Clinical Outcomes and Risk Factors for Carbapenem-resistant Enterobacterales Bloodstream Infection in Solid Organ Transplant Recipients

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Abstract

Background.—The clinical outcomes associated with, and risk factors for, carbapenem-resistant Enterobacterales (CRE) bloodstream infections (BSIs) in solid organ transplant (SOT) recipients remain ill-defined.

Methods.—A multicenter retrospective cohort study was performed, including SOT recipients with an Enterobacterales BSI between 2005 and 2018. Exposed subjects were those with a CRE BSI. Unexposed subjects were those with a non-CRE BSI. A multivariable survival analysis was performed to determine the association between CRE BSI and risk of all-cause mortality within 60

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d. Multivariable logistic regression analysis was performed to determine independent risk factors for CRE BSI.

Results.—Of 897 cases of Enterobacterales BSI in SOT recipients, 70 (8%) were due to CRE. On multivariable analysis, CRE BSI was associated with a significantly increased hazard of all-cause mortality (adjusted hazard ratio, 2.85; 95% confidence interval [CI], 1.68-4.84; $P < 0.001$). Independent risk factors for CRE BSI included prior CRE colonization or infection (adjusted odds ratio [aOR] 9.86; 95% CI, 4.88-19.93; $P < 0.001$), liver transplantation (aOR, 2.64; 95% CI, 1.23-5.65; $P = 0.012$), lung transplantation (aOR, 3.76; 95% CI, 1.40-10.09; $P = 0.009$), and exposure to a third-generation cephalosporin (aOR, 2.21; 95% CI, 1.17-4.17; $P = 0.015$) or carbapenem (aOR, 2.80; 95% CI, 1.54-5.10; $P = 0.001$) in the prior 6 months.

Conclusions.—CRE BSI is associated with significantly worse outcomes than more antibiotic-susceptible Enterobacterales BSI in SOT recipients.

INTRODUCTION

Carbapenem-resistant Enterobacterales (CRE) infections have been designated an urgent antibiotic resistance threat by the Centers for Disease Control and Prevention.[1] Although the prevalence varies by region, CRE are increasingly endemic throughout the United States[2] and globally.[3–5]

CRE infections have disproportionately affected the solid organ transplant (SOT) population. SOT recipients experience rates of CRE infection up to five-times greater than the general population.[6–8] This is likely driven by SOT recipients' multicomorbidity, frequent healthcare and antibiotic exposures, frequent procedures, and chronic indwelling medical devices.[9–12] Notably, however, several studies have identified transplant status as an independent risk factor for CRE infection, even after adjusting for other risk factors,[7] suggesting there may be issues unique to transplantation that increase the risk for CRE infection.[12] Furthermore, prior studies have indicated that outcomes following CRE infection in SOT recipients are poor, with rates of graft failure and death ranging between 12% and 66%, depending on the transplant cohort, the type of CRE infection studied, and the duration of follow-up.[6,13–16]

Despite the outsized impact of CRE on SOT recipients, there is a limited understanding of the clinical risk factors for CRE infection and the impact of CRE infection on SOT recipient outcomes. Much of the data regarding CRE infections in SOT recipients are derived from small single-center studies, limited to abdominal organ transplant recipients, include heterogeneous infection types (eg, CRE urinary tract infections and bloodstream infections [BSIs]), and have limited durations of patient follow-up.[6,17,18]

As a result, in this study, we sought to determine (1) the impact of CRE BSI on the risk of all-cause mortality and new-onset graft failure and (2) the risk factors for developing CRE BSI in SOT recipients, using a large multicenter cohort of all organ transplant types. This is the largest and only multicenter cohort of SOT recipients with CRE BSI reported to date.[14,17,19–21]

MATERIALS AND METHODS

Study Design and Setting

A multicenter retrospective cohort study was performed at three tertiary care transplant centers in the United States: The Hospital of the University of Pennsylvania (HUP) (776 beds), The Johns Hopkins Hospital (JHH) (1154 beds), and the University of Maryland Medical Center (UMMC) (767 beds).

Study Population

The initial source population included all SOT recipients with an Enterobacterales (EB) BSI identified at HUP or UMMC between January 1, 2007, and June 30, 2018, and at JHH between January 1, 2005, and December 31, 2015 (with the varying time periods being due to differences in data availability). Because the microbiology laboratories at each institution process both inpatient and outpatient cultures, the cohort included any SOT recipient with an EB BSI regardless of the geographic location at which the BSI was identified, although all subjects were ultimately hospitalized. For those SOT recipients with multiple EB BSI during the study period, only the first episode was included.

For the determination of the impact of CRE BSI on clinical outcomes, the cohort was divided into exposed and unexposed subjects: Exposed subjects were those with a CRE BSI. CRE BSI was defined by any EB on blood culture that exhibited *in vitro* nonsusceptibility to any carbapenem, that is, minimum inhibitory concentration [MIC] 2 μg/mL for ertapenem or MIC 4 μg/mL for meropenem, doripenem, or imipenem before 2011, or MIC 1 μg/mL for ertapenem or MIC 2 μg/mL for meropenem, doripenem, or imipenem after 2011 per Clinical and Laboratory Standards Institute guidelines.[22] EB isolates were not routinely screened for carbapenemase production. Unexposed subjects were those with a non-CRE EB BSI, defined as any EB on blood culture that exhibited *in vitro* susceptibility to all carbapenems. This control population was selected to focus on the impact of carbapenem resistance, rather than EB BSI, on outcomes.

