Infection (2019) 47:417–424
https://doi.org/10.1007/s15010-018-1260-z

ORIGINAL PAPER

Enterococcal bacteremia in febrile neutropenic children and adolescents with underlying malignancies, and clinical impact of vancomycin resistance

Kil-Seong Bae[1,2] · Ju Ae Shin[1] · Seong koo Kim[1,3] · Seung Beom Han[1,2] · Jae Wook Lee[1,3] · Dong-Gun Lee[2,3,4] · Nack-Gyun Chung[1,3] · Bin Cho[1,3] · Dae Chul Jeong[1,2] · Jin Han Kang[1,2]

Received: 28 August 2018 / Accepted: 15 December 2018 / Published online: 19 December 2018

Abstract

Purpose Enterococci are a common cause of bacteremia in immunocompromised patients. Although the increase of vancomycin-resistant enterococci (VRE) makes appropriate antibiotic therapy difficult, clinical characteristics of enterococcal bacteremia and the impact of VRE infection on outcomes have rarely been reported in immunocompromised children.

Methods We enrolled children and adolescents (< 19 years of age) with underlying malignancies who were diagnosed with enterococcal bacteremia during febrile neutropenia between 2010 and 2017. Medical records of the enrolled children were retrospectively reviewed to evaluate the clinical characteristics of enterococcal bacteremia and impact of VRE infection on outcomes.

Results Thirty-six episodes of enterococcal bacteremia were identified in 30 patients. VRE infection was identified in 11 episodes (30.6%); the 7- and 30-day mortalities were 27.8% and 44.4%, respectively. Acute lymphoblastic leukemia (50.0%) and acute myeloid leukemia (30.6%) were the most common underlying disorders. Three (8.3%) of the patients were in complete remission, and palliative and reinduction chemotherapies were administered in 47.2% and 36.1% of episodes, respectively. Empirical antibiotic therapy was appropriate in 64.0% of patients with vancomycin-susceptible enterococcal infection and in none of the VRE-infected patients ($p = 0.001$). However, the 30-day mortality was not significantly different between the two patient groups (44.0% vs. 45.5%, $p = 1.000$).

Conclusions Most episodes of enterococcal bacteremia occurred in advanced stages of underlying malignancies, and still showed high mortality. The prognosis seemed to be related to the underlying disease condition rather than vancomycin resistance of the isolated enterococci, although the number of enrolled patients was small.

Keywords Enterococcus · Vancomycin resistance · Neutropenia · Child

Introduction

Enterococcus species reside in the gastrointestinal (GI) tract of humans as normal flora [1]. These species have not been considered major human pathogens owing to their low virulence [1]; however, morbidity and mortality caused by enterococcal bacteremia have been reported since the 1980s [2, 3]. *Enterococcus* spp. cause invasive infection in immunocompromised patients, burn patients, patients with indwelling catheters, and neonates [1]. Most patients diagnosed with enterococcal bacteremia have underlying diseases, with hematologic/oncologic diseases comprising a large proportion of these [3–5]. *Enterococcus* spp. are the second most common Gram-positive bacterial pathogen causing bacteremia in patients with hematologic/oncologic

✉ Seung Beom Han
beomsid@catholic.ac.kr

1 Department of Pediatrics, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea

2 The Vaccine Bio Research Institute, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

3 The Catholic Hematology Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

4 Division of Infectious Diseases, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

diseases, following *Staphylococcus* spp. [6]; a total 6.0% of bacteremia cases diagnosed in febrile neutropenic children and adolescents at our hospital are caused by enterococci [7].

Enterococcus spp. are intrinsically resistant to commonly used antibiotics such as cephalosporins and can acquire resistance to ampicillin and high-level resistance to aminoglycoside, although most strains of *Enterococcus faecalis* remain susceptible to ampicillin [1]. Furthermore, an increase in vancomycin-resistant enterococci (VRE) has made appropriate antibiotic therapy for invasive enterococcal infection more difficult. Hematologic/oncologic diseases are considered a risk factor for VRE colonization and infection [8, 9]. Immunocompromised patients with these diseases usually have additional risk factors for VRE colonization and infection, such as use of vancomycin, anti-pseudomonal cephalosporins, and metronidazole; central venous catheter; anti-cancer chemotherapy; neutropenia; GI dysfunction; and prolonged hospitalization [10–15]. Therefore, the early prediction and early antibiotic treatment of VRE infection in patients with hematologic/oncologic diseases seem to be important. However, the prognostic impact of vancomycin resistance in patients with enterococcal bacteremia has not been established. Some reports have showed significantly higher mortality in patients with VRE infection than in patients infected with vancomycin-susceptible enterococci (VSE) [16–19]. However, other studies have reported higher mortality in patients with VRE infection than VSE infection, arising from the severity of underlying diseases rather than vancomycin resistance [8, 13, 15, 20–22]. This discrepancy regarding the impact of vancomycin resistance in previous studies may have resulted from differences in the type and severity of underlying diseases, age of enrolled patients, and antibiotics administered for VRE infection; therefore, the prognostic impact of VRE infection in specific patient groups should be determined separately. In immunocompromised children and adolescents, however, there were very few reports on enterococcal bacteremia [23] or on the efficacy of newly approved antibiotics for VRE infection such as linezolid, quinupristin/dalfopristin, and daptomycin [24]. This study was performed to evaluate the clinical characteristics and prognosis of febrile neutropenic children and adolescents with underlying malignancies in whom enterococcal bacteremia was diagnosed.

