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MAJOR ARTICLE

Daptomycin-Resistant *Enterococcus* Bacteremia Is Associated With Prior Daptomycin Use and Increased Mortality After Liver Transplantation

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Background. Risk factors for acquisition of vancomycin-resistant *Enterococcus* (VRE) include immunosuppression, antibiotic exposure, indwelling catheters, and manipulation of the gastrointestinal tract, all of which occur in liver transplant recipients. VRE infections are documented in liver transplantation (LT); however, only one single center study has assessed the impact of daptomycin-resistant *Enterococcus* (DRE) in this patient population.

Methods. We conducted a retrospective multicenter cohort study comparing liver transplant recipients with either VRE or DRE bacteremia. The primary outcome was death within 1 year of transplantation. Multivariable logistic regression analyses were performed to calculate adjusted odds ratios for outcomes of interest.

Results. We identified 139 cases of *Enterococcus* bacteremia following LT, of which 78% were VRE and 22% were DRE. When adjusted for total intensive care unit days in the first transplant year, liver-kidney transplantation, and calcineurin inhibitor use, patients with DRE bacteremia were 2.65 times more likely to die within 1 year of transplantation (adjusted odds ratio [aOR], 2.648; 95% CI, 1.025–6.840; $P = .044$). Prior daptomycin exposure was found to be an independent predictor of DRE bacteremia (aOR, 30.62; 95% CI, 10.087–92.955; $P < .001$).

Conclusions. In this multicenter study of LT recipients with *Enterococcus* bacteremia, DRE bacteremia was associated with higher 1-year mortality rates when compared with VRE bacteremia. Our data provide strong support for dedicated infection prevention and antimicrobial stewardship efforts for transplant patients. Further research is needed to support the development of better antibiotics for DRE and practical guidance focusing on identification and prevention of colonization and subsequent infection in liver transplant recipients at high risk for DRE bacteremia.

Keywords. bacteremia; daptomycin; *Enterococcus*; liver transplant.

Vancomycin-resistant enterococci (VRE) have been named by the Centers for Disease Control and Prevention as pathogens that pose a significant public health threat [1]. Risk factors for VRE acquisition include immunosuppression, receipt of prior antibiotics, indwelling catheters, and manipulation of the gastrointestinal (GI) tract—all common occurrences for liver transplant recipients [2–4]. The prevalence of VRE colonization among waitlisted liver transplant candidates ranges from 11.9% to 13%, and in one study of the candidates who went on to liver transplantation, 32% developed post-transplant VRE infection, which was associated with increased 90-day mortality [5–7].

Except for infective endocarditis, published guidelines for the duration and selection of antimicrobial agents for the treatment of VRE infection do not exist. In practice, either linezolid, an oxazolidinone, or daptomycin, a lipopeptide, is typically chosen for ampicillin-resistant VRE infections, including bacteremia [4, 8–10]. Linezolid treatment duration is limited by bone marrow toxicity, and while daptomycin is relatively safe, controversy persists regarding optimal dosing in VRE infection [11]. Comparisons of the efficacy of linezolid vs daptomycin in the treatment of VRE bacteremia in immunocompetent and immunocompromised hosts have had conflicting results, though this may be due to heterogeneity in daptomycin dosing [10, 12–15]. A recent multicenter prospective study of VRE bacteremia found that, in comparison with lower-dose daptomycin, both higher-dose daptomycin (≥9 mg/kg) and linezolid were

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associated with decreased mortality risk [16]. Finally, emerging studies have demonstrated synergistic activity of daptomycin and beta-lactams, but there are no clear guidelines to determine when clinicians should consider combination therapy [17].