For the determination of risk factors for CRE BSI, a case-control study design was employed. Case subjects were those with a CRE BSI, and control subjects were those with a non-CRE EB BSI (as defined above). All cases and controls were included in the analysis; no matching was performed.

This study was approved by the Institutional Review Board at each of the participating transplant centers (see Text S1, SDC, http://links.lww.com/TP/C498).

Primary Outcomes

There were two primary outcomes: (1) all-cause mortality within 60 d after the EB BSI, and (2) new-onset graft failure within 60 d after the EB BSI. Graft failure was defined by retransplantation of the same organ, relisting for transplantation of the same organ, return to dialysis for kidney transplant recipients,[23] or a cardiac index 2 or ejection fraction 40% with need for inotropes or persistent mechanical support in heart transplant recipients.[24] For the analysis of new-onset graft failure, those SOT recipients with graft failure before the

EB BSI onset were excluded from the cohort. We chose not to restrict graft failure or death to those that were thought to be directly attributable to the EB BSI episode because the relatedness of graft failure or death to a single infectious event can be difficult to ascertain retrospectively and can lead to misclassification of outcomes. Subjects were followed for 60 d because this is a timeframe in which subsequent graft failure or death may be attributable, at least in part, to the EB BSI. The follow-up period began immediately after the first positive blood culture was collected.

Data Collection

Data on SOT recipients were abstracted from the electronic medical records at each study site by a combination of electronic data extraction, with validation of variables, and manual chart review. Information was collected on demographics, comorbidities, medications, and details of the EB BSI episode (see Text S2 parts B1 and B2, SDC, http://links.lww.com/TP/C498 for details).

Susceptibility Testing of EB Isolates

All EB isolates identified from study subjects were tested as part of routine care for susceptibility to antibiotics at each of the centers' clinical microbiology laboratories. At HUP, the semiautomated Vitek 2 identification and susceptibility system (bioMerieux, Inc, Durham, NC) was utilized; at JHH, the BD Phoenix Automated System (BD Diagnostics, Sparks, MD) was used; and at UMMC, disk diffusion was used before 2010 and the Vitek 2 (bioMerieux, Inc, Durham, NC) was used after 2010.

Statistical Analysis

Continuous variables were summarized using median and interquartile range, and categorical variables were summarized using proportions. Continuous variables were compared using the Wilcoxon rank-sum test (because distributions were non-normal), and categorical variables were compared using the χ^2 or Fisher exact test.

For the determination of the association between CRE BSI and risk of death, we performed a survival analysis. Time zero was defined as the date of the first blood culture that grew an EB organism, and the time at risk was measured in days. The day on which the SOT recipient first met criteria for the outcome (ie, date of death) following the EB BSI was the failure date, and subjects were censored after 60 d of follow-up. For the unadjusted analyses, a Kaplan Meier curve was plotted to assess the time to the primary outcome (death), stratified by exposure status (CRE versus non-CRE EB BSI), and a log-rank test was performed. For the adjusted analysis, a mixed-effects multivariable frailty model using the Weibull distribution was developed, with a random effect for study site. Bivariate regression was used to examine the relationship between the primary exposure, as well as other baseline factors, and the outcome. Variables from bivariate analyses with $P < 0.20$ were considered for inclusion in the final multivariable model. Variables were retained in the final multivariable model if they were confounders of the primary association (defined by a 15% or more change in the effect estimate of the association between the primary exposure and outcome) or had a P of <0.05 in the multivariable model. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of any associations.

For the determination of the association between CRE BSI and risk of new-onset graft failure, we again performed a survival analysis, but used multivariable competing risks regression, with death modeled as a competing risk. Study site was incorporated as a fixed effect. Measurement of time at risk, duration of follow-up, and variable selection for the multivariable model were performed in the same manner as described above. For this analysis, subhazard ratios (SHRs) and 95% CIs were calculated.

For the determination of risk factors for CRE BSI, we performed mixed-effects multivariable logistic regression analyses. Bivariate mixed-effects logistic regression was used to examine the relationship between each potential risk factor and CRE BSI. Variables from bivariate analyses with $P < 0.20$ were considered for inclusion in the final multivariable model. Manual forward selection was performed to build the multivariable model. Variables were retained in the final model if they were significantly associated with the outcome ($P < 0.05$). Odds ratios (ORs) and 95% CIs were calculated to evaluate the strength of any association.

Secondary Analyses

We performed several secondary analyses, including: (1) Stratified analyses by organ transplant type. (2) An analysis of outcomes after further stratifying the exposure into three groups: CRE BSI, extended-spectrum beta-lactamase (ESBL)–producing EB BSI (with ESBL status determined by either confirmatory testing using the double disk method with both cefotaxime and ceftazidime,[25] the ESBL ETEST [bioMerieux, Durham, NC], or a ceftriaxone MIC of ≥ 8 μg/mL[26]), and susceptible EB BSI. (3) An analysis of outcomes after stratifying the CRE exposure into two mutually exclusive groups: CRE BSI nonsusceptible to all carbapenems and CRE BSI nonsusceptible to ertapenem only.

