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Title Risk Factors for Mortality in Carbapenem-resistant Enterobacterales in Georgia, 2011 – 2020

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Risk Factors for Mortality in Carbapenem-resistant Enterobacterales in Georgia, 2011 – 2020

By

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Abstract

Risk Factors for Mortality in Carbapenem-resistant Enterobacterales in Georgia, 2011 – 2020

By Lucy Sabrin Witt

Background
Carbapenem-resistant Enterobacterales (CRE) are an urgent public health threat. Although the high mortality from CRE is well described, modifiable risk factors for mortality, such as possession of an indwelling medical device, have not yet been consistently identified. Furthermore, prior studies have disagreed on the impact carbapenemase enzymes have on mortality.

Methods
Using data from the Georgia Emerging Infections Program, we created a cohort of patients with sterile-site CRE infections between 2012 – 2019. We described the incidence of infection and demographics of the patients. Using log-binomial multivariable modeling, we investigated whether having an indwelling medical device was associated with an increased risk of 90-day mortality when controlling for confounders.

A second, adjacent cohort consisted of isolates from CRE infections (both sterile-site and urine) between 2011 – 2020 for which whole genome sequencing (WGS) was available. Using this data we described the frequency of carbapenemase genes (CP) and evaluated whether having a CP was associated with 90-day mortality when controlling for confounders. We completed time-to-event analyses using a Kaplan Meier analysis and a Cox proportional hazards modeling.

Results
There were 154 patients with sterile-site CRE infections between 2012– 2019. Having an indwelling medical device was not associated with increased mortality (adjusted risk ratio [aRR] 1.29, 95% Confidence Interval [CI] 0.57 – 2.81), however having at least two devices was (aRR 2.00, 95% CI 1.18 – 3.38). For isolates from both sterile-site and urine CRE infections with WGS available (n=284), CPs were not associated with increased 90-day mortality compared to infections with isolates without CPs (aRR 0.92, 95% CI 0.62 – 1.34). Cox proportional hazard modeling found no relationship between survival and CP gene possession (adjusted hazard ratio 1.23, 95% CI 0.75 – 2.01).

Discussion
Indwelling medical devices are not a clear risk for mortality. Although having at least two indwelling devices was associated with mortality, it is unclear whether increased device usage is a true risk factor or simply a marker of more severe illness. Similarly, CPs were not associated with increased risk of mortality as all patients with CRE had limited treatment options during this time period regardless of the mechanism of resistance.

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Introduction

In 2017 the World Health Organization declared carbapenem-resistant Enterobacterales (CRE), with an estimated mortality as high as 65%[1,2], an urgent public health threat.[3] Enterobacterales are common bacterial causes of infections ranging from minor urinary tract infections to life-threatening bloodstream infections. CRE have resistance to carbapenems which are considered the routine "last line" antibiotics for Enterobacterales. In 2019 there were approximately 6,000 of cases of CRE in the United States, with rates of infections rising over the last three years.[4]

Although the high mortality from CRE is well described, modifiable risk factors for mortality have not yet been consistently identified. Currently clinicians and hospital systems use contact precautions for patients if CRE is identified in a clinical culture to prevent spread and treat infections (as able) when they arise. Identifying novel and modifiable risk factors for mortality in patients infected with CRE could aid in decreasing the burden of these infections.

Furthermore, the mechanism of carbapenem resistance can impact transmissibility and guide treatment. CRE may have resistance due to genetic mutations in carbapenemases, enzymes that can inactivate carbapenems. Because carbapenemases are frequently encoded on plasmids, which are transmissible mobile genetic elements, mutations in these enzymes can easily be transferred.[1,3] Thus understanding the local landscape of carbapenem producing (CP) CRE can help clinicians better choose empiric antimicrobial therapy and inform infection prevention strategies.

The Georgia Emerging Infection Program (EIP) performs active population- and laboratory-based surveillance in the Atlanta metropolitan area (Figure 1) to identify cases of CRE. Using data collected by the EIP we aimed to first describe longitudinal trends and

demographic and clinical characteristics of patients with invasive CRE infections in the Atlanta metropolitan area between 2012 and 2019 and identify risk factors for 90-day mortality. We specifically focused on the risk afforded by having an indwelling medical device, as this has been postulated as a risk factor for CRE acquisition and progression to invasive disease and may be an intervenable risk factor for mortality. In our second aim we describe the rates of CP in our cohort using whole genome sequencing (WGS) and examine whether possessing a CP gene is associated with higher mortality compared to patients infected with a non-CP CRE.

Background

Enterobacterales and Carbapenem Resistance

Enterobacterales are an order of Gram-negative bacteria which can be part of the natural microbiome in the gastrointestinal (GI) and genitourinary (GU) tracts of both humans and animals. These bacteria can cause disease when present in sterile sites such as blood or cerebrospinal fluid, or even within the GI and GU systems. Carbapenems are a broad class of antibiotics generally reserved for drug resistant bacteria including those producing *AmpC* β-lactamase or with extended-spectrum β-lactamase (ESBL) genes. Unfortunately, due to inappropriate use and overuse of antibiotics, the rates of carbapenem-resistant infections are increasing.[4] Professional societies including the Infectious Disease Society of America (IDSA) and the Society for Healthcare Epidemiology of America, as well as government agencies such as the US Centers for Disease Control and Prevention (CDC) and the Agency for Healthcare Research and Quality have recognized CRE as a necessary focus of research to identify and assess practice changes to prevent these infections.[5–8]

Carbapenem resistance in Enterobacterales is of particular concern as these infections are 1) associated with a high mortality rate and 2) may harbor transmissible resistance mechanisms if the resistance is conferred by a CP gene found on a plasmid, a highly mobile genetic element in Gram-negative bacteria (Figure 2). This transmissible resistance mechanism facilitates not only transfer of the CP between organisms within the same host, but potentially from one patient to another. This mechanism of resistance transmission has been implicated in multiple outbreaks[9–12] and has led to recommendations for contact precautions for patients infected with CRE.[5,13] Other mechanisms of resistance to carbapenems may arise from over-expression of other β-lactamase genes (ESBL or *AmpC)* often paired with mutations in porin channels or efflux pumps which

respectively allow passive entry and active expulsion of an antibiotic.[14–17] Although the mechanism of resistance can guide treatment of CRE, all patients infected with CRE have limited treatment options and are at higher risk for mortality compared to patients with infections from carbapenem-susceptible Enterobacterales.[2,8,18–20]

Indwelling Medical Devices

Indwelling medical devices including urinary catheters, central venous catheters, and endotracheal tubes are common in the modern US healthcare system and are frequently encountered in critically ill or healthcare exposed patients. Prior studies have suggested that indwelling devices may be a risk factor for acquiring CRE [21] as well as for CRE progression to invasive disease.[22] Indwelling medical devices, however, have not been consistently linked to mortality risk in patients with CRE.[23] As many indwelling medical devices may not be indicated or may be able to be removed earlier in a patient's hospital course, these present a potentially modifiable risk factor for mortality in patients with CRE infections.

Carbapenemases

Carbapenemases are a group of β-lactam hydrolyzing enzymes found in Gram-negative bacteria; they areidentified by their gene symbols and divided by their Ambler class, a classification system of β-lactamases based on peptide sequencing.[24] *Klebsiella pneumoniae* carbapenemase (KPC) is an Ambler molecular class A carbapenemase encoded by the *bla*$_{KPC}$ gene. The KPC-2 enzyme was first recognized in North Carolina in 2001, has since become endemic in parts of the US and, along with KPC-3, is the most common carbapenemase in the US.[21] In the last 20 years a group of Ambler class B carbapenemases, the metallo-β-lactamases (MBL), have emerged as an increasingly common and distinct set of carbapenemases in the US.

