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ORIGINAL ARTICLE

Bloodstream infections with vancomycin-resistant enterococci are associated with a decreased survival in patients with hematological diseases

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Abstract

Enterococcus species are commensals of the human gastrointestinal tract with the ability to cause invasive infections. For patients with hematological diseases, enterococcal bloodstream infections (BSI) constitute a serious clinical complication which may even be aggravated if the pathogen is vancomycin-resistant. Therefore, we analyzed the course of BSI due to vancomycin-susceptible enterococci (VSE) in comparison to vancomycin-resistant enterococci (VRE) on patient survival. In this retrospective single-center study, BSI were caused by VRE in 47 patients and by VSE in 43 patients. Baseline patient characteristics were similar in both groups. Concerning infection-related characteristics, an increased CRP value and an increased rate of prior colonization with multidrug-resistant organisms were detected in the VRE BSI group. More enterococcal invasive infections were found in the VSE group. The primary endpoint, overall survival (OS) at 30 days after BSI, was significantly lower in patients with VRE BSI compared to patients with VSE BSI (74.5% vs. 90.7%, $p = 0.039$). In a multivariate regression analysis, VRE BSI and a Charlson comorbidity index higher than 4 were independent factors associated with 30-day mortality. Moreover, we found that VRE with an additional teicoplanin resistance showed a trend towards an even lower OS.

Keywords Bloodstream infections · Hematological diseases · Multidrug-resistant organisms · Vancomycin-resistant enterococci · Survival

Introduction

Enterococci are commensals of the human gastrointestinal tract of which *Enterococcus faecalis* and *Enterococcus faecium* represent the most common *Enterococcus* spp. in human infections such as bloodstream infections (BSI), endocarditis, urinary tract infections, and other invasive infections [1]. Enterococci have many intrinsic antibiotic resistances against commonly used antibiotics based on chromosomal genes, but can also acquire additional resistance traits, which are usually transposon or plasmid encoded [2, 3]. Glycopeptide-resistance is mainly mediated via the

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transferrable *VanA* (primarily vancomycin and teicoplanin resistance) and *VanB* (primarily conferring vancomycin resistance only) genes which lead to an alteration of the peptidoglycan synthesis pathway [4]. The prevalence of vancomycin-resistant enterococci (VRE) has increased dramatically worldwide since its first discovery in the 1980s [5–9]. In Germany, 13.4% of all enterococci bloodstream isolates in 2016 were detected to be VRE with a regional belt of higher VRE prevalence from western to eastern Germany, including Frankfurt am Main, Hesse [10, 11].

Disease- or therapy-related changes of the human gut microbiota, damage of the mucosal barrier, and the presence of virulence factors can lead to enterococcal infections [12–14]. In a meta-analysis, patients with a pre-existing VRE colonization had a 24-fold higher risk of developing VRE bloodstream infections [15]. For patients with hematological diseases, BSI due to *Enterococcus* spp. can represent a serious clinical complication. These patients have an increased risk for VRE colonization and infections due to well-described risk factors such as long hospitalization, immunodeficiency and the frequent use of antibiotics [16–18]. Results from previous studies with mixed patient cohorts indicate that VRE infections are associated with a worse outcome in comparison to infections with vancomycin susceptible enterococci (VSE) [19, 20]. However, up-to-date studies for patients with hematological diseases in Europe are missing.

The aim of this study was to investigate the impact of VRE BSI in comparison to VSE BSI on patient survival in our center in Frankfurt, Germany, during the last decade. Additionally, we investigated the impact of teicoplanin resistance on the outcome of enterococcal BSI.

Methods

Study design

In this retrospective single-center study, 90 patients with hematological diseases and a blood culture positive for *Enterococcus* spp. were included. All patients were treated at the University Hospital Frankfurt between March 2007 and May 2017. The primary endpoint of the study was overall survival (OS) after 30 days. Patient medical records were reviewed to obtain clinical and laboratory information as approved by the local ethical committee (approval: SHN-10-2017).

Definitions

VSE was defined as *Enterococcus faecium* (*E. faecium*) or *E. faecalis* without resistance against vancomycin, VRE as *E. faecium* or *E. faecalis* with resistance against vancomycin. Teicoplanin-resistant (TR)-VRE exhibited an additional resistance against teicoplanin. TS-VRE is defined as all VRE except TR-VRE. The term *multidrug resistant organisms* (MDRO) was used as a generic term for VRE, *methicillin-resistant Staphylococcus aureus* and multidrug resistant gram-negative bacteria (MDRGN).

MDRO colonization was defined as a positive pharyngeal, nasal, rectal, or skin swab with evidence of any MDRO. BSI was defined as at least one positive blood culture except for blood cultures positive for commensals of the skin (in particular coagulase-negative staphylococci). Here, two positive cultures were needed. In case of repeated VRE/VSE detection in blood cultures, the first isolate was used as timepoint for further analysis. Patients with both, VRE and VSE BSI were assigned to the VRE BSI group. Polymicrobial BSI was defined as the detection of at least two different pathogens in one or more blood cultures taken within 24 h. Nosocomial acquisition of the BSI was assumed, when the BSI was detected more than 72 h after hospital admission. Primary BSI was defined as the BSI being the primary site of detection of this germ in a patient (pharyngeal, nasal, rectal, or skin colonization excluded).

