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ORIGINAL ARTICLE

Clinical characteristics and treatment outcomes of *Enterococcus durans* bacteremia: a 20-year experience in a tertiary care hospital

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Abstract

While the clinical characteristics and treatment outcomes of *Enterococcus faecalis* and *E. faecium* bacteremia are well known, those of *E. durans* bacteremia are still largely unclear. We retrospectively identified 80 adult *E. durans* bacteremia cases treated at our 2700-bed tertiary care hospital between January 1997 and December 2016. We compared the clinical characteristics and treatment outcomes of the adult patients with *E. durans* bacteremia (case group) with those of *E. faecalis* and *E. faecium* bacteremia cases (two control groups). The case and control groups were matched for sex, age, and date of onset of bacteremia. *E. durans* was responsible for 1.2% of all enterococcal bacteremia cases at our hospital. Of 80 cases, 39 (48.8%) had biliary tract infection and 18 (22.5%) had urinary tract infection. Community-onset bacteremia was more frequent in the case group than in the control groups (56.2% vs. 35.0% vs. 21.2%, $p < 0.01$). Infective endocarditis tended to be more common in the *E. durans* group (7.5% vs. 1.2% vs. 1.2%, $p = 0.05$). 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%). The case 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 the control groups. *E. durans* bacteremia mainly originates from the biliary or urinary tract and is associated with a lower risk of mortality.

Keywords *Enterococcus durans* · *Enterococcus faecalis* · *Enterococcus faecium* · Bacteremia · Mortality

Introduction

Enterococcus species represent part of the normal flora in the gastrointestinal tracts of humans and other animals. These organisms are major causative pathogens of community-acquired endocarditis and intraabdominal infection. Owing to their high viability in the nosocomial environment and ability to colonize surrounding medical devices, enterococci are among the leading causes of nosocomial infection, especially in immunocompromised patients [1, 2]. Of the more than 30 known *Enterococcus* species, *E. faecalis* and *E. faecium* are the most frequently isolated in clinical specimens, and the vast majority of the clinical and microbiological studies of enterococcal infections have thus focused on these organisms.

E. durans, formerly known as *Streptococcus durans*, was first described in the 1930s [3] and is commonly found in the intestinal tract and in the dairy products of domestic animals. It has been suggested that *E. durans* is associated with encephalomalacia and diarrhea in livestock [4–6]. Unlike *E. faecalis* or *E. faecium*, *E. durans* is not a common pathogen in humans [7]. A Taiwanese group reported that among 1887 cases of enterococcal bacteremia over 9 years, only 2 cases of *E. durans* bacteremia were identified [8]. This may be due to the low carriage rate of *E. durans* among the microflora of the human intestine (2.5–6.7%) [9, 10], and the low virulence of this bacteria inferred from its insufficient insecticidal activity against moth larvae [11]. In this context, there are few case

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reports on *E. durans* bacteremia [12–16], and no prior studies on the clinical characteristics or treatment outcomes of *E. durans* bacteremia series have been published. We therefore reviewed our own experiences with 80 consecutive episodes of *E. durans* bacteremia over 20 years.

Methods

This retrospective matched case-control study was performed at the Asan Medical Center (Seoul, Republic of Korea), a 2700-bed tertiary care teaching hospital that includes 170 intensive care unit beds. From January 1997 to December 2016, 80 adult patients (≥ 16 years) with positive blood cultures for *E. durans* had been treated at our hospital. These cases were identified by reviewing the computerized database from our clinical microbiology units and were categorized as our study case group. Infectious disease specialists reviewed the electronic medical record of each patient and collected data on the patient demographics, the underlying disease or condition, severity of illness at the time of bacteremia, portal of entry, co-infecting microorganism, antibiogram findings, prior antimicrobial use, prescribed antimicrobials, and clinical outcomes. These results were compared with those from two control groups of patients with *E. faecalis* and *E. faecium* bacteremia. The case and control groups were 1:1:1 matched for sex, age (difference not exceeding ± 5 years), and date of onset of bacteremia (within 1 month).

