Enterococcal Bacteremia is Associated with Prolonged Stay in the Medical Intensive Care Unit

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ABSTRACT

Background: Although enterococci are relatively common nosocomial pathogens in surgical intensive care units (ICUs), their significance in blood cultures from patients in the medical ICU is unclear. **Materials and Methods:** In this retrospective study spanning 2 years, the clinical and microbiological characteristics of enterococcal bacteremia among medical ICU patients were evaluated. **Results:** Of 1325 admissions, 35 with enterococcal bacteremia accounted for 14.8% of positive blood cultures. They were significantly older (*P*=0.03) and had various co-morbidities. Most had vascular (96.9%) and urinary (85.3%) catheters, and 67.7% were mechanically ventilated. In addition to blood, enterococci were isolated from vascular catheters (8.6%) and other sites (20%), while no focus was identified in 77% of patients. Prior use of broad-spectrum antimicrobials was nearly universal. All isolates tested were sensitive to vancomycin and linezolid. Resistance to ampicillin and gentamicin were 44.7% and 52.6%, respectively. Compared with other medical ICU patients, patients with enterococcal bacteremia had a longer ICU stay (*P*<0.0001) and a trend toward higher ICU mortality (*P*=0.08). **Conclusions:** Enterococcal bacteremia is an important nosocomial infection in the medical ICU, with a predilection for older patients with multiple comorbidities. Its occurrence is associated with a significantly longer ICU stay and a trend to a higher mortality. The choice of antibiotics should be dictated by local susceptibility data.

Key words: Bacteremia, Duration, Enterococcal, Medical intensive care unit, Mortality

INTRODUCTION

Enterococci are commensals in the human alimentary tract, traditionally considered to have low virulence. However, they are increasingly recognized as an important pathogen in the intensive care unit (ICU). It has been shown that the isolation of enterococci from blood–even of doubtful clinical significance–is associated with mortality, especially in elderly patients with underlying diseases like malignancy and diabetes.[1]

Enterococci rank third among nosocomial infections in the United States and are the third most common isolated bacteria in blood stream infections in developed nations.[2,3] The progressive development of resistance by enterococci to various antimicrobial agents in the past two decades has further heightened the importance of their isolation from critically ill patients.[4,5] Enterococcal infections have a predominantly nosocomial source in developing countries too,[6] where, like in developed nations, their treatment is frequently complicated by antimicrobial resistance.[7] The substantial costs associated with enterococcal infections were recently estimated by Butler and colleagues.[8]

The significance of enterococci in surgical ICUs is well established; it is the single most frequently reported pathogen from surgical site infections.[3] However, the importance of this isolate in patients admitted to the medical ICU is not well established. It is also unclear if enterococcal infections in a medical ICU patient impact outcome.[9] Our study seeks to describe the characteristics of patients with enterococcal bacteremia in the medical ICU in the setting of a developing country, the antibiotic susceptibility patterns of the organisms involved, and the risk factors for an adverse outcome.

MATERIALS AND METHODS

This retrospective descriptive study was performed in the

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11-bed medical ICU of a tertiary care university teaching hospital in South India. The study was approved by the Institutional Review Board (IRB) and the Ethics Committee. Adult and adolescent patients, 15 years or older, with enterococcal bacteremia during ICU stay were included. The electronic medical records of patients admitted to the medical ICU over a 2-year period (January 2006 to December 2007), as well as the microbiology database, were screened for enterococci in blood cultures. A data abstraction form was developed after reviewing the available literature and scanning a sample of the patient records. Data were extracted from the charts and the electronic records of laboratory reports, radiologic studies and discharge summaries of patients. The demographic profile of patients, diagnosis at admission, baseline characteristics, risk factors for acquisition of enterococcal infections, antibiotic susceptibility, and outcomes were recorded. Severity of illness was determined with physiological variables from the ICU monitoring flow charts using APACHE II and SAPS scores. The primary end point was hospital mortality. Other outcomes included duration on ventilator and duration of ICU and hospital stay.

