Master of Medicine

Clinical Characteristics and Treatment Outcomes of *Enterococcus durans* Bacteremia

Enterococcus durans 균혈증의 임상적 특징과 치료 결과

The Graduate School

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Clinical Characteristics and Treatment Outcomes of *Enterococcus durans* Bacteremia

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Summary

Introduction: *Enterococcus* species is one of the major pathogens causing various infections, especially in immunocompromised patients. Of these, clinical characteristics and treatment outcomes of *Enterococcus faecalis* and *E. faecium* bacteremia are well known. However, those of *E. durans* bacteremia are still uncertain.

Methods: I performed this case-control study through retrospective review of medical records at the Asan Medical Center, a 2,700-bed tertiary-care teaching hospital, Seoul, Korea, from December 1997 to October 2016. I analyzed the clinical characteristics and treatment outcomes of a case group: patients with *E. durans* bacteremia. These results were compared with those of two randomly selected control groups of patients with *E. faecalis* and *E. faecium* bacteremia. The case and two control groups were 1:1:1 matched for sex, similar age, and similar date of onset of bacteremia. Risk factors for mortality of *E. durans* bacteremia were also analyzed.

Results: *E. durans* caused 1.2% of total enterococcal bacteremia. A total of 80 patients with *E. durans* bacteremia were identified. Of these patients, 39 (48.8%) had biliary tract infection, 18 (22.5%) had urinary tract infection. Six patients (7.5%) had infective endocarditis. Twenty-four cases (30.0%) were associated with polymicrobial bacteremia. Community-onset bacteremia was more frequent in *E. durans* bacteremia than control groups (56.2% vs. 35.0% vs. 21.2%, p <0.01; versus *E. faecalis* and *E. faecium*, respectively). The majority of *E. durans* isolates were susceptible to penicillin (66/76, 86.8%), ampicillin (67/76, 88.2%), and vancomycin (75/76, 98.7%). *E. durans* bacteremia group had significantly lower all-cause mortality (20.0% vs. 31.2% vs. 42.5%, p <0.01) and bacteremia-related mortality (2.5% vs. 16.2% vs. 18.8%, p <0.01) than control groups. In the

multivariate analysis, independent risk factors for mortality of patients with *E. durans* bacteremia were ultimately or rapidly fatal underlying disease (adjusted OR, 5.30; 95% CI, 1.29-21.72; p =0.02) and a Pitt bacteremia score≥4 (adjusted OR, 13.52; 95% CI, 1.05-174.26; p =0.046).

Conclusion: *E. durans* bacteremia mainly originated from the biliary tract or urinary tract disease and associated with lower risk of mortality.

Keywords: *Enterococcus durans*, bacteremia, mortality, antibiotic susceptibility

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INTRODUCTION

Enterococcus species are normal flora in the gastrointestinal tracts of humans and animals. Although low virulence of enterococci has a minor impact on an immunocompetent person, high viability in the nosocomial environment and well characterized colonization onto surrounding medical devices made these bacteria one of the important nosocomial pathogen in immunocompromised patients.[1,2] Moreover, due to rapid emergence and potential for transmission of acquired resistance to newer classes of antibiotics, enterococci have become an important issue for infection control in healthcare facilities.[3]

Of more than 30 known *Enterococcus* species, *E. faecalis* and *E. faecium* are the most frequently isolated species in clinical specimens, and numerous studies on these bacteria have been published. In previous studies which included patients with *E. faecalis* and *E. faecium* bacteremia mainly, those with the severe underlying disease were found to have a high mortality rate.[4-6]

E. durans, formerly known as *Streptococcus durans*, was first described in the literature published in 1930's.[7] Since then, it has been reported encephalomalacia and diarrhea in livestock caused by *E. durans* found in the intestinal tract and dairy products of domestic animals.[8-10] Unlike *E. faecalis* or *E. faecium*, *E. durans* is not a common pathogen in human.[11] According to a study conducted in Taiwan, only 2 cases of *E. durans* bacteremia were found among 1,887 cases of enterococcal bacteremia over 9 years.[12] This may be due to the low carriage rate of *E. durans* among the microflora in human intestine (2.5-6.7%)[13,14] and low virulence of this bacteria.[15] In this context, there are only a few case reports on *E. durans* bacteremia mainly associated with endovascular infection until the present,[16-20] and no studies on clinical characteristics and treatment outcomes of *E. durans* bacteremia series have been published. Therefore, I performed this study reviewing experiences with 80 consecutive episodes of *E. durans* bacteremia.

METHODS

Patient selection and data collection

This retrospective case-control study was performed at the Asan Medical Center (Seoul, Republic of Korea), a 2,700-bed tertiary-care teaching hospital with 170 beds of intensive care unit. From December 1997 to October 2016, all adult patients (≥16 years) with blood cultures positive for *E. durans* who were identified by reviewing computerized database of clinical microbiology units were categorized as a case group. Infectious disease specialists reviewed the electronic medical record of each patient and collected data regarding patient demographic characteristics, underlying disease or condition, the severity of illness at the time of bacteremia, portal of entry, co-infecting microorganism, antibiogram findings, prior antibiotic use, prescribed antibiotics, and clinical outcome. These results were compared with those of randomly selected two control groups of patients with *E. faecalis* and *E. faecium* bacteremia. The case and two control groups were 1:1:1 matched on the basis of the 3 following criteria: patients with the same sex, similar age (age difference not exceeding ±5 years) and similar date of onset of bacteremia (time interval within a month-period).

Blood culture, species identification, and susceptibility testing

All blood cultures were processed by the hospital microbiology laboratory using a standard blood culture system (BACTEC 730 or BACTEC 9240; Becton Dickinson). *Enterococcus* species were identified based on tolerance to 6.5% NaCl, bile-esculin hydrolysis, and growth rate at 45°C. *E. durans* was identified based on the positivity for arginine dihydrolase test, and failure of fermentation tests for arabinose, mannitol, sucrose, methyl-α-D-glucopyranoside, sorbitol, and raffinose.[21,22] The species of organism and the susceptibility to antimicrobial agents were determined using the Vitek (bioMérieux-Vitek) or MicroScan (Dade Behring, Deerfield, IL) system, based on standard criteria of the Clinical and

Laboratory Standards Institute (CLSI).[23] Intermediate susceptibility to an antimicrobial agent was considered to indicate resistance.

Definitions

Clinically significant bacteremia was defined as ≥2 blood cultures yielding *E. durans, E. faecalis* or *faecium*, or a single blood culture yielding these bacteria together with a clinically apparent culture-positive source of infection. Date of onset of bacteremia was defined as the date on which the blood sample was obtained for the first positive culture result. Place of bacteremia acquisition was categorized as following two groups; community-onset group or hospital-acquired group, as previously described.[24] Bacteremia was considered to be community-onset if the first sample of positive blood culture was obtained within the 48 hours from hospital admission. It was re-assorted into community-acquired or healthcare-associated bacteremia. Otherwise, bacteremia was considered to hospital-acquired. Polymicrobial bacteremia was defined as isolation of >1 organism from the same blood culture specimen. Patients' underlying comorbidities were classified as "rapidly fatal," "ultimately fatal," or "nonfatal," by the McCabe and Jackson criteria.[25] Bacteremia without sepsis, sepsis, and septic shock were defined as described in the most recent international consensus (Sepsis-3).[26] A localized infection was regarded as the portal of entry if it was microbiologically and clinically documented. Recurrent bacteremia was defined as the isolation of the same organism from the blood 5 days after initial bacteremia. In cases of recurrent bacteremia, only the first episode of bacteremia was included in the analysis. Prior antibiotic use was defined as receipt of antibiotics for more than 24 hours during the previous month. Appropriate therapy was defined as the use of antibiotics susceptible in vitro more than 24 hours, within 5 days after the positive blood culture was obtained (index day).[27] Outcomes were evaluated at the time of discharge from the hospital. Death was considered to have been related with bacteremia if the patient without other identified cause

of death died within 14 days from the onset of bacteremia.