Patients and methods

Study design and patients

For this study, we considered all children and adolescents aged less than 19 years who were admitted to the Department of Pediatrics of Seoul St. Mary's Hospital, College of Medicine, the Catholic University of Korea in Seoul, Republic of Korea between January 2010 and December 2017. Among them, we enrolled patients with underlying malignancies in whom enterococcal bacteremia was diagnosed during neutropenic fever (NF). Medical records of the enrolled patients were retrospectively reviewed. Patients' age and sex were collected as demographic data. The following clinical data were also collected: type and remission state of the underlying malignancy, anti-cancer therapy for the underlying malignancy administered prior to enterococcal bacteremia, duration of fever and neutropenia, local symptoms and signs consistent with focal infection, polymicrobial infection, C-reactive protein (CRP) levels during the diagnosis of enterococcal bacteremia, appropriateness of empirical antibiotic therapy, time of administration of appropriate antibiotic agents, and development of complications or death during enterococcal bacteremia. As microbiological data, we reviewed antibiotic susceptibilities of the isolated enterococci to penicillin, ampicillin, imipenem, gentamicin, erythromycin, tigecycline, teicoplanin, vancomycin, linezolid, and quinupristin/dalfopristin. The enrolled patients were divided into VSE and VRE groups, based on susceptibility of the isolated strain to vancomycin. The investigated data were compared between the two groups. In addition, the enrolled patients were also divided into surviving and deceased groups, based on mortality within 30 days after the development of enterococcal bacteremia, and the data were compared between the two groups.

In our hospital, antibiotic therapy for patients with NF has been administered in accordance with the recommendations of the "Guidelines for the Empirical Therapy of Neutropenic Fever Patients based on Literature in Korea" [25]. Piperacillin/tazobactam and isepamicin were empirically given for the first episode of NF, and meropenem was given if NF persisted for more than 2–3 days without a definite cause. Glycopeptide has been administered for selected conditions in which Gram-positive bacterial infection is identified or expected, in accordance with the above guideline [25]. The administered glycopeptide was teicoplanin rather than vancomycin in most instances, and administration was stopped in 3–5 days if there is no evidence of Gram-positive bacterial infection. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, under a waiver of the requirement for obtaining informed consent (Approval number: KC18RESI0231).

Microbiological tests

For culture studies, blood samples were collected aseptically from a peripheral vein and each lumen of a central venous catheter. A volume of 1–3 mL from each blood sample was immediately inoculated into a culture bottle (BD BACTEC™ Peds Plus Culture Vial, Becton Dickinson,

Sparks, MD, USA), and an automated system (BACTEC™ FX, Becton Dickinson) was used for culturing pathogens. The identification of enterococcal growth was performed using the VITEK®2 automated system (bioMériux, Hazelwood, MO, USA), and antibiotic susceptibility was determined using a VITEK®2 antibiotic susceptibility test card (bioMériux). The results reported as "intermediate" were considered "resistant" in this study.

Definitions

NF was defined based on the aforementioned Korean guideline [25]: neutropenia was defined as an absolute neutrophil count < 500/mm^3 or expected count < 500/mm^3 within 2–3 days, and fever was defined as tympanic membrane temperature > 38.0 °C or axillary temperature > 37.5 °C. Enterococcal bacteremia was defined as growth of *Enterococcus* spp. from at least one of the obtained blood samples. Recurrent enterococcal bacteremia was considered a separate episode if *Enterococcus* spp. were re-grown after three consecutive blood cultures were negative for *Enterococcus* spp. that were performed with an interval of 1 week or more during the previous episode. Empirical antibiotic therapy was considered appropriate if any antibiotics to which the isolated enterococci were susceptible had been administered within 48 h of bacteremia. Polymicrobial infection was defined when any other bacterial, viral, or fungal infections were diagnosed during the episode of enterococcal bacteremia. Complications consisted of oxygen therapy, shock, and renal and hepatic dysfunction. Shock was defined when the patient received volume expansion or inotropic agents to maintain normal blood pressure [26]. Renal dysfunction was defined as an increase in serum creatinine level to more than twice the level prior to enterococcal bacteremia [27]. Hepatic dysfunction was defined as an increase in serum aspartate or alanine transaminase levels to more than twice the levels prior to enterococcal bacteremia, with serum total bilirubin level ≥ 2.0 mg/dL and prothrombin time-international normalized ratio ≥ 1.5 [28]. Crude mortality included deaths from any cause occurring within 30 days after the onset of enterococcal bacteremia. Mortality attributable to enterococcal bacteremia could not be determined because enterococcal bacteremia usually occurs in patients with severe underlying disease and complications that can lead to death.

