SUPPLEMENTAL DIGITAL CONTENT

A. TEXT S1. INSTITUTIONAL REVIEW BOARD (IRB) APPROVALS

The IRB approvals for each participating center are listed below:

1. University of Pennsylvania: Protocol # 826458
2. Johns Hopkins University: Protocol # IRB001050712
3. University of Maryland: Protocol # HP-00072951

B. TEXT S2

B.1. Clinical data collection. Data on solid organ transplant (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 the following: demographics (eg, age, gender), comorbidities (eg, diabetes, asthma), medications (including current and prior immunosuppressants and antibiotics), viral serologies (eg, cytomegalovirus [CMV]), transplanted organ, date of transplant, induction immunosuppression, primary graft dysfunction, need for re-operation posttransplant, donor type, prior rejection episodes within 3 months prior to the Enterobacterales (EB) bloodstream infection (BSI), microbiology results for the 1 year prior to the EB BSI, and details of the EB BSI episode (including dates of positive blood cultures, organism(s) that grew on culture, in vitro susceptibilities, and a determination of the source of the EB BSI by each site-PI using standardized criteria). Inpatient and outpatient antibiotic therapy in the 6 months preceding the BSI was documented and categorized as described below.

B.2. Antimicrobial classification. For the purposes of the analysis, antibiotics were categorized as follows: aminoglycosides; amoxicillin and ampicillin; amoxicillin-clavulanate or ampicillin-sulbactam; aztreonam; first-generation cephalosporins; second-generation cephalosporins; third-generation cephalosporins; fourth-generation cephalosporins; ceftaroline; carbapenems; clindamycin; daptomycin; fosfomycin; fluoroquinolones; macrolides; metronidazole; anti-staphylococcal penicillins; polymyxins (colistin and polymyxin B); nitrofurantoin; penicillin; piperacillin-tazobactam; tetracyclines; linezolid; rifampin; trimethoprim-sulfamethoxazole; intravenous vancomycin; oral vancomycin; rifaximin; dapsone; and atovaquone. Antifungals were categorized as fluconazole; voriconazole and posaconazole; echinocandins; amphotericin.

B.3. Effective antibiotic therapy classification. Subjects were considered to have been given "effective antibiotic therapy" if they were administered at least one dose an antibiotic to which the EB organism was susceptible in vitro with the following guidelines and exceptions:

EB susceptibility category	Effective antibiotics (if susceptible in vitro)[a]	Not effective antibiotics (regardless of in vitro susceptibility)
Carbapenem-resistant Enterobacterales (CRE)	• Meropenem, imipenem-cilastatin, doripenem *if EB only resistant to ertapenem* • Fluoroquinolones • Polymyxins • Tigecycline • Aminoglycosides • Ceftazidime-avibactam[b]	• Amoxicillin or ampicillin • Amoxicillin-clavulanate or Ampicillin-sulbactam • First-, third-, and fourth-generation cephalosporins • Piperacillin-tazobactam • Ertapenem

	• Ceftolozane-tazobactam[b] • Meropenem-vaborbactam[b]	
Extended-spectrum beta-lactamase (ESBL)-producing EB	• Carbapenems • Fluoroquinolones • Aminoglycosides • Polymyxins • Tigecycline • Ceftazidime-avibactam[b] • Ceftolozane-tazobactam[b] • Meropenem-vaborbactam[b]	• Amoxicillin or ampicillin • Amoxicillin-clavulanate or Ampicillin-sulbactam • Third-generation cephalosporings • Fourth-generation cephalosporins • Piperacillin-tazobactam
Susceptible EB (ie, not ESBL-producing or CRE)	• Amoxicillin or ampicillin • Amoxicillin-clavulanate or Ampicillin-sulbactam • First-, third-, and fourth-generation cephalosporins • Aztreonam • Fluoroquinolones • Piperacillin-tazobactam • Polymyxins • Carbapenems • Tigecycline	N/A

Time to effective antibiotic therapy was defined as the number of days between the first positive blood culture and the first dose of an effective antibiotic, where day 0 was defined as the day that the first positive blood culture was collected. Antibiotics were evauated through 90 days post-EB BSI onset.

[a]Antibiotics in this category were only considered “effective” if the EB organism exhibited in vitro susceptibility to the antibiotic administered.

