Eur J Clin Microbiol Infect Dis (2014) 33:1995–2003
DOI 10.1007/s10096-014-2167-y

ARTICLE

Is a single positive blood culture for *Enterococcus* species representative of infection or contamination?

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Received: 13 February 2014 / Accepted: 16 May 2014 / Published online: 11 June 2014

Abstract Data on the clinical outcomes of patients with a single compared with multiple positive blood cultures for *Enterococcus* species is limited. We undertook a retrospective cohort study in adults with at least one positive blood culture for *Enterococcus* species in a single institution. Clinical outcomes included death and elimination of infection. We included 471 positive blood cultures from 206 enterococcal positive blood culture episodes in 189 patients. Multiple positive blood cultures for *Enterococcus* species occurred in 110/206 (53.4 %) episodes; 31.6 % of patients had diabetes mellitus; 42.9 % of patients had solid or hematologic malignancy; 26.5 % of patients were solid organ transplant recipients; hospital-acquired and healthcare-associated acquisition represented 55.3 % and 33.0 % of episodes, respectively. Thirty-five patients died and 110 episodes of enterococcal bloodstream infection were successfully treated. In the multivariable analysis, multiple positive blood cultures were not statistically significantly associated with an increased likelihood of in-hospital death [odds ratio (OR) 1.00, 95 % confidence interval (CI) 0.42–2.40] or elimination (OR 1.41, 95 % CI 0.76–2.64) compared with single positive blood cultures. Hematologic malignancy and diabetes mellitus were independently associated with in-hospital death (OR 2.83, 95 % Cl 1.02–7.82; OR 2.79, 95 % Cl 1.16–6.70, respectively). Infectious disease consultation was associated with a greater likelihood of elimination (OR 2.50, 95 % Cl 1.32–4.72). The clinical outcomes of patients with single versus multiple positive blood cultures with *Enterococcus* species were similar in our institution. Further studies should examine efficient methods to detect contamination versus true infection.

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Introduction

Enterococcus species are a major cause of healthcare-associated infections (HAIs), especially bloodstream infections (BSIs) [1, 2], often device-related, with a crude in-hospital mortality as high as 36 % in recent studies [3, 4]. While, in most instances, *Enterococcus* species in positive blood cultures represents true BSI, studies have found that *Enterococcus* species may be a contaminant in blood cultures in 10–15 % of cases [3, 5]. It has been suggested that a single positive blood culture in the presence of other negative blood cultures or co-isolation with skin organisms may suggest contamination rather than a true BSI [6, 7]. We undertook a retrospective cohort study to examine clinical patient outcomes comparing patients with a single positive blood culture to those with multiple positive blood cultures for *Enterococcus* species in a single large academic tertiary care institution. We hypothesized that, if a single blood culture is usually representative of contamination, then the clinical outcomes of patients with single positive blood cultures would be better than the outcomes of patients with multiple positive blood cultures.

Methods

Study design

Patients who had at least one positive blood culture for *Enterococcus* species from 1/1/2008 though 10/31/2010 at a

single large academic medical center were included. All subjects were identified using the institution's microbiology database. Eligible subjects were hospitalized patients aged≥18 years old. The clinical outcomes of single versus multiple positive blood cultures with *Enterococcus* species were compared, which included death during the index hospitalization and elimination of BSI. This study was conducted as a quality improvement project, was submitted to the institutional review board, and was considered exempt from institutional review board review.

Microbiology methods

Blood cultures were processed in the microbiology laboratory using standard microbiology methods [8].

Data collection

The medical charts of each subject were reviewed by two authors (KJ, MS) via the electronic health record system. Data were abstracted in a standardized Excel file worksheet. Clinical information included: age, sex, source of infection and clinical significance, location of acquisition, species of *Enterococcus* including susceptibility to vancomycin, blood drawn via peripheral vein versus central catheter, co-infection [additional bacterial or fungal specie(s) isolated from the same blood culture bottle], pre-antibiotics (antibiotics administered prior to culture draw), presence of infectious disease consultation, and patient outcome (discharge alive, death during the index hospitalization, and bacteremia elimination). The pre-existing medical conditions of interest included diabetes mellitus, solid organ malignancy, hematologic malignancy, hematopoietic stem cell transplantation, solid organ transplantation, and cirrhosis. We did not evaluate the presence of endocarditis due the fact that an echocardiogram was not routinely done in all the enterococcal BSIs in our facility.