In the past 10 years, daptomycin-resistant enterococci (DRE; previously daptomycin-nonsusceptible enterococci) have been increasingly reported and are associated with high mortality rates in patients with bacteremia [18–21]. The mechanism of daptomycin resistance in *Enterococcus* is thought to be due to genetic mutations in the regulation of cell envelope homeostasis and phospholipid metabolism [22–25]. Recent single-center studies compared outcomes of daptomycin-susceptible (DS-VRE) and DRE infection in liver transplant recipients and concluded that DRE infections in this population were associated with bleeding complications after surgery and more complex hospitalizations, including biliary interventions [18, 26]. Although these studies did not find a statistically significant difference in mortality, they have driven the hypothesis that DRE bacteremia may portend a worse prognosis compared with VRE bacteremia. Donor-derived resistant *Enterococcus* infection, de novo DRE infection, and DRE after daptomycin use have been reported in the literature, but to date there has only been one single-center study of liver transplant patients with DRE who had prior daptomycin exposure, and further work is needed to fully understand the risk factors associated with DRE bacteremia in the liver transplant patient population [26]. To clarify the risk factors and clinical consequences of DRE bacteremia, we performed a multicenter retrospective study of DRE and VRE bacteremia in liver transplant recipients. We hypothesize that DRE bacteremia is associated with increased mortality in liver transplant recipients and is associated with prior daptomycin use.

METHODS

Study Design

We conducted a retrospective multicenter cohort study of liver transplant recipients at 9 acute care academic hospitals with active transplant programs across the United States. Sites were recruited through the American Society of Transplantation Infectious Diseases Community of Practice. The Institutional Review Board approved this study at each institution. Patients ≥18 years of age with a history of liver transplantation (including multivisceral transplantation) and a history of resistant enterococcal bacteremia, defined as at least 1 positive blood culture for VRE or DRE after the date of liver transplant during the period from January 1, 2006, to December 31, 2016, were included in the study. If patients had DRE bacteremia at any point during the study period, they were assigned to the DRE group. Data were obtained by transplant infectious disease clinicians from patients' electronic medical records at each site and entered into a REDCap database hosted by the University of Alabama at Birmingham. Collected data included patient demographics, comorbidities, microbiological data, transplant clinical variables, antibiotic treatment, and clinical outcomes. We defined prior daptomycin exposure as post-transplant daptomycin prescribed before the initial episode of *Enterococcus* bacteremia. VRE infection was defined as post-transplant infection, and the source of infection was determined by trained infectious disease physicians during the year of review (2017–2018).

Microbiology

Microbiologic data provided by clinical laboratories were collected, including results of antibiotic susceptibility testing. Routine daptomycin susceptibility testing of *Enterococcus* isolates was performed at each site according to recommendations by the Clinical and Laboratory Standards Institute (CLSI) [27]. Susceptibility testing was confirmed at each institution with both broth microdilution and E-test [28]. Daptomycin resistance was defined as minimum inhibitory concentration (MIC) >4 μg/mL, per CLSI guidelines [27]. The study period occurred before the recent update of CLSI breakpoints of daptomycin nonsusceptibility.

Outcomes

The primary outcome was death within 1 year of transplantation. Secondary outcomes included death-censored graft failure within 1 year of transplantation and death within 30 days of final episode of bacteremia (VRE or DRE) captured during the study period.

Statistical Analysis

Comparison of categorical variables was performed using chi-square analysis or Fisher exact test where appropriate. Continuous variables were tested for normality and were compared using either the Mann-Whitney *U* test for nonparametric results or the Student *t* test for parametric results. *P* values <.05 were considered statistically significant. Risk factors were determined for DRE bacteremia, and multivariable logistic regression models were performed to calculate adjusted odds ratios (ORs) for the development of DRE bacteremia. For the outcome analyses, multivariable logistic regression models were performed to calculate adjusted odds ratios (aORs) for the primary and secondary outcomes. Covariates were selected for regression models if found to have $P < .10$ on bivariate analysis or if they were deemed clinically relevant with regard to predicting the primary outcome. If inclusion of a variable in the model induced confounding, as determined by a change in the β-coefficient of a covariate of >10%, the confounding variable was retained. Each model was assessed for fitness and collinearity. All statistical analyses were completed using SAS, version 9.4 (SAS Institute, Inc.).

