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Clinical epidemiology of carbapenem-resistant Gram-negative sepsis among hospitalized patients: shifting burden of disease?

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Abstract

Background—Infections due to carbapenem-resistant Gram-negative bacilli are an emerging public health threat. However, there remains a paucity of data examining comparative incidence rates, risk factors, and outcomes in this population.

Methods—This was a single-center retrospective cohort study conducted at an urban tertiary care academic medical center. We included patients admitted (2012–2015) with: i) age ≥ 18 years; and ii) culture positive for CRE or CRNE from any site. Exclusion criteria were: i) < 2 systemic inflammatory response criteria; ii) cystic fibrosis; and iii) no targeted treatment. We evaluated hospital survival by Cox regression and year-by-year differences in the distribution of cases by Cochran-Armitage test.

Results—448 patients were analyzed (CRE, *n*=111 [24.8%]; CRNE, *n*=337 [75.2%]). CRE sepsis cases increased significantly over the study period (*P*<0.001), driven primarily by increasing

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incidence of *Enterobacter* spp. infection (*P*=0.004). There was no difference in hospital survival between patients with CRE versus CRNE sepsis (hazard ratio [HR], 1.29; 95% confidence interval [CI], 0.83–2.02; *P*=0.285), even after adjusting for confounding factors (adjusted HR, 1.08; 95% CI, 0.62–1.87; *P*=0.799).

Conclusions—Clinical outcomes did not differ between patients with CRE versus CRNE sepsis. Dramatic increases in CRE, particularly *Enterobacter* spp., appear to be causing a shift in the burden of clinically significant carbapenem-resistant Gram-negative infection.

Keywords

carbapenem resistance; multidrug resistance; sepsis; carbapenem-resistant *Enterobacteriaceae*; *Pseudomonas aeruginosa*

INTRODUCTION

Infections due to multidrug-resistant Gram-negative bacilli (MDR-GNB) are becoming an increasingly common clinical problem [1–4]. Carbapenem-resistant *Enterobacteriaceae* (CRE) represent an urgent threat to public health according to the latest report from the United States Centers for Disease Control and Prevention (CDC) [5]. While CRE infections are an important concern, infections due to non-fermenting MDR-GNB, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* complex, are also on the rise [5, 6]. Whether these carbapenem-resistant non-*Enterobacteriaceae* (CRNE) infections affect different patient populations than CRE has not been extensively evaluated.

Resistance mechanisms and production of virulence factors significantly differ between CRE and CRNE [7]. *Pseudomonas aeruginosa* in particular is able to produce a multitude of exotoxins which may influence clinical outcomes [8, 9]. Carbapenemase production is an emerging plasmid-mediated resistance mechanism among CRE, but is rare among non-*Enterobacteriaceae* [4, 10]. Whilst carbapenem resistance has been associated with worse clinical outcomes among patients with Gram-negative infections in multiple meta-analyses, whether outcomes differ between CRE and CRNE infections is unclear [11–13]. The objectives of this study were to quantify the burden of carbapenem-resistant Gram-negative sepsis in a cohort of hospitalized patients, as well as to compare risk factors and clinical outcomes between patients with CRE or CRNE infection.

METHODS

The present study was a single-center retrospective cohort study conducted at Barnes-Jewish Hospital, an urban tertiary care academic medical center in St. Louis, Missouri, USA. This design was chosen to allow for comparison of CRE versus CRNE and most accurately quantify and evaluate trends in the epidemiology of these infections. All adult (age ≥ 18 years) hospitalized patients with a Gram-negative organism isolated from any site were initially screened for inclusion. We included those patients with a corresponding clinical isolate from January 2012 through December 2015 that displayed phenotypic non-susceptibility to any carbapenem agent tested (ertapenem, doripenem, imipenem, or meropenem) in accordance with the current CRE definition endorsed by CDC [14]. For