Study definitions

An episode of enterococcal BSI was defined by a positive blood culture which must have occurred >7 days after any previous positive result, unless the infectious disease clinicians (KJ, NS) agreed that any previous positive result was part of the same episode. Death refers to death during the index hospitalization. Elimination was defined as elimination of bacteria from the blood, requiring blood culture draw post-treatment. Acquisition was categorized as community-acquired, hospital-acquired (hospitalized >48 h at the time the blood culture was drawn), or other healthcare-associated (e.g., previous hospitalization within 90 days, attending a hemodialysis or intravenous chemotherapy clinic within 30 days, home intravenous therapy or specialized nursing care within 30 days, or resident of a long-term care facility) [9]. The source of enterococcal BSI was categorized as follows: urinary tract infection (UTI), central line-associated bloodstream infection (CLABSI), gastrointestinal/hepatobiliary origin, and other. The latter category was subdivided into five categories, as follows: the presence of other identifiable source, no documentation or evaluation available for decision, no identifiable source despite appropriate evaluation, presence of >1 possible identifiable source, and BSI with uncertain clinical significance or presumed central line colonization. Central line colonization was defined as a positive blood culture obtained via a central line without a positive peripheral blood culture and no signs or symptoms of infection. To determine the source of enterococcal BSI and to distinguish between true BSI and an episode of BSI with uncertain clinical significance or central line colonization, one investigator independently assessed the documentation in the electronic medical records (KJ). Any conflict between the electronic health record documentation and our assessment was reviewed further by the other investigator (NS).

Statistical methods

Univariate summaries of all data were tabulated with both the patient and the episode as the unit of analysis. The χ^2 test or Fisher's exact test was used to assess the statistical significance for categorical variables and the Wilcoxon rank-sum test was used for continuous variables to assess the statistical significance of all variables between the respective outcome cohorts.

To assess whether single versus multiple positive blood cultures had any impact on death or elimination, we first conducted a stepwise model-building analysis using all the variables included in Tables 1 and 2 for possible inclusion using a logistic regression model. In the elimination model, where episode was the unit of analysis, an exchangeable covariance structure was employed to model possible repeated episodes within the same individual using generalized estimating equations. The criteria for both entry into the model and remaining in the model were set using a significance of $\alpha=0.10$. First-level interactions between predictors were also allowed. Once final models were found, an indicator of single versus multiple positive cultures was added, along with possible interactions. Odds ratios (ORs) and corresponding 95 % confidence intervals (CIs) were calculated. Statistical analyses were performed using the R statistical computing environment, version 2.13.

Results

Incidence

We found 236 patients who had at least one positive blood culture for *Enterococcus* species at the University of

Table 1 Features of the study population with the patient as the unit of analysis comparing death to survival

Variable	Total, *N*=189	Alive, *n*=153	Death, *n*=35	*p*-Value
Age mean ± SD years	57.1 ± 15.9	56.8 ± 16.1	58 ± 15.5	0.589
Female, *n* (%)	71/189 (37.6)	61/153 (39.9)	10/35 (28.6)	0.214
Diabetes mellitus, *n* (%)	59/187 (31.6)	45/151 (29.8)	14/35 (40.0)	0.243
Cirrhosis, *n* (%)	24/188 (12.8)	17/153 (11.1)	7/34 (20.6)	0.157
Solid organ malignancy, *n* (%)	47/189 (24.9)	35/153 (22.9)	12/35 (34.3)	0.160
Hematologic malignancy, *n* (%)	34/189 (18.0)	24/153 (15.7)	10/35 (28.6)	0.074
Bone marrow transplant recipient, *n* (%)	10/189 (5.3)	8/153 (5.2)	2/35 (5.7)	1.000
Liver transplantation recipient, *n* (%)	30/189 (15.9)	23/153 (15.0)	7/35 (20.0)	0.469
Other transplantation recipient, *n* (%)	20/189 (10.6)	15/153 (9.8)	5/35 (14.3)	0.542
Species, *n* (%)				
Enterococcus faecium	107/189 (56.6)	79/153 (51.6)	27/35 (77.1)	0.006
Enterococcus faecalis	75/189 (39.7)	68/153 (44.4)	7/35 (20.0)	0.008
Other species[a]	5/189 (2.6)	4/153 (2.6)	1/35 (2.9)	1.000
Multiple species[b]	5/189 (2.6)	4/153 (2.6)	1/35 (2.9)	1.000
VRE[c], *n* (%)	75/189 (39.7)	55/153 (35.9)	19/35 (54.3)	0.045
Multiple positive blood cultures, *n* (%)	94/189 (49.7)	75/153 (49.0)	18/35 (51.4)	0.797
Place of acquisition, *n* (%)				
Community-acquired	25/189 (13.2)	22/153 (14.4)	3/35 (8.6)	0.580
Healthcare-associated	65/189 (34.4)	58/153 (37.9)	7/35 (20.0)	0.044
Hospital-acquired	104/189 (55.0)	78/153 (51.0)	25/35 (71.4)	0.028
ID consultation[d], *n* (%)	106/189 (56.1)	86/153 (56.2)	20/35 (57.1)	0.920
Central line[e], *n* (%)	108/189 (57.1)	83/153 (54.2)	24/35 (68.6)	0.123
Pre-antibiotics[f], *n* (%)	95/189 (50.3)	72/153 (47.1)	22/35 (62.9)	0.092
Source of infection *n* (%)				
GI/hepatobiliary system	52/189 (27.5)	42/153 (27.5)	10/35 (28.6)	0.894
Urinary tract infection	18/189 (9.5)	17/153 (11.1)	1/35 (2.9)	0.204
CLABSI	35/189 (18.5)	30/153 (19.6)	4/35 (11.4)	0.257
Other				
Other identifiable source present	4/189 (2.1)	4/153 (2.6)	0/35 (0.0)	1.000
Not enough data available to make a decision	39/189 (20.6)	27/153 (17.6)	12/35 (34.3)	0.029
No identifiable source	12/189 (6.3)	10/153 (6.5)	2/35 (5.7)	1.000
More than one possible source identified	11/189 (5.8)	8/153 (5.2)	3/35 (8.6)	0.432
BSI with uncertain clinical significance or central line colonization	26/189 (13.8)	24/153 (15.7)	2/35 (5.7)	0.175
Co-infection, *n* (%)				
Skin co-infection[g]	25/189 (13.2)	21/153 (13.7)	4/35 (11.4)	1.000
Other co-infection[h]	24/189 (12.7)	19/153 (12.4)	5/35 (14.3)	0.780
No co-infection	154/189 (81.5)	126/153 (82.4)	27/35 (77.1)	0.475