RESULTS

During the study period, we identified 139 cases of resistant enterococcal bacteremia following liver transplantation (LT), of which 108 (78%) were VRE and 31 (22%) were DRE. Two institutions accounted for >50% of the DRE cases as well as a large portion of VRE cases (Table 1). Both cohorts were similar in gender, age, and race distributions. Hepatitis C, sclerosing cholangitis, and nonalcoholic steatohepatitis (NASH) were the most common indications for liver transplantation in both cohorts. There were similar proportions of multivisceral transplantation in both cohorts (16% in both VRE and DRE). Liver transplant patients with VRE and DRE bacteremia did not differ in type of induction therapy or in type of maintenance immunosuppression agents, including corticosteroids. Patients with VRE bacteremia were more likely to have a model for end-stage liver disease (MELD) score >20 at the time of transplantation (69% vs 48%; $P = .04$), but median MELD scores did not significantly differ between the 2 cohorts (24.0 vs 20.0, respectively; $P = .24$). Median MELDs in both the DRE and VRE cohorts were slightly less than median MELDs for liver transplants across the reporting institutions (median reported MELD, 28) [29]. Although types of post-transplant surgical complications were similar between the 2 cohorts, we identified increased rates of surgical complications in liver transplant recipients with DRE bacteremia compared with VRE bacteremia (unadjusted OR, 2.57; 95% CI, 1.06–6.26; $P = .03$). These surgical complications were largely due to anastomotic leaks (18% in VRE vs 32% in DRE; $P = .10$).

There were similar rates of rejection in both cohorts before bacteremia episodes (19% vs 19%; $P = .93$). The initial bacteremia episode occurred at similar times following transplantation in both cohorts, with 80% documented within the first year of transplantation (Table 1). In the first year following transplantation, LT recipients with DRE bacteremia did not have significantly longer hospital lengths of stay (median, 66 vs 85 days; $P = .18$). At the time of the initial identification of enterococcal bloodstream infection (BSI), liver transplant patients in both cohorts were equally likely to be hospitalized in the intensive care unit (ICU; 61% vs 51%; $P = .25$); however, liver transplant recipients with DRE bacteremia were more likely to be hospitalized in the ICU for longer periods of time compared with liver transplant recipients with VRE bacteremia (median, 36 days vs 14 days in the first year post-transplantation; $P = .006$). An intra-abdominal source was identified as the etiology of bacteremia in nearly 50% of patients in both cohorts.

Eighty-one percent of liver transplant recipients with DRE bacteremia had prior post-transplant exposure to daptomycin (unadjusted OR, 27.98; 95% CI, 9.76–80.2; $P < .001$). Furthermore, 22/31 (71%) of patients with DRE bacteremia had a prior post-transplant VRE infection, compared with only 2/76 (2.6%) of patients with VRE bacteremia. Prior post-transplant daptomycin exposure was found to be independently associated with subsequent DRE bacteremia (aOR, 30.62; 95% CI, 10.087–92.955; $P < .001$), when adjusted for natural MELD at the time of transplantation and surgical complications following transplantation (Table 2). Although not included in the bivariate analysis, we observed that patients with VRE bacteremia were treated predominantly with daptomycin (66%) and linezolid (31%), while patients with DRE bacteremia were more likely to receive linezolid (67%), combination therapy (daptomycin/beta-lactams, daptomycin/linezolid, or triple therapies, 17%), high-dose daptomycin (defined as ≥8 mg/kg, 7%), or other therapies such as quinupristin/dalfopristin or tigecycline (10%).

For the primary outcome of interest (death within 1 year of transplantation), initial unadjusted analysis identified liver-kidney transplantation, hospitalization in the ICU at the time of initial positive blood culture, and greater number of ICU days as being associated with increased risk (Supplementary Table 1). Rates of death within 1 year of transplantation were higher in the DRE bacteremia cohort, although this did not reach statistical significance (19% vs 7%; $P = .08$). When adjusted for total ICU days in the first year of transplantation, liver-kidney transplantation, and calcineurin inhibitor use, patients with DRE bacteremia were 2.65 times more likely to die within 1 year of transplantation when compared with patients with VRE bacteremia (aOR, 2.648; 95% CI, 1.025–6.840; $P = .044$) (Table 3).

