacteriuria (20% vs. 16%, respectively, $P = 0.73$). Kaplan–Meier analysis revealed no difference in time from transplantation to graft failure comparing CRKP and CSKP bacteriuria ($P = 0.91$). Rates of rejection after *K. pneumoniae* bacteriuria were also similar between the 2 groups (CRKP 20% vs. CSKP 18%, $P = 0.47$).

Outcomes of post-transplant CRKP bacteriuria episodes

Study subjects developed 128 episodes of *K. pneumoniae* bacteriuria (25 CRKP and 103 CSKP), most of which were treated with at least 3 days of active antimicrobial therapy (CRKP 72% vs. CSKP 70%, $P = 0.84$). The characteristics of treated episodes of CRKP ($n = 18$) and CSKP ($n = 72$) bacteriuria were similar except for antimicrobial susceptibility patterns, with CRKP isolates demonstrating higher rates of resistance to levofloxacin, ceftriaxone, cefepime, aztreonam, piperacillin-tazobactam, amikacin, gentamicin, tobramycin, and TMP-SMX than CSKP isolates; all tested CRKP isolates were susceptible to polymyxin B (PMB) (Table 3). The median time from *K. pneumoniae* bacteriuria to the initiation of active antimicrobials was 3 days for both CRKP and CSKP episodes ($P = 1.00$), and the median duration of antimicrobial therapy was 15 days (IQR 7–31 days) for CRKP episodes and 12 days (IQR 8–15 days) for CSKP episodes ($P = 0.23$).

Compared to treated episodes of CSKP bacteriuria, treated episodes of CRKP bacteriuria were less likely to achieve microbiologic clearance within 1 month of antimicrobial initiation (83% vs. 97%, $P = 0.05$) and were more likely to recur within 3 months (50% vs. 22%, $P = 0.02$). One-month clearance of CRKP bacteriuria was similar, comparing episodes treated with monotherapy and combination therapy (83% vs. 100%, $P = 0.45$), as were 3-month recurrence rates (50% vs. 75%, $p = 0.58$). No difference as seen in 1-month clearance and 3-month recurrence of CRKP bacteriuria, comparing aminoglycoside (AG)-containing, PMB-containing, and non-AG, non-PMB-containing treatment regimens ($P = 0.33$ and $P = 0.84$, respectively; Table 4).

Nephrotoxicity developed during treatment of 4 (22%) episodes of CRKP bacteriuria (Table 4), including 3 of 7 episodes treated with non-AG, non-PMB-containing regimens and 1 of 6 episodes treated with PMB-containing regimens. Renal function recovered in 1 of 3 patients after completion of therapy with a non-AG, non-PMB containing regimen, and did not recover in the patient receiving a PMB-containing regimen. Nephrotoxicity did not occur in any of the 5 episodes treated with AG-containing regimens.

Discussion

To our knowledge, this is the largest study to evaluate the incidence of and risk factors for CRKP bacteriuria in KT recipients, the impact of CRKP bacteriuria on mortality and graft failure, and assess treatment outcomes in this population. We analyzed data from 2 large KT centers located in a CRKP-endemic area and identified a 1.1% incidence of post-transplant CRKP bacteriuria. This incidence is lower than that of other published reports of CRKP UTI in KT recipients (17–20) and may relate to the large number of KT recipients in our cohort and the lack of a clear CRKP outbreak during the study period. Although KT recipients were closely monitored at both centers, it is possible that our incidence is lower than the actual incidence because patients could have presented to other institutions with post-transplant CRKP bacteriuria. Given the microbiology data available, the definition of carbapenem resistance in this study was based on the 2009 CLSI interpretive breakpoints. It is possible that we would have observed a higher incidence of CRKP bacteriuria if we had applied the current CLSI carbapenem breakpoints (21).