These include Verona-integron-encoded MBL (*bla*$_{VIM}$), imipenemase (*bla*$_{IMP}$) and New Delhi MBL (*bla*$_{NDM}$).[21,25] Another carbapenemase more recently recognized in the U.S is the OXA-48-like carbapenemase, a class D enzyme that hydrolyzes carbapenems and is not inhibited by β-lactamase inhibitors.[26] Identifying the particular gene that confers carbapenem resistance has important treatment implications[8], may predict transmissibility[27,28] and/or mortality risk[29], and can aid in outbreak investigations[30].

A study in 2012-2013 examining all 10 US EIP sites found (using polymerase chain reaction [PCR]) that half of the identified CRE harbored CPs.[1] A connected investigation of EIP data across the US from 2011-2015 found that 90% of the CRE isolates that had undergone WGS in Georgia possessed a CP gene suggesting that the landscape of CRE may be changing.[31] Prior studies are inconsistent on whether CP-CRE have higher rates of mortality compared to non-CP CRE.[16,32–34] As such, it is imperative to identify any variations in CP distribution and associated mortality.

Whole Genome Sequencing

Historically, identifying CP in CRE isolates relied on PCR technology or phenotypic laboratory tests such as the modified Hodge test, Carba-NP test, or modified carbapenem inactivation method, but these may not detect all carbapenemases.[35,36] In the last five years WGS has become more accessible and less costly.[37] With WGS we can more accurately identify a larger number of CP genes, as well as the associated plasmids, allowing a more complete description of the burden of potentially transmissible carbapenem resistance mechanisms. This improved detection allows for a more robust analysis of risk factors for the acquisition of CP

genes and evaluation of differences between patients with CP (CP CRE) and those without CP (non-CP CRE).

Study Design

Using data from the Georgia EIP, we created two cohorts to answer these pressing questions. The first cohort consisted of patients with sterile site CRE infections between 2012-2019. With this cohort we sought to describe current trends and demographics in CRE infections, as well as to identify risk factors for mortality, specifically focusing on indwelling medical devices. As CRE can be found in the natural microbiota of the GI and GU tracts, it can be difficult to assess whether CRE identified in non-sterile sites such as urine, wounds, or the lungs are truly pathogenic. By focusing on sterile site infections and eliminating potential colonization, we can more accurately examine risk factors for mortality associated with a CRE infection. Furthermore, risk factors for mortality are often not modifiable, such as age or admission to the intensive care unit (ICU). Identifying these non-modifiable risk factors may be informative, but modifiable risk factors can provide clinicians or public health professionals with a route to decrease the burden of mortality from CRE infections.

Our second, adjacent cohort consisted of CRE isolates collected by EIP between 2011-2020 for which WGS was available. This cohort was used to explore the frequency and epidemiology of CP genes within CRE isolates and assess for mortality difference between infections caused by CP CRE compared to infections caused by non-CP CRE. The true epidemiology of CP in CRE infections is still being clarified, as prior studies were outdated[1,31], included many isolates thought to represent colonization[16], and relied on less sensitive techniques to identify CP[1]. By using WGS and limiting our investigation to infections, we sought

to accurately describe the frequency of CP in CRE infections, identify risk factors for CP presence, and assess whether these genes confer any difference in mortality risk compared to patients with non-CP CRE infections.

Methods

Study Aims

In the first aim, we described the longitudinal trends and the clinical characteristics of invasive CRE infections in the Atlanta metropolitan area between 2012-2019 and identified risk factors for 90-day all-cause mortality in patients with invasive CRE infections. We hypothesized that indwelling medical devices would be independently associated with mortality after controlling for confounders. Our second related aim was to evaluate risk factors for having a CRE infection with a CP gene and examine whether 90-day all-cause mortality and survival time differed between patients with CP CRE infections compared to those with non-CP CRE infections.

Study Design and Setting

This is a retrospective observational cohort study utilizing data obtained by the Georgia EIP (funded by the CDC). The CDC EIP is an active population- and laboratory-based surveillance program for many pathogens including CRE with 10 sites across the US including Georgia. The Georgia EIP performs active surveillance for CRE in both sterile sites and urine across the eight counties surrounding metropolitan Atlanta (Figure 1). EIP staff routinely query laboratory testing instruments at each associated microbiology laboratory and identify all relevant organisms that are carbapenem resistant including *Escherichia coli*, *Klebsiella spp.*, and *Enterobacter spp.* Only the first isolate of CRE from each patient in a 30-day period is included. EIP staff then captures basic demographic information, clinical syndromes, presence of medical devices, antibiotic susceptibilities, comorbidities, admission to an intensive care unit (ICU), and discharge disposition in a standard 29-item case report form.

Our study included two, overlapping cohorts. To complete our first aim, we created a cohort of all isolates from normally sterile sites, such as blood, within the Georgia EIP between 2012-2019.

Our second aim was limited to isolates that had undergone WGS. All isolates collected between 2011-2020 were eligible for inclusion, including sterile sites and urine. The CDC completes WGS on a some, but not all, isolates collected as part of the EIP, as described previously (Karlsson 2022). For our study, the Investigational Clinical Microbiology Core at Emory University prepared an additional randomly selected 96 isolates without WGS results from CDC for additional WGS, which was completed by Seq Center (Pittsburgh, PA, USA). Isolates processed by Emory were extracted using either the Qiagen DNAeasy Blood and Tissue Kit (Qiagen, Hilden, Germany) or KingFisher Apex System (ThermoFisher Scientific, Waltham, MA, USA) using the MagMax 2.0 viral DNA kit with the following modifications: a 10ul loopful of bacteria from a fresh overnight agar plate was resuspended in 500 ul of nuclei lysis buffer, vortexed and incubated at 80 degrees C for 15 min, cooled to RT and vortexed. 400 ul was used in the MagMax kit as directed. Library construction and sequencing were completed using Illumina Nextera DNA sample prep kit with 150 bp paired-end read length, and libraries were sequenced on the NextSeq WGS platform (Illumina, San Diego, CA, USA). This data was then processed through the Bactopia analysis pipeline (https://github.com/bactopia/bactopia) for gene identification.[38] Three isolates had discordant results between CDC completed PCR testing and WGS completed at either Emory or CDC. These were removed from the analysis to avoid misclassification. Thirty-nine isolates classified by EIP as potentially colonization rather than infection were removed prior to analysis (all were from urine). 284 isolates were included in our final analysis.

Carbapenem Resistance

In 2012, the EIP definition for CRE required non-susceptibility to meropenem, doripenem, and imipenem (MIC ≥ 4 μg/mL) with resistance to all tested third generation cephalosporins. However, in 2016 EIP simplified their definition to better align with state public health definitions and included any relevant organism resistant to meropenem, doripenem, imipenem, *or ertapenem* (MIC ≥ 2 μg/mL) and updated susceptibility breakpoints. For Aim 1, to avoid confounding due to this definition change, only patients meeting the previously used definition across the full time period (2012 - 2019) were included.

For Aim 2, to enrich our sample for potentially non-CP possessing CRE [39] and increase our sample size, we included *any* isolate classified as a CRE by EIP with WGS results.

Variable Definitions

The exposures of interest were (1) use of an indwelling medical device and (2) presence of a CP gene. Indwelling medical devices were defined as a central venous catheter (CVC), urinary catheter, or any other indwelling device including nasogastric tubes, endotracheal tubes, nephrostomy tubes, tracheostomies, or percutaneous gastrostomy tubes (PEG) in place up to, or at any time within, the two calendar days prior to infection. CP presence was determined by WGS as described above. Co-variates were obtained from EIP data. Clinical and demographic data including race and ethnicity were abstracted from the medical chart. ICU admission was defined as the patient being in an ICU at any time in the seven days prior to isolate collection. Length of stay was calculated from admission and discharge date (if admitted). Ninety-day all-cause mortality, the primary outcome, was elicited from the Georgia office of Vital Records, which is linked to the Georgia EIP. For the time-to-event analysis, the day of specimen

collection was considered the date of entrance to the cohort, with the date of death being time of event. All those not deceased at day 91 were censored.

