

Infectious Diseases Consultation Is Associated With Decreased Mortality in Enterococcal Bloodstream Infections

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Background. *Enterococcus* species frequently cause health care–associated bacteremia, with high attributable mortality. The benefit of consultation with infectious disease (ID) specialists has been previously illustrated with *Staphylococcus aureus* bacteremia. Whether ID consultation (IDC) improves mortality in enterococcal bacteremia is unknown.

Methods. This is a retrospective cohort single-center study from January 1, 2015, to June 30, 2016, that included all patients >18 years of age admitted with a first episode of *Enterococcus* bacteremia. Patients were excluded if death or transfer to palliative care occurred within 2 days of positive blood culture.

Results. Two hundred five patients were included in the study, of whom 64% received IDC. Participants who received IDC were more likely to undergo repeat cultures to ensure clearance (99% vs 74%; $P < .001$), echocardiography (79% vs 45%; $P < .001$), surgical intervention (20% vs 7%; $P = 0.01$), and have appropriate antibiotic duration (90% vs 46%; $P < .001$). Thirty-day mortality was significantly higher in the no-IDC group (27% vs 12%; $P < .007$). In multivariate analysis, 30-day in-hospital mortality was associated with both *E. faecium* bacteremia (adjusted odds ratio [aOR], 2.39; 95% confidence interval [CI], 1.09–5.23) and IDC (aOR, 0.35; 95% CI, 0.16–0.76).

Conclusions. Patients who received IDC for *Enterococcus* bacteremia had significantly lower 30-day mortality. Further prospective studies are necessary to determine if these outcomes can be validated in other institutions for patients who receive IDC with *Enterococcus* bacteremia.

Keywords. bacteremia; *Enterococcus*; infectious diseases consultation.

Enterococcus spp. are gram-positive bacteria typically present in low abundance in the normal gut flora, but are known for their ability to cause serious infections in hospitalized patients [1, 2]. They are frequently a cause of health care–associated bloodstream infections and are associated with mortality rates as high as 68%, high rates of antibiotic resistance, increased length of stay, and associated health care costs [3, 4]. Globally, they account for up to 10% of all bacteremias and are the second most common cause of health care–associated infections reported to the National Healthcare Safety Network [5–7]. Timely effective antimicrobial therapy, especially within the first 48 hours, has been associated with reduced mortality in patients

with enterococcal bloodstream infections (EBSIs) even after adjusting for severity of illness and medical comorbidities [8].

Infectious disease consultation (IDC) has been associated with improved outcomes in patients with *Staphylococcus aureus* bacteremia, resulting in decreased mortality, lower incidence of treatment failure, and fewer episodes of recurrent bacteremia, without any effect on length of stay [9–15]. These improved clinical outcomes have been attributed to better adherence to quality measures and treatment guidelines with increased use of follow-up blood cultures, echocardiogram, and other radiographic studies [10]. In addition to *S. aureus* bacteremia, IDC has been associated with improved outcomes in patients with infections from multidrug-resistant pathogens, *Cryptococcus* and *Candida* species, and, recently, enterococcal bacteremia in children [16–19].

Currently, there are no professional society or national guidelines for the treatment of EBSIs other than bacteremia associated with endocarditis [20]. The purpose of this study was to determine the impact of IDC on the clinical outcome of patients with EBSI.

METHODS

The institutional review board (IRB) of the University of Alabama at Birmingham approved this study and waived informed consent (IRB #X160222002).

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Study Design

We conducted a retrospective cohort study of all patients with EBSI admitted to the University of Alabama at Birmingham (UAB) Hospital—a 1157-bed tertiary care teaching hospital located in Birmingham, Alabama—between January 1, 2015, and June 30, 2016. Patients who had at least 1 positive blood culture for *Enterococcus* species were identified through a review of the electronic medical record for inclusion into the study. Only the first episode of EBSI was included in the analysis. Patients were excluded if age <18 years or if death or transfer to palliative care occurred within 2 days of positive blood culture.