We identified a number of factors associated with post-transplant CRKP bacteriuria, including diabetes, increased transplant admission length of stay, and recent receipt of an antimicrobial agent other than TMP-SMX. These variables were statistically significant in both univariate and multivariate analysis, despite the limited sample size. Diabetes, prolonged hospital stay, and receipt of antimicrobials, namely anti-pseudomonal penicillins, cephalosporins, carbapenems, and fluoroquinolones, have been associated with CRKP infection in previous studies (8–10, 12) and likely represent underlying severity of illness and a consequence of antimicrobial selection pressure. The relationship between the use of deceased-donor renal allografts and the development of post-transplant UTI has been previously described (22, 23), although this is the first study to our knowledge to identify an association between deceased-donor grafts and CRKP bacteriuria. This association may be related to the use of more potent immunosuppression in recipients of deceased-donor kidneys, pre-transplant colonization or infection in the donor, or prolonged ischemic time in deceased-donor vs. living-donor transplantation. The association between multiple organ transplantation and CRKP bacteriuria may partially be attributable to the use of deceased-donor allografts. An association between the receipt of simultaneous kidney-pancreas transplant and infections caused by extended-spectrum-beta-lactamase-producing gram-negative rods has previously been described, and attributed in part to the possibility of fecal content exposure as well as more potent immunosuppression (24).

Finally, we demonstrated a strong association between pre-transplant history of CRKP infection or colonization and post-transplant CRKP bacteriuria in univariable analysis. Given that only 5 patients had pre-transplant CRKP infection or colonization, we believe that the multivariable analysis had insufficient power to identify a statistically significant association between this variable and post-transplant CRKP bacteriuria. Knowledge of CRKP carriage status before KT may, at a minimum, assist in stratification of post-transplant CRKP infection risk. However, pre-transplant CRKP screening in this population is not routinely performed, and no standards presently exist for decolonization or alteration of perioperative prophylactic antimicrobial protocols in the setting of CRKP colonization before transplantation (25). In this study, crude mortality was 30% among KT recipients with CRKP bacteriuria. This rate was 3-fold higher than that of patients with CSKP bacteriuria, and similar to the 33% mortality described in KT recipients with CRKP UTI and the 29% in-hospital mortality previously described among a general inpatient population with CRKP bacteriuria (19, 26). Simkins et al. (27) also recently reported decreased cumulative survival in KT recipients with CRKP infections compared to those with CSKP infections. The degree to which this increased mortality is directly related to CRKP bacteriuria is unclear, although 2 of our patients died of subsequent septic shock due to CRKP.

We did not demonstrate an association between CRKP bacteriuria and renal allograft failure, nor any difference in time from CRKP or CSKP bacteriuria to graft failure. To date, the relationship between UTIs or bacteriuria and renal allograft failure remains controversial (22, 28–30), and additional studies evaluating the impact of CRKP bacteriuria on long-term outcomes in KT recipients are needed.

The optimal treatment of CRKP UTI remains undefined. Our microbiologic clearance data are consistent with those of Brizendine and colleagues (31), who found an increased rate of microbiologic failure with CRKP UTI among recipients of any type of solid organ transplant. The decreased rates of microbiologic clearance and increased recurrence rates compared to CSKP bacteriuria, as well as the relatively high rate of nephrotoxicity associated with treatment (22%), highlight the need for more effective and less toxic therapies for CRKP UTI.

This study had limited power to identify a statistically significant difference in clearance or recurrence rates of CRKP bacteriuria by treatment regimen used, because of small numbers of cases and variability in regimens. However, all 3 cases that failed to achieve microbiologic clearance were not treated with an AG. Previously published data suggest that AG use is associated with a higher rate of microbiologic clearance of CRKP bacteriuria than treatment with PMB or tigecycline (32). Doxycycline may also be an effective option for CRKP (33).

Several limitations of this study deserve mention. This study was conducted in a region of CRKP endemicity, and our findings may not be applicable to areas where the prevalence of CRKP is low. The small numbers of patients who developed CRKP bacteriuria only allowed for detection of large effect sizes in risk factor analysis, and potentially clinically significant risk factors for CRKP bacteriuria may have not met statistical significance in univariable or multivariable analyses. We chose KT recipients with post-transplant CSKP bacteriuria as controls, instead of KT recipients who did not develop CRKP UTI. Thus, our controls were likely more ill than the average KT recipient who did not develop *K. pneumoniae* bacteriuria, and rates of graft loss and mortality in the controls were higher than the average rates at the transplant centers. We selected this control group in order to better identify factors related to developing CRKP bacteriuria, and not factors related to bacteriuria in general. We did not collect data on expanded-criteria donor allografts, which may serve as additional risk factors for CRKP acquisition. The small sample size also limited our ability to compare the efficacy of treatment regimens.