The Charlson-comorbidity index was used for classifying predicted mortality due to comorbidities [21, 22]. Severe neutropenia was defined as an absolute neutrophil count of < 500/μl. Mucositis was assessed and graded according to the common terminology criteria for adverse events (CTCAE) [23]. Grade 3 or 4 mucositis was classified as severe.

The cause of death was defined as the most important disease(s) or event(s) directly initiating the lethal sequence.

Microbiologic testing and antibiotic treatment

All microbiologic procedures were performed under quality-assured conditions (accredited standards according to ISO 15189:2007; certificate number D–ML–13102–01–00, valid through 2021). For the identification of different species in patient samples matrix-assisted-laser desorption ionization–time of flight analysis was used (MALDI–TOF; VITEK MS, bioMérieux, Nürtingen, Germany). Antibiotic susceptibility was analyzed using VITEK 2 and/or antibiotic gradient tests (bioMérieux).

All patients were screened for colonization with MDRO on the day of admission and weekly during their inpatient stay by pharyngeal, nasal, and rectal swabs.

Blood cultures were taken in case of fever or any other signs of infectious diseases at discretion of the treating physician. Therefore, blood was inoculated into culture vials (BD BACTEC Lytic/10 Anaerobic/F and BD BACTEC Plus Aerobic/F, Becton Dickinson, Heidelberg, Germany).

Patients with an estimated prolonged neutropenia (more than 10 days) received an antimicrobial prophylaxis with levofloxacin. For patients during allogeneic

hematopoietic stem cell transplantation, cefotaxime was used as antimicrobial prophylaxis. In case of clinical signs of infection, an empirical antibiotic therapy was given: patients with neutropenia routinely received piperacillin/tazobactam, and patients with a previous colonization status of MDRGN received imipenem or meropenem. Antibiotic treatment was adjusted, if necessary, according to the antibiotic susceptibility of the microorganisms. If fever was persistent or recurrent, the anti-infective therapy was escalated after 48 h to imipenem or meropenem if empirical therapy had been initiated with piperacillin/tazobactam. If there were indications of a central venous catheter infection, soft tissue infections or a grade 3/4 mucositis, vancomycin (in VRE-screening-negative), teicoplanin or linezolid (in VRE-colonized patients) was added. In case of fever and metabolic acidosis, hypotension or any signs of organ dysfunction, imipenem or meropenem and teicoplanin or linezolid was administered.

Statistics

Descriptive and comparative analysis of categories was performed via SPSS (version 24.0; IBM, SPSS Institute Inc., Chicago, USA). The comparison between nominal categories was performed via chi-square test; for categories with an estimated value less than 5 in over 20% of the cells, the Fisher exact test (2×2 tables) or the likelihood-ratio ($> 2 \times 2$ tables) was used, respectively. The comparison of metric values was performed via Mann-Whitney-U test.

For the survival analysis, R (version 3.4.2.) was used. Kaplan–Meier curves were plotted and compared via the log-rank test. Cox proportional hazards were calculated for multivariate analysis. Factors likely to be relevant for modeling mortality in addition to VRE BSI were first tested in a simple cox analysis and variables with a p value < 0.1 were included into a multivariate analysis.

All statistical tests were two-tailed and considered to be significant if $p < 0.05$.

Results

Patient characteristics

The cohort consisted of 90 patients with hematological diseases. During the study period from 2007 until 2017, 43 patients (47.8%) met the criteria for VSE BSI, and 47 patients (52.2%) met the criteria for VRE BSI.