Statistical analysis

Statistical analysis was performed using the χ^2 test or 2-tailed Fisher's exact test for binary variables. For continuously scaled variables, a one-way analysis of variance or Kruskal-Wallis test were used. When the statistical analysis result was significant (p-value of <0.05), a *post hoc* analysis with the Bonferroni correction for multiple comparisons was performed, and p-value of <0.025 was considered to indicate statistical significance. Continuous data were expressed as the mean ± standard deviation (SD) or as the median and interquartile range (IQR). The time-to-mortality analyses were performed using Kaplan-Meier estimates and the log-rank test. Multivariate analyses to determine independent risk factors for mortality were performed using the logistic regression models with statistically significant factors (p-value of <0.1) in univariate analysis. A 2-tailed p-value of <0.05 I considered to statistically significant. All tests were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, N.Y., USA).

RESULTS

Study Population

From December 1997 to October 2016 at the Asan Medical Center, 82,158 blood cultures were positive for bacteria. *Enterococcus* species, including in combination with other organisms, were present in 7,438 (9.1%) of these cultures and the incidence of *Enterococcus* bacteremia was 3.9 cases per 1,000 admissions. Of 7,438 *Enterococcus*-positive cultures, 4,598 (61.8%) were identified as *E. faecium* and 1,981 (26.6%) as *E. faecalis*. Of the remaining 859 (11.5%) non-*faecium* and non-*faecalis* isolates, 332 (4.5%) were identified as *E. casseliflavus*, 263 (3.6%) as *E. gallinarum*, 119 (1.6%) as *E. avium*, 91 (1.2%) as *E. durans*, 44 (0.6%) as *E. raffinosus*, 4 (0.1%) as *E. hirae*, and 6 (0.1%) was undetermined *Enterococcus* species. The incidence of bacteremia due to *E. durans* was 0.05 cases per 1,000 admissions. Among 91 cultures of *E. durans* bacteremia from 83 patients, 8 cultures collected from same patients were excluded. In addition, 3 patients under the age of 16 were also excluded. Therefore, a total of 80 cultures of *E. durans* from 80 adult patients were included in a case group. As control groups, 80 cultures were selected from 1,981 cultures of *E. faecalis*, as well as from 4,598 cultures of *E. faecium*. The incidence of *E. durans* bacteremia was not significantly different by year (Figure 1).

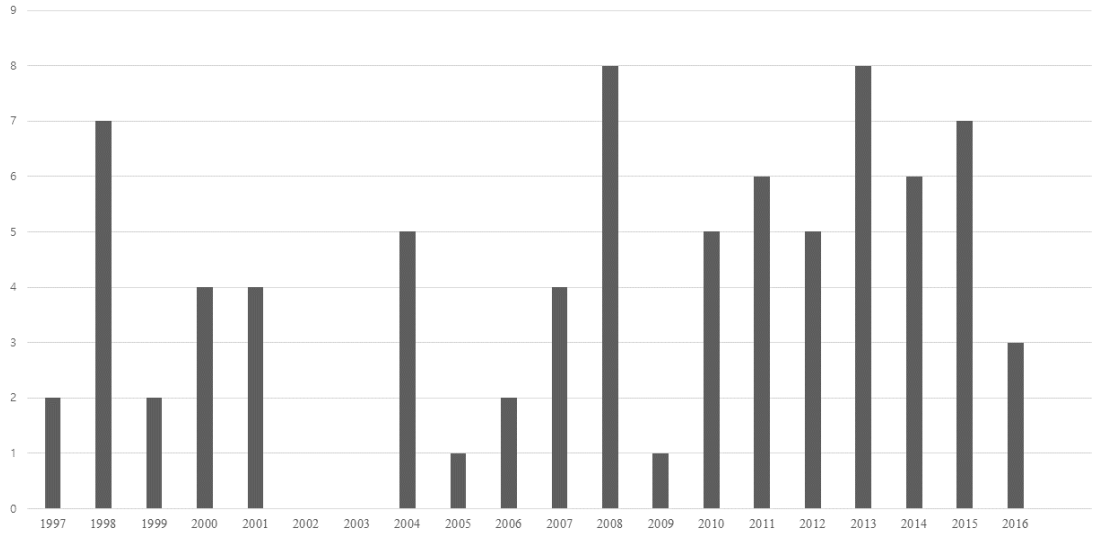

Figure 1. The incidence of *E. durans* bacteremia by year.

Demographic data and underlying disease/condition

The demographic characteristics and underlying disease/conditions of 80 patients with *E. durans* bacteremia are provided in Table 1. Forty-one patients (51.2%) were men, and the mean age was 64.3 years (standard deviation, 12.1 years). All patients had underlying illnesses; the most common underlying illness was solid cancer (48.8%), followed by biliary disease (46.2%), diabetes mellitus (28.7%), chronic kidney disease (17.5%), liver cirrhosis (12.5%), alcoholism (10.0%), congestive heart failure (7.5%), history of solid-organ transplantation (6.2%), neurologic disease (5.0%), hematologic malignancy (2.5%), chronic obstructive pulmonary disease (2.5%), and end-stage renal disease (1.2%). The overall distribution of underlying illnesses among three groups of bacteremia were not significantly different, except the significant difference in patients with hematologic malignancy between *E. durans* and *E. faecium* bacteremia (2.5% vs. 20.0%, p <0.01). Forty-seven patients (58.8%) were classified as having the nonfatal disease, 33 (41.2%) as ultimately fatal, and none as rapidly fatal. The nonfatal disease was significantly frequent in *E. durans* bacteremia than in other two groups of bacteremia (58.8% vs. 43.8% vs. 32.5%, p <0.01), with the significant difference between *E. durans* and *E. faecium* bacteremia (58.8% vs. 32.5%, p <0.01) was noticed. Regarding factors that predisposed patients to *E. durans* bacteremia, 42 patients (52.5%) had a history of prior hospital admission within 6 months, 27 (33.8%) had biliary drainage catheter in place, 10 (12.5%) had a history of cancer chemotherapy, 9 (11.2%) had a history of recent surgery within a month, 8 (10.0%) had leukopenia at the time of bacteremia, 8 (10.0%) received immunosuppressive therapy within a month, 7 (8.8%) had a central venous catheter in place, 7 (8.8%) had an indwelling urinary catheter in place, 6 (7.5%) had a history of bleeding within 2 weeks, 5 (6.2%) had prior ICU care within a month, and 2 (2.5%) received mechanical ventilation at the time of bacteremia. Significant differences in possession of following risk factors among three groups were as follows; prior hospital admission within 6 months (52.5% vs. 56.2% vs. 76.2%, p <0.01; versus *E. faecalis*

and *E. faecium*, respectively), history of cancer chemotherapy (12.5% vs. 7.5% vs. 26.2%, p <0.01), central venous catheter in place (8.8% vs. 31.2% vs. 50.0%, p <0.01), indwelling urinary catheter in place (8.8% vs. 22.5% vs. 40.0%, p <0.01), prior ICU care within a month (6.2% vs. 25.0% vs. 32.5%, p <0.01), and received mechanical ventilation at the time of bacteremia (2.5% vs. 10.0% vs. 22.5%, p< 0.01). *E. durans* bacteremia was associated with community-onset bacteremia more frequently than *E. faecalis* or *E. faecium* bacteremia (56.2% vs. 35.0% vs. 21.2%, p <0.01), while hospital-acquired bacteremia was less frequent in *E. durans* bacteremia than other groups of bacteremia (43.8% vs. 65.0% vs. 78.8%, p <0.01). *E. durans* bacteremia showed a lower frequency of prior antibiotic use within one month than *E. faecalis* or *E. faecium* bacteremia (32.5% vs. 65.0% vs. 88.8%, p <0.01).