[a] *Enterococcus* species other than *faecium* or *faecalis*, such as *gallinarum*

[b] Multiple *Enterococcus* species isolated from one blood culture draw

[c] Vancomycin-resistant enterococci

[d] Infectious disease consultation obtained

[e] Blood drawn via central venous cannulation

[f] Antibiotics administered prior to culture draw

[g] Coagulase-negative *Staphylococcus* species (spp.), *Corynebacterium* spp., *Bacillus* spp., *Propionibacterium* spp., *Lactobacillus* spp., *Bifidobacterium* spp., viridans streptococcal spp.

[h] *Candida* spp., Enterobacteriaceae, *Pseudomonas* spp., *Streptococcus* spp. other than viridans streptococcal spp., *Staphylococcus aureus*, *Bacteroides* spp., *Stenotrophomonas* spp.

Table 2 Features of the study population with the episode as the unit of analysis comparing elimination to no elimination

Variable	Total, *N*=206	Elimination, *n*=110	No elimination, *n*=95	*p*-Value
Age mean ± SD years	56.6 ± 15.6	55.9 ± 15.9	57.4 ± 15.3	0.364
Female, *n* (%)	82/206 (39.8)	42/110 (38.2)	40/95 (42.1)	0.567
Diabetes mellitus, *n* (%)	65/204 (31.9)	35/109 (32.1)	30/94 (31.9)	0.976
Cirrhosis, *n* (%)	24/205 (11.7)	11/109 (10.1)	13/95 (13.7)	0.427
Solid organ malignancy, *n* (%)	48/206 (23.3)	22/110 (20.0)	26/95 (27.4)	0.214
Hematologic malignancy, *n* (%)	38/206 (18.4)	18/110 (16.4)	20/95 (21.1)	0.389
Bone marrow transplant recipient, *n* (%)	12/206 (5.8)	9/110 (8.2)	3/95 (3.2)	0.127
Liver transplantation recipient, *n* (%)	37/206 (18.0)	20/110 (18.2)	17/95 (17.9)	0.957
Other transplantation recipient, *n* (%)	24/206 (11.7)	16/110 (14.5)	8/95 (8.4)	0.174
Species, *n* (%)				
Enterococcus faecium	119/206 (57.8)	59/110 (53.6)	59/95 (62.1)	0.221
Enterococcus faecalis	78/206 (37.9)	44/110 (40.0)	34/95 (35.8)	0.536
Other species[a]	5/206 (2.4)	3/110 (2.7)	2/95 (2.1)	1.000
Multiple species[b]	5/206 (2.4)	2/110 (1.8)	3/95 (3.2)	0.665
VRE[c], *n* (%)	81/206 (39.3)	40/110 (36.4)	40/95 (42.1)	0.401
Multiple positive blood cultures, *n* (%)	110/206 (53.4)	62/110 (56.4)	47/95 (49.5)	0.324
Place of acquisition, *n* (%)				
Community-acquired	25/206 (12.1)	13/110 (11.8)	12/95 (12.6)	0.859
Healthcare-associated	68/206 (33.0)	42/110 (38.2)	26/95 (27.4)	0.101
Hospital-acquired	114/206 (55.3)	56/110 (50.9)	57/95 (60.0)	0.192
ID consultation[d], *n* (%)	116/206 (56.3)	71/110 (64.5)	45/95 (47.4)	0.013
Central line[e], *n* (%)	113/206 (54.9)	59/110 (53.6)	53/95 (55.8)	0.757
Pre-antibiotics[f], *n* (%)	103/206 (50.0)	49/110 (44.5)	53/95 (55.8)	0.108
Source of infection, *n* (%)				
GI/hepatobiliary system	54/206 (26.2)	28/110 (25.5)	26/95 (27.4)	0.756
Urinary tract infection	19/206 (9.2)	12/110 (10.9)	7/95 (7.4)	0.383
CLABSI	38/206 (18.4)	24/110 (21.8)	13/95 (13.7)	0.131
Other				
Other identifiable source present	4/206 (1.9)	3/110 (2.7)	1/95 (1.1)	0.625
Not enough data available to make a decision	40/206 (19.4)	11/110 (10.0)	29/95 (30.5)	<0.001
No identifiable source	12/206 (5.8)	8/110 (7.3)	4/95 (4.2)	0.352
More than one possible source identified	12/206 (5.8)	8/110 (7.3)	4/95 (4.2)	0.352
BSI with uncertain clinical significance or central line colonization	26/206 (12.6)	15/110 (13.6)	11/95 (11.6)	0.659
Co-infection, *n* (%)				
Skin co-infection[g]	26/206 (12.6)	14/110 (12.7)	12/95 (12.6)	0.984
Other co-infection[h]	24/206 (11.7)	13/110 (11.8)	11/95 (11.6)	0.958
No co-infection	168/206 (81.6)	91/110 (82.7)	76/95 (80.0)	0.616