Statistical analysis

Categorical and continuous factors were compared using a Chi square test and Mann–Whitney test, respectively, for comparisons between the VSE and VRE groups and between the surviving and deceased groups. The annual frequency of VRE infection was compared using a linear by linear association test. Multivariate analysis using a binary logistic regression test was performed for statistically significant factors derived from a univariate analysis to determine factors related to mortality. The SPSS 21 program (IBM Corporation, Armonk, NY, USA) was used for statistical analyses, and statistical significance was defined as a p value < 0.05.

Results

Clinical characteristics of enterococcal bacteremia

During the study period, a total of 36 episodes of enterococcal bacteremia were diagnosed in 30 febrile neutropenic children and adolescents with underlying malignancies; of these, 21 (58.3%) episodes occurred in males. The median age of enrolled patients was 10 years (range 1–17). Thirty-four (94.4%) bacteremia episodes were caused by *Enterococcus faecium*, and one (2.8%) episode each was caused by *Enterococcus gallinarum* and *Enterococcus avium*, respectively. Two patients experienced two episodes of enterococcal bacteremia and the other two patients experienced three episodes. Twenty-five (69.4%) isolated strains of *Enterococcus* spp. were VSE, and 11 (30.6%), including one isolate of vancomycin-intermediate *E. gallinarum*, were VRE (Table 1). Among the VSE, one isolate of *E. faecium* that was susceptible to vancomycin and resistant to teicoplanin was identified in one patient. He received empirical teicoplanin therapy and died the day after the occurrence of enterococcal bacteremia. Among the VRE, one isolate of *E. faecium* that was susceptible to teicoplanin and one isolate of *E. gallinarum* that was intermediate to vancomycin and susceptible to teicoplanin were identified in each patient. The annual frequency of VRE was between 14.3% and 80.0%, showing a significantly decreasing trend year by year ($p = 0.027$) (Fig. 1). Acute lymphoblastic leukemia (50.0%) and acute myeloid leukemia (30.6%) were the most common underlying malignancies. Only three (8.3%) underlying malignancies were in a state of complete remission/response. Accordingly, palliative (47.2%) and reinduction chemotherapies (36.1%) were frequently administered preceding enterococcal bacteremia. Local symptoms and signs accompanied by enterococcal bacteremia were observed in 33 (91.7%) episodes, with GI symptoms and signs (63.9%) as the most common. Thirty-three (91.7%) episodes of enterococcal bacteremia occurred during antibiotic administration, and 10 (27.8%) episodes occurred during glycopeptide administration. Antibiotic therapy had been initiated due to previously unexplained NF in 20 (60.6%) episodes and previously diagnosed bacteremia in 13 (39.4%) episodes. Previous bacteremia persisted until the occurrence of enterococcal bacteremia in only one episode.

Five (13.9%) patients (three in the VSE group, two in the VRE group) died before the administration of appropriate

Table 1 Comparison of vancomycin-susceptible enterococci (VSE) and vancomycin-resistant enterococci (VRE) groups