The following protocol was used for enterococcal isolates from blood cultures. Growth-positive blood cultures with Gram-positive oval cocci in tetrads and short chains were subcultured onto blood and MacConkey agar plate and incubated overnight at 37°C. Magenta pink colored fine colonies were further speciated and subjected to antimicrobial susceptibility testing using standard recommended biochemical tests as per the Clinical and Laboratory Standards Institute guidelines.[10] Enterococcal bacteremia was defined as enterococci isolated from one or more blood cultures obtained by separate venipuncture drawn with strict aseptic precautions.[1] Nosocomially acquired bacteremia was defined as a blood culture drawn 48 hours after admission to the hospital yielding enterococci. Community acquired bacteremia was defined as a blood culture drawn within 48 hours of hospital admission being positive for enterococci.[11] Where two isolates from the same patient showed different sensitivities, the one with the higher resistance was used for statistical analyses in the study.

Data on age, ICU mortality and duration of stay in the ICU for the entire medical ICU population during the study period 2006–2007 were available from audit records and used for comparing patients with and without enterococcal bacteremia. Statistical analysis was performed using R statistical software version 2.11.[12] Continuous variables were assessed using the Mann–Whitney test for non-parametric data. Dichotomous variables were analyzed using Fisher's exact test.

RESULTS

Of 1327 patients admitted to the medical ICU over 2 years, 237 (17.89%) had positive blood cultures, among whom 35 (14.8%) patients had enterococcal bacteremia, yielding 41 enterococcal blood culture isolates. Patients with enterococcal bacteremia were older than those without enterococcal bacteremia (P=0.03; 95% CI=1–14) and the ratio of males to females was 0.88 [Table 1].

The commonest comorbidity was diabetes mellitus (45.5%). The rates of comorbidities and interventions previously identified as risk factors for acquisition of enterococcal infection[6,13,14] are listed in Table 2. Non-invasive (25%) and invasive ventilation (67.7%) were prominent among these.[13] Six (21.9%) patients underwent a surgical procedure during the month before the appearance of enterococcal bacteremia, including five (15.6%) patients who had surgery during the current hospitalization. The majority of patients (90.6%) had received antibiotics prior to isolation of enterococci from blood [Table 2].

Thirty-nine of 41 isolates underwent antibiotic susceptibility testing. *In vitro* resistance to ampicillin was observed in 17 (44.7%) isolates and to gentamicin [high level gentamicin resistance (HLGR)][15] in 20 (52.6%). None of the isolates demonstrated resistance to vancomycin or linezolid [Figure 1]. Fourteen (40%) patients were treated for enterococcal

Table 1: Baseline characteristics of patients with enterococcal bacteremia

Variable*	Rate†
Age (years)	
Entire MICU population, *N*=1310	43.77 (17.79)
Patients with enterococcal bacteraemia, *N*=35	50.17 (15.98)
Patients without enterococcal bacteraemia, *N*=1275	43.59 (17.81)
Sex (male:female)	0.88
APACHE II Score, *N*=31	29.7 (6.46)
SAPS, *N*=30	57.3 (17.53)
Site of acquisition of enterococcal infection	
Community	1 (2.86)
Present hospital	26 (74.29)
Referring hospital	8 (22.86)
Source of enterococcal bacteraemia, *N*=35	
Vascular catheter	3 (8.57)
Pus	2 (5.71)
Pleural fluid	1 (2.86)
Ascitic fluid	1 (2.86)
Bone marrow	1 (2.86)
Urine	1 (2.86)
Sputum	1 (2.86)
Primary enterococcal bacteraemia	27 (77.14)

*N denotes denominator; †Mean (standard deviation) are indicated for continuous variables; Frequency (percentage of total) is indicated for categorical variables; Two patients had two positive sites besides bacteraemia; APACHE: Acute physiology and chronic health evaluation; SAPS: Simplified acute physiology score. Figures in parenthesis are in percentage

Table 2: Comorbidities and co-interventions among patients with enterococccal bacteraemia

