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Carbapenem-Resistant *Klebsiella pneumoniae* Urinary Tract Infection following Solid Organ Transplantation

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Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is an emerging pathogen with a devastating impact on organ transplant recipients (OTRs). Data describing urinary tract infections (UTIs) due to CRKP, compared to extended-spectrum β-lactamase (ESBL)-producing and susceptible *K. pneumoniae*, are lacking. We conducted a retrospective cohort study comparing OTRs with a first episode of UTI due to CRKP, ESBL-producing *K. pneumoniae*, or susceptible *K. pneumoniae*. We identified 108 individuals; 22 (20%) had UTIs due to CRKP, 22 (20%) due to ESBL-producing *K. pneumoniae*, and 64 (60%) due to susceptible *K. pneumoniae*. Compared to susceptible *K. pneumoniae* (27%), patients with UTIs due to CRKP or ESBL-producing *K. pneumoniae* were more likely to have a ≥24-hour stay in the intensive care unit (ICU) before or after development of the UTI (64% and 77%, respectively; $P < 0.001$). Among 105/108 hospitalized patients (97%), the median lengths of stay prior to UTI with CRKP or ESBL-producing *K. pneumoniae* (7 and 8 days, respectively) were significantly longer than that for susceptible *K. pneumoniae* (1 day; $P < 0.001$). Clinical failure was observed for 8 patients (36%) with CRKP, 4 (18%) with ESBL-producing *K. pneumoniae*, and 9 (14%) with susceptible *K. pneumoniae* ($P = 0.073$). Microbiological failure was seen for 10 patients (45%) with CRKP, compared with 2 (9%) with ESBL-producing *K. pneumoniae* and 2 (3%) with susceptible *K. pneumoniae* ($P < 0.001$). In multivariable logistic regression analyses, CRKP was associated with greater odds of microbiological failure (versus ESBL-producing *K. pneumoniae*: odds ratio [OR], 9.36, 95% confidence interval [CI], 1.94 to 72.1; versus susceptible *K. pneumoniae*: OR, 31.4, 95% CI, 5.91 to 264). In conclusion, CRKP is associated with ICU admission, long length of stay, and microbiological failure among OTRs with UTIs. Greater numbers are needed to determine risk factors for infection and differences in meaningful endpoints associated with carbapenem resistance.

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is a serious emerging global pathogen with very limited therapeutic options. Its impact on organ transplant recipients (OTRs) in particular is potentially devastating, given their use of immunosuppression and the frequency of their exposure to the health care system, where *Klebsiella* spp. cause approximately 8% of health care-associated infections in the United States. Twenty-seven percent of health care-associated infections are catheter-associated urinary tract infections (UTIs) and, among facilities reporting these to the National Healthcare Safety Network (NHSN), 20% observed that at least one *Klebsiella* sp. was carbapenem resistant (1). CRKP UTIs among OTRs present diagnostic and therapeutic challenges, and data addressing these issues are lacking. In particular, data describing the clinical significance of CRKP UTIs, compared to extended-spectrum β-lactamase (ESBL)-producing and susceptible *K. pneumoniae* UTIs, are needed to provide new insights into the treatment and prevention of these complicated infections. Herein we review first episodes of UTI due to CRKP, ESBL-producing *K. pneumoniae*, or susceptible *K. pneumoniae* in all OTRs, with the aim of comparing microbiological and clinical outcomes.

MATERIALS AND METHODS

Cases. We identified cases of UTI diagnosed at Cleveland Clinic, a 1,400-bed academic medical center in Cleveland, Ohio, between 2006 and 2012 through a retrospective review of microbiology reports and electronic medical records of every OTR with positive urine culture results for *K. pneumoniae*. Only the first episode of UTI following transplantation was considered. A standardized case report form was used to collect data on demographic characteristics, clinical features, treatments, and outcomes. This study was approved by the Cleveland Clinic institutional review board.

