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Research Article

Nosocomial Enterococcal Bacteremia: Predictors of Resistance and Mortality

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Abstract

Objectives: This study aims to identify the risk factors associated with 14-day mortality in nosocomial *Enterococci* bacteremia.

Methods: This retrospective study was conducted in a tertiary training hospital. Patients aged 16 or older, with nosocomial bacteremia due to *Enterococci* between January 2012 and January 2018 were included. Analyses were performed using SPSS version 21. Pearson's chi-square, and Fisher's Exact tests were used for the comparison of categorical data. Parameters found to be statistically significant in univariate analyses were further tested with multivariate logistic regression to predict the risk of mortality. Statistical significance is interpreted as p-values lower than 0.05.

Results: The mean age in our study was 64.82±16.76. Patients were diagnosed in intensive care unit (44%), internal medicine wards (41.3%) or surgical wards (14.7%). Reasons of admittance included medical problems (52.7%), surgery (14.1%), cerebrovascular occlusion (12.5%), burns (7.1%) and community acquired infections (6.5%). We found that increase in both Charlson and Pitt bacteremia scores; the presence of neutropenia, severe sepsis, septic shock, or other concurrent infections significantly increased the risk of death. Gentamicin sensitivity yielded more favorable therapeutic outcomes regarding mortality.

Conclusion: Mortality is higher in patients with higher Charlson comorbidity indices and Pitt bacteremia scores, in neutropenic cases, and patients with concomitant infections and sepsis. Interestingly, mortality in gentamicin-sensitive cases is significantly lower.

Keywords: *Enterococcus*, nosocomial bacteremia, mortality

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In humans, *enterococci* are part of intestinal microbiota; they can be found in smaller proportions in secretions (oropharyngeal and vaginal) and on skin. The wide spectrum of clinical infections caused by these bacteria can include urinary tract and intra-abdominal infections, endocarditis, and bacteremia. In the last two decades, enterococcal species have emerged as opportunistic pathogens in severe human infections.[1,2] The majority of invasive enterococcal infections are caused by *Enterococcus faecalis*, and *Enterococcus faecium*.[3–6]

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Throughout the world, a number of major trends in the epidemiology of invasive enterococcal infection are demonstrated. These include the emergence of *enterococci* as important nosocomial pathogens, the development of resistance to commonly used antimicrobial agents, including penicillins, aminoglycosides and glycopeptides.[3] According to the National Hospital Infections Surveillance Network (UHESA) 2017 Bacteria Distribution and Antibiotic Resistance Summary Report, *Enterococci* strains were accounted for 10.8% of all episodes of nosocomial bacteremia in Turkey.[7] Little data exist regarding epidemiology of nosocomial enterococcal bacteremias and risk factors related mortality in Turkey.[8–11] In this perspective, we aimed to investigate the local epidemiology of *Enterococcus* bacteremia, in order to determine rates of antimicrobial resistance, mortality rates and, the impact of various risk factors on outcomes and comorbidities among affected patients.

Methods

Study Design

This retrospective study was conducted following the approval of local ethics committee, in a 571-bed tertiary training hospital, in the west of Turkey. We extracted relevant data from our prospective bloodstream database of Infection Control Commitee routine active surveillance, which includes microbiological, laboratory and clinical data of all patients with a positive blood culture. Patients ≥16 years with nosocomial bacteremia due to *Enterococci* between January 2012 and January 2018 were eligible for the study. Patients younger than 16 years were excluded from the analyses.

We aimed to determine demographic and clinical characteristics of the patients diagnosed with nosocomial infection as established by positive blood cultures of *enterococci*, antibiotic resistances and the risk factors associated with 14-day mortality patients. We chose to use 14 day mortality because it is difficult to examine impact on the outcomes of various risk factors which is particularly problematic in patients with many comorbid conditions and severe general status.

In our hospital, active surveillance of hospital - acquired infections is routinely performed by a team of two infectious diseases specialists and four infection control nurses by reviewing daily patient visits and electronic patient files and interviewing with treating physicians. The obtained data are regularly entered in patient follow-up forms. Patient follow-up forms include data regarding age, sex, comorbid diseases, admission ward and time, history of nosocomial infections, isolated microorganisms and susceptibility to various antimicrobials, previous surgical interventions and antibiotic treatment regimens undertaken. We classified admission wards as internal medicine wards, surgical care wards and intensive care units, as our hospital does not accept obstetrics and gynecology, pediatrics or cardiology patients.