Factor	VSE group ($n=25$)	VRE group ($n=11$)	p value
Sex, male	12 (48.0)	9 (81.8)	0.077
Age, years, median (range)	10 (1–17)	9 (1–16)	0.520
Enterococcus species isolated			
Enterococcus faecium	24 (96.0)	10 (90.9)	0.275
Enterococcus avium	1 (4.0)	0 (0.0)	
Enterococcus gallinarum	0 (0.0)	1 (9.1)	
Underlying malignancy			
Acute lymphoblastic leukemia	13 (52.0)	5 (45.5)	0.327
Acute myeloid leukemia	7 (28.0)	4 (36.4)	
Chronic myeloid leukemia	1 (4.0)	1 (9.1)	
Lymphoma	0 (0.0)	1 (9.1)	
Solid tumors	4 (16.0)	0 (0.0)	
Remission state of underlying malignancy			
Complete remission/response	1 (4.0)	2 (18.2)	0.216
Non-complete remission/response	24 (96.0)	9 (81.8)	
Anti-cancer therapy preceding enterococcal bacteremia			
Induction chemotherapy	1 (4.0)	0 (0.0)	0.613
Reinduction chemotherapy	10 (40.0)	3 (27.3)	
Consolidation chemotherapy	1 (4.0)	1 (9.1)	
Maintenance chemotherapy	0 (0.0)	1 (9.1)	
Palliative chemotherapy	11 (44.0)	6 (54.5)	
Autologous hematopoietic cell transplantation	1 (4.0)	0 (0.0)	
Allogeneic hematopoietic cell transplantation	1 (4.0)	0 (0.0)	
Central venous catheter			
Hickman catheter	16 (64.0)	9 (81.8)	0.439
Subcutaneously implanted chemoport	9 (36.0)	2 (18.2)	
Neutropenia duration, days, median (range)			
Before bacteremia	16 (1–98)	26 (4–80)	0.839
Total duration	37 (2-106)	49 (7–88)	0.477
Polymicrobial infection	12 (48.0)	2 (18.2)	0.142
Breakthrough infection			
During any type of antibiotic therapy	22 (88.0)	11 (100.0)	0.538
During glycopeptide therapy	4 (16.0)	6 (54.5)	0.039
Local symptoms and signs			
Gastrointestinal	14 (56.0)	9 (81.8)	0.259
Respiratory	12 (48.0)	4 (36.4)	0.718
Urological	1 (4.0)	0 (0.0)	1.000
Cutaneous	6 (24.0)	3 (27.3)	1.000
C-reactive protein level on the diagnosis of bacteremia[a]	9.12 (0.44–34.1)	16.63 (6.81–25.67)	0.072
Appropriateness of empirical antibiotic therapy[b]	16 (64.0)	0 (0.0)	0.001
Time of appropriate antibiotic therapy after bacteremia days, median (range)[b]	0 (0–3)	3 (2–4)	<0.001
Complications			
Hypoxia	8 (32.0)	5 (45.5)	0.475
Shock	4 (16.0)	0 (0.0)	0.290
Renal dysfunction	4 (16.0)	0 (0.0)	0.290
Hepatic dysfunction	3 (12.0)	0 (0.0)	0.538
Mortality			
7-Day mortality	7 (28.0)	3 (27.3)	1.000
30-Day mortality	11 (44.0)	5 (45.5)	1.000

Data are presented as number (%), unless otherwise indicated

[a]The C-reactive protein level was not measured in one patient in the VSE group

[b]Six patients (four in the VSE group, two in the VRE group) who were not administered appropriate antibiotics were excluded

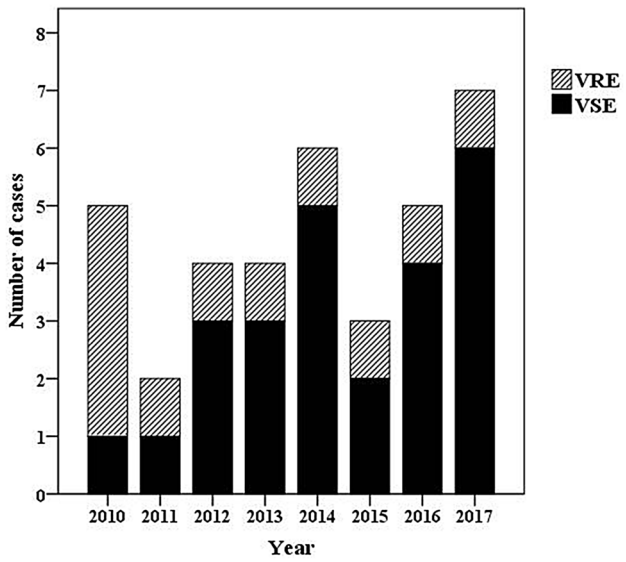

Fig. 1 Annual distribution of vancomycin-susceptible enterococci (VSE) and vancomycin-resistant enterococci (VRE)

antibiotics. In the remaining 31 episodes, empirical antibiotic therapy was appropriate in 16 (51.6%) episodes; the appropriate antibiotic agent was administered a median of 1 day (range 0–4) after the development of enterococcal bacteremia. A total of 10 (27.8%) and 16 (44.4%) patients died within 7 and 30 days after the development of enterococcal bacteremia, respectively. One patient who had never received appropriate antibiotic therapy survived with cefepime administration for VSE bacteremia.

All isolated *Enterococcus* spp. were resistant to ampicillin, and high-level resistance to gentamicin was identified in 22 (62.9%) of 35 tested isolates. All isolates were susceptible to linezolid, and one (2.8%) isolate each was resistant to quinupristin/dalfopristin and tigecycline.