A comparison of patient characteristics is depicted in Table 1. Of all patients, 58.9% were male and the median age was 58.5 years with a range from 21 to 86 years. The main diagnosis was acute myeloid leukemia (AML) with 54.4% (VSE 25/43, VRE 24/47). 14.4% of the patients (VSE 5/43, VRE 8/47) suffered from lymphomas, 13.3% (VSE 6/43, VRE 6/47) from acute lymphatic leukemia (ALL), 6.7% (VSE 3/43, VRE 3/47) from myeloproliferative diseases, 5.6% (VSE 2/43, VRE 3/47) from myelodysplastic syndrome (MDS), and 5.6% (VSE 2/43, VRE 3/47) had a benign hematological disease (agranulocytosis or very severe aplastic anemia). In 53.5% of these patients, the underlying disease was newly diagnosed; 3.3% had a stable disease and 43.3% had a refractory disease or a relapse. The majority (93.3%) was treated with curative intention. 55.6% of the patients received first-line therapy, 26.7% second-line, and 17.8% third- or further line therapies. VSE BSI was detected in two and VRE BSI in none of the patients during autologous hematopoietic stem cell transplantation (HSCT). During allogeneic HSCT, VSE BSI was detected in 17 and VRE BSI in 11 patients. Ten percent of all patients were post-allogeneic HSCT. Patient comorbidities were collected and clustered (Table S1). Most common were heart diseases, amounting to 23.3% of the patients (VSE 12/43, VRE 9/47). Ten percent (VSE 6/43, VRE 3/47) were diagnosed with diabetes mellitus (DM), 8.9% (VSE 5/43, VRE 3/47) with lung diseases, 6.7% (VSE 4/43, VRE 2/47) with liver diseases, 6.7% (VSE 1/43, VRE 5/47) with renal diseases, and 2.2% (VSE 1/43, VRE 1/47) were HIV-positive. The overall prognostic influence of the comorbidities for each patient was estimated using the Charlson comorbidity index (CCI). The median CCI was 4 in both, the VSE and VRE BSI group. The length of the hospital stay until BSI detection was tendentially longer in the VRE BSI group (median VSE 18 days, median VRE 22 days, $p = 0.063$). Hospital admission within 90 days prior to BSI detection was found in 55.6% of all patients, and 3.3% of all patients (one patient with VSE BSI and two with VRE BSI) were admitted to the intensive care unit (ICU) within the previous 90 days. Most patients (78.9%) had a central venous catheter at the timepoint of BSI detection; 15.6% were receiving parenteral nutrition. In 20% of the patients, corticosteroids were given within 7 days before BSI; 38.9% were receiving an immunosuppressive therapy, and 85.6% had chemotherapy within the previous 30 days. All in all, no significant differences in patient characteristics between VSE and VRE group were found.

Infection-related characteristics

Within the VSE BSI group, 33 patients were detected with *E. faecalis* and 10 with *E. faecium*. Within the VRE BSI group, all patients were detected with *E. faecium* ($n = 47$). Infection-related characteristics are shown in Table 2. In most cases, the acquisition of BSI was nosocomial (94.4%). In some cases, the BSI causing organism was detected at another site prior to the BSI (pharyngeal, nasal, rectal, or skin colonization excluded): The most frequent locus was the urinary

Table 1 Baseline patient characteristics. If not indicated otherwise, all characteristics are reported with regard to the timepoint of BSI. *BSI*, bloodstream infection; *VRE*, vancomycin-resistant enterococci; *VSE*, vancomycin-susceptible enterococci; *MDS*, myelodysplastic syndrome; *AML*, acute myeloid leukemia; *ALL*, acute lymphoblastic leukemia; *MPN*, myeloproliferative neoplasia; *VSAA*, very severe anaplastic anemia; *AG*, agranulocytosis; *HSCT*, hematopoietic stem cell transplantation; *HIV*, human immunodeficiency virus; *CCI*, Charlson comorbidity index; *ICU*, intensive care unit. *p* values indicate differences between VRE BSI and VSE BSI

Characteristics	All patients ($n = 90$)	VSE BSI ($n = 43$)	VRE BSI ($n = 47$)	*p* value
Male sex, *n* (%)	53 (58.9)	29 (67.4)	24 (51.1)	0.115
Age, median (range)	58.5 (21–86)	57 (21–76)	59 (22–86)	0.997
Underlying hematological disease, *n* (%)				0.967
MDS	5 (5.6)	2 (4.7)	3 (6.4)	
AML	49 (54.4)	25 (58.1)	24 (51.1)	
ALL	12 (13.3)	6 (14.0)	6 (12.8)	
Lymphoma	13 (14.4)	5 (11.6)	8 (17.0)	
MPN	6 (6.7)	3 (7.0)	3 (6.4)	
VSAA/AG	5 (5.6)	2 (4.7)	3 (6.4)	
Phase of hematological disease, *n* (%)				0.641
Newly diagnosed	48 (53.3)	25 (58.1)	23 (48.9)	
In complete remission	3 (3.3)	1 (2.3)	2 (4.3)	
Refractory disease/relapse	39 (43.3)	17 (39.5)	22 (46.8)	
Curative treatment approach, *n* (%)	84 (93.3)	41 (95.3)	43 (91.5)	0.679
Therapy line, *n* (%)				0.660
1st line	50 (55.6)	26 (60.5)	24 (51.1)	
2nd line	24 (26.7)	11 (25.6)	13 (27.7)	
Further line	16 (17.8)	6 (14.0)	10 (21.3)	
Autologous HSCT	2 (2.2)	2 (4.7)	0	0.225
Allogeneic HSCT	28 (31.1)	17 (39.5)	11 (23.4)	0.099
Post-autologous HSCT	1 (1.1)	1 (2.3)	0	0.478
Post-allogeneic HSCT	9 (10.0)	4 (9.3)	5 (10.6)	1.000
Comorbidities, *n* (%)				
Diabetes mellitus	9 (10.0)	6 (14.0)	3 (6.4)	0.301
HIV	2 (2.2)	1 (2.3)	1 (2.1)	1.000
Heart disease	21 (23.3)	12 (27.9)	9 (19.1)	0.326
Liver disease	6 (6.7)	4 (9.3)	2 (4.3)	0.420
Lung disease	8 (8.9)	5 (11.6)	3 (6.4)	0.472
Renal failure	6 (6.7)	1 (2.3)	5 (10.6)	0.206
CCI, median (range)	4 (0–16)	4 (1–8)	4 (0–16)	0.591
Length (days) of hospital stay, median (range)	20 (0–160)	18 (0–56)	22 (2–160)	0.063
Hospital admission within previous 90 days, *n* (%)	50 (55.6)	24 (26.7)	26 (55.3)	0.962
ICU admission within previous 90 days, *n* (%)	3 (3.3)	1 (2.3)	2 (4.2)	1.000
Central venous catheter, *n* (%)	71 (78.9)	35 (81.4)	36 (76.6)	0.577
Parenteral nutrition, *n* (%)	14 (15.6)	6 (14.0)	8 (17.0)	0.688
Corticosteroids within previous 7 days, *n* (%)	18 (20.0)	9 (20.9)	9 (19.1)	0.833
Immunosuppressive therapy, *n* (%)	35 (38.9)	20 (46.5)	15 (31.9)	0.156
Chemotherapy within previous 30 days, *n* (%)	77 (85.6)	36 (83.7)	41 (87.2)	0.636