However, the risk factors identified for CRKP bacteriuria and crude mortality appear to carry a high degree of biologic and clinical plausibility. The ratio of KT recipients with CRKP and CSKP bacteriuria differed by site and may have represented inherent differences in practices at each center. However, matching by study site likely eliminated confounding by center. In addition, this study evaluated all KT recipients with *K. pneumoniae* bacteriuria, but did not differentiate between asymptomatic bacteriuria and UTI. We conservatively included all individuals with bacteriuria because KT recipients are less likely to present with symptomatic UTIs than the general population (22, 30).

Finally, although the mechanism of carbapenem resistance was not routinely performed for CRKP isolates, *K. pneumoniae* carbapenemase production likely predominated, as this is the most common mechanism of carbapenem resistance among *K. pneumoniae* in the New York City metropolitan area (34–37).

As the largest study to evaluate CRKP bacteriuria in KT recipients to our knowledge, this report contributes to our understanding of the epidemiology and impact of this important, highly drug-resistant pathogen. We estimated the incidence of post-KT CRKP bacteriuria in an endemic area, identified potential risk factors for post-transplant CRKP bacteriuria, and demonstrated that CRKP bacteriuria is associated with increased mortality, a lower microbiologic clearance rate, and a higher recurrence rate compared to treated episodes of CSKP bacteriuria. Larger prospective multicenter studies are needed to better inform our understanding of the epidemiology of CRKP bacteriuria in KT recipients, to further assess the efficacy and outcomes of treatment regimens utilized in the management of CRKP bacteriuria, and to address the role of pre-transplant screening for CRKP colonization in this patient population.

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Fig. 1. Kaplan–Meier analysis of mortality comparing renal transplant recipients with carbapenem-resistant *Klebsiella pneumoniae* (CRKP) bacteriuria and carbapenem-susceptible *K. pneumoniae* (CSKP) bacteriuria. Time is measured from first episode of post-transplant *K. pneumoniae* bacteriuria until death. Log-rank $P = 0.01$.

Table 1

Characteristics of the study population with *Klebsiella pneumoniae* bacteriuria and associations with CRKP bacteriuria