Sample Size and Power Calculation

Our sample size estimate was calculated based on our primary aim to investigate the risk of mortality for patients with invasive CRE infections, specifically comparing those with and without indwelling medical devices. Prior data suggested that approximately 70% of the invasive CRE cases had a central venous catheter at or around the time of diagnosis. Previous studies found a 10 - 40% difference in mortality between patients with and without indwelling devices.[40,41] Using a two-sided confidence interval with α =0.05 and an estimated 25% mortality difference between those with and without indwelling medical devices, we would require approximately 143 participants to obtain 80% power (openepi.com).

Data Analysis (by Aim)

Aim 1: Indwelling medical devices and mortality

Trends over time were assessed using a longitudinal analytic approach including generalized estimating equations to evaluate rates of infection per population as well as patient demographics. Descriptive univariable analyses were completed for the entire cohort detailing frequencies with standard deviations for categorical variables and medians with interquartile ranges (IQR) for continuous variables to account for non-normality in the data. Bivariate analyses of continuous and categorial variables' association with 90-day mortality were conducted using Wilcoxon rank sum or chi-squared test (or Fisher's exact test) as appropriate. The proportion of patients identified as Black race was compared to the catchment area

population using student's t-test. An investigator created directed acyclic graph (DAG) based on prior knowledge of CRE was used to inform variable inclusion in the multivariable analysis (Figure 3). Patients with missing data regarding whether they were admitted to the hospital and patients never admitted to the hospital were not included in analyses involving hospital length of stay.

Multivariable log binomial regression was used to estimate risk ratios (RR) for the association of multiple demographic and clinical risk factors including Charlson co-morbidity index (CCI) score, ICU admission, long-term acute care hospital (LTACH) stays in the last year, and presence of an indwelling medical device on 90-day mortality. Secondary analysis was completed limiting the primary exposure of any medical device to only a central venous catheter as it may pose a unique risk for infection. Another secondary analysis was completed examining only patients with at least two indwelling medical devices. ICU admission was not included in the multivariable model for the subgroup analysis of patients with at least two indwelling devices due to concern for co-linearity. A sensitivity analysis was completed that included ICU admission in this secondary multivariable model to assess its effect on the relationship and the assumption of collinearity. Chronic dialysis was not included in any multivariable model due to collinearity with possession of an indwelling device. Finally, the association between indwelling medical devices and 90-day mortality was stratified by chronic dialysis to assess for interaction.

Aim 2: Carbapenemase genes and mortality

Descriptive statistics were generated for the entire cohort including frequencies with standard deviations for categorical variables and medians with IQR for continuous variables. Bivariate analysis examining the relationship between basic demographic, clinical, and

microbiologic information along with CP presence was analyzed using Wilcoxon rank sum test, chi-square (or Fisher's exact test) as appropriate. A directed acyclic graph (DAG) was created based on prior knowledge of risk factors for mortality and the bivariate analysis of factors associated with CP-possession (Figure 4). This DAG informed variable inclusion in multivariable analysis to assess the relationship between CP and mortality.

Multivariable log binomial regression estimated RRs for the association of carbapenemase gene on 90-day mortality when controlling for CCI score and being on chronic dialysis. A Kaplan-Meier analysis was completed to assess survival time for those with and without CP. An adjusted Cox proportional hazard model controlling for the CCI score and chronic dialysis was performed.

For all analyses a two-sided p-value of 0.05 was considered significant. All analyses were completed using SAS 9.4 (SAS Institute, Cary NC).

Institutional Review Board

This study was approved the Emory Institutional Review Board.

Results

Aim 1: Indwelling medical devices and mortality

Clinical Characteristics and Trends Over Time

There were 154 cases of invasive CRE infections in the Georgia catchment area between 2012 and 2019. A majority of patients with invasive CRE infections were male (53.2%) and were hospitalized for an average of 20 days (Table 1). Patients identified as Black race were over-represented compared to the population of the catchment area, composing 66.9% of those with invasive CRE infections compared to 42.5% of the catchment area population during this study period (p-value < 0.0001). Most infections occurred in the bloodstream (84.4%) and 65.6% were *Klebsiella pneumoniae* (Table 1).Indwelling devices were frequent (87.7%) with the most common device being a central venous catheter (70.8%). One fifth of patients had both a tracheostomy tube and a percutaneous enteric gastronomy (PEG) tube in place around the time of infection, and 78% of those also had a CVC in place. 53.6% of patients were admitted to the ICU at any time during their hospitalization and 31.2% had been in the ICU in the seven days prior to isolate collection. Most patients had been admitted to a hospital (81.2%) and 24% had stayed in a long-term acute care hospital (LTACH) in the last year (Table 1).

In-hospital mortality was 23.4% for the entire cohort and 90-day mortality was 42.2%. The annual incidence rate of invasive CRE infections per 100,000 patients decreased over the study time period from 0.576 to 0.361 (Table 2, Figure 3).

Indwelling medical devices and mortality

Factors statistically associated with 90-day mortality on bivariate analysis included older age, higher CCI score, admission to the ICU, bloodstream infection, having at least two

indwelling devices, and being on chronic dialysis (Table 3). Each additional indwelling medical device above one provided an additional 53% increased odds of mortality (OR 1.53, 95% Confidence Interval [CI] 1.09 - 2.17). In unadjusted models to assess an association with 90-day mortality, ICU admission was associated with mortality with a risk ratio of 1.73 (95% CI 1.22 - 2.45) (Table 4). Having an indwelling device present (RR 1.69, 95% CI 0.78 - 3.67), CCI score (RR 1.06, 95% CI 0.91 - 1.24), and previous stay at an LTACH (RR 1.31, 95% CI 0.89-1.92) were not associated with 90-day mortality in unadjusted models. In a multivariable model adjusting for these four factors, admission to the ICU remained associated with mortality (aRR 1.65, 95% CI 1.14 - 2.38) while CCI score (aRR 1.30, 95% CI 0.58 - 2.92), previous stay at LTACH (aRR 1.45, 95% CI 0.63 - 3.34), and having an indwelling device present (aRR 1.29, 0.57 – 2.81) were not (Table 4).

Secondary Analyses

Limiting the exposure of interest to central venous catheters (N=109) there was no increased risk of 90-day mortality for patients with a CVC in the unadjusted (RR 1.26, 95% CI 0.81 - 1.97) or adjusted model (aRR 1.02, 95% CI 0.57 - 2.81) (Table 4).

Of the 106 patients who had two indwelling medical devices, 86% had central venous catheters and 72% had urinary catheters (Table 4). An unadjusted model showed an association between having at least two indwelling medical devices and 90-day mortality (RR 2.00, 95% CI 1.18 – 3.38) (Table 5). In the adjusted model, without ICU admission included, this relationship persisted (aRR 1.88, 95% CI 1.10 - 3.20). A sensitivity analysis which included ICU admission in the multivariable model showed a diminished effect estimate with a wider confidence interval (aRR of 1.64, 95% CI 0.95 - 2.82).

Chronic Dialysis and Interaction Analysis

Approximately one-third of the cohort was on chronic dialysis (n=54). Patients on chronic dialysis were older, median age 61 (IQR 54 - 69) years, and more likely to be identified as Black race (79.3%) as compared to the total cohort. Almost all the patients on chronic dialysis (92.5%) had an indwelling medical device. When stratified by dialysis, the odds ratio for all-cause 90-day mortality in patients with indwelling medical devices was 4.35 (95% CI 0.42 – 44.88) for patients on chronic dialysis and 1.55 (95% CI 0.46 – 5.28) for patients not on chronic dialysis.

Aim 2: Carbapenemase genes and mortality

Clinical Characteristics

A total of 284 CRE isolates with WGS completed were included in our analysis. A majority of the cohort were female (60.6%) and black (51.1%) (Table 6). 64.9% were hospitalized at time of specimen collection with a median length of stay of 11 days. A majority of isolates were from urine (82.4%), and *Klebsiella pneumoniae* was the most common pathogen. Most had been hospitalized, stayed at an LTACH, or resided at a long-term care facility (LTCF) in the last year. The 10.6% of the cohort who were on chronic dialysis were younger, median age 63.5 (IQR 47 - 71) years, and more likely to be identified as Black race (76.7%) than the general cohort. Only four patients with CRE reported travel outside the US, all of whom possessed CP (three NDM and one KPC). In-hospital mortality for the entire cohort was 6.7% while 90-day mortality was 25.4%.