patients with infections due to *Proteus* spp., *Providencia* spp., or *Morganella* spp., which are known to have intrinsic reduced susceptibility to imipenem, resistance to another carbapenem agent was required for the isolate to be deemed carbapenem-resistant [14]. Inclusion dates were chosen to allow for evaluation of carbapenem-resistant cases after the 2012 carbapenem breakpoint revisions by the Clinical and Laboratory Standards Institute (CLSI) [15]. To limit analysis to cases of true infection rather than colonization, we excluded patients without sepsis, defined as ≥2 systemic inflammatory response syndrome (SIRS) criteria [16]. Furthermore, we excluded patients with cystic fibrosis and those that were discharged to home alive without ever having received targeted antimicrobial therapy [16]. We also excluded patients with polymicrobial infection (> 1 organism isolated) and in cases of recurrent infection, only the first case encountered during the study period was analyzed.

Patients were classified into CRE or CRNE groups for analysis. The primary outcome was hospital survival. We hypothesized survival would be lower for patients with CRNE sepsis compared to CRE sepsis due to the virulence of this group of organisms and known differences in mechanisms of resistance [17, 18]. Thus, the CRNE sepsis group was designated as the comparator group for all tests. Secondary outcomes were 7-day, 28-day, and 90-day all-cause mortality, chosen to evaluate the comparative risk of death at early, intermediate, and late timepoints. All outcomes were assessed from the beginning of CRE or CRNE sepsis, defined at the time of index positive culture while meeting sepsis criteria.

Clinical data recorded during routine care were abstracted by a bioinformatics specialist (NBH) via electronic query of a database available at our institution and audited by the primary investigator (NSB) to ensure accuracy and concordance with the electronic medical record. Variables collected included patient demographics, setting of onset (hospital-acquired defined as culture date > 48 hours after admission), comorbidities and Charlson comorbidity index (defined according to diagnosis codes), invasive devices and procedures, previous antimicrobial exposures, previous hospitalizations, immunosuppression, vital signs, microbiological data, laboratory data, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and vital status [19, 20]. Prior to 2013, bacterial identification was performed using phenotypic methods, typically VITEK2. After 2013, organism identification was performed using the Bruker Biotyper matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) system [21, 22]. Susceptibility testing was performed during routine clinical care using the disk diffusion method according to CLSI guidelines current at the time. *Enterobacteriaceae* isolates which were phenotypically non-susceptible to our reference carbapenem agent (meropenem) were further characterized using polymerase chain reaction (PCR) to detect carbapenemase genes [23, 24]

Baseline characteristics were compared using the chi-squared test for categorical data and Student's t-test or Mann-Whitney *U* test for continuous data. We analyzed year-by-year differences in the distribution of sepsis cases caused by CRE versus CRNE infection using the Cochran-Armitage test for trend. Hospital survival was first evaluated by univariable Cox regression. Two multivariable Cox proportional hazards models for hospital survival were then derived. In the first, CRNE sepsis was forced into the model as the exposure variable of

interest. Other variables associated with CRNE sepsis or hospital survival (P<0.2) were entered into the model manually using an iterative process as described by Hosmer, *et al* [25]. Only variables which were significant confounders (≥10% change in the associated hazard ratio [HR]) were retained in the final parsimonious model [25]. In the second, CRNE sepsis was not forced into the model, and factors independently associated with hospital survival (P<0.05) were identified using a backward stepwise approach. Dichotomous secondary outcomes were compared by chi-squared test. A subgroup analysis evaluating the impact of carbapenemase production on hospital survival among patients with CRE sepsis was also performed. Statistical analyses were performed using SPSS software (IBM Corporation; Armonk, New York, USA; version 22) and GraphPad Prism (version 7, GraphPad software, La Jolla, California, USA). The level of significance was designated as 0.05 for all statistical tests. The Washington University in St. Louis institutional review board approved this study.