Clinical outcomes of patients in the VRE group

Two (18.2%) patients in the VRE group died before the administration of appropriate antibiotics 2 and 5 days after the development of bacteremia, respectively. The remaining nine (81.8%) patients received linezolid therapy. In five (55.6%) patients, bacteremia resolved after linezolid administration; four (80.0%) patients, including one with vancomycin-resistant, teicoplanin-susceptible *E. faecium* infection survived, and one (20.0%) patient died. Three (33.3%) patients had persistent enterococcal bacteremia despite linezolid administration: one of these patients died 9 days after development of bacteremia, another patient survived for more than 30 days after bacteremia, and the third cleared bacteremia after administration of quinupristin/dalfopristin and eventually survived. The remaining one (11.1%) patient, in whom vancomycin-intermediate, teicoplanin-susceptible *E. gallinarum* was isolated, died 5 days after developing bacteremia owing to uncontrolled, relapsed acute leukemia, although enterococcal bacteremia resolved during the teicoplanin therapy.

Comparison between VSE and VRE groups

Age, sex, the type and remission state of underlying malignancy and administered anti-cancer therapy for underlying diseases showed no significant difference between the VSE and VRE groups (Table 1). Empirical antibiotic therapy was appropriate more frequently in the VSE group than in the VRE group ($p < 0.001$); however, the frequencies of complications and death were not significantly different between the two groups.

Comparison between surviving and deceased groups

Patients in the deceased group were significantly older ($p = 0.021$), more likely to receive palliative chemotherapy ($p = 0.027$), and had higher CRP levels ($p < 0.001$) than those in the surviving group (Table 2). However, a multivariate analysis showed no significant factors for mortality. The frequency of VRE infection was not significantly different between the two groups.

Discussion

In this study, the clinical characteristics and outcome of enterococcal bacteremia in febrile neutropenic children and adolescents were investigated. Most cases of enterococcal bacteremia in patients with underlying malignancies occurred in a relapsed or refractory state of the underlying disease, in accordance with previous reports [9, 23]. Enterococcal bacteremia still showed high mortality, which seemed to be related to the disease state of the underlying malignancy rather than to VRE infection.

Nearly all *Enterococcus* spp. isolated in this study were *E. faecium*, and none was *E. faecalis*. Previous studies have showed a predominance of *E. faecium* in patients with hematologic/oncologic diseases [19, 20], or a different predominance of *E. faecium* and *E. faecalis* in different hospitals [5, 21]. Aminopenicillins, ureidopenicillins, penicillin G, and imipenem have an antibiotic effect on *Enterococcus* spp [1]. Among the 36 episodes of enterococcal bacteremia in this study, 33 occurred during antibiotic therapy with β-lactam agents: 16 during meropenem, 13 during piperacillin/tazobactam, and 4 during cefepime administration. All of the four patients administered cefepime and two of the three patients not receiving antibiotic therapy during the occurrence of enterococcal bacteremia had received meropenem

Table 2 Comparison between surviving and deceased groups

Factor	Surviving group ($n=20$)	Deceased group ($n=16$)	p value
Sex, male	10 (50.0)	11 (68.8)	0.257
Age, years, median (range)	6 (1–16)	14 (1–17)	0.021
Enterococcus species isolated			
Enterococcus faecium	19 (95.0)	15 (93.8)	0.359
Enterococcus avium	1 (5.0)	0 (0.0)	
Enterococcus gallinarum	0 (0.0)	1 (6.3)	
Vancomycin-resistant enterococci	6 (30.0)	5 (31.3)	1.000
Underlying malignancy			
Acute lymphoblastic leukemia	11 (55.0)	7 (43.8)	0.332
Acute myeloid leukemia	6 (30.0)	5 (31.3)	
Chronic myeloid leukemia	0 (0.0)	2 (12.5)	
Lymphoma	0 (0.0)	1 (6.3)	
Solid tumors	3 (15.0)	1 (6.3)	
Remission state of underlying malignancy			
Complete remission/response	3 (15.0)	0 (0.0)	0.238
Non-complete remission/response	17 (85.0)	16 (100.0)	
Anti-cancer therapy preceding enterococcal bacteremia			
Induction chemotherapy	1 (5.0)	0 (0.0)	0.027
Reinduction chemotherapy	10 (50.0)	3 (18.8)	
Consolidation chemotherapy	2 (10.0)	0 (0.0)	
Maintenance chemotherapy	1 (5.0)	0 (0.0)	
Palliative chemotherapy	4 (20.0)	13 (81.3)	
Autologous hematopoietic cell transplantation	1 (5.0)	0 (0.0)	
Allogeneic hematopoietic cell transplantation	1 (5.0)	0 (0.0)	
Neutropenia duration, days, median (range)			
Before bacteremia	16 (2–88)	32 (1–98)	0.158
Total duration	36 (8–105)	41 (2–106)	0.888
Polymicrobial infection	7 (35.0)	7 (43.8)	0.593
Breakthrough infection			
During any type of antibiotic therapy	17 (85.0)	16 (100.0)	0.238
During glycopeptide therapy	7 (35.0)	3 (18.8)	0.456
Local symptoms and signs			
Gastrointestinal	15 (75.0)	8 (50.0)	0.121
Respiratory	6 (30.0)	10 (62.5)	0.051
Urological	0 (0.0)	1 (6.3)	0.444
Cutaneous	6 (30.0)	3 (18.8)	0.700
C-reactive protein level on the diagnosis of bacteremia[a]	6.85 (0.4–25.67)	18.35 (6.81–34.10)	<0.001
Appropriateness of empirical antibiotic therapy[b]	11 (55.0)	5 (31.3)	0.154
Time of appropriate antibiotic therapy after bacteremia, days, median (range)[b]	1 (0–4)	2 (0–4)	0.966

