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MAJOR ARTICLE

Carbapenem-Resistant Enterobacteriaceae Infections in Patients on Renal Replacement Therapy

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Background. Patients on chronic intermittent renal replacement therapy (RRT) are at risk for infection with carbapenem-resistant Enterobacteriaceae (CRE). However, the impact of RRT on outcomes after CRE infections remains to be defined. Here we perform a comparison of outcomes for CRE-infected patients with preserved renal function compared with CRE-infected patients on RRT.

Methods. Cases and controls were defined from a prospective cohort of CRE-infected patients from the Consortium on Resistance against Carbapenems in *Klebsiella* and other Enterobacteriaceae (CRACKLE). Cases were defined as CRE-infected patients on RRT at hospital admission, while controls were defined as CRE-infected patients with serum creatinine <2 mg/dL and not receiving RRT at admission. Risk factors for 28-day in-hospital mortality were assessed using multivariable logistic regression. An ordinal ranking of outcomes by desirability analysis was performed.

Results. Patients on RRT were more likely to have diabetes mellitus and cardiac disease than controls. Urinary sources of infection were less common in the RRT group. In RRT patients, 28-day in-hospital mortality was increased as compared with controls: 22/71 (31%) vs 33/295 (11%). RRT remained significantly associated with 28-day in-hospital mortality after adjustment for source of infection, prehospitalization origin, and severity of illness (adjusted odds ratio, 2.27; 95% confidence interval [CI], 1.09–4.68; $P = .03$). Using univariable desirability of outcome ranking analysis, RRT status was associated with a 68% (95% CI, 61%–74%) chance of a worse disposition outcome.

Conclusions. Chronic RRT in CRE-infected patients is associated with increased in-hospital mortality and worse disposition outcomes at 28 days.

Keywords. carbapenem-resistant Enterobacteriaceae; *Klebsiella pneumoniae*; mortality; renal failure; renal replacement therapy.

Nearly 500 000 Americans with end-stage renal disease (ESRD) required chronic intermittent renal replacement therapy (RRT) in 2013. Prevalence rates are rising, with more than 100 000 new patients initiating chronic RRT in 2013 [1]. RRT patients typically engage with the health care setting 3 times weekly and face more than 1.5 hospital admissions/person-year [2]. The majority (79%) of ESRD patients initiate hemodialysis via intravascular catheter, which increases the risk for line-related bloodstream infection [3]. According to a meta-analysis, RRT patients face intravenous antibiotic start rates ranging from 3.1–7.7 per 100 patient-months [4].

ESRD is associated with impaired innate and adaptive immune responses [5, 6]. In addition, ESRD may lead to bacterial overgrowth, particularly in the duodenum and jejunum [7]. Beyond increased bacterial counts in the gut, an increase in abundance of potentially pathogenic bacterial families such as Enterobacteriaceae is observed. This occurs at the expense of Lactobacillaceae and Prevotellaceae, both normal components of healthy gut flora [8].

These increased opportunities for acquisition in ESRD patients translate into higher incidence of infection with multidrug-resistant organisms than the general population, particularly methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE) [9]. There are no published studies of incidence of CRE infections in the ESRD population. Outcomes of CRE infections in ESRD patients

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on RRT are also poorly studied. In a sample in which gram-negative bacteria comprised 52% of the cases, 30-day mortality of 15.1% was observed among patients with ESRD on RRT [10]. Compared with patients not on RRT, ESRD patients on RRT face mortality rates more than 2 times higher for sepsis, pneumonia, and endocarditis [11–13]. ESRD patients on RRT are also more likely to die from antibiotic-resistant organisms such as MRSA (adjusted odds ratio [aOR], 5.4; 95% confidence interval [CI], 1.5–18.7) and *Clostridium difficile* (aOR, 2.15; 95% CI, 2.07–2.24) [14, 15]. For CRE, 1 study identified a median survival of 1 month for CRE-infected patients with ESRD on RRT compared with more than 24 months for the control group of ESRD patients on RRT without infection [16]. The aim of this study was to examine outcomes in CRE-infected patients on RRT compared with CRE-infected patients with normal renal function in a large prospective, multicenter cohort of CRE-infected patients.