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, Franklin Lakes, NJ). *Enterococcus* species were identified based on their tolerance to 6.5% NaCl, bile-esculin hydrolysis, and growth rate at 45 °C. *E. durans* was identified based on a positive arginine dihydrolase test, and fermentation test failure with arabinose, mannitol, sucrose, methyl-α-D-glucopyranoside, sorbitol, and raffinose [17]. The species of organism and its susceptibility to antimicrobial agents were determined using the Vitek (bioMérieux, Marcy-l'Etoile, France) or MicroScan (Dade Behring, Deerfield, IL) system, based on standard criteria of the Clinical and Laboratory Standards Institute (CLSI) [18]. 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 *E. faecium*, or a single blood culture yielding these bacteria together with a clinically apparent culture-positive source of infection. The date of onset of bacteremia was defined as the date on which the blood sample was obtained for the first positive culture result. The origin of bacteremia was categorized as community-onset or hospital-acquired, as previously described [19]. Community-onset bacteremia was subgrouped into community-acquired or healthcare-associated bacteremia. Underlying comorbidities were classified as "rapidly fatal," "ultimately fatal," or "nonfatal," in accordance with the McCabe and Jackson criteria [20]. Bacteremia without sepsis, sepsis, and septic shock were defined in accordance with the most recent international consensus (Sepsis-3) [21]. A localized infection was regarded as the portal of entry if microbiologically and clinically documented. Prior antimicrobial use was defined as receipt of antimicrobials for more than 24 h during the previous month. Outcomes were evaluated at the time of hospital discharge. Death was considered to have been related to bacteremia if the patient died within 14 days of onset with no other identifiable cause.

Statistical analysis

Statistical analysis was performed using the χ^2 test or 2-tailed Fisher's exact test for binary variables. One-way analysis of variance or Kruskal-Wallis test was used for continuously scaled variables. When the overall statistical analysis result among the three groups was significant (p value of < 0.05), a *post hoc* analysis with the Bonferroni correction for multiple comparisons (*E. durans* vs. *E. faecalis* and *E. faecium*, respectively) was performed, and a p value of < 0.025 was considered to indicate statistical significance. Continuous data were expressed as a mean ± standard deviation (SD) or as the median and interquartile range (IQR). 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) determined by univariate analysis. A 2-tailed p value of < 0.05 was considered to indicate statistical significance. All tests were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY).

Results

Study population

Between January 1997 and December 2016 at the Asan Medical Center, 82,158 blood cultures tested positive for bacteria. *Enterococcus* species, including in combination with other organisms, were present in 7438 (9.1%) of these cultures, and the incidence of *Enterococcus* bacteremia was 3.9

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[a]
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[b]						
Solid cancer	39 (48.8)	39 (48.8)	36 (45.0)	1.00	0.64	0.86
Hepatobiliary and pancreatic	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**[f]	**< 0.01**
COPD	2 (2.5)	2 (2.5)	3 (3.8)	1.00	1.00	1.00
ESRD	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[b]						
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[c]	10 (12.5)	6 (7.5)	21 (26.2)	0.29	0.03	**0.003**
Recent surgery[c]	9 (11.2)	16 (20.0)	16 (20.0)	0.13	0.13	0.24
Leukopenia[d]	8 (10.0)	8 (10.0)	17 (21.2)	1.00	0.05	0.06
Immunosuppressive therapy[e]	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[c]	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 antimicrobial use[c]	26 (32.5)	52 (65.0)	71 (88.8)	**< 0.01**	**< 0.01**	**< 0.01**

Data represent the numbers (%) of patients, unless otherwise indicated. *SD*, standard deviation; *COPD*, chronic obstructive pulmonary disease; *ESRD*, end-stage renal disease on dialysis; *ICU*, intensive care unit

[a] Overall p values are for the overall comparison among the three groups

[b] Some patients had more than one underlying disease or risk factor

[c] Within the previous month

[d] Leukocyte count, < 4000 leukocytes/mm^3

[e] Receipt of steroid therapy for > 10 days or use of other immunosuppressant for > 1 week within the previous 1 month

[f] Statistically significant p values are presented in boldface

cases per 1000 admissions. Of the 7438 *Enterococcus*-positive cultures, 4598 (61.8%) were identified as *E. faecium* and 1981 (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%) as an undetermined *Enterococcus* species. The incidence of bacteremia due to *E. durans* was 0.05 cases per 1000 admissions. Among the 91 cultures of *E. durans* bacteremia from 83 patients, 8

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[a]
Initial manifestation within 24 h						
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**[b]	**< 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 ($\times 10^3/mm^3$)	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**

Data are the numbers (%) of patients, unless otherwise indicated. *IQR*, interquartile range; *WBC*, white blood cell; *CRP*, C-reactive protein

[a] Overall *p* values are for the overall comparison among the three groups

[b] Statistically significant *p* values are presented in boldface

cultures collected from same patients were excluded. In addition, 3 patients who were under the age of 16 were also excluded from further analysis. A total of 80 cultures of *E. durans* from 80 adult patients were finally included as our study case group. As control groups, 80 cultures each were selected from 1981 cultures of *E. faecalis* and 4598 cultures of *E. faecium*.

