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Approval Sheet

Evaluation of Risk Factors for Invasive Carbapenem Resistant Enterobacteriaceae Infections and Resultant Mortality in Atlanta, 2011-2015

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Abstract Cover Page

Evaluation of Risk Factors for Invasive Carbapenem Resistant Enterobacteriaceae Infections and Resultant Mortality in Atlanta, 2011-2015

By

Mary Elizabeth Sexton

B.S., Georgetown University, 2005

M.D., Emory University, 2011

Advisor: Jesse Jacob, M.D., M.Sc.

An abstract of

A thesis submitted to the Faculty of the

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ABSTRACT

Evaluation of Risk Factors for Invasive Carbapenem Resistant Enterobacteriaceae Infections and Resultant Mortality in Atlanta, 2011-2015
By Mary Elizabeth Sexton

Background

Carbapenem-resistant Enterobacteriaceae (CRE) have become an increasing public health concern, given limited treatment options and associated high mortality. Understanding risk factors for CRE infections of sterile sites (invasive infection) and for mortality may have important implications for prevention. A retrospective cohort study was performed using the Georgia Emerging Infections Program (EIP) CRE surveillance data to evaluate risk factors associated with invasive infection and mortality.

Methods

The study population comprised incident CRE cases from 8/2011 to 12/2015. A case required isolation, from urine or a normally-sterile site, of *E. coli*, *Klebsiella spp.*, or *Enterobacter spp*. that was carbapenem-nonsusceptible and resistant to third-generation cephalosporins. Cases were incident if the patient resided in the surveillance area and had no prior positive cultures in 30 days, with only the first incident case for each patient included. Cases were considered invasive infection if the patient had a sterile site culture positive during the 30-day period. Mortality was defined as in-hospital mortality for admitted patients, or 30-day mortality in long-term care facility or dialysis patients. Demographic characteristics and CRE risk factor prevalence were compared using chi-square analysis between patients with sterile site versus urinary cultures positive, and patients with fatal versus non-fatal outcomes. Multivariable logistic regression was performed to evaluate whether particular risk factors were associated with invasive infection and mortality.

Results

Of 567 CRE patients, 91 (16.0%) had an invasive infection and 476 (84.0%) had only urinary cultures positive. Central line presence, indwelling devices, and recent surgery were associated with invasive infection in multivariable analysis. The overall mortality rate was 9.0% (51/567), including 30 deaths in patients with urinary cultures positive (6.3%) and 21 deaths in patients with invasive infection (23.1%). In multivariable analysis, ICU stay, a central line, or invasive infection predicted mortality.

Conclusions

Device use was common and was associated with invasive infection. Patients with invasive infection and markers of severity of illness were more likely to die. Future research should focus on whether removal of unnecessary devices decreases risk of invasive infection with CRE, and whether early identification and initiation of appropriate antibiotic therapy in high-risk patients decreases mortality.

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INTRODUCTION

Antibiotic resistance among the Enterobacteriaceae, a family of gram-negative bacteria that includes *Enterobacter* species, *E. coli*, and *Klebsiella* species, has been increasing over the last 15 years with serious public health consequences. The Enterobacteriaceae are responsible for both relatively mild infections such as urinary tract infections, and invasive infections including bacteremia, meningitis, peritonitis, and osteomyelitis (1). Historically, these pathogens were susceptible to many antibiotics, including most β-lactams, with carbapenems considered last-line therapy. Carbapenem resistance has, however, been documented in the United States with surveillance systems identifying rising incidence since 2000 (1-3). The Center for Disease Control and Prevention's National Healthcare Safety Network (NHSN) found that the proportion of Enterobacteriaceae isolates in the United States that were carbapenem-resistant (CRE) rose from 1.2% in 2001 to 4.2% in 2011 (1). This increasing incidence of CRE infections is concerning because treatment options are limited and toxic, and the associated mortality is high (4, 5). In one early study, 48% of patients with a sterile-site infection with carbapenem-resistant *K. pneumoniae* died during their hospital stay (6).

Given these documented poor outcomes, earlier studies have attempted to identify risk factors for acquisition of CRE, progression from colonization to infection, and mortality. Most studies have identified patient comorbidities, prior healthcare exposures, and recent invasive devices or procedures as associated with CRE infections, but the specific associations have not always been

consistent among different studies. Further elucidation of these risk factors for severe CRE infections and associated mortality may have important implications for targeting of prevention interventions. The Georgia Emerging Infections Program (EIP) therefore began performing active, population-based laboratory surveillance for CRE in the eight-county Atlanta metropolitan area in August 2011, in order to determine disease burden and clarify patient characteristics.

The Georgia EIP collects data on all patients with urinary or sterile site cultures positive for CRE within the surveillance area. EIP staff complete a retrospective review of the medical chart once a case is identified, and document patient demographic characteristics and risk factors for CRE, based on those that have been identified in earlier studies, in a computerized database. This database was utilized to perform two retrospective cohort analyses comparing patients who had CRE present only in the urine to patients who had CRE present at a sterile site, and patients who had a fatal outcome to those who survived. These comparisons were done to achieve the following study aims: 1) To evaluate for differences between patients with only urinary cultures positive and those with invasive infection and to estimate the association between invasive CRE infection and healthcare exposures, medical device presence, and patient comorbidities; and 2) Among those who have acquired CRE, to estimate the association between mortality and potential risk factors, including patient demographic factors, healthcare exposures and devices, the presence of immunosuppression, and infection type.

BACKGROUND

The Enterobacteriaceae: Mechanisms of Carbapenem Resistance

The Enterobacteriaceae, including *Klebsiella* species, *Enterobacter* species, and *E. coli*, typically colonize the gastrointestinal tract but can be pathogenic in other locations (1). Treatment of infections caused by the Enterobacteriaceae has traditionally involved a wide range of antibiotic options but, as noted above, progressively increasing incidence of carbapenem resistance has been documented in the United States since 2000 (1, 3). There are several mechanisms by which Enterobacteriaceae can become carbapenem-resistant, including acquisition of bacterial genes coding for carbapenemases, and acquisition of combinations of genetic mutations that together decrease carbapenem efficacy.

Carbapenemases are enzymes that allow bacteria to render antibiotics in the carbapenem class ineffective via hydrolysis (1, 7, 8). Carbapenemase genes are particularly problematic because they are often carried on bacterial plasmids, and therefore are transferable not only between Enterobacteriaceae, but also to a variety of other bacterial species (1, 7-9). For example, during a CRE outbreak at the NIH Clinical Center in 2011, a patient infected with a carbapenemase-producing *Klebsiella* isolate spread the same isolate to another patient, and also had *Enterobacter* and *Citrobacter* species isolated from environmental cultures of his hospital room that were carrying a genetically-identical carbapenemase (9).

Not all CRE isolates carry a carbapenemase gene, however. Enterobacteriaceae can also become resistant to carbapenems via simultaneous

possession of a gene coding for a β-lactamase (an enzyme that hydrolyzes other classes of β-lactam antibiotics but in isolation does not usually affect carbapenem susceptibility) and a mutation in the bacterial cell membrane that makes it more difficult for antibiotics to enter (8, 10). Carbapenem-resistant Enterobacteriaceae isolates are considered CRE regardless of resistance mechanism, although a distinction is often drawn because of the potential for carbapenemase-producing isolates to cause outbreaks (1, 7, 11-13).