Mediation Analysis

A mediation analysis was performed in which we evaluated whether time to effective antibiotic therapy (measured in days) was the primary driver of the association between CRE BSI and all-cause mortality and/or new-onset graft failure. Effective antibiotic therapy is defined in Text S2 part B3, SDC, http://links.lww.com/TP/C498.

Risk Factors for Death Following CRE BSI

An exploratory analysis was performed in which we identified the risk factors for death among those with CRE BSI. In this analysis, only those with a CRE BSI were included in the cohort. Cases were those who died within 60 d after the CRE BSI, and controls were those who did not.

The same statistical approach was used for all secondary analyses as is described for the primary analyses. All analyses were performed with STATA/SE 15.1 (StataCorp, College Station, TX).

RESULTS

Study Population

A total of 897 SOT recipients developed an EB BSI during the study period, of which 70 (8%) cases were due to CRE. Among those with a CRE BSI (Table 1), the median age was 56 y old (interquartile range [IQR], 48–63), 24 (34%) were women, 40 (57%) had received a liver transplant, 13 (19%) a kidney, 12 (17%) a lung, 4 (6%) a heart, and 1 (1%) a pancreas transplant. The remainder of the cohort has been described previously.[12]

Overview of CRE BSI Microbiology

Among those with a CRE BSI (Table 2), the most common identifiable sources were biliary (19, 27%), genitourinary (13, 19%), lower respiratory tract (13, 19%), and intra-abdominal (12, 17%). The most common CRE organisms were *Klebsiella* (37, 53%) and *Enterobacter* (25, 36%) species. The median duration of bacteremia was 1 d (IQR, 1–2). The microbiology of the remainder of the cohort has been described previously.[12]

Impact of CRE BSI on Risk of All-cause Mortality

Among those SOT recipients with a CRE BSI, 33 (47%) died within 60 d of the BSI, compared to 102 (12%) among those with a non-CRE EB BSI (Figure 1A, log-rank $P <$ 0.001). On multivariable analysis (Table 3A), CRE BSI was associated with a significantly increased hazard of death within 60 d (adjusted hazard ratio [aHR] 2.85; 95% CI, 1.68-4.84; $P <$ 0.001), after adjusting for age, organ type, prior CRE and EB colonization/infection, prior exposure to polymyxins, graft failure before the EB BSI, and recent allograft rejection treated with corticosteroids. Notably, the year of transplant and year of EB BSI were not confounders or significantly associated with the outcome.

Impact of CRE BSI on Risk of New-onset Graft Failure

There were 663 SOT recipients with a functioning graft at the time of their EB BSI, of which 44 (7%) had a CRE BSI. Among those with a CRE BSI, 15 (34%) developed new-onset graft failure within 60 d of the EB BSI, compared to 72 (12%) in the non-CRE BSI group (Figure 1B, log-rank $P <$ 0.001). On multivariable analysis, in which death was modeled as a competing risk (Table 3B), CRE BSI was associated with a significantly increased hazard of new-onset graft failure within 60 d (aSHR, 2.42; 95% CI, 1.33-4.39; $P =$ 0.004), after adjusting for organ type, study site, prior antibiotic exposures, prior EB colonization/infection, and recent allograft rejection.

Risk Factors for CRE BSI

On multivariable analysis, the independent risk factors for CRE BSI (compared to non-CRE EB BSI) included (Table 4) prior CRE colonization/infection (adjusted odds ratio [aOR], 9.86; 95% CI, 4.88-19.93; $P <$ 0.001), liver transplantation (aOR, 2.64; 95% CI, 1.23-5.65; $P =$ 0.012), lung transplantation (aOR, 3.76; 95% CI, 1.40-10.09; $P =$ 0.009), exposure to a third-generation cephalosporin in the prior 6 mo (aOR, 2.21; 95% CI, 1.17-4.17; $P =$ 0.015), and exposure to a carbapenem in the prior 6 mo (aOR, 2.80; 95% CI, 1.54-5.10; $P =$ 0.001). Conversely, there was a significantly decreased odds of CRE BSI in SOT recipients

on mycophenolate immunosuppression (aOR, 0.47; 95% CI, 0.25-0.89; $P = 0.021$), and a reduction in the odds of CRE BSI with increasing time posttransplant (aOR, 0.99; 95% CI, 0.99-1.00; $P = 0.051$ per day forward posttransplant).

Secondary Analyses

Among liver transplant recipients, there was not a significant association between CRE BSI and the hazard of all-cause mortality (aHR, 1.60; 95% CI, 0.83-3.05; $P = 0.158$) or new-onset graft failure (aHR, 0.70; 95% CI, 0.25-1.99; $P = 0.506$) (Table S1, SDC, http://links.lww.com/TP/C498). In examining risk factors for CRE BSI in liver recipients, there was a significantly decreased odds of CRE BSI among those who received their allograft from a living donor (aOR, 0.18; 95% CI, 0.05-0.72; $P = 0.016$) (Table S2, SDC, http://links.lww.com/TP/C498).

Among kidney, lung, and pancreas transplant recipients (Table S3A, SDC, http://links.lww.com/TP/C498), CRE BSI was associated with a significantly increased hazard of all-cause mortality on bivariate analysis. Among all non–liver transplant recipients (Table S3B, SDC, http://links.lww.com/TP/C498), CRE BSI was associated with a significant increase in the hazard of new-onset graft failure on bivariate analysis.

