ORIGINAL ARTICLE

Is Enterococcal Bacteremia a Cause or Corollary of Severe Illness? 5 Years' Experience from an Indian Teaching Hospital

Gauri Kumar[1], Muralidhar Varma[2], Chiranjay Mukhopadhyay[3], Vandana K Eshwara[4]

Received on: 29 May 2024; *Accepted on:* 19 April 2025; *Published on:* 08 May 2025

Abstract

Background and aims: Enterococci have emerged as successful pathogens in healthcare-associated infections due to their hardiness and survival ability in environments with high background antimicrobial pressure. Enterococcal bacteremia (EB) present an intriguing link between the host, environmental and healthcare practices. We present here the detailed clinical epidemiology of EB from an Indian hospital.

Patients and methods: We retrospectively studied adult patients diagnosed with bacteremia by Enterococcal species for 5 years. The details of clinical characteristics, implicated species, factors contributing to the development of bacteremia and the underlying source were analyzed. All the clinical and laboratory findings and antimicrobial therapy associated with clinical outcome were assessed.

Results: *Enterococcus faecium* was the predominant pathogen in 82(42.5%) of the total 193 cases. Prior healthcare exposure was evident in 136(70.46%). Direct admission to intensive care during initial presentation was noted in 107(55.4%) of study cohort. Among 82(42.5%) of EB, source could be identified and central line infection was the commonest source in 45(23.3%). In-hospital mortality was 47, 23%, while 40(21%) left the hospital due to poor clinical outcome. Multivariate analysis indicated age >60 years, intra-abdominal disease as initial presentation, staying in the ICU during bacteremia, presence of central line and invasive mechanical ventilation as independent risk factors for fatality and poor clinical outcome.

Conclusion: Enterococcal bacteremia can present both as cause and outcome of severe illness. Multiple comorbidities, healthcare acquisition, and limited therapy options suggest the need for strategies to prevent the invasive infections by enterococci.

Keywords: Bacteremia, Enterococci, *Enterococcus faecalis*, *Enterococcus faecium*, Vancomycin-resistant enterococci.

Indian Journal of Critical Care Medicine (2025): 10.5005/jp-journals-10071-24969

Highlights

Enterococcal bacteremia (EEB) is a non-negligible health event in patients with increasing clinical complexity. Broad spectrum antimicrobial use, multiple comorbidities and invasive devices contribute to its occurrence and adds to poor clinical outcome.

Introduction

Enterococci have emerged as successful pathogens in healthcare-associated infections due to their hardiness and survival ability in environments with high background antimicrobial pressure.[1] Despite not being highly virulent bacteria, enterococci harbor several factors enabling them to colonize medical devices, therefore, contributing to healthcare-associated blood stream infections (BSI).[1–3] Emergence of vancomycin-resistant Enterococci (VRE) has narrowed the therapeutic options leading to unfavorable clinical outcomes.[4–6] The World Health Organization has categorized VRE as a priority pathogen deeming the urgent need of collaborative efforts of new drug development, infection prevention, and antimicrobial stewardship.[7]

Among several species, *Enterococcus faecalis* (*E. faecalis*) and *Enterococcus faecium* (*E. faecium*), are frequently encountered in BSIs.[8] In the recent years, *E. faecium* overhauling *E. faecalis* is has been reported in several national surveillance registries.[3,9,10] This is a disturbing trend as *E. faecium* are more likely to demonstrate multidrug resistance including to glycopeptides, weakening effective management strategies. Several factors have influenced the occurrence of EB and the subsequent healthcare events. Historically, severe underlying illness, immunocompromised status, malignancy, and indwelling devices are considerably associated

[1]Department of Microbiology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India

[2]Department of Infectious Diseases, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal; Center for Antimicrobial Resistance and Education (CARE), Manipal Academy of Higher Education, Manipal, Karnataka, India

[3]Department of Microbiology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal; Center for Antimicrobial Resistance and Education (CARE), Center for Emerging and Tropical Diseases (CETD), Manipal Academy of Higher Education, Manipal, Karnataka, India

[4]Department of Microbiology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal; Center for Antimicrobial Resistance and Education (CARE), Manipal Academy of Higher Education, Manipal, Karnataka, India

Corresponding Author: Vandana K Eshwara, Department of Microbiology, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal; Center for Antimicrobial Resistance and Education (CARE), Manipal Academy of Higher Education, Manipal, Karnataka, India, Phone: +91 8202922717, e-mail: vandana.ke@manipal.edu

How to cite this article: Kumar G, Varma M, Mukhopadhyay C, Eshwara VK. Is Enterococcal Bacteremia a Cause or Corollary of Severe Illness? 5 Years' Experience from an Indian Teaching Hospital. Indian J Crit Care Med 2025;29(5):441–448.