[a] *Enterococcus* species other than *faecium* or *faecalis*, such as *gallinarum*

[b] Multiple *Enterococcus* species isolated from one blood culture draw

[c] Vancomycin-resistant enterococci

[d] Infectious disease consultation obtained

[e] Blood drawn via central venous cannulation

[f] Antibiotics administered prior to culture draw

[g] Coagulase-negative *Staphylococcus* species (spp.), *Corynebacterium* spp., *Bacillus* spp., *Propionibacterium* spp., *Lactobacillus* spp., *Bifidobacterium* spp., viridans streptococcal spp.

[h] *Candida* spp., Enterobacteriaceae, *Pseudomonas* spp., *Streptococcus* spp. other than viridans streptococcal spp., *Staphylococcus aureus*, *Bacteroides* spp., *Stenotrophomonas* spp.

Wisconsin, Madison from 1/1/2008 through 10/31/2010. Forty-seven patients were excluded from analysis: 39 patients were younger than 18 years old, three patients were not hospitalized, and five patients had no documentation available for data analysis. Hence, a total of 471 blood cultures isolates from 206 enterococcal BSI episodes in 189 patients were analyzed. Thirty-five patients died during the index hospitalization. One hundred and ten episodes of BSI were considered eliminated by our definition.

Demographic and clinical characteristics

The demographic and clinical features are summarized in Tables 1 and 2. The median age at the time of BSI was 57 years. A total of 71 patients were female (37.6 %). Most patients were white (91.5 %). We found that 31.6 % of patients had diabetes mellitus, 12.8 % of patients had cirrhosis, 42.9 % of patients had solid or hematologic malignancy, 26.5 % of patients were solid organ transplant recipients, and 5.3 % of patients received bone marrow transplantation.

Furthermore, 53.4 % of BSI episodes comprised multiple blood cultures for *Enterococcus* species. *Enterococcus faecium*, *Enterococcus faecalis*, and vancomycin-resistant enterococci (VRE), either *faecium* or *faecalis*, accounted for 57.8 %, 37.9 %, and 39.3 % of all BSI episodes, respectively.

The majority of the BSIs (88.3 %) occurred in hospital or healthcare settings. Blood cultures were obtained through a central line in 54.9 %. Infectious disease consultation was obtained in 56.3 % of the episodes. In half of the episodes, antimicrobial agents had been started before blood cultures were drawn. The source of BSI was identified in 53.8 % of episodes and gastrointestinal or hepatobiliary origin accounted for 26.2 %, followed by CLABSI (18.4 %) and UTI (9.2 %). Despite extensive chart review, we were not able to find the source of the BSI in 45.5 % of episodes and 12.6 % of episodes were considered to be BSI with uncertain clinical significance or central line colonization. We also found that 24.3 % of enterococcal BSI episodes were concomitant with BSI resulting from other pathogens.

Univariate risk factor analysis

The univariate analysis for death as an outcome is shown in Table 1. There were no major differences in patients' demographics and pre-existing medical conditions comparing patients who died during the index hospitalization and those who were discharged alive. Patients with *Enterococcus faecalis* BSI were more frequently alive at discharge (44 %, $p=0.008$), whereas hospital death was more common for patients with *Enterococcus faecium* BSI (77 %, $p=0.006$). Moreover, hospital death was common in patients with VRE BSI (54 %, $p=0.045$). Death was common in hospital-acquired BSI (71 %, $p=0.028$). Healthcare-associated BSI patients were more likely to be discharged home alive (37.9 %, $p=0.044$).

The univariate analysis for elimination as an outcome is shown in Table 2. The elimination of BSI occurred more frequently in the episodes when infectious disease consultation was obtained (64.5 %, $p=0.013$). When the source was not identified due to the absence of documentation or evaluation available for decision, the elimination of BSI was less likely to occur (30.5 %, $p<0.001$).

