Comparing the Outcomes of Patients with Carbapenemase-Producing and Non-Carbapenemase-Producing Carbapenem-Resistant *Enterobacteriaceae* Bacteremia

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Running title: Mortality with CP-CRE bacteremia

40-word summary: In a cohort of 83 CRE bacteremic patients, the odds of dying within 14 days were four times greater for carbapenemase-producing (CP) CRE compared with non-CP-CRE patients, adjusting for severity of illness, underlying medical conditions, and differences in antibiotic regimens.

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Abstract

Background: Carbapenem-resistant *Enterobacteriaceae* (CRE) are associated with considerable mortality. As mechanisms of carbapenem resistance are heterogeneous, it is unclear if mortality differs based on resistance mechanisms. Our objective was to evaluate whether CRE resistance mechanism determination is prognostically informative.

Methods: We conducted an observational study of patients comparing 14-day mortality between patients with carbapenemase-producing (CP)-CRE compared with non-CP-CRE bacteremia. Extensive clinical data were collected on all patients. A comprehensive DNA microarray-based assay was performed on all isolates to identify β-lactamase-encoding genes.

Results: There were 83 unique episodes of monomicrobial CRE bacteremia during the study period: 37 (45%) CP-CRE and 46 (55%) non-CP-CRE episodes. The majority of CP-CRE isolates were *bla*$_{\text{KPCs}}$ (92%), followed by *bla*$_{\text{NDMs}}$ (5%) and *bla*$_{\text{OXA-48-type}}$ (3%). CP-CRE isolates were more likely to demonstrate meropenem MICs of ≥16 mcg/ml, while non-CP-CRE isolates were more likely to have meropenem MICs of ≤1 mcg/ml (both p-values <0.001). A total of 18 (22%) patients died within 14 days, including 12 (32%) in the CP-CRE group and 6 (13%) in the non-CP-CRE group. Adjusting for severity of illness on day 1 of bacteremia, underlying medical conditions, and differences in antibiotic treatment administered, the odds of dying within 14 days were more than four times greater for CP-CRE compared with non-CP-CRE bacteremic patients (aOR 4.92; 95% CI 1.01-24.81).

Conclusion: Our findings suggest that CP-CRE may be more virulent than non-CP-CRE and are associated with poorer outcomes. This underscores the added importance of delineating underlying resistance mechanisms of CRE to direct antibiotic treatment decisions.

Key words: KPC; carbapenemases; CRE; MDRGN

Introduction

Resistance to carbapenem antibiotics is recognized globally as one of the most pressing concerns facing the healthcare community[1]. Carbapenem-resistant *Enterobacteriacea*e (CRE) bacteremia is associated with considerable mortality, approaching 60% in published studies[2-14]. Mechanisms of carbapenem resistance are heterogeneous: chiefly, resistance can be mediated via carbapenemase production (CP-CRE) or via production of extended-spectrum β-lactamases (ESBLs) and/or AmpC cephalosporinases (AmpC) combined with altered membrane permeability (non-CP-CRE)[15]. Available studies evaluating outcomes associated with CRE bacteremia generally analyze CRE as a single composite category without discriminating between underlying resistance mechanisms[2,4,5,10]. To date, there have been no studies comparing the clinical outcomes of CP-CRE and non-CP-CRE bacteremia.

Understanding the implications of CRE resistance mechanism heterogeneity has assumed newfound clinical relevance as reliable phenotypic and genotypic carbapenemase assays are increasingly becoming available. Clear differences in outcomes between CP-CRE and non-CP-CRE infections would underscore the importance of delineating underlying resistance mechanisms in CRE as this may impact antibiotic treatment decisions (e.g., prioritizing who should receive newer CP-CRE active antibiotic agents). Conversely, if differences do not exist, then additional resistance testing may not be necessary to guide the clinical management of patients. Our objective was to compare mortality in patients with CP-CRE and non-CP-CRE bacteremia in order to evaluate whether CRE resistance mechanism determination is prognostically informative.

Methods

Study population. We conducted a retrospective, observational cohort study including 83 unique patients with monomicrobial CRE bacteremia who were hospitalized at The Johns Hopkins Hospital between March 2013 and April 2016. Six patients with CRE in their bloodstream during this time period were excluded as their clinical isolates could not be located for additional genotypic testing. Patient data were collected via chart review, including the following: demographics, preexisting medical conditions, source of bacteremia and source control measures, microbiological data, antibiotic therapy, and outcomes data. Source control was defined as the removal of infected hardware or drainage of infected fluid collections within the first 7 days of receiving antibiotic therapy. Consistent with the current United States Centers for Disease Control and Prevention (CDC) definition, ‘CRE’ was defined as an

Enterobacteriaceae isolate demonstrating resistance to any carbapenem (ertapenem, meropenem, imipenem, and/or doripenem), based upon antimicrobial susceptibility testing (AST).