Carbapenemase genes

Most isolates possessed a CP gene (60.2%). Patients with a CP gene were younger, more likely to be identified as Black, less likely to be immunocompromised, more likely to be infected with *Klebsiella pneumoniae,* and have stayed at an LTACH, LTCF or been hospitalized in the last year (Table 6). CP positivity was also associated with chronic dialysis and having an indwelling medical device. 84.3% of infections with *Klebsiella pneumoniae* were found to have a CP and a majority of CP genes were KPC-3 (Table 7). No isolates possessed more than one CP gene. None of the *Klebsiella oxytoca* and only one of the *Klebsiella aerogenes* isolates had a CP gene identified.

Mortality and Survival Analyses

In unadjusted models, having a CP gene was not associated with 90-day mortality (RR 1.04, 95% CI 0.69 - 1.57). On multivariable analysis, after controlling for CCI and being on chronic dialysis, having a CP gene was not associated with 90-day mortality (RR 0.92, 95% CI 0.62 - 1.34). A Kaplan Meier analysis showed no relationship between CP positivity and 90-day survival (Figure 4). Cox proportional hazard modeling found no relationship between survival and CP gene possession (adjusted hazard ratio 1.23, 95% CI 0.75 – 2.01) when controlling for CCI or chronic dialysis.

Discussion

Aim 1: Indwelling medical devices and mortality

In patients with invasive CRE infections in Georgia between 2012 and 2019, risk factors associated with all-cause 90-day mortality in multivariable modeling included admission to the ICU in the prior seven days, having at least two indwelling devices, and being on chronic dialysis. These findings reflect that patients with CRE infections are chronically and often acutely ill. Our mortality rate, 42.2%, was slightly higher than previously reported national and local rates.[1,42] The rates of invasive CRE infection decreased during our study period, which is reflected in national data.[43] Conversely, the national rates of ESBL Enterobacterales increased during our study time period.[43] Potential mechanisms for the decrease in rates of CRE include increased focus on antimicrobial stewardship and improved infection control practices from national campaigns. These efforts have not been focused upon antibiotics linked to the development of ESBL resistance patterns such as ceftriaxone, and ESBL organisms do not require contact precautions. Unfortunately, this trend was reversed after our study period in the wake of the COVID-19 pandemic.[4]

Our primary exposure, possession of an indwelling medical device, was prevalent in our cohort (87.7%) and in multivariable analysis was not associated with an increased risk of 90-day mortality, although having at least two medical devices was. Central venous catheters have been shown to be associated with lower mortality in *S. aureus* infections when not accompanied by endocarditis[44–46], however their role in CRE infections is less clear. Howard-Anderson et al. used Georgia EIP data to show that patients with CRE bacteriuria who had urinary catheters were more likely to develop CRE bacteremia, however they did not examine risk of mortality.[22] Prior studies have suggested that central venous catheters may be a risk factor for mortality in patients

with drug resistant Gram-negative bacteremia, however these were not limited to CRE and focused on catheter-associated blood stream infections.[41,47] Having at least two indwelling medical devices may simply be a surrogate marker of acute and chronic illness; therefore, it is unclear whether removing one device would improve survival in patients with invasive CRE infections.

The other risk factors we identified for mortality, specifically ICU admission, are consistent with those previously described in the literature. Babiker et al described carbapenem-resistant Gram-negative infections over almost 20 years at a single center in Pennsylvania that included *Pseudomonas and Acinetobacter spp.* and found an association between 30-day mortality and chronic renal disease, ICU admission, chronic liver disease, and bloodstream infection.[48] A single-site retrospective cohort study in India with a high rate of mortality among children found that ICU admission, intubation, ionotropic support, and infection from a respiratory source were associated with increased mortality.[49] A single center cohort study in Spain found that ICU admission and inadequate initial antimicrobial therapy were associated with increased mortality.[50] A similar association between ICU admission and prior hospitalization and 90-day mortality was noted in an observational study in New York City.[51] Unfortunately, a majority of the risk factors described are not easily intervened upon.

Patients with invasive CRE infections in Georgia between 2012 - 2019 were highly healthcare experienced with significant chronic and acute illness. This reflects the well described pathogenesis of CRE which involves exposure to multiple antibiotics and healthcare facilities where multi-drug resistant pathogens are known to reside on surfaces, the hands of personnel, and in-patient rooms.[16,52–54] Our findings reflect an excess burden of disease among the Black population of Georgia which a new finding, and likely due to the contribution of patients on

chronic dialysis in our study, who were more likely to be qualified as Black race than the general cohort. Further study is required to understand the role of social determinants of health on CRE acquisition and mortality. The distribution of organisms in our study reflects previously reported national trends in CRE, with a majority of cases being caused by *Klebsiella pneumoniae.*[16,31]

Limitations

The direction of the relationship between an indwelling device and infection with CRE is also difficult to ascertain. Our data describe indwelling devices in place in the two days prior to culture of CRE, therefore we cannot elucidate whether the device was placed prior to CRE infection or potentially due to abnormal physiology that developed in the setting of CRE infection. Our study could suggest that limiting the use of invasive medical devices may decrease mortality, however having numerous medical devices may simply be a surrogate for illness severity. Although our investigation is unique in its description of invasive CRE infections, it only represents one urban, southern US region. The risk factors identified through our study may not be generalizable to other geographic areas. Furthermore, prior studies have suggested that appropriate antibiotic therapy contributes to survival in patients with CRE infections, however information regarding antibiotic therapy was not available in our dataset, therefore this risk factor could not be included in our analysis.

Aim 2: Carbapenemase genes and mortality

In this retrospective observational cohort of CRE infections between 2010 and 2020 we found a high percentage of CRE isolates with CP genes. Previously reported rates of CP have varied markedly and may be dependent on the region of the US, however our results are similar

to national rates.[1,16,17,31] Notably Karlsson et al found that 90% of EIP CRE isolates from Georgia collected between 2011 - 2015 that underwent WGS possessed CP genes. Their investigation was limited to isolates meeting the older, more stringent definition of CRE, which likely enriched their cohort for CP CRE.[31] These variations in rates may reflect changes over the study time period as well as differences in laboratory techniques for CP identification.

Similar to prior studies, we found that interaction with the healthcare system, whether through a prior hospitalization, stay at an LTACH or LTCF, being on chronic dialysis, or having an indwelling medical device was associated with CP positivity.[40,55] However, our study found novel demographic relationships including male sex, Black race (per medical record), and younger average age. A multicenter retrospective cohort of American veterans between 2013 and 2018 found that being African American, being diagnosed in 2017 or 2018, having congestive heart failure, and gastrointestinal reflux disease (GERD) were associated with CP CRE.[35] Interestingly, GERD and proton-pump inhibitors (PPI) use were found to be a risk factor for CP CRE colonization in a 2019 Johns Hopkins cohort of patients admitted to the medical ICU or solid organ transplant unit.[56] Unfortunately, we did not have data on GERD diagnosis or PPI usage. Our finding that CP-CRE was associated with Black race and younger age is likely due to the association between CP-CRE and dialysis. Patients identified as Black race made up a large majority of those on chronic dialysis in our study, and they were on average younger than the general cohort.