tract in 7.8% (VSE 2/43; VRE 5/47), the gastrointestinal tract in 4.4% (VSE 1/43, VRE 3/47), the lung in 2.2% (VSE 1/43, VRE 1/47), and the soft tissues in 2.2% (VSE 2/43, VRE 0/47) of the cases. However, most cases were primary BSI (83.3%, VSE 37/43, VRE 40/47). Severe neutropenia at the timepoint of BSI was common in 86.7% of the patients. The median duration of neutropenia before the detection of BSI was 11 days (range 0–204 days). A significant difference between the VSE and VRE BSI group was detected in the level of C-reactive protein (CRP) at BSI, which was nearly twice as high

Table 2 Infection-related characteristics. *BSI*, bloodstream infection; *VRE*, vancomycin-resistant enterococci; *VSE*, vancomycin-susceptible enterococci; *ANC*, absolute neutrophil count; *CRP*, C-reactive protein; *ICU*, intensive care unit; *MDRO*, multidrug-resistant organism. *p* values indicate differences between VRE BSI and VSE BSI

Characteristics	All patients ($n = 90$)	VSE BSI ($n = 43$)	VRE BS ($n = 47$)	*p* value
Nosocomial acquisition of BSI, *n* (%)	85 (94.4)	39 (90.7)	46 (97.9)	0.189
Primary site of the BSI causing organism, *n* (%)				0.289
Lung	2 (2.2)	1 (2.3)	1 (2.1)	
Urinary tract	7 (7.8)	2 (4.7)	5 (10.6)	
Abdominal	4 (4.4)	1 (2.3)	3 (6.4)	
Soft tissue	2 (2.2)	2 (4.7)	0	
Primary BSI	75 (83.3)	37 (86.0)	38 (80.9)	
Severe neutropenia, *n* (%)	78 (86.7)	38 (88.4)	40 (85.1)	0.649
Duration of severe neutropenia before BSI (days), median (range)	11 (0–204)	9 (0–204)	11.5 (0–123)	0.374
CRP (mg/dl), median (range)	7.9 (0.1–32.3)	5.6 (0.1–29.2)	10.5 (0.3–32.3)	0.009
Creatinine over upper limit, *n* (%)	14 (15.6)	4 (9.3)	10 (21.3)	0.117
Albumin (g/dl), median (range)	3.2 (1.5–196.0)	3.3 (2.1–4.2)	3.1 (1.5–196.0)	0.295
Severe (grade 3/4) mucositis at BSI, *n* (%)	14 (15.6)	5 (11.6)	9 (19.1)	0.325
ICU admission, *n* (%)	19 (21.1)	6 (14.0)	13 (27.7)	0.111
ICU admission due to infection, *n* (% of all ICU admissions)	14 (73.7)	5 (83.3)	9 (69.2)	0.325
Additional antimicrobial resistances, $n_{resistant}/n_{tested}$ (%)				
Teicoplanin		0/37 (0)	9/47 (19.1)	
Linezolid		0/37 (0)	0/47 (0)	
Tigecycline		1/38 (2.6)	1/46 (2.2)	
Daptomycin		0/5 (0)	3/23 (13.0)	
Polymicrobial BSI, *n* (%)	14 (15.6)	9 (20.9)	5 (10.6)	0.178
Other non-VSE/VRE invasive infections within ± 7 days to VRE/VSE BSI, *n* (%)	33 (36.7)	21 (48.8)	12 (25.5)	0.022
Prior colonization with any MDRO, *n* (%)	37 (41.1)	13 (30.2)	24 (51.1)	0.045
Prior colonization with non-VRE-MDRO, *n* (%)	19 (21.1)	9 (20.9)	10 (21.3)	0.986
Prior colonization with VRE, *n* (%)	33 (36.7)	12 (27.9)	21 (44.7)	0.099