Active empiric antibiotic therapy was defined as at least one antibiotic with *in vitro* activity, based on AST against the isolate within 24 hours of the time the first positive blood culture was obtained. For meropenem minimum inhibitory concentrations (MICs) of ≤4 mcg/ml, standard-infusion meropenem administered at 2 grams every 8 hours was considered active based on existing pharmacokinetic-pharmacodynamic studies[16,17]. Meropenem treatment for MICs of 8 mcg/ml was considered active if extended-infusion meropenem (2 grams every 8 hours over at least 3 hours) was administered, as modeling of extended-infusion strategies suggest that reasonable target attainment can be anticipated with meropenem MICs of up to 8 mcg/ml, and possibly 16 mcg/ml[16,17]. Active directed antibiotic therapy was defined as at least one antibiotic with *in vi*tro activity against the isolate any time after AST results were available, up to 7 days after the first positive blood culture was obtained.

The primary exposure was identification of a CP-CRE via carbapenemase gene detection in a CRE isolate. The primary outcome was 14-day mortality, with day 1 as the day the first positive blood culture was collected. Fourteen-day mortality was selected as the primary endpoint, as it was thought to be most reflective of death attributable to CRE bacteremia. Secondary outcomes included 30-day mortality and 30-day recurrence of CRE bacteremia. This study was approved by the Johns Hopkins University School of Medicine Institutional Review Board, with a waiver of informed consent.

Resistance Mechanism Identification. Bacterial genus, species, and AST results were identified using matrix-assisted laser-desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics Inc., Billerica, MA) and the BD Phoenix Automated System (BD Diagnostics, Sparks, Maryland). For isolates demonstrating resistance to any carbapenem antibiotic, using the Clinical Laboratory and Standards Institute criteria, carbapenem MICs were confirmed with Etests (bioMérieux, Durham, North Carolina). Carbapenem resistance was defined as an ertapenem MIC ≥2 mcg/ml and meropenem, and/or imipenem MIC ≥4 mcg/ml.

Genomic DNA was extracted from isolates using the DNeasy Blood & Tissue Kit (QIAGEN, Inc., Valencia, California). Identification of β-lactamase-encoding genes was assessed utilizing a

comprehensive DNA microarray-based assay, the Check-MDR CT103XL kit (CheckPoints, Wageningen, Netherlands). The CheckPoints assay can detect the following plasmid-mediated β-lactamase genes: (1) Extended-spectrum β-lactamases (ESBLs): *bla*$_{\text{CTX-M-1 group}}$, *bla*$_{\text{CTX-M-1-like}}$, *bla*$_{\text{CTX-M-15-like}}$, *bla*$_{\text{CTX-M-32-like}}$, *bla*$_{\text{CTX-M-2 group}}$, *bla*$_{\text{CTX-M-8, \&-25 group}}$, *bla*$_{\text{CTX-M-9 group}}$, *bla*$_{\text{TEM-types}}$, *bla*$_{\text{SHV-types,}}$ *bla*$_{\text{VEB}}$, *bla*$_{\text{PER}}$, *bla*$_{\text{BEL}}$, *bla*$_{\text{GES}}$; (2) plasmid-mediated AmpC cephalosporinases (pAmpCs): *bla*$_{\text{CMY I/MOX}}$, *bla*$_{\text{ACC}}$, *bla*$_{\text{DHA}}$, *bla*$_{\text{ACT/MIR}}$, *bla*$_{\text{CMY II}}$, *bla*$_{\text{FOX}}$; and (3) carbapenemases: *bla*$_{\text{KPC}}$, *bla*$_{\text{NDM}}$, *bla*$_{\text{VIM}}$, *bla*$_{\text{IMP}}$, *bla*$_{\text{GES}}$, *bla*$_{\text{GIM}}$, *bla*$_{\text{SPM}}$, and *bla*$_{\text{OXA-48-like,}}$ *bla*$_{\text{OXA-23-like}}$, *bla*$_{\text{OXA-24/40-like}}$, *bla*$_{\text{OXA-58-like}}$. The modified Hodge test (MHT), metallo-β-lactamase (MβL) Etest (imipenem/imipenem & EDTA; bioMérieux), and the Carba NP test were performed on all isolates to determine if there were any bacteria that appeared to produce carbapenemases by phenotypic methods but were negative by genotypic methods, or vice versa.