The distribution of CP genes in our study reflect known CP gene frequencies in the US A multicenter study in New York and New Jersey found 77% of patients with a CRE infection had a CP, a majority of which was KPC.[57] A single center cohort from Maryland found that 45% of their CRE possessed CP, with 92% having a KPC gene as identified through a DNA microarray-

based assay.[32] The national CRACKLE-2 cohort found that 59% of their CRE isolates were CP with 51% having KPC-2 and 41% having KPC-3 genes[16] and Karlsson's evaluation of national EIP data found a majority of isolates harbored KPC genes, with KPC-3 predominating[31]. Similar to other national studies, we found that very few other *Klebsiella* species other than *K. pneumoniae* possessed CP genes.[16] All four patients who traveled internationally possessed CPs and three had NDMs. These comprised 50% of the isolates with NDM in the cohort, which is not surprising given NDMs are more common outside of the US.[58]

Our finding that rates of mortality with CP CRE were not different from non-CP CRE is not consistently reflected in the literature. Mariappan et al studied 111 patients in an Indian hospital and found that those infected with CP CRE had a mortality rate of 64.4% compared to 35.6% for those with non-CP CRE infections.[33] However, their study employed PCR for identification of CP, included mostly NDM-type CP, and occurred in 2010.[33] Similarly, Tamma et al found higher rates of 30-day mortality in patients with CP-CRE bacteremia (identified by a DNA microarray assay) at a single center in Baltimore (adjusted odds ratio [aOR] 3.19, 95% CI 0.99 - 10.25, p-value 0.05).[32] Conversely, Hovan et al performed a retrospective cohort study of patients with CRE bacteremia at a single medical center in New Jersey and found that non-CP CRE was associated with increased hazard of death compared to CP CRE (Hazard ratio 2.4, 95% CI 1.2 - 4.6) when adjusting for receipt of active and targeted antimicrobial therapy within seven days.[59] The CRACKLE-2 study, a multi-center prospective cohort of CRE infection and colonization showed no difference in desirability of outcome ratings for patients with and without CP.[16] This may be a result of the regional CRE differences as well as the introduction of new antibiotics in recent years which have greatly expanded treatment options for CRE.[8] Specific antibiotics are known to be effective against particular CPs, which is reflected in current

guidance on treatment for CRE.[8] With these differences, it is possible that mortality advantages could emerge dependent on the mechanism of resistance or specific CP. However, as these novel antibiotics including new β-lactam/β-lactamase inhibitors, the siderophore cephalosporin cefiderocol, and newer tetracyclines tigecycline and eravacycline become more easily accessible, the mortality rates for all CRE will likely continue to improve.

Limitations

Processing the results of whole genome sequencing is limited in that it can only identify known CP genes that exist in the gene library employed. Ours was a convenience sample of isolates with WGS available and may not reflect the entire population CRE. Furthermore, our cohort included mostly isolates from urine and, although we attempted to eliminate isolates that represented colonization rather than infection, some of the included isolates may not represent true infections, likely decreasing the frequency of mortality in our cohort, and limiting our ability to detect a difference between those with and without CP genes. Although Black race was associated with CP gene positivity in our study, this is likely a surrogate for other factor(s) involving interaction with the healthcare system (such as chronic dialysis). Therefore, it was not included in any multivariable modeling.

Future Directions

The coronavirus pandemic has increased hospitalizations, exposure to antibiotics, and led to increased multidrug resistant infections in some hospitals.[60–63] This study can serve as a preliminary investigation to compare rates of CRE and factors associated with mortality after

2020. Furthermore, a larger national cohort of invasive CRE infections could more fully describe the relationship between indwelling medical devices and mortality. As antibiotic therapy is known to influence survival in patients with CRE infections, further study could include incorporating antibiotic appropriateness and timing as covariates.

Our investigation of CP positivity will be expanded to examine sub-groups including only patients with infections with *Klebsiella pneumoniae* and only isolates from sterile sites. Furthermore, we plan to examine the rates of plasmids in these isolates to assess risk of transmissibility of identified CP genes. Lastly, we will investigate alternative mechanisms of resistance such as *AmpC* and ESBL genes to describe alternative mechanisms for carbapenem resistance in isolates with CP as this may have treatment implications.

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Tables and Figures

Table 1. Characteristics of patients with carbapenem resistant isolates by those with and without indwelling medical devices

	Total	Without Indwelling Device	With Indwelling Device
	n=154	n= 19	n= 135
Age, median (IQR)	59 (48-69)	54 (33-67)	61 (48 - 69)
Female, n (%)	72 (46.8)	11 (57.9)	61 (45.2)
Race, n (%)			
Black	103 (66.9)	12 (63.2)	91 (67.4)
White	40 (26.0)	6 (31.6)	34 (25.2)
Pacific Islander	5 (3.3)	0 (0)	5 (3.7)
Ethnicity, n (%)			
Hispanic	4 (2.6)	0 (0)	4 (3.0)
Non-Hispanic	122 (79.2)	16 (84.2)	106 (78.5)
Charlson Comorbidity Index Score, median (IQR)	2 (1-3)	2 (0-2)*	2 (1-3)*
Length of Stay, median (IQR)**	20 (10-39)	16 (5.5-23.5)	21 (10-40)
Intensive Care Unit Admission in 7d prior n (%) ***	48 (31.2)	2 (10.5%)	46 (34.1%)
Immunocompromised, n (%)	36 (23.4)	5 (26.3)	30 (22.2)
HIV or AIDS, n (%)	5 (3.3)	1 (5.3)	4 (3.0)
Transplant (bone marrow), n (%)	1 (0.7)	0 (0)	1 (0.8)
Transplant (solid organ), n (%)	2 (1.3)	0 (0)	2 (1.5)
Solid Tumor, n (%)	15 (9.7)	1 (5.3)	14 (10.4)
Metastatic Cancer, n (%)	10 (6.5)	2 (10.5)	8 (6.0)
Hematologic Malignancy, n (%)	5 (3.3)	1 (5.3)	4 (3.0)
Specimen Source, n (%)			
Blood	130 (84.4)	14 (73.7)	116 (85.9)
Other	24 (15.6)	5 (26.3)	19 (14.1)
Organism, n (%)			
Escherichia coli	16 (10.4)	4 (21.1)	12 (8.9)
Enterobacter cloacae	19 (12.3)	6 (31.6)	13 (9.6)
Klebsiella aerogenes	10 (6.5)	0 (0)	10 (7.4)
Klebsiella pneumoniae	101 (65.6)	7 (36.8)	94 (69.6)
Klebsiella oxytoca	8 (5.2)	2 (10.5)	6 (4.4)
Polymicrobial Infection, n (%)*	58 (37.9)	6 (31.6)	52 (38.8)
History, n (%)			
Previous stay in hospital (1 year)	125 (81.2)	13 (68.4)	112 (83.0)
Previous stay in long term care facility (1 year)	57 (37.0)	2 (10.5)	55 (40.7)
Previous stay in long term acute care (1 year)	37 (24.0)	0 (0)	37 (27.4)
Surgery	75 (48.7)	6 (31.6)	69 (51.1)
Chronic Dialysis	53 (34.4)	4 (21.1)	49 (36.3)
Hemodialysis, n (% of dialysis)	*51 (96.2)*		
Central or hemodialysis line	*39 (76.4)*		
Aorto-venous fistula or graft	*12 (23.5)*		
Peritoneal, n (% of dialysis)	*2 (3.8)*		
Previously Isolated same organism (1 year)	23 (14.9)	0 (0)	23 (17.0)
Invasive Devices, n (%)			
Any	135 (87.7)		
Central line	109 (70.8)		
Urinary Catheter	80 (52.0)		
PEG	53 (34.4)		
Trach	51 (33.1)		
Both Tracheostomy and PEG	32 (20.8)		
Invasive Devices - Numerical, n (%)			
None	19 (12.3)		
One	29 (18.8)		
Two	58 (37.7)		
Three	48 (31.2)		
At least Two Devices	106 (68.8)		

Race: 6 unknown, Ethnicity: 28 unknown

Other site of infection: bone (1), deep tissue (1), joint/synovial (1), liver (2), ovary (1), peritoneal fluid(12), pleural fluid (2), other normally sterile site (4)

*1 missing, ** did not include 16 patients who were never admitted to the hospital and 2 with missing data, ***3 missing