METHODS

Patients

The Consortium on Resistance against Carbapenems in *Klebsiella* and other Enterobacteriaceae (CRACKLE) is a prospective, multicenter, observational study of hospitalized patients with CRE in the Great Lakes Region of the United States [17–20]. The study period for the current study was December 2011 to July 2016. Two nonoverlapping nested cohorts of patients with CRE infection were constructed. Patients who did not meet criteria for infection and were deemed to have CRE colonization were excluded. Standardized, a priori definitions of infection were used, as previously described [21]. The first cohort ("RRT patients") contained all patients who were on RRT at the time of admission for the index hospitalization. The second cohort ("control patients") consisted of all patients who did not have renal failure upon or during hospital admission. Renal failure was defined as either a need for RRT and/or a serum creatinine >2 mg/dL. In both cohorts, unique patients were included only once, at the time of their first CRE infection. All the health systems involved in this study had approval from their respective institutional review boards.

Microbiology

CRE was defined as Enterobacteriaceae isolates with nonsusceptibility to any of the following carbapenems: meropenem, imipenem, or ertapenem, as outlined by the Clinical and Laboratory Standards Institute (CLSI) [22]. Bacterial identification and routine antimicrobial susceptibility testing was performed with MicroScan (Siemens Healthcare Diagnostics) or Vitek2 (bioMérieux) at the clinical sites. Additional susceptibilities were obtained by GN4F Sensititre tray (Thermo Fisher) or Etest (bioMérieux), as indicated. In more than 90% of tested isolates, carbapenem resistance was mediated through bla_{KPC-2} or bla_{KPC-3}, as previously described [18, 19].

Clinical Data

Clinical data from the electronic medical record were entered into a centralized database. The index hospitalization was defined as the first hospital stay within the study period during which a CRE infection occurred. Critical illness was determined as a Pitt bacteremia score ≥4 points on the day of the index culture [23]. The Pitt bacteremia score has previously been validated for nonbacteremic infections [24]. The Charlson comorbidity index was calculated at hospital admission, as described [25]. Outcomes at 28 days after the date of the index culture were categorized as follows: discharged home, discharged to a skilled nursing facility, remains admitted, discharged to long-term acute care hospital (LTACH), dead or discharged to hospice. For this purpose, the status at hospital discharge was carried forward, and patients who were transferred to another hospital prior to the 28-day mark were considered "remains admitted."

Statistics

Differences between groups were analyzed using the Wilcoxon rank sum test for continuous variables. Fisher's exact test and Pearson testing were used for categorical variables where appropriate. Nominal logistic regression was performed to determine the univariable association of each variable of interest and 28-day in-hospital mortality. All variables that were associated at a level of $P < .1$ were included in a multivariable model. An ordinal outcome was constructed based on the 28-day outcomes, with the following order of categories: "discharged home" (best), "discharged to skilled nursing facility," "remains admitted," "discharged to long-term acute care hospital," "dead or discharged to hospice" (worst) [26]. P values of ≤.05 were considered statistically significant. JMP 10.0.1 software (SAS, Inc, Cary, NC) was used for all analyses.

RESULTS

Patient Characteristics

The study population included 71 case patients with end-stage renal disease (ESRD) requiring RRT and 295 control patients without renal failure, selected as shown in Figure 1. Carbapenem-resistant *Klebsiella pneumoniae* comprised 90% of infections (n = 330). In the remaining 10% of patients, *Enterobacter* spp. (n = 20; 5%), *Morganella morgannii* (n = 6; 2%), *Proteus mirabilis* (n = 3; 1%), *Providencia stuartii* (n = 3; 1%), *Escherichia coli* (n = 2; 1%), and *Citrobacter* spp. (n = 2; 1%) were isolated. The characteristics of the study population are shown in Table 1. The distributions of age, sex, and race did not differ significantly between the RRT and control groups. Besides renal failure, other comorbid conditions were also more common in RRT patients. Specifically, diabetes mellitus (DM) and cardiac disease were associated with the RRT group; the rates of DM and cardiac disease were 62% and 63% in RRT patients, respectively, compared with 37% and 34%, respectively, in the control