Of note, the MHT was performed on CRE isolates during the study period to distinguish CP-CRE and non-CP-CRE for infection control purposes, but The Johns Hopkins Hospital Antibiotic Treatment Guidelines[18] do not differentiate treatment recommendations for CP-CRE and non-CP-CRE. All molecular testing, as well as the MβL Etest, Carba NP test, and a repeat MHT test, was performed retrospectively. Clinicians were unaware of carbapenemase gene results when selecting antibiotic therapy for CRE bacteremic patients.

Statistical Methods. Descriptive statistics for patient variables were calculated using median (interquartile range) or frequency count (percentage), as appropriate. Comparisons between CP-CRE and non-CP-CRE groups were made using the Wilcoxon-Mann-Whitney test for continuous variables, and the Pearson χ^2 test and Fisher's exact test, for cells with a frequency of five or fewer, for categorical variables. The relationship between carbapenemase status and study outcomes was evaluated using univariable logistic regression, as summarized by odds ratios and corresponding 95% confidence intervals. *A priori* confounders to be included in the multivariable model for the primary outcome were day 1 Pitt bacteremia score ≥4[19], receipt of combination antibiotic therapy, receipt of active *in vitro* empiric antibiotic therapy, and receive of active *in vitro* directed antibiotic therapy. Covariates found to have a p-value <0.10 on univariable analysis and that resulted in a 10% or greater change in the parameter estimate of the CP-CRE group were retained in the final multivariable logistic regression models for each of the outcomes. All tests were 2-tailed and p-values ≤0.05 were used for statistical significance testing. Analyses were performed using the STATA 13.0 (Stata Corp) statistical package.

Results

Microbiological Characteristics. There were a total of 83 unique episodes of monomicrobial CRE bacteremia during the study period: 37 (45%) CP-CRE and 46 (55%) non-CP-CRE episodes (Table 1). Although the ratio of CP-CRE and non-CP-CRE bacteremia across the study years was relatively constant, the overall proportion of CRE bacteremia steadily increased and more than tripled over the study period: 2.01 per 100, 3.66 per 100, 6.50 per 100, and 7.00 per 100 episodes of *Enterobacteriaceae* bacteremia episodes in 2013, 2014, 2015, and 2016, respectively. The AST results for CRE bloodstream isolates are displayed in Table 2.

For CP-CRE bacteremic isolates, the predominant genus and species were *Klebsiella* spp. (76%) and *Enterobacter* spp. (19%); there was one (3%) isolate each of *Escherichia coli* and *Citrobacter amalonaticus*. For non-CP-CRE, the genus and species distribution was slightly more diverse but largely reversed: 59% *Enterobacter* spp., 30% *Klebsiella* spp., 7% *E. coli*, and one each (2%) of *Proteus mirabilis* and *Serratia marcescens*. The majority of CP-CRE isolates were bla_{KPC} (92%), followed by bla_{NDM} (5%) and $bla_{OXA\text{-}48\text{-}type}$ (3%) (Table 1). CP-CRE isolates were more likely to require meropenem MICs of ≥ 16 mcg/ml for growth inhibition while non-CP-CRE isolates were more likely to require meropenem MICs of ≤ 1 mcg/ml (both p-values <0.001), Table 2.

For 21 isolates categorized in the non-CP-CRE group, no plasmid-mediated β-lactamase gene (i.e., carbapenemase, ESBL, pAmpC) was identified. The CheckPoints assay was repeated on these isolates by different trained users with consistent results. These isolates also yielded negative results by MHT, MβL Etest, and the Carba NP test, indicating they were unlikely to be carbapenemase-producing. The organisms involved were as follows: *Enterobacter* spp. (n=16), *K. pneumoniae* (n=3), *S. marcescens* (n=1), and *P. mirabilis* (n=1). The median meropenem MIC for this group was 1 mcg/ml (IQR 1-2 mcg/ml), meeting criteria for carbapenem resistance generally because of ertapenem resistance.