Abbreviations: IQR – Interquartile Range, PEG – percutaneous enteric gastronomy

Table 2. Annual case count and incidence of invasive carbapenem resistant Enterobacterales infections, Atlanta, Georgia, 2012 - 2019

Year	N	% Total Specimens	Population	Annual Incidence Rate*
2012	22	14%	3,821,534	0.576
2013	27	18%	3,864,091	0.699
2014	19	12%	3,925,130	0.484
2015	19	12%	3,991,607	0.476
2016	19	12%	4,036,982	0.471
2017	13	8%	4,098,115	0.317
2018	20	13%	4,126,399	0.485
2019	15	10%	4,160,864	0.361

**per 100,000 people*

Table 3. Characteristics as related to 90-day mortality in patients with invasive carbapenem resistant Enterobacterales infections, Atlanta, Georgia, 2012 - 2019

	Survived n = 89 (57.8%)	**Deceased n = 65 (42.2%)**	*p-value*
Age, mean (IQR)	55 (44-69)	60 (53 - 68)	0.005
Female, n (%)	42 (47.2)	30 (46.2)	0.9
Race, n (%)			0.52
Black	61 (68.5)	42 (64.6)	
White	24 (27.0)	16 (24.6)	
Pacific Islander	3 (2.3)	3 (4.6)	
Ethnicity, n (%)			0.55
Hispanic	3 (3.4)	1 (1.5)	
Non-Hispanic	68 (76.4)	54 (83.3)	
Charlson Comorbidity Index Score, median (IQR)	2 (1-3)*	3 (1-3)*	<0.001
Length of Stay, median (IQR)**	20 (10-36)	20 (8-40)	0.16
Intensive Care Unit Admission, n (%) ***	40 (44.9)	43 (66.2)	*<0.01*
Specimen Source, n (%)			0.04
Blood	72 (80.9)	58 (89.2)	
Other	17 (19.1)	7 (10.8)	
Immuncompromised	18 (20.2)	18 (27.7)	0.28
Organism, n (%)			0.28
Escherichia coli	13 (14.6)	3 (4.6)	
Enterobacter cloacae	10 (11.2)	9 (13.9)	
Klebsiella aerogenes	7 (7.9)	3 (4.6)	
Klebsiella pneumoniae	55 (61.8)	46 (70.8)	0.34
Klebsiella oxytoca	4 (4.5)	4 (6.2)	
Polymicrobial Infection, n (%)	33 (37.5)	25 (38.5)	1
Invasive Devices, n (%)			
Any	75 (84.3)	60 (92.3)	0.13
Urinary Catheter	44 (48.9)	36 (40.0)	0.04
Central line	60 (67.4)	49 (75.4)	0.28
≥ Two devices	75 (63.6)	31 (86.1)	0.004
Number of Indwelling devices	2 (1-3)	2 (2-3)	0.01
History, n (%)			
Previous stay in hospital (1 year)	71 (79.8)	54 (83.1)	0.61
Previous stay in long term care facility (1 year)	31 (34.8)	26 (40.0)	0.51
Previous stay in long term acute care (1 year)	18 (11.7)	19 (12.3)	0.2
Surgery	50 (56.2)	25 (38.5)	0.03
Chronic Dialysis	23 (25.8)	30 (46.2)	*0.009*
Previously Isolated same organism (1 year)	13 (14.6)	10 (15.4)	1

Race: 6 unknown, Ethnicity: 28 unknown

*1 missing, ** did not include 16 patients who were never admitted to the hospital and 2 with missing data, ***3 missing

Abbreviations: IQR - interquartile range

Table 4. Frequency of devices present in patients with at least two indwelling medical devices in patients with invasive carbapenem resistant Enterobacterales infections, Atlanta, Georgia, 2012 - 2019

Device	**n**	**%**
Central Venous Catheter	91	86%
Hemodialysis Catheters	39	37%
Urinary Catheter	76	72%
Other	19	18%
Endotracheal tube	11	10%
Tracheostomy tube	46	43%
Gastrostomy tube	51	48%
Nasogastric tube	25	24%

Table 5. Risk ratios for 90-day mortality in patients with invasive carbapenem resistant Enterobacterales infections, Atlanta, Georgia, 2012 - 2019

	Unadjusted RR (95% CI)	Adjusted [1] RR (95% CI)	Adjusted [2] RR (95% CI)	Adjusted [3] RR (95% CI)
Indwelling Device Present	1.69 (0.78, 3.67)	**1.29 (0.57, 2.81)**		
Central Venous Catheter Present	1.26 (0.81, 1.97)		**1.02 (0.64, 1.62)**	
>/= 2 Indwelling Devices	2.00 (1.18, 3.38)			**1.88 (1.10, 3.20)**
Charlson Comorbidity Index Score	1.06 (0.91, 1.24)	1.30 (0.58, 2.92)	1.04 (0.95, 1.13)	1.02 (0.95, 1.11)
Intensive Care Unit Admission	1.73 (1.22, 2.45)	1.65 (1.14, 2.38)	1.69 (1.17, 2.46)	
Previous stay in LTACH (1 year)	1.31 (0.89, 1.92)	1.45 (0.63, 3.34)	1.17 (0.80, 1.72)	1.16 (0.79, 1.70)

1 Adjusted for Indwelling device, Charlson comorbidity score, Intensive care admission, previous stay at long term acute care

2 Secondary analysis - adjusted for central venous catheter, Charlson comorbidity score, Intensive care admission, previous stay at long term acute care

3 Secondary analysis - adjusted for at least two indwelling devices, Charlson comorbidity score, previous stay at long term acute care

Abbreviations: LTACH - Long Term Acute Care hospital

Table 6. Characteristics of patients with carbapenem resistant isolates with available whole genome sequencing, stratified by presence of a carbapenemase gene

	Total	Carbapenemase (CP)	No Carbapenemase (non-CP)
	n= 284	n= 171 (60.2%)	n= 113 (39.8%)
Age, median (IQR)	68 (56-77)	67 (52-74)	70 (60-80)
Female, n (%)	172 (60.6%)	92 (53.8%)	80 (70.8%)
Race, n (%)			
Black	145 (51.1%)	105 (61.4%)	40 (35.4%)
White	112 (39.4%)	50 (29.2%	62 (54.9%)
Asian or Pacific Islander	10 (3.5%)	4 (3.5%)	6 (3.5%)
Ethnicity, n (%)			
Hispanic	5 (1.8%)	2 (1.2%)	3 (2.7%)
Non-Hispanic	230 (81.9%)	137 (80.1%)	93 (82.3%)
Charlson Comorbidity Index Score, median (IQR)	2 (1-4)	2 (1-4)	2 (1-3)
Hospitalized n (%)	183 (64.9%)	114 (67.5%)	69 (61.1%)
Length of Stay, median (IQR)	11 (5-24)	11 (6-24)	10 (5-26)
Intensive Care Unit Admission Prior to culture, n (%)	32 (11.7%)	18 (10.4%)	14 (13.0%)
Immunocompromised, n (%)	49 (17.3%)	23 (13.5%)	26 (23.0%)
HIV or AIDS, n (%)	6 (2.1%)	6 (3.5%)	0
Transplant (solid organ), n (%)	2 (0.7%)	0	2 (1.8%)
Solid Tumor, n (%)	26 (9.2%)	12 (7.0%)	14 (12.4%)
Metastatic Cancer, n (%)	12 (4.2%)	6 (2.1%)	6 (5.3%)
Hematologic Malignancy, n (%)	6 (2.1%)	4 (2.4%)	2 (1.8%)
Cirrhosis	2 (0.7%)	0	2 (1.8%)
Specimen Source, n (%)			
Blood	40 (14.1%)	25 (14.6%)	15 (13.3%)
Urine	234 (82.4%)	143 (83.6%)	91 (80.5%)
Peritoneal fluid	5 (1.8%)	2 (1.1%)	3 (2.7%)
Other	5 (1.8%)	1 (0.6%)	4 (3.5%)
Organism, n (%)			
Escherichia coli	47 (16.6%)	17 (10.0%)	30 (26.6%)
Enterobacter cloacae	50 (17.7%)	8 (4.7%)	42 (37.2%)
Klebsiella aerogenes	13 (3.6 %)	1 (0.6%)	12 (10.6%)
Klebsiella pneumoniae	172 (60.8%)	144 (84.7%)	28 (24.8%)
Klebsiella oxytoca	1 (0.4%)	0	1 (0.9%)
Polymicrobial Infection, n (%)	84 (29.8%)	61 (35.7%)	23 (20.7%)
History, n (%)			
Previous stay in hospital (1 year)	215(75.7%)	142 (83.0%)	73 (64.6%)
Previous stay in long term care facility (1 year)	143 (50.4%)	106 (62.0%)	37 (32.7%)
Previous stay in long term acute care (1 year)	39 (13.7%)	36 (21.1%)	3 (2.7%)
Surgery	85 (29.9%)	47 (27.5%)	38 (33.6%)
Chronic Dialysis	30 (10.6%)	24 (14.0%)	6 (5.3%)
Previously Isolated same organism (1 year)	29 (10.4%)	27 (16.0%)	2 (1.8%)
Indwelling Devices, n (%)			
Any	200 (70.4%)	139 (81.3%)	61 (54.0%)
Central line	91 (72.8%)	69 (49.6%)	32 (51.6%)
Urinary Catheter	148 (84.1%)	112 (80.6%)	36 (58.1%)
Both Tracheostomy and PEG	45 (15.9%)	42 (28.1%)	6 (9.8%)
90-day Mortality	72 (25.4%)	44 (25.7%)	28 (24.8%)
In-hospital Mortality	19 (6.7%)	12 (7.0%)	7 (6.2%)