After stratifying the exposure into 3 groups based on resistance to carbapenems and extended-spectrum cephalosporins (namely, CRE, ESBL-EB, and susceptible EB BSI) (Figure S1, SDC, http://links.lww.com/TP/C498), an unadjusted analysis showed that CRE BSI was associated with a significant increase in the hazard of all-cause mortality (HR, 5.46; 95% CI, 3.56-8.36; $P < 0.001$), whereas ESBL-EB BSI was not (HR, 1.22; 95% CI, 0.81-1.84; $P = 0.348$).

After stratifying the CRE exposure into 2 groups, namely, CRE nonsusceptible to all carbapenems and CRE nonsusceptible to ertapenem only (Figure S2, SDC, http://links.lww.com/TP/C498), an unadjusted analysis showed that both CRE types were associated with a significantly increased hazard of all-cause mortality (CRE BSI nonsusceptible to all carbapenems HR, 6.64; 95% CI, 4.32-10.18; $P < 0.001$; CRE nonsusceptible to only ertapenem HR, 2.48; 95% CI, 1.09-5.65; $P = 0.031$).

Mediation Analysis of Time to Effective Antibiotic Therapy

Among those with a CRE BSI, 27 (39%) received effective antibiotic therapy within 24 h of their first positive blood culture, compared to 597 (72%) among those with a non-CRE EB BSI (χ^2 $P < 0.001$) (Table S4, SDC, http://links.lww.com/TP/C498). Among those with a CRE BSI, the median time to effective antibiotics was 3 d (IQR, 0–90) compared to 1 d (IQR, 0–2) among those with a non-CRE EB BSI (Wilcoxon rank-sum $P < 0.001$). However, among those with a CRE BSI, the median time to effective antibiotics was reduced to 1 d (IQR, 0–4) for those with prior CRE colonization/infection. Furthermore, among those with a CRE BSI, the median time to effective antibiotics was 2 d (IQR, 0–8) in liver recipients, compared to 4 d (IQR, 1–90) in non–liver recipients (Wilcoxon rank-sum $P = 0.058$). There was no significant multicollinearity observed between prior CRE colonization/infection, liver transplantation, prior polymyxin exposure, and time to effective antibiotics (variance inflation factor values, 1.00–1.29; tolerance values, 0.78–1.14).

When time to effective therapy was incorporated into the analysis of CRE BSI and its impact on all-cause mortality and new-onset graft failure (Table S5, SDC, http://links.lww.com/TP/C498), we found that (1) with increasing time to effective antibiotics, there was a significant increase in the hazard of all-cause mortality (aHR, 1.01; 95% CI, 1.00-1.01; *P* = 0.034 per day without effective antibiotics) and new-onset graft failure (aSHR, 1.01; 95% CI, 1.00-1.02; *P* = 0.009); (2) there remained a significant association between CRE BSI and all-cause mortality (aHR, 2.60; 95% CI, 1.54-4.41; *P* < 0.001) and new-onset graft failure (aSHR, 2.03; 95% CI, 1.09-3.78; *P* = 0.025).

Risk Factors for Death Following CRE BSI

In the subgroup with a CRE BSI (N = 70), there were 33 (47%) who died within 60 d of the BSI. The independent risk factors for death within 60 d included (Table S6, SDC, http://links.lww.com/TP/C498): polymyxin exposure in the prior 6 mo (aOR, 6.44; 95% CI, 1.01-40.93; *P* = 0.049), Pitt bacteremia score (aOR, 1.36; 95% CI, 1.00-1.84; *P* = 0.053 per additional point), and graft failure before the CRE BSI (aOR, 7.66; 95% CI, 1.16-50.33; *P* = 0.034). Conversely, a genitourinary source of the CRE BSI (eg, urinary tract infection) was associated with a reduced odds of death (aOR, 0.05; 95% CI, 0.002-0.93; *P* = 0.045). Time to effective antibiotics was not significantly associated with the odds of death (aOR, 1.00; 95% CI, 0.98-1.02; *P* = 0.966).

DISCUSSION

In this multicenter retrospective cohort study of SOT recipients, we demonstrated a significant reduction in graft and patient survival—with over twice the hazard of all-cause mortality and new-onset graft failure—in the 60 d following a CRE BSI compared to those with a more antibiotic-susceptible EB BSI. After adjusting for time to effective antibiotics, this relationship was slightly attenuated, but remained significant, suggesting that poor outcomes with CRE BSI are not simply due to delays in detection and treatment. We further identified several important risk factors for CRE BSI in SOT recipients, including prior colonization or infection with a CRE organism, a history of liver or lung transplantation (as compared to other transplant types), and recent exposure to third-generation cephalosporins or carbapenems.