Baseline and Treatment Characteristics. The CP-CRE and non-CP-CRE groups were well-balanced on demographic information and most pre-existing medical conditions (Table 3). CP-CRE patients were less likely to receive active empiric antibiotic therapy compared with patients with non-CP-CRE bacteremia, although this difference did not achieve statistical significance (32% vs. 52%, p=0.07). Excluding the nine patients who expired within three days of bacteremia onset, before AST results would have become available to treating clinicians, patients with CP-

CRE were less likely to receive active directed antibiotic therapy compared with patients in the non-CP-CRE group (84% vs. 100%; p=0.01). A carbapenem-containing regimen was administered to 62% and 76% (p=0.17) patients in the CP-CRE and non-CP-CRE groups, respectively. All patients in the cohort who received meropenem received 2 grams every 8 hours, in compliance with The Johns Hopkins Antibiotic Treatment Guidelines. Additionally, all patients with meropenem MICs of 8 mcg/ml or higher who received meropenem, received it as an extended-infusion. CP-CRE bacteremic patients were more likely to receive combination antibiotic therapy (78% vs. 30%, p<0.001), and for a longer duration of time. CP-CRE and non-CP-CRE patients received combination therapy for a median of 5 (IQR: 1-13) and 0 (IQR: 0-2) days, respectively (p<0.001). Empiric and directed antibiotic regimens are described in Supplemental Table 1.

14-day and 30-day Mortality. A total of 18 (22%) patients died within 14 days, including 12 (32%) in the CP-CRE group and 6 (13%) in the non-CP-CRE group. No correlation was observed with increasing meropenem MICs and mortality (Table 3). In univariable logistic regression analysis, the odds of dying within 14 days were more than three times greater for CP-CRE compared with non-CP-CRE bacteremic patients (OR 3.20; 95% CI, 1.07–9.61), Table 4. Decreased survival in the CP-CRE group persisted after adjusting for Pitt bacteremia score ≥4, active empiric therapy, and active directed therapy, days of combination antibiotic therapy, diabetes, and polymixin therapy (aOR 4.92; 95% CI 1.01-24.81). In addition, Pitt bacteremia score ≥4 and polymixin therapy remained independent predictors of 14-day mortality (aOR 11.89; 95% CI 2.38-59.30 and aOR 5.57; 95% CI 1.07-28.96). Each additional day of combination antibiotic therapy was associated with a 27% decreased odds of death within 14 days. Of note, mortality differences at 30 days were also higher in the CP-CRE group (aOR=3.19, 95% CI: 0.99 – 10.25; p=0.05).

Because of the notable differences in MIC distributions and *in vitro* activity of the empiric and directed antibiotic regimens between the CP-CRE and non-CP-CRE groups, we repeated the analysis restricting the cohort to patients infected with CRE bacteremia with meropenem MICs ≤4 mcg/ml. There were 7 (35%) deaths and 6 (14%) deaths in the CP-CRE and non-CP-CRE groups within 14 days (and 9 (45%) and 8 (18%) deaths within 30 days). All patients in this restricted cohort who survived until day 3 received appropriate directed antibiotic therapy so this variable was no longer included in the multivariable analysis. Adjusting for receipt of active empiric therapy and Pitt bacteremia score ≥4, the aOR was 3.39 times higher (95% CI 0.85-

12.80; p=0.08) and 3.79 times higher (95% CI 1.02-14.02; p=0.04) for the CP-CRE group when evaluating 14-day and 30-day mortality, respectively.

30-day Recurrent CRE Bacteremia. Excluding the 20 patients who died within 30 days, without first experiencing a bacteremia recurrence, there were 12 episodes of recurrent CRE bacteremia within 30 days: 9 (38%) and 3 (8%) in the CP-CRE and non-CP-CRE groups, respectively (p=0.003). After adjusting for receipt of active empiric therapy and active directed therapy, CP-CRE patients remained at increased odds of bacteremia recurrence within 30 days, relative to non-CP-CRE patients (OR= 2.67, 95% CI: 0.54-13.2). No other variables in multivariable analysis were independently associated with CRE bacteremia recurrence within 30 days.

Discussion

Our results suggest that patients with CP-CRE bacteremia have about 4 times the odds of dying within 14 days compared to patients with non-CP-CRE bacteremia after accounting for severity of illness on day 1 of bacteremia, underlying medical conditions, and antibiotic treatment administered. These findings suggest that CP-CRE isolates may be more virulent than non-CP-CRE mechanisms of resistance. As more antibiotic agents with activity against CP-CRE are in advanced phases of drug development[20], distinguishing CP-CRE from non-CP-CRE will be increasingly important as patients infected with the former should be prioritized for these newer agents. Rather, if these newer agents are indiscriminately prescribed for patients infected with CRE, increasing resistance to these agents, rendering them ineffective, may result.