Table 1. Demographic and clinical characteristics of study patients with enterococcal bacteremia

Characteristic	Group 1 *E. durans* bacteremia (n = 80)	Group 2 *E. faecalis* bacteremia (n = 80)	Group 3 *E. faecium* bacteremia (n = 80)	Group 1 vs 2 *p*-value	Group 1 vs 3 *p*-value	Overall *p*-value*
Male sex	41 (51.2)	41 (51.2)	41 (51.2)	1.00	1.00	1.00
Age (mean years ± SD)	64.3 ± 12.1	64.5 ± 11.2	64.0 ± 11.4	1.00	1.00	0.96
Underlying disease or condition‡						
Solid cancer	39 (48.8)	39 (48.8)	36 (45.0)	1.00	0.64	0.86
Hepatobiliary & pancreas	26 (32.5)	25 (31.3)	26 (32.5)	0.87	1.00	0.98
Gastrointestinal	8 (10.0)	5 (6.3)	2 (2.5)	0.39	0.05	0.15
Others	7 (8.8)	9 (11.3)	8 (10.0)	0.60	0.79	0.87
Biliary disease†	37 (46.2)	35 (43.8)	41 (51.2)	0.75	0.53	0.63
Diabetes mellitus	23 (28.7)	20 (25.0)	15 (18.8)	0.59	0.14	0.33
Chronic kidney disease	14 (17.5)	7 (8.8)	13 (16.2)	0.10	0.83	0.23
Liver cirrhosis	10 (12.5)	5 (6.2)	6 (7.5)	0.18	0.29	0.33
Alcoholism	8 (10.0)	6 (7.5)	6 (7.5)	0.58	0.58	0.80
Congestive heart failure	6 (7.5)	3 (3.8)	5 (6.2)	0.50	0.76	0.70
Solid-organ transplantation	5 (6.2)	3 (3.8)	6 (7.5)	0.72	0.76	0.70
Neurologic disease	4 (5.0)	5 (6.2)	4 (5.0)	1.00	1.00	1.00
Hematologic malignancy	2 (2.5)	4 (5.0)	16 (20.0)	0.68	**<0.01****	**<0.01**
Chronic obstructive pulmonary disease	2 (2.5)	2 (2.5)	3 (3.8)	1.00	1.00	1.00
End-stage renal disease on dialysis	1 (1.2)	6 (7.5)	5 (6.2)	0.12	0.21	0.16
Multiple trauma	0	2 (2.5)	1 (1.2)	0.50	1.00	0.78
McCabe and Jackson criteria						
Nonfatal disease	47 (58.8)	35 (43.8)	26 (32.5)	0.06	**<0.01**	**<0.01**
Ultimately or rapidly fatal disease	33 (41.2)	45 (56.2)	54 (67.5)	0.06	**<0.01**	**<0.01**
Underlying risk factor‡						
Prior hospital admission within 6 months	42 (52.5)	45 (56.2)	61 (76.2)	0.63	**<0.01**	**<0.01**
Biliary drainage catheter	27 (33.8)	25 (31.2)	26 (32.5)	0.74	0.87	0.95
Cancer chemotherapy§	10 (12.5)	6 (7.5)	21 (26.2)	0.29	0.03	**0.003**
Recent surgery§	9 (11.2)	16 (20.0)	16 (20.0)	0.13	0.13	0.24
Leukopenia‖	8 (10.0)	8 (10.0)	17 (21.2)	1.00	0.05	0.06
Immunosuppressive therapy¶	8 (10.0)	9 (11.2)	14 (17.5)	0.80	0.17	0.32
Central venous catheter	7 (8.8)	25 (31.2)	40 (50.0)	**<0.01**	**<0.01**	**<0.01**
Indwelling urinary catheter	7 (8.8)	18 (22.5)	32 (40.0)	**0.017**	**<0.01**	**<0.01**
Bleeding in prior 2 weeks	6 (7.5)	4 (5.0)	11 (13.8)	0.51	0.20	0.13
Prior ICU care§	5 (6.2)	20 (25.0)	26 (32.5)	**<0.01**	**<0.01**	**<0.01**
Mechanical ventilation	2 (2.5)	8 (10.0)	18 (22.5)	0.05	**<0.01**	**<0.01**
Place of bacteremia acquisition						
Hospital-acquired	35 (43.8)	52 (65.0)	63 (78.8)	**<0.01**	**<0.01**	**<0.01**
Community-onset	45 (56.2)	28 (35.0)	17 (21.2)	**<0.01**	**<0.01**	**<0.01**
Community-acquired	18 (22.5)	8 (10.0)	5 (6.2)	0.03	**<0.01**	**<0.01**
Healthcare-associated	27 (33.8)	20 (25.0)	12 (15.0)	0.22	**<0.01**	**0.02**
Prior antibiotic use within 1 month	26 (32.5)	52 (65.0)	71 (88.8)	**<0.01**	**<0.01**	**<0.01**

Note. Data are no. (%) of patients, unless otherwise indicated. ICU, intensive care unit.

* Overall *p*-values are for the overall comparison among the three groups.

† Biliary disease was considered to include hepatobiliary or pancreatic cancer.

‡ Some patients had >1 underlying disease or risk factor.

[§] Within the past month.
[‖] Leukocyte count, <4000 leukocytes/mm^3.
[¶] Receipt of steroid therapy for >10 days or use of other immunosuppressant (tacrolimus, mycophenolate mofetil, azathioprine, cyclosporin A, anti-CD3 monoclonal antibody [OKT-3], or anti-TNF-α inhibitor) for >1 week within the previous 1 month.
[**] Statistically significant *p*-values are presented in boldface.

Clinical and laboratory manifestations

Clinical and laboratory manifestations of patients are shown in Table 2. In *E. durans* bacteremia, clinical sepsis at the time of bacteremia was not evident in 59 (73.8%) of the patients, 14 (17.5%) had cases that met the criteria for sepsis, and 7 (8.8%) presented with septic shock. Fewer patients with *E. durans* bacteremia were manifested as a septic shock than those with *E. faecalis* or *E. faecium* bacteremia, but it was not statistically significant (8.8% vs. 13.8% vs. 17.5%, p =0.26). Four (5.0%) of *E. durans* bacteremia had a Pitt bacteremia score≥4 points. The proportion of patients with Pitt bacteremia score≥4 points was significantly lower in *E. durans* bacteremia than other two groups (5.0% vs. 8.8% vs. 20.0%, p <0.01), especially than *E. faecium* bacteremia (5.0% vs. 20.0%, p <0.01). The biliary tract was the most common portal of entry (39/80, 48.8%) of *E. durans* bacteremia, followed by urinary tract (18/80, 22.5%), unknown focus (10/80, 12.5%), abdomen (7/80, 8.8%). Urinary tract infection was significantly associated with *E. durans* bacteremia compared with *E. faecalis* or *E. faecium* bacteremia (22.5% vs. 10.0% vs. 2.5%, p <0.01). There was no catheter-related infection or soft tissue and skin infection in *E. durans* bacteremia, catheter-related infection was more common in *E. faecalis* or *E. faecium* bacteremia (0% vs. 16.2% vs. 12.5%, p <0.01). Table 3 describes information on the concomitantly identified microorganisms. Concomitant bacteremia due to another kind of microorganisms were 24 (30.0%), 28 (35.0%) and 17 (21.5%) cases for *E. durans*, *E. faecalis*, and *E. faecium* bacteremia, respectively. Of these, 7 (8.8%), 7 (8.8%), and 2 (2.5%) cases were associated with 2 or more other organisms, respectively. The most frequently observed organisms with study patients were gram-negative bacilli in all three groups of bacteremia, among which *Escherichia coli* was the most commonly identified. The organisms identified concomitantly with *E. durans* bacteremia are listed in decreasing order of frequency as follows; *E. coli, Klebsiella pneumoniae, E. faecium* (3 patients each), *Enterobacter cloacae* (2 patients), *Pseudomonas aeruginosa, Citrobacter freundii,*

Acinetobacter baumannii, Clostridium perfringenes, Staphylococcus warneri, and *Bacteroides caccae* (1 patient each). The multiple organisms identified concomitantly with *E. durans* bacteremia are listed as described above; *E. coli* and *K. pneumoniae, E. coli* and *E. faecium* (2 patients each), *E. coli* and *P. aeruginosa, E. coli* and *K. oxytoca, P. aeruginosa* and *C. perfringenes* (1 patient each). The presence of concomitant bacteremia was not related with the initial manifestation of *E. durans* bacteremia (p >0.05; data not shown). Rate of recurrent bacteremia was not different among three groups (2.5% vs. 3.8% vs. 11.2%, p =0.07). Infective endocarditis was diagnosed in six patients (6/80, 7.5%) with *E. durans* bacteremia. The overall significant differences in the levels of white blood cell count and procalcitonin among three groups were detected, but there were no significant differences in the *post hoc* analysis between the three groups.