Although studies have previously demonstrated poor outcomes in SOT recipients with CRE infections,[6,13–16,27,28] our study adds meaningfully to this literature by quantifying the specific impact of carbapenem resistance, even after accounting for antibiotic appropriateness and timing, on the risk of graft failure and death in the largest and only multicenter cohort of SOT recipients with CRE BSI reported to date. The reason for such poor outcomes is likely multifactorial: First, those with CRE BSI are less likely to receive early effective antibiotic therapy; indeed, we found that the time to effective antibiotic therapy was longer for those with CRE BSI than non-CRE BSI, was predictive of poor outcomes, and served as a partial mediator between CRE BSI and patient outcomes. Another possible mechanism is via increased pathogenicity: some CRE have been shown to be more pathogenic than antibiotic-susceptible EB organisms, due to harboring additional virulence factors such as those affecting iron scavenging or adhesion factors.[29–31] *Klebsiella*

pneumoniae is the most common organism in the CRE group, and is also among the most pathogenic of EB organisms.[32–34] Third, it is likely that a CRE BSI results in a cascade of necessary management decisions, such as reduction in immunosuppression or use of antibiotics with greater potential toxicity (eg, polymyxins, as shown in the secondary analysis of risk factors for death following CRE BSI), that may compromise graft function and subsequently result in poorer outcomes.

In two secondary analyses, we found a stepwise relationship between the degree of EB resistance and clinical outcomes, where ESBL-EB did not significantly affect mortality, CRE with nonsusceptibility to only ertapenem increased the hazard of mortality 2-fold, and CRE with nonsusceptibility to all carbapenems increased the hazard of mortality 6-fold. This stepwise increase in the risk of mortality with increasing degree of antibiotic resistance further underscores the finding that the drug resistance itself contributes to poor outcomes. Taken together, these data suggest that it will be imperative to not only more rapidly detect and treat CRE BSI but also develop novel approaches to preventing CRE infection, to improve SOT recipient outcomes.

In one subgroup analysis of note, we found that CRE BSI did not significantly affect outcomes in liver transplant recipients. We hypothesized that this was likely due to earlier effective antibiotic therapy in this subgroup because liver recipients are known to be at higher risk for CRE infection.[35,36] Our analysis of time to effective antibiotic therapy confirmed this hypothesis, showing that liver recipients had a shorter median time to effective antibiotics in the setting of CRE BSI.

In our analysis of risk factors for CRE BSI, the single most predictive factor was colonization or infection with CRE in the prior 12 months, which increased the odds more than nine-fold. CRE colonization has been shown previously to be a risk factor for CRE infection in SOT recipients,[17,19,21,37–39] but the magnitude of this risk, particularly for thoracic organ recipients and after adjusting for other risk factors, has not been previously quantified. Although none of the transplant centers included in this study perform routine fecal sample surveillance for CRE colonization, this finding raises the question of whether transplant recipients should be proactively screened for CRE colonization pretransplantation or posttransplantation to guide antibiotic stewardship and infection prevention efforts as well as empiric antibiotic therapy choices.

Interestingly, we found that chronic immunosuppression with mycophenolate was associated with a reduced odds of CRE BSI. Although this finding is perhaps counterintuitive, it is possible that mycophenolate immunosuppression is a marker of those SOT recipients who have had fewer prior infectious complications, and fewer antibiotic exposures, because mycophenolate is often discontinued when infectious complications occur.[40,41] We also found that the risk of CRE BSI decreased with increasing time posttransplant, which is consistent with prior studies that have shown that multidrug-resistant Gram-negative infections are most common in the first year posttransplant and decrease thereafter,[27] likely due to the reduction in immunosuppression, hospital exposures, and antibiotic exposures with increasing time posttransplant.

There are several limitations to this work: (1) We chose to employ a control group with susceptible EB BSI, rather than including all hospitalized SOT recipients, which can result in an overestimation of the risk of antibiotic exposures.[42] (2) None of the included hospitals perform surveillance cultures for CRE colonization, so our analyses of prior CRE colonization/infection are limited to those CRE captured on clinical cultures. (3) Before the adjustment of MIC breakpoints for CRE in 2011, the incidence of CRE may have been underestimated because of limitations in the ability of automated susceptibility platforms to reliably detect carbapenem resistance.[43] Furthermore, because of the changes in MIC breakpoints in 2011, there may be some heterogeneity in the CRE exposure distribution based on era. However, the year of BSI was not significantly associated with the primary outcomes and did not significantly alter the association between CRE status and the primary outcomes, suggesting the change in definitions in 2011 did not significantly alter our findings. (4) We were not able to perform molecular analyses to identify the carbapenemases produced by CRE organisms because of the retrospective nature of this study. (5) We chose not to limit the primary outcomes to EB BSI-related graft failure or death because this can be difficult to classify accurately, but, as a result, the proportion of death and graft failure outcomes that were directly due to the EB BSI are unknown. (6) Because this was a retrospective observational study, there may have been residual unmeasured confounders that if measured, might account for the differences in outcomes observed with CRE BSI. (7) Though this is a large multicenter cohort, the results may not be generalizable to other transplant centers in other geographic regions.