Definitions. UTIs were defined according to the Centers for Disease Control and Prevention/NHSN surveillance definition (2). The date of diagnosis was the date on which the urine culture was obtained. Relapse was defined as the development of UTI with the same pathogen within 30 days after diagnosis of the initial episode. The time to adequate antibiotic therapy was the number of days between the date on which the urine culture was obtained and the date on which an appropriate agent with *in vitro* activity was administered. Intensive care unit (ICU) admission was defined by a stay of ≥24 h at any time during hospitalization, before or after development of the UTI. A urinary catheter was considered present if there was documentation of a catheter at the time the urine culture was obtained. Predictors of the primary outcomes included age, sex, transplant type, bacteremia, length of stay (LOS) prior to UTI, ICU admission at any time during hospitalization, and the presence of a urinary catheter. The primary outcomes were clinical failure and microbiological failure. Clinical failure was defined as continued fever or urgency, frequency, dysuria, suprapubic tenderness, or costovertebral angle pain or tender-

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TABLE 1 Characteristics of 108 OTRs with a first episode of UTI due to CRKP, ESBL-producing *K. pneumoniae*, or susceptible *K. pneumoniae* at Cleveland Clinic in 2006 to 2012

Characteristic[a]	CRKP ($n = 22$)	ESBL-producing *K. pneumoniae* ($n = 22$)	Susceptible *K. pneumoniae* ($n = 64$)	Total cohort ($n = 108$)	*P*
Age (mean ± SD) (yr)	56 ± 10.3	56 ± 10.9	51 ± 12.8	53 ± 12.1	0.104
Male (no. [%])	16 (73)	12 (55)	14 (22)	42 (39)	<0.001
Time to UTI (median [IQR]) (days)	66 (22–208)	90 (34–512)	306 (59–984)	185 (38–712)	0.004
Transplant type (no. [%])					
Kidney	7 (32)	6 (27)	27 (42)	40 (37)	
Liver	7 (32)	12 (55)	15 (23)	34 (31)	
Heart	2 (9)	0 (0)	4 (6)	6 (6)	
Lung	3 (14)	2 (9)	7 (11)	12 (11)	
Pancreas	0 (0)	0 (0)	2 (3)	2 (2)	
Intestine	0 (0)	1 (5)	0 (0)	1 (1)	
Kidney-liver	3 (14)	1 (5)	4 (6)	8 (7)	
Kidney-pancreas	0 (0)	0 (0)	4 (6)	4 (4)	
Kidney-heart	0 (0)	0 (0)	1 (2)	1 (1)	
Clinical features					
Bacteremia (no. [%])	7 (32)	4 (18)	8 (13)	19 (18)	0.150
ICU admission (no. [%])	14 (64)	17 (77)	17 (27)	48 (44)	<0.001
Urinary catheter (no. [%])	6 (27)	6 (27)	6 (9)	18 (17)	0.049
Relapse (no. [%])	7 (32)	4 (18)	7 (11)	18 (17)	0.075
LOS prior to UTI (median [IQR]) (days)	7 (2–26)	8 (1–14)	1 (1–4)	2 (1–11)	<0.001
Time to adequate antibiotics (mean ± SD) (days)	2.73 ± 2.1	1.36 ± 1.1	1.31 ± 1.9	1.61 ± 1.9	0.006
Outcome (no. [%])					
Clinical failure	8 (36)	4 (18)	9 (14)	21 (19)	0.073
Microbiological failure	10 (45)	2 (9)	2 (3)	14 (13)	<0.001
All-cause death during hospitalization	4 (18)	4 (18)	1 (2)	9 (8)	NS

[a] UTI, urinary tract infection; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; ESBL, extended-spectrum β-lactamase; SD, standard deviation; IQR, interquartile range; ICU, intensive care unit; LOS, length of stay; NS, nonsignificant.

ness 72 h after receiving adequate antimicrobial therapy. Microbiological failure occurred if positive urine culture results of $\geq 10^5$ CFU/ml of the original organism were found ≥72 h after appropriate antibiotic treatment (3).