Patient characteristics	CRKP bacteriuria (n = 20)	CSKP bacteriuria (n = 80)	Post-KT CRKP bacteriuria	
			OR (95% CI)	P-value
Median age at transplant, yrs (IQR)	57 (51, 67)	54 (40, 63)	1.0 (1.0–1.1)	0.17
Male gender, n (%)	11 (55)	31 (39)	1.9 (0.7–5.1)	0.19
Race/ethnicity, n (%)				
White	11 (55)	35 (44)	1.0 (Ref)	
African-American	2 (10)	18 (23)	0.4 (0.1–1.8)	0.22
Hispanic	4 (20)	23 (29)	0.5 (0.2–1.9)	0.34
Asian	2 (10)	1 (1)	6.3 (0.5–75.9)	0.14
Other	1 (5)	3 (4)	1.0 (0.1–10.6)	0.99
Primary etiology of kidney disease, n (%)				
Diabetes mellitus	9 (45)	18 (23)	1.0 (Ref)	
Hypertension	5 (25)	15 (19)	0.7 (0.2–2.4)	0.54
Systemic lupus erythematosus	1 (5)	7 (9)	0.3 (0.0–2.7)	0.28
Polycystic kidney disease	0 (0)	8 (10)	0.1 (0.1–100.0)	0.97
Other	5 (25)	32 (40)	0.3 (0.1–1.1)	0.07
Diabetes mellitus, n (%)	9 (45)	18 (23)	2.8 (1.0–7.8)	0.04
Renal replacement therapy prior to transplant, n (%)				
Hemodialysis	15 (75)	66 (83)	1.00 (Ref)	
Peritoneal dialysis	1 (5)	6 (8)	0.5 (0.1–1.7)	0.25
None	4 (20)	8 (10)	0.3 (0.1–3.8)	0.38
Kidney retransplantation, n (%)	3 (15)	17 (22)	0.7 (0.2–2.5)	0.76
Simultaneous solid organ transplant, n (%) ¹	4 (20)	4 (5)	4.7 (1.1–20.4)	0.04
Deceased-donor transplant, n (%)	18 (90)	48 (60)	5.9 (1.3–26.8)	0.01
Ureteral stent placement, n (%)	12 (60)	54 (68)	0.7 (0.2–2.1)	0.48
Stent removed, n (%)	10 (83)	52 (96)	0.5 (0.2–1.4)	0.19
Median stent duration, days (IQR)	54 (29, 86)	47 (39, 63)	1.0 (0.9–1.01)	0.63
Delayed graft function, n (%)	7 (35)	23 (29)	1.3 (0.5–3.7)	0.59
Median transplant admission length of stay, days (IQR)	17 (9, 43)	7 (5, 10)	1.1 (1.0–1.1)	<0.01
Reoperation within 30 days of transplant, n (%)	6 (30)	12 (15)	2.5 (0.8–7.7)	0.19
Induction Immunosuppression				
Anti-thymocyte globulin	14 (70)	55 (69)	1.0 (Ref)	
Interleukin-2 antagonist	4 (20)	24 (30)	0.7 (0.2–2.2)	0.49
None	2 (10)	1 (1)	7.9 (0.7–93.0)	0.10
Steroid-containing maintenance immunosuppression, n (%) ²	6 (30)	16 (20)	1.7 (0.6–5.0)	0.34
Median hospitalizations within 1 yr of transplant, n (IQR)	1 (0, 3)	2 (1, 3)	0.8 (0.6–1.1)	0.34

Patient characteristics	CRKP bacteriuria (n = 20)	CSKP bacteriuria (n = 80)	Post-KT CRKP bacteriuria	
			OR (95% CI)	P-value
Positive CRKP culture prior to transplant, n (%) ³	4 (20)	1 (1)	18.3 (2.0–170.5)	<0.01
Kidney allograft rejection prior to <i>K. pneumoniae</i> bacteriuria	4 (20)	14 (18)	0.9 (0.2–2.9)	0.79
Prednisone use within 30 days of <i>K. pneumoniae</i> bacteriuria, n (%)	10 (50)	26 (33)	2.1 (0.8–5.8)	0.15
TMP/SMX use within 30 days of <i>K. pneumoniae</i> bacteriuria, n (%)	9 (45)	42 (53)	0.7 (0.3–2.0)	0.55
Other antimicrobial use within 30 days of <i>K. pneumoniae</i> bacteriuria, n (%)	12 (60)	20 (25)	4.3 (1.6–12.0)	<0.01

¹ Concomitant transplants: liver, 4; pancreas, 3; heart, 1.

² Tacolimus or cyclosporine and an anti-metabolite (mycophenolate mofetil or azathioprine) were used in maintenance immunosuppression. No patients received sirolimus.

³ Previous sites of CRKP isolation: sputum, 4; urine, 2; blood, 1; liver abscess, 1; peritoneal fluid, 1; wound culture, 1.

CRKP, carbapenem-resistant *K. pneumoniae*; CSKP, carbapenem-susceptible *K. pneumoniae*; KT, kidney transplant; OR, odds ratio; CI, confidence interval; no, number; yrs, years; IQR, interquartile range; TMP/SMX, trimethoprim-sulfamethoxazole.

Table 2Multivariable analysis of risk factors for *Klebsiella pneumoniae* bacteriuria after kidney transplant

Risk factor	Post-KT CRKP bacteriuria	
	Adjusted OR (95% CI)	P-value
Diabetes mellitus	5.5 (1.4–21.6)	0.01
Simultaneous solid organ transplant	0.2 (0.01–2.2)	0.17
Deceased-donor transplant	3.3 (0.6–17.1)	0.16
Transplant admission length of stay	1.1 (1.0–1.1)	0.03
Positive CRKP culture prior to transplant	9.8 (0.7–138.0)	0.09
Other antimicrobial use within 30 days of <i>K. pneumoniae</i> bacteriuria	4.9 (1.1–20.9)	0.03

KT, kidney transplant; CRKP, carbapenem-resistant *K. pneumoniae*; OR, odds ratio; CI, confidence interval.