RESULTS

A total of 84,955 patients met inclusion criteria and were assessed for eligibility over the course of the study period. Patients were excluded due to carbapenem-susceptible infection (n=82,260), <2 SIRS criteria (n=1,700), recurrent or polymicrobial infection (n=392), cystic fibrosis (n=91), and lack of treatment prior to discharge (n=64). A total of 448 patients were included in the final analysis, including 124 patients (27.7%) in 2012, 98 patients (21.9%) in 2013, 92 patients (20.5%) in 2014, and 134 patients (29.9%) in 2015. Overall, CRNE infections were more common than CRE infections (75.2% [n=337/448] versus 24.8% [n=111/448] over the 4-year study period. However, a significant shift in the distribution of CRE and CRNE cases occurred from 2012 to 2015 (Figure 1; P<0.001). CRE infections comprised only 13/124 (10.5%) of carbapenem-resistant Gram-negative infections in 2012, but this increased to 56/134 (41.8%) by 2015 (Figure 1).

Baseline characteristics among patients with CRE or CRNE sepsis were compared and multiple factors distinguished these groups of patients (Table 1). Genitourinary infections were significantly more common among patients with CRE sepsis (41.4% [46/111] versus 20.5% [69/337]; P<0.001), whereas respiratory tract infections were significantly more common among patients with CRNE sepsis (26.1% [29/111] versus 49.0% [165/337]; P<0.001; Table 1). Patients with CRE sepsis also experienced significantly longer delays in initiation of appropriate antimicrobial therapy than patients with CRNE sepsis (Table 1). Conversely, patients with CRNE sepsis were significantly more likely be admitted to the ICU, mechanically ventilated, have been previously hospitalized within the preceding 6 months, and have previous antibiotic (including carbapenem) exposure within the preceding 3 months (Table 1).

Overall, hospital mortality was 21.7% (n=97/448). Median duration of hospitalization was 17 days (interquartile range [IQR], 7–34 days) among patients with CRE sepsis and 20 days (IQR, 9–36 days) for those with CRNE sepsis (P=0.267). There was no difference in hospital survival between patients with CRE or CRNE sepsis (Figure 2; HR, 1.29; 95% CI, 0.83–2.02; P=0.285). Factors associated with poorer survival in univariable analysis were increased age, ICU admission, prolonged duration of hospitalization prior to infection,

hospital-acquired infection, prolonged time to appropriate treatment, respiratory tract infection, previous hospitalization within the preceding 6 months, urinary catheterization, prior antibiotic (including carbapenem) exposure within the preceding 3 months, vasopressor requirement, immunosuppression, increased Charlson comorbidity index, and increased APACHE II score. Patients with genitourinary infections had a lower risk of mortality compared to those with other types of infections in univariable analysis.

Multivariable Cox proportional hazards models for hospital survival were derived and are displayed in Table 2. After adjusting for confounding factors, CRNE infection was not associated with a significant difference in hospital survival compared to CRE infection (Table 2, model 1). Factors significantly associated with worse hospital survival (Table 2, model 2) included time to appropriate treatment (HR, 1.01; 95% CI, 1.01–1.02; P=0.13), vasopressor requirement (HR, 9.75; 95% CI, 4.39–21.7; P<0.001), immunosuppression (HR, 1.82; 95% CI, 1.15–2.87; P=0.010), and increased Charlson comorbidity index (HR, 1.14; 95% CI, 1.07–1.21; P<0.001). Genitourinary infection was associated with significantly better survival compared to other types of infection in this model (Table 2, model 2; HR, 0.23; 95% CI, 0.10–0.59; P=0.002). Regarding secondary outcomes, there were no significant differences in early (odds ratio [OR], 1.23; 95% CI, 0.57–2.66; P=0.598), intermediate (OR, 1.27; 95% CI, 0.79–1.82; P=0.385), or late (OR, 1.15; 95% CI, 0.72–1.84; P=0.564) all-cause mortality between patients with CRE versus CRNE sepsis (Table 3).