In summary, in this multicenter retrospective cohort study, we found that CRE BSI significantly reduced graft and patient survival in SOT recipients, even after accounting for antibiotic appropriateness and timing. More intensive antibiotic stewardship and rapid antimicrobial susceptibility testing are urgently needed in the transplant population to mitigate the burden and impact of CRE infections on SOT recipient outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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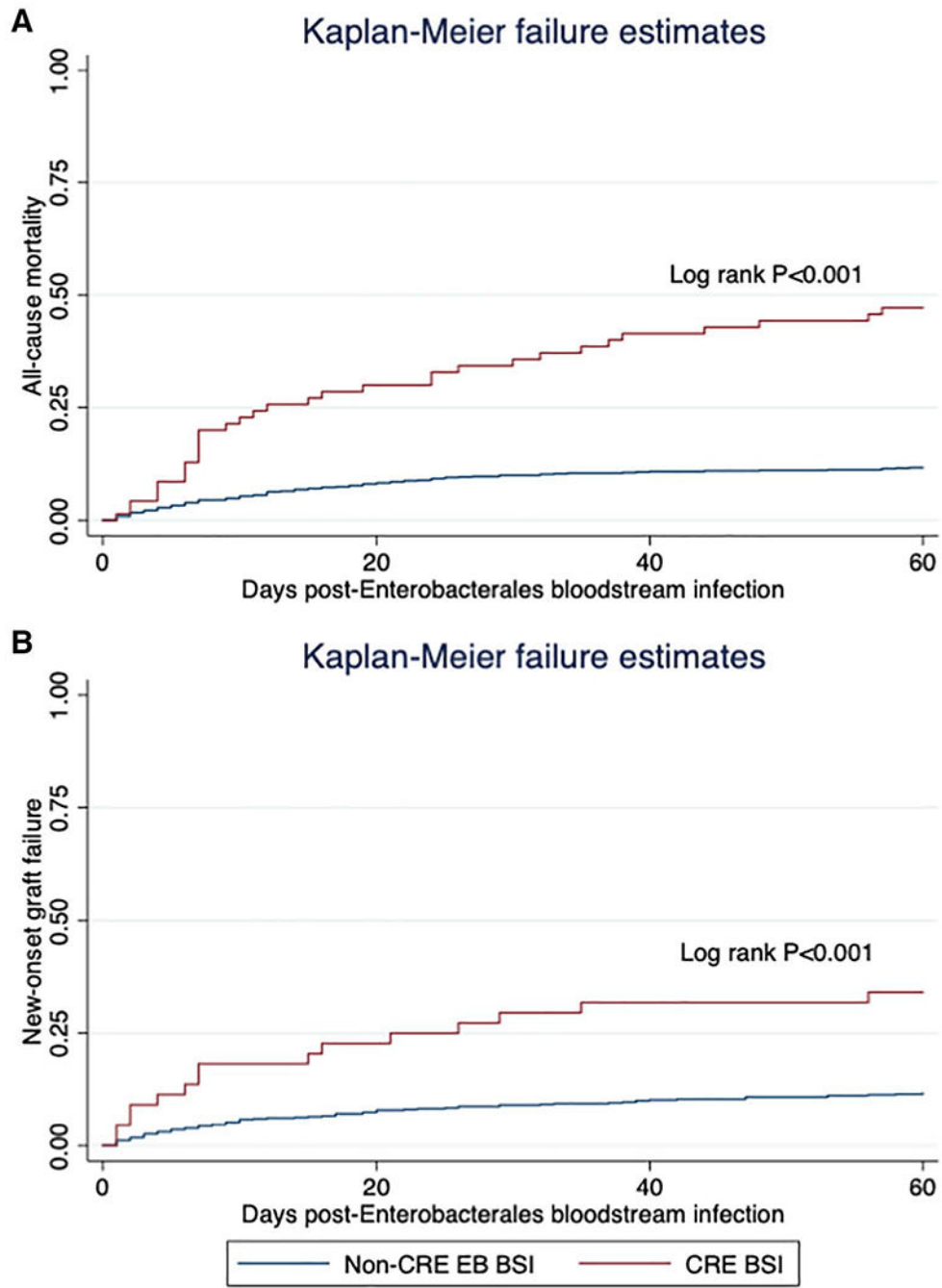**FIGURE 1.**

Kaplan Meier curve of (A) all-cause mortality and (B) new-onset graft failure following EB BSI, stratified by carbapenem resistance. BSI, bloodstream infection; CRE, carbapenem-resistant Enterobacterales; EB, Enterobacterales.

TABLE 1.

Baseline characteristics of solid organ transplant recipients with CRE and non-CRE BSI

Baseline characteristic [a,b]	CRE BSI (N = 70)	Non-CRE EB BSI (N = 827)	P [c]
Study site			
Site 1	24 (34%)	250 (30%)	0.057
Site 2	12 (17%)	253 (31%)	
Site 3	34 (49%)	324 (39%)	
Demographics			
Age, y, median (IQR)	56 (48–63)	57 (47–64)	0.721
Female gender	24 (34%)	346 (42%)	0.218
Black/African American	7 (10%)	219 (26%)	0.002
White/Caucasian	23 (33%)	265 (32%)	0.889
Hispanic ethnicity	4 (6%)	18 (2%)	0.085
Comorbidities [d]			
Diabetes mellitus	21 (30%)	398 (48%)	0.004
Chronic kidney disease (not on dialysis)	2 (3%)	92 (11%)	0.025
End-stage kidney disease requiring dialysis	19 (27%)	276 (33%)	0.287
Cirrhosis	14 (20%)	137 (17%)	0.461
Heart failure	3 (4%)	82 (10%)	0.140
Chronic pulmonary disease	7 (10%)	60 (7%)	0.350
Malignancy requiring chemotherapy in the prior 6 mo	8 (11%)	58 (7%)	0.174
Weight, kg, median (IQR)	76 (60–86)	74 (62–88)	0.500
Organ transplant type			
Kidney	21 (30%)	503 (61%)	<0.001
Liver	40 (57%)	238 (29%)	<0.001
Heart	4 (6%)	65 (8%)	0.645
Lung	12 (17%)	46 (6%)	<0.001
Pancreas	1 (1%)	26 (3%)	0.716
Transplant characteristics			
Time from transplant to BSI, d, median (IQR)	120 (50–462)	760 (122–3062)	<0.001
Induction immunosuppression given at time of transplantation	15 (23%)	345 (49%)	<0.001