Recurrent bacteremia with the same organism occurred more frequently in patients with DRE bacteremia (unadjusted OR, 2.35; 95% CI, 1.04–5.31). Death-censored graft failure occurred more frequently in the DRE bacteremia group than the VRE bacteremia group (OR, 4.12; 95% CI, 1.58–11.2; $P = .005$). DRE bacteremia was associated with death within 30 days of final culture in bivariate analysis (48%; unadjusted OR, 2.33; 95% CI, 1.03–5.28) (Supplementary Table 2). Both rejection before bacteremia (aOR, 3.269; 95% CI, 1.282–8.334) and admission to the ICU at the time of bacteremia (aOR, 4.024; 95% CI, 1.691–9.575) were strongly associated with 30-day mortality following the last episode of bacteremia in multivariate analysis (Table 4).

DISCUSSION

In this multicenter study of liver transplant recipients with resistant *Enterococcus* bacteremia, DRE bacteremia was associated with high 1-year mortality rates following liver transplantation when compared with patients with VRE bacteremia. Due to intrinsic and acquired antibiotic resistance, particularly to vancomycin and ampicillin, *Enterococcus faecium* poses a therapeutic challenge, particularly for those isolates that are multidrug-resistant [30]. In our cohort, patients with DRE bacteremia were more likely to have recurrent bacteremia, higher rates of death-censored graft failure, and higher rates of 30-day mortality by unadjusted analyses. Nearly 30% of DRE bacteremia patients received combination therapy alternative therapies such as tigecycline and quinopristin-dalfopristin. Given few antimicrobial choices for treatment, these data underscore

Table 1. Epidemiology and Outcomes of Patients With VRE and DRE Bacteremia

	Total	VRE	DRE	Unadjusted OR	
	n = 139	n = 108 (78%)	n = 31 (22%)	(95% CI)	*P* Value
Demographics					
Institution					.06
A	16 (12)	14 (13)	2 (7)	Ref	
B	23 (16)	13 (12)	10 (33)	5.39 (0.99–29.34)	
C	31 (22)	24 (22)	7 (23)	2.04 (0.37–11.22)	
D	7 (5)	5 (5)	2 (7)	2.80 (0.31–25.52)	
E	23 (16)	19 (17)	4 (13)	1.47 (0.24–9.21)	
F	4 (3)	2 (2)	2 (7)	7.00 (0.60–81.68)	
G	9 (6)	7 (6)	2 (7)	2.00 (0.23–17.34)	
H	17 (12)	17 (16)	0 (0)	…	
I	9 (6)	8 (7)	1 (3)	0.88 (0.07–11.24)	
Male, No. (%)	91 (66)	68 (63)	23 (74)	1.69 (0.69–4.14)	.25
Race					.66
Caucasian	107 (77)	81 (75)	26 (84)	Ref	
Black	21 (15)	17 (16)	4 (13)	0.73 (0.23–2.37)	
Asian	2 (1)	2 (2)	0 (0)	…	
Latino	4 (3)	3 (3)	1 (3)	1.04 (0.10–10.4)	
Other	5 (4)	5 (4)	0 (0)	…	
Age at time of transplant					.18
Mean ± SD, y	54.8 ± 10.9	55.5 ± 10.9	52.4 ± 10.6		
Median (IQR), y	56 (48–63)	57 (48–64)	52 (47–59)		
Primary liver diagnosis, No. (%)					.6
Hepatitis C	32 (23)	25 (23)	7 (22)	Ref	
Sclerosing cholangitis	23 (16)	16 (15)	7 (23)	1.56 (0.46–5.30)	
NASH	19 (14)	14 (13)	5 (16)	1.28 (0.34–4.78)	
Alcohol	18 (13)	15 (14)	3 (10)	0.71 (0.16–3.19)	
Cryptogenic	12 (9)	11 (10)	1 (3)	0.32 (0.04–2.97)	
Primary biliary cirrhosis	6 (4)	4 (4)	2 (6)	1.79 (0.27–11.86)	
Autoimmune	6 (4)	5 (5)	1 (3)	0.72 (0.07–7.16)	
Drug/toxin	2 (1)	2 (2)	0 (0)	…	
Cystic fibrosis	1 (0.5)	0 (0)	1 (3)	…	
Biliary atresia	1 (0.5)	1 (1)	0 (0)	…	
Hepatitis B	1 (0.5)	1 (1)	0 (0)	…	
Wilson's disease	1 (0.5)	1 (1)	0 (0)	…	
Alpha 1- antitrypsin	1 (0.5)	1 (1)	0 (0)	…	
Hepatocellular carcinoma	1 (0.5)	1 (1)	0 (0)	…	
Multiple	6 (4)	6 (6)	0 (0)	…	
Other	9 (6)	5 (5)	4 (13)	2.86 (0.60–13.59)	
Natural MELD at time of transplantation					
Mean ± SD	24.8 ± 9.2	25.2 ± 8.8	23.4 ± 10.8		.24
Median (IQR)	23 (19–31)	24 (20–32)	20 (17–30)		
Natural MELD >20, No. (%)	86 (64)	71 (69)	15 (48)	0.42 (0.19–0.96)	.04
Transplant organ, No. (%)					
Liver	117 (84)	91 (84)	26 (84)	Ref	.31
Liver-kidney	16 (11)	13 (12)	3 (10)	0.81 (0.21–3.05)	
Liver-pancreas	1 (1)	0 (0)	1 (3)	…	
Liver-pancreas-intestine	5 (4)	4 (4)	1 (3)	0.875 (0.09–8.17)	
Donor type, No. (%)					.20
Deceased	125 (90)	99 (92)	26 (84)	1.09 (0.93–1.29)	
Living	14 (10)	9 (8)	5 (16)	0.52 (0.19–1.43)	
Induction, No. (%)	96 (72)	74 (71)	22 (73)	1.12 (0.45–2.78)	.82
Immunosuppression following transplantation, No. (%)					
Calcineurin inhibitor	113 (81)	89 (82)	24 (77)	0.73 (0.28–1.94)	.53
Antiproliferative agents	74 (53)	61 (56)	13 (42)	0.56 (0.25–1.25)	.15
mTOR inhibitor	9 (6.5)	8 (7)	1 (3)	0.42 (0.05–3.45)	.40
Steroids	109 (78)	82 (76)	27 (87)	2.14 (0.69–6.69)	.18
≥3 immunosuppressants	52 (37)	43 (40)	9 (29)	0.62 (0.26–1.47)	.28
Surgical complication (total)	80 (58)	57 (53)	23 (74)	2.57 (1.06–6.26)	.03