[b]Ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem-vaborbactam were the only antibiotics containing novel beta-lactamase inhibitors available at the time that this data was collected.

BSI, bloodstream infection; EB, Enterobacterales.

C. SUPPLEMENTAL TABLES

Table S1. Multivariable survival analysis among liver transplant recipients evaluating the association between CRE BSI, (A) all-cause mortality, and (B) new-onset graft failure.

A. All-cause mortality			
Characteristic	**aHR**	**95% CI**	***P***
CRE BSI (compared to non-CRE EB BSI)	**1.60**	**0.83-3.05**	**0.158**
Prior CRE colonization/infection[a]	1.77	0.84-3.69	0.131
Hepatitis C infection as the indication for Liver transplantation	2.33	1.39-3.92	0.001
Living organ donor	0.32	0.12-0.90	0.031
Primary graft dysfunction after transplant	1.92	1.03-3.56	0.039
B. New-onset graft failure			
Characteristic	**aSHR**	**95% CI**	***P***
CRE BSI (compared to non-CRE EB BSI)	0.70	0.25-1.99	0.506
Hepatitis C infection as the indication for Liver transplantation	1.87	1.00-3.49	0.050
Prior exposure to metronidazole[b]	2.61	1.34-5.09	0.005
Prior exposure to rituximab[c]	2.97	0.95-9.35	0.062

Study site			
Site 1	*ref*		
Site 2	0.90	0.40-2.06	0.809
Site 3	0.46	0.20-1.05	0.065

[a]Organism isolated on any microbiological culture from any anatomical site in the 1 year prior to the EB BSI. (No surveillance cultures performed at the included study sites.)

[b]Exposure within the 6 months prior to the EB BSI.

[c]Exposure within the 12 months prior to the EB BSI.

aHR, adjusted hazard ratio; aSHR, adjusted subhazard ratio; BSI, bloodstream infection; CI, confidence interval; CRE, carbapenem-resistant Enterobacterales; EB, Enterobacterales; ref, reference.

Table S2. Mixed effects multivariable logistic regression of risk factors for CRE BSI among liver transplant recipients.

Baseline characteristic	aOR	95% CI	*P*
Prior exposure to a carbapenem[a]	3.74	1.70-8.22	0.001
Prior CRE colonization/infection[b]	4.99	1.85-13.49	0.002
Living donor	0.18	0.05-0.72	0.016
Time from transplant to EB BSI (per day)	0.99	0.998-0.999	0.019

[a]Exposure within the 6 months prior to the EB BSI.

[b]Organism isolated on any microbiological culture from any anatomical site in the 1 year prior to the EB BSI. (No surveillance cultures performed at the included study sites.)

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

Table S3. Mixed effects bivariate survival analysis of the association between CRE BSI, (A) all-cause mortality, and (B) new-onset graft failure stratified by organ transplant type.

A. All-cause mortality			
Characteristic	**HR**	**95% CI**	***P***
CRE BSI (compared to non-CRE EB BSI) in *kidney transplant recipients*	13.68	5.55-33.75	<0.001
CRE BSI (compared to non-CRE EB BSI) in *heart transplant recipients*	3.17	0.34-29.64	0.311
CRE BSI (compared to non-CRE EB BSI) in *lung transplant recipients*	6.78	2.44-18.87	<0.001
CRE BSI (compared to non-CRE EB BSI) in *pancreas transplant recipients*	15.85	1.53-163.70	0.020
B. New-onset graft failure[a]			
Characteristic	**SHR**	**95% CI**	***P***
CRE BSI (compared to non-CRE EB BSI) in *kidney transplant recipients*	5.42	1.51-19.45	0.009
CRE BSI (compared to non-CRE EB BSI) in *heart transplant recipients*	7.30	1.21-44.11	0.030
CRE BSI (compared to non-CRE EB BSI) in *lung transplant recipients*	12.65	2.36-67.79	0.003

[a]Pancreas transplant recipients omitted due to insufficient numbers for analysis.

BSI, bloodstream infection; CI, confidence interval; CRE, carbapenem-resistant Enterobacterales; EB, Enterobacterales; HR, hazard ratio; SHR, subhazard ratio.

Table S4. Management of EB BSIs, stratified by carbapenem-resistance.