Baseline characteristic[a,b]	CRE BSI (N = 70)	Non-CRE EB BSI (N = 827)	P[c]
Graft failure before the EB BSI	26 (38%)	200 (25%)	0.018
Primary graft dysfunction after transplant	18 (28%)	105 (15%)	0.005
Reoperation within 4 wk of transplant	27 (45%)	210 (31%)	0.024
Living donor	9 (13%)	190 (23%)	0.050
CMV infection before the EB BSI[e]	23 (34%)	168 (21%)	0.012
Rejection episode before the EB BSI[f]	5 (7%)	85 (10%)	0.387
Chronic immunosuppression at the time of the EB BSI			
Azathioprine	6 (9%)	31 (4%)	0.051
Corticosteroids	57 (81%)	559 (68%)	0.017
Cyclosporine	4 (6%)	44 (5%)	0.784
Mycophenolate	25 (36%)	500 (60%)	<0.001
Sirolimus	6 (9%)	66 (8%)	0.861
Tacrolimus	48 (69%)	593 (72%)	0.577
Prior healthcare and antibiotic exposures[g]			
Hospitalization in prior 6 mo	54 (77%)	587 (71%)	0.273
Antimicrobial exposure in prior 6 mo	66 (94%)	614 (74%)	<0.001
Aminoglycoside	32 (46%)	63 (8%)	<0.001
Third-generation cephalosporin	26 (37%)	139 (17%)	<0.001
Fourth-generation cephalosporin	31 (44%)	193 (23%)	<0.001
Fluoroquinolone	31 (44%)	233 (28%)	0.005
Polymyxin	15 (21%)	13 (2%)	<0.001
Carbapenem	39 (56%)	156 (19%)	<0.001
Piperacillin-tazobactam	42 (60%)	312 (38%)	<0.001
Tigecycline	17 (24%)	15 (2%)	<0.001
TMP-SMX	47 (67%)	271 (33%)	<0.001
IV vancomycin	55 (79%)	358 (43%)	<0.001
Prior colonization with EB[h]			
Prior ESBL-EB colonization/infection	38 (54%)	99 (12%)	<0.001
Prior CRE colonization/infection	29 (41%)	25 (3%)	<0.001
EB on prior culture	46 (67%)	378 (48%)	0.003

Baseline characteristic[a,b]	CRE BSI (N = 70)	Non-CRE EB BSI (N = 827)	P[c]
EB on prior respiratory tract culture	17 (24%)	76 (9%)	<0.001
EB on prior genitourinary tract culture	17 (24%)	255 (31%)	0.252
EB on prior biliary culture	2 (3%)	10 (1%)	0.239
EB on prior intra-abdominal culture	12 (17%)	26 (3%)	<0.001
EB on prior blood culture	16 (23%)	67 (8%)	<0.001
Severity of illness[i]			
Pitt bacteremia score, median (IQR), points	3 (1–4)	1 (0–3)	0.001
Intensive care unit admission	40 (61%)	240 (31%)	<0.001
Neutropenic[j]	10 (14%)	56 (7%)	0.021
Creatinine, median (IQR), mg/dL among nonkidney transplant recipients	1.2 (0.8–2.0)	1.6 (1.0–2.5)	0.079
Creatinine, median (IQR), mg/dL among kidney transplant recipients	2.0 (1.0–2.7)	2.1 (1.4–3.3)	0.162

[a]Data are presented as n(%) except where noted. The percentages represent the proportion of exposed and unexposed subjects with the specified baseline characteristic, except where noted.

[b]Only those variables with a P<0.20 and those of notable biologic importance are included in this table.

[c]Continuous variables were compared using the Wilcoxon rank-sum test (because distributions were non-normal), and categorical variables were compared using the χ^2 or Fisher exact test.

[d]Comorbidities assessed at the time of EB BSI.

[e]CMV infection assessed through 6 mo before the EB BSI.

[f]Acute rejection assessed through 3 mo before the EB BSI.

[g]Hospital and antibiotic exposures assessed through 6 mo before the EB BSI.

[h]Microbiological results assessed through 1 y before the EB BSI. No surveillance cultures for ESBL-EB or CRE are performed at any of the included study sites.

[i]Severity of illness measures were assessed on day 1 of the EB BSI (the day that the first positive blood culture was collected).

[j]Neutropenia defined by an absolute neutrophil count <1500 cells/μL.

BSI, bloodstream infection; CMV, cytomegalovirus; CRE, carbapenem-resistant EB; EB, Enterobacterales; ESBL, extended-spectrum beta-lactamase; IQR, interquartile range; IV, intravenous; TMP-SMX, trimethoprim-sulfamethoxazole.

TABLE 2.