Variable*	Rate†
Comorbidities	
Diabetes mellitus, *N*=33	15 (45.5)
COPD, *N*=33	3 (9.1)
Renal failure, *N*=33	6 (18.2)
Dialysis, *N*=32	6 (18.8)
Heart failure, *N*=33	2 (6.1)
Immunosuppressive drugs, *N*=33	2 (6.1)
Prior corticosteroid therapy, *N*=33	4 (12.1)
Chronic liver disease, *N*=33	1 (3)
Bronchial asthma, *N*=33	1 (3)
Chronic Hepatitis C, *N*=33	1 (3)
Malignancy, *N*=33	4 (12.1)
Lines and tubes, *N*=32	
Central venous lines	31 (96.9)
Arterial lines, *N*=32	17 (53.1)
Dialysis catheter, *N*=32	6 (18.8)
Urinary catheter, *N*=34	29 (85.3)
Intercostal drains, *N*=32	2 (6.3)
Prior ventilatory support	
Prior NIV, *N*=32	8 (25)
Prior mechanical ventilation, *N*=34	23 (67.7)
Surgical procedures, *N*=32	
During this hospitalization	5 (15.6)
During the last 1 month	2 (6.3)
Prior Antibiotic use, *N*=32	29 (90.6)

*N denotes denominator where <35; †Frequency (percentage of total) is indicated for categorical variables; COPD: Chronic obstructive pulmonary disease. Figures in parenthesis are in percentage; NIV: Non-invasive ventilation

Table 3: Comparison of patients with and without enterococcal bacteremia

Variable*	Patients without EB†	Patients with EB†	Odds ratio	*P* value	95% CI
Age (years), N=1310	45 (28-57)	50 (39.5-60)	N/A	0.03	1-14
Survival, N=1326	760 (58.87%)	15 (42.86%)	1.9	0.08	0.92-4.04
Duration of ICU stay (days), N=1327	4 (2-7)	13 (7-25)	N/A	<0.0001	5-11

*N for each variable denotes the number of cases with data; †Continuous variables are listed as mean (inter-quartile range) and dichotomous variables as rate (percentage within each category). CI: confidence interval; N/A: Not applicable, ICU: intensive care unit

bacteremia with either vancomycin or teicoplanin. The rest received combinations of ampicillin and gentamicin.

There was a trend toward a higher ICU mortality amongst patients who developed enterococcal bacteremia compared with those who did not develop enterococcal bacteremia in the medical ICU (*P*=0.08). The mean stay in the ICU was significantly longer in those who developed enterococcal bacteremia compared with patients who did not develop enterococcal bacteremia (15.9 vs. 5.7 days; *P*<0.0001) [Table 3]. In-hospital mortality among patients with enterococcal bacteremia was 62.9% (*n*=22); their mean duration of stay in hospital was 33.2±25.6 days (that of

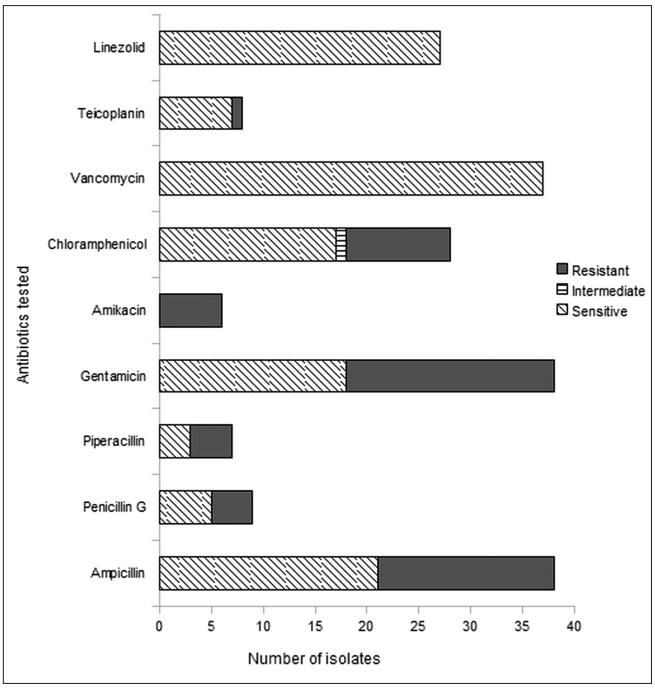

Figure 1: Antibiotic resistance profile of enterococci isolated in blood cultures from the medical ICU during 2006–2007. The vertical axis shows the antibiotics for which sensitivity testing was done. The horizontal axis shows the number of isolates tested for each antibiotic, classified as resistant, sensitive and (for chloramphenicol) intermediate

survivors was 37±26.7 days). In univariate analysis, a trend toward increased mortality was noted among patients with renal failure (*P*=0.08; 95% CI=0.64–∞). There were no statistically relevant differences between survivors and non-survivors in other parameters [Table 4].