Data collected included baseline patient characteristics and clinical data, such as repeating blood cultures and echocardiogram use, interventions for source control, microbiology data, appropriate antibiotic treatment, and outcomes. Data were collected from the electronic medical record system and managed using the REDCap electronic data capture tool hosted at UAB.

Definitions

Enterococcal bloodstream infection (EBSI) was defined as isolation of *Enterococcus* spp. in 1 or more blood culture bottles. Microbiologic identification and susceptibility testing were performed using Clinical and Laboratory Standards Institute (CLSI) standards. Definitive identification was done by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS), and antimicrobial susceptibility was performed by the MicroScan system. The date of onset of EBSI was defined as the date of the first positive blood culture for *Enterococcus* sp. Fever, hypotension, leukocytosis, neutropenia, and acute kidney injury were documented within 24 hours of cultures being drawn. Fever was defined as a single recorded internal body temperature $\geq 100.4^{\circ}\text{F}$. Hypotension was defined as a single blood pressure <90/60 mmHg. Leukocytosis was defined as a total white blood cell count $>11 \times 10^9$ cells/L, and neutropenia was defined as an absolute neutrophil count (ANC) of $<1000 \times 10^9$ cells/L. Acute kidney injury was defined as an increase in serum creatinine ≥ 0.3 mg/dL or >1.5 times the baseline creatinine. An episode of bacteremia was considered to be hospital-acquired if the blood culture was drawn >48 hours after admission. Recurrence of bacteremia was calculated from the date of onset of EBSI, and treatment failure was defined as persistent bacteremia for ≥ 5 days. Microbiological and clinical criteria were used by an ID-trained physician (R.A.L.) to define the source of each case of bacteremia. The source was deemed unclear/unknown if no other source of infection was identified or documentation was not clear. Uncomplicated EBSI was defined as having at least 1 positive blood culture and being without evidence of infection of deeper tissue structures, metastatic infection, or endocarditis. Complicated EBSI was defined as having a positive blood culture with evidence

of deep tissue structure involvement (including but not limited to osteomyelitis, septic arthritis, complex intra-abdominal infection, or abscess), metastatic infection, or endocarditis.

Appropriate antibiotic therapy was defined as receipt of an active bioavailable antimicrobial agent based on in vitro microbiology susceptibility testing. Appropriate duration of antibiotic therapy was evaluated using available guidelines or local standard of care [20–27]. We defined appropriate duration of therapy as 14 days for uncomplicated bacteremia and at least 28 days for complicated bacteremia. Antibiotic duration was confirmed in the medication administration records during the inpatient stay and by the discharge summary if patients were discharged before completion of therapy. Length of stay (LOS) was defined as time from admission to discharge; if a patient died during the index hospitalization, LOS was not calculated.

Infectious Diseases Specialist Consultation

Infectious diseases consultation (IDC) was readily available and performed upon request from the primary service/physician. The expectation was for bedside IDC to take place within 24 hours of request, as documented by completion of the consult note in the electronic medical record.

Outcome

The primary outcome was defined as in-hospital mortality within 30 days. Secondary outcomes included length of stay, treatment failure, recurrence of bacteremia within 60 days, and readmission within 60 days.

Statistical Methods

Categorical variables were analyzed with the Fisher exact test, and continuous variables were analyzed with the *t* test or Wilcoxon rank-sum test when appropriate. Multivariable analysis was performed using logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for factors associated with 30-day in-hospital mortality. Only variables found to be statistically significant were included in the model. A *P* value $<.05$ was considered significant. Analyses were done with SAS, version 9.4, statistical software (Cary, NC, USA).