The Pitt Bacteraemia Score (PBS) is a widely used severity of illness score, which is mainly used to estimate short term mortality in gram-negative bacteremia and is not pathogen-specific.[12] The PBS is calculated at initial patient evaluation from distinct clinical variables (range 0–14 points), such as; temperature of 35.1-36.0°C or 39.0-39.9°C (1 point), temperature of ≤35°C or ≥40°C (2 points), mental status (alert, 0 points; disoriented, 1 point; stupor, 2 points; coma, 4 points), hypotension (2 points), mechanical ventilation (2 points) and cardiac arrest (4 points). Charlson comorbidity score for each patient was calculated.[13]

Healthcare-associated infections (HAI), primary or secondary bacteremia diagnoses were established according to relevant Centers for Disease Control and Prevention (CDC) definitions.[14] Severe sepsis and septic shock definitions according to American Society of Chest Physicians/ Society of Critical Care Medicine were used for diagnosis.[15] Use of an adequate dosage of an antibacterial agent with in vitro activity against the isolate initiated within 72 h of the onset of infection was considered appropriate treatment.

Microbiology

Blood culture bottles (BD BACTEC™ PLUS Aerobic/F Medium; Becton-Dickinson Diagnostic Systems) were incubated for 7 days in a BD BACTEC™ FX device (Becton-Dickinson Diagnostic Systems) in microbiology laboratory of our hospital. Samples with positive signals during this period, were gram stained, and then samples were incubated in 5% sheep blood agar (Salubris, Turkey), Eosin methylene blue (EMB) agar (Salubris), and chocolate agar (Salubris) at 37°C for 18–24 h. We further processed all positive cultures for identification of pathogens by colonial morphology, and biochemical tests. We used conventional methods and the BD Phoenix™ Automated Microbiology System (BD Diagnostics, France) for identification of the bacterial colonies. We used BD Phoenix™ Automated Microbiology System (BD Diagnostics) for susceptibility testing. While CLSI criteria are used to determine antibiotic susceptibility until 2016, EUCAST criteria have been used since January 2016.[16]

Cultures were regarded as contamination and excluded from analysis in the absence of clinical data supporting infection. All patients with a non-*enterococcus* blood stream infection within ±2 days of the blood culture with *Enterococcus* spp. were assumed to be 'polymicrobial.'

Statistical Analysis

Analyses were performed using IBM SPSS Statistics 21 version (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). We expressed quantitative data as mean, standard deviation, minimum and maximum values; while frequency values were tabulated for qualitative data. We used Pearson's chi-square, and Fisher's Exact tests for the comparison of categorical data. Data were evaluated at a level of 95% confidence level, Statistical significance is interpreted as p-values lower than 0.05. Parameters found to be statistically significant in univariate analyses were further tested with multivariate logistic regression to predict the risk of mortality. For our primary outcome parameter, 14-day mortality, we measured the overall discriminative power of the Pitt bacteremia score at bacteremia onset by receiver-operating characteristics analysis, with an area under the curve (AUC) of 0.5 indicating a random prediction and a value of 1.0 denoting a perfect prediction; for the validation, only the highest PBS was taken at BSI onset.

Results

In the 6-year study period, a total of 184 patients identified and included. None of them were excluded. Number of male patients were only slightly greater in frequency (n=110, 59.8%), with ages ranging from 18 to 92 (64.82±16.76). Patients were diagnosed in intensive care unit (n=81, 44%), internal medicine wards (n=76, 41.3%) or surgical wards (n=27, 14.7%). Reasons of admittance included medical problems (52.7%), surgery (14.1%), cerebrovascular occlusion (12.5%), burns (7.1%) and community acquired infections (6.5%). Identified strains of *enterococci* were *E. faecium* (54.3%), *E. faecalis* (41.8%), *E. casseliflavus* (1.6%), *E. gallinarum* (1.6%), and *E. hirae* (0.5%).

Overall mortality rate was 35%3. We found that the presence of neutropenia, severe sepsis, septic shock, or other concurrent infections significantly increased the risk of death. Gentamicin sensitivity yielded more favorable therapeutic outcomes regarding mortality (Table 1).