The majority of CRE infections were caused by *Enterobacter* spp. (38.7% [n=43/111]) and the majority of CRNE infections were caused by *Pseudomonas aeruginosa* (77.4% [n=261/337]). There was a statistically significant increase in CRE infections due to *Enterobacter* spp. (P=0.004) and a significant decrease in CRE infections due to *Klebsiella pneumoniae* (P<0.001) observed over the 4-year study period. Of CRE infections, 29/111 (26.1%) were carbapenemase-producing (CP), including 27 KPC-producing, 1 NDM-producing, and 1 OXA-48-like producing organism. There was no significant difference in hospital survival between patients with sepsis due to CP-CRE versus non-CP-CRE (HR, 1.65; 95% CI, 0.69–3.95; P=0.269) in this cohort. No year-by-year differences in carbapenemase production among CRE were observed over the course of the 4-year study period (P=0.246).

DISCUSSION

In this study of hospitalized patients with carbapenem-resistant Gram-negative sepsis, we identified unique factors distinguishing patients who developed CRE sepsis versus those with CRNE sepsis. Patients with CRE sepsis were more likely to have genitourinary infection, whereas patients with CRNE sepsis were more likely to be admitted to the ICU, have respiratory tract infection, and previous hospitalization and antibiotic exposures. Hospital mortality was slightly higher for patients with CRNE sepsis compared to CRE sepsis, although this did not reach statistical significance. Moreover, the risk of hospital mortality associated with CRNE sepsis was diminished in multivariable analysis adjusting for baseline characteristics. Therefore, any potential differences in outcomes between patients with CRNE sepsis versus those with CRE sepsis would likely be attributable to

other patient-specific characteristics. Delayed time to appropriate antibiotic treatment was the only modifiable factor associated with poorer hospital survival in this cohort of patients with carbapenem-resistant Gram-negative sepsis. Immunosuppression and higher comorbidity burden were also important contributors to poorer hospital survival in the present study.

Although CRE represent a more urgent threat to public health according to the most recent CDC report, 75% of clinically significant carbapenem-resistant Gram-negative infections were caused by CRNE in this study. Thus, the clinical impact of CRNE, particularly carbapenem-resistant *Pseudomonas aeruginosa*, may be underappreciated. Nonetheless, perhaps the most striking finding from the present study was the apparent shift in the burden of carbapenem-resistant Gram-negative disease observed over the 4-year study period. CRNE infections comprised nearly 90% of cases in 2012, but only 60% of cases by 2014. This occurred without an increase in the incidence of carbapenemase production detected by our screening methods. A profound increase in cases of sepsis due to infection with *Enterobacter* spp. was observed over the course of the present study for uncertain reasons. Although the epidemiology of CRE infections can vary widely by geographic region, a recent analysis of national data from the Veterans Health Administration healthcare system noted a significant increase in the incidence of carbapenem-resistant *E. cloacae* from 2006–2015 [26]. Concerns for increased carbapenem resistance among *Enterobacter* spp. have also been raised in multiple reports across distinct regions of the United States [27–29]. Several studies have also reported decreased or stable incidence rates of carbapenem-resistant *K. pneumoniae* infection, which is consistent with our data [26, 27, 30].

The present study is not without limitations which should be considered. This was a retrospective investigation of a single tertiary care academic medical center. Therefore, prior antibiotic exposures and hospitalizations occurring outside our health care system would not have been captured. As the epidemiology of carbapenem-resistant Gram-negative infections varies geographically, our results may not be generalizable to other regions or hospitals with dissimilar patient populations. Additionally, the single-center design limited the number of included cases and we may have been underpowered to detect small differences in risk factors and outcomes between patients with CRE versus CRNE sepsis. Results from microbiological analyses were limited to those provided during routine clinical care and carbapenem minimum inhibitory concentration data were not available. It is difficult to discern active infection from colonization in a large-scale retrospective analysis. We attempted to overcome this by analyzing only patients with signs of sepsis and excluding patients with cystic fibrosis and those who were not treated with antibiotic therapy. Although we expect the degree of any misclassification to be small, we cannot exclude for this possibility. The inclusion and exclusion criteria used may have selected for a more severely ill patient population, although the mortality rates we observed were modest.