RESULTS

Study Population

A total of 205 patients met the inclusion criteria during the study period, of whom 131 (64%) received IDC (Table 1). The median age was 59 years, with 52% being male. Baseline demographics and medical comorbidities were similar between the 2 groups, with the exception of diabetes mellitus, which was more prevalent in the no-IDC group (45% vs 30%; *P* = .04). The median Charlson comorbidity index score was 3. *E. faecalis* accounted for 65% of cases, and *E. faecium* accounted for

Table 1. Baseline Demographics of 205 Episodes of Enterococcal Bacteremia

Variable	All Patients (n = 205)	No IDC (n = 74)	IDC (n = 131)	P Value
Age, median (IQR), y	59 (23)	59 (15)	59 (27)	.54
Male, No. (%)	107 (52)	36 (49)	71 (54)	.44
White, No. (%)	112 (55)	44 (60)	68 (52)	.23
IVDU, No. (%)	10 (5)	1 (1)	9 (7)	.10
COPD, No. (%)	40 (20)	11 (15)	29 (22)	.21
CAD, No. (%)	40 (20)	14 (19)	26 (20)	.87
CHF, No. (%)	54 (26)	17 (23)	37 (28)	.41
Connective tissue disease, No. (%)	8 (4)	3 (4)	5 (4)	1.00
Diabetes, No. (%)	73 (36)	33 (45)	40 (30)	.04
Hypertension, No. (%)	118 (58)	42 (57)	76 (58)	.86
CKD, No. (%)	58 (28)	24 (32)	34 (26)	.32
Hemodialysis, No. (%)	26 (13)	8 (11)	18 (14)	.54
PVD, No. (%)	13 (6)	7 (10)	6 (5)	.17
Malignancy, No. (%)	47 (23)	20 (27)	27 (20)	.29
Cirrhosis, No. (%)	19 (9)	6 (8)	13 (10)	.67
Hepatitis, No. (%)	15 (7)	5 (7)	10 (8)	1.00
HIV, No. (%)	4 (2)	1 (1)	3 (2)	1.00
Immunocompromised, No. (%)	52 (25)	16 (22)	36 (27)	.35
• Hematologic malignancy	16 (8)	6 (8)	10 (8)	.83
• Solid organ transplantation	24 (12)	7 (10)	17 (13)	
• Immunosuppressive agents	11 (5)	3 (4)	8 (6)	
• CD4 <200	1 (0.5)	0 (0)	1 (1)	
Charlson comorbidity index, median (IQR)	3 (4)	2 (4)	3 (3)	.84
Hospitalization <30 d before bacteremia	107 (53)	37 (50)	70 (53)	.64
Invasive procedure 30 d before bacteremia	62 (30)	23 (31)	39 (30)	.84
Bacteremia diagnosed ≥48 h after admission	172 (84)	57 (77)	115 (88)	.04
Admitting service				
• ICU	58 (28)	21 (28)	37 (28)	.24
• Medical	97 (48)	30 (41)	67 (51)	
• Surgical	29 (14)	15 (20)	14 (11)	
• Transplant/IC	21 (10)	8 (11)	13 (10)	
ICU placement within 72 h	109 (53)	40 (54)	69 (53)	.85
Symptoms within 24 h of bacteremia				
• Fever	105 (51)	42 (57)	63 (48)	.23
• Hypotension	76 (37)	28 (38)	48 (37)	.86
• Leukocytosis	116 (57)	47 (64)	69 (53)	.13
• Neutropenia	12 (6)	2 (3)	10 (8)	.22
• AKI	67 (32)	30 (40)	37 (28)	.07
Mechanical ventilation	44 (22)	17 (23)	27 (21)	.69
<i>Enterococcus</i> species				
• <i>Enterococcus faecalis</i>	133 (65)	49 (66)	84 (64)	.88
• <i>Enterococcus faecium</i>	68 (33)	24 (33)	44 (34)	
• Other	4 (2)	1 (1)	3 (2)	
Vancomycin-resistant <i>Enterococcus</i>	67 (33)	24 (32)	43 (33)	.95
Time from admission to bacteremia, median (IQR), d	5 (19)	5 (16)	6 (19)	.05

Abbreviations: AKI, acute kidney injury; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IC, immunocompromised; ICU, intensive care unit; IDC, infectious diseases consultation; IQR, interquartile range; IVDU, intravenous drug user; PVD, peripheral vascular disease.