Sensitivity of *Enterococcus* strains to ampicillin, gentamicin, streptomycin, vancomycin and teicoplanin were 53.3% (98/814), 66.3% (122/184), 47.8% (88/184), 93.5% (172/184) and 93.5% (172/184). All strains (%100) were sensitive to linezolid and daptomycin.

Univariate logistic regression analyses demonstrated that sensitivity to ampicillin (p=0.003), streptomycin (p=0.007), and gentamicin (p<0.001) were associated with decreased rate of mortality on the 14th day. Sensitivity to vancomycine (p=0.636) and teicoplanin (p=0.636) were not related to a decrease in mortality rate. Sensitivity to linezolid was also not associated with mortality (p=0.478).

Multivariate logistic regression analyses showed that only *enterococci* with gentamicin sensitivity yielded more favorable therapeutic outcomes regarding 14-day mortality (p=0.009). Similar outcomes were not observed with vancomycin, ampicillin or teicoplanin therapies.

We found that increase in both Charlson and Pitt bacteremia scores significantly increased the risk of death (p=0.006, p<0.001). Table 2 presents the data regarding the relationship between scores and mortality in detail. We performed multivariate logistic regression analyses in order to explore the magnitude of effects of variables on 14-day mortality (Table 3). Our analysis showed that one point increase in Charlson score increases the risk of death in 14 days by 1.361 times (p=0.014). As the score increases, the risk of death increases significantly. Likewise, one point increase in Pitt bacteremia score causes an increase of the risk of death in 14 days by 1.499 times (p<0.001). The presence of neutropenia, also increases the risk of death in 14 days increases four times (p=0.024). Presence of septic shock increases the risk of death in 14 days by nearly 15 times (p<0.001). In presence of severe sepsis, the risk of death in 14 days increases at about three times (p=0.038). The risk of death in 14 days is approximately 4.5 fold higher in presence of other concurrent infections (p=0.008). Infection with a strain that is susceptible to gentamicin decreases 14-day mortality by about 3 (1/0.331) times (p=0.011). Thus, sensitivity to gentamicin seems to display a protective effect.

Our analyses to determine the predictive value of Pitt bacteremia score on 14-day mortality showed that sensitivity of the score is 67.7% and the specificity is 75.6% (Table 4). ROC analysis for the analysis of the association between Pitt bacteremia score were shown in Figure 1.

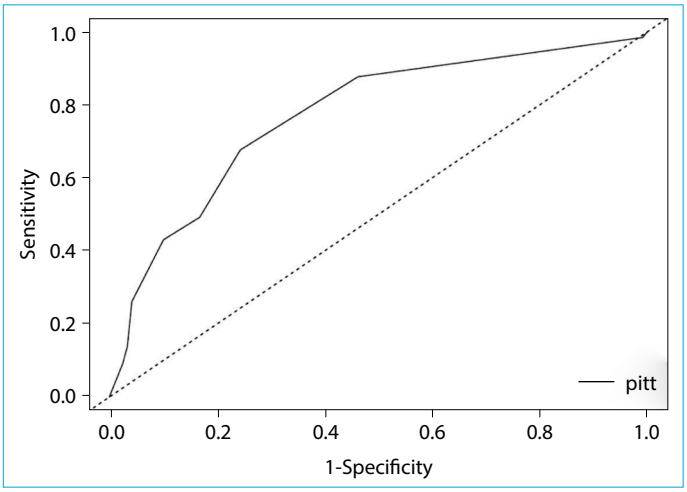

Figure 1. ROC analysis for the analysis of the association between Pitt bacteremia score and 14-day mortality (Area under the curve: 0.77; standard error: 0.036; z: 7.496; p<0.001; lower and upper limits for confidence interval: 0.699 and 0.841).

Table 1. Relationship between variables and mortality on 14th day in patients with nosocomial entereococcal bacteremia