Table 2. Clinical and microbiological features of patients with enterococcal bacteremia

Characteristic	Group 1 *E. durans* bacteremia (n = 80)	Group 2 *E. faecalis* bacteremia (n = 80)	Group 3 *E. faecium* bacteremia (n = 80)	Group 1 vs 2 *p*-value	Group 1 vs 3 *p*-value	Overall *p*-value*
Initial manifestation within 24 hours						
Bacteremia without sepsis	59 (73.8)	54 (67.5)	56 (70.0)	0.39	0.60	0.68
Sepsis	14 (17.5)	15 (18.8)	10 (12.5)	0.84	0.38	0.53
Septic shock	7 (8.8)	11 (13.8)	14 (17.5)	0.32	0.10	0.26
Pitt bacteremia score≥4	4 (5.0)	7 (8.8)	16 (20.0)	0.35	**<0.01**†	**<0.01**
Portal of entry						
Biliary tract infection	39 (48.8)	34 (42.5)	37 (46.2)	0.43	0.75	0.73
Urinary tract infection	18 (22.5)	8 (10.0)	2 (2.5)	0.03	**<0.01**	**<0.01**
Primary unknown infection	10 (12.5)	13 (16.2)	19 (23.8)	0.50	0.07	0.16
Gastrointestinal tract infection	7 (8.8)	10 (12.5)	9 (11.2)	0.44	0.60	0.74
Catheter related infection	0	13 (16.2)	10 (12.5)	**<0.01**	**<0.01**	**<0.01**
Skin and soft tissue infection	0	1 (1.2)	2 (2.5)	1.00	0.50	0.78
Concomitant bacteremia	24 (30.0)	28 (35.0)	17 (21.5)	0.50	0.22	0.15
Recurrent bacteremia	2 (2.5)	3 (3.8)	9 (11.2)	1.00	0.03	0.07
Infective endocarditis	6 (7.5)	1 (1.2)	1 (1.2)	0.12	0.12	0.05
Laboratory findings, median (IQR)						
WBC, x 10^3/mm^3	11.25 (6.78-15.50)	10.80 (6.33-15.68)	9.10 (4.40-12.80)	0.45	0.05	**0.04**
CRP, mg/dL	6.72 (3.92-12.56)	9.44 (2.94-18.37)	7.40 (3.91-13.95)	0.34	0.74	0.40
Procalcitonin, ng/mL	0.69 (0.21-3.58)	3.75 (0.57-23.80)	0.81 (0.28-4.19)	0.22	0.81	**0.04**

Note. Data are no. (%) of patients, unless otherwise indicated.

* Overall *p*-values are for the overall comparison among the three groups.

† Statistically significant *p*-values are presented in boldface.

Table 3. Concomitantly identified microorganisms with each *Enterococcus* group

Concomitant bacteremia	Group 1 *E. durans* bacteremia (n = 80)	Group 2 *E. faecalis* bacteremia (n = 80)	Group 3 *E. faecium* bacteremia (n = 80)
Escherichia coli	3 (3.8)	6 (7.5)	3 (3.8)
Klebsiella pneumoniae	3 (3.8)	2 (2.5)	0
Enterococcus faecium	3 (3.8)	0	N/A
Enterobacter cloacae	2 (2.5)	2 (2.5)	1 (1.3)
Pseudomonas aeruginosa	1 (1.3)	1 (1.3)	2 (2.5)
Citrobacter freundii	1 (1.3)	0	0
Acinetobacter baumannii	1 (1.3)	2 (2.5)	1 (1.3)
Clostridium perfringenes	1 (1.3)	1 (1.3)	0
Staphylococcus warneri	1 (1.3)	0	0
Bacteroides caccae	1 (1.3)	0	0
S. aureus	0	4 (5.0)	1 (1.3)
K. oxytoca	0	1 (1.3)	1 (1.3)
S. epidermidis	0	1 (1.3)	1 (1.3)
Chryseobacterium meningosepticum	0	0	1 (1.3)
Bacillus species	0	0	1 (1.3)
Agrobactrium radiobacter	0	0	1 (1.3)
E. faecalis	0	N/A	1 (1.3)
Morganella morgannii	0	0	1 (1.3)
Candida tropicalis	0	1 (1.3)	0
E. coli + *K. pneumoniae*	2 (2.5)	1 (1.3)	0
E. coli + *E. faecium*	2 (2.5)	0	0
E. coli + *P. aeruginosa*	1 (1.3)	1 (1.3)	0
E. coli + *K. oxytoca*	1 (1.3)	0	0
P. aeruginosa + *C. perfringenes*	1 (1.3)	0	0
E. coli + *Aeromonas hydrophila*	0	1 (1.3)	1 (1.3)
E. aerogenes + *M. morganii*	0	1 (1.3)	0
A. baumannii + *S. aureus*	0	1 (1.3)	0
E. faecium + *C. difficile*	0	1 (1.3)	0
K. pneumoniae + *C. freundii*	0	0	1 (1.3)
E. coli + *Proteus mirabilis* + *E. avium*	0	1 (1.3)	0

N/A, not available.

Antibiotic susceptibility

Antibiotic susceptibility data of *Enterococcus* species is presented in Table 4. Most *E. durans* isolates were susceptible to penicillin (66/76, 86.8%), ampicillin (67/76, 88.2%), vancomycin (75/76, 98.7%), linezolid (62/62, 100%), gentamicin (66/73, 90.4%), and streptomycin (69/73, 94.5%). Susceptibility of *E. durans* isolates to other antibiotics were as follows; quinupristin-dalfopristin (42/61, 68.9%), tetracycline (56/76, 73.7%), erythromycin (61/76, 80.3%), ciprofloxacin (63/76, 82.9%), rifampin (65/76, 85.5%), imipenem (13/14, 92.9%), respectively. *E. durans* isolates were less susceptible to ampicillin than *E. faecalis* isolates (88.2% vs. 98.7%, p <0.01), however, susceptibility to following antibiotics were more common than *E. faecalis* isolates; quinupristin-dalfopristin (68.9% vs. 0%, p <0.01), tetracycline (73.7% vs. 34.2%, p <0.01), erythromycin (80.3% vs. 27.8%, p <0.01), ciprofloxacin (82.9% vs. 59.5%, p <0.01), rifampin (85.5% vs. 50.6%, p <0.01), gentamicin (90.4% vs. 48.7%, p <0.01), and streptomycin (94.5% vs. 76%, p <0.01), respectively. *E. durans* isolates showed higher rate of susceptibility to most antibiotics, such as penicillin (86.6% vs. 21.1%, p <0.01), ampicillin (88.2% vs. 23.4%, p <0.01), vancomycin (98.7% vs. 68.8%, p <0.01), erythromycin (80.3% vs. 11.7%, p <0.01), ciprofloxacin (82.9% vs. 16.9%, p <0.01), rifampin (85.5% vs. 37.7%, p <0.01), imipenem (92.9% vs. 68.8%, p <0.01), and gentamicin (90.4% vs. 48.7%, p <0.01). The rate of quinupristin-dalfopristin (31.1% vs. 19.7%, p =0.15), tetracycline (26.3% vs. 22.1%, p =0.54), and streptomycin (94.5% vs. 84.4%, p =0.05) susceptibility of *E. durans* isolates were not significantly different from those of *E. faecium* isolates. Linezolid was susceptible to all enterococcal isolates of three groups underwent susceptibility test.