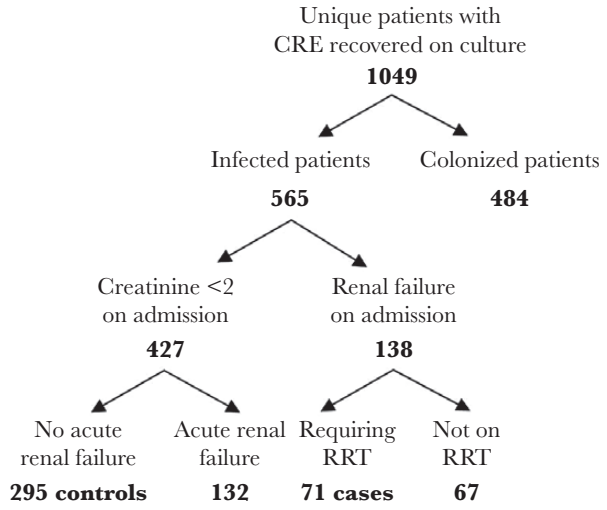

Figure 1. Selection of isolates. Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; RRT, renal replacement therapy.

group ($P < .0001$ for both). The distribution of infections also differed between the groups ($P = .01$), which was primarily driven by a higher proportion of urinary tract infections in the control group (34%) compared with the RRT population (14%). Furthermore, the 2 groups varied significantly by origin at time of admission, with 40% of control patients admitted from home compared with 30% of RRT patients and 5% of control patients admitted from LTACH compared with 20% of RRT patients.

Table 1. Clinical Characteristics

	All	RRT	Control	*P*[a]
n	366	71	295	
Age, median (IQR), y	62 (50–74)	62 (53–71)	62 (49–75)	.99
Female	189 (52)	36 (51)	153 (52)	.90
Race				.10
White	198 (54)	32 (45)	166 (56)	
Black	140 (38)	35 (49)	105 (36)	
Other	28 (8)	4 (6)	24 (8)	
Charlson comorbidity index, median (IQR)	3 (1–5)	6 (4–7)	2 (1–4)	<.0001
Diabetes mellitus	152 (42)	44 (62)	108 (37)	<.0001
Cardiac disease[b]	144 (39)	45 (63)	99 (34)	<.0001
Type of infection				.01
Bloodstream infection	92 (25)	21 (30)	71 (24)	
Pneumonia	80 (22)	16 (23)	64 (22)	
Urinary tract infection	109 (30)	10 (14)	99 (34)	
Wound infection	40 (11)	11 (15)	29 (10)	
Other infection	45 (12)	13 (18)	32 (11)	
Origin				<.01
Home	138 (38)	21 (30)	117 (40)	
Skilled nursing facility	137 (37)	25 (35)	112 (38)	
Hospital transfer	63 (17)	11 (15)	52 (18)	
Long-term acute care hospital	28 (8)	14 (20)	14 (5)	
Critical illness[c]	147 (40)	39 (55)	108 (37)	<.01
Length of stay, median (IQR), d	12 (7–24)	13 (9–24)	11 (6–25)	.24

All data expressed as n (%), unless otherwise indicated.

Abbreviations: IQR, interquartile range; RRT, renal replacement therapy.

[a]Univariable relationship between variable of interest and RRT.

[b]Cardiac disease defined as the presence of coronary artery disease and/or congestive heart failure.

[c]Critical illness defined as Pitt bacteremia score ≥4 at the time of index culture.

Antibacterial Treatment

Directed anti-CRE treatment given within 14 days after index culture is summarized in Table 2. Upon comparison of the usage of specific antibiotics, colistin use was more common in the RRT group, with 23/71 (32%) receiving colistin as compared with 25/295 (8%) in the control patients ($P < .0001$). Other specific antibiotic usage was not different between groups. Of note, critical illness was more common in patients treated with colistin; 28/48 (58%) patients who received colistin were critically ill, as compared with 119/318 (37%) patients who did not receive colistin ($P < .01$). Furthermore, colistin use was more common in patients with bloodstream infections (22/92; 24%), compared with patients with other types of infection (26/274; 9%; $P = .001$). Similar proportions of cases and controls received agents without in vitro susceptibility to CRE.