Variable	Total (n=184) n	Survivors (n=119) n (%)	Nonsurvivors (n=65) n (%)	Odds ratio	p
Age >65	99	64 (64.6)	35 (35.4)	1.003	0.993
Male gender	110	71 (64.5)	39 (35.5)	0.986	0.965
Intensive care unit patient	81	40 (48.4)	41 (50.6)	3.587	0.013
Comorbidities					
Diabetes mellitus	40	27(67.5)	13 (32.5)	0.852	0.673
Chronic renal failure	34	27 (79.4)	7 (20.6)	0.411	0.051
Solid organ malignancy	28	15 (53.6)	13 (46.4)	1.733	0.185
Hematological malignacy	30	16 (53.3)	14 (46.7)	1.767	0.159
Neutopenia	19	8 (42.1)	11 (57.9)	2.826	**0.035**
Chronic obstructive pulmonary disease	17	10 (58.8)	7 (41.2)	1.316	0.597
Cardiac failure	23	17 (73.9)	6 (26.1)	0.610	0.325
Cirrhosis	3	1 (33.3)	2 (66.6)	3.746	0.285
Coronary artery disease	29	21 (72.4)	8 (27.6)	0.655	0.344
Acute cerebrovascular disease	61	33 (54.1)	28 (45.9)	1.972	0.036
Renal transplant	2	1 (50)	1 (50)	1.844	0.667
Demantia	21	14 (66.7)	7 (33.3)	0.905	0.839
Extrinsic factors					
Trauma	10	4 (40)	6 (60)	2.924	0.107
Surgical intervention in the last month	50	29 (58)	21 (42)	1.481	0.249
Hospital acquired infection in the last month	36	24 (66.7)	12 (33.3)	0.896	0.780
Exposure to beta-lactam group antibiotic treatment in the past 30 days	42	24 (57.1)	18 (42.9)	1.516	0.247
Corticosteroid use treatment in the past 30 days	3	1 (33.3)	2 (66.7)	3.746	0.285
Chemotherapy in the past 30 days	32	17 (53.1)	15 (46.9)	1.8	0.136
Mechanical ventilation	52	23 (44.2)	29 (55.8)	3.362	**<0.001**
Central venous catheter	114	62 (54.4)	52 (45.6)	3.677	**<0.001**
Abdominal drainage	8	6 (75)	2 (25)	0.598	0.536
Extraventricular drainage	10	5 (50)	5(50)	1.9	0.325
Percutaneous enterogastrostomy feeding	7	6 (85.5)	1 (14.3)	0.292	0.259
Nephrostomy / ureterostomy	5	4 (80)	1 (20)	0.449	0.478
Appropriate empirical therapy	105	75 (71.4)	30 (28.6)	0.503	**0.028**
Severe sepsis	36	15 (41.7)	21(58.3)	3.309	**0.002**
Septic shock	23	3 (13)	20 (87)	17.185	**<0.001**
Polymicrobial bacteremia	15	8 (53.3)	7 (46.7)	1.675	0.342
Probable source of infection					
Primary	89	49 (55.1)	40 (44.9)		
Catheter	27	21 (77.8)	6 (22.2)		
Lung	9	5 (55.6)	4 (44.4)	0.394	0.083
Urinary	28	23 (82.1)	5 (17.9)		
Gastrointestinal	15	11 (73.3)	4 (26.7)		
Skin and soft tissue	16	10 (62.5)	6 (37.5)		
Concomittent infection	7	4	3	4.329	**0.001**
Antibiotic sensitivity					
Ampicillin sensitive	98	73 (74.5)	25 (25.5%)	0.394	**0.003**
Gentamicin sensitive	122	91 (74.6)	31(25.4%)	0.281	**<0.001**
Streptomycin sensitive	88	66 (75)	22 (25%)	0.421	**0.007**
Vancomycin sensitive	172	112 (65.1)	60 (34.9%)	0.750	0.636
Teicoplanin sensitive	172	112 (65.1)	60 (34.9%)	0.750	0.636

Table 2. Relationship between PBS and Charlston scores, and mortality on 14th day in patients with nosocomial entereococcal bacteremia

Score	Total (n=184) n	Survivors (n=119) n (%)	Nonsurvivors (n=65) n (%)	Odds ratio	p
Charlson comorbidity score					
1	44	29 (65.9)	15 (34.1)		
2	71	51 (71.8)	20 (28.2)		
3	28	19 (67.9)	9 (32.1)		
4	20	13 (65)	7 (35)	1.308	**0.006**
5	5	3 (60)	2 (40)		
6	10	3 (60)	40		
7	2	0 (0)	2 (100)		
8	4	1 (25)	3 (75)		
Pitt bacteremia score					
0	2	1 (50)	1 (50)		
1	70	63 (90)	7 (10)		
2	39	26 (66.7)	13 (33.3)		
3	21	9 (42.9)	12 (57.1)		
4	12	8 (66.7)	4 (33.3)	1.618	**<0.001**
5	18	7 (38.8)	11 (61.1)		
6	9	1 (11.1)	8 (88.9)		
7	4	1 (25)	3 (75)		
8	9	3 (33.3)	6 (66.7)		