Overview of CRE and non-CRE BSI microbiology

Microbiology characteristic[a]	CRE BSI (N = 70)	Non-CRE EB BSI (N = 827)	P
Source of BSI[b]			
Genitourinary	13 (19%)	363 (43%)	<0.001
Central venous catheter	7 (10%)	102 (12%)	0.566
Intra-abdominal	12 (17%)	91 (11%)	0.122
Biliary/hepatic	19 (27%)	95 (27%)	<0.001
Lower respiratory tract	13 (19%)	44 (5%)	<0.001
Skin or soft tissue	3 (4%)	20 (2%)	0.415
Organism on blood culture			
Klebsiella spp	37 (53%)	334 (40%)	0.042
Escherichia coli	5 (7%)	333 (40%)	<0.001
Enterobacter spp	25 (36%)	94 (11%)	<0.001
Serratia spp	1 (1%)	29 (4%)	0.724
Proteus spp	0 (0%)	22 (3%)	0.406
Citrobacter spp	2 (3%)	12 (1%)	0.299
In vitro susceptibilities			
Resistant to extended-spectrum cephalosporins	70 (100%)	286 (35%)	<0.001
Resistant to piperacillin-tazobactam	59 (84%)	92 (11%)	<0.001
Resistant to fluoroquinolones	47 (67%)	180 (22%)	<0.001
Resistant to polymyxins	5 (7%)	0 (0%)	<0.001
Duration of bacteremia, d, median (IQR)	1 (1–2)	1 (1–1)	0.007

[a] Data are presented as n(%) except where noted.

[b] The source of the EB BSI is displayed for those episodes in which it was possible to determine.

The source was determined by an infectious diseases–trained physician at each study site.

BSI, bloodstream infection; CRE, carbapenem-resistant Enterobacterales; EB, Enterobacterales; IQR, interquartile range; spp, species.

TABLE 3.

Multivariable survival analysis of the association between CRE BSI and (A) all-cause mortality, (B) new-onset graft failure

A. All-cause mortality

Characteristic	aHR	95% CI	P
CRE BSI (compared to non-CRE EB BSI)	2.85	1.68-4.84	<0.001
Prior CRE colonization/infection[a]	0.90	0.45-1.77	0.749
Age (per y)	1.03	1.01-1.05	<0.001
Prior EB on respiratory culture[a]	3.08	2.00-4.74	<0.001
Prior exposure to a polymyxin[b]	2.51	1.32-4.79	0.005
Rejection before the EB BSI, treated with corticosteroids[c]	1.91	1.05-3.47	0.034
Graft failure before the EB BSI	1.90	1.30-2.77	0.001
Organ transplant type			
Kidney	Ref		
Liver	2.68	1.72-4.19	<0.001
Heart	1.22	0.54-2.77	0.631
Lung	1.45	0.73-2.89	0.293
Pancreas	3.79	1.46-9.82	0.006

B. New-onset graft failure

Characteristic	aSHR	95% CI	P
CRE BSI (compared to non-CRE EB BSI)	2.42	1.33-4.39	0.004
Rejection before the EB BSI[c]	1.86	1.03-3.36	0.040
Prior EB on genitourinary culture[a]	0.43	0.23-0.81	0.009
Prior EB on respiratory culture[a]	2.53	1.31-4.87	0.006
Prior exposure to metronidazole[b]	1.77	1.05-2.96	0.030
Prior exposure to an aminoglycoside[b]	0.90	0.46-1.80	0.756
Organ transplant type			
Kidney	Ref		
Liver	2.00	1.10-3.65	0.024
Heart	1.41	0.53-3.71	0.491
Lung	1.47	0.59-3.64	0.408
Pancreas	3.49	1.40-8.69	0.007
Study site			
Site 1	Ref		
Site 2	0.59	0.35-1.02	0.059
Site 3	0.47	0.28-0.80	0.005

[a]Organism isolated on any clinical culture from any anatomical site in the 12 mo before the EB BSI. (No surveillance cultures performed at the included study sites.)

Table 4.

Mixed-effects multivariable logistic regression model of risk factors for CRE BSI

Baseline characteristic	aOR	95% CI	P
Prior exposure to a third-generation cephalosporin[a]	2.21	1.17-4.17	0.015
Prior exposure to a carbapenem[a]	2.80	1.54-5.10	0.001
Prior CRE colonization/infection[b]	9.86	4.88-19.93	<0.001
Time from transplantation to EB BSI (per d)	0.99	0.99-1.00	0.051
Chronic immunosuppression with mycophenolate[c]	0.47	0.25-0.89	0.021
Organ transplant type			
Kidney	*Ref*		
Liver	2.64	1.23-5.65	0.012
Heart	2.69	0.80-9.02	0.108
Lung	3.76	1.40-10.09	0.009
Pancreas	0.68	0.08-6.57	0.740

[a]Exposure within the 6 mo before the EB BSI.

[b]CRE organism isolated on any microbiological culture from any anatomical site in the 12 months before the EB BSI. No surveillance cultures were performed at the included study sites.

[c]Immunosuppression assessed at the time of the EB BSI.

aOR, adjusted odds ratio; BSI, bloodstream infection; CI, confidence interval; CRE, carbapenem-resistant Enterobacterales; EB, Enterobacterales; ref, reference.