CRE Epidemiology in the United States

Existing surveillance systems demonstrate an increasing incidence of CRE infections in the United States in the last 15 years, with the emergence of carbapenemase-producing isolates starting in 2000 (7, 8). Among US academic medical centers submitting Enterobacteriaceae isolates from 1999-2008 to a voluntary international surveillance system, no meropenem resistance was found in 1999, but 2.3% of *Enterobacter* isolates and 5.6% of *Klebsiella* isolates were resistant by 2008 (2). This phenomenon has also not been limited to teaching hospitals. In 25 community hospitals in the southeastern US, the rate of CRE per 100,000 patient-days increased from 0.26 to 1.4 cases between 2008 and 2012 (3).

These increases in prevalence have been accompanied by reports of healthcare-associated infections with CRE in both hospitals and long-term care facilities, although the risk to patients likely differs by facility type and location. The Center for Disease Control and Prevention's (CDC) National Healthcare Safety Network (NHSN), which conducts national surveillance for multidrug-

resistant pathogens and healthcare-associated infections, found that 4.6% of acute care hospitals and 17.8% of long-term acute-care hospitals (LTACHs) who report data identified at least one central line-associated bloodstream infection or catheter-associated urinary tract infection caused by CRE from January through June of 2012 (1). CRE infections were more commonly reported in hospitals in the northeastern United States compared to other regions, and in academic medical centers compared to non-teaching hospitals (1).

While CRE cases were only reported in <5% of hospitals (1), a detailed examination of a small number of these cases demonstrates significant associated morbidity. 82% of affected patients in these cases required hospitalization, and 22% needed to be in an intensive care unit (ICU) (1). Prior studies have also shown high mortality in the setting of CRE infection. In a 2003-2006 study, 44% of patients with an infection caused by carbapenem-resistant *K. pneumoniae* died during their hospital stay, compared to 12.5% of those with an infection caused by carbapenem-sensitive *K. pneumoniae* (12). These observed increases in mortality may be multifactorial, with underlying patient characteristics and comorbidities, inappropriate empiric antibiotic therapy, and virulence of CRE all potentially playing a role (5).

Risk Factors for CRE Colonization

Given the above data regarding CRE incidence in U.S. hospitals, it would not make sense to empirically cover all infected patients for CRE since the infections are rare, but it is important to identify and treat high-risk patients given the associated morbidity and mortality. Therefore, an understanding of

risk factors for CRE is critical, and has been the subject of multiple prior studies. Most of these studies have consistently found that patient comorbidities, prior healthcare exposures, prior antibiotic use, and recent invasive devices or procedures are associated with CRE acquisition.

With respect to patient comorbidities, renal disease, diabetes, prior organ transplant, and autoimmune disease have all been documented as risk factors for CRE, suggesting that immunosuppression may play a role (6, 14-16). Immunosuppressed patients likely have high rates of hospitalization and antibiotic administration, however, and so it is difficult to assess the impact of immunosuppression itself on CRE risk.

Exposure to healthcare settings, length of hospital stay, and being in an ICU may also raise a patient's risk of acquiring CRE (12, 15, 17-22). Studies additionally suggest that residence in skilled nursing facilities (SNFs) and long-term acute-care hospital (LTACH) facilities may increase the risk of CRE infection. A study of 675 CRE cases in Los Angeles found that while the majority were identified in hospitalized patients, 34% were isolated in LTACHs and 8% in SNFs (23).

Patients' antibiotic exposures also appear to be a risk factor for CRE acquisition. In a case-case-control study comparing patients with a CRE infection to patients with carbapenem-susceptible Enterobacteriaceae infection and to uninfected controls, antibiotic use was associated with CRE infection in multivariable analysis (OR 4.4,p=0.05) (12). When a subgroup analysis of specific classes of antibiotics was performed, fluoroquinolone use was also associated with CRE infection (OR 7.2, p=0.04). None of the control group

patients were given a carbapenem, and so carbapenem use was not assessed as part of the multivariable analysis. However, almost one-third of the patients with CRE infection had been prescribed a carbapenem, which the study authors argued is suggestive of a relationship between use and development of CRE infection (12).

Invasive devices and procedures have additionally been shown to increase risk of CRE acquisition. Patients in one study in Greece with carbapenem-resistant *Klebsiella* infections were more likely to have a Foley catheter, an endotracheal tube, or a central line than uninfected controls (15). Another study found that the only significant predictor of infection with a carbapenem-resistant *Enterobacter* rather than with a carbapenem-sensitive *Enterobacter* was endotracheal intubation or the presence of more than one invasive device (24).

Risk Factors for Developing Invasive Infection

The CRE risk factors described above have been associated with acquisition of CRE, both in cases of asymptomatic colonization and in cases of true infection. Several studies have also explored risk factors for progression from colonization with CRE to invasive infection, as colonization is thought to be an intermediate step in invasive infection development. One of the largest studies done of patients positive for CRE evaluated 464 patients found to be colonized with resistant *Klebsiella* on surveillance rectal swabs, and found that 9% went on to develop invasive infection during the study period of almost three years. These patients were more likely to have diabetes or an underlying malignancy, and/or to have had an invasive procedure (25). An Israeli case-

control study of patients with positive rectal screening cultures for CRE during a hospital admission compared those who progressed to have a positive clinical culture to those who did not. Patients who progressed to infection were more likely to require an ICU stay, to have a diagnosis of diabetes, to have antibiotics administered, or to have a central line (11).

In a smaller study, it also appears that the presence of significant immunocompromise may influence progression from colonization to invasive infection. A study of nine liver transplant recipients in Germany with a history of CRE colonization found that eight of them (89%) ultimately developed a CRE infection, with five (56%) having bacteremia (14).

Risk Factors for Mortality

Mortality in the setting of CRE infection appears to be high, with rates of 30-50% documented in severe infections (4-6, 13). Several studies suggest that underlying patient comorbidities likely determine which patients are at highest risk (4-6). For example, a retrospective cohort study of 175 liver transplant patients compared those who acquired a CRE infection post-transplant to those who did not, and found a mortality rate of 71% in the group with CRE and 14% in the group without (26). This mortality rate is higher than what had been reported in prior studies, which may argue that underlying immunosuppression and other comorbidities in these transplant patients played a significant role. In two additional studies, patients with CRE infections appeared to have higher mortality than matched cases with carbapenem-susceptible infections and matched controls without infection in univariable analysis, but this effect was not

significant in multivariable analysis when controlling for patient characteristics (5, 27).

Severity of illness is also unsurprisingly associated with mortality in these patients. In one study of 99 patients with documented CRE infection, patients who required an ICU admission were more likely to die (6). The presence of invasive CRE infection rather than colonization also appears to impact mortality rates (5, 28). When seven surveillance sites across the United States compiled data reviewing cases of CRE present in urine and sterile site cultures, the overall mortality rate was 9%. However, that reflected a predominance of patients with only a urinary culture positive, in whom the mortality rate was 5.5%, compared to a rate of 27.5% in patients with a sterile site cultures positive (28).

