Epidemiology, Management, and Risk-Adjusted Mortality of ICU-Acquired Enterococcal Bacteremia

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Background. Enterococcal bacteremia has been associated with high case fatality, but it remains unknown to what extent death is caused by these infections. We therefore quantified attributable mortality of intensive care unit (ICU)–acquired bacteremia caused by enterococci.

Methods. From 2011 to 2013 we studied consecutive patients who stayed >48 hours in 2 tertiary ICUs in the Netherlands, using competing risk survival regression and marginal structural modeling to estimate ICU mortality caused by enterococcal bacteremia.

Results. Among 3080 admissions, 266 events of ICU-acquired bacteremia occurred in 218 (7.1%) patients, of which 76 were caused by enterococci (incidence rate, 3.0 per 1000 patient-days at risk; 95% confidence interval [CI], 2.3–3.7). A catheter-related bloodstream infection (CRBSI) was suspected in 44 (58%) of these, prompting removal of 68% of indwelling catheters and initiation of antibiotic treatment for a median duration of 3 (interquartile range 1–7) days. Enterococcal bacteremia was independently associated with an increased case fatality rate (adjusted subdistribution hazard ratio [SHR], 2.68; 95% CI, 1.44–4.98). However, for patients with CRBSI, case fatality was similar for infections caused by enterococci and coagulase-negative staphylococci (CoNS; adjusted SHR, 0.91; 95% CI, .50–1.67). Population-attributable fraction of mortality was 4.9% (95% CI, 2.9%–6.9%) by day 90, reflecting a population-attributable risk of 0.8% (95% CI, .4%–1.1%).

Conclusions. ICU-acquired enterococcal bacteremia is associated with increased case fatality; however, the mortality attributable to these infections is low from a population perspective. The virulence of enterococci and CoNS in a setting of CRBSI seems comparable.

Keywords. bacteremia; intensive care unit; enterococcus; bloodstream infection; mortality.

The clinical management of bacteremia depends on the presumed source of infection. Bacteremia that occurs more than 48 hours after intensive care unit (ICU) admission and is thus assumed to be newly acquired in the ICU can often be related to catheter-related bloodstream infections (CRBSIs) or ventilator-associated pneumonias [1] but may frequently also be of unknown source and significance. As critically ill patients frequently have indwelling central venous and arterial catheters, critical care physicians often face questions regarding optimal catheter management and antimicrobial treatment in patients with ICU-acquired bacteremia [2, 3]. Heterogeneity of the underlying conditions and clinical presentation of infection, uncertainty about the interpretation of blood culture results (ie, pathogen or contaminant), and various assumptions about the virulence of the cultured microorganism all contribute to variability in the clinical management of ICU-acquired bacteremia [4, 5]. A more aggressive

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clinical response will typically be triggered in case of a highly virulent pathogen compared with microorganisms with presumed low virulence. These differences are also reflected by international guidelines [6, 7].

Enterococci are frequent causes of ICU-acquired bacteremia [8], but their clinical significance is not self-evident. Although enterococcal bacteremia most frequently occurs in severely ill patients and has been associated with mortality rates ranging from 23% to 48% [9–11], many physicians consider this pathogen to be of low virulence. In fact, enterococci are natural colonizers of the human gastrointestinal tract and have been used as a probiotic for decades [12]. It remains uncertain whether enterococcal bacteremia is a true cause of mortality or merely a marker of morbidity associated with higher risk of dying. Therefore, we describe the epidemiology and clinical management of ICU-acquired enterococcal bacteremia and estimate the mortality that is caused by this infection from both the individual patient and the population perspective.

METHODS

Patients and Measurements

This evaluation was performed as part of an ongoing prospective observational cohort study in the mixed ICUs of 2 tertiary care hospitals in the Netherlands [13]. Selective digestive decontamination was part of standard care in both centers [14]. The institutional review board approved an opt-out consent method by which participants and family members were notified of the study by a brochure provided at ICU admission with an attached opt-out card that could be completed by the patient or by his/her legal representative in case they declined to participate (protocol number 10–056C).