Source of support: Nil

Conflict of interest: None

Patient consent statement: As this was a retrospective record-based study, need for written informed consent from the patients

with EB.[11–13] While the case fatality and attributable mortality show differing results, EB is consistently associated with prolonged hospital stay and excessive healthcare costs.[14,15]

In Indian subcontinent, high burden of multidrug resistant Gram-negative infections has led to the excess use of carbapenems and other last resort antimicrobial agents. The high antimicrobial selection pressure in healthcare settings is a favored ecological niche for *Enterococci*, which are intrinsically resistant to several antimicrobial agents and promote the subsequent development of healthcare associated infections. We undertook this study to describe the occurrence, clinical characters, and risk factors for EB and explore the various factors influencing clinical outcome in a teaching hospital. We further assessed the differences in the clinical epidemiology of bacteremia by *E. faecium* and *E. faecalis.*

Patients and Methods

This retrospective study included adult in-patients (>18 years) diagnosed with EB between January 2014 and December 2018 from a teaching hospital with 2030 beds in Southern India. After clearance from the Institutional Ethics Committee (IEC No 326-2019), patients who developed bacteremia by any *enterococcus* spp. were identified from the laboratory database. Only the first episode of bacteremia was included in the analysis. Due to the retrospective nature of the study, informed consent from the patients was waived. Details of patients' demography, clinical characteristics, laboratory findings, management and outcome were collected in a pre-designed proforma from the medical records. The source of bacteremia was determined if there were microbiological cultures performed from the clinically apparent sites of infections and yielded same bacteria as in blood cultures. Whenever, the source site cultures were inconclusive, the clinical assessment details were used to determine the source of bacteremia if detailed in the medical records.

Approximately, 18–20 mL of blood from the patients was collected in two BacT/ALERT FA Plus® bottles from different venepuncture sites according to the hospital practice. Blood culture bottles flagging positive were further processed by performing a Gram stain and subculturing on 5% sheep blood agar and MacConkey agar. *Enterococcus* spp. was identified using MALDI-TOF (Vitek MS, bioMérieux Inc., Durham, NC) and antibiotic sensitivity testing was done by Vitek® 2 Systems (bioMérieux Inc., Durham, NC).

Median and interquartile range was calculated for the continuous variables, and frequency along with percentage was calculated for categorical variables. Mann–Whitney test was used to compare continuous variables with prognosis and Chi-square test (or Fisher exact test, wherever necessary) was used for categorical variables. All variables in the univariate analysis that had a *p*-value of <0.1 were included in logistic regression for multivariate analysis. All analysis was performed on Statistical Package for Social Science (IBM® SPSS® v.16, Chicago, IL, USA).

Results

During the study period, we identified 248 cases of EB, of which 193 records were available for final analysis. Rate of enterococcal isolation over 5 years of study period was 0.35%. The median annual incidence EB was 3.66 (±0.282)/1000 blood cultures performed. The rate of EB was comparable to the rate of MRSA bacteremia during the same period in our center (unpublished data). Prognosis was poor in 87 (45%) patients, of whom 47 (23%) died in the hospital, while 40 (21%) left the hospital against medical advice (LAMA) due to lack of affordability to treatment and, or poor prognosis. Largely, patients were admitted to medical specialties (62.6%) while the remaining in surgical specialties.

Majority of EB was caused by *E. faecium* (82, 42.5%) and *E. faecalis* (69, 35.8%) while *E. gallinarum, E. avium and E. raffinosus* were less frequently isolated (3, 1.6%; 1, 0.5%; and 1, 0.5%, respectively). Polymicrobial bacteremia was detected in 27(14%) of patients. Penicillin resistance was found in 7.6% of *E. faecalis* and 100% *E. faecium*. Barring *E. gallinarum* due to intrinsic resistance, there were 12 vancomycin resistant enterococcal isolates (6.3%), first case was detected in 2014. The rates were 2(2.9%) and 8(9.8%) among *E. faecalis* and *E. faecium*, respectively. Linezolid resistance was detected in 2/4 VR *E. faecalis*. High level gentamicin resistance was found in 56% *E. faecalis* and 85% of *E. faecium* isolates. Admission diagnosis were predominantly intra-abdominal disease (57, 29.5%) and lower respiratory tract disease/infection (36, 18.7%). Hypertension and diabetes mellitus were the commonest co morbidities in 84(43.5%) and 79(40.9%), respectively. More than 2 comorbidities were present in 77(40%) patients. Among 36 patients that underwent surgery before the bacteremia episodes, 11(30%) had surgery involving large bowel and urinary tract, 16(44%) other contaminated surgery and 9(25%) clean surgeries. Bacteremia was detected before and after 48 h of hospitalization in equal number of patients, nevertheless in the former group, 40(41%) of patients had some form of healthcare exposure in the 3 months prior to current hospitalization. Despite careful search for the source, majority, 111(57.5%) cases did not show demonstrable source and hence categorized as noncentral line-associated primary bacteremia.

Among 107(55.4%) of patients that received any antimicrobial agents prior to the detection of bacteremia, 58, 54% received ≥ 2 agents and the most frequent therapy were beta lactam-inhibitor combinations, 31.8%, cephalosporins, 14.9%, fluoroquinolones, 12.8% and carbapenems, 10.3% among other agents. Antimicrobial therapy potentially active against enterococci was initiated after a median 3 days of blood culture collection in 120(62.2%), of whom only 101(52.3%) received therapy deemed appropriate for bacteremia based on susceptibility tests. More details of the clinical characters, management, and factors contributing to poor outcomes are provided in Tables 1 and 2.