Missing values: Race - 17, Ethnicity - 49, Charlson Comorbidity Index - 6, Hospitalized - 2, Polymicrobial - 2, Organism source - 1, Previous organism- 6

Abbreviations: IQR – Interquartile Range, PEG – percutaneous enteric gastronomy

Table 7. Type and frequency of carbapenemase genes by organism in patients with carbapenem resistant isolates with available whole genome sequencing

Species	**CP-CRE (%)**	**Carbapenemase genes (n)**
Klebsiella pneumoniae	145 (84.3%)	KPC-3 (120), KPC-2 (19), KPC-38 (1), NDM-5 (2), NDM-1 (1), NDM-4 (1), NDM-9 (1)
Escherichia coli	17 (36.2%)	KPC-3 (13), KPC-2 (1), KPC-4 (1), NDM-5 (2)
Enterobacter cloacae	8 (16.0%)	KPC-3 (4), KPC-4 (3), IMP-13 (1)
Klebsiella aerogenes	1 (7.7%)	KPC-3 (1)

Figure 1. Georgia Emerging Infections Program catchment area

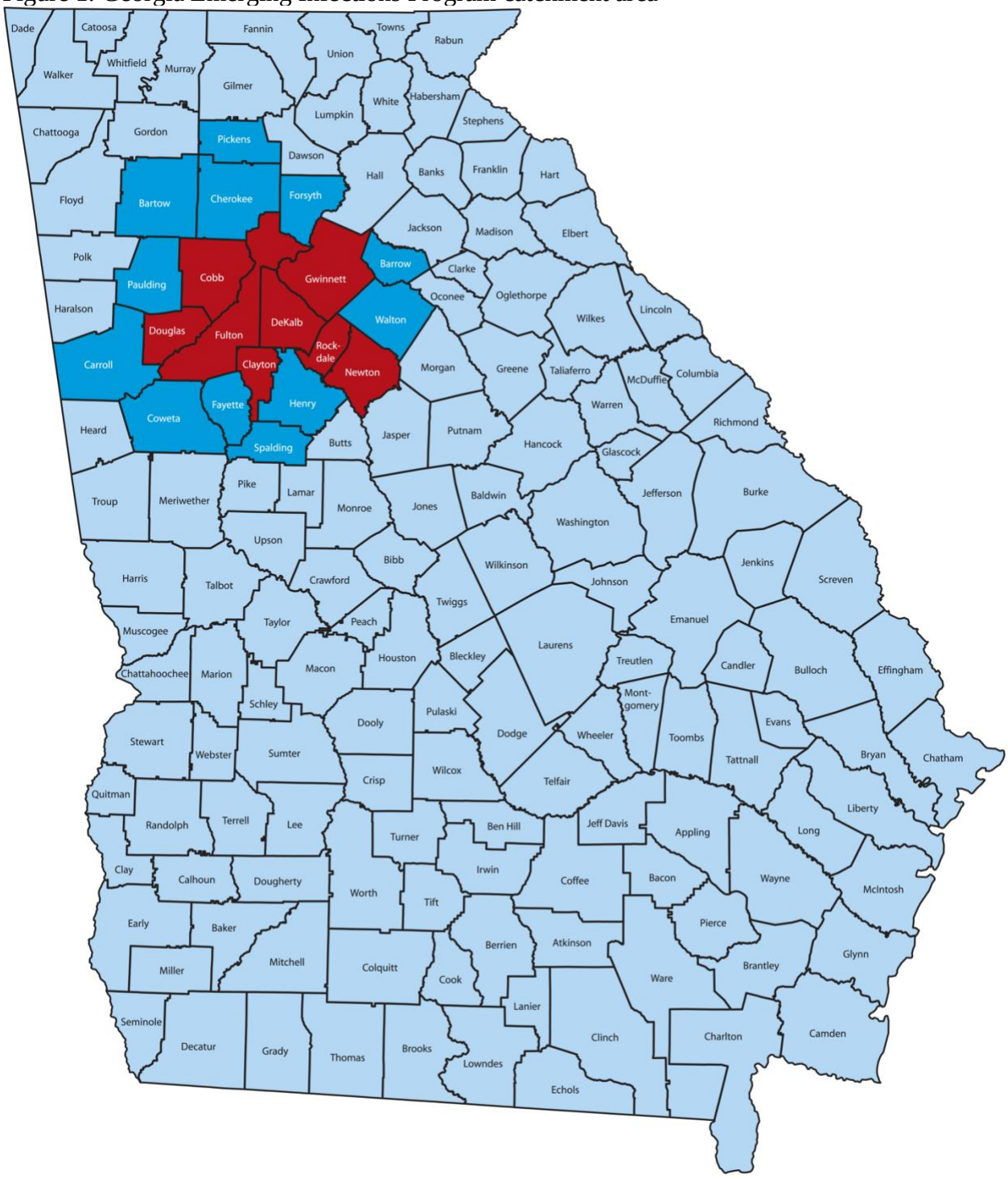

Figure 2. Plasmid with a transmissible genetic element

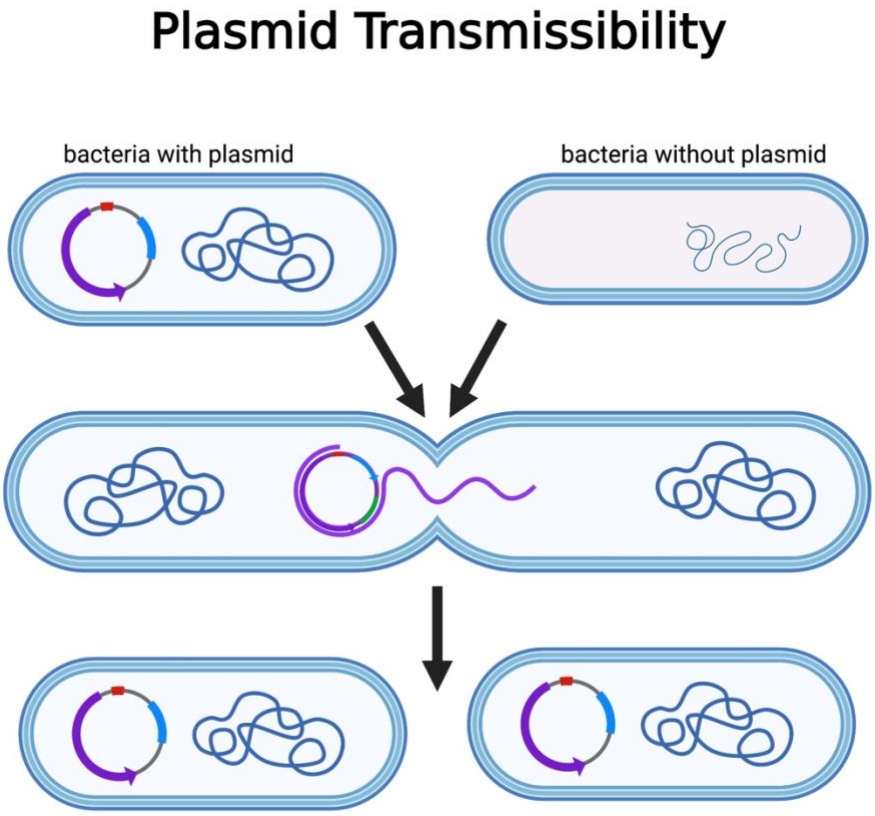