Current Knowledge Gaps

Risk factors for CRE acquisition have been well-studied, but studies of risk factors for progression from colonization to invasive infection have been more limited, and it remains unclear which risk factors are most critical as they have differed between studies (11, 25). In particular, the role of immunosuppression in CRE progression might benefit from additional evaluation, as studies have often focused on only one etiology of immunosuppression (i.e. solid organ transplant), or have included only small numbers of patients with CRE, resulting in small sample sizes of immunosuppressed patients that have made it difficult to draw significant conclusions (14, 15, 29). Further clarification of these risk factors might be helpful in targeting efforts to prevent progression, which is important as it appears that invasive infections have significantly higher mortality rates (28).

Studies of risk factors for mortality in the setting of CRE infection have suggested that underlying patient conditions play a role, as described above, but have had inconsistent results with respect to the particular comorbidities that place patients at highest risk (5, 6, 27). Additionally, it appears that invasive infections are associated with higher mortality than urinary infections or colonization, but mortality rates in patients who progress from non-invasive to invasive infection and in patients who have recurrent episodes of CRE infection have not been well-studied. This information could be particularly helpful in the development of targeted interventions to limit mortality in a very high-risk patient population.

METHODS

Study Aims

This study was designed to achieve two aims. First, to evaluate whether differences exist between patients with invasive CRE infection and those with only positive urine cultures, and to estimate the association between invasive CRE infection and patient comorbidities, healthcare exposures, and the presence of medical devices. Second, in patients with CRE, to estimate the association between mortality and patient demographic factors, immunosuppression, healthcare exposures and devices, and infection type.

Study Population

The Georgia Emerging Infections Program (EIP) has performed active population-based laboratory surveillance for CRE cases in the 8-county Atlanta metropolitan area since August 2011. EIP surveillance identified 567 patients who had at least one incident case of CRE from August 2011 to December 2015, and a retrospective chart review was conducted of the first incident case during that time period for each of these patients. A case required isolation, from urine or a normally-sterile site, of *E. coli*, *Klebsiella spp*., or *Enterobacter spp*. that was carbapenem-nonsusceptible, and resistant to all tested third-generation cephalosporins. Cases were considered incident if the patient resided in the surveillance area and had no history of a prior culture positive for the same CRE organism in the past 30 days.

Laboratory Procedures

Carbapenem-nonsusceptibility was defined using the Clinical and Laboratory Standards institute breakpoints as a minimum inhibitory concentration (MIC) >1 to either meropenem, imipenem, or doripenem (30). Isolates also had to be resistant to all tested third generation cephalosporins. Isolates that were resistant only to ertapenem but susceptible to the other carbapenem antibiotics were not considered CRE cases. CRE isolates meeting this definition were identified using an electronic query validated on automated testing instruments present in each of the twenty-three participating laboratories, as previously described (31).

Data Collection and Variable Definitions

Once a CRE isolate was identified, a case report was completed by EIP staff via a retrospective review of the patient's medical record. Information was collected via chart review regarding the patient's demographic information, location at the time of the culture (inpatient facility versus outpatient clinic), organism present on culture and whether it was carbapenemase-producing, culture site and type of infection, comorbidities, risk factors for CRE, and outcome at discharge. EIP staff then entered the information from that case report into an electronic database, which was utilized for this study.

CRE risk factors that were assessed for each case included: hospitalization for at least three days prior to the positive culture; ICU admission in the seven days prior to the positive culture; prior hospitalization or surgery within the last year; residence in a long-term care facility or long-term acute care facility in the

last year; the presence of a central venous catheter, a urinary catheter, or another indwelling device (including endotracheal tubes, tracheostomies, nasogastric or gastric tubes, and nephrostomy tubes) in the two days prior to positive culture; and underlying immunocompromise.

All cases were assessed for documentation in the chart of the presence any of the following immune-compromising conditions on admission: diabetes mellitus; chronic renal failure; cirrhosis or liver failure; hematologic malignancy; solid tumor malignancy; history of solid organ transplant; AIDS; and/or a connective tissue disease. Patients were considered diabetic if they had a history of type I or type II diabetes noted in the medical record. Chronic renal failure designation required a creatinine ≥3 mg/dl, a documentation of end-stage renal disease and/or a need for dialysis, or a history of renal transplant. Cirrhosis required documentation of cirrhosis in the medical record without current clinical manifestations; patients were considered to have liver failure if they were symptomatic. Patients were classified as having a hematologic malignancy if they had a history of leukemia, lymphoma, or multiple myeloma within the last year, and as having a solid tumor malignancy if they had any history of cancer involving a solid organ (excluding non-melanoma skin cancers and *in situ* cervical carcinoma) within the last five years. Patients with metastatic solid tumors were categorized separately and were also included in the definition of immunosuppression. Patients were classified as having had a solid organ transplant if they had ever had a kidney, liver, heart, lung, or pancreas transplant. An AIDS designation required either a documented diagnosis of AIDS in the medical record or a CD4 count <200 at admission in a patient known to be HIV

positive. Patients were considered to have connective tissue disease if they had a documented history of lupus, rheumatoid arthritis, polymyositis, polymyalgia rheumatica, or mixed connective tissue disease.

Cases with a positive culture from a normally-sterile site (blood, cerebrospinal fluid, pericardial fluid, pleural fluid, peritoneal fluid, synovial fluid, or bone) were considered to represent invasive infection. In the event that the initial positive culture for a case was urinary but a subsequent culture from a sterile site was positive within the same 30-day period, the case was included in the invasive infection group.

Mortality was defined as in-hospital mortality for admitted patients, or 30-day mortality for those in a long-term care or dialysis center. Patients with unknown outcomes were presumed to have survived for the purposes of the analysis. In order to be able to compare mortality rates in different clinical scenarios, two additional variables of progression and recurrence were also defined. Patients with an initial positive urine culture and a subsequent invasive infection within 30 days were considered to have progressed, and patients with multiple positive cultures for the same organism >30 days apart were considered to have recurred.

Institutional Review Board Approval

CRE surveillance and data collection by the Georgia Emerging Infections Program has been evaluated by the Emory University Institutional Review Board and was considered exempt from IRB review at the time of this study.

Data Management/Statistical Analysis

CRE cases entered into the EIP database were classified as invasive infection or urinary infection as discussed above. Baseline demographic characteristics of sex, age, race, and residence (defined as location four days prior to positive culture) were compared between patients with invasive infection and urinary infection and between patients with fatal and non-fatal outcomes, using chi-square analysis for categorical variables and t-tests for continuous variables, with $p<0.05$ considered significant.

The prevalence of suspected risk factors for CRE, including recent healthcare exposures, long-term care facility residence, hospitalization or surgery in the last year, hospitalization for three or more days prior to culture, ICU stay prior to culture, presence of indwelling devices (such as urinary catheters, central venous catheters, tracheostomy tubes, or gastrostomy tubes), and baseline immunocompromised status, was also compared between patients with invasive and urinary infections. The prevalence of these risk factors was also compared between patients with fatal and non-fatal outcomes, with one adjustment (any ICU stay before or after culture was assessed) and two additions (the presence of a carbapenemase-producing organism and whether the infection was invasive or non-invasive). Chi-square analyses or Fisher's exact tests were utilized as appropriate to evaluate for differences, again with $p<0.05$ considered statistically-significant.