Table 4. Antibiotic susceptibility of *Enterococcus* species isolated in study patients

Antibiotic*	Group 1 *E. durans* (n = 80)	Group 2 *E. faecalis* (n = 80)	Group 3 *E. faecium* (n = 80)	Group 1 vs 2 *p*-value	Group 1 vs 3 *p*-value	Overall *p*-value†
Penicillin	66/76 (86.8)	71/79 (89.9)	16/76 (21.1)	0.56	**<0.01**‖	**<0.01**
Ampicillin	67/76 (88.2)	78/79 (98.7)	18/77 (23.4)	**<0.01**	**<0.01**	**<0.01**
Vancomycin	75/76 (98.7)	79/79 (100)	53/77 (68.8)	0.49	**<0.01**	**<0.01**
Linezolid	62/62 (100)	61/61 (100)	61/61 (100)	1.00	1.00	1.00
Quinupristin-dalfopristin	42/61 (68.9)	0/61 (0)	49/61 (80.3)	**<0.01**	0.15	**<0.01**
Tetracycline	56/76 (73.7)	27/79 (34.2)	60/77 (77.9)	**<0.01**	0.54	**<0.01**
Erythromycin	61/76 (80.3)	22/79 (27.8)	9/77 (11.7)	**<0.01**	**<0.01**	**<0.01**
Ciprofloxacin	63/76 (82.9)	47/79 (59.5)	13/77 (16.9)	**<0.01**	**<0.01**	**<0.01**
Rifampin	65/76 (85.5)	40/79 (50.6)	29/77 (37.7)	**<0.01**	**<0.01**	**<0.01**
Imipenem	13/14 (92.9)	18/18 (100)	5/16 (68.8)	0.44	**<0.01**	**<0.01**
Gentamicin‡	66/73 (90.4)	50/75 (66.7)	38/78 (48.7)	**<0.01**	**<0.01**	**<0.01**
Streptomycin§	69/73 (94.5)	57/75 (76.0)	65/77 (84.4)	**<0.01**	0.05	**<0.01**

Data are *n*/*N* (%) of patients.

* Not all isolates underwent susceptibility testing.

† Overall *p*-values are for the overall comparison among the three groups.

‡ Isolates did not show high-level resistance to gentamicin.

§ Isolates did not show high-level resistance to streptomycin.

‖ Statistically significant *p*-values are presented in boldface.

Antibiotic therapy

Antibiotic treatment regimens are shown in Table 5. Forty-seven patients (58.8%) with *E. durans* bacteremia received appropriate therapy, 42 of whom received monotherapy, with ampicillin being the most common antibiotic (23/47, 48.9%), followed by vancomycin (15/47, 31.9%), teicoplanin (3/47, 6.4%), and linezolid (1/47, 2.1%). Compared with other two groups of bacteremia, the frequencies of prescribed single appropriate antibiotic to *E. durans* bacteremia were significantly different in ampicillin (48.9% vs. 66.7% vs. 10.0%, p <0.01; versus *E. faecalis* and *E. faecium*, respectively) and linezolid (2.1% vs. 1.9% vs. 35.0%, p <0.01). For prescription of vancomycin (31.9% vs. 46.3% vs. 48.3%, p =0.2), and teicoplanin (6.4% vs. 1.9% vs. 10.0%, p =0.2), there were no distinct differences among three groups. Compared with *E. faecalis* bacteremia, there were no significant differences in the frequency of prescribed single appropriate antibiotic. However, prescription of ampicillin (48.9% vs. 10.0%, p <0.01) and linezolid (2.1% vs. 35.0%, p <0.01) were significantly different compared with *E. faecium* bacteremia. Combination antibiotic therapy was administered to 7 of patients with *E. durans* bacteremia. Among these patients, 4 (8.5%) received ampicillin with gentamicin, 2 (4.3%) received penicillin with gentamicin, and remaining 1 (2.1%) received vancomycin with gentamicin. I could not find a difference in the frequency of ampicillin plus gentamicin combination regimen (8.5% vs. 3.7% vs. 1.7%, p =0.51; versus *E. faecalis* and *E. faecium*, respectively) among the three groups. No patient with *E. faecalis* or *E. faecium* bacteremia received combination therapy containing penicillin or vancomycin. The proportion of patients received appropriate antibiotics was high in the order of *E. durans*, *E. faecalis* and *E. faecium* bacteremia (58.8% vs. 67.5% vs. 75.0%, p =0.09), without significant differences among the three groups. Thirty-five patients of 47 *E. durans* bacteremia (35/47, 74.5%) who received appropriate therapy were administered such antibiotics within three days from index day. The median duration of adequate therapy was 11 days (IQR, 4–18 days). There were no significant differences regarding the proportion of

patients received appropriate antibiotics within three days from the onset of bacteremia and duration of appropriate antibiotics among the three groups.

Outcomes

Clinical outcomes are summarized in Table 5. The all-cause 60-day mortality rate of patients with *E. durans* bacteremia was 20.0% (16 of 80 patients), with only two deaths (2.5%) considered to be related to bacteremia. The first patient had diabetes mellitus as an underlying disease with concomitant bacteremia due to *E. coli*. The second patient was received recent chemotherapy for head and neck cancer, with concomitant bacteremia due to *P. aeruginosa* and *C. perfringenes*. The initial manifestation of these two patients was categorized as septic shock. The all-cause 60-day mortality of the *E. durans* bacteremia was lower than those of the *E. faecalis* or *E. faecium* bacteremia (20.0% vs. 31.2% vs. 42.5%, p <0.01), and the difference in mortality rate was particularly significant between day 14 and 28. Kaplan-Meier curve illustrates the overall survival rates of these three groups (Figure 2). Bacteremia-related mortality of *E. durans* bacteremia was significantly lower than that of other two groups (2.5% vs. 16.2% vs. 18.8%, p <0.01; versus *E. faecalis* and *E. faecium*, respectively). In-hospital mortality of three groups also showed similar results (15.0% vs. 28.7% vs. 31.6%, p =0.04).

Table 5. Treatment and outcomes of patients with enterococcal bacteremia

Characteristic	Group 1 *E. durans* bacteremia (n = 80)	Group 2 *E. faecalis* bacteremia (n = 80)	Group 3 *E. faecium* bacteremia (n = 80)	Group 1 vs 2 *p*-value	Group 1 vs 3 *p*-value	Overall *p*-value*
Received appropriate therapy†	47 (58.8)	54 (67.5)	60 (75.0)	0.25	0.03	0.09
Monotherapy						
Ampicillin	23/47 (48.9)	36/54 (66.7)	6/60 (10.0)	0.07	**<0.01**‡	**<0.01**
Vancomycin	15/47 (31.9)	25/54 (46.3)	29/60 (48.3)	0.16	0.09	0.20
Teicoplanin	3/47 (6.4)	1/54 (1.9)	6/60 (10.0)	0.34	0.73	0.17
Linezolid	1/47 (2.1)	1/54 (1.9)	21/60 (35.0)	1.00	**<0.01**	**<0.01**
Combination therapy						
Ampicillin plus gentamicin	4/47 (8.5)	2/54 (3.7)	1/60 (1.7)	0.41	0.17	0.26
Penicillin plus gentamicin	2/47 (4.3)	0	0	0.21	0.19	0.09
Vancomycin plus gentamicin	1/47 (2.1)	0	0	0.47	0.44	0.29
Intervals to appropriate therapy ≤3 days	35/47 (74.5)	44/54 (81.5)	49/60 (81.7)	0.66	0.37	0.6
Duration of appropriate therapy, median days (IQR)	11.00 (4.00-18.00)	11.00 (5.00-14.25)	13.00 (8.00-18.75)	0.96	0.28	0.28
Day 1 mortality	2 (2.5)	4 (5.0)	2 (2.5)	0.68	1.00	0.74
Day 7 mortality	5 (6.2)	12 (15.0)	10 (12.5)	0.07	0.18	0.20
Day 14 mortality	5 (6.2)	15 (18.8)	16 (20.0)	**0.02**	**0.01**	**0.03**
Day 21 mortality	7 (8.8)	21 (26.2)	20 (25.0)	**<0.01**	**<0.01**	**<0.01**
Day 28 mortality	7 (8.8)	21 (26.2)	23 (28.7)	**<0.01**	**<0.01**	**<0.01**
Day 60 mortality	16 (20.0)	25 (31.2)	34 (42.5)	0.10	**<0.01**	**<0.01**
Bacteremia-related mortality	2 (2.5)	13 (16.2)	15 (18.8)	**<0.01**	**<0.01**	**<0.01**
In-hospital mortality	12 (15.0)	23 (28.7)	25 (31.6)	0.04	**0.01**	**0.04**