Table 3Characteristics of treated episodes of *Klebsiella pneumoniae* bacteriuria

Characteristic	CRKP (n = 18) ¹	CSKP (n = 72) ²	P-value
Timing of positive urine culture from kidney transplant, n (%)			0.12
<1 month	7 (39)	11 (15)	
1–6 months	4 (22)	27 (38)	
6–12 months	3 (17)	9 (13)	
>1 year	4 (22)	25 (35)	
Fever within 48 h of urine culture, n (%)	5 (28)	25 (35)	0.55
Colony count, n (%)			0.91
10–100 K	7 (39)	27 (38)	
>100 K	11 (61)	45 (63)	
Polymicrobial urine culture, n (%)	1 (6)	12 (17)	0.23
Pyuria (>10 WBC/hpf), n (%)	13 (76)	40 (60)	0.20
Antibiotic susceptibility, n (%)			
Levofloxacin	2 (11)	65 (90)	<0.01
Ceftriaxone	0 (0)	59 (82)	<0.01
Cefepime	4 (22)	72 (100)	<0.01
Aztreonam	0 (0)	33 (46)	<0.01
Piperacillin-tazobactam	0 (0)	58 (81)	<0.01
Amikacin	6 (33)	71 (99)	<0.01
Gentamicin	10 (56)	69 (96)	<0.01
Tobramycin	2 (11)	68 (94)	<0.01
Trimethoprim-sulfamethoxazole	3 (18)	32 (44)	0.04
Polymyxin B	16 (100) ³	Susceptibilities not performed	
Median time from <i>K. pneumoniae</i> bacteriuria to receipt of antimicrobials, days (IQR)	3 (1, 4)	3 (1, 4)	1.00
Median duration of antimicrobials for <i>K. pneumoniae</i> bacteriuria, days (IQR)	15 (7, 31)	12 (8, 15)	0.23

¹These 18 treated episodes of CRKP bacteriuria all occurred in different patients.²These 72 treated episodes of CRKP bacteriuria occurred among 57 patients.³Polymyxin B susceptibility testing was performed for 16/18 treated isolates.CRKP, carbapenem-resistant *K. pneumoniae*; CSKP, carbapenem-susceptible *K. pneumoniae*; K, thousand; WBC, white blood cells; hpf, high power field; IQR, interquartile range.

Table 4

Outcomes of treated episodes of carbapenem-resistant *Klebsiella pneumoniae* bacteriuria in kidney transplant recipients by treatment regimen

Outcome	AG-containing regimen (n = 5) ¹	PMB-containing regimen (n = 6) ²	Non-AG, non-PMB-containing regimen (n = 7) ³	P-value
Clearance within 1 month, n (%)	5 (100)	4 (67)	6 (86)	0.33
Recurrence within 3 months, n (%)	2 (40)	3 (50)	4 (57)	0.84
Nephrotoxicity by RIFLE criteria, n (%)	0 (0)	1 (20) ⁴	3 (43) ⁵	0.38
Recovery of renal function after completion of therapy, n (%)	N/A	0 (0)	1 (33)	1.00

Regimens received:

¹ Aminoglycoside (AG)-containing regimens: AG + cephalosporin, 2; AG monotherapy, 1; AG + tigecycline, 1; AG + tigecycline + fosfomycin, 1.

² Polymyxin B (PMB)-containing regimens: PMB + tigecycline, 3; PMB + cephalosporin, 1; PMB + tigecycline + cephalosporin, 1; PMB + tigecycline + carbapenem, 1.

³ Non-AG, non-PMB-containing regimens: tigecycline + carbapenem, 2; tigecycline + cephalosporin, 1; tigecycline monotherapy, 1; carbapenem monotherapy, 1; carbapenem + cephalosporin, 1; fluoroquinolone monotherapy, 1.

Degree of nephrotoxicity by RIFLE criteria (15):

⁴ Injury.

⁵ Risk, 1; Injury, 2.