If demographic and risk factor data could not be verified in the medical record, that information was categorized as "unknown." This information was not considered to be missing at random, as data were more likely to be missing in

some of the sickest patients (who might have required transfer from a hospital outside the surveillance area without access to those records) and in the healthiest patients (who were likely in a community facility for the duration of their illness with more limited medical record-keeping). Sensitivity analyses were performed for the risk factor variable of being in the ICU prior to culture (5.47% missing) and the outcome variable (3.88% missing) to assess whether there was a significant impact of the missing information on the comparisons of the invasive and urinary infection groups for the former, or the fatal and non-fatal outcome groups for the latter. If there was no significant impact, the chi-square comparisons were performed with patients with unknown ICU stay prior to culture assumed not to have required the ICU, and with patients with unknown outcomes assumed to have survived.

The relationship between each of the suspected CRE risk factors and both invasive infection and mortality was assessed using univariable logistic regression. Crude odds ratios were calculated for the odds of a patient having invasive infection with CRE compared to urinary infection, and for a patient having a fatal outcome compared to a non-fatal one, in the presence of each of the CRE risk factors.

A multivariable logistic regression model was constructed for the primary outcome of invasive infection, initially using ten variables thought most likely to have clinical significance based on prior studies. Several models were considered to evaluate which of the variables had remained significant in multivariable analysis with $p<0.05$, initially using backward and stepwise selection. The addition of interaction terms of potential clinical significance was also performed.

The best-fitting model was then selected based on evaluation of the c-statistic, the results of the Hosmer-Lemeshow goodness of fit test, and assessment of clinical relevance.

Multivariable logistic regression was similarly performed for the primary outcome of mortality, initially using twelve risk factor variables thought most likely to be significant, based on univariable analysis and suspected clinical importance. Backward, stepwise, and manual selection were again utilized to select the best-fitting model as described above, with goodness of fit evaluated on the basis of the c-statistic and Hosmer-Lemeshow test.

Statistical analysis was performed using SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

Population Demographic Characteristics and CRE Risk Factor Prevalence

768 cases were identified in 567 unique patients from August 2011-December 2015. The majority of these patients were female (57.5%) and black (51.9%), with an average age of 63.2 years±18.0 years. Four days prior to positive CRE culture, 37.2% were living in a LTCF, 32.8% were living in a private residence, 16.0% were already admitted to the hospital, and 7.2% were living in a LTACH (see Table 1). More than 60% had been hospitalized in the last year, 49.9% had lived in a LTCF in the last year, 24.9% had surgery in the last year, and 10.6% had lived in an LTACH in the last year (see Table 1). More than 50% had a urinary catheter in place two days prior to culture, 30.2% had a central venous catheter, and 36.3% had another indwelling device. 20.1% had been hospitalized for at least three days prior to the culture, and 13.2% had been in the ICU in the week prior (see Table 1). 63.1% of the patients qualified as immunosuppressed, with diabetes mellitus (44.1%) and chronic renal disease (26.1%) the most common immune-suppressing conditions.

Microbiologic Data and Infection Type

The majority of positive cultures were *Klebsiella pneumoniae* (58.6%), followed by *E. coli* (18.2%), *Enterobacter cloacae* (13.9%), *Enterobacter aerogenes* (7.2%), and *Klebsiella oxytoca* (2.1%). 476 patients (84.0%) had a urinary culture positive, while 91 (16.0%) had a sterile site culture positive. 75/91 of the sterile site cultures were from the blood (82.4%), while 10 (11.0%) were

from peritoneal fluid, 3 (3.3%) were from another sterile drainage site, 2 (2.2%) were from pleural fluid, and 1 (1.1%) was from a bone culture. There were not significant differences in organism type between patients with urine and sterile site cultures positive, with the exception of *E. coli*, which had higher prevalence among patients with urinary cultures positive (p=0.03).

CRE Incidence in Atlanta

Data collection in 2011 did not begin until August, but from 2012-2015 all incident CRE cases in the eight-county metropolitan Atlanta area were included. From 2012-2013, the population of the metropolitan area was ~3.9 million people, and so crude incidence ratios reflect that population (28). There were 175 incident cases in 2012 (4.58 cases/100,000 people), 181 incident cases in 2013 (4.68 cases/100,000), 171 incident cases in 2014 (4.43 cases/100,000), and 149 incident cases in 2015 (3.86 cases/100,000) (see Figure 1).

Univariable Analysis of Risk Factors for Invasive Infection

Patients with invasive infection were more likely to be male (53.9% vs 39.9% of those with urinary cultures positive, p=0.01), to be younger (average age 55.8±16.3 years, versus 64.6±18.0 years in the group with urinary cultures positive, p<0.0001), and to have been admitted to either an LTACH (15.4% vs 5.7%, p=0.001) or the hospital (29.7% vs 13.4%, p=0.0001) four days prior to their positive culture (see Table 1).

The prevalence of 10 suspected CRE risk factors, including healthcare exposures, devices, and underlying patient conditions, was also compared

between the group of 91 patients with invasive infections, and the group of 476 patients with only urinary cultures positive (see Table 1). Hospitalization for ≥3 days (40.7% vs 16.2%, p<0.0001), surgery within the last year (42.9% vs 21.4%, p<0.0001), ICU stay prior to positive culture (28.6% vs 10.3%, p<0.0001), central venous catheter presence (65.9% vs 23.3%, p<0.0001), other indwelling device presence (63.7% vs 31.1%, p<0.0001), LTACH stay in the last year (18.7% vs 9.0%, p=0.006), immunocompromised status (75.8% vs 60.7%, p=0.006), and hospitalization in the last year (74.7% vs 60.1%, p=0.008) were all more common in the group of patients with invasive infection. LTCF stay in the last year was more common in patients with urinary cultures positive (53.6% compared to 30.8% of patients with invasive infection, p<0.0001). Urinary catheters were present in the majority of both groups (53.9% of those with invasive infection vs 50.2% of those with urinary cultures positive), and there was no statistically-significant difference between the groups (p=0.53).

In univariable logistic regression, the presence of a central venous catheter (OR 6.36, 95% CI 3.93-10.31), presence of another indwelling device (OR 3.90, 95% CI 2.44-6.23), hospitalization for ≥3 days (OR 3.55, 95% CI 2.19-5.76), ICU stay prior to culture (OR 3.35, 95% CI 1.94-5.78), surgery in the last year (OR 2.75, 95% CI 1.72–4.40), LTACH stay in the last year (OR 2.31, 95% CI 1.25–4.27), immunocompromised status (OR 2.03, 95% CI 1.21-3.39), and hospitalization in the last year (OR 1.96, 95% CI 1.18-3.26) all had statistically-significant association with invasive infection rather than urinary infection, as shown in Table 2. LTCF residence in the last year appeared protective against invasive infection (OR 0.39, 95% CI 0.24-0.64), and the presence of a urinary

catheter (OR 1.16, 95% CI 0.74-1.81) did not significantly predict invasive infection rather than urinary infection.

Multivariable Modeling of Risk Factors for Invasive Infection

In multivariable logistic regression, the presence of a central venous catheter (OR 3.58, 95% CI 2.06-6.23), the presence of another indwelling device (OR 2.34, 95% CI 1.35-4.06), and surgery within the last year (OR 1.81, 95% CI 1.08-3.05) were significantly associated with invasive infection, while LTCF residence in the last year was protective against invasive infection (OR 0.44, 95% CI 0.26-0.75), using both backward selection and stepwise selection modeling (see Table 2). This model had AUC = 0.80 with a Hosmer-Lemeshow goodness of fit p=0.06. While hospitalization ≥3 days, ICU stay prior to culture, and immunocompromised status were significant in univariable logistic regression, none was significantly associated with invasive infection in multivariable analysis, and their addition to the model did not change the AUC.