Multivariate risk factor analysis

Hematologic malignancy and diabetes mellitus were independently associated with in-hospital death (OR 2.83, 95 % Cl 1.02–7.82; OR 2.79, 95 % Cl 1.16–6.70, respectively) (Table 3). *Enterococcus faecium* BSI was associated with death compared with *Enterococcus faecalis* BSI (OR 3.89, 95 % Cl 1.24–12.20). Cirrhosis showed a higher rate of in-hospital death, but this was not statistically significant. Hospital-acquired and healthcare-associated enterococcal BSI had a lower in-hospital death trend, but this was also not statistically significant. These findings are summarized in Table 3 and Fig. 1.

Infectious disease consultation was associated with BSI elimination (OR 2.50, 95 % Cl 1.32–4.72) (Table 4). Antibiotic treatment prior to blood culture draw was associated with decreasing the likelihood of BSI elimination (OR 0.48, 95 % Cl 0.25–0.90). Hematologic malignancy had a lower likelihood of elimination, although this was not statistically significant. Bone marrow transplant recipients were more likely to eliminate BSI (OR 8.82, 95 % Cl 1.76–44.21). Multiple positive blood cultures were not statistically significantly associated with an increased likelihood of in-hospital death (OR 1.00, 95 % CI 0.42–2.40) or elimination (OR 1.41, 95 % CI 0.76–2.64) compared with single positive blood cultures. These findings are summarized in Table 4 and Fig. 2.

Discussion

Enterococcus species remain as major pathogens for nosocomial infection in the United States [2, 10–12]. They are classically considered to be relatively avirulent pathogens [13, 14]. However, multiple studies in recent years have shown a mortality rate ranging from 6 to 40 % [3, 4, 15–19]. In our study, we found that 35 patients out of 189 enterococcal BSI patients (18.5 %) died during the index hospitalization. We found that 110 episodes of BSI out of 206 episodes (53.4 %) were cleared. A previous comprehensive case series conducted at our institution from the 1970s to the 1980s revealed that 77 % of enterococcal BSIs were hospital-

Table 3 Predictors of death in the multivariable analysis

Variable	Odds ratio of death	
	95 % Confidence interval	*p*-Value
Multiple positive blood cultures	1.00	
	0.42, 2.40	0.993
Healthcare acquisition[a]	0.25	
	0.06, 1.09	0.065
Hospital-associated acquisition[a]	0.61	
	0.15, 2.53	0.496
Solid organ malignancy	2.34	
	0.93, 5.85	0.070
Hematologic malignancy	2.83	
	1.02, 7.82	0.045
Cirrhosis	3.04	
	0.98, 9.37	0.053
Diabetes mellitus	2.79	
	1.16, 6.70	0.022
Enterococus faecium[b]	3.89	
	1.24,12.20	0.020
Other and multiple enterococcal species[c]	2.54	
	0.40, 16.24	0.325

[a] Odds ratio compared to community acquisition

[b] Odds ratio compared to *Enterococcus faecalis*

[c] Odds ratio of the combination of both other and multiple *Enterococcus* species to *Enterococcus faecalis*

acquired; and there was 46 % in-hospital mortality among patients with enterococcal BSIs [20]. Similarly, other studies conducted in the 1980s observed higher rates of mortality, though it would be difficult to directly compare these studies given their heterogeneity in research populations [21–23]. The improved mortality rate over time likely reflects advances in medical care and antimicrobial therapy.