For the current study, we included consecutive patients having an ICU length of stay of more than 2 days between January 2011 and March 2013. From this cohort, patients with enterococcal bacteremia occurring during the first 2 days in the ICU were excluded. Trained observers prospectively collected baseline patient characteristics and markers of disease severity as well as daily clinical events and illness characteristics during the ICU admission. ICU-acquired bacteremia was defined as a first positive blood culture occurring more than 2 days after ICU admission (without a prior positive blood culture with the same pathogen for at least 30 days). Recurrent bacteremia was defined as 1 or more consecutive positive blood culture(s) with the same pathogen taken more than 3 days after the first positive sample. The most likely source of each bacteremia was determined by post hoc physician assessment, using strict diagnostic criteria [13]. In addition, the clinical management of indwelling catheters, the initiation of antimicrobial therapy, and various clinical outcomes related to the bacteremia event were recorded.

Descriptive Analyses

The incidence of ICU-acquired enterococcal bacteremia and associated patient characteristics are reported in comparison to other commonly isolated bloodstream pathogens using nonparametric descriptive statistics (ie, χ^2 and Kruskal–Wallis tests). Because decisions regarding catheter management and antibiotic therapy depend on the presumed source of bacteremia, we restricted the reporting of management practices to cases of bacteremia that were attributed to CRBSIs only.

Association With Outcome

Cox proportional hazards models were used to assess the association between enterococcal bacteremia and mortality. For this analysis, ICU discharge and death were considered as competing events [15], and the occurrence of enterococcal bacteremia was fitted as a time-dependent variable [16]. A competing risks analysis provides 2 measures of association. First, the cause-specific hazard ratio (CSHR) describes the instantaneous effect on the outcome of interest, given that the patient is still at risk. In our case, it estimates the direct effect of enterococcal bacteremia on the rate of death in the ICU. Second, the subdistribution hazard ratio (SHR) describes the risk of dying from enterococcal bacteremia while accounting for the competing risk of ICU discharge. To correct for confounding, we decided a priori to adjust for age, gender, non-European ethnicity, Charlson comorbidity index, surgical reason for admission, previous ICU admission, and acute physiology and chronic health evaluation (APACHE) IV score, which were considered to be likely associated with both enterococcal bacteremia as well as mortality based on careful consideration of the literature [8, 17, 18].

As confounding may remain because markers of illness at the time of ICU admission may not be fully representative of the disease state at the time of bacteremia (which typically does not occur until the second week of admission), marginal structural modeling was subsequently performed to adjust for the evolution of disease severity prior to the onset of bacteremia [19, 20]. First, such analysis involves the estimation of daily probabilities of acquiring enterococcal bacteremia in the ICU using a multivariable logistic regression model that includes markers of disease severity on a daily basis. In a second analysis step, these probabilities are used to calculate patient-specific inversed probability weights, which are then included as a summary measure of all relevant covariables in the final Cox regression model.

Comparative Analysis of Enterococci vs Coagulase-Negative Staphylococci

To further evaluate the impact of ICU-acquired enterococcal bacteremia on patient outcome, we compared mortality rates between patients with CRBSI due to either enterococci or

coagulase-negative staphylococci (CoNS). We restricted this analysis to CRBSI cases in order to reduce confounding. We chose a direct comparison to CoNS because this group of microorganisms represents the most frequent cause of ICU-acquired bacteremia and is widely considered to be of low virulence [21]. As for the primary analysis, competing risk survival regression was used, with the follow-up time starting at the time of bacteremia and ending at either death or discharge from the ICU [15]. We adjusted for both baseline patient characteristics (age, surgical reason for ICU admission, and Charlson comorbidity index) as well as illness characteristics at the time of bacteremia (sequential organ failure assessment [SOFA] score from the day before bacteremia, immunosuppression, and presence of intravascular or orthopedic implants).

Population-Attributable Mortality

Finally, we used a multistate model to estimate the fraction of ICU mortality that was attributable to enterococcal bacteremia on the population level, again taking both the time-dependent nature of bacteremia occurrence and competing events into account [22]. For formal definitions of risk difference, population-attributable risk, and population-attributable fraction of ICU mortality, refer to the Supplementary Materials. Bootstrapping was used to estimate the confidence intervals (CI) for the population-attributable risk and population-attributable fraction of mortality [23].

All analyses were performed using SAS 9.2 (Cary, North Carolina) and R 2.15.1 software (R Foundation for Statistical Computing, Vienna, Austria; package "mstate"). *P* values <.05 were considered to be statistically significant.

RESULTS

Incidence

Among 3080 included patients, 218 (7.1%) had 266 episodes of ICU-acquired bloodstream infection (Figure 1). Enterococci were responsible for 76 of these episodes, yielding an incidence rate of 3.0 (95% CI, 2.3–3.7) events per 1000 patient-days at risk (Table 1). Median time from ICU admission to bacteremia onset was 9.5 (interquartile range [IQR], 7.0–17.5) days. Thirty-two patients acquired bacteremia with 2 different pathogens and 8 patients acquired 3 different pathogens at any time during their ICU admission.