Management[a]	**CRE BSI (N = 70)**	**Non-CRE EB BSI (N = 827)**	***P***
Antibiotics[b]			
Days to effective therapy, median (IQR), days	3 (0-90)	1 (0-2)	<0.001
Effective antibiotics within 24 hours	27 (39%)	597 (72%)	<0.001
First effective antibiotic received			
Aminoglycoside	17 (24%)	31 (4%)	<0.001
Aztreonam	0 (0%)	8 (1%)	0.409
Carbapenem	10 (14%)[c]	200 (24%)	0.060
Fluoroquinolone	7 (10%)	125 (15%)	0.246
Fourth-generation cephalosporin	0 (0%)	170 (21%)	<0.001
Piperacillin-tazobactam	0 (0%)	194 (23%)	<0.001
Polymixin	4 (6%)	4 (0.5%)	<0.001
Third-generation cephalosporin	0 (0%)	50 (6%)	0.034
Tigecycline	12 (17%)	6 (1%)	<0.001
Source control			
Abscess drainage[d]	5 (7%)	27 (3%)	0.096
Central venous catheter removed[e]	6 (9%)	69 (8%)	0.947

[a]Data are presented as numbers (percentages) except where noted.

[b]Effective antibiotics defined as per Text S2 part B3.

[b]There were 10 cases in which the Enterobacterales organism was nonsusceptible to ertapenem but susceptible to meropenem and was treated with meropenem.

[c]Only assessed in those in whom in intra-abdominal abscess was the source of the EB BSI.

[d]Only assessed in those in whom a central venous catheter was the source of the EB BSI.

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

Table S5. Mixed effects survival analysis of the association between CRE BSI, (A) all-cause mortality, and (B) new-onset graft failure after adjusting for time to effective antibiotic therapy.

A. All-cause mortality			
Characteristic	**aHR**	**95% CI**	***P***
CRE BSI (compared to non-CRE EB BSI)	**2.60**	**1.54-4.41**	**<0.001**
Prior CRE colonization/infection[a]	0.91	0.46-1.80	0.795
Age (per year)	1.03	1.02-1.05	<0.001
Prior EB on respiratory culture[a]	3.10	2.02-4.78	<0.001
Rejection prior to the EB BSI treated with corticosteroids[b]	1.89	1.04-3.43	0.038
Prior polymyxin exposure[b]	2.53	1.32-4.83	0.005
Graft failure prior to the EB BSI	1.86	1.27-2.72	0.001
Days to effective antibiotic therapy	**1.01**	**1.00-1.01**	**0.034**
Organ transplant type			
Kidney	*ref*		
Liver	2.77	1.78-4.31	<0.001
Heart	1.26	0.56-2.86	0.575
Lung	1.50	0.75-3.00	0.246
Pancreas	3.87	1.49-10.04	0.005
B. New-onset graft failure			

Characteristic	aSHR	95% CI	*P*
CRE BSI (compared to non-CRE EB BSI)	2.03	1.09-3.78	0.025
Rejection prior to the EB BSI[c]	1.79	0.99-3.22	0.053
Prior EB on genitourinary culture[a]	0.44	0.23-0.82	0.010
Prior EB on respiratory culture[a]	2.65	1.42-4.94	0.002
Prior exposure to metronidazole[b]	1.74	1.03-2.93	0.039
Prior exposure to an aminoglycoside[b]	1.01	0.50-2.05	0.978
Days to effective antibiotic therapy	**1.01**	**1.00-1.02**	**0.009**
Organ transplant type			
Kidney	*ref*		
Liver	2.00	1.10-3.66	0.024
Heart	1.38	0.51-3.68	0.524
Lung	1.60	0.66-3.86	0.296
Pancreas	3.21	1.34-7.72	.009
Study site			
Site 1	*ref*		
Site 2	0.55	0.31-0.96	0.034
Site 3	0.46	0.27-0.79	0.004

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

[b]Within the 6 months prior to the EB BSI.

[c]Within the 3 months prior to the EB BSI.

aHR, adjusted hazard ratio; aSHR, adjusted subhazard ratio; BSI, bloodstream infection; CI, confidence interval; CRE, carbapenem-resistant Enterobacterales; EB, Enterobacterales; ref, reference.