When individual components of immunocompromised status were evaluated in the model, the subset of chronic renal failure patients on chronic dialysis had a significant association with invasive infection (OR 3.61, 95% CI 1.89-6.87). Central venous catheter presence (OR 2.85, 95% CI 1.60-5.08) and other indwelling device presence (OR 2.51, 95% CI 1.43-4.39) were associated with invasive infection but surgery within the last year was not significant in this model. Long-term care facility residence in the last year was protective (OR 0.40, 95% CI 0.23-0.67). This model also had an AUC =0.80, but had improved goodness-of-fit assessed via the Hosmer-Lemeshow test (p=0.43). No interaction

terms between the significant predictors remained in this model using backward selection with $p<0.05$.

Patient Outcomes and Mortality Rates

The overall mortality rate was 11.3% (64/567), including 33 deaths in 463 patients with only urine cultures positive (7.1%) and 31 deaths in 104 patients with at least one invasive infection (29.8%) (see Figure 2). 51 patients died at the time of their initial infection, and 13 died during a recurrent infection. Of deaths in patients with a history of invasive infection, 17 occurred in 77 patients at initial infection (22.1%), 4 occurred in 14 patients with progression (28.6%), and 10 occurred in 29 patients with a urinary or invasive recurrence (34.5%) (see Figure 2). While mortality rates were higher in progression and recurrence than in initial invasive infection, these differences were not statistically-significant ($p=0.41$).

Univariable Analysis of Risk Factors for Mortality

Patients with a fatal outcome did not differ from patients who survived with respect to gender (92.9% of women survived compared to 88.3% of men, $p=0.06$), race (90.1% of white patients survived compared to 90.5% of black patients, $p=0.89$), or average age ($p=0.91$). Patients who died were more likely to have been in an LTACH (19.6% vs 6.0%, $p=0.002$) or hospitalized (39.2% vs 13.8%, $p<0.0001$) four days prior to positive culture, while patients who survived were more likely to have been at home (34.5% vs 15.7%, $p=0.006$) or in a LTCF (38.6% vs 23.5%, $p=0.03$) (see Table 3).

The prevalence of twelve additional potential risk factors was compared in patients with fatal and non-fatal outcomes (see Table 3). ICU stay (64.7% vs 22.1%, p<0.0001), a central line (70.6% vs 26.2%, p<0.0001), a non-urinary indwelling device (70.6% vs 32.9%), an invasive infection (41.2% vs 13.6%, p<0.0001), hospitalization for ≥3 days (43.1% v 17.8%, p<0.0001), LTACH stay in the year prior (21.6% vs 9.5%, p=0.008), and immunocompromised status (78.4% vs 61.6%, p=0.02) were more common in patients who died (see Table 3).

In univariable logistic regression, central venous catheter presence (OR 6.77, 95% CI 3.60-12.76), ICU stay (OR 6.47, 95% CI 3.51-11.91), presence of another indwelling device (OR 4.88, 95% CI 2.60-9.17), invasive rather than urinary infection (OR 4.46, 95% CI 2.42-8.22), hospitalization for ≥3 days (OR 3.50, 95% CI 1.92-6.36), LTACH stay in the year prior (OR 2.62, 95% CI 1.26-5.44), and immunocompromised status (OR 2.26, 95% CI 1.14-4.52) were all significantly associated with a fatal outcome (see Table 4).

Multivariable Modeling of Risk Factors for Mortality

In multivariable analysis, ICU stay (OR 3.51, 95% CI 1.79-6.88), the presence of a central venous catheter (OR 3.26, 95% CI 1.59-6.70), and having an invasive rather than a urinary infection (OR 2.24, 95% CI 1.14-4.40) were associated with mortality with p<0.05, using both backward and stepwise selection modeling (see Table 4). This model had AUC=0.80, with goodness of fit confirmed using the Hosmer-Lemeshow test (p=0.58). Addition of other variables with high odds ratios in univariable analysis (i.e. the presence of another indwelling device) to the model did not significantly improve model fit,

as measured by the change in the c-statistic. No interaction terms were statistically-significant associations with mortality as the outcome.

DISCUSSION

CRE Incidence Trends

Crude annual incidence of CRE in the Atlanta metropolitan area does not appear to be increasing from 2012-2015, which is inconsistent with earlier national data that suggested steadily increasing rates from 2000-2012. There are several possible explanations for this finding, which may be multifactorial. First, because of the way EIP surveillance is done using an automated query of the microbiology lab instruments in all participating laboratories, all CRE cases in Atlanta should have been captured from the beginning of the study period. Because data collection was not dependent on institutional reporting, any apparent increase in incidence due to increased awareness over time is eliminated. Additionally, it is possible that there is truly a plateau in CRE incidence. As seen in this study, patients who acquire CRE infections tend to be chronically-ill with multiple comorbidities, and so there are only a limited number of patients who are at risk. This incidence plateau could also be the result of increased awareness and successful infection control interventions at healthcare institutions. The Meropenem Yearly Susceptibility Test Information Collective (MYSTIC) surveillance program in the United States similarly found that incidence of carbapenemase-producing Klebsiella increased from 2004-2007 but then decreased in 2008, which the study authors attributed to dedicated prevention efforts (2). It would be interesting to survey the Atlanta hospitals in the EIP catchment area regarding policies for screening and isolation of CRE

patients and for antimicrobial stewardship, to see if there is any relationship between implementation of these policies and changes in CRE incidence.

Invasive Infection Risk Factors

The strongest associations with invasive infection in this study were non-urinary device use, chronic dialysis, and surgery in the last year, which all involve procedural interventions. This is not surprising, given data from prior CRE studies also suggested that invasive manipulations were associated with progression from colonization to sterile site infection (11, 25). This emphasizes the need for an ongoing focus on minimizing device use in high-risk patients, promoting good device maintenance practices, and removing devices as quickly as possible when they are no longer necessary for patient care. It also raises questions about what best practices should be in patients known to be colonized. For example, chronic dialysis patients with a history of CRE colonization could be a priority for creation of arteriovenous fistulae for dialysis access, rather than pursuing dialysis through indwelling central venous catheters.

Based on prior study results, we had expected to see an association between immunosuppression and invasive infection, but this was not statistically-significant in multivariable analysis. There may be several reasons that we did not see this association, including the use of a composite variable for immunocompromised status. It is possible that certain immune-suppressing conditions pose higher risk than others, and that there are gradations of risk based on the severity of the underlying illness. For example, diabetes mellitus was included in this variable, but this could have captured both well-controlled

patients taking oral hypoglycemic medications, and poorly-controlled patients requiring insulin. Also, approximately 43% of the invasive infections were considered hospital-onset, with cultures not positive until three or more days into an admission, which may indicate again that things we do to a patient from a procedural standpoint have more impact than their underlying conditions. Finally, because their underlying conditions lead to frequent contact with the healthcare system, immunocompromised patients may have an increased likelihood of having the risk factors identified as most important in this study. For example, among the diabetic patients, 34.4% had a central venous catheter, 44% had another indwelling device, and 28.4% had had surgery in the last year. This could help to explain why prior studies have identified immunosuppression as a CRE risk factor.