Table 1. Continued

	Total	VRE	DRE	Unadjusted OR	
	n = 139	n = 108 (78%)	n = 31 (22%)	(95% CI)	*P* Value
Bleeding	18 (13)	15 (12)	5 (16)	Ref	.24
Anastomotic leak	30 (22)	20 (18)	10 (32)	1.30 (0.36–4.68)	
Thrombosis	11 (8)	7 (6)	4 (13)	1.49 (0.30–7.39)	
Reoperation	8 (6)	7 (6)	1 (3)	0.37 (0.04–3.84)	
Other	13 (9)	10 (9)	3 (10)	0.78 (0.15–4.07)	
Year 1 transplant hospital days					
Mean ± SD	89.3 ± 62.5	87.8 ± 65.9	94.5 ± 49.7		
Median (IQR)	68 (46–118)	66 (40–115)	85 (56–124)		.18
Year 1 transplant ICU days					
Mean ± SD	33.4 ± 37.4	32.4 ± 40.8	37.2 ± 18.5		.006
Median (IQR)	21.5 (8–43.5)	14 (7–41)	36 (28–49)		
Culture data					
Rejection before first bacteremia, No. (%)	25 (18)	20 (19)	6 (19)	1.04 (0.38–2.88)	.93
Time from initial transplant to bacteremia					.15
Mean ± SD	269.3 ± 502.4	270.4 ± 517.2	268.3 ± 454.8		
Median (IQR)	75 (19–248)	56.5 (15–248)	111.5 (35–226)		
Primary culture source, No. (%)					
Primary BSI	47 (34)	35 (32)	10 (32)	Ref	.79
CLABSI	22 (16)	14 (13)	6 (19)	1.50 (0.46–4.92)	
Intra-abdominal	64 (46)	53 (49)	15 (48)	0.99 (0.40–2.45)	
SSI	1 (1)	1 (1)	0 (0)	…	
Other	5 (3)	5 (5)	0 (0)	…	
ICU at time of first bacteremia, No. (%)	73 (53)	54 (51)	19 (61)	1.52 (0.67–3.45)	.41
Daptomycin exposure before first bacteremia, No. (%)	39 (28)	14 (13)	25 (81)	27.98 (9.76–80.2)	<.001
History of VRE infection before first bacteremia, No. (%)	24 (22) (out of 85)	2 (3)	22 (71)	92.9 (18.7–461.9)	<.001
Outcomes					
Recurrent bacteremia	58 (42)	40 (37)	18 (58)	2.35 (1.04–5.31)	.036
Death-censored graft failure	21 (15)	11 (10)	10 (32)	4.12 (1.58–11.2)	.005
Death-censored 1-year graft failure	14 (10)	8 (7)	6 (19)	3.00 (0.95–9.43)	.08
1-year mortality from transplantation	43 (31)	29 (27)	14 (45)	2.24 (0.98–5.12)	.08
30-day mortality from first bacteremia	34 (24)	24 (22)	10 (32)	1.67 (0.69–4.01)	.25
30-day mortality from last bacteremia	46 (33)	31 (29)	15 (48)	2.23 (1.03–5.28)	.04