33% of bacteremia, with similar rates of vancomycin-resistant *Enterococcus* (VRE) in both groups. A total of 172 episodes (84%) were identified >48 hours after admission, which was significantly different in the 2 groups (77% in no IDC vs 88% in IDC; $P = .04$). The mean time to IDC after bacteremia (SD) was 3.73 (3.18) days.

Clinical Features

Patients who received IDC were more likely to have repeat blood cultures drawn (99% vs 74%; $P < .001$) and were more likely to have an echocardiogram performed (79% vs 45%; $P < .001$) (Table 2). Patients who received IDC were more likely to be diagnosed with endocarditis as the primary source of

Table 2. Clinical Features and Outcomes in *Enterococcus* Bacteremia

	All Patients (n = 205)	No IDC (n = 74)	IDC (n = 131)	P Value
Repeat cultures	185 (90)	55 (74)	130 (99)	<.001
Echocardiogram performed	136 (66)	33 (45)	103 (79)	<.001
Unknown primary source	65 (32)	40 (54)	25 (19)	<.001
Primary source (among known)				
• Intravascular catheter	43 (21)	7 (10)	36 (28)	.016
• Skin/soft tissue	7 (3)	4 (5)	3 (2)	
• GI	29 (14)	8 (10)	21 (16)	
• Bone and joint	6 (3)	0 (0)	6 (5)	
• Endocarditis	17 (8)	0 (0)	17 (13)	
• Urinary tract	21 (10)	9 (12)	12 (9)	
• Other	14 (7)	6 (8)	8 (6)	
Removal of catheter	34 (16)	6 (75)	28 (70)	1.00
Time to definitive antibiotics, median (IQR), d	0 (2)	0 (1)	1 (2)	.30
Inappropriate antibiotic duration	53 (26)	40 (54)	13 (10)	<.001
Inappropriate or no antibiotics	14 (7)	14 (19)	0 (0)	<.001
Treatment failure	15 (7)	8 (11)	7 (5)	.12
Surgical intervention	31 (15)	5 (7)	26 (20)	.01
Recurrent bacteremia within 60 d	10 (5)	5 (7)	5 (4)	.50
Readmission within 60 d	67 (41)	24 (42)	43 (40)	.81
30-d mortality	36 (18)	20 (27)	16 (12)	.007
90-d mortality	56 (27)	25 (34)	31 (24)	.12
LOS, median (IQR), d	14.5 (32)	11 (27)	18 (35)	.09
Postbacteremia LOS, median (IQR), d	10.5 (16)	10.5 (15)	10.5 (22)	.004

Abbreviations: GI, gastrointestinal; IDC, infectious diseases consultation; IQR, interquartile range; LOS, length of stay.

infection (13% vs 0%; $P < .001$) as well as documented intravascular catheter infection (28% vs 10%; $P < .001$), although the rates of catheter removal were similar in both groups (75% vs 70%; $P = 1.00$). Interventions for source control including drain placement and surgical interventions were more frequently performed in the IDC group (20% vs 7%; $P = .01$). Definitive antibiotics were prescribed within 48 hours in 77% of patients, with no differences in IDC vs no IDC (79% vs 74%; $P = .48$). Patients who did not receive IDC were more likely to have received inappropriate or no antibiotic treatment at all (19% vs 0%; $P < .001$) and inappropriate duration of therapy based on the source of bacteremia (54% vs 10%; $P < .001$).

All-cause 30-day mortality was lower in patients who received IDC (12% vs 27%; $P = .007$), although this did not hold true at 90 days (34% vs 24%; $P = .12$). Patients with VRE BSI were 2.8 times more likely to die at 30 days compared with vancomycin-sensitive *Enterococcus* (28% vs 17%; odds ratio [OR], 2.82; 95% confidence interval [CI], 1.35–5.87; $P = .005$). Upon evaluating secondary outcomes, the IDC cohort was noted to have a longer LOS, but LOS was not statistically significant (median, 18 days vs 11 days; $P = .09$). There were no differences in the rate of treatment failure, recurrent bacteremia, or readmission within 60 days.