DISCUSSION

Enterococcal bacteremia is nosocomially acquired, with rare exceptions. This condition, often associated with ICU patients having surgical problems particularly intra-abdominal pathology, is not uncommon amongst patients with medical problems admitted to the ICU, as demonstrated in this study. Our study found that nearly 15% of positive blood cultures of patients admitted to the medical ICU were due to enterococci. In the medical ICU, enterococcal bacteremia occurred in older patients who were very ill (as reflected by the severity scores) with multiple comorbidities, and was associated with a prolonged stay in ICU and high mortality.

In our study, patients who developed enterococcal bacteremia were significantly older than patients without enterococcal bacteremia (*P*=0.03). Our observations are in keeping with a recent study that demonstrated age to be an independent risk factor (OR 1.2; *P*=0.009) for the acquisition of enterococcal infections including

Table 4: Comparison of survivors and non-survivors

Variable*	Non-survivors,† *N*=22	Survivors,† *N*=13	Odds ratio	*P* value	95% CI
Age (years)	54 (41.8-59.8)	48 (40-60)	N/A	0.4	-9-15
APACHE, *N*=31	31.5 (27-34)	25.5 (25-30.8)	N/A	0.1	-1-8
Comorbidities and risk factors					
Diabetes mellitus, *N*=33	10 (45.5%)	5 (45.5%)	1	1	0.19-5.54
Renal failure, *N*=33	6 (27.3%)	0 (0%)	∞	0.08	0.64-∞
Dialysis, *N*=32	6 (27.3%)	0 (0%)	∞	0.14	0.58-∞
Corticosteroid therapy during this hospitalization, *N*=32	13 (59.1%)	3 (30%)	3.24	0.25	0.55-24.84
Malignancy, *N*=33	3 (13.6%)	1 (9.1%)	1.56	1	0.11-91.02
Prior antibiotics					
Any prior antibiotics, *N*=33	20 (90.9%)	9 (90%)	1.1	1	0.02-23.96
Cephalosporin, *N*=31	13 (61.9%)	5 (50%)	1.6	0.7	0.27-9.61
Fluoroquinolones, *N*=31	5 (23.8%)	3 (30%)	0.74	1	0.1-6.08
Aminoglycoside, *N*=31	2 (9.5%)	1 (10%)	0.95	1	0.04-62
Carbapenem, *N*=31	5 (23.8%)	2 (20%)	1.24	1	0.16-15.78
Metronidazole, *N*=31	6 (28.6%)	2 (20%)	1.58	1	0.21-19.52
Surgery within the last 1 month, *N*=32	4 (18.2%)	2 (20%)	0.89	1	0.1-11.78
Antimicrobial susceptibility‡					
Ampicillin resistance, *N*=33	9 (45%)	7 (53.9%)	0.71	0.73	0.14-3.52
High level gentamicin resistance, *N*=33	13 (65%)	5 (38.5%)	2.87	0.17	0.57-16.2
Enterococci concurrently isolated in other sites, *N*=35	6 (27.3%)	2 (15.4%)	2.02	0.68	0.29-24.13
Source of other enterococcal isolates					
Vascular sites, *N*=35	4 (18.2%)	0 (0%)	∞	0.27	0.4-∞
Other sites, *N*=35	3 (13.6%)	2 (15.4%)	0.87	1	0.09-11.96
Concurrent non enterococcal bacteremias, *N*=35	13 (59.1%)	6 (46.2%)	1.66	0.5	0.34-8.37
Prior mechanical ventilation, *N*=34	14 (63.6%)	9 (69.2%)	0.59	0.7	0.08-3.4

*N for each variable denotes number of cases with data; †Continuous variables are listed as mean (inter-quartile range) and dichotomous variables as rate (percentage within each category); ‡Susc eptibility of enterococcus to both vancomycin and linezolid were 100% among the 32 and 22 patients respectively whose isolates were tested. Amikacin resistance was noted in all the 6 patients whose isolates were tested; APACHE: Acute physiology and chronic health evaluation; CI: Confidence interval; N/A: Not applicable

bacteremia.[14] However, age *per se* was not associated with mortality in our cohort with enterococcal bacteremia or in other studies.[5,14,16] The increased predilection for enterococcal bacteremia among the elderly may be related to the need for more intensive monitoring with invasive vascular devices, indwelling urinary catheters and the greater risk of skin breakdown at pressure sites.