Data are presented as number (%), unless otherwise indicated

[a]The C-reactive protein level was not measured in one patient in the deceased group

[b]Six patients (one in the surviving group and five in the deceased group) who were not administered appropriate antibiotics were excluded

or piperacillin/tazobactam within a month before the onset of enterococcal bacteremia. We assumed that previous recurrent administration of meropenem and piperacillin/tazobactam in patients with underlying malignancies inhibited colonization of *E. faecalis*, which is more susceptible to these antibiotics than *E. faecium* [1], and eventually reduced the onset of invasive infection by *E. faecalis*.

The frequency of VRE in this study was 30.6%, which is higher than the 15.3% reported in patients with NF in the 2000s [21]; however, this frequency is similar to the 38.0%

recently reported in pediatric allogeneic hematopoietic cell transplant recipients and 26.4% reported in adult patients with NF at our hospital [20, 29]. Fortunately, the frequency of VRE infection showed a decreasing trend each year in this study. This may reflect the appropriateness of the recent infection control strategies adopted at our hospital since the opening of the new hospital building in 2009 because the following infection control strategies for VRE have been kept in our hospital: early cessation of glycopeptide therapy in patients without evidence of Gram-positive bacterial infection, and contact isolation or cohorting of VRE-positive patients. Routine surveillance for VRE colonization has not been performed in our hospital. A recent study reported that active surveillance for VRE colonization did not prevent VRE bacteremia in patients with hematologic malignancies [30]. Therefore, infection control measures targeting VRE-colonized and VRE-infected patients, rather than extensive routine surveillance, should be emphasized.

Enterococcal bacteremia exhibits high mortality even in the era of VSE, with mortality of 26.3% reported in children with VSE bacteremia [4]. Enterococcal bacteremia in this study, including both VSE and VRE infections, had a mortality of 44.4%. The type of administered chemotherapy, rather than VRE infection, was associated with mortality in this study. Considering that most of the deceased patients received palliative chemotherapy, the prognosis of enterococcal bacteremia in immunocompromised patients seems to be related to the outcome of the underlying disease itself. Before the use of new antibiotics that are effective against VRE, such as linezolid, quinupristin/dalfopristin, daptomycin, and tigecycline, vancomycin resistance was reported as a significant risk factor for mortality in patients with enterococcal bacteremia [17–19]. However, in recent studies where the severity of the underlying disease was considered and adjusted for, no significant association between vancomycin resistance and mortality was reported [8, 15, 20, 22]. In addition, the appropriateness of empirical antibiotic therapy for VRE infection was not significantly related to mortality [20, 22, 31, 32]. Therefore, intensive therapy for uncontrolled underlying malignancies, beyond early identification of VRE infection and early administration of antibiotics targeting VRE bacteremia, should be emphasized to improve prognosis of patients with VRE infection. Fundamentally, preventive strategies for VRE infection and spread are of great importance because correction of the deteriorated or uncontrolled state of underlying malignancy observed in most patients with enterococcal bacteremia is often impossible.

This study had several limitations, including its retrospective study design. First, the number of enrolled patients was small. If we consider that the occurrence rate of enterococcal bacteremia in immunocompromised patients is lower in children than in adults [33, 34], future studies on enterococcal infection in pediatric patients should be performed as a multicenter study. Second, there was no isolate of *E. faecalis* in this study, as mentioned above; therefore, the clinical characteristics and prognosis of *E. faecalis* infection could not be evaluated. Because most cases of enterococcal bacteremia were caused by *E. faecalis* before the emergence of VRE [3, 4] and there were some reports of an unfavorable prognosis in *E. faecium* bacteremia in comparison with *E. faecalis* bacteremia [35, 36], the clinical impact of enterococcal bacteremia might be modified if cases of *E. faecalis* infection were included. Finally, genetic studies of the isolated enterococci and vancomycin-resistant genes were not performed in this study. Further genetic studies should be helpful to increase epidemiologic knowledge and to establish strategies for infection control and prevention.