On multivariate analysis, IDC was associated with a 13-fold increased likelihood of repeat blood cultures (adjusted odds

ratio [aOR], 12.83; 95% CI, 1.52–108.03), 2.5-fold increased likelihood of echocardiogram (aOR, 2.45; 95% CI, 1.13–5.31), 6.6-fold increased likelihood of treatment with an appropriate antibiotic duration (aOR, 6.65; 95% CI, 2.90–15.27), and 60% decreased likelihood of having an unknown source (aOR, 0.31; 95% CI, 0.14–0.70). Thirty-day in-hospital mortality was found to be associated with *E. faecium* bacteremia (aOR, 2.39; 95% CI, 1.09–5.23), and IDC was associated with decreased odds of death (aOR, 0.35; 95% CI, 0.16–0.76) (Table 3).

DISCUSSION

In our retrospective single-center cohort study, infectious diseases consultation was associated with a 65% reduction of 30-day in-hospital mortality. This finding is similar to the results of other well-established studies that have identified improvement in mortality and adherence to guidelines when ID specialists are consulted for *S. aureus* bacteremia, as well as recent evidence showing improvement in mortality in other infections such as candidemia and cryptococcosis [10, 12–15, 17, 19, 28–30]. In enterococcal BSI, IDC has been shown to improve mortality in both pediatric and adult populations, but this is the first study that we are aware of that focuses specifically on IDC as a primary outcome of interest in an adult population [8, 18, 31].

Table 3. Multivariable Logistic Regression Model of Variables Associated With 30-Day Mortality

Variable	Crude Odds Ratio	Adjusted Odds Ratio	P Value
	(95% Confidence Interval)	(95% Confidence Interval)	
Infectious diseases consultation	0.38 (0.181–0.782)	0.35 (0.16–0.76)	.007
Hypotension	2.20 (1.06–4.55)	1.85 (0.83–4.12)	.13
Ventilation at time of bacteremia	2.95 (1.36–6.42)	2.20 (0.93–5.23)	.07
<i>Enterococcus</i> species			
<i>Enterococcus faecium</i>	2.38 (1.14–4.95)	2.39 (1.09–5.23)	.03
Other <i>Enterococcus</i> species	1.58 (0.16–15.65)	2.18 (0.18–26.04)	.55
<i>Enterococcus faecalis</i>	Referent	Referent	

EBSI has been associated with high attributable mortality, ranging from 13% to 68%, and treating EBSI has become increasingly difficult due to rising prevalence of vancomycin resistance and emergence of multidrug-resistant enterococci [4, 8, 32, 33]. Receipt of early effective therapy within 48 hours has been associated with reduced mortality in hospital-onset EBSI; however, our cohort did not show a difference in 30-day mortality with receipt of appropriate empiric therapy within 48 hours. This may be due to 2 reasons: First, our cohort includes both hospital-onset and community-acquired bacteremias and thus may reflect differences in patient populations. Second, we noted that nearly 80% of patients received appropriate empiric therapy within 48 hours, likely due to the inclusion of *E. faecalis*, which is less likely to be vancomycin resistant based on our institution's antibiogram. Although appropriate empiric therapy was not different between the 2 groups, 99% of patients in the IDC had blood cultures to prove clearance of EBSI, which may contribute to lower 30-day mortality; Jindai et al. noted similarly that patients who received IDC had more cultures taken, and thus assessment of elimination of bacteremia was more accurate in these cases [31]. Finally, although we observed differences in 30-day in-hospital mortality, there was no difference in 90-day mortality. This may be reflective of other unmeasured variables in the outpatient setting, including lack of a formal OPAT program at the time of the study, recurrent bacteremia, and other patient-specific factors.