The absence of vancomycin and linezolid resistance and the high rate of ampicillin and aminoglycoside resistance in our cohort is similar to the findings by Indian[6,7] and other[16] investigators reporting on general hospital populations. However, vancomycin-resistant enterococci (VRE) have been detected in fecal and urine samples in Indian hospitals as early as 2007.[17] Experience from South Korea suggests that an outbreak of VRE would require multifaceted interventions for effective control, including cohorting of infected patients, active rectal and environmental surveillance cultures, daily extensive cleaning of environmental surfaces, antibiotic restriction, and education of hospital staff.[18]

We would echo Agrawal's caution against the empiric use of amikacin for synergy with cell wall-active agents, given the much higher prevalence of resistance to amikacin/kanamycin than to gentamicin/tobramycin/netilmicin among enterococci (48.8% vs. 8.3% in their study).[19,20] The variation in aminoglycoside susceptibility profiles among Indian studies probably arises from varying antimicrobial usage practices and emphasizes the importance of referring to data on local antimicrobial susceptibility patterns when deciding empiric therapy. The high rate of resistance to first-line drugs (ampicillin and aminoglycosides) observed by us may warrant the inclusion of vancomycin or teicoplanin in the initial treatment of life-threatening enterococcal infections while awaiting sensitivity reports, in centers with antimicrobial susceptibility profiles similar to ours.

Ninety percent of the patients in our study received antibiotics for various indications prior to the enterococcal bacteremia. A number of studies link prior antibiotic use to the acquisition of enterococcal infections and the selection of antibiotic resistance among enterococci. The use of carbapenems and cefepime in the first 48 hours in ICU has been independently associated with acquisition of enterococcal infections in the ICU.[14] Third-generation cephalosporins, quinolones, and carbapenems have been associated with HLGR enterococcal bacteremia in a hospital setting.[5,20] In spite of these concerns, prior

antibiotic use did not appear to directly correlate with mortality in our cohort, as well as in other ICU and hospital environments.[5,14,20] Nevertheless, care should be taken in the initiation and choice of antibiotics.

Patients with enterococcal bacteremia had a longer ICU stay (P<0.0001) and a trend toward higher mortality (P=0.08), when compared with other patients in the medical ICU. A review of the literature identified several risk factors for death among patients with enterococcal bacteremia, including surgery, presence of a nasogastric tube, arterial lines, higher APACHE score, renal replacement therapy, cirrhosis, malignancy, and immunosuppression.[14,16,21,22] Many of these appear to be markers of severity of the primary illness.[14] Our findings on the impact of enterococcal bacteremia on outcome support the observation of Hoge and colleagues that early and appropriate treatment of enterococcal bacteremia significantly reduces mortality (relative risk 0.46; 95% CI=0.27–0.77).[1]

The study has a few limitations. As it was retrospective, antimicrobial susceptibility data were incomplete, being governed by clinical requirements, and species were not routinely characterized. Nevertheless, relevant analyses and inferences were possible in this area. Only limited information from audit records could be obtained for the "control" population (medical ICU patients without enterococcal bacteremia). The subgroup of medical ICU patients with positive blood cultures other than enterococci would have been a better group against which to compare our study cohort, but these data were unavailable. The paucity of significant associations precluded multivariate analysis of risk factors for mortality in the study cohort.

CONCLUSION

Enterococci cause 15% of the bacteremias in the medical ICU, with a predilection for older patients with multiple comorbidities. Enterococcal bacteremia is associated with a longer ICU stay and a trend toward increased mortality. The wide variation in their resistance profiles in various centers in India calls for close attention to local antimicrobial susceptibility patterns when initiating treatment.

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