Outcomes

Total length of stay of the index hospitalization was not different between RRT patients and control patients. The RRT group had illness of significantly higher severity at the time of first positive CRE culture. The impact of risk factors on 28-day mortality is shown in Table 3. The all-cause 28-day in-hospital mortality rates were 22/71 (31%) in RRT patients, compared with 33/295 (11%) in control patients ($P < .0001$). Risk factors associated with increased mortality on multivariable analysis include bloodstream infection, transfer from hospital or LTACH, high levels of critical illness, and RRT. Notably, RRT remained

Table 2. Treatment Characteristics

	All	RRT	Control	*P*[a]
n	366	71	295	
Colistin	48 (13)	23 (32)	25 (8)	<.0001
Tigecycline	117 (32)	22 (30)	95 (32)	.88
Amikacin	58 (16)	13 (18)	45 (15)	.59
Gentamicin	65 (18)	12 (17)	53 (18)	1.0
Trimethoprim/sulfamethoxazole	37 (10)	9 (13)	28 (9)	.39
Carbapenem	130(36)	31 (44)	99 (34)	.13
Fosfomycin[b]	16 (4)	1 (1)	15 (5)	.33
Ceftazidime/avibactam	28 (8)	3 (4)	25 (8)	.32
Antibiotics without in vitro anti-CRE activity	62 (17)	11 (15)	51 (17)	.86
None of above	22 (7)	2 (3)	20 (7)	.59

All data expressed as n (%), unless otherwise indicated. Shown is the number of patients who received a given antibiotic in the 14 days following index culture. Percentages accumulated exceed 100% as patients may have received more than 1 antibiotic.

Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; RRT, renal replacement therapy.

[a]Univariable relationship between variable of interest and RRT.

[b]Fosfomycin use was only recorded in patients with urinary tract infections.

Table 3. Risk Factors for 28-Day In-Hospital Mortality

	Survivor	Nonsurvivor	P^a	aOR	95% CI	P^b
n	311	55				
Age, median (IQR)	62 (49–74)	63 (53–74)	.85			
Female	161 (52)	28 (51)	1.0			
Race			.31			
White	173 (56)	25 (45)				
Black	114 (37)	26 (47)				
Other	24 (8)	4 (7)				
Charlson comorbidity index ≥3	160 (51)	31 (56)	.56			
Diabetes mellitus	128 (41)	24 (44)	.77			
Cardiac disease[c]	120 (39)	24 (44)	.54			
Source			<.0001			.001
Blood (ref.)	66 (21)	26 (47)		-	-	
Urine	105 (34)	4 (7)		0.16	0.05–0.51	
Respiratory	66 (21)	14 (25)		0.27	0.12–0.65	
Other	74 (24)	11 (20)		0.39	0.16–0.92	
Origin						.001
Home (ref.)	122 (39)	15 (27)		-	-	
Skilled nursing facility	125 (40)	12 (22)		0.63	0.26–1.48	
Hospital transfer	49 (16)	15 (27)		1.93	0.81–4.66	
Long-term acute care hospital	15 (5)	13 (24)		4.53	1.60–12.97	
Critical illness[d]	107 (34)	40 (73)	<.0001	4.28	2.15–8.93	<.0001
RRT	49 (16)	22 (40)	<.001	2.27	1.09–4.68	.03

All data expressed as n (% of survivors and nonsurvivors, respectively), unless otherwise indicated.

Abbbreviations: aOR, adjusted odds ratio; CI, confidence interval; IQR, interquartile range; RRT, renal replacement therapy.

[a] *P* value for univariable relationship with 28-day in-hospital mortality.

[b] *P* value for multivariable relationship with 28-day in-hospital mortality.