Comparison between the two major bacterial species, *E. faecalis* and *E. faecium* indicated that *E. faecalis* was associated with community acquired bacteremia occurring <48 h [*p* 0.003, *OR* 2.27 (1.41–5.27)] while *E. faecium* was more likely to be detected in patients already receiving broad spectrum antimicrobial therapy although the results were not statistically significant. *E. faecalis* contributed to all the six cases of infective endocarditis which were community acquired. *E. faecium* bacteremia was more likely to be found in patients presenting with intra-abdominal diseases when compared to *E. faecalis* (30, 36.6% and 12, 17.4%, respectively; *p*: 0.009). Of the patients who developed bacteremia by *E. faecium* and *E. faecalis*, the former were more likely to be sicker and hence were directly admitted to ICUs, (63 vs 45%, $p = 0.023$). In addition, they were more likely to be in the ICUs during the detection of bacteremia (73 vs 51%, $p = 0.004$) and on Foley's catheter (84 vs 70%, $p = 0.033$). Due to the low number, we could not assess the influence of vancomycin resistance on clinical outcome.

Table 1: Details of patient characteristics of Enterococcal bacteremia

Variables	*All patients (N = 193) n (%)*	*Improved (N = 106) n (%)*	*LAMA and death combined as outcome (N = 87, 40 + 47) n (%)*	*p-value*	*Odds ratio (Confidence interval)*	*p-value*	*Adjusted odds ratio (Confidence interval)*	*Only death as outcome (N = 47) n (%)*	*p-value*	*Odds ratio (Confidence interval)*
Age in years, median (IQR)	58 (45, 68)	57 (44.8, 65)	62 (45, 72)	0.182	–	–	–	56 (40, 69)	0.916	–
Patients <60 years of age	105 (54.4)	64 (60.4)	41 (47.1)	–	–	–	–	26 (55.3)	–	–
Patients ≥60 years of age	88 (45.6)	42 (39.6)	46 (52.9)	0.066	1.71 (0.96, 3.03)	**0.028**	**2.22 (1.08, 4.52)**	21 (44.7)	0.558	–
Female	74 (38.3)	40 (37.7)	34 (39.1)	–	–	–	–	23 (48.9)	–	–
Male	119 (61.7)	66 (62.3)	53 (60.9)	0.848	–	–	–	24 (51.1)	0.194	–
Major syndromic presentations at the time of hospitalization										
Intra-abdominal disease	57 (29.5)	26 (24.5)	31 (35.6)	0.092	1.70 (0.91, 3.17)	**0.024**	**2.58 (1.13, 5.86)**	13 (27.7)	0.682	–
Lower respiratory tract disease/infection	36 (18.7)	21 (19.8)	15 (17.6)	0.648	–	–	–	9 (19.1)	0.924	–
Neurological disease	29 (15)	14 (13.2)	15 (17.2)	0.435	–	–	–	9 (19.1)	0.343	–
Trauma	20 (10.4)	7 (6.5)	13 (14.9)	0.059	2.48 (0.94, 6.53)	–	–	9 (19.1)	**0.019**	0.229 (0.1, 0.85)
Renal disease	17 (8.8)	10 (9.3)	7 (8)	0.735	–	–	–	4 (8.5)	1.000	–
Soft tissue infection	13 (6.7)	5 (4.6)	8 (9.4)	0.217	–	–	–	6 (12.8)	0.094	–
Cardiac manifestations	10 (5.2)	7 (6.5)	3 (3.5)	0.325	–	–	–	1 (2.1)	0.436	–
Non-specific illness	26 (13.5)	20 (18.9)	6 (6.9)	0.015	0.32 (0.12, 0.83)	–	–	3 (6.4)	**0.052**	3.411 (0.96, 12.1)
Comorbidities and risk factors										
Hypertension	84 (43.5)	48 (45.3)	36 (41.1)	0.586	–	–	–	16 (34)	0.193	–
Type 2 diabetes mellitus	79 (40.9)	47 (44.3)	32 (36.8)	0.288	–	–	–	15 (31.9)	0.149	–
Chronic liver disease	22 (11.4)	11 (10.2)	11 (12.6)	0.622	–	–	–	7 (14.9)	0.424	–
Malignancy	20 (10.4)	10 (9.4)	10 (11.5)	0.640	–	–	–	6 (12.8)	0.534	–
Chronic kidney disease (Stage IV/V)	20 (10.4)	12 (11.1)	8 (9.4)	0.630	–	–	–	4 (8.5)	0.777	–
COPD	15 (7.8)	6 (5.6)	9 (10.6)	0.226	–	–	–	5 (10.6)	0.314	–
No comorbidities	56 (29)	31 (29.2)	25 (28.7)	0.938	–	–	–	15 (31.9)	0.740	–
Patients with any one comorbidity	60 (31)	38 (35.8)	22 (25.2)	0.382	–	–	–	16 (34)	0.829	–
Patients with 2 or more comorbidities	77 (39.9)	37 (34.9)	40 (46)	0.406	–	–	–	16 (34)	0.918	–
Acute kidney injury	117 (60.6)	51 (53.7)	66 (76.7)	**<0.001**	**2.85 (1.49, 5.4)**	–	–	34 (72.3)	**0.033**	0.44 (0.20, 0.94)
Liver function derangement	48 (24.9)	25 (23.6)	23 (26.4)	0.648	–	–	–	14 (29.8)	**0.033**	0.73 (0.33, 1.57)
Surgical procedures	36 (18.7)	20 (18.9)	16 (18.4)	0.933	–	–	–	15 (31.9)	0.137	–