Infections were categorized into 3 groups, i.e., CRKP, ESBL-producing *K. pneumoniae*, or susceptible *K. pneumoniae*, based on the results of susceptibility testing performed using the automated Vitek 2 system (bioMérieux, Inc., Durham, NC) supplemented by manual methods. Isolates with ertapenem MICs of ≥4 μg/ml and positive modified Hodge test results were considered CRKP (4). ESBL production was determined by the Vitek 2 test detection of reduction of growth in wells containing cephalosporins with clavulanic acid, compared to wells with the cephalosporin alone. Isolates with positive ESBL test results were reported as resistant to penicillins, cephalosporins, and aztreonam regardless of the MICs. Fosfomycin susceptibility was determined by the Etest method (bioMérieux, Inc., Durham, NC) performed with Mueller-Hinton agar (BBL; Becton, Dickinson). This methodology represented the workflow in the microbiology laboratory and generated results incorporated by clinicians into the care of patients in a real-world setting at our institution.

Statistical analyses. Descriptive statistics were computed, and differences in characteristics across groups were analyzed by the chi-square test, analysis of variance techniques, and nonparametric median comparisons as appropriate. Multivariable analyses for factors associated with microbiological failure and clinical failure were performed using stepwise multiple logistic regression analyses. The criterion for entering the model was significance at the $\alpha = 0.20$ level, while the criterion for remaining in the model was significance at the $\alpha = 0.05$ level. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. Model fits were assessed using the Hosmer-Lemeshow goodness-of-fit statistic. All statistical tests were two-tailed and utilized a 5% significance level. Analyses were performed using JMP Pro 10 (SAS Institute, Cary, NC).

RESULTS

We identified 108 individuals; 22 (20%) had UTIs due to CRKP, 22 (20%) due to ESBL-producing *K. pneumoniae*, and 64 (60%) due to susceptible *K. pneumoniae*. There were 40 kidney-only transplants (37%) and 68 transplants of other solid organs (63%). The mean age was 53 years, and 42 patients (39%) were male. Overall, the median time from transplantation to UTI was 185 days (interquartile range [IQR], 38 to 712 days). As shown in Table 1, bacteremic UTI was found in 7 patients with CRKP (32%), 4 with ESBL-producing *K. pneumoniae* (18%), and 8 with susceptible *K. pneumoniae* (13%) ($P = 0.150$). Compared to susceptible *K. pneumoniae* (27%), patients with UTIs due to CRKP or ESBL-producing *K. pneumoniae* were more likely to have a ≥24-hour stay in the ICU before or after development of the UTI (64% and 77%, respectively; $P < 0.001$). Patients with UTIs due to susceptible *K. pneumoniae* were significantly less likely to have a urinary catheter. Relapse of UTI occurred for 7 patients with CRKP (32%), 4 with ESBL-producing *K. pneumoniae* (18%), and 7 with susceptible *K. pneumoniae* (11%) ($P = 0.075$). Among 105/108 hospitalized patients (97%), the median LOS prior to UTI for CRKP and ESBL-producing *K. pneumoniae* (7 and 8 days, respectively) were significantly longer than that for susceptible *K. pneumoniae* (1 day; $P < 0.001$). The mean time to adequate antibiotic

TABLE 2 Treatment and outcomes for 22 OTRs with a first episode of UTI due to CRKP at Cleveland Clinic in 2006 to 2012

Patient no.	Organ(s) transplanted	Treatment length (days)					Outcome[a]
		Colistin	Tigecycline	Carbapenem	Aminoglycoside	Fosfomycin	
1[b]	Heart		14		7		Clin and micro failure
2	Heart		30				Clin failure
3[b]	Kidney	7	3	3			Clin and micro failure
4	Kidney					7	Response
5	Kidney				10	7	Response
6	Kidney				16	12	Response
7	Kidney	24	35			20	Clin and micro failure
8	Kidney	3	21			8	Micro failure
9	Kidney	4	120			10	Clin and micro failure
10	Liver		14		14		Micro failure
11[b]	Liver	40	40				Clin failure
12[b]	Liver	9					Clin failure
13	Liver					8	Micro failure
14	Liver	14					Response
15	Liver		26			7	Micro failure
16	Liver	6					Response
17	Liver and kidney		35				Micro failure
18	Liver and kidney		3			7	Response
19	Liver and kidney		14			7	Response
20	Lung	12	42		14		Response
21	Lung	3					Response
22	Lung		50		18		Clin and micro failure