Similarly, solid organ transplant recipients, particularly liver transplant patients, have been previously studied as a high-risk population for CRE infection (14, 26), and the results from this portion of the study suggest several reasons that this association between transplant and CRE infection could exist. Renal transplant patients may require chronic dialysis in the months and years leading up to their transplant, and then they often have several indwelling lines and devices at the time of transplant surgery, in addition to undergoing the surgery itself.

Long-term care facility residence has been identified as a risk factor for CRE in multiple studies (16, 23, 28), but appeared protective against invasive infection here. These two ideas are not necessarily mutually-exclusive, as long-term care facility exposure may increase risk of CRE acquisition, but invasive

infection risk may be more dependent on subsequent invasive procedures that are more common in inpatient settings. Additionally, this apparent protective effect of LTCF residence against invasive infection may simply reflect a strong association between LTCF residence and CRE urinary colonization and infections. LTCFs may not use the same guidelines for when to perform urinary cultures that are utilized in the hospital, and so may identify higher rates of urinary colonization. It is also possible that their urinary catheter use differs from the inpatient setting.

Mortality Risk Factors

The overall mortality rate of 11.3% seen in this study is lower than has previously been reported, although it is similar to the rate seen in the national EIP surveillance study from 2012-2013, likely because the majority of CRE cases in both studies were urinary rather than invasive disease (28). Attributable mortality in patients with CRE is also very difficult to determine, because the typical patient population who acquires infection has many medical comorbidities, which may contribute to differences in reported mortality among multiple studies. Additionally, some of initial data on CRE mortality rates is now more than ten years old -- for example, the study that identified a 48% mortality of invasive disease was conducted from 2004-2006 (6) -- and so it is also possible that increased recognition of CRE as a possible diagnosis, improved diagnostic testing, and new antibiotic options contributed to the decreased mortality rate seen in this study.

The strongest predictors of mortality were markers of illness severity (ICU stay and the presence of an invasive infection) and central venous catheter presence. This is unsurprising, as it would be expected for the sickest patients to have the highest risk of death. However, confirming that these risk factors are the most strongly associated with mortality in the setting of CRE infection has important implications for patient prognosis and prevention. It is possible that identification of CRE colonization or infection in an ICU patient may offer information regarding the severity of their illness that could give the medical team and the patient's family assistance in healthcare decision-making. Patients with CRE and these risk factors for mortality would also be targets for aggressive treatment interventions, including device removal when possible.

Mortality rates were also higher in patients who progressed from urinary to invasive infection and in patients with invasive CRE recurrence, although these differences were not statistically-significant. The lack of statistical significance may be attributable to small sample sizes in these categories, as there were only 14 patients with progression in the study. It would therefore be interesting to look at these data across the national EIP surveillance to see if significant differences exist with increased power. Regardless, given that the mortality rate in patients with progression and invasive recurrence approached one-third, these may also be important groups for targeting of interventions. The high mortality in patients with progression may reflect difficulties in identifying and treating CRE early in a patient's course, and so improvements in CRE diagnostic testing might have benefit in those cases. Given that rates are also high with recurrent disease, patients with a history of CRE could also be a focus for interventions

after their initial episode, including ensuring that their history is clearly identified in their medical record (32) so that they receive CRE-specific treatment with any subsequent severe infections, and possibly attempting decolonization.

Study Strengths

To our knowledge, this is one of the largest cohorts of CRE cases in the literature. Cases were identified via active population-based surveillance, allowing for descriptions of CRE incidence in the Atlanta metropolitan area. Additionally, while some prior studies have focused on CRE risk factors in patients in a single healthcare setting (i.e. inpatient or a long-term care environment), this study included data from multiple institutions across the healthcare spectrum, which strengthens the generalizability of the results.

Generalizability may also be increased because this surveillance was conducted in an area without an established CRE outbreak leading to high-level spread. While crude annual incidence in the Atlanta area was higher than the incidence reported by the EIP sites in Colorado, Minnesota, New Mexico, New York, and Oregon on 2012-2013 surveillance (28), there have not been documented outbreaks, and so the Georgia EIP data allows for analysis of CRE risk factors in a metropolitan area where transmission dynamics should be relatively stable.

Finally, the surveillance and data collection methods utilized by the Georgia EIP support the reliability of the data. The use of an automated query of microbiology lab data to compile the list of cases eliminates any reliance on institutional reporting, and so all cases that meet the surveillance definition

should be captured. Medical record reviews were subsequently carried out by trained personnel using a standardized process, leading to only a small number of variables for which there was missing data. Given the large cohort size and the robustness of the data capture, CRE risk factors that are statistically-significant in the analysis should provide good starting points for future intervention design.

Limitations

There are several study limitations with respect to characterization of the positive urine cultures, missing data for a small number of variables, mortality estimates, and the potential for unmeasured confounding.

Positive sterile site cultures for CRE clearly represent an infection, but it is difficult to differentiate between infection and colonization when only the urinary culture is positive. It is highly likely that some of the patients with positive urine cultures were colonized in the urine without any related clinical syndrome, but it is difficult to make that determination based on data collected from the medical record retrospectively. The chart review does include recording of information about patient-reported symptoms, such as dysuria, suprapubic tenderness, and urinary frequency, but these are both non-specific and difficult to assess in patients who are altered, non-verbal, or critically-ill. Patients with urinary colonization may have differences in risk factors, likelihood of progression to invasive infection, and mortality when compared to patients with urinary infection, but it was not possible to make that distinction in this study.

While overall there was a limited amount of missing data, there were several variables for which data collection was more challenging. Patient race

was missing in >10% of cases, and carbapenemase testing was only reported to have been performed on <50% of isolates, which did not allow for a robust assessment of whether resistance mechanism impacted development of invasive infection or mortality in this cohort.

Mortality rates may also be underestimated in the EIP cohort, as the data reflect only in-hospital mortality for patients who were admitted to the hospital, and 30-day mortality in patients who were admitted to a long-term care facility or utilized a dialysis center. Patients who were discharged from a hospital to a hospice facility, or who otherwise died within 30 days of infection but after hospital discharge, are not captured.

Finally, it is possible that there are unmeasured confounders impacting the multivariable modeling. For example, antibiotic administration appears to be a risk factor for the acquisition of CRE (12), and so could play a role in both invasive infection and mortality. However, it is difficult to accurately account for all recent antibiotic administration in patients who may access care at a variety of inpatient and outpatient facilities, and so this data is not routinely collected as part of EIP surveillance.

Future Directions

The study results provide a starting point for the development of predictive modeling and for design of future investigations of CRE transmission dynamics and CRE prevention interventions.