[c] Cardiac disease defined as the presence of coronary artery disease and/or congestive heart failure.

[d] Critical illness defined as Pitt bacteremia score ≥4 at the time of index culture.

significantly associated with 28-day in-hospital mortality after adjustment for source of infection, prehospitalization origin, and critical illness (aOR, 2.27; 95% CI, 1.09–4.68; $P = .03$).

The ordinal outcome of disposition at 28 days by desirability of outcome ranking (DOOR) analysis (dead/hospice, LTACH, admitted, nursing home, and home) is shown as a mosaic plot in Figure 2. The probability of a worse outcome in the RRT patient group was 68% (95% CI, 61%–74%) when compared with the control group.

DISCUSSION

In our cohort, CRE-infected patients receiving RRT have a higher likelihood of death and increased in-hospital mortality compared with controls, even after adjusting for source of infection, level of care at admission, infection type, and level of critical illness. RRT patients tended to have more comorbid conditions, which likely contributed to the observed increased hospital mortality. RRT patients with CRE infections were more likely to be admitted from higher levels of care than control

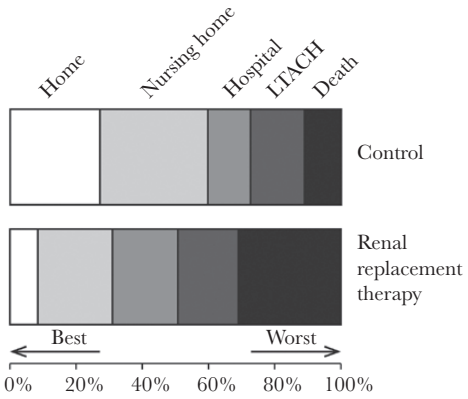

Figure 2. Mosaic plot of outcomes at 28 days. If a patient was discharged prior to 28 days, the last observation was carried forward. Using desirability of outcome ranking analysis, renal replacement therapy patients had a 68% (95% confidence interval, 61%–74%) likelihood of a worse outcome at 28 days as compared with controls. Abbreviation: LTACH: long-term acute care hospital.

patients and less likely than controls to be admitted from home. In addition, they are more acutely ill at the time of their CRE infection when compared with control patients with normal renal function. RRT patients also have a lower proportion of low-mortality urinary tract infections and higher proportions of bloodstream infections.

In addition, a DOOR analysis was performed to rank patients based on the range of possible dispositions following treatment of CRE infection [26]. In a DOOR analysis, when comparing outcomes between 2 groups, a likelihood of 50% of a worse outcome is indicative of no numerical difference between the groups. Similarly, if the 95% confidence interval crosses 50%, there is no statistically significant difference between the groups. In our study, the likelihood of a worse outcome for a patient in the RRT group as compared with a patient in the control group was 68%. DOOR analysis is a novel method of analyzing outcomes on a spectrum of patient experiences. We have recently used DOOR analysis to compare patients treated with colistin vs ceftazidime-avibactam [27]. DOOR analysis provides an opportunity to analyze several states between alive and dead that are important to patients. In this study, we have used DOOR analysis to give a visual and statistical association between the exposure of interest (RRT in this case) and outcomes after CRE infection. While this is an association that does not imply causality, the robust observation of poor outcomes in this vulnerable patient population and the quantification of this effect add to the existing literature of impact of infections on patients with chronic renal failure. Furthermore, these findings add to existing studies to emphasize the clear need for infection control measures and antibiotic stewardship in patients on RRT [28].