COPD, chronic obstructive pulmonary disease; LAMA, left against medical advice; Statistically significant *p*-values, odds ratio and adjusted odds ratios are shown in boldface values

Table 2: Association of clinical progress, source of bacteremia, and management with clinical outcome among the patients diagnosed with EB

Variables	*All patients (N = 193) n (%)*	*Improved (N = 106) n (%)*	*LAMA and death combined (N = 87, 40 + 47) n (%)*	*p-value*	*Odds ratio (Confidence interval)*	*p-value*	*Adjusted odds ratio (Confidence interval)*	*Only death (N = 47) n (%)*	*p-value*	*Odds ratio (Confidence interval)*
Antimicrobial therapy before onset of bacteremia										
Yes	107 (55.4)	52 (49.1)	55 (63.2)	–	–	–	–	32 (68.1)	–	–
No	86 (44.6)	54 (50.9)	32 (36.8)	**0.05**	**1.79 (1.0, 3.18)**	–	–	15 (31.9)	**0.029**	0.45 (0.21–0.92)
Occurrence of bacteremia	–	–	–	–	–	–	–	–	–	–
<48 h of hospitalization	97 (50.3)	58 (54.7)	39 (44.8)	–	–	–	–	28 (59.6)	–	–
>48 of hospitalization	96 (49.7)	48 (45.3)	48 (55.2)	0.172	1.49 (0.84, 2.63)	–	–	19 (40.4)	0.103	1.78 (0.88, 3.57)
Direct admittance to ICU	107 (55.4)	45 (42.5)	62 (71.3)	**0.001**	**3.36 (1.83, 6.14)**	–	–	34 (72.3)	**0.001**	0.28 (0.13, 0.59)
ICU admittance any time during hospitalization	134 (69.4)	58 (54.7)	76 (87.4)	**<0.001**	**5.72 (2.73, 11.97)**	–	–	45 (95.7)	**<0.001**	**18.62 (4.29, 80.75)**
Total days hospitalized before EB (Median, IQR)	2 (0, 10)	2 (0, 10)	4 (1, 11)	0.083	1.11 (0.98, 1.04)	–	–	6 (2, 12)	**0.025**	1.03 (0.99, 1.06)
Number of days in ICU before EB (Median, IQR)	1 (0, 7)	0 (0, 6)	2 (0, 8)	0.049	–	–	–	3 (1, 8)	**0.012**	1.03 (0.99, 1.07)
Staying in ICU at the time of EB	121 (62.7)	51 (48.1)	70 (80.5)	**<0.001**	0.18 (0.08, 0.33)	**0.011**	**2.79 (1.26, 6.17)**	41 (87.2)	**<0.001**	0.136 (0.05, 0.34)
Length of stay in hospital (Median, IQR)	13 (7, 24)	15 (9, 29)	10 (5, 21)	**0.001**	0.97 (0.95, 0.99)	–	–	12 (6, 25)	**0.052**	0.98 (0.95, 1)
Length of stay in ICU (Median, IQR)	7 (3, 14)	7 (4, 12)	6 (3, 14)	0.688	–	–	–	7 (4, 16)	0.753	–
Enterococcal species										
E. faecium	82 (42.5)	38 (35.8)	44 (50.6)	**0.039**	**1.83 (1.02, 3.26)**	–	–	19 (40.4)	0.589	–
E. faecalis	69 (35.8)	38 (35.8)	31 (35.6)	0.975	(reference)	–	–	21 (44.7)	0.3	–
E. gallinarum	3 (1.6)	3 (2.8)	0 (0)	0.114	–	–	–	0 (0)	0.553	–
E. avium	1 (0.5)	0 (0)	1 (1.2)	0.268	–	–	–	1 (2.1)	0.307	–
E. raffinosus	1 (0.5)	0 (0)	1 (1.2)	0.268	–	–	–	0 (0)	–	–
Undifferentiated	37 (19.2)	27 (25)	10 (11.8)	**0.014**	**2.6 (1.19, 5.8)**	–	–	6 (12.8)	0.078	2.34 (0.89, 6.11)
Details of invasive devices										
Mechanical ventilation (MV)	75 (38.9)	27 (25.5)	48 (55.2)	**<0.001**	**3.6 (1.96, 6.61)**	**0.005**	**3.36 (1.43, 7.83)**	31 (66)	<0.001	0.18 (0.08, 0.37)
Foleys catheter (FC)	142 (73.6)	65 (61.3)	77 (88.5)	**<0.001**	**4.8 (2.25, 10.44)**	**–**	**–**	41 (87.2)	0.001	0.23 (0.09, 0.59)
Central line (CL)	58 (30.1)	20 (18.9)	38 (43.7)	**<0.001**	0.3 (0.16, 0.59)	**0.011**	**2.85 (1.26, 6.42)**	25 (53.2)	<0.001	0.21 (0.09, 0.43)
Hemodialysis access line	39 (20.2)	16 (15.1)	23 (26.4)	**0.051**	2.02 (0.99, 4.12)	–	–	16 (34)	0.079	0.51 (0.23, 1.09)
Tracheostomy	20 (10.4)	8 (7.4)	12 (13.8)	0.162	1.96 (0.76, 5.03)	–	–	11 (23.4)	0.006	0.27 (0.1, 0.71)
Source of EB	–	–	–	–	–	–	–	–	–	–
Central line	45 (23.3)	18 (17)	27 (31)	**0.022**	**2.2 (1.11, 4.34)**	–	–	19 (40.4)	0.002	0.30 (0.13, 0.65)
Urinary tract	17 (8.8)	10 (9.3)	7 (8.2)	0.72	–	–	–	3 (6.4)	0.755	–

(Contd...)