Ideally, patients at highest risk for development of invasive infection with CRE and associated mortality could be identified early in a hospitalization. These

are patients in whom high-risk procedures like central venous catheter placement should be avoided whenever possible. They likely should also receive empiric antibiotic therapy that includes coverage for CRE immediately upon having any signs or symptoms of infection. Therefore, the ability to do predictive modeling could be helpful both in prevention efforts and in targeting of appropriate early antibiotic therapy in patients who do become infected. It would be interesting to trial combinations of risk factors identified in this study (for example, chronic dialysis, central venous catheter presence, and other indwelling device presence) to construct a predictive model for development of invasive infection with CRE in someone known to be colonized, and then to prospectively validate this model. If progression to invasive infection could be predicted, that might in turn suggest a role for screening at-risk patients for the presence of CRE colonization on hospital admission. Similarly, predictive models could be constructed for mortality in patients with CRE infection, which could again help with trying to avoid high-risk interventions like device placement in these patients. Additionally, since CRE infections occur most often in chronically-ill patients, predictive modeling of mortality could help medical teams and families to assess patient prognosis when making decisions regarding the goals of care.

The Georgia EIP data also suggest that both inpatient facilities and long-term care facilities play a role in CRE transmission among patients, and similar findings were identified in the 2012-2013 national EIP surveillance compilation (28). The majority of patients in this study had been in a LTCF or LTACH in the year prior to their positive culture, and similar numbers of patients were discharged to a facility following hospitalization for CRE infection. LTACH

residence in particular was also a risk factor for both invasive infection and mortality in univariable analysis, although the association was not significant in multivariable modeling. Therefore, starting with the 2016 EIP CRE surveillance data, there is a plan to utilize geocoding to evaluate how CRE is spreading in Atlanta and whether cases concentrate in particular facilities, as these locations would then be ideal sites for implementation of prevention interventions. Attempts are also being made to collect larger numbers of culture isolates in addition to performing chart reviews, so that genetic sequencing can be performed to support evidence for CRE spread.

Finally, the data provided about CRE risk factors by this study argue that some of the most effective interventions may involve aggressive infection control measures and antibiotic stewardship. Future studies could involve targeting interventions, such as education of healthcare staff about device use and device handling (for example, the importance of hand hygiene, central venous catheter maintenance and access strategies, and endotracheal and PEG tube maintenance) to facilities with the highest incidence of CRE, and then evaluating for subsequent changes in incidence rates, particularly of invasive infections, and mortality.

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TABLES AND FIGURES

Table 1. Comparison of Baseline Demographic Information and the Prevalence of Risk Factors for CRE in Patients with Urinary and Sterile Site Cultures Positive, 2011-2015

	Overall Number (%) N=567	Invasive Infection Number (%) N=91	Urinary Infection Number (%) N=476	p-value+
Sex				
Women	326 (57.5)	42 (46.2)	284 (59.7)	0.02
Men	239 (42.2)	49 (53.9)	190 (39.9)	0.01
Average Age, years (mean ± SD)	63.2 ± 18.0	55.8 ±16.3	64.6 ± 18.0	<0.0001
Race				
White	192 (33.9)	27 (29.7)	165 (34.7)	0.36
Black	294 (51.9)	55 (60.4)	239 (50.2)	0.07
Location prior to culture:				
Residence	186 (32.8)	30 (33.0)	156 (32.8)	0.97
LTCF	211 (37.2)	18 (19.8)	193 (40.5)	0.0002
LTACH	41 (7.2)	14 (15.4)	27 (5.7)	0.001
Inpatient	91 (16.0)	27 (29.7)	64 (13.4)	0.0001
Hospitalized for ≥3 days	114 (20.1)	37 (40.7)	77 (16.2)	<0.0001
Hospitalized in the last year	354 (62.4)	68 (74.7)	286 (60.1)	0.008
Surgery within the last year	141 (24.9)	39 (42.9)	102 (21.4)	<0.0001
In the ICU prior to positive culture	75 (13.2)	26 (28.6)	49 (10.3)	<0.0001
Urinary catheter present	288 (50.8)	49 (53.9)	239 (50.2)	0.53
Central venous catheter present	171 (30.2)	60 (65.9)	111 (23.3)	<0.0001
Other indwelling device present	206 (36.3)	58 (63.7)	148 (31.1)	<0.0001
In a LTCF in the year prior	283 (49.9)	28 (30.8)	255 (53.6)	<0.0001
In an LTACH in the year prior	60 (10.6)	17 (18.7)	43 (9.0)	0.006
Immunocompromised	358 (63.1)	69 (75.8)	289 (60.7)	0.006

Immunocompromised = patient history of diabetes, renal failure, cirrhosis or liver failure, hematologic or solid tumor malignancy, solid organ transplant, or AIDS; LTACH = long-term acute care hospital; LTCF = long-term care facility; Other indwelling device: tracheostomy tube, gastrostomy tube, or nephrostomy tube; Residence = private residence.

Figure 1. Incident CRE Cases in Atlanta By Year and Infection Type, 2011-2015

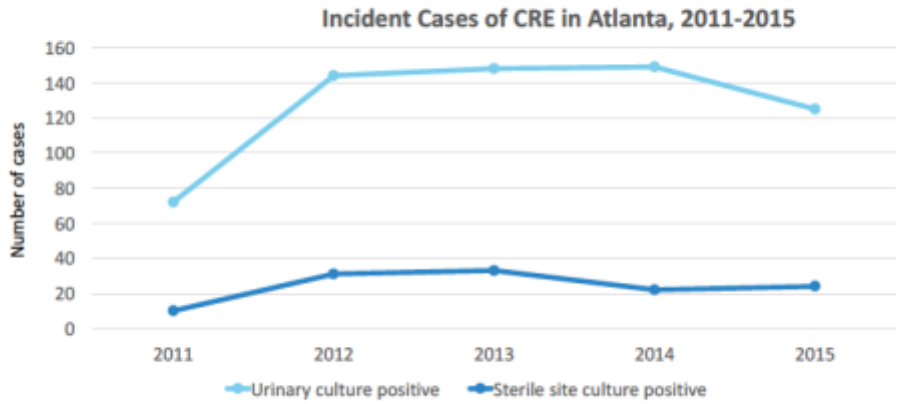

Figure 1 displays the number of incident cases of positive urine cultures (light blue line) and positive sterile site cultures (dark blue line) seen in the Atlanta metropolitan area in each year from 2011-2015. 2011 was an incomplete year in which data collection started in August.

Table 2. Univariable and Multivariable Logistic Regression Analysis of Risk Factors for Invasive Infection in Patients with a Positive Culture for CRE

	Crude Odds Ratio[+]	95% Confidence Interval	Adjusted Odds Ratio[++]	95% Confidence Interval
Central venous catheter present	6.36	3.93 – 10.31	3.58	2.06 – 6.23
Other indwelling device present	3.90	2.44 – 6.23	2.34	1.35 – 4.06
Hospitalized for ≥3 days	3.55	2.19 – 5.76	--	--
In the ICU prior to positive culture	3.35	1.94 – 5.78	--	--
Surgery within the last year	2.75	1.72 – 4.40	1.81	1.08 – 3.05
In an LTACH in the year prior	2.31	1.25 – 4.27	--	--
Immunocompromised	2.03	1.21 – 3.39	--	--
Hospitalized within the last year	1.96	1.18 – 3.26	--	--
Urinary catheter present	1.16	0.74 – 1.81	--	--
In a LTCF in the year prior	0.39	0.24 – 0.62	0.44	0.26 – 0.75

+Crude odds ratio calculated using univariable logistic regression, with each risk factor as the sole predictor of invasive infection.
++Adjusted odds ratios calculated using multivariable logistic regression, with backward and stepwise selection ($p<0.05$) used to identify risk factors that remained associated with invasive infection when controlling for confounding variables. Only adjusted odds ratios that remained significant are reported.