Table 3. Multivariate logistic regression analysis demonstrating relationship between variables and mortality on 14th day in patients with nosocomial entereococcal bacteremia

Variable	Odds ratio	Confidence interval		p
		Upper limit	Lower limit	
Charlson comorbidity index	1.361	1.063	1.743	0.014*
Pitt bacteremia score	1.499	1.201	1.871	<0.001*
Neutropenia	4.388	1.213	15.877	0.024*
Severe sepsis	2.751	1.055	7.170	0.038*
Septic shock	15.393	3.882	65.445	<0.001*
Concomittent infection	4.546	1.485	13.915	0.008*
Gentamycine sensitivity	0.331	0.142	0.773	0.011*

Hint: *: statistically significant.

Table 4. Sensitivity, specificity, predictive values of Pitt bacteremia score for mortality on 14th day

Variable	Result	Confidence interval	
		Upper limit	Lower limit
Sensitivity	0.677	0.549	0.788
Specificity	0.756	0.669	0.830
Positive predictive value	0.603	0.497	0.729
Negative predictive value	0.811	0.714	0.871
Positive likelihood ratio	2.778	1.941	3.975
Negative likelihood ratio	0.427	0.296	0.616

Discussion

Enterococci are opportunistic bacteria mainly effecting elderly patients with comorbidities, and immune-compromised patients with long hospitalization periods, receiving invasive treatments or broad-spectrum antibiotics.[1–3] In this study, we aimed to determine demographic and clinical characteristics, resistance to various antibiotics and the risk factors related to 14-day mortality of patients with proven nasocomial enterococcal infection.

Enterococcal bacteremia is usually associated with higher mortality rates, which is often due to underlying factors. Shlaes et al.[17] reported a mortality rate of 34% in their study. Burns, underlying systemic diseases, and hospi-

tal acquired infections were found to be associated with increased mortality. However, gender of the patients or presence polymicrobial infections did not effect mortality. Malone et al.[18] reported a mortality rate of 44%, but factors in previous studies were not discussed, and they reported that the underlying disease or gender was not associated with mortality. Maki et al.[19] found a mortality rate of 46%. Age (>56 years), polymicrobial bacteremia, underlying serious disease, previous antibiotic treatment, intraabdominal origin, and a high number of local infections were associated with higher mortality rates.[8] Consistent with relevant literature,[23] our results showed that Pitt bacteremia score and Charlson morbidity index were predictors of 14-day mortality in enterococcal bacteremia.[20,21] We found one point increase in Charlson score increases the risk of death by 1.361 times and one point increase in Pitt bacteremia score increases the risk of death by 1.499 times. Hence, use of Charlson score and Pitt bacteremia score might prove to be useful for physicians in follow up of patients with nosocomial Enterococcal bacteremia. Moreover, clinical circumstances such as neutropenia, severe sepsis, septic shock and concomittent infection must be taken into account while analyzing the course of the disease. These factors are all indicators of poor host conditions and the severity of blood stream infections, and therefore, are associated with a poor outcome.

In this study, episodes of bacteremia were mainly without identifiable source, followed by documented sources such as intravascular catheters, urinary tract infections, and skin-soft tissue infections. Shlaes et al.[17] followed 13 patients with pure *enterococci* growth in blood cultures for 4 years. They found endocarditis in 6 of these (32%) cases. Malone et al.[18] examined 55 cases with enterococcal bacteremia. In 5 of them (9.3%) they found endocarditis. Maki et al.[19] reported endocarditis in 13 (8%) of 153 cases with enterococcal bacteremia. In their studies, 8-32% of enterococcal bacteremia cases were accompanied by endocarditis.[17–19] In the absence of endocarditis, the source of the enterococcal bacteremia is mostly the urinary system.[9] Shlaes et al.[17] (23%), Garrison et al.[23] (19%), Malone et al.[18] (24%) found the urinary system as the source of enterococcal bacteremia in indicated percentages of their cases.[6,7,10] In Maki et al.[19] study, the source of enterococcal bacteremia was either urinary system or intravascular catheter in 77% of the cases with enterococcal bacteremia. Other than these regions, bacteremias originating from the intra-abdominal region, gastrointestinal tract, biliary tract, pelvis, wound, and bone were also described.[23]