Demographic data and underlying disease/condition

The demographic characteristics and underlying disease/conditions of the 80 study patients with *E. durans* bacteremia are provided in Table 1. Forty-one of the case group patients (51.2%) were men, and the mean age was 64.3 years. All patients had underlying illnesses, the most common being a solid cancer (48.8%), followed by biliary disease (46.2%). The overall incidence of underlying illnesses among the three groups was not significantly different other than hematologic malignancy between patients with *E. durans* and those with *E. faecium* bacteremia (2.5% vs. 20.0%, $p < 0.01$). Forty-seven patients (58.8%) with *E. durans* bacteremia had the nonfatal disease which was a significantly higher frequency than the control groups ($p < 0.01$). Regarding the 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 1 month, 8 each (10.0%) had leukopenia or received immunosuppressive therapy within 1 month, 7 each (8.8%) had a central venous catheter or an indwelling urinary catheter in place, and 5 (6.2%) had prior ICU care within 1 month. Patients with *E. durans* bacteremia were less likely to have a prior history of hospital admission within 6 months ($p < 0.01$), history of chemotherapy ($p = 0.003$) or ICU care ($p < 0.01$) within 1 month, mechanical ventilation ($p < 0.01$), CVC ($p < 0.01$), and urinary catheter ($p < 0.01$) compared with the control groups. *E. durans* bacteremia was also associated with community-onset bacteremia more frequently than the control groups ($p < 0.01$). In addition, fewer patients with *E. durans* bacteremia received

Table 3 Antimicrobial susceptibility of *Enterococcus* species isolated in the study patients

Antimicrobial[a]	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[b]
Penicillin	66/76 (86.8)	71/79 (89.9)	16/76 (21.1)	0.56	**< 0.01**[e]	**< 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[c]	66/73 (90.4)	50/75 (66.7)	38/78 (48.7)	**< 0.01**	**< 0.01**	**< 0.01**
Streptomycin[d]	69/73 (94.5)	57/75 (76.0)	65/77 (84.4)	**< 0.01**	0.05	**< 0.01**

Data are proportions (%) of patients

[a] Not all isolates underwent susceptibility testing

[b] Overall p values are for the overall comparison among the three groups

[c] Isolates did not show high-level resistance to gentamicin

[d] Isolates did not show high-level resistance to streptomycin

[e] Statistically significant p values are presented in boldface

antimicrobial therapy within 1 month compared with the control groups ($p < 0.01$).

Clinical and laboratory manifestations

The recorded clinical and laboratory manifestations of our study patients are listed in Table 2. In the *E. durans* group, clinical sepsis at the time of bacteremia was not evident in 59 (73.8%) of the patients, 14 (17.5%) cases met the criteria for sepsis, and 7 (8.8%) individuals presented with septic shock. There were no significant differences in sepsis grades according to the type of enterococcal bacteremia. Four (5.0%) patients of the *E. durans* group had a Pitt bacteremia score ≥ 4 points, which was a significantly lower proportion than in the control groups ($p < 0.01$). The most common portal of entry of *E. durans* bacteremia was biliary tract (48.8%), followed by the urinary tract (22.5%), unknown focus (12.5%), and gastrointestinal tract (8.8%). Urinary tract infection was more frequent in the *E. durans* group than in the control groups ($p < 0.01$). There were no catheter-related infections or soft tissue/skin infections in the *E. durans* group. Infective endocarditis was diagnosed in six of patients (7.5%) with *E. durans* bacteremia. The incidence of infective endocarditis was marginally more frequent in *E. durans* bacteremia than other enterococcal bacteremia ($p = 0.05$). Concomitant bacteremia was present in 24 (30.0%) of the *E. durans* bacteremia cases, and the most frequently observed organisms were gram-negative bacilli, among which *Escherichia coli* was the most commonly identified. The presence of concomitant bacteremia was not related with the initial manifestation of *E. durans* bacteremia ($p > 0.05$; data not shown). More detailed information on concomitant bacteremia is presented in Table S1. Significant differences in the white blood cell count ($p = 0.04$) and procalcitonin ($p = 0.04$) levels were detected among the study groups, but not in the *post hoc* analysis between these three groups.