Previous studies have demonstrated mortality from CRE bacteremia ranging from approximately 20% to 70%[2-14]. Considerable variability in definitions of carbapenem-resistance, limited to no description of the mechanisms of carbapenem resistance included, variability in treatment administered, differences in casemix data, and variability in outcome definitions, make comparisons between studies difficult. Villegas and colleagues previously compared clinical outcomes of patients with CP bacteremia and non-CP bacteremia in a multicenter, observational study across 7 Latin American countries[21]. They found that patients with CP bacteremia had four times the odds of death within 28 days compared with non-CP bacteremia. However, over 90% of patients in the non-CP group had isolates susceptible to carbapenems using the current CLSI breakpoints. To our knowledge, no previous studies have compared outcomes of patients with CP-CRE and non-CP-CRE bacteremia.

The aggressiveness of CP-CRE pathogens is highlighted by their ability to hydrolyze carbapenems to a greater extent compared with non-CP-CRE. There were notable differences in the carbapenem MIC distributions in our cohort. For example, CP-CRE were more likely to have meropenem MICs ≥16 mcg/ml compared with non-CP-CRE isolates (38% vs. 2%). CP-CRE were also less likely to be susceptible to other non-β-lactam agents considered for the treatment of CRE such as aminoglycosides, fluoroquinolones, tigecycline, and polymixins. Because of these resistance profiles, empiric therapy regimens were less likely to be active against CP-CRE isolates. Additionally, clinicians were more likely to resort to agents like polymixins and tigecycline as directed therapy for CP-CRE bacteremia. Because of the substantial differences in MIC distributions between CP-CRE and non-CP-CRE and differences in the *in vitro* activity of the antibiotic regimens prescribed, we repeated the analysis limiting inclusion to patients with meropenem MICs ≤4 mcg/ml and still observed differences in mortality between CP-CRE and non-CP-CRE. This suggests that underlying microbial characteristics may have an important role in poor outcomes of patients with CP-CRE infections.

For 21 patients categorized in the non-CP-CRE group growing *Enterobacter* spp., *K. pneumoniae*, *S. marcescens*, and *P. mirablis*, no plasmid-mediated β-lactamase gene was identified. Like all molecular methods, this assay can only recognize β-lactamase genes that have been previously characterized and would be unable to identify new targets. However, the CheckPoints assay used in this study includes a comprehensive group of narrow spectrum β-lactamases, ESBLs, pAmpCs, and carbapenemases and it would be unlikely that a large number of novel, unrelated (as AST patterns differed in these 21 isolates) β-lactamase genes were present. Additionally, MHT, MβL Etest, and Carba NP testing were negative suggesting these isolates were unlikely to harbor carbapenemases. Rather, we suspect that the most likely explanation was the induction of the chromosomally-mediated AmpC cephalosporinases in addition to outer membrane protein mutations - particularly as 76% of these isolates were *Enterobacter* spp., the organisms most commonly associated with chromosomally-mediated AmpC inducible resistance. The chromosomal *ampC* gene is not included in the Check-MDR CT103XL assay. a*mpC* genes have also been identified with other *Enterobacteriaceae*[22], including *S. marcensens*[23]. Another β-lactamase that has been produced by *Klebsiella* spp. and not present in the Check-MDR CT103XL panel are the chromosomal K1 β-lactamase genes, $bla_{\text{OXY-1}}$ and $bla_{\text{OXY-2}}$[24,25]. As whole genome sequencing was not performed on these 21 isolates, we cannot say with any certainty what the mechanisms of carbapenem resistance were, but feel

that misclassification bias was unlikely based on the negative CheckPoints, MHT, MβL, Carba NP, and meropenem MIC results of these isolates.

There are several limitations with this work. First, although we attempted to include all variables that have been previously identified as associated with poor outcomes for patients with CRE bacteremia, we cannot exclude the possibility that there was residual confounding that we did not account for which influenced treatment outcomes between CP-CRE and non-CP-CRE cases. Second, our limited sample size precluded exploration of certain subgroup analyses, such as differences that may exist due to bacterial genus and species, differences in carbapenemase-specific genes, differences in polymixin dosing. Additionally, this work included patients from a single center in the United States. Although we anticipate that our carbapenemase-gene distribution will be similar to most US institutions (i.e., mainly bla_{KPCs})[26], they will differ from other regions of the world where bla_{NDM} or $bla_{OXA\text{-}48\text{-}types}$ predominate[1], compromising generalizability. We encourage others to repeat these analyses with a larger cohort to both explore these lingering issues and to determine if our results are reproducible. Finally, we did not characterize the plasmids carrying the β-lactamase genes identified in this study. It is possible that these plasmids may harbor virulence characteristics that are independent of the actual carbapenemase genes, resulting in poorer outcomes of patients with non-CP-CRE infections. Future work characterizing the associated plasmids will be helpful to explore this hypothesis.