Figure 3. Directed acyclic graph of relationship between indwelling medical devices and 90-day mortality in patients with invasive carbapenem resistant Enterobacterales infections, Atlanta, Georgia, 2012 – 2019

Figure 3. Directed acyclic graph of relationship between indwelling medical devices and 90-day mortality

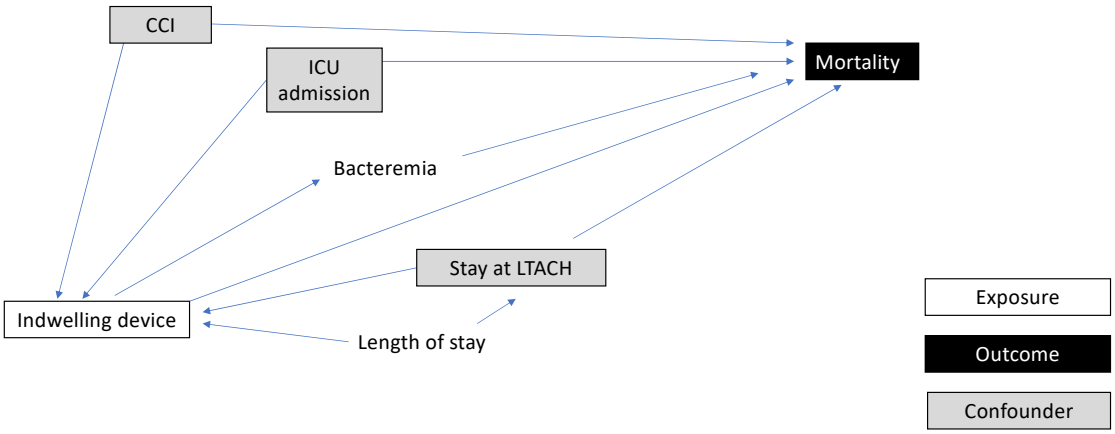

Figure 4. Directed acyclic graph of relationship between carbapenemase gene positivity and 90-day mortality in patients with carbapenem resistant isolates with available whole genome sequencing

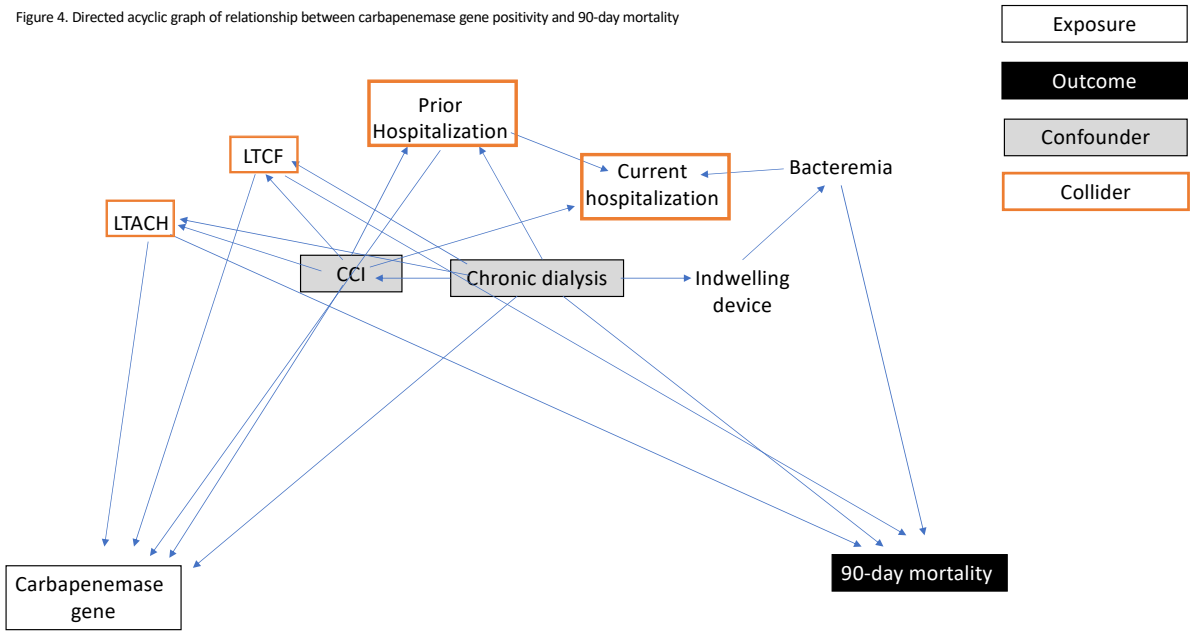

Figure 5. Annual case count and incidence of invasive carbapenem resistant Enterobacterales infections, Atlanta, Georgia, 2012 - 2019

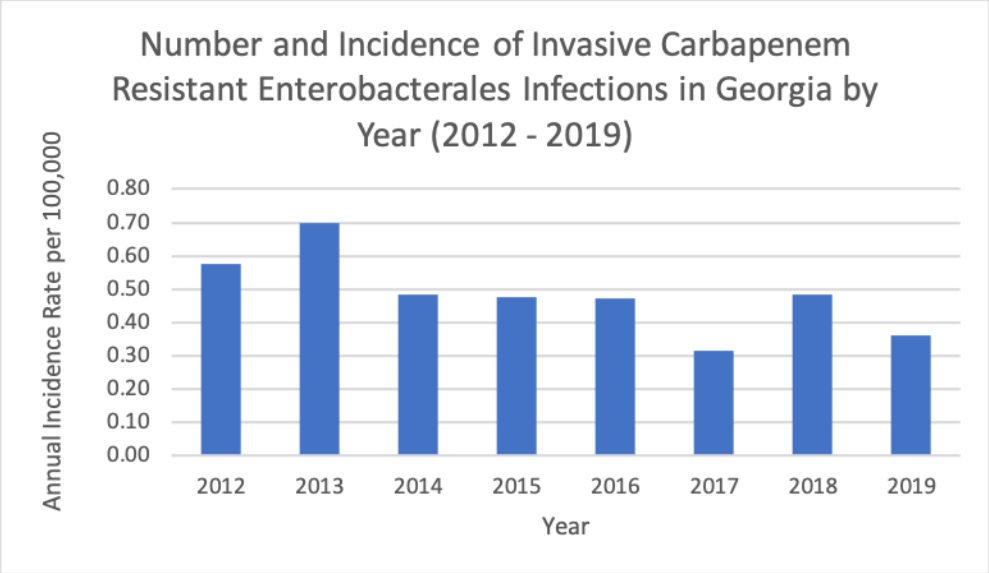

Figure 6. Kaplan Meier survival curve for those with versus those without carbapenemase genes in patients with carbapenem resistant isolates with available whole genome sequencing