Antimicrobial susceptibility

Antimicrobial susceptibility data for *Enterococcus* species are presented in Table 3. 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%). *E. durans* isolates showed a higher rate of susceptibility to most tested antimicrobials than other enterococcal isolates, but susceptibility to ampicillin was less common than with *E. faecalis* isolates (88.2% vs. 98.7%, $p < 0.01$).

Antimicrobial therapy

Antimicrobial treatment regimens are listed in Table 4. Forty-seven patients (58.8%) with *E. durans* bacteremia received appropriate therapy. Monotherapy was used in 42 cases, with ampicillin being the most common antimicrobial (23/47, 48.9%). Appropriate combination antimicrobial therapy was

Table 4 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[a]
Received appropriate therapy[b]	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**[c]	**< 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**

Data are numbers (%) of patients or proportions (%) of patients. *IQR* interquartile range

[a] Overall *p* values are for the overall comparison among the three groups

[b] Some patients received > 1 antimicrobial

[c] Statistically significant *p* values are presented in boldface

administered to 7 of the *E. durans* bacteremia cases. Among these 7 patients, 4 (8.5%) received ampicillin with gentamicin, 2 (4.3%) received penicillin with gentamicin, and 1 (2.1%) received vancomycin with gentamicin. The proportion of patients with *E. durans* bacteremia who received appropriate antimicrobial therapy tended to be lower than that with other enterococcal bacteremia (58.8% vs. 67.5% vs. 75.0%, $p = 0.09$, versus *E. faecalis* and *E. faecium*, respectively). The median duration of adequate therapy was 11 days (IQR, 4–18 days).

Outcomes

The clinical outcomes in our current patient series are summarized in Table 4. The all-cause 60-day mortality rate of patients with *E. durans* bacteremia was 20.0%, with only two deaths (2.5%) considered to be related to the bacteremia (these two patients had polymicrobial bacteremia with other gram-negative bacilli). The all-cause 60-day mortality (20.0% vs. 31.2% vs. 42.5%, $p < 0.01$) and bacteremia-related mortality (2.5% vs. 16.2% vs. 18.8%, $p < 0.01$) of the *E. durans* bacteremia were lower than those of *E. faecalis* or *E. faecium* bacteremia. Figure 1 presents Kaplan-Meier curves for the survival outcomes in the three groups.

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

By univariate analysis, we found that a prior hospital admission within 6 months, an underlying solid cancer, ultimately or rapidly fatal underlying disease, septic shock, and a Pitt bacteremia score ≥ 4 were related to the 60-day mortality of *E. durans* bacteremia. Urinary tract infection was associated with lower mortality. Using multivariate analysis, we found that an ultimately or rapidly fatal underlying disease and a Pitt bacteremia score ≥ 4 were independent risk factors for 60-day mortality (Table 5).

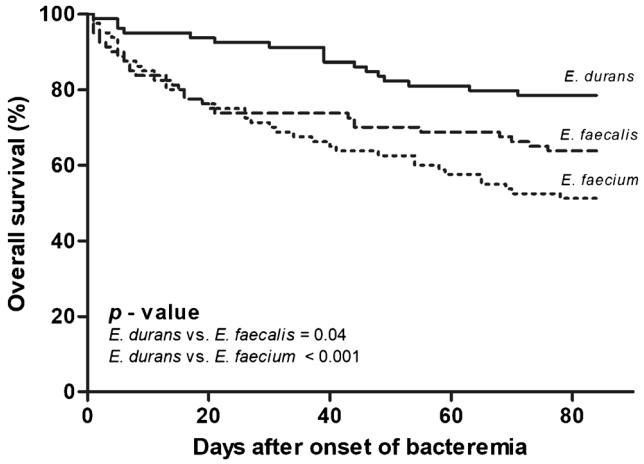

Fig. 1 Kaplan-Meier survival curves for the patients with enterococcal bacteremia

Discussion

We have here investigated the clinical characteristics and treatment outcomes of *E. durans* bacteremia. To our knowledge, our current study is the first to analyze an *E. durans* bacteremia series. In our analyses, *E. durans* was found to cause only 1.2% of the total enterococcal bacteremia cases at our hospital and to mainly originate from a biliary or urinary tract infection. The mortality rate was also found to be lower with *E. durans* than with other types of enterococcal bacteremia.

Enterococci are generally considered to account for approximately 10% of all bacteremia cases [22–24], and our result was consistent with this (9.1%). However, we noted a much higher proportion of *E. durans* bacteremia among the total enterococcal bacteremia at our institution than reported in previous studies (1.2% vs. 0–0.2%) [8, 24, 25]. Different patient populations or more comprehensive microbiological diagnostic techniques in the laboratory may have contributed to this difference.