These limitations notwithstanding, our findings suggest that bacteremia due to CP-CRE may be independently associated with unfavorable patient outcomes, compared with non-CP-CRE bacteremia. Determining solely whether a clinical isolate is carbapenem resistant, as is the practice at most US healthcare institutions, may not be sufficient. Rather, understanding whether isolates are carbapenemase-producers may be necessary to guide treatment decisions. This is particularly relevant as newer agents with activity against CP-CRE are anticipated to be available in upcoming years and must be prioritized for patients infected with pathogens with confirmed carbapenemase-production. It may be some time before rapid, accurate, user-friendly, and affordable options for detecting the comprehensive list of carbapenemase genes present in common *Enterobaceriaceae* become available to the average diagnostic laboratory. However, we believe our work gives credence to the potential for precision medicine, the approach for disease treatment that accounts for individual variability in

genes, amongst other unique patient characteristics, to ultimately result in improved patient outcomes.

NOTES

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Disclosures

None of the authors report any conflicts of interest.

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Table 1: Identification of β-lactamase genes in 83 carbapenem-resistant *Enterobacteriaceae* (CRE) bloodstream isolates including both carbapenemase-producing (CP) and non-carbapenemase-producing (non-CP-CRE) isolates

	Type of plasmid-mediated β-lactamase	CP-CRE bloodstream isolates (n=37)	non-CP CRE bloodstream isolates (n=25)[1]
Class A			
bla$_{\text{TEM wild type}}$	Narrow spectrum β-lactamase	--	5
bla$_{\text{TEM}}$, *bla*$_{\text{ACT/MIR}}$	ESBL + AmpC	--	2
bla$_{\text{SHV wild type}}$	Narrow spectrum β-lactamase	--	2
bla$_{\text{SHV}}$, *bla*$_{\text{ACT/MIR}}$	ESBL + AmpC	--	1
bla$_{\text{SHV}}$, *bla*$_{\text{DHA}}$	ESBL + AmpC	--	1
bla$_{\text{CTX-M}}$, *bla*$_{\text{SHV}}$	ESBL	--	3
bla$_{\text{TEM wild type}}$, *bla*$_{\text{SHV wild type}}$	Narrow spectrum β-lactamase	--	1
bla$_{\text{TEM}}$, *bla*$_{\text{CTX-M}}$, *bla*$_{\text{SHV}}$	ESBL	--	4
bla$_{\text{KPC}}$	Carbapenemase	3	--
bla$_{\text{KPC}}$, *bla*$_{\text{TEM}}$, *bla*$_{\text{CTX-M}}$, *bla*$_{\text{SHV}}$	ESBL + Carbapenemase	7	--
bla$_{\text{KPC}}$, *bla*$_{\text{CTX-M}}$, *bla*$_{\text{SHV}}$	ESBL + Carbapenemase	3	--
bla$_{\text{KPC}}$, *bla*$_{\text{SHV}}$, *bla*$_{\text{TEM}}$	ESBL + Carbapenemase	7	--
bla$_{\text{KPC}}$, *bla*$_{\text{ACT/MIR}}$	AmpC + Carbapenemase	1	--
bla$_{\text{KPC}}$, *bla*$_{\text{ACT/MIR}}$, *bla*$_{\text{TEM}}$	ESBL + AmpC + Carbapenemase	1	--
bla$_{\text{KPC}}$, *bla*$_{\text{ACT/MIR}}$, *bla*$_{\text{CMY II}}$, *bla*$_{\text{SHV}}$, *bla*$_{\text{TEM}}$	ESBL + AmpC + Carbapenemase	1	--
bla$_{\text{KPC}}$, *bla*$_{\text{TEM}}$	ESBL + Carbapenemase	3	--
bla$_{\text{KPC}}$, *bla*$_{\text{SHV}}$	ESBL + Carbapenemase	8	--
Class B			--
bla$_{\text{NDM}}$, *bla*$_{\text{TEM}}$, *bla*$_{\text{CTX-M}}$, *bla*$_{\text{SHV}}$	ESBL + Carbapenemase	1	--
bla$_{\text{NDM}}$, *bla*$_{\text{DHA}}$, *bla*$_{\text{CTX-M}}$, *bla*$_{\text{SHV}}$	ESBL + AmpC +Carbapenemase	1	--
Class C			
bla$_{\text{CMY}}$	AmpC	--	1
bla$_{\text{ACT/MIR}}$	AmpC	--	5
Class D			
bla$_{\text{OXA-48-type}}$, *bla*$_{\text{CTX-M}}$, *bla*$_{\text{SHV}}$, *bla*$_{\text{TEM}}$		1	--