In conclusion, enterococcal bacteremia usually occurred during the uncontrolled state of underlying disease in pediatric patients with malignancies. In the era of linezolid, enterococcal infection exhibited a grave outcome; however, the prognosis seemed to be related to the underlying disease condition rather than vancomycin resistance of the isolated enterococci. Therefore, effective preventive strategies for VRE infection in patients with uncontrolled underlying malignancies should be emphasized beyond efforts for early diagnosis of VRE infection and early administration of new antibiotic agents.

Acknowledgements This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, under a waiver of the requirement for obtaining informed consent (Approval number: KC18RESI0231).

Compliance with ethical standards

Conflict of interest There is no conflict of interest for all authors.

References

1. English BK, Shenep JL. Enterococcal and viridans streptococcal infections. In: Cherry JD, Harrison GJ, Kaplan SL, Steinbach WJ, Hotez PJ, editors. Feigin and Cherry's textbook of pediatric infectious diseases. 7th edn. Philadelphia: Elsvier; 2014. pp. 1170–97.
2. Hoge CW, Adams J, Buchanan B, Sears SD. Enterococcal bacteremia: to treat or not to treat, a reappraisal. Rev Infect Dis. 1991;13:600–5.
3. Maki DG, Agger WA. Enterococcal bacteremia: clinical features, the risk of endocarditis, and management. Medicine (Baltimore). 1988;67:248–69.
4. Christie C, Hammond J, Reising S, Evans-Patterson J. Clinical and molecular epidemiology of enterococcal bacteremia in a pediatric teaching hospital. J Pediatr. 1994;125:392–9.
5. Gray J, Marsh PJ, Stewart D, Pedler SJ. Enterococcal bacteraemia: a prospective study of 125 episodes. J Hosp Infect. 1994;27:179–86.
6. Mikulska M, Viscoli C, Orasch C, Livermore DM, Averbuch D, Cordonnier C, et al. Aetiology and resistance in bacteraemias