CONCLUSIONS

We report significant changes in the epidemiology of carbapenem-resistant Gram-negative sepsis observed from 2012 to 2015 at a single center in the central United States. Infections due to carbapenem-resistant *Enterobacter* spp. are rising, whereas infections due to

carbapenem-resistant *Klebsiella pneumoniae* are decreasing. These changes appear to be occurring in the absence of appreciable increases in the incidence of infection due to carbapenemase-producing organisms. Dramatic increases in the incidence of CRE infection appear to be causing a shift in the burden of clinically significant carbapenem-resistant Gram-negative disease. More extensive infection control and antibiotic stewardship interventions, particularly targeting *Enterobacter* spp., may be needed to curb this worrisome trend. Future research should seek to address these questions in other healthcare settings and geographic regions.

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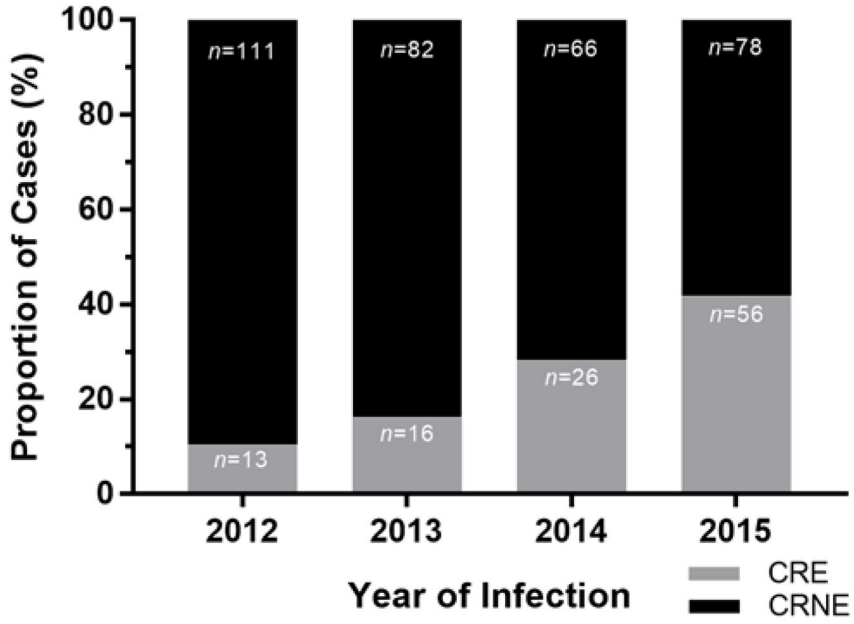

Figure 1. Distribution of carbapenem-resistant Gram-negative sepsis cases by year and organism category

Infections due to carbapenem-resistant non-*Enterobacteriaceae* (CRNE) comprised the majority of sepsis cases from 2012–2015. However, a significant shift in the distribution of carbapenem-resistant *Enterobacteriaceae* (CRE) and CRNE cases occurred from 2012 to 2015 ($P<0.001$).