[1]No β-lactamase genes identified in 21 isolates including *Enterobacter* spp. (n=16), *Klebsiella pneumoniae* (n=3), *Serratia marcescens* (n=1), and *Proteus mirabilis* (n=1).

Table 2: Antibiogram evaluating percentage of carbapenem resistant *Enterobacteriaceae* isolates susceptible to various antibiotics using the Clinical Laboratory and Standards Institute criteria for antibiotic susceptibility

Plasmid-mediated β-lactamase genes identified	**Piperacillin-tazobactam** ≤16 mcg/mL	**Ceftriaxone** ≤1 mcg/mL	**Cefepime** ≤8 mcg/mL	**Aztreonam** ≤4 mcg/mL	**Ertapenem** ≤0.5 mcg/mL	**Meropenem** ≤1 mcg/mL	**Imipenem** ≤1 mcg/mL	**Gentamicin** ≤4 mcg/mL	**Tobramycin** ≤4 mcg/mL	**Amikacin** ≤16 mcg/mL	**Ciprofloxacin** ≤1 mcg/mL	**Tigecycline** ≤2 mcg/mL	**Colistin** ≤2 mcg/mL
Carbapenemase-producing carbapenem resistant *Enterobacteriaceae*													
bla$_{KPC}$ (n=32)	0	0	23	6	0	41	30	38	19	84	23	58	75
bla$_{NDM}$ (n=2)	0	0	0	50	0	0	0	100	0	100	0	50	100
bla$_{OXA-48-type}$ (n=1)	0	0	0	100	0	0	0	0	0	0	0	100	100
Non-carbapenemase-producing carbapenem resistant *Enterobacteriaceae*													
None identified[1] (n=21)	9	5	79	14	0	90	71	95	86	95	71	100	100
Narrow or extended-spectrum β-lactamase (n=17)	0	6	35	19	0	41	55	71	59	100	35	89	100
AmpC β-lactamase (n=8)	33	0	88	25	0	100	50	100	100	100	88	100	100
ESBL + AmpC (n=2)	0	0	50	0	0	50	0	50	50	100	0	100	100

[1]The majority of these are presumed to be derepressed chromosomally-mediated *ampC* β-lactamases

Table 3: Baseline characteristics of patients and clinical isolates with carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* (CP-CRE) and non-carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* (non-CP-CRE) bacteremia