among adult and paediatric haematology and cancer patients. J Infect. 2014;68:321–31.
7. Lee JH, Kim SK, Kim SK, Han SB, Lee JW, Lee DG, et al. Increase in antibiotic-resistant gram-negative bacterial infections in febrile neutropenic children. Infect Chemother. 2016;48:181–9.
8. Shay DK, Maloney SA, Montecalvo M, Banerjee S, Wormser GP, Arduino MJ, et al. Epidemiology and mortality risk of vancomycin-resistant enterococcal bloodstream infections. J Infect Dis. 1995;172:993–1000.
9. Theilacker C, Jonas D, Huebner J, Bertz H, Kern WV. Outcomes of invasive infection due to vancomycin-resistant *Enterococcus faecium* during a recent outbreak. Infection. 2009;37:540–3.
10. Edmond MB, Ober JF, Weinbaum DL, Pfaller MA, Hwang T, Sanford MD, et al. Vancomycin-resistant *Enterococcus faecium* bacteremia: risk factors for infection. Clin Infect Dis. 1995;20:1126–33.
11. Singh-Naz N, Sleemi A, Pikis A, Patel KM, Campos JM. Vancomycin-resistant *Enterococcus faecium* colonization in children. J Clin Microbiol. 1999;37:413–6.
12. Tornieporth NG, Roberts RB, John J, Hafner A, Riley LW. Risk factors associated with vancomycin-resistant *Enterococcus faecium* infection or colonization in 145 matched case patients and control patients. Clin Infect Dis. 1996;23:767–72.
13. Lucas GM, Lechtzin N, Puryear DW, Yau LL, Flexner CW, Moore RD. Vancomycin-resistant and vancomycin-susceptible enterococcal bacteremia: comparison of clinical features and outcomes. Clin Infect Dis. 1998;26:1127–33.
14. Peel T, Cheng AC, Spelman T, Huysmans M, Spelman D. Differing risk factors for vancomycin-resistant and vancomycin-sensitive enterococcal bacteraemia. Clin Microbiol Infect. 2012;18:388–94.
15. Lautenbach E, Bilker WB, Brennan PJ. Enterococcal bacteremia: risk factors for vancomycin resistance and predictors of mortality. Infect Control Hosp Epidemiol. 1999;20:318–23.
16. Prematunge C, MacDougall C, Johnstone J, Adomako K, Lam F, Robertson J, et al. VRE and VSE bacteremia outcomes in the era of effective VRE Therapy: a systematic review and meta-analysis. Infect Control Hosp Epidemiol. 2016;37:26–35.
17. Vergis EN, Hayden MK, Chow JW, Snydman DR, Zervos MJ, Linden PK, et al. Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia. a prospective multicenter study. Ann Intern Med. 2001;135:484–92.
18. Bhavnani SM, Drake JA, Forrest A, Deinhart JA, Jones RN, Biedenbach DJ, et al. A nationwide, multicenter, case-control study comparing risk factors, treatment, and outcome for vancomycin-resistant and -susceptible enterococcal bacteremia. Diagn Microbiol Infect Dis. 2000;36:145–58.
19. DiazGranados CA, Jernigan JA. Impact of vancomycin resistance on mortality among patients with neutropenia and enterococcal bloodstream infection. J Infect Dis. 2005;191:588–95.
20. Cho SY, Lee DG, Choi SM, Kwon JC, Kim SH, Choi JK, et al. Impact of vancomycin resistance on mortality in neutropenic patients with enterococcal bloodstream infection: a retrospective study. BMC Infect Dis. 2013;13:504.
21. Todeschini G, Tecchio C, Borghero C, D'Emilio A, Pegoraro E, de Lalla F, et al. Association between *Enterococcus* bacteraemia and death in neutropenic patients with haematological malignancies. J Infect. 2006;53:266–73.
22. Han SH, Chin BS, Lee HS, Jeong SJ, Choi HK, Kim CO, et al. Vancomycin-resistant enterococci bacteremia: risk factors for mortality and influence of antimicrobial therapy on clinical outcome. J Infect. 2009;58:182–90.
23. Kosack A, Riedel E, Kiehn TE, Small TN, Wexler LH, Dunkel IJ. Vancomycin-resistant enterococcus in pediatric oncology patients: an analysis of potential consequences of colonization and infection. Pediatr Blood Cancer. 2009;52:300–2.
24. Tamma PD, Hsu AJ. Optimizing therapy for vancomycin-resistant enterococcal bacteremia in children. Curr Opin Infect Dis. 2014;27:517–27.
25. Lee DG, Kim SH, Kim SY, Kim CJ, Park WB, Song YG, et al. Evidence-based guidelines for empirical therapy of neutropenic fever in Korea. Korean J Intern Med. 2011;26:220–52.
26. Turner D, Cheifetz I. Shock. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF, editors. Nelson textbook of pediatrics. 20th edn. Philadelphia: Elsevier; 2016. pp. 516–28.
27. Sreedharan R, Avner E. Renal failure. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF, editors. Nelson textbook of pediatrics. 20th edn. Philadelphia: Elsevier; 2016. pp. 2539–47.
28. Suchy F. Fulminant hepatic failure. In: Kliegman RM, Stanton BF, St. Geme JW, Schor NF, editors. Nelson textbook of pediatrics. 20th edn. Philadelphia: Elsevier; 2016. pp. 1966–8
29. Satwani P, Freedman JL, Chaudhury S, Jin Z, Levinson A, Foca MD, et al. A multicenter study of bacterial blood stream infections in pediatric allogeneic hematopoietic cell transplantation recipients: the role of acute gastrointestinal graft-versus-host disease. Biol Blood Marrow Transplant. 2017;23:642–7.
30. Almyroudis NG, Osawa R, Samonis G, Wetzler M, Wang ES, McCarthy PL, et al. Discontinuation of systematic surveillance and contact precautions for vancomycin-resistant *Enterococcus* (VRE) and its impact on the incidence of VRE faecium bacteremia in patients with hematologic malignancies. Infect Control Hosp Epidemiol. 2016;37:398–403.
31. Erlandson KM, Sun J, Iwen PC, Rupp ME. Impact of the more-potent antibiotics quinupristin-dalfopristin and linezolid on outcome measure of patients with vancomycin-resistant *Enterococcus* bacteremia. Clin Infect Dis. 2008;46:30–6.
32. McKinnell JA, Patel M, Shirley RM, Kunz DF, Moser SA, Baddley JW. Observational study of the epidemiology and outcomes of vancomycin-resistant *Enterococcus* bacteraemia treated with newer antimicrobial agents. Epidemiol Infect. 2011;139:1342–50.
33. Kamboj M, Chung D, Seo SK, Pamer EG, Sepkowitz KA, Jakubowski AA, et al. The changing epidemiology of vancomycin-resistant *Enterococcus* (VRE) bacteremia in allogeneic hematopoietic stem cell transplant (HSCT) recipients. Biol Blood Marrow Transpl. 2010;16:1576–81.
34. Vydra J, Shanley RM, George I, Ustun C, Smith AR, Weisdorf DJ, et al. Enterococcal bacteremia is associated with increased risk of mortality in recipients of allogeneic hematopoietic stem cell transplantation. Clin Infect Dis. 2012;55:764–70.
35. Noskin GA, Peterson LR, Warren JR. *Enterococcus faecium* and *Enterococcus faecalis* bacteremia: acquisition and outcome. Clin Infect Dis. 1995;20:296–301.
36. Hayakawa K, Marchaim D, Martin ET, Tiwari N, Yousuf A, Sunkara B, et al. Comparison of the clinical characteristics and outcomes associated with vancomycin-resistant *Enterococcus faecalis* and vancomycin-resistant *E. faecium* bacteremia. Antimicrob Agents Chemother. 2012;56:2452–8.