in the VRE BSI group (median VSE 5.6 mg/dl, median VRE 10.5 mg/dl, $p = 0.009$). No significant differences were detected in creatinine or albumin levels. 15.6% of all patients suffered from severe mucositis. The number of ICU admissions after BSI tended to be higher in the VRE group (VSE 14.0%, VRE 27.7%, $p = 0.111$). 73.7% of admissions to the ICU were due to infections without a significant difference between groups. Beside the vancomycin-resistance, 9 (19.1%) VRE isolates showed an additional teicoplanin resistance and were subclassified as TR-VRE. None of the tested VSE/VRE were resistant to linezolid. Tigecycline resistance was found in overall two isolates (VSE 2.6% of 38 tested, VRE 2.2% of 46 tested). Three isolates (13.0%) of 23 tested VRE were resistant to daptomycin. A polymicrobial BSI was detected in 15.6%. Other non-enterococcal invasive infections within ± 7 days to VSE/VRE BSI were significantly more frequent in the VSE BSI group (VSE 48.8%, VRE 25.5%, $p = 0.022$). Moreover, the proportion of patients with prior colonization with any MDRO was significantly higher in the VRE BSI group (VSE 30.2%, VRE 51.1%, $p = 0.046$). In this respect, prior colonization with VRE was tendentially more frequent in the VRE BSI group (VSE 28.9%, VRE 44.7%, $p = 0.099$). However, no difference in prior colonization with MDRO other than VRE was detected between the groups (VSE 20.9%, VRE 21.3%).

Survival

The outcomes of patients after BSI are depicted in Table 3. OS at 30 days after BSI was 82.2% [95% CI 74.4, 90.5] for all patients included. OS at 30 days was significantly lower in the VRE BSI group compared to the VSE group (VSE 90.7% [95% CI 82.4, 99.8]; VRE 74.5% [95% CI 63.0, 88.0], $p = 0.039$) (Fig. 1). During that time, 16 patients (VSE 4, VRE 12) died. 81.3% of them died during neutropenia. The main causes of death were infectious diseases in both, the VSE and the VRE group, with 100% and 83.3% of all deaths, respectively. All but one infection in the VSE group were hospital-acquired. 3/4 patients in the VSE group and 1/10 patients in the VRE group also showed a relapse or progressive disease. Additionally, one patient in the VRE group died from an intracerebral hemorrhage in combination with an

Table 3 Outcomes. *BSI*, bloodstream infection; *VRE*, vancomycin-resistant enterococci; *VSE*, vancomycin- susceptible enterococci; *CI*, confidence interval; *PD*, progressive disease. *p* values indicate differences between VRE BSI and VSE BSI

Characteristics	All patients ($n = 90$)	VSE BSI ($n = 43$)	VRE BSI ($n = 47$)	*p* value
Overall survival, % (95% CI)				0.039
10 days	91.1 (85.4–97.2)	97.7 (93.3–100.0)	85.1 (75.5–95.9)	
20 days	86.7 (79.9–94.0)	95.3 (89.3–100.0)	78.7 (67.9–91.3)	
30 days	82.2 (74.7–90.5)	90.7 (82.4–99.8)	74.5 (63.0–88.0)	
Death in neutropenia, *n* (%)	13 (81.3)	4 (100.0)	9 (75.0)	0.529
Death	All patients ($n = 16$)	VSE BSI ($n = 4$)	VRE BSI ($n = 12$)	*p* value
Cause of death, *n* (%) (referring to dead patients only)				
Infection only + relapse/PD and infection + intracerebral hemorrhage and infection	14 (87.5)	1 + 3 + 0 (100)	8 + 1 + 1 (83.3)	1.000
Relapse/PD without sign of infection	1 (6.3)	0 (0)	1 (8.3)	1.000
Cardiac arrest	1 (6.3)		1 (8.3)	1.000

infection and one from a sudden cardiac arrest. Besides the primary endpoint of OS at 30 days after BSI, OS during the complete time span following, revealed a long-term difference in the outcome between the VRE BSI and VSE BSI group with both curves progressively diverging ($p = 0.002$) (Fig. 2).

In a multivariate cox regression analysis considering all factors with $p < 0.1$ in a simple cox regression analysis (Table 4), VRE BSI and a CCI > 4 were identified as independent factors associated with 30-day mortality (VRE BSI, HR 3.546 [95% CI 1.054, 11.932], $p = 0.041$; curative treatment approach: HR 0.322 [95% CI 0.098, 1.061], $p = 0.062$; CCI > 4, HR 2.783 [95% CI 0.921, 8.413], $p = 0.029$; other invasive infection within ± 7 days to VSE/VRE BSI, HR 2.577 [95% CI 0.874, 7.604], $p = 0.086$).