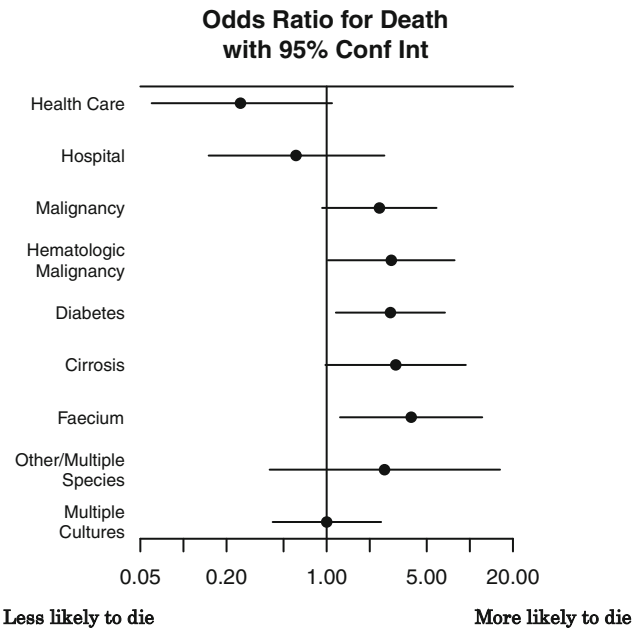

Fig. 1 The odds ratios of independent risk factors for death

We found that multiple positive blood cultures were not statistically significantly associated with an increased likelihood of in-hospital death or elimination compared with single positive blood cultures. BSIs with uncertain clinical significance or central line colonization was 12.6 % in our study, and this had no influence on the likelihood of in-hospital death or elimination in both the univariate and the multivariate analysis. From the infection control surveillance standpoint, the National Healthcare Safety Network (NHSN) definition for laboratory-confirmed enterococcal BSI requires at least one or more positive blood cultures [24]. Sexton et al. have suggested that the NHSN definition may be overly sensitive in detecting enterococcal CLABSI [7]. Freeman et el. showed that enterococci from blood cultures could indicate contamination when skin organisms were co-isolated [6]. This study, however, was based on microbiology data without clinical data collection. Our study, conducted at a single tertiary care center, combined microbiology data with extensive clinical data review to examine the outcomes of patients with single positive blood cultures to those with multiple positive blood cultures for *Enterococcus* species. We found no significant difference in the clinical outcomes between single versus multiple positive blood cultures. In our study, about 90 % of BSI episodes were hospital-acquired or healthcare-associated. Intra-abdominal sources, including the gastrointestinal tract or hepatobiliary system, were the most common sources of BSIs, followed by CLABSIs and UTIs. Our study results are compatible with a recent study reviewing a large number of BSIs, including enterococcal BSIs [3]. *Enterococcus faecium* infection was

Table 4 Predictors of elimination in the multivariable analysis

Variable	Odds ratio of elimination	
	95 % Confidence interval	*p*-Value
Multiple positive blood cultures	1.41	
	0.76, 2.64	0.278
Hematologic malignancy	0.43	
	0.17, 1.09	0.074
Enterococus faecium[a]	0.65	
	0.34, 1.25	0.198
Infectious disease consultation	2.50	
	1.32, 4.72	0.005
Pre-antibiotics[b]	0.48	
	0.25, 0.90	0.023
Bone marrow transplant recipient	8.82	
	1.76, 44.21	0.008
Other and multiple enterococcal species[c]	1.01	
	0.25, 4.13	0.993

[a] Odds ratio compared to *Enterococcus faecalis*

[b] Antibiotics administered prior to culture draw

[c] Odds ratio of the combination of both other and multiple *Enterococcus* species to *Enterococcus faecalis*

the most common, followed by *Enterococcus faecalis* in BSIs. VRE, either *faecium* or *faecalis*, accounted for about 40 % of all enterococcal BSIs in our facility. Since the first report of VRE 25 years ago, VRE have remained major nosocomial pathogens, and infection with VRE is associated with higher mortality compared with infection caused by vancomycin-susceptible enterococci [25–27]. In our study, however, we did not find that VRE was a statistically significant risk for in-hospital death or failure of clearance of BSIs.

Independent risk factors associated with in-hospital death among patients with enterococcal BSI in our study were hematologic malignancy, diabetes mellitus, and *Enterococcus faecium* BSI. Our findings are similar to and extend those of other studies, which found that comorbid illnesses, not receiving active antimicrobial therapy, *Enterococcus faecium*, enterococci with high-level gentamicin resistance, and intensive care unit admission increased the risk of mortality [4, 16, 17, 19, 28–31]. We found that infectious disease consultation was associated with a higher likelihood of elimination. While this has not been shown in the literature specifically for enterococcal BSI, our observation is similar to findings of studies in the management and outcomes of *Staphylococcus aureus* BSI [32, 33]. Infectious disease consultation for patients with *Staphylococcus aureus* BSI was associated with greater adherence to guidelines, more detailed evaluation and detection of metastatic sites of infection, and reduction in mortality. It is possible that, in our study, infectious disease consultation resulted in obtaining more blood cultures in order to prove blood clearance, which would result in a more accurate assessment of elimination. In our study, we found that the elimination of BSI was more likely in bone marrow transplant recipients, probably because of the early initiation of appropriate broad-spectrum antibiotic therapy and aggressive source control.