In this study we found sensitivity to *Enterococcus* spp ampicillin, gentamicin, streptomycin, vancomycin and teicoplanin were 53.3%, 66.3%, 47.8%, 93.5% and 93.5%. All strains were sensitive to linezolid and daptomycin. The resistance *E. faecalis* strains, isolated from nosocomial bacteremias, is listed in the National Hospital Infections Surveillance Network (UHESA) 2017 Bacteria Distribution and Antibiotic Resistance Summary Report[7] for ampicillin, gentamicin, linezolid, teicoplanin and vancomycin, as 16.2%, 52.3%, 0.6%, 2.7% and 1.8%. The resistance of E.faecium strains, isolated from nosocomial bacteremias, is listed in the report for ampicillin, gentamicin, linezolid, teicoplanin and vancomycin, as 91.4%, 55%, 2%, 24.9% and 25.1%. In our study, the rates of resistance were similar to those in the country, except that linezolid and daptomycin resistant strains were not detected. Ampicillin remains the choice for the treatment of infections caused by ampicillin-susceptible *E. faecium*, although their proportion is very small. During the last three decades, resistance to glycopeptides has progressively emerged as a major clinical issue. In Europe, surveillance data show a large variability between the various countries with vancomycin-resistant *Enterococcus* strains ranging from 4.2% (Italy) to 20% (Ireland, Greece, Portugal). According to the National Healthcare Safety Network (NHSN) in 2006-2007 (10), overall 33% of *enterococci* were resistant to vancomycin İn USA. Infections caused by vancomycin resistant *Enterococci* are more serious and associated to a higher mortality rate and economic burden compared to those caused by vancomycin susceptible *enterococci*.[24]

We noted that only gentamicin sensitivity was associated with the improved outcome related to nosocomial *Enterococcus* bacteremia on 14-day mortality based on final logistic regression analysis. In the literature, effect of high level gentamycin resistance (HLGR) on *Enterococcus* bacteremia outcome was controversial. HLGR was reported to be associated with increased mortality in invasive enterococcal disease in a recent study,[25] but not in other studies.[26,27] Combined treatment with gentamicin and beta lactam group antibiotic for invasive enterococcal infection is traditionally regarded as important for the treatment of conditions requiring bactericidal activity, such as endocarditis and bacteremia. Gentamicin resistance may be associated with high mortality in these cases. However, HLGR in nosocomial strains of *enterococci* may be an indicator of additional resistance and/or virulence determinants, and therefore, may be associated with a higher mortality than expected.[3] Since we did not perform any molecular or genetic analyses in our study, it is impossible to determine whether this high mortality is due solely to the HLGR, or to other additional genetic factors.

Hospital staff should be trained on routes, and severity of infection, as well as prophylactic strategies to prevent Enterococcal bacteremia. The microbiology laboratory should

periodically follow the distribution of resistant *enterococci*, particularly in transplantation units, intensive care units and hematology and oncology departments to detect and report the agent at an early stage. Infection control measures should be implemented to prevent and control infection at the hospital. For this purpose, infected or colonized patients with resistant *enterococci* should be isolated in single rooms, and when entering the room, gloves should be used when coming in contact with body secretions, and non-critical devices (such as a stethoscope) should be reserved for an individual patient.[3,22]

Limitations of the present study involve its single center and retrospective design; Thus, our results may not be applicable in other settings. Moreover, impacts of social, environmental and ethnic parameters and the role of uninvestigated variables may have important effects on the outcomes.

Conclusion

In conclusion, mortality is higher in patients with Enterococcal bacteremia who have high Charlson comorbidity index and Pitt bacteremia scores, in neutropenic cases, and patients with concomitant infections and sepsis. Interestingly, mortality in gentamicin-sensitive cases is found to be significantly lower. Early diagnosis of nosocomial enterococcal bacteremia, as well as identification and treatment of the risk factors for mortality have critical importance. It appears that there is a need to conduct further multi-center studies in large series concerning enterococcal bacteremia and risk factors.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.C.; Design – S.C.; Supervision – A.A.; Materials – O.O.; Data collection &/or processing – R.Y.; Analysis and/or interpretation – A.A.; Literature search – S.C.; Writing – S.C., O.O.; Critical review – S.T.

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