To further investigate a potential impact on survival of a combined vancomycin and teicoplanin resistance, the VRE BSI group was split into two subgroups depending on their susceptibility to teicoplanin (TR-VRE and TS-VRE). OS at 30 days after BSI, again, was significantly lower in the TR-VRE BSI subgroup (55.6% [95% CI 31.0, 99.7]) compared to patients of the VSE group (90.7% [95% CI 82.4, 99.8], $p = 0.028$) (Fig. 3). Additionally, although the difference was not significant in this small cohort, a trend towards a decreased survival of the TR-VRE BSI group in comparison to the TS-VRE BSI group could be detected (78.9% [95% CI 67.0, 93.9], $p = 0.13$).

Discussion

In this study, we analyzed the outcomes of 90 patients at our center with hematological diseases suffering from VSE BSI or VRE BSI, respectively, during the last decade. The patient population in our study was very well balanced. No differences in other risk factors that may have affected the primary endpoint, the 30-day OS, (e.g., age, underlying disease, therapy line, and comorbidities) were observed. Patients were mainly diagnosed with acute leukemias (54.4% with AML and 13.3% with ALL), reflecting the high risk of acquiring a BSI in patients with those diseases [24]. Additionally, for

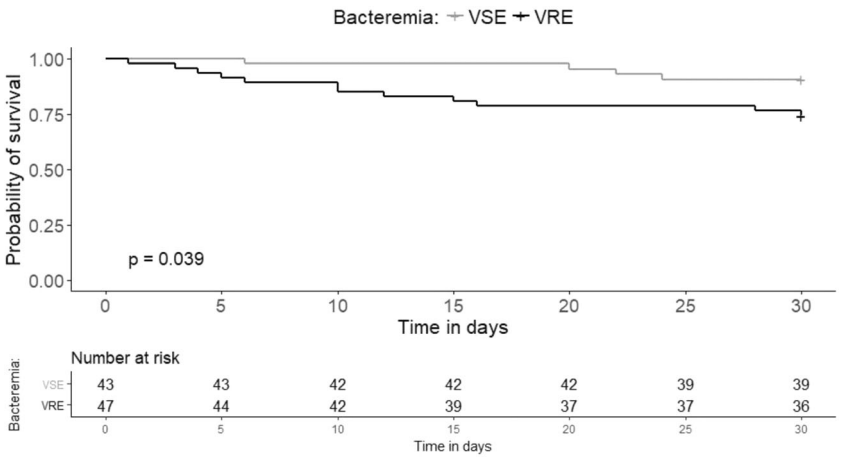

Fig. 1 Kaplan–Meier plot depicting the overall survival after 30 days for patients stratified for VSE (gray line) and VRE (black line) BSI

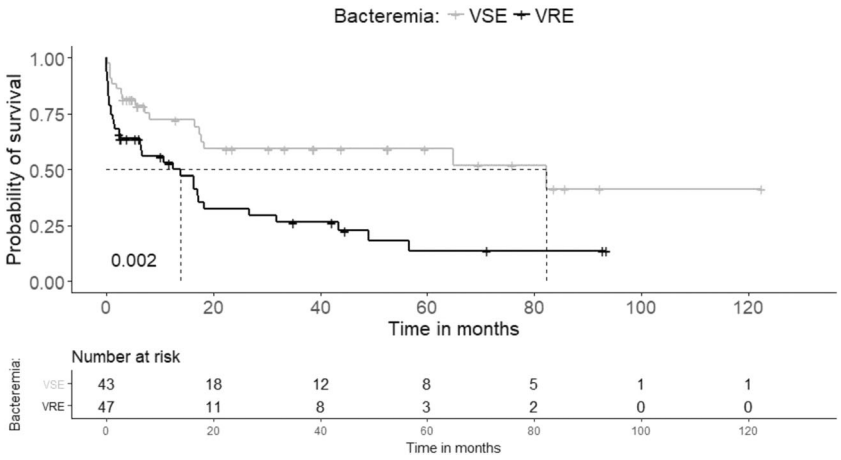

Fig. 2 Kaplan–Meier plot depicting the overall survival during the complete time span of follow-up for patients stratified for VSE (gray line) and VRE (black line) BSI

patients receiving an allogeneic hematopoietic stem cell transplantation, at that time, cefotaxime was used as antimicrobial prophylaxis, which has been identified as an independent risk factor for the emergence of enterococcal bacteremia [25, 26].

Of all patients included, 47.8% had VSE BSI and 52.2% had VRE BSI, respectively. In other studies, the reported rates of VRE BSI are varying from 5.9% in patients on the ICU [27] up to 26.4% in neutropenic patients [28]. However, patients in hematology departments have an increased risk for VRE infections due to repeated hospitalization, a long duration of the inpatient stay, and frequent use of antibiotics. Therefore, several studies demonstrated the particularly high risk for VRE infections in patients with hematological malignancies [29, 30]. Vydra et al. reported in their cohort of allogeneic hematopoietic stem cell recipients that 54% of all patients with BSI due to *Enterococcus* spp. suffered from VRE BSI and 46% from VSE BSI [31] which is in line with the results demonstrated here. Furthermore, our center is located in a region with a higher prevalence of VRE wound infections and bloodstream isolates [11], which might also contribute to the high rates of VRE BSI.