Table S6. Mixed effects multivarible logistic regression analysis of risk factors for death within 60 days of a CRE BSI (N = 70).

Characteristic	aOR	95% CI	*P*
Genitourinary source of CRE BSI	0.05	0.002-0.93	0.045
Prior exposure to a polymyxin[a]	6.44	1.01-40.93	0.049
Pitt bacteremia score (per additional point)	1.36	1.00-1.84	0.053
Graft failure prior to the CRE BSI	7.66	1.16-50.33	0.034
Organ transplant type[b]			
Kidney	*ref*		
Liver	0.23	0.03-1.85	0.165
Heart	0.43	0.02-11.32	0.612
Lung	0.29	0.02-4.45	0.371

Table S6 Footnote.

[a]Exposure within the 6 months prior to the EB BSI.

[b]Pancreas transplant recipients were not included in this analysis due to insufficient sample size.

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

D. SUPPLEMENTAL FIGURES

Figure S1. Kaplan-Meier curve of all-cause mortality following an EB BSI, stratified by resistance to carbapenems and extended-spectrum cephalosporins. BSI, bloodstream infection; CRE, carbapenem-resistant Enterobacterales; EB, Enterobacterales; ESBL, extended-spectrum beta-lactamase.

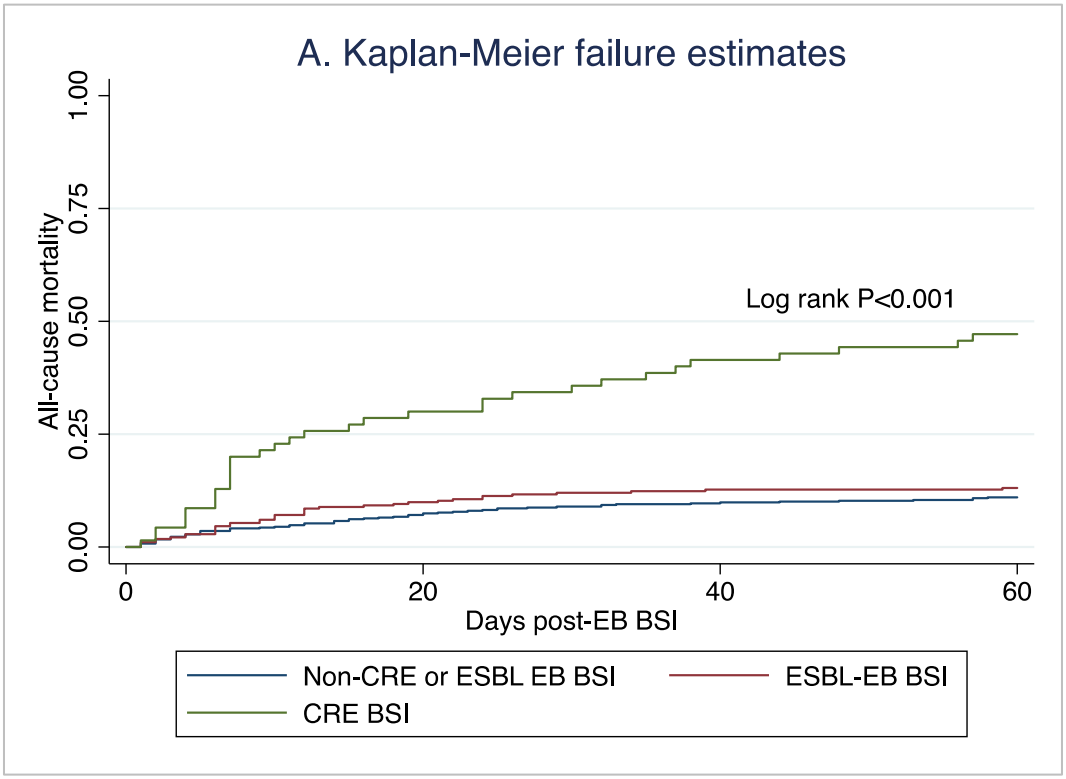

Figure S2. Kaplan-Meier curve of all-cause mortality following an EB BSI, stratified by degree of resistance to carbapenems. BSI, bloodstream infection; CRE, carbapenem-resistant Enterobacterales; EB, Enterobacterales.