Note. Data are no. (%) of patients or *n*/*N* (%) of patients.

* Overall *p*-values are for the overall comparison among the three groups.

† Some patients received >1 antibiotics.

‡ Statistically significant *p*-values are presented in boldface.

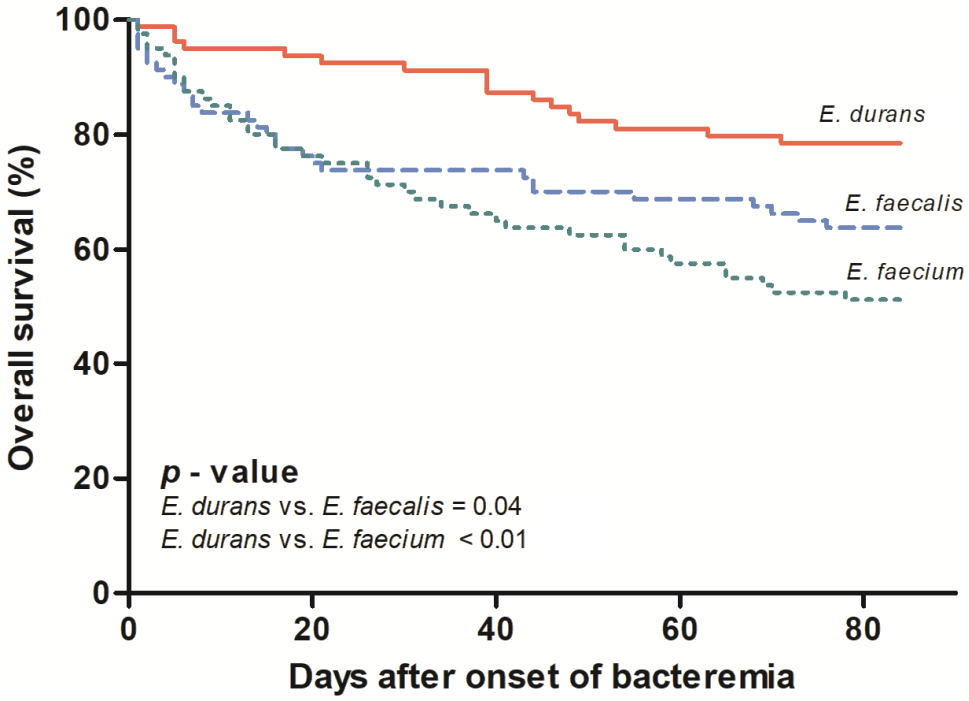

Figure 2. Kaplan-Meier survival curve of patients with enterococcal bacteremia.

Risk factors for mortality of patients with *E. durans* bacteremia

Table 6 presents a univariate analysis of risk factors for 60-day mortality of patients with *E. durans* bacteremia. Prior hospital admission within 6 months (OR, 3.40; 95% CI, 0.99-11.67; p =0.04), underlying solid cancer (OR, 4.11; 95% CI, 1.20-14.14; p =0.02), ultimately or rapidly fatal underlying disease according to McCabe and Jackson criteria (OR, 6.14; 95% CI, 1.77-21.36; p <0.01), septic shock as initial manifestation (OR, 6.78; 95% CI, 1.34-34.24; p =0.03), a Pitt bacteremia score≥4 at the onset of bacteremia (OR, 14.54; 95% CI, 1.40-151.02; p =0.02) were related with 60-day mortality of *E. durans* bacteremia. Urinary tract infection was associated with reduced 60-day mortality (OR, 0.72; 95% CI, 0.62-0.84; p =0.02). Resistance to ampicillin was associated with a higher mortality rate (44.4%) than that of ampicillin-susceptible (17.9%) group. However, the difference was not statistically significant (p =0.09). Inadequate antibiotic therapy was not related to mortality (p =0.82).

Multivariate analysis (Table 7) showed that ultimately or rapidly fatal underlying disease (adjusted OR, 5.30; 95% CI, 1.29-21.72; p =0.02) and a Pitt bacteremia score≥4 (adjusted OR, 13.52; 95% CI, 1.05-174.26; p =0.046) were independent risk factor for 60-day mortality. Although the mortality rate was significantly lower among patients with urinary tract infection (0%) than among those involved with infections other than urinary tract infection (25.8%), this factor was not considered as a significant risk factor in multivariate analysis. The median length of hospital stay after bacteremia for surviving patients was 13.5 days (range, 0–131 days).

Table 6. 60-day outcomes of patients with *Enterococcus durans* bacteremia

Variable	No. of death* / No. of episodes (%)	*p-value*	OR (95% CI)
Sex			
Male	11/41 (26.8)	0.12	2.49 (0.78-8.00)
Female	5/39 (12.8)		
Polymicrobial bacteremia			
Yes	3/24 (12.5)	0.37	0.47 (0.12-1.84)
No	13/56 (23.2)		
Location			
ICU	1/5 (20.0)	1.00	1.00 (0.10-9.61)
Non-ICU	15/75 (20.0)		
Place of acquisition			
Hospital-acquired	6/35 (17.1)	0.57	0.72 (0.24-2.23)
Community-onset	10/45 (22.2)		
Prior hospital admission within 6 months			
Yes	12/42 (28.6)	0.04	3.40 (0.99-11.67)
No	4/38 (10.5)		
Solid cancer			
Yes	12/39 (30.8)	0.02	4.11 (1.20-14.14)
No	4/41 (9.8)		
Ultimately or rapidly fatal disease			
Yes	12/33 (36.4)	<0.01	6.14 (1.77-21.36)
No	4/47 (8.5)		
Septic shock			
Yes	4/7 (57.1)	0.03	6.78 (1.34-34.24)
No	12/73 (16.4)		
Pitt bacteremia score≥4			
Yes	3/4 (75.0)	0.02	14.54 (1.40-151.02)
No	13/76 (17.1)		
Portal of entry - Biliary tract			
Yes	10/39 (25.6)	0.22	2.01 (0.65-6.20)
No	6/41 (14.6)		
Portal of entry – Infective endocarditis			
Yes	1/6 (16.7)	1.00	0.79 (0.09-7.25)
No	15/74 (20.3)		
Portal of entry - Urinary tract			
Yes	0/18 (0)	0.02	0.72 (0.62-0.84)
No	16/62 (25.8)		
Resistance to ampicillin			
Yes	4/9 (44.4)	0.09	3.67 (0.86-15.72)
No	12/67 (17.9)		
Resistance to vancomycin			
Yes	0/1 (0)	1.00	0.98 (0.95-1.02)
No	16/75 (21.3)		
Inadequacy of antibiotic therapy			
Yes	7/33 (21.2)	0.82	0.88 (0.29-2.66)
No	9/47 (19.1)		
Total†	16/80 (20.0)		

* Death from any cause.