Table 2: *(Contd...)*

Variables	*All patients (N = 193) n (%)*	*Improved (N = 106) n (%)*	*LAMA and death combined (N = 87, 40 + 47) n (%)*	*p-value*	*Odds ratio (Confidence interval)*	*p-value*	*Adjusted odds ratio (Confidence interval)*	*Only death (N = 47) n (%)*	*p-value*	*Odds ratio (Confidence interval)*
Infective endocarditis	6 (3.1)	4 (3.7)	2 (2.4)	0.557	–	–	–	1 (2.1)	1	–
Vascular device (other than CL)	9 (4.7)	6 (5.6)	3 (3.4)	0.502	–	–	–	–	–	–
Intra-abdominal	3 (1.6)	0 (0)	3 (3.4)	0.054	–	–	–	3 (6.4)	0.028	1.07 (0.99, 1.15)
Wound	2 (1)	1 (0.9)	1 (1.2)	1	–	–	–	1 (2.1)	0.521	–
Source identified	82 (42.5)	39 (36.7)	43 (49.4)	–	–	–	–	–	–	–
Source not identified	111 (57.5)	67 (63.2)	44 (50.6)	0.085	0.60 (0.34, 1.08)	–	–	20 (42.6)	0.005	**2.74 (1.35, 5.54)**
Polymicrobial bacteremia	27 (14)	11 (10.4)	16 (18.4)	**0.048**	**2.33 (1, 5.3)**	–	–	9 (19.1)	0.138	0.49 (0.18, 1.27)
Severity scores										
Pitt's bacteremia score (Median, IQR)	0 (0, 2)	0 (0, 0)	0 (0, 2)	**<0.01**	**1.6 (1.25, 2.22)**	–	–	2 (0, 2)	<0.001	**1.67 (1.25, 2.23)**
Pitt's bacteremia score <2	141 (73.1)	90 (84.9)	51 (58.6)	–	–	–	–	22 (46.8)	–	–
Pitt's bacteremia score ≥2	52 (26.9)	16 (15.1)	36 (41.4)	**<0.001**	**3.97 (2, 7.8)**	–	–	25 (53.2)	<0.001	**6.39 (2.92, 13.96)**
Appropriate antimicrobial therapy										
Received	101 (52.3)	64 (60.4)	37 (42.5)	–	–	–	–	43 (91.5)	–	–
Not received	92 (47.7)	42 (39.6)	50 (57.5)	**0.014**	**2.06 (1.16, 3.66)**	–	–	27 (57.4)	0.028	0.30 (0.09, 0.9)
Time to appropriate therapy (median days, IQR)	3 (1, 4)	3 (2, 4)	2 (1, 4)	**0.012**	1.29 (0.9, 1.6)	–	–	1 (1, 3)	0.004	0.75 (0.57, 1)

EB, enterococcal bacteremia; ICU, intensive care unit; IQR, interquartile range; LAMA, left against medical advice; Statistically significant *p*-values, odds ratio and adjusted odds ratios are shown in boldface values

Table 3: Comparison of salient features of bacteremia by two common species, *E. faecium and E. faecalis*

Variables	*Overall (N = 151)*	*E. faecium (N = 82)*	*E. faecalis (N = 69)*	*p-value*	*Odds ratio (Confidence interval)*
Age <60 years	81 (53.6)	41 (50)	40 (58)	–	–
Age ≥60 years	70 (46.4)	41 (50)	29 (42)	0.328	–
Female	63 (41.7)	39 (47.6)	24 (34.8)	–	–
Male	88 (58.3)	43 (52.4)	45 (65.2)	0.113	1.70 (0.88, 3.28)
Healthcare acquired EB	77 (51)	51 (62.2)	26 (37.7)	–	–
Community acquired EB	74 (49)	31 (37.8)	43 (62.3)	**0.003**	**2.72 (1.41, 5.27)**
Intra-abdominal disease at initial presentation	42 (27.8)	30 (36.6)	12 (17.4)	**0.009**	**2.74 (1.27, 5.90)**
Direct admission to ICU	83 (55)	52 (63.4)	31 (44.9)	**0.023**	**2.13 (1.10, 4.08)**
Staying in ICU at the time of EB	95 (62.9)	60 (73.2)	35 (50.7)	**0.004**	**2.65 (1.34, 5.22)**
Mechanical ventilation	60 (39.7)	35 (42.7)	25 (36.2)	0.42	–
Foleys catheter	117 (77.5)	69 (84.1)	48 (69.6)	**0.033**	**2.32 (1.06, 5.08)**
Central line	52 (34.4)	28 (34.1)	24 (34.8)	0.935	–
Other vascular devices	43 (28.5)	27 (32.9)	16 (23.2)	0.187	1.63 (0.78, 3.35)
Hemodialysis access line	35 (23.2)	22 (26.8)	13 (18.8)	0.247	–
Tracheostomy	19 (12.6)	7 (8.5)	12 (17.4)	0.102	0.44 (0.16, 1.19)
Central line as source of EB	41 (27.2)	23 (28)	18 (26.1)	0.787	–
Urinary source EB	14 (9.3)	8 (9.8)	6 (8.7)	0.823	–
Infective endocarditis	6 (4)	0 (0)	6 (8.7)	**0.008**	**2.30 (1.91, 2.77)**

EB, enterococcal bacteremia; ICU, intensive care unit; Statistically significant *p*-values, odds ratio and adjusted odds ratios are shown in boldface values

Out of the 12 EB by VRE, 3 patients had died (20%). Majority, 84%, of bacteremia by VRE were healthcare associated and central line was the predominant source of infection. Comparison of clinical characteristics and outcomes of EB by *E. faecalis* and *E. faecium* are shown in Table 3.