Only 33% of isolates included in our study were vancomycin resistant, with similar prevalence of vancomycin-resistant *Enterococcus* (VRE) occurring in both groups. A previously published systematic review compared VRE with vancomycin-sensitive *Enterococcus* (VSE) bacteremia, noting a nearly 2-fold increased risk of mortality, despite more anti-VRE antimicrobial agents on the market such as daptomycin and linezolid [2]. Similar to this meta-analysis, *E. faecium* (known for its high rate of vancomycin resistance) in our study was associated with a 2.4-fold higher likelihood of death at 30 days. In addition to increased risk of mortality, LOS is longer in VRE when compared with VSE bacteremia [2]. The median LOS in our whole cohort was notably long at 14.5 days and was slightly longer in the IDC group, but there was no difference in LOS in VRE vs

VSE bacteremia (median LOS, 20 days vs 13 days; $P = .105$). Our median LOS is similar to older studies that found the mean duration of hospital stay to be nearly 40 days [3]. Interestingly, LOS after bacteremia was significantly different in the IDC cohort. This may be due to the fact that although the Charlson comorbidity index scores were similar, there were more patients with bacteremia diagnosed after 48 hours in the IDC group; and thus may reflect a chronically ill population. Additionally, more surgical interventions were performed on patients in the IDC group, which may have increased the LOS postbacteremia.

Higher identification of the source of bacteremia in the IDC group likely reflects both proper documentation of a source within the electronic medical record in order to guide treatment duration and a potential increase in surgical interventions for source control (20% vs 7%; $P < .001$). IDC occurred more frequently for patients in whom either intravascular catheter or infective endocarditis (IE) was identified as the source. The proportion of infective endocarditis ranges from 5.7% to 13.3%, which is similar to our cohort of 8% [5]. ID consultation occurred before the diagnosis of IE in 41% of our cohort. Echocardiography is essential in the diagnosis of IE, but in *Enterococcus* bacteremia, there are no set guidelines similar to *S. aureus* bacteremia. Both transthoracic and transesophageal echocardiography are typically used to identify IE, with TEE typically being reserved for higher-risk patients [20]. A bedside predictive score (NOVA score) has been developed to predict which patients with *E. faecalis* BSI will develop infective endocarditis and includes the number (N) of positive blood cultures, unknown origin (O) of bacteremia, prior valve disease (V), and auscultation of a heart murmur (A) [34]. External validation of the score identified that several risk factors associated with IE, including monomicrobial bacteremia, community acquisition, prosthetic heart valve, and male sex, were associated with IE [35]. We did not obtain NOVA scores in this cohort given the retrospective nature of this study; we could not confirm if all aspects of the score were assessed. Use of the NOVA score would be helpful in future studies to assess appropriate utilization of transesophageal echocardiography in EBSI.

This study has several limitations. This is a single-center retrospective study, and the findings may not be generalizable to

other institutions. Although every effort was made to collect all variables for each patient, the source of the bacteremia that remained “unknown” or “unclear” is higher than in other published studies, as the source could not be ascertained from a review of the medical records. In our regression model for 30-day mortality, there was noted multicollinearity with both repeat blood cultures and inappropriate duration, likely due to the fact that both are associated with IDC and thus were removed from the model. Additionally, repeat blood cultures may have occurred more often in the IDC group if patients in the no-IDC group died before repeat draw of cultures. Finally, the optimal treatment of EBSI and treatment courses recommended in the published guidelines may not necessarily apply to all cases. In this study, however, we chose specified cutoffs based on guidelines to determine appropriate duration of therapy for bacteremia, which was reviewed by 1 unblinded ID physician (RAL); thus, review by a second ID physician may differ in these choices.

CONCLUSIONS

In conclusion, in our retrospective cohort study, we observed a significant decrease in 30-day in-hospital mortality in patients with EBSI who received IDC. This observation may be attributed to better workup (including blood cultures and echocardiography), more surgical interventions, and an increase in appropriate durations of therapy determined by primary source of infection. Based on our findings, we have implemented automatic consultation for *Enterococcus* bacteremia at our institution. Further multisite studies are necessary to assess outcomes in this patient population and validate these findings.

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