† Two death were related to bacteremia (2/80 [2.5%])

Table 7. Multivariate analysis of risk factors for 60-day mortality in *E. durans* bacteremia

	Univariate analysis		Multivariate analysis	
Character	OR (95% CI)	*p-value*	aOR (95% CI)	*p-value*
Prior hospital admission within 6 months	3.40 (0.99-11.67)	0.04	0.96 (0.21-4.43)	0.96
Ultimately or rapidly fatal disease	6.14 (1.77-21.36)	<0.01	5.30 (1.29-21.72)	0.02
Pitt bacteremia score≥4	14.54 (1.40-151.02)	0.02	13.52 (1.05-174.26)	0.046
Urinary tract infection	0.72 (0.62-0.84)	0.02	NA	>0.99
Resistance to ampicillin	3.67 (0.86-15.72)	0.09	2.57 (0.49-13.46)	0.26

This model fit the data well in terms of discrimination (C-static = 0.84) and calibration (Hosmer-Lemeshow goodness of fit statistic = 0.34; $p = 0.95$).

* Two potential confounding variables (solid cancer for rapidly fatal disease and septic shock for Pitt bacteremia score≥4) were excluded from the multivariate analysis.

OR, odds ratio; aOR, adjusted odds ratio; N/S, not significant.

Risk factors for mortality of all study patients with enterococcal bacteremia

Table 8 shows a univariate analysis of risk factors for 60-day mortality of all study patients with enterococcal bacteremia. *E. durans* bacteremia (OR, 0.43; 95% CI, 0.23-0.81; p <0.01) and urinary tract infection (OR, 0.07; 95% CI, 0.01-0.52; p <0.01) were associated with survival. Prior hospital admission within 6 months (OR, 1.94; 95% CI, 1.08-3.51; p =0.03), ultimately or rapidly fatal disease (OR, 3.14; 95% CI, 1.73-5.71; p <0.01), septic shock (OR, 6.43; 95% CI, 2.86-14.46; p <0.01), a Pitt bacteremia score≥4 (OR, 8.21; 95% CI, 3.30-20.47; p <0.01), resistance to ampicillin (OR, 2.82; 95% CI, 1.56-5.10; p <0.01) and vancomycin (OR, 3.19; 95% CI, 1.37-7.44; p <0.01) were associated with 60-day mortality.

Independent risk factors for 60-day mortality of all study patients identified by multivariate analysis (Table 9) were ultimately or rapidly fatal underlying disease (adjusted OR, 3.60; 95% CI, 1.82-7.09; p <0.01) and a Pitt bacteremia score≥4 (adjusted OR, 8.11; 95% CI, 3.03-21.75; p <0.01). Urinary tract infection was related with reduced 60-day mortality (adjusted OR, 0.10; 95% CI, 0.01-0.74; p =0.02). Enterococcal species and resistance to antibiotics were not included in the independent risk factors for mortality of enterococcal bacteremia.

Table 8. 60-day outcomes of all study patients with enterococcal bacteremia

Variable	No. of death* / No. of episodes (%)	*p-value*	OR (95% CI)
Organism			
E. durans	16/80 (20.0)	<0.01	0.43 (0.23-0.81)
E. faecalis or *E. faecium*	59/160 (36.9)		
Sex			
Male	34/123 (27.6)	0.22	0.71 (0.41-1.23)
Female	41/117 (35.0)		
Polymicrobial bacteremia			
Yes	18/69 (26.1)	0.27	0.71 (0.38-1.32)
No	57/171 (33.3)		
Location			
ICU	8/26 (30.8)	0.96	0.98 (0.40-2.35)
Non-ICU	67/214 (31.3)		
Place of acquisition			
Hospital-acquired	50/150 (33.3)	0.37	1.30 (0.73-2.31)
Community-onset	25/90 (27.8)		
Prior hospital admission within 6 months			
Yes	54/148 (36.5)	0.03	1.94 (1.08-3.51)
No	21/92 (22.8)		
Solid cancer			
Yes	40/114 (35.1)	0.22	1.41 (0.81-2.43)
No	35/126 (27.8)		
Ultimately or rapidly fatal disease			
Yes	55/132 (41.7)	<0.01	3.14 (1.73-5.71)
No	20/108 (18.5)		
Septic shock			
Yes	22/32 (68.8)	<0.01	6.43 (2.86-14.46)
No	53/208 (25.5)		
Pitt bacteremia score≥4			
Yes	20/27 (74.1)	<0.01	8.21 (3.30-20.47)
No	55/213 (25.8)		
Portal of entry - Biliary tract			
Yes	29/110 (26.4)	0.13	0.65 (0.38-1.14)
No	46/130 (35.4)		
Portal of entry – Infective endocarditis			
Yes	1/8 (12.5)	0.44	0.31 (0.04-2.52)
No	74/232 (31.9)		
Portal of entry - Urinary tract			
Yes	1/28 (3.6)	<0.01	0.07 (0.01-0.52)
No	74/212 (34.9)		
Resistance to ampicillin			
Yes	33/69 (47.8)	<0.01	2.82 (1.56-5.10)
No	40/163 (24.5)		
Resistance to vancomycin			
Yes	14/25 (56.0)	<0.01	3.19 (1.37-7.44)
No	59/207 (28.5)		
Inadequacy of antibiotic therapy			
Yes	23/79 (29.1)	0.62	1.16 (0.65-2.09)
No	52/161 (32.3)		
Total	75/240 (31.3)		

* Death from any cause.

Table 9. Multivariate analysis of risk factors for 60-day mortality in total enterococcal bacteremia

Character	Univariate analysis OR (95% CI)	*p-value*	Multivariate analysis aOR (95% CI)	*p-value*
E. durans bacteremia	0.43 (0.23-0.81)	<0.01	0.80 (0.38-1.65)	0.54
Prior hospital admission within 6 months	1.94 (1.08-3.51)	0.03	0.89 (0.44-1.82)	0.76
Ultimately or rapidly fatal disease	3.14 (1.73-5.71)	<0.01	3.60 (1.82-7.09)	<0.01
Pitt bacteremia score≥4	8.21 (3.30-20.47)	<0.01	8.11 (3.03-21.75)	<0.01
Urinary tract infection	0.07 (0.01-0.52)	<0.01	0.10 (0.01-0.74)	0.02
Resistance to ampicillin	2.82 (1.56-5.10)	<0.01	1.65 (0.76-3.57)	0.21
Resistance to vancomycin	3.19 (1.37-7.44)	<0.01	0.77 (0.25-2.42)	0.66

This model fit the data well in terms of discrimination (C-static = 0.78and calibration (Hosmer-Lemeshow goodness of fit statistic = 1.87; $p = 0.41$).

* A potential confounding variable (septic shock for Pitt bacteremia score≥4) were excluded from the multivariate analysis.

OR, odds ratio; aOR, adjusted odds ratio; N/S, not significant.

DISCUSSION

I demonstrated clinical characteristics and treatment outcomes of *E. durans* bacteremia. To my knowledge, this is the first study to date. In this study, *E. durans* caused only 1.2% of the total enterococcal bacteremia. *E. durans* bacteremia mainly originated from biliary tract or urinary tract infection and was frequently associated with concomitant bacteremia. All-cause and bacteremia-related mortality were lower compared with *E. faecalis* and *E. faecium* bacteremia.

Enterococci are generally considered to account for approximately 10% of all bacteremia[28-31] and my result also showed a similar result (9.1%). I noted a higher proportion of *E. durans* bacteremia among all enterococcal bacteremia than those of previous studies (1.2% vs. 0% – 0.2%).[12,31,32] Different patient populations or more exquisite microbiological diagnostic techniques in the laboratory may have contributed to this difference.