We further sought to explore the risk factors for mortality/poor prognosis leading to LAMA among the study patients. In univariate analysis, direct ICU admission, prior antimicrobial therapy, acute kidney injury, *E. faecium* as an implicating agent, CLABSI, presence of devices such as mechanical ventilation, central venous catheter and Foley's catheter, not receiving appropriate anti-enterococcal therapy, presence of polymicrobial bacteremia, acute kidney injury and Pitt's bacteremia score ≥2 were associated with poor outcome combining fatality and LAMA in our cohort. Multivariate analysis indicated age >60 years, intra-abdominal disease as initial presentation, staying in the ICU during bacteremia detection, presence of central line and invasive mechanical ventilation as independent risk factors for poor clinical outcome. Direct comparison between clinical improvement and fatality, excluding LAMA, could recognize only disease severity and inability to identify the source of bacteremia as a contributing factor in univariate analysis. However, none of the previous risk factors scored significance in multivariate model.

Discussion

Our observational study from a large Indian teaching hospital analyzed the clinico-microbiological details of EB and assessed the risk factors for poor outcomes. Positioned in the list of top six causes of bacteremia, the overall frequency was comparable to MRSA bacteremia. Our results showed a shift toward *E. faecium* predominance over *E. faecalis* and its association with prior healthcare exposure. Advanced age, higher severity scores along with presence of several invasive devices, and intra-abdominal disease as initial presentation were independently contributed to poor outcomes.

Enterococcus has emerged as a major nosocomial pathogen across the continents including Indian subcontinent and implicated in nosocomial bacteremia especially central line associated.[2,3,10] Several of our findings are similar to the reported characteristics of EB such as increased occurrence in patients with several comorbidities, healthcare acquisition, and severe underlying illnesses during bacteremia among others.[16,17] Initial presentations were predominantly related to the abdominal, lower respiratory, neurological diseases, and trauma. Surgical procedures involving abdominal and genitourinary tract which are the usual colonization sites of *enterococci*, did not present an increased risk of bacteremia over other surgeries or without surgeries in our cohort. Studies have presented an increased occurrence of EB in patients undergoing surgery for biliary tract disease and biliary carcinoma.[18,19] In our study, bacteremia occurred before and after 48 h of hospitalization in similar number of cases, however, 41% of assumed community-acquired cases had healthcare exposure in recent past, thus accounting for healthcare acquisition of bacteremia in 70% of cases. *E. faecium* was increasingly detected in this category. Prior antimicrobial therapy is another important risk for EB, especially by *E. faecium* and its reported that carbapenem and antipseudomonal penicillin therapy were strongly implicated in its occurrence.[17] In our cohort, 55% cases received any antimicrobial therapy before EB and an overall 30% received ≥2 antimicrobial agents. We could not identify any specific antimicrobial group as a contributing factor, however, the major classes received by these cases were beta lactam-inhibitor combinations, cephalosporins, fluoroquinolones and carbapenems. Bacteremia was diagnosed at a median of 2 days (IQR 0, 10) after hospitalization. In all the cases, blood culture was performed while investigating increased blood leucocytes, pyrexia or worsening primary clinical condition and detection of enterococci was an inconspicuous finding. Commensalism in gastrointestinal tract, resistance to biocides, selection due to multiple prior antimicrobial therapy along with several virulence factors favoring adhesion, biofilm formation, and invasion have led

to the endogenous infections by enterococci particularly urinary tract infection, intra-abdominal infections, infective endocarditis, and vascular device-associated bacteremia.[1,20] It's also a successful healthcare-associated pathogen due to several combinatorial factors of virulence and multiple antimicrobial resistance.[1] A recent report provides evidence through longitudinal genome studies for the endogenous acquisition of *E. faecium* in bacteremia and additionally supports nosocomial transmission among patients.[21]