Regarding the overall 30-day mortality after BSI due to Enterococcus spp., mortality was significantly higher in the VRE BSI group than in the VSE BSI group with 25.5% and 9.3%, respectively. According to other studies, the mortality of VRE BSI varies strongly from 9 to 67% [28, 31–33]. Three meta-analyses have identified vancomycin resistance to be significantly associated with increased mortality in patients with enterococcal BSI [19, 20, 34]. Remarkably, in these meta-analyses, studies from different countries and with different underlying diseases have been included. Cho et al. included only patients with neutropenia, which might be more comparable to our patient cohort, as in our study 86.7% of all patients had a severe neutropenia at the time of BSI. However, they only report a slightly higher 30-day mortality rate of 27% in the VRE patients compared to 23% in the VSE patients [28].

Table 4 Simple and multivariate regression analysis of risk factors for death after 30 days. *CI*, confidence interval; *VRE*, vancomycin-resistant enterococci; *BSI*, bloodstream infection; *ANC*, absolute neutrophil count; *CCI*, Charlson comorbidity index; *VSE*, vancomycin- susceptible enterococci; *MDRO* multidrug-resistant organism

Characteristics	Descriptive (*n*, %)		Simple regression			Multivariate regression		
	Survivors (30 days) (*n* = 76)	Non-survivors (30 days) (*n* = 16)	HR	95% CI	*p* value	HR	95% CI	*p* value
Male sex	45 (59.2)	8 (50.0)	0.629	9.236–1.677	0.354	–	–	–
Age ≥ 60 years	33 (43.4)	8 (50.0)	1.215	0.456–3.238	1.215	–	–	–
VRE BSI	35 (46.1)	12 (75.0)	3.086	0.995–9.573	0.051	3.546	1.054–11.932	0.041
Curative treatment approach	71 (93.4)	11 (68.8)	0.133	0.046–0.388	0.000	0.322	0.098–1.061	0.062
CCI > 4 points	14 (18.4)	10 (62.5)	5.403	1.959–14.898	0.001	2.783	0.921–8.413	0.029
ANC < 500/μl	63 (82.9)	15 (93.8)	2.398	0.317–18.158	0.397	–	–	–
Other non-VSE/VRE invasive infections within ± 7 days to VRE/VSE BSI, *n* (%)	24 (31.6)	9 (56.3)	2.391	0.890–6.426	0.084	2.577	0.874–7.604	0.086
Prior colonization with any MDRO	29 (38.2)	8 (50.0)	1.479	9.555–3.943	0.434	–	–	–

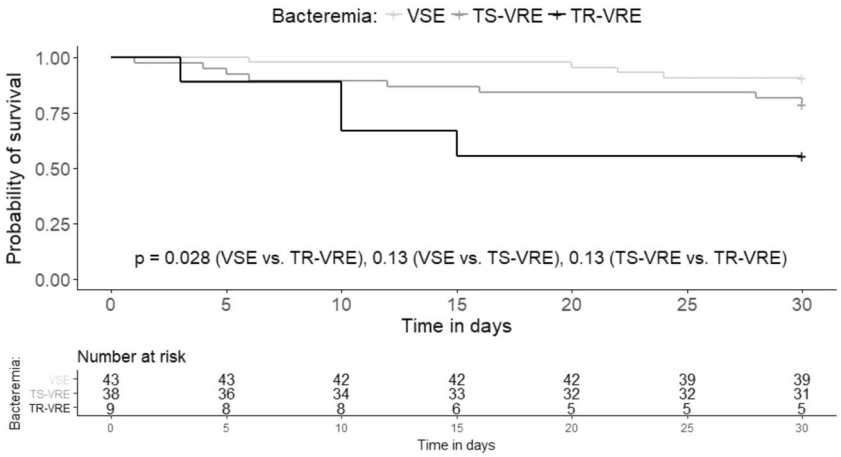

Fig. 3 Kaplan–Meier plot depicting the overall survival after 30 days for patients stratified for VSE (light gray line), TS-VRE (dark gray line), and TR-VRE (black line) BSI

In accordance with that, Yoo et al. also describe a similar clinical course for patients with VRE BSI and VSE BSI in a hematology unit [35], and Vydra et al. show a 30-day mortality rate of 38% for both, patients with VRE and VSE BSI, after allogeneic hematopoietic stem cell transplantation [31]. In contrast to that, Chen et al. and Diaz Granados show VRE BSI to be a predictor of mortality in patients with hematological malignancies and neutropenic patients, respectively [19, 36]. The different results of these studies might be explained by different underlying diseases, different wards (e.g., ICU vs. non-ICU), different antimicrobial treatment strategies at certain centers, and different definitions for the control groups and the outcome.