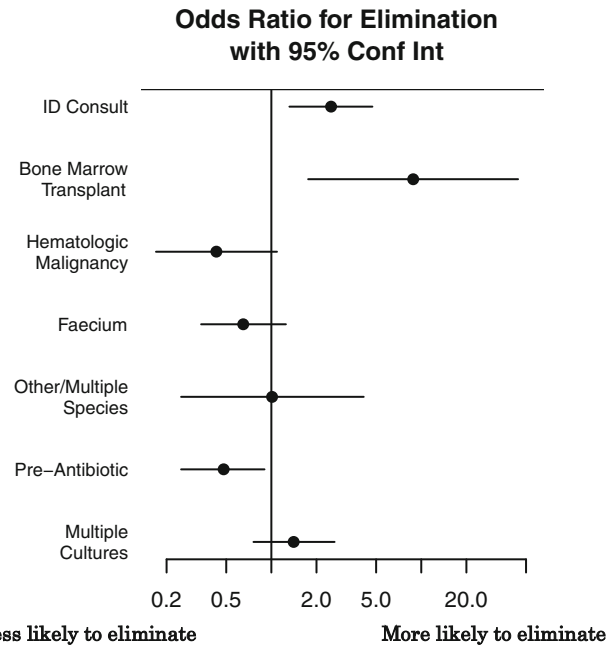

Fig. 2 shows the odds ratios of independent predictors for elimination

Our study has some limitations. First, this is a retrospective single-center study, which may limit the generalizability of the findings. Second, although we had a large number of enterococcal BSI episodes, the sample size was not large enough to detect small differences in outcome comparing single and multiple blood cultures. Third, we were not able to determine a source for all the episodes of BSI due to limitations of data availability in the electronic medical records. Fourth, we did not evaluate attributable or excess mortality from enterococcal BSI to examine whether the in-hospital death of patients with

enterococcal BSI was truly caused by enterococcal BSI, rather than other factors. While this would have been of value, in practice, it is difficult to examine the contribution of an infection to the demise of a patient with multiple underlying comorbid illnesses and who is immunocompromised, as was the case with many of our patients. These limitations notwithstanding, our findings suggest that it is not possible to routinely consider a single enterococcal blood culture as a contaminant without a review of the underlying clinical condition. As the clinical outcomes of patients with single versus multiple positive blood cultures with *Enterococcus* species were similar at our institution, it is likely that single blood cultures with *Enterococcus* represent true infection rather than contamination. Further studies should examine efficient methods to determine the likelihood of contamination versus true infection in patients with enterococcal BSIs.

Acknowledgments Part of this study was presented at IDWeek 2013, San Francisco, CA, October 2013.

Conflict of interest All authors: no reported conflict.

Funding No financial support.

References

1. Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA, Fridkin SK; National Healthcare Safety Network Team; Participating National Healthcare Safety Network Facilities (2008) NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. Infect Control Hosp Epidemiol 29(11):996–1011
2. Sievert DM, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A, Kallen A, Limbago B, Fridkin S; National Healthcare Safety Network (NHSN) Team and Participating NHSN Facilities (2013) Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. Infect Control Hosp Epidemiol 34(1):1–14
3. Pien BC, Sundaram P, Raoof N, Costa SF, Mirrett S, Woods CW, Reller LB, Weinstein MP (2010) The clinical and prognostic importance of positive blood cultures in adults. Am J Med 123(9):819–828
4. Cheah AL, Spelman T, Liew D, Peel T, Howden BP, Spelman D, Grayson ML, Nation RL, Kong DC (2013) Enterococcal bacteraemia: factors influencing mortality, length of stay and costs of hospitalization. Clin Microbiol Infect 19(4):E181–E189
5. Weinstein MP, Towns ML, Quartey SM, Mirrett S, Reimer LG, Parmigiani G, Reller LB (1997) The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. Clin Infect Dis 24(4):584–602
6. Freeman JT, Chen LF, Sexton DJ, Anderson DJ (2011) Blood culture contamination with Enterococci and skin organisms: implications for surveillance definitions of primary bloodstream infections. Am J Infect Control 39(5):436–438
7. Sexton DJ, Chen LF, Anderson DJ (2010) Current definitions of central line-associated bloodstream infection: is the emperor wearing clothes? Infect Control Hosp Epidemiol 31(12):1286–1289
8. Versalovic J; American Society for Microbiology (2011) Manual of clinical microbiology, 10th edn. ASM Press, Washington, DC
9. Siegman-Igra Y, Fourer B, Orni-Wasserlauf R, Golan Y, Noy A, Schwartz D, Giladi M (2002) Reappraisal of community-acquired bacteremia: a proposal of a new classification for the spectrum of acquisition of bacteremia. Clin Infect Dis 34(11):1431–1439
10. Hughes JM, Culver DH, White JW, Jarvis WR, Morgan WM, Munn VP, Mosser JL, Emori TG (1983) Nosocomial infection surveillance, 1980–1982. MMWR CDC Surveill Summ 32(4):1SS–16SS
11. Banerjee SN, Emori TG, Culver DH, Gaynes RP, Jarvis WR, Horan T, Edwards JR, Tolson J, Henderson T, Martone WJ (1991) Secular trends in nosocomial primary bloodstream infections in the United States, 1980–1989. National Nosocomial Infections Surveillance System. Am J Med 91(3B):86S–89S
12. Maki DG (1981) Nosocomial bacteremia. An epidemiologic overview. Am J Med 70(3):719–732
13. Bartlett JG, Louie TJ, Gorbach SL, Onderdonk AB (1981) Therapeutic efficacy of 29 antimicrobial regimens in experimental intraabdominal sepsis. Rev Infect Dis 3(3):535–542
14. Onderdonk AB, Bartlett JG, Louie T, Sullivan-Seigler N, Gorbach SL (1976) Microbial synergy in experimental intra-abdominal abscess. Infect Immun 13(1):22–26
15. Conde-Estévez D, Grau S, Albanell J, Terradas R, Salvadó M, Knobel H (2011) Clinical characteristics and outcomes of patients with vancomycin-susceptible Enterococcus faecalis and Enterococcus faecium bacteraemia in cancer patients. Eur J Clin Microbiol Infect Dis 30(1):103–108
16. Hayakawa K, Marchaim D, Martin ET, Tiwari N, Yousuf A, Sunkara B, Pulluru H, Kotra H, Hasan A, Bheemreddy S, Sheth P, Lee DW, Kamatam S, Bathina P, Nanjireddy P, Chalana IK, Patel S, Kumar S, Vahia A, Ku K, Yee V, Swan J, Pogue JM, Lephart PR, Rybak MJ, Kaye KS (2012) Comparison of the clinical characteristics and outcomes associated with vancomycin-resistant Enterococcus faecalis and vancomycin-resistant E. faecium bacteremia. Antimicrob Agents Chemother 56(5):2452–2458
17. McBride SJ, Upton A, Roberts SA (2010) Clinical characteristics and outcomes of patients with vancomycin-susceptible Enterococcus faecalis and Enterococcus faecium bacteraemia—a five-year retrospective review. Eur J Clin Microbiol Infect Dis 29(1):107–114
18. Caballero-Granado FJ, Becerril B, Cuberos L, Bernabeu M, Cisneros JM, Pachón J (2001) Attributable mortality rate and duration of hospital stay associated with enterococcal bacteremia. Clin Infect Dis 32(4):587–594
19. Pinholt M, Ostergaard C, Arpi M, Bruun NE, Schønheyder HC, Gradel KO, Søgaard M, Knudsen JD; Danish Collaborative Bacteraemia Network (DACOBAN) (2014) Incidence, clinical characteristics and 30-day mortality of enterococcal bacteraemia in Denmark 2006–2009: a population-based cohort study. Clin Microbiol Infect 20(2):145–151
20. Maki DG, Agger WA (1988) Enterococcal bacteremia: clinical features, the risk of endocarditis, and management. Medicine (Baltimore) 67(4):248–269
21. Landry SL, Kaiser DL, Wenzel RP (1989) Hospital stay and mortality attributed to nosocomial enterococcal bacteremia: a controlled study. Am J Infect Control 17(6):323–329
22. Garrison RN, Fry DE, Berberich S, Polk HC Jr (1982) Enterococcal bacteremia: clinical implications and determinants of death. Ann Surg 196(1):43–47
23. Malone DA, Wagner RA, Myers JP, Watanakunakorn C (1986) Enterococcal bacteremia in two large community teaching hospitals. Am J Med 81(4):601–606