Variables	**CP-CRE (n=37; 45%)**	**Non-CP-CRE (n=46; 55%)**	**P-value**
Age (median, IQR)	58 (48 – 68)	58 (43 – 62)	0.24
Male (n, %)	22 (59%)	29 (63%)	0.74
Race/ethnicity			
White	16 (43%)	25 (54%)	0.32
Black	15 (41%)	19 (41%)	0.94
Asian	2 (5%)	1 (2%)	0.58
Latino	2 (5%)	1 (2%)	0.58
Middle Eastern	2 (5%)	0 (0%)	0.20
Pitt bacteremia score ≥4 on day 1	20 (54%)	18 (39%)	0.19
Intensive care unit, day 1	23 (62%)	24 (52%)	0.36
Likely source of bacteremia			
Central-line associated	9 (24%)	7 (15%)	0.30
Urinary tract	5 (14%)	7 (15%)	1.00
Biliary	1 (3%)	4 (9%)	0.36
Intra-abdominal	16 (43%)	22 (48%)	0.68
Pneumonia	2 (5%)	3 (7%)	1.00
Skin and soft tissue	2 (5%)	2 (4%)	1.00
Osteoarticular	2 (5%)	1 (2%)	0.58
Inappropriate source control during therapy[1]	2 (5%)	1 (2%)	0.43
Pre-existing medical conditions			
Diabetes	12 (32%)	6 (13%)	0.03
End-stage liver disease	3 (8%)	6 (13%)	0.73
End-stage renal disease	3 (8%)	2 (4%)	0.65
Structural lung disease	2 (5%)	1 (2%)	0.58
Congestive heart failure	3 (8%)	3 (7%)	1.00
Immunocompromised[2]	12 (32%)	23 (50%)	0.11
Solid organ transplant	4 (11%)	6 (13%)	1.00
Hematopoietic stem cell transplantation within the previous 12 months	2 (5%)	1 (2%)	0.58
Chemotherapy within the previous 6 months	6 (16%)	13 (28%)	0.19
Human immunodeficiency virus infection	0 (0%)	2 (4%)	0.50
Immunomodulator therapy within the previous 30 days	0 (0%)	3 (7%)	0.25
Chronic corticosteroid therapy	0 (0%)	1 (2%)	1.00
Absolute neutrophil count <200 cells/ml on day 1 of bacteremia	5 (14%)	5 (11%)	0.75
Days of combination antibiotic therapy (median, IQR)	5 (1 – 13)	0 (0 – 2)	<0.001
Carbapenem-containing regimen administered as directed therapy	31 (84%)	44 (95%)	0.13
Polymixin therapy administered as directed therapy	8 (22%)	8 (18%)	0.78
Empiric[3] antibiotic therapy active *in vitro*	12 (32%)	24 (52%)	0.07
Directed[4] antibiotic therapy active *in vitro*	27 (84%)	46 (100%)	<0.001
Meropenem minimum inhibitory concentration (MIC)			
Meropenem MIC ≤1 mcg/ml	13 (36%)	35 (76%)	<0.001
Meropenem MIC 2 mcg/ml	4 (11%)	4 (9%)	1.00
Meropenem MIC 4 mcg/ml	3 (8%)	4 (9%)	1.00
Meropenem MIC 8 mcg/ml	3 (8%)	2 (4%)	0.65
Meropenem MIC ≥16 mcg/ml	14 (38%)	1 (2%)	<0.001

[1]Inappropriate source control was defined as retained infected hardware or lack of drainage of infected fluid collections within the first 7 days of antibiotic therapy.

[2]"Immunocompromised" is a composite category of conditions listed below it; conditions below it are not mutually exclusive

[3]At least one antibiotic demonstrating *in vitro* activity to the isolate recovered within 24 hours of the time the first positive blood culture was obtained; meropenem MICs up to 8 mcg/ml considered active *in vitro* as modeling of extended infusion-strategies suggest that reasonable target attainment can be anticipated with MICs up to 8-16 mcg/ml

[4]At least one antibiotic demonstrating *in vitro* activity to the isolate any time after antibiotic susceptibility results were available, up to 7 days after the first positive blood culture was obtained; meropenem MICs up to 8 mcg/ml were considered *active in vitro* (excluding 5 patients in the CP-CRE group and 4 patients in the non-CP-CRE group who died in the first 72 hours, before antibiotic susceptibility test would have returned)

Table 4: Fourteen-day mortality for patients with carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* (CP-CRE) compared with non-carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* (non-CP-CRE) bacteremia

	Odds Ratio (95% CI)	**p-value**	**Adjusted Odds Ratio**[1] (95% CI)	**p-value**
CP-CRE bacteremia	3.20 (1.06-9.61)	0.04	4.92 (1.01-24.81)	0.05
Pitt bacteremia score ≥4	9.13 (2.39-34.86)	0.001	11.89 (2.38-59.30)	0.005
Active empiric antibiotic therapy	0.79 (0.27-2.29)	0.67	2.46 (0.53-11.48)	0.25
Active directed antibiotic therapy	0.17 (0.04-0.72)	0.01	0.10 (0.004-2.22)	0.14
Days of combination antibiotic therapy	0.89 (0.79-1.00)	0.07	0.73 (0.59-0.93)	0.01
Polymixin therapy administered	4.61 (1.16-18.3)	0.03	5.57 (1.07-28.96)	0.04
Diabetes	3.12 (0.99-9.84)	0.05	3.42 (0.62-19.07)	0.16
Immunocompromised	0.45 (0.14-1.40)	0.17	--	--
Carbapenem therapy administered	0.82 (0.27-2.52)	0.74	--	--
Meropenem MIC ≥16 mcg/ml	1.40 (0.38-5.01)	0.61	--	--

[1]Potential confounders identified *a priori* to include in the multivariable model were day 1 Pitt bacteremia score ≥4, receipt of combination antibiotic therapy, receipt of active *in vitro* empiric antibiotic therapy, and receipt of active *in vitro* directed antibiotic therapy. Colistin therapy was found to have a p-value <0.10 on univariable analysis and resulted in a 10% or greater change in the parameter estimate of the CP-CRE group so was retained in the multivariable model.