Abbreviations: BSI, bloodstream infection; CLABSI, central line bloodstream infection; DRE, daptomycin-resistant Enterococcus; ICU, intensive care unit; IQR, interquartile range; MELD, model for-end stage liver disease; mTOR, mechanistic target of rapamycin; NASH, nonalcoholic steatohepatitis; SSI, surgical site infection; VRE, vancomycin-resistant *Enterococcus*.

the need to understand risk factors for acquisition of DRE in the liver transplant recipient and the need for further treatment options for drug-resistant *Enterococcus*.

Solid organ transplant recipients experience a high burden of bacterial infections within the first year of solid organ transplantation, particularly from *Enterococcus* [31]. With increasing VRE infections among transplant recipients, daptomycin is a common therapeutic agent used for treatment [32]. Patients with DRE bacteremia were 30 times more likely to have received daptomycin before developing infection when compared with patients with VRE bacteremia. In patients with recurrent *E. faecium* BSI, recent literature has documented an association between daptomycin exposure and subsequent increase in daptomycin MIC, suggesting that prior daptomycin exposure is a major driver of resistance [33–35]. There is further evidence that an MIC of 3–4 µg/mL in enterococcal isolates may predict microbiological failure of daptomycin therapy at

Table 2. Binary Logistic Regression for Predictors of Daptomycin-Resistant *Enterococcus* Bacteremia

Variable	aOR (95% CI)	*P* Value
Daptomycin exposure before first bacteremia	30.62 (10.087–92.955)	<.001
Natural MELD at time of transplantation	0.961 (0.907–1.018)	.173
Surgical complication following transplantation	1.750 (0.565–5.423)	.332

Abbreviations: aOR, adjusted odds ratio; MELD, model for end-stage liver disease.

Table 3. Binary Logistic Regression of Risk Factors Associated With Death Within 1 Year of Liver Transplantation

Variable	aOR (95% CI)	*P* Value
DRE bacteremia	2.648 (1.025–6.840)	.044
Total ICU days in the first year of transplantation	1.017 (1.006–1.029)	.003
Liver-kidney transplantation	3.737 (1.172–11.917)	.026
Calcineurin inhibitor use	0.449 (0.165–1.221)	.117

Abbreviations: aOR, adjusted odds ratio; DRE, daptomycin-resistant *Enterococcus*; ICU, intensive care unit.