24. Horan TC, Andrus M, Dudeck MA (2008) CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 36(5):309–332
25. Uttley AH, Collins CH, Naidoo J, George RC (1988) Vancomycin-resistant enterococci. Lancet 1(8575–8576):57–58
26. DiazGranados CA, Zimmer SM, Klein M, Jernigan JA (2005) Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal bloodstream infections: a meta-analysis. Clin Infect Dis 41(3):327–333
27. Salgado CD, Farr BM (2003) Outcomes associated with vancomycin-resistant enterococci: a meta-analysis. Infect Control Hosp Epidemiol 24(9):690–698
28. Suppli M, Aabenhus R, Harboe ZB, Andersen LP, Tvede M, Jensen JU (2011) Mortality in enterococcal bloodstream infections increases with inappropriate antimicrobial therapy. Clin Microbiol Infect 17(7): 1078–1083
29. Jang HC, Lee S, Song KH, Jeon JH, Park WB, Park SW, Kim HB, Kim NJ, Kim EC, Oh MD, Choe KW (2010) Clinical features, risk factors and outcomes of bacteremia due to enterococci with high-level gentamicin resistance: comparison with bacteremia due to enterococci without high-level gentamicin resistance. J Korean Med Sci 25(1):3–8
30. Shaked H, Carmeli Y, Schwartz D, Siegman-Igra Y (2006) Enterococcal bacteraemia: epidemiological, microbiological, clinical and prognostic characteristics, and the impact of high level gentamicin resistance. Scand J Infect Dis 38(11–12): 995–1000
31. Vydra J, Shanley RM, George I, Ustun C, Smith AR, Weisdorf DJ, Young JA (2012) Enterococcal bacteremia is associated with increased risk of mortality in recipients of allogeneic hematopoietic stem cell transplantation. Clin Infect Dis 55(6):764–770
32. Honda H, Krauss MJ, Jones JC, Olsen MA, Warren DK (2010) The value of infectious diseases consultation in Staphylococcus aureus bacteremia. Am J Med 123(7):631–637
33. Jenkins TC, Price CS, Sabel AL, Mehler PS, Burman WJ (2008) Impact of routine infectious diseases service consultation on the evaluation, management, and outcomes of Staphylococcus aureus bacteremia. Clin Infect Dis 46(7):1000–1008