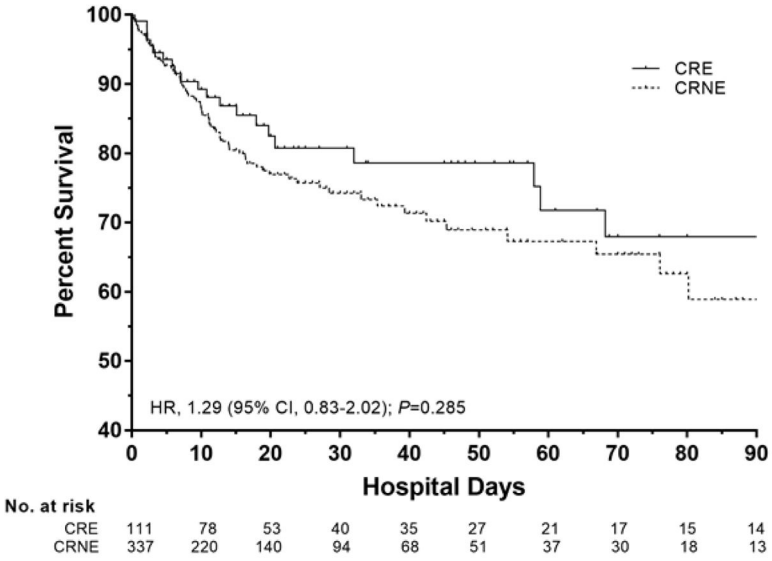

Figure 2. Comparison of hospital survival between patients with carbapenem-resistant *Enterobacteriaceae* (CRE) versus carbapenem-resistant non-*Enterobacteriaceae* (CRNE) sepsis

No difference in hospital survival was observed between patients with CRE sepsis compared to those with CRNE sepsis (hazard ratio [HR], 1.29; 95% confidence interval [CI], 0.83–2.02; *P*=0.285).

Table 1

Baseline characteristics of patients with carbapenem-resistant Gram-negative sepsis

Characteristic (*N*=448)	CRE (*n*=111)	CRNE (*n*=337)	*P*-value
Age (years), median (IQR)	58 (48–65)	58 (46–68)	0.526
Age ≥ 65, *n* (%)	28 (25.2)	111 (32.9)	0.128
Year of infection, *n* (%)	---	---	<0.001
2012	13 (11.7)	111 (32.9)	<0.001
2013	16 (14.4)	82 (24.3)	0.028
2014	26 (23.4)	66 (19.6)	0.385
2015	56 (50.5)	78 (23.1)	<0.001
ICU admission, *n* (%)	46 (41.4)	180 (53.4)	0.029
Length of stay (days)[a], median (IQR)	2.4 (0.2–19.0)	3.4 (0.4–18.0)	0.376
Hospital-acquired[b], *n* (%)	58 (52.3)	203 (60.2)	0.139
Time to appropriate treatment (hours)[c], mean (SD)	36.9 (14.2)	21.4 (14.6)	<0.001
No appropriate treatment[d]	5 (4.5)	10 (3.0)	0.542
Infection type, *n* (%)	---	---	<0.001
Abdominal/gastrointestinal	8 (7.2)	18 (5.3)	0.466
Respiratory tract	29 (26.1)	165 (49.0)	<0.001
Bloodstream/endovascular	14 (12.6)	36 (10.7)	0.575
Genitourinary	46 (41.4)	69 (20.5)	<0.001
Skin/soft tissue/osteomyelitis	14 (12.6)	49 (14.5)	0.561
Previous hospitalization[e], *n* (%)	90 (81.1)	313 (92.9)	<0.001
Invasive surgical procedure[f], *n* (%)	54 (48.6)	170 (50.4)	0.743
Central venous catheter[f], *n* (%)	69 (62.2)	259 (76.9)	0.002
Urinary catheter[f], *n* (%)	76 (68.5)	221 (65.6)	0.576
Other invasive device[f], *n* (%)	25 (22.5)	76 (22.6)	0.995
Mechanical ventilation, *n* (%)	56 (50.5)	225 (67.1)	0.002
Previous antibiotic exposure[g], *n* (%)	78 (70.3)	275 (81.6)	0.011
Carbapenem[g]	36 (32.4)	168 (50.3)	0.001
Vasopressor requirement, *n* (%)	54 (48.6)	171 (50.5)	0.702
Immunosuppression, *n* (%)	45 (40.5)	132 (29.2)	0.798
Solid organ transplantation	8 (7.2)	38 (11.3)	0.221
Stem cell transplantation	7 (6.3)	34 (10.1)	0.231
SIRS criteria, median (IQR)	2 (2–3)	2 (2–3)	0.633
Charlson comorbidity index, median (IQR)	6 (3–8)	6 (4–9)	0.672
APACHE II, median (IQR)	12 (9–16)	13 (9–17)	0.217