[a] Clin, clinical; micro, microbiological.
[b] Death during hospitalization.

therapy for CRKP (2.73 days) was significantly longer than those for ESBL-producing *K. pneumoniae* or susceptible *K. pneumoniae* (1.36 and 1.31 days, respectively; $P = 0.006$).

Clinical failure was observed for 8 patients with CRKP (36%), compared with 4 patients with ESBL-producing *K. pneumoniae* (18%) and 9 patients with susceptible *K. pneumoniae* (14%) ($P = 0.073$). Microbiological failure was seen for 10 patients with CRKP (45%), compared with 2 patients with ESBL-producing *K. pneumoniae* (9%) and 2 patients with susceptible *K. pneumoniae* (3%) ($P < 0.001$). The all-cause mortality rate during hospitalization was 8% (9/108 patients). There were 4 deaths among patients with CRKP and 4 among those with ESBL-producing *K. pneumoniae*. In multivariable logistic regression analyses controlling for age, sex, ICU admission, and transplant type, UTI caused by CRKP was independently associated with greater odds of microbiological failure (versus ESBL-producing *K. pneumoniae*: OR, 9.36 [95% CI, 1.94 to 72.1]; versus susceptible *K. pneumoniae*: OR, 31.4 [95% CI, 5.91 to 264]). Controlling for age, sex, ICU admission, and urinary catheters, there were greater odds of clinical failure associated with CRKP, but that finding did not reach statistical significance (versus ESBL-producing *K. pneumoniae*: OR, 2.26 [95% CI, 0.57 to 10.2]; versus susceptible *K. pneumoniae*: OR, 2.17 [95% CI, 0.61 to 7.53]).

With regard to treatment, considering only OTRs with UTIs due to CRKP, 10 patients (45%) received an antibiotic regimen containing colistin, 14 (64%) tigecycline, 1 (5%) a carbapenem, 6 (27%) an aminoglycoside, and 10 (45%) fosfomycin (Table 2). Fourteen patients (64%) received combination antibiotic therapy with at least 2 different classes of drugs. Notably, both clinical and microbiological responses occurred for 3/14 patients (21%) treated with tigecycline, 4/10 (40%) treated with colistin, 3/6 (50%) treated with aminoglycosides, and 5/10 (50%) treated with fosfomycin. Generally, too few patients received any specific agent to permit meaningful comparisons among drugs. Therefore, no individual agent could be shown to be associated with the primary outcomes in any of the multiple models evaluated (data not shown).

DISCUSSION

To our knowledge, the present study is the largest detailed clinical characterization and comparison of OTRs with UTIs due to CRKP, ESBL-producing *K. pneumoniae*, or susceptible *K. pneumoniae*. We observed that UTIs caused by CRKP were associated with greater odds of microbiological failure. We documented that UTIs due to CRKP or ESBL-producing *K. pneumoniae* occurred significantly earlier after transplantation than those due to susceptible *K. pneumoniae* and were associated with a urinary catheter at diagnosis, a ≥24-hour stay in the ICU either before or after development of the UTI, and longer LOS prior to the UTI. These data support the idea that, during the study period, CRKP was largely a nosocomial pathogen. We further observed a trend toward an increased likelihood of patients with CRKP experiencing relapse within 30 days and continued fever or urgency, frequency, dysuria, suprapubic tenderness, or costovertebral angle pain or tenderness 72 h after receiving adequate antimicrobial therapy. The mean time to initiation of that therapy was significantly longer for CRKP.