Enterococci are relatively less virulent in comparison to other Gram-positive bacteria such as *Staphylococcus aureus* and pneumococcus. In the absence of identifiable source, it is challenging to plan appropriate management protocols in EB. In our analysis, a significant, 57.5% of cases did not show a befitting source of bacteremia. In another 14%, blood culture showed additional bacteria, therefore, raising suspicion on the clinical significance of isolated bacteria. These factors would influence the administration of appropriate antimicrobial therapy and source control, both of which are particularly important for favorable outcome. Published reports give a conflicting overview of the significance of enterococci in blood cultures. One study assesses the association of bacterial clearance as determined by isolation of enterococci in one or more time points and the clinical outcomes. They did not find any difference, and therefore, suggested a possible contamination of blood culture by this bacteria.[22] Another study indicated a possible epiphenomenon after comparing the outcomes of enterococcal vs *S. aureus* and *Escherichia coli* bacteremia, where the latter had higher fatality while the former contributed to increased clinical severity.[15] Their findings were suggestive of mucosal translocation augmented due to invasive device use. Amidst the complexities involved in understanding the clinical significance of positive blood cultures, the undeniable importance of detection of source is highlighted in our analysis. Enterococcus in blood cultures is likely to be viewed with doubt when the source is not detected or not sought for. In 42% of our cases, culture result had a poor correlation to the clinical condition as the blood culture prompts had several other overarching reasons in critically ill patients rather than implicating enterococcal causality. Moreover, 14% of cases had other concomitant bacterial isolation in blood cultures, further weakening the enterococcal diagnosis. Incidentally, this might have led to the overlooking of EB and delayed appropriate therapy. We noticed that a significant number of patients that did not receive appropriate therapy experienced unfavorable outcome including fatality (p = 0.014; OR = 2.059, CI = 1.157–3.664) although it was not an independent contributory factor. Vancomycin resistance is another factor influencing the clinical outcome, possibly due to delayed therapy and a threefold increase in 30-day mortality is reported if therapy is delayed > 48 h.[5,23] We could not ascertain this due to a small number of VRE in our study.

We report a few limitations in this study. Our case-mix did not have sufficient number in subgroups showing similar risk factors or comorbidities, and hence we could not associate the underlying diseases leading to the development of EB. Clinical endpoints could not be stated clearly considering that a reasonably high number of patients left the hospital due to non-affordability and/poor prognosis. Moreover, the source of EB remained inconclusive in many cases due to the retrospective nature of the study. Despite these limitations, we could highlight the importance of this hardy bacteria harboring several resistance traits in the bacteremia episodes. Resource constrained healthcare facilities in low- and middle-income countries will increasingly encounter this infection amid the outrageously high Gram-negative infections.[24]

Conclusion

Our results indicate an overt problem growing parallelly alongside the growing threat of other Gram-negative infections further triggering the overuse of broad spectrum antimicrobial agents. Despite being a relatively low virulent bacteria, *E. faecium* is a dominating pathogen in the healthcare-associated infections in severely ill patients. Lack of availability and affordability will further limit the therapeutic options in these patients. Identifying patients at risk of developing EB should be prioritized along with infection prevention and antimicrobial stewardship to reduce the additional damage caused by EB.

Clinical Significance

Bacteremia by *Enterococcus* spp. particularly occurs in patients with severe illness leading to poor prognosis. Low index of suspicion and inability to identify the source of infection might further delay the appropriate intervention in these patients.

Acknowledgment

Authors thank all the healthcare professionals involved in the management of the cases included in this study.

Ethical Approval

The ethical approval was taken from the Institutional Ethics Committee (IEC No 326-2019).

Orcid

Gauri Kumar https://orcid.org/0000-0002-5796-237X
Muralidhar Varma https://orcid.org/0000-0002-5546-5353
Chiranjay Mukhopadhyay https://orcid.org/0000-0003-0402-1143
Vandana K Eshwara https://orcid.org/0000-0001-7561-4435

References

1. García-Solache M, Rice LB. The Enterococcus: A model of adaptability to its environment. Clin Microbiol Rev 2019;32(2):e00058–18. DOI: 10.1128/CMR.00058-18.
2. Mathur P, Malpiedi P, Walia K, Srikantiah P, Gupta S, Lohiya A, et al. Health-care-associated bloodstream and urinary tract infections in a network of hospitals in India: A multicentre, hospital-based, prospective surveillance study. Lancet Glob Health 2022;10(9):e1317–e1325. DOI: 10.1016/S2214-109X(22)00274-1.
3. European Centre for Disease Prevention and Control. Annual Epidemiological Report for 2019 – Healthcare associated infections acquired in intensive care units. ECDC. Annual epidemiological report for 2018. Stockholm: ECDC; 2023. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/healthcare-associated-infections-intensive-care-units-annual-epidemiological-report-2019.pdf.
4. Cheah AAY, Spelman T, Liew D, Peel T, Howden BP, Spelman D, et al. Enterococcal bacteraemia: Factors influencing mortality, length of stay and costs of hospitalization. Clin Microbiol Infect 2013;19(4):E181–E189. DOI: 10.1111/1469-0691.12132.
5. Russo A, Picciarella A, Russo R, d'Ettorre G, Ceccarelli G. Time to effective therapy is an important determinant of survival in bloodstream infections caused by vancomycin-resistant Enterococcus spp. Int J Mol Sci 2022;23(19):11925. DOI: 10.3390/ijms231911925.
6. Bhatti JM, Raza SA, Alam AF, Khan YN, Mala A, Batool I, et al. Antibiotic choices among healthcare professionals for enterococcal bacteremia with patterns of resistance and risk factors of mortality, in settings of poor antibiotic stewardship program — A five-year retrospective