E. durans bacteremia was most commonly related to biliary tract infection (48.8%). My colleagues previously reported that biliary tract was a common route of *E. gallinarum/casseliflavus* and *E. avium* bacteremia.[33,34] A Taiwanese study on non-*faecalis*, non-*faecium* enterococcal bacteremia, most of which were *E. casseliflavus*, *E. gallinarum*, and *E. avium*, also showed high proportion of biliary tract infection (32.7%–55.9%).[12] Considerable proportion of biliary tract infection as portal of *E. durans* bacteremia in this study may reflect distinct characteristics of the study-conducted hospital where many patients with hepatobiliary cancer or diseases are hospitalized.

Despite smaller numbers of patients with an indwelling urinary catheter in *E. durans* bacteremia, urinary tract infection (UTI) was the second most common cause (22.5%) of *E. durans* bacteremia and occurred more frequently than *E. faecalis* or *E. faecium* bacteremia. When I compared my result with those of other studies on non-*faecalis*, non-*faecium* enterococcal bacteremia,[12,34] I detected a higher proportion of UTI to the entire source of

bacteremia (22.5% vs. 1.9%–4.4%). The biofilm-forming mechanism of *E. faecalis* which linked to tropism for human urinary tract is well known,[35-38] but the factors involved in biofilm formation of *E. durans* is still veiled. Although the relationship between the pathogenesis of UTI and *E. durans* has not been elucidated yet, my result suggests that the potential of *E. durans* for triggering UTI may surpass that of *E. faecalis*.

Another notable finding in this study was that the incidence of infective endocarditis in *E. durans* bacteremia tended to be higher than that of other enterococcal bacteremia. The complex interactions of various factors such as microbial surface components recognizing adhesive matrix molecule (MSCRAMM), enterococcal surface protein (Esp), and gelatinase appears to contribute to the capability of biofilm formation by *E. faecalis*.[39-41] According to a recent study, *E. durans* can also possess *esp*, *fsrA*, *fsrC*, *gelE* and other genes which encode proteins involving biofilm formation of *E. faecalis*.[42] These findings suggest that infective endocarditis should be considered as one of the differential diagnoses when *E. durans* bacteremia is found. Further studies on the relationship between possession of genes involved in biofilm formation of *E. durans* and incidence of infective endocarditis are needed.

Patients with *E. durans* bacteremia showed a lower risk of mortality compared with *E. faecalis* or *E. faecium* bacteremia and none of the patients with monomicrobial *E. durans* bacteremia died. Following explanations may support these findings. First, low intrinsic virulence of *E. durans* may have contributed to the favorable outcome of the study patients. It has been suggested that intrinsic virulence of *E. durans* may be lower compared with *E. faecalis*.[15] Several factors such as hemolysin, gelatinase and enterococcal surface protein (Esp) have been suggested to induce virulence of *E. faecalis*.[43-45] However, no studies have described the effects of the virulence factors of *E. durans*. Second, lower incidence of antimicrobial resistance among *E. durans* isolates could result in lower mortality. Most *E. durans* isolates were susceptible to penicillin and only one *E. durans* isolate showed

resistance to vancomycin in this study. Previous meta-analyses on enterococcal bacteremia, which demonstrated a significant association between vancomycin resistance and mortality support my result.[46-48] Third, the relatively high proportion of UTI in patients with *E. durans* bacteremia may influence the outcome. Approximately quarter of *E. durans* bacteremia (18/80, 22.5%) were related with UTI, and no all-cause mortality among these patients was identified. Besides, low incidence of catheter-associated UTI (considered as a subcategory of complicated UTI) among total UTI in patients with *E. durans* bacteremia may affect this result as well. Last, more favorable underlying condition and bacteremia severity could be another reason for lower mortality of patients with *E. durans* bacteremia than those with other enterococcal bacteremia. As shown in the multivariate analysis on mortality of all study patients, underlying disease, severity of bacteremia, and urinary tract infection may have mediated lower mortality of *E. durans* bacteremia. Enterococcal species and resistance to antibiotics were excluded from the multivariate analysis, but further studies are needed on this issue in the future.

This study has several limitations. Due to retrospective data collection from a single tertiary center at a specific location and small sample size, my data may not reflect whole aspects of *E. durans* bacteremia. Especially, these limitations may have been affected by the sources of *E. durans* bacteremia. In addition, some of *E. durans* isolates identified by Microscan system were reported as *E. durans/hirae*. Another weak point is that molecular typing and susceptibility test for teicoplanin has not been performed in the laboratory.

CONCLUSION

The present study provides new information on clinical characteristics and treatment outcome of *E. durans* bacteremia. *E. durans* bacteremia accounts for a minor proportion of the total enterococcal bacteremia, and mainly originate from biliary tract or urinary tract infection. The mortality of *E. durans* bacteremia is significantly lower than that of *E. faecalis* or *E. faecium* bacteremia.

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국문요약

Enterococcus durans 균혈증의 임상적 특징과 치료 결과

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배경: 장구균은 특히 면역저하환자들에게 다양한 종류의 감염증을 일으키는 주요 원인균들 중 하나이다. 장구균 중 대부분을 차지하는 *E. faecalis*와 *E. faecium*에 의한 균혈증의 임상적 특징과 치료결과는 잘 알려져 있으나, *E. durans* 균혈증에 대해서는 일부 증례 보고들을 제외하면 알려진 바가 없는 실정이다.

방법: 저자들은 2,700 병상 규모의 3차 수련병원인 서울아산병원에서 1997년 12월부터 2016년 10월까지 작성된 전자의무기록을 후향적으로 분석하여 본 환자-대조군 연구를 수행하였다. 환자군으로 16세 이상의 성인 *E. durans* 균혈증 환자들을 설정하였다. 두 대조군으로는 *E. durans* 균혈증 환자들과 성별, 연령, 균혈증 발생시기가 상응하는 *E. faecalis*와 *E. faecium* 균혈증 환자들을 무작위로 선택하였다. 환자군과 두 대조군의 환자 비율은 1:1:1로 설정하였고, 각각의 임상적 특징과 치료 결과를 확인한 뒤 서로 비교 분석하였다. *E. durans* 균혈증의 사망과 관련된 위험인자도 분석하였다.

결과: 연구 기간 동안 확인된 모든 장구균 균혈증의 1.2%가 *E. durans* 균혈증이었고, 총 80명의 성인 *E. durans* 균혈증 환자가 확인되었다. 이들 중 39명 (48.8%)에서 담도계 감염증이, 18명 (22.5%)에서 요로계 감염증이 진단되었다. 6명 (7.5%)은 감염성 심내막염이 진단되었다. *E. durans* 균혈증 중 24건 (30.0%)은 복합균에 의한 균혈증으로 발현하였다. 지역사회발생 균혈증은 대조군에 비해 *E. durans* 균혈증군에서 더 흔하였다 (56.2% 대 35.0% 대 21.2%, p <0.01; *E. faecalis*, *E. faecium* 순서로 비교함). *E. durans* 균주의 대부분은 penicillin (66/76, 86.8%), ampicillin (67/76, 88.2%), 그리고 vancomycin (75/76, 98.8%)에 감수성이 있었다. *E. durans* 균혈증군은 대조군보다 모든 원인에 의한 사망률 (20.0% 대 31.2% 대 42.5%, p <0.01)과 균혈증 연관 사망률 (2.5% 대 16.2% 대 18.8%, p <0.01)이 유의하게 낮았다. 다변량분석을 통하여 심각한 (ultimately fatal or rapidly fatal disease) 기저질환 (adjusted OR, 5.30; 95% CI, 1.29−21.72; p =0.02)과 4점 이상의 Pitt bacteremia score (adjusted OR, 13.52; 95% CI, 1.05−174.26; p =0.046)가 *E. durans* 균혈증 환자들의 사망과 관련된 독립적 위험인자로 확인되었다.

결론: *E. durans* 균혈증은 주로 담도계 또는 요로계 감염이 원인이 되며, 사망 위험이 낮았다.