CRE, carbapenem-resistant *Enterobacteriaceae*; CRNE, carbapenem-resistant non-*Enterobacteriaceae*; IQR, interquartile range; SD, standard deviation; APACHE II, Acute Physiology and Chronic Health Evaluation II

[a] Prior to index culture

[b] Hospitalized > 48 hours prior to index culture without previous evidence of infection

[c] Treatment with an agent to which the organism was susceptible *in vitro*

[d] No treatment with an agent to which the organism was susceptible *in vitro* prior to patient death

[e] Within the preceding 6 months

[f] During the index hospitalization prior to index culture

[g] Within the preceding 3 months

Table 2

Multivariable Cox proportional hazards models of factors associated with hospital survival in carbapenem-resistant Gram-negative sepsis

Factor (*N*=448)	Adjusted Hazard Ratio (95% CI)	*P*-value
Model 1[b]		
CRNE infection[c]	1.08 (0.62–1.87)	0.799
Length of stay (days)[d]	1.01 (0.98–1.01)	0.052
Genitourinary infection	0.42 (0.16–1.08)	0.071
Mechanical ventilation	3.06 (1.15–8.15)	0.025
Vasopressor requirement	3.98 (1.82–8.72)	0.001
Immunosuppression	1.51 (0.96–2.37)	0.072
Charlson comorbidity index	1.13 (1.07–1.20)	<0.001
Model 2[e]		
Time to appropriate treatment (hours)[f]	1.01 (1.01–1.02)	0.013
Genitourinary infection	0.23 (0.10–0.59)	0.002
Vasopressor requirement	9.75 (4.39–21.7)	<0.001
Immunosuppression	1.82 (1.15–2.87)	0.010
Charlson comorbidity index	1.14 (1.07–1.21)	<0.001

CI, confidence interval; CRNE, carbapenem-resistant non-*Enterobacteriaceae*

[a] Hazard ratio > 1 indicates poorer survival

[b] Variables considered for inclusion in multivariable model: age, age ≥ 65, year of infection, intensive care unit admission, time to appropriate therapy, length of stay prior to infection, hospital-acquired infection, infection type, previous hospitalization, previous antibiotic (including carbapenem) use, central venous catheter, urinary catheter, mechanical ventilation, vasopressor requirement, immunosuppression, Charlson comorbidity index, Acute Physiology and Chronic Health Evaluation (APACHE) II score

[c] Variable forced into model

[d] Prior to index culture

[e] Variables considered for inclusion in multivariable model: age, age ≥ 65, intensive care unit admission, time to appropriate therapy, length of stay prior to infection, hospital-acquired infection, infection type, previous hospitalization, previous antibiotic (including carbapenem) use, urinary catheter, mechanical ventilation, vasopressor requirement, immunosuppression, Charlson comorbidity index, APACHE II score

[f] Treatment with an agent to which the organism was susceptible *in vitro*

Table 3

Comparison of early (7-day), intermediate (28-day), and late (90-day) all-cause mortality endpoints among patients with carbapenem-resistant Gram-negative sepsis

Outcome (*N*=448), *n* (%)	**CRE (*n*=111)**	**CRNE (*n*=337)**	**Odds Ratio (95% CI)**	***P*-value**
Early mortality	9 (8.1)	33 (9.8)	1.23 (0.57–2.66)	0.598
Intermediate mortality	21 (18.9)	77 (22.8)	1.27 (0.79–1.82)	0.385
Late mortality	32 (28.8)	107 (31.8)	1.15 (0.72–1.84)	0.564

CRE, carbapenem-resistant *Enterobacteriaceae*; CRNE, carbapenem-resistant non-*Enterobacteriaceae*