UTI occurs more frequently in OTRs than in the nontransplant population. For example, UTI, estimated to be associated with approximately 44 to 47% of all infectious complications (5), is the most common infection following kidney transplantation, but published studies of UTI due to CRKP in OTRs are lacking. Sim-

kins and colleagues compared 9 kidney transplant recipients with UTIs due to CRKP and 34 with carbapenem-susceptible *K. pneumoniae* (6). They observed a trend toward more bacteremia among cases of CRKP, as well as a significantly higher mortality rate at 6.5 months. Unfortunately, other investigations into CRKP among OTRs excluded UTIs (7–10). Still others included both OTRs and nontransplant patients but focused on a particular therapy (11), bacteremia (12, 13), or factors associated with the development of UTIs among patients with asymptomatic bacteriuria (14). Extrapolating from data for nontransplant patients is problematic. It has been shown that, among mostly (81%) nontransplant patients with UTIs due to CRKP, microbiological failure occurred in only 5 cases (24%) and bacteremia in 3 (14%) (15). In contrast, we observed microbiological failure for 45% of OTRs and bacteremic UTI due to CRKP for 32%. In addition, it was shown that aminoglycosides were associated with clearance of CRKP bacteriuria among nontransplant patients (16), but our data demonstrated that 3/6 aminoglycoside-exposed OTRs (50%) experienced microbiological failure. We hypothesize that immunosuppressive medication enhances the importance of early active antimicrobial therapy and accounts in part for the increased rates of microbiological failure and bacteremia.

Our results are generally in agreement with the other very limited published studies. In Brazil, Argentina, and Israel, 12 OTRs with UTIs due to CRKP have been described, 6 (50%) of whom were bacteremic (17–19). Mortality rates ranged from 0 to 33%. Finally, in a recent study of patients from the United States, there were 11 OTRs with UTIs due to CRKP (14). While detailed clinical characterizations were not provided, multivariate logistic regression analyses identified solid organ transplantation as independently associated with UTI among all patients with CRKP bacteriuria (OR, 4.50 [95% CI, 1.39 to 14.52]).

In the present study, we report an additional 22 OTRs with UTIs due to CRKP, with ESBL-producing *K. pneumoniae* and susceptible *K. pneumoniae* for comparison. As shown, many features of UTIs due to ESBL-producing *K. pneumoniae* were similar to those for CRKP; however, important differences emerged, particularly in the increased odds of microbiological failure associated with CRKP. Failure to include ESBL-producing *K. pneumoniae* would have placed the findings in an improper context, and the results would have been much less informative. Although our study provides some advantages, the observational design is limited by unmeasured confounders, such as the presence of ureteral stents and confounding by indication. Therefore, some of our observations should be interpreted cautiously. These data reflect the biases of the clinicians at our institution. For example, providers more often repeated urine cultures for OTRs with UTIs due to CRKP or ESBL-producing *K. pneumoniae*, which could bias the results with regard to microbiological failure, in comparison to susceptible *K. pneumoniae*. Finally, ESBL-producing *K. pneumoniae* and carbapenem resistance were defined phenotypically. During the study period, testing for *K. pneumoniae* carbapenemase (KPC) production through detection of bla_{KPC} was not performed; however, subsequent PCR testing of the isolates with positive results from the modified Hodge test revealed the overwhelming majority to be bla_{KPC} positive. While the phenotypic definitions may be somewhat limited, results reflect the information available to providers caring for these patients in a real-world setting. Therefore, our data incorporating these definitions remain largely informative and relevant.

In conclusion, CRKP is associated with microbiological failure among OTRs with UTIs and may be an important predictor of clinical outcomes. There are few therapeutic options for CRKP, and use of the available agents is limited by the parenteral route of administration and toxicity, particularly among patients with recent or ongoing organ failure syndromes, which are frequently encountered among OTRs. This underscores the importance of infection prevention. Additional studies with OTRs, with greater patient numbers and an emphasis on determining modifiable risk factors for the development of infection, are needed. These will permit discovery of significant differences in clinically meaningful endpoints associated with carbapenem resistance, which would be invaluable to clinicians caring for OTRs.

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