It has been speculated by others earlier whether VRE BSI is only a predictive parameter for more critically ill patients or also the reason for the worse survival itself [17, 20]. As this is a retrospective study, we cannot fully answer that question. However, in our cohort, other factors such as curative treatment intention, other non-VSE/VRE invasive infections within ± 7 days to VRE/VSE BSI, and a higher CCI also showed an impact on mortality, but VRE BSI besides a CCI > 4 was an independent predictor of mortality in the multivariate cox regression model. Therefore, we speculate that the higher mortality in the VRE BSI group might be mainly attributable to the vancomycin resistance itself.

There are several considerations before choosing the best empiric antibiotics, including the development of antibiotic resistances. However, for vancomycin, a large review did not show that vancomycin restriction reduces the rate of invasive VRE infections [37]. At our department, only patients with previous VRE colonization and suspected central venous catheter infection assumed soft tissue infections or grade 3/4 mucositis receive teicoplanin or linezolid as part of their first-line antibiotic treatment. In our cohort, less than half (44.9%) of all VRE BSI patients were previously identified as colonized with VRE, which might explain treatment delays in the VRE group, and therefore, a worse survival in this group. Because we found patients with TR-VRE BSI to have a trend towards an even worse OS at 30 days in comparison to the TS-VRE group, the teicoplanin resistance might also be accountable for the difference. This might lead to the question if an earlier application of drugs of last resort as linezolid could prevent mortality in patients with a presumed BSI due to a glycopeptide resistant germ. Nonetheless, in hematologic and hematopoietic stem cell transplantation, patients with known VRE colonization, early empirical use of linezolid for febrile neutropenia seems to have no impact on mortality or duration of VRE BSI [38, 39]. Therefore, the use of linezolid, and probably also tigecycline and daptomycin, should be further on carefully considered and limited to the detection of a (TR-)VRE infection.

All patients of the VRE BSI group were detected with *E. faecium*, whereas most patient in the VSE group were detected with *E. faecalis*. This unequal distribution resembles the different frequency of vancomycin resistance in this two species in Germany [10]. However, due to the study of Todeschini et al., these different enterococci species do not seem to significantly affect the fatality rate in patients with hematologic malignancies [40].

We report in our cohort that most of the patients (80.9%) suffered from primary BSI. Other studies also reported rates over 50% of unknown or primary BSI [41, 42]. Therefore, our rates appear very high but might be explained by the different study settings (retrospective vs. prospective) and different definitions of the primary site (we defined primary BSI as the BSI being the primary site of detection of this germ in a patient except for pharyngeal, nasal, rectal, or skin colonization). In line with our results, Gudiol et al. were not able to identify a defined source of BSI in over 70% of hematopoietic stem cell recipients [43]. Concerning other first sites of detection in our study, no final conclusion about the source of the BSI can be drawn. Moreover, the presence of enterococci at an organ site must not necessarily lead to an infection of this organ.

We found a significant difference between the VRE and VSE BSI group concerning prior colonization with a MDRO. This effect seems to be mainly caused by differences in prior colonization with VRE. VRE colonization has emerged as a major challenge in many fields of healthcare since the last years. The role of previous colonization with VRE and subsequent infections has been widely discussed in the literature, and previous colonization has clearly been described as risk factor for subsequent VRE infection [15, 44]. This is congruent with our finding that 44.7% of the patients with VRE BSI and 27.9% of the patients with VSE BSI were previously colonized by VRE. The colonization rate in general is in range with other reported rates of VRE colonization in adult patients with hematological diseases varying from 0% [45] up to 45.7% in Europe [46].

Other non-VSE/VRE invasive infections within ± 7 days to VSE/VRE BSI were significantly more frequent in the VSE BSI group and may have confounded the outcome. Yet, this did not mask the decrease in survival in the VRE BSI group. Higher CRP levels were observed in VRE BSI compared to VSE BSI patients. This might reflect the worse outcome of patients with VRE BSI since it is well known that high CRP levels are associated with an inferior survival and are predictors of mortality in patients with infections [47–49]. Albumin levels did not differ in our study between VRE and VSE patients. Albumin, as a liver acute phase protein which decreases in response to an infection, is also a known to be associated with a worse outcome [50–52]. We may not have found differences in the albumin-levels because of (i) our relatively small patient cohort and (ii) the fact, that the albumin level is related to the nutrition condition of patients. Patients undergoing chemotherapy due to a malignant disease may eat insufficiently because of chemotherapy-induced nausea and vomiting and may therefore have rather low albumin levels.

Summarizing our results, we have shown that VRE compared to VSE BSI is independently associated with a decreased 30-day OS in patients with hematological diseases. Moreover, we have demonstrated that TR-VRE BSI is associated with a decreased survival in comparison to other enterococcal BSI. However, our study has several limitations: First of all, it was a retrospective study and causal conclusions can therefore hardly be drawn. Furthermore, though homogenous, our group size was rather small. Therefore, further prospective studies are needed to elucidate the role of VRE and especially TR-VRE BSI in patients with hematological diseases and investigate whether certain subclones of enterococci might be spread and transmitted in these patients.

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Compliance with ethical standards

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. For this type of study formal consent is not required.

Conflict of interest The authors declare that they have no conflicts of interest.

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