cohort study. BMC Infect Dis 2023;23(1):514. DOI: 10.1186/s12879-023-08498-0.
7. World Health Organization. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017. ISBN 978-92-4-002643-8. [Online]. Available from: https://www.who.int/publications/i/item/WHO-EMP-IAU-2017.12. [Last accessed April, 2025].
8. Sivaradjy M, Gunalan A, Priyadarshi K, Madigubba H, Rajshekar D, Sastry A. Increasing trend of vancomycin-resistant enterococci bacteremia in a tertiary care hospital of south India: A three-year prospective study. Indian J Crit Care Med 2021;25(8):881–885. DOI: 10.5005/jp-journals-10071-23916.
9. Indian Council of Medical Research. Annual Report 2021: Antimicrobial Resistance Research and Surveillance Network. [Online]. Available from: https://main.icmr.nic.in/sites/default/files/upload_documents/AMR_Annual_Report_2021.pdf. [Last accessed April, 2025].
10. Coombs GW, Daley DA, Lee YT, Pang S. Australian Group on Antimicrobial Resistance (AGAR) Australian Enterococcal Sepsis Outcome Programme (AESOP) Annual Report 2017. Commun Dis Intell (2018) 2019;43. DOI: 10.33321/cdi.2019.43.42.
11. Suzuki H, Hase R, Otsuka Y, Hosokawa N. A 10-year profile of enterococcal bloodstream infections at a tertiary-care hospital in Japan. J Infect Chemother 2017;23(6):390–393. DOI: 10.1016/j.jiac.2017.03.009.
12. Ceci M, Delpech G, Sparo M, Mezzina V, Sánchez Bruni S, Baldaccini B. Clinical and microbiological features of bacteremia caused by Enterococcus faecalis. J Infect Dev Ctries 2015;9(11):1195–203. DOI: 10.3855/jidc.6587.
13. Kajihara T, Nakamura S, Iwanaga N, Oshima K, Takazono T, Miyazaki T, et al. Clinical characteristics and risk factors of enterococcal infections in Nagasaki, Japan: A retrospective study. BMC Infect Dis 2015;15(1):426. DOI: 10.1186/s12879-015-1175-6.
14. Moses V, Jerobin J, Nair A, Sathyendara S, Balaji V, George I, et al. Enterococcal bacteremia is associated with prolonged stay in the medical intensive care unit. J Glob Infect Dis 2012;4(1):26. DOI: 10.4103/0974-777X.93758.
15. Frickmann H, Köller K, Veil I, Weise M, Ludyga A, Schwarz NG, et al. On the role of enterococci in the bloodstream: Results of a single-center, retrospective, observational study at a German University Hospital. Eur J Microbiol Immunol 2017;7(4):284–295. DOI: 10.1556/1886.2017.00030.
16. McBride SJ, Upton A, Roberts SA. Clinical characteristics and outcomes of patients with vancomycin-susceptible Enterococcus faecalis and Enterococcus faecium bacteraemia—a five-year retrospective review. Eur J Clin Microbiol Infect Dis 2010;29(1):107–114. DOI: 10.1007/s10096-009-0830-5.
17. Uda A, Shigemura K, Kitagawa K, Osawa K, Onuma K, Yan Y, et al. Risk factors for the acquisition of enterococcus faecium infection and mortality in patients with enterococcal bacteremia: A 5-year retrospective analysis in a tertiary care university hospital. Antibiotics (Basel) 2021;10(1):64. DOI: 10.3390/antibiotics10010064.
18. Fukuda J, Tanaka K, Matsui A, Nakanishi Y, Asano T, Noji T, et al. Bacteremia after hepatectomy and biliary reconstruction for biliary cancer: The characteristics of bacteremia according to occurrence time and associated complications. Surg Today 2022;52(9):1373–1381. DOI: 10.1007/s00595-022-02462-2.
19. Mussa M, Martínez Pérez-Crespo PM, Lopez-Cortes LE, Retamar-Gentil P, Sousa-Dominguez A, Goikoetxea-Aguirre AJ, et al. risk factors and predictive score for bacteremic biliary tract infections due to Enterococcus faecalis and Enterococcus faecium: A multicenter cohort study from the PROBAC project. MicrobiolSpectr 2022;10(4):e00051–22. DOI: 10.1128/spectrum.00051-22.
20. Strateva T, Atanasova D, Savov E, Petrova G, Mitov I. Incidence of virulence determinants in clinical Enterococcus faecalis and Enterococcus faecium isolates collected in Bulgaria. Braz J Infect Dis 2016;20(2):127–133. DOI: 10.1016/j.bjid.2015.11.011.
21. Gouliouris T, Coll F, Ludden C, Blane B, Raven KE, Naydenova P, et al. Quantifying acquisition and transmission of Enterococcus faecium using genomic surveillance. Nat Microbiol 2020;6(1):103–111. DOI: 10.1038/s41564-020-00806-7.
22. Jindai K, Strerath MS, Hess T, Safdar N. Is a single positive blood culture for Enterococcus species representative of infection or contamination? Eur J Clin Microbiol Infect Dis 2014;33(11):1995–2003. DOI: 10.1007/s10096-014-2167-y.
23. Zasowski EJ, Claeys KC, Lagnf AM, Davis SL, Rybak MJ. Time Is of the essence: The impact of delayed antibiotic therapy on patient outcomes in hospital-onset enterococcal bloodstream infections. Clin Infect Dis 2016;62(10):1242–1250. DOI: 10.1093/cid/ciw110.
24. Kumar R, Sen M, Das A, Agarwal J, Nath SS, Singh V. Reversing the trend of antimicrobial resistance in ICU: Role of antimicrobial and diagnostic stewardship. Indian J Crit Care Med 2021;25(6):635–641. DOI: 10.5005/jp-journals-10071-23861.