Figure 2. Outcomes in Patients With Cultures Positive for CRE, 2011-2015

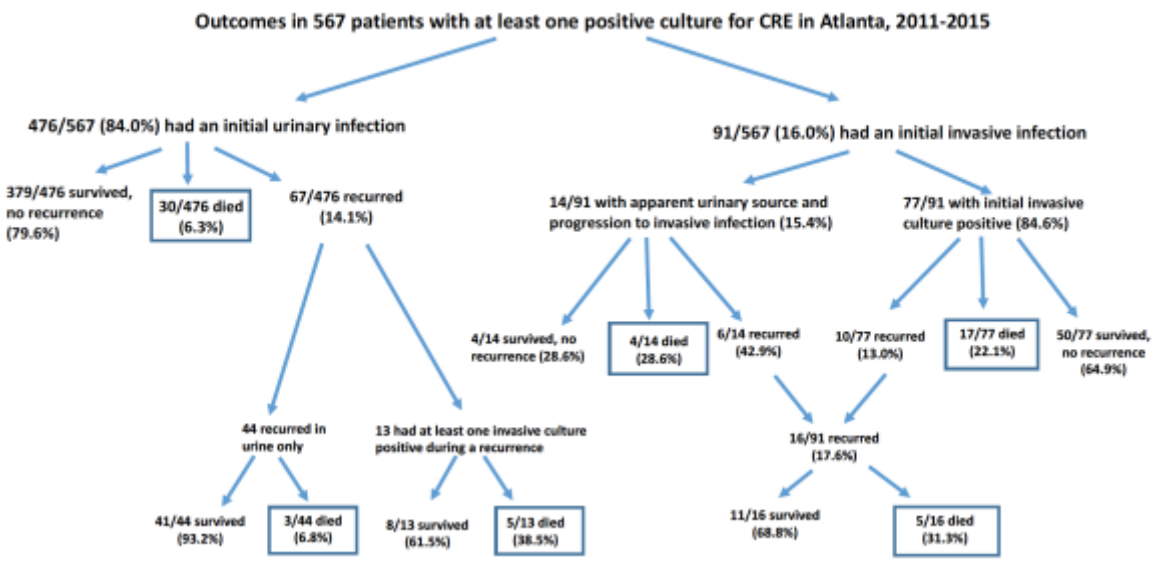

Figure 2 displays the outcomes of unique patients with at least one culture positive for CRE from 2011-2015, first with respect to whether their initial infection was urinary or invasive, and then what the outcome of that infection was (survival without recurrence, survival with recurrence, or death). Mortality was defined as in-hospital mortality for hospitalized patients, or 30-day mortality in patients in a long-term care facility or dialysis center. Recurrence was defined as a second positive culture for the same CRE organism more than 30 days after the initial culture was positive. Patients with an initial invasive infection are further separated into those who appeared to progress from a positive urinary culture to an invasive infection in the same thirty-day period, and those who just had a sterile site culture positive. For patients who recurred, the subsequent infection type (urinary vs invasive) and the outcome (survival vs death) is also shown.

Table 3. Comparison of Risk Factor Prevalence with Fatal and Non-Fatal Outcomes*

	Overall Number (%) N=567	Patient Died Number (%) N=51	Patient Survived Number (%) N=516	p-value+
Sex				
Women	326 (57.5)	23 (45.1)	303 (58.7)	0.06
Men	239 (42.2)	28 (54.9)	211 (40.9)	
Average Age, years (mean ± SD)	63.2 ± 18.0	62.9 ± 15.1	63.2 ± 18.3	0.90
Race				
White	192 (33.9)	19 (37.3)	173 (33.5)	0.89
Black	294 (51.9)	28 (54.9)	266 (51.6)	
Location prior to culture:				
Residence	186 (32.8)	8 (15.7)	178 (34.5)	0.006
LTCF	211 (37.2)	12 (23.5)	199 (38.6)	0.03
LTACH	41 (7.2)	10 (19.6)	31 (6.0)	0.002
Inpatient	91 (16.1)	20 (39.2)	71 (13.8)	<0.0001
Risk Factors:				
Hospitalized for ≥3 days	114 (20.1)	22 (43.1)	92 (17.8)	<0.0001
Any ICU Stay	147 (25.9)	33 (64.7)	114 (22.1)	<0.0001
Central venous catheter	171 (30.2)	36 (70.6)	135 (26.2)	<0.0001
Other indwelling device	206 (36.3)	36 (70.6)	170 (32.9)	<0.0001
Invasive Infection	91 (16.1)	21 (41.2)	70 (13.6)	<0.0001
In an LTACH in the year prior	60 (10.6)	11 (21.6)	49 (9.5)	0.008
Immunocompromised	358 (63.1)	40 (78.4)	318 (61.6)	0.02
In a LTCF in the year prior	283 (49.9)	19 (37.3)	264 (51.2)	0.06
Urinary catheter present	288 (50.8)	32 (62.8)	256 (49.6)	0.07
Hospitalized in the last year	354 (62.4)	36 (70.6)	318 (61.6)	0.21
Carbapenemase testing positive	85 (15.0)	10 (19.6)	75 (14.5)	0.33
Surgery in the last year	141 (24.9)	14 (27.5)	127 (24.6)	0.65

*Mortality = in-hospital mortality for hospitalized patients, or 30-day mortality in patients in a long term care or dialysis center.
+Chi-square tests used to compare demographic and risk factor prevalence in patients with and without a fatal outcome, with the exceptions of LTACH residence, for which a Fisher's exact test was used, and age, for which a t-test was used.

Table 4. Univariable and Multivariable Logistic Regression Analysis of Risk Factors for Mortality in Patients with a Positive CRE Culture

	Crude Odds Ratio[+]	95% Confidence Interval	Adjusted Odds Ratio[++]	95% Confidence Interval
Central venous catheter present	6.77	3.60 – 12.76	3.26	1.59 – 6.70
ICU stay	6.47	3.51 – 11.91	3.51	1.79 – 6.88
Other indwelling device present	4.88	2.60 – 9.17	----	----
Invasive Infection	4.46	2.42 – 8.22	2.24	1.14 – 4.40
Hospitalized for ≥3 days	3.50	1.92 – 6.36	----	----
In an LTACH in the year prior	2.62	1.26 – 5.44	----	----
Immunocompromised	2.26	1.14 – 4.52	----	----
Urinary catheter present	1.71	0.95 – 3.10	----	----
Hospitalized in the last year	1.49	0.80 – 2.80	----	----
Carbapenemase positive	1.43	0.69 – 2.97	----	----
Surgery in the last year	1.16	0.61 – 2.21	----	----
In a LTCF in the year prior	0.57	0.31 – 1.03	----	----

Mortality = in-hospital mortality for hospitalized patients, or 30-day mortality for patients in a long-term care or dialysis center.
+Crude odds ratio calculated using univariable logistic regression, with each risk factor as the sole predictor of mortality.
++Adjusted odds ratios calculated using multivariable logistic regression, with backward and stepwise selection ($p<0.05$) used to identify risk factors that remained associated with mortality when controlling for confounding variables. Only adjusted odds ratios that remained significant are reported.