E. durans bacteremia was found in our present analysis to be most commonly related to biliary tract infection (48.8%). We previously reported that the biliary tract is a common route of *E. gallinarum*/*casseliflavus* and *E. avium* bacteremia [26, 27]. A prior Taiwanese study on non-*faecalis*, non-*faecium* enterococcal bacteremia, most of which were *E. casseliflavus*, *E. gallinarum*, and *E. avium*, also described a high proportion of biliary tract infections (32.7%–55.9%) [8]. The high proportion of biliary tract infection as a portal of *E. durans* bacteremia in this study may reflect distinct characteristics of the hospital where the study was conducted where many patients with hepatobiliary diseases are hospitalized.

Although a smaller number of patients with *E. durans* bacteremia had an indwelling urinary catheter, urinary tract infection (UTI) was the second most common cause (22.5%) of *E. durans* bacteremia and was more frequently associated with *E. durans* bacteremia than with *E. faecalis* or *E. faecium* bacteremia. When we compared our findings with those of other studies on non-*faecalis*, non-*faecium* enterococcal bacteremia [8, 27], we detected a higher proportion of UTI cases among the sources of bacteremia (22.5% vs. 1.9–4.4%). The biofilm-forming mechanism of *E. faecalis* is well known to be linked to tropism for the human urinary tract [28, 29], but the factors involved in the biofilm formation of *E. durans* are still unknown. Our current data suggest that the potential of *E. durans* to trigger a UTI may surpass that of *E. faecalis*.

Another notable finding in our present study is that the incidence of infective endocarditis in *E. durans* bacteremia tended to be higher than that in other enterococcal bacteremia. The complex interactions between various factors appear to contribute to the capability of biofilm formation by *E. faecalis* [30, 31]. A recent study has reported that *E. durans* could also

Table 5 Multivariate analysis of risk factors for 60-day mortality in *E. durans* bacteremia

Variable	Univariate analysis OR (95% CI)	*p* value	Multivariate analysis 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
Solid cancer[a]	4.11 (1.20–14.14)	0.02		
Ultimately or rapidly fatal disease	6.14 (1.77–21.36)	< 0.01	5.30 (1.29–21.72)	0.02
Septic shock[a]	6.78 (1.34–34.24)	0.03		
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 fitted the data well in terms of discrimination (C-statistic = 0.84) and calibration (Hosmer-Lemeshow goodness of fit statistic = 0.34; p = 0.95)

[a] 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; *NA*, not available

possess *esp*, *fsrA*, *fsrC*, *gelE*, and other genes that encode proteins involved in the biofilm formation of *E. faecalis* [32]. These findings suggest that infective endocarditis should be considered when *E. durans* bacteremia is encountered. There is a need for further molecular and clinical investigation in this regard.

Patients with *E. durans* bacteremia showed a lower risk of mortality compared with those with *E. faecalis* or *E. faecium* bacteremia, and none of the patients with monomicrobial *E. durans* bacteremia died. There are a number of possible explanations for this. First, it has been suggested previously that the intrinsic virulence of *E. durans* may be lower compared with *E. faecalis* [11]. Several factors such as hemolysin, gelatinase, and enterococcal surface protein have been suggested to induce the virulence of *E. faecalis* [33, 34]. However, there are no detailed studies on virulence factors of *E. durans*. Second, the lower incidence of antimicrobial resistance among *E. durans* isolates could result in a lower mortality. Previous meta-analyses on enterococcal bacteremia have demonstrated a significant association between vancomycin resistance and mortality [35–37]. Finally, the relatively high proportion of UTI among our *E. durans* bacteremia cases may have influenced this outcome. Approximately a quarter of the *E. durans* bacteremia cases in our current series (22.5%) was related with UTI, and none of these patients died.

This study has several limitations of note. First, our retrospective data collection from a single tertiary center limits the generalization of our results. Second, improvements in patient care over the 20 years may have influenced the mortality. However, we found no significant differences in the annual mortality rate of each group. It should be mentioned also that molecular typing of the isolates and susceptibility testing for teicoplanin were not performed in the laboratory.

In summary, *E. durans* bacteremia accounts for a minor proportion of the total enterococcal bacteremia and mainly originates from a biliary tract or urinary tract infection. The mortality rates among patients with *E. durans* bacteremia are significantly lower than those with *E. faecalis* or *E. faecium* bacteremia.

Compliance with ethical standards This study was approved by the Asan Medical Center Institutional Review Board.

Conflict of interest The authors declare that they have no competing interests.

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