Table 4. Binary Logistic Regression of Death Within 30 Days Following Last Episode of Bacteremia

	aOR (95% CI)	*P* Value
DRE bacteremia	1.982 (0.803–4.896)	.138
ICU at time of last episode of bacteremia	4.024 (1.691–9.575)	<.001
Rejection before bacteremia	3.269 (1.282–8.334)	.013
Calcineurin inhibitors	0.400 (0.146–1.101)	.076

Abbreviations: DRE, daptomycin-resistant *Enterococcus*; ICU, intensive care unit.

standard dosing for bacteremia, and thus the CLSI has recently updated the breakpoints for enterococci to guide clinicians in optimal daptomycin dosing [36–39]. It is important to note that our study occurred before the updated CLSI breakpoints, and there is some likelihood that post-transplant daptomycin was used to treat enterococcal isolates with higher MICs. Thus, it will be important to confirm our findings in the in current era of updated CLSI breakpoints. Interestingly, 30% of patients with DRE bacteremia in our study did not have documented exposure to daptomycin, which may potentially be due to sporadic emergence and clonal spread [40]. Studies have documented institution-wide increases of daptomycin MICs among vancomycin-resistant *Enterococcus faecium* isolates, which may correlate to increased usage of daptomycin within health care facilities [33, 41]. Antimicrobial stewardship programs should prioritize reducing prescriptions of broad antimicrobial agents in transplant recipients, which will be important in combatting multidrug-resistant pathogens such as DRE.

Infection prevention practices including robust hand hygiene programs and active antimicrobial stewardship programs have improved overall rates of VRE colonization in hospitalized patients. Active surveillance screening (ie, rectal swabs) and subsequent isolation have been shown to reduce VRE infections with potential for reduced costs, but further studies are needed, particularly in liver transplant recipients [42]. Pre–liver transplant colonization with VRE has been associated with higher rates of post–liver transplant VRE infection as well as increased length of stay, morbidity, and mortality when compared with noncolonized recipients [6, 7, 43, 44]. Recent data have shown that daptomycin resistance can develop in screening fecal cultures and that the development of daptomycin resistance is 50% higher in those exposed to daptomycin [45, 46]. However, to date, there are limited data focusing on infection prevention strategies in DRE-colonized and -infected liver transplant patients. Further research is needed to understand the role of pre- and post-transplant screening as well as potential donor screening for resistant bacteria such as DRE. The latter is an emerging area of focus as antibiotic-experienced deceased donors have been shown to be at increased risk of colonization with multidrug-resistant organisms (MDROs) that can be transmitted to the recipient [47].

The strengths of our study include its multicenter design and robust transplant infectious disease clinician–directed data capture. Our study differed in design from that of Lewis et al., who retrospectively reviewed liver transplant recipients who developed daptomycin-resistant infections following exposure to daptomycin; thus, we were able to identify potential risk factors for the development of DRE, including daptomycin exposure [26]. Our study does have some limitations to note. Despite our multicenter design, we had a relatively small sample size, which limited our ability to adjust for confounding variables, including identifying risk factors such as ICU exposure before the development of DRE. We did not rigorously capture prior daptomycin dosing in these patients, and therefore we could not fully elucidate whether prior lower-dose daptomycin (<6 mg/kg) is associated with DRE bacteremia. Further, we did not limit the time of prior exposure of daptomycin before infection or the number of days received. There is also incomplete information regarding pretransplant VRE or DRE colonization and infection in our cohort. In terms of treatment, we did not capture immunosuppressive medication changes, attempts at any source control in response to enterococcal bacteremia, or the effect of different therapies on mortality. Given the small sample size and variability of treatment in our cohort, more data are needed to determine if combination therapy is beneficial. Finally, both cohorts were infected with *Enterococcus* bacteremia following transplantation, and the data presented here may be reflective of a sicker population, as the length of stay in the ICU for both cohorts was longer than what has been reported on average for liver transplant recipients [48]. Further studies are needed to elucidate the effect of drug-resistant infections in liver transplantation.

CONCLUSIONS

Liver transplant recipients with DRE bacteremia have high rates of graft failure, 1-year mortality following transplantation, and 30-day mortality following bacteremia when compared with liver transplant recipients with VRE bacteremia. Prior daptomycin receipt predicts development of DRE bacteremia in the liver transplant patient population. Collectively, our data provide strong support for dedicated infection prevention and antimicrobial stewardship efforts for solid organ transplant patients. Further research is needed to support the development of better antibiotics and delineate optimal treatment strategies for DRE and practical guidance focusing on identification and prevention of colonization and subsequent infection in liver transplant recipients at high risk for DRE bacteremia.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Patient consent. The study above does not include factors necessitating patient consent.

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