RRT patients have been shown to have a higher risk for the acquisition of multidrug-resistant (MDR) organisms than patients with normal renal function. For instance, receipt of RRT

was associated with an aOR of 2.34 for infection with *ampC*-carrying organisms [29]. More data exist for higher rates of infection with MRSA and VRE in the RRT population when compared with patients with normal renal function [30, 31]. Outcomes in resistant *Enterobacteriaceae* infections in the chronic RRT population are rare in the literature. A 42-month study of French RRT patients showed that 42% developed any bloodstream infection during the study period, 32/93 experienced hospitalization or death, and isolation of an MDR pathogen was associated with an increased chance of hospitalization or death (OR, 2.75; 95% CI, 1.01–7.48) [32]. An Israeli study found higher mortality in CRE-infected patients than those infected with carbapenem-susceptible strains (OR, 1.9; 95% CI, 1.2–3.1). Thirty-day mortality was associated with several comorbid conditions, including dialysis (OR, 5.6; 95% CI, 2.7–11.5) and chronic renal failure (OR, 3.1; 95% CI, 1.9–5.1), though they did not compare RRT and non-RRT patients with CRE infections [33]. Bacteremic RRT patients in the United Kingdom experienced worse outcomes than bacteremic renal transplant patients in a setting where *Enterobacteriaceae* comprised the majority (57/77; 74%) of the infecting strains; of which 15/57 (26%) were ESBL-producing Enterobacteriaceae [34].

The difference in distribution of infections between the 2 groups was driven primarily by the lower share of urinary tract infections in the RRT group; this finding is expected as 72% of RRT patients are anuric at 1 year from RRT initiation [35]. We have previously shown that within the various sources of CRE infection in hospitalized patients, bacteremia and pneumonia are associated with the highest mortality risk, and urinary tract infection the lowest [21]. Similarly, proportions of in-hospital mortality observed in patients with CRE urinary tract infections were similar to controls with CRE urinary tract colonization [21]. Adjustment for source was, therefore, an important part of our multivariable analysis. Even after this adjustment, there was a large excess risk of death associated with RRT.

The increased use of colistin in the RRT population may have several explanations that are not mutually exclusive. First, it may reflect the acuity of illness at the time of index culture. An association between critical illness and colistin use was noted. In 1 study of colistin use in a 2200-bed health system, patients receiving colistin had high proportions of sepsis/severe sepsis/septic shock (80%), mechanical ventilation (62%), and baseline renal insufficiency (25%), suggesting that colistin is used principally in a critically ill population [36]. Second, a lack of concern for nephrotoxicity in RRT patients may play a role. This is difficult to assess from the literature as no studies have specifically surveyed providers' use of colistin. One study of antibiotic choice in health care–associated pneumonia treatment identified only duration of admission >5 days and *Acinetobacter baumanii* prevalence >10% in respiratory cultures as predictors of colistin use; renal replacement therapy was not a studied variable; however, prevalence of chronic renal failure in the study population was 15% [37]. Furthermore, patients requiring any kind of renal replacement therapy including RRT are typically excluded from studies of colistin use. Third, colistin may be used more for specific infection types. We observed an association between colistin use and bloodstream infections but not pneumonia, which may reflect a lower propensity for CRE to cause pneumonia as compared with *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.

The study had several limitations as a result of its observational design and geographical origin. The etiology of carbapenem resistance in the hospitals studied is predominantly bla_{KPC}; therefore, these results may not be generalizable to infecting isolates with other mechanisms of carbapenem resistance. Also, the study was conducted in the Great Lakes region of the United States, and other patterns may be observed elsewhere. Our choice of a serum creatinine <2 mg/dL for inclusion in the control group does not ensure normal renal function. However, this level would be unusual in a patient with moderate to severe renal failure.

Previous studies have identified both carbapenem resistance and chronic RRT as risk factors for poor outcomes during infection episodes. Gram-negative multidrug resistance has been previously associated with increased mortality in bacteremic episodes, and chronic RRT has been associated with increased risk of acquiring MDR infection and an increased risk of death. Here we show that chronic RRT is associated with higher mortality in CRE infections compared with control CRE-infected patients with serum creatinine <2 mg/dL. Furthermore, by DOOR analysis, we show that RRT patients have a 68% likelihood of an overall worse outcome. Beyond the human and financial costs of increased levels of care at discharge, this analysis highlights the impact of spread of CRE to nursing homes, LTACH, and, in chronic RRT patients, RRT centers. Because CRE infections result in such high levels of morbidity and mortality, further attention is needed to prevent infection by CRE, particularly in the RRT population and in the RRT centers they frequent.

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