Patient Characteristics

Patients with ICU-acquired enterococcal bacteremia tended to have more chronic comorbidities (median Charlson comorbidity score, 7.4 vs 5.5; $P = .08$) and higher severity of disease at baseline (median APACHE IV score, 91 vs 86; $P = .13$) compared with patients who had ICU-acquired bacteremia caused by other pathogens (Table 1). Furthermore, these patients had more often been previously admitted to the ICU (22% vs 13%; $P = .05$). On the day that bacteremia was acquired, those with enterococcal bacteremia also had higher median SOFA scores (10 vs 7; $P < .01$) and more frequently had intravascular or orthopedic implants (41% vs 24%; $P < .01$) compared with those with bacteremia caused by other pathogens (Table 2).

Crude Associations With Mortality

Observed ICU mortality was 47% in patients with enterococcal bacteremia vs 15% in those without enterococcal bacteremia ($P < .01$), yielding a crude risk difference of 32% (95% CI, 21%–44%). The mortality associated with enterococci was also higher than the 33% crude mortality in patients with ICU-acquired bacteremia caused by other pathogens combined ($P = .03$). In 55 of 76 patients with enterococcal bacteremia, more than 50% of all blood cultures taken on the first day of bacteremia grew enterococci (indicating a high bacterial load). ICU mortality in these patients was 53% compared with 33% in patients having fewer positive blood cultures ($P = .12$). A second (concurrent) pathogen was cultured in 33 of 76 (43%) patients with enterococcal bacteremia. ICU mortality was 52% and 44%

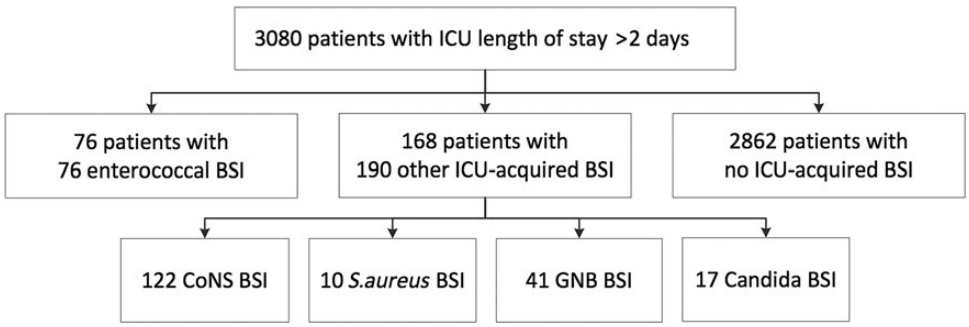

Figure 1. Patient inclusion. Abbreviations: BSI, bloodstream infection; CoNS, coagulase-negative staphylococci; GNB, gram-negative bacteria; ICU, intensive care unit.

Table 1. Patient Characteristics at Baseline

Characteristic	ICU-Acquired Bacteremia					Reference
	Enterococci (n = 76)	Coagulase-Negative Staphylococci (n = 122)	*Staphylococcus aureus* (n = 10)	Gram-Negative Rods (n = 41)[a]	Candida Species (n = 17)	No Bacteremia (n = 2862)
Age, yr	66 (54–73)	59 (49–69)	57 (42–78)	64 (52–71)	52 (43–65)	62 (50–71)
Male sex	50 (66)	83 (68)	6 (60)	21 (51)	11 (65)	1743 (61)
Non-European ethnicity	9 (12)	24 (20)	4 (40)	6 (15)	3 (18)	300 (10)
Charlson comorbidity index	7.4 (3.0–12.4)	5.6 (2.0–12.6)	5.7 (0.0–8.1)	6.4 (2.5–10.4)	3.9 (2.0–6.4)	4.6 (1.0–10.9)
Surgical reason for admission	27 (36)	47 (39)	1 (10)	18 (44)	7 (41)	1234 (43)
Previous ICU admission	17 (22)	18 (15)	0 (0)	3 (7)	3 (18)	373 (13)
Acute physiology and chronic health evaluation IV score	91 (71–114)	86 (66–103)	86 (60–115)	86 (65–100)	78 (69–97)	72 (54–92)
ICU mortality	36 (47)	37 (30)	4 (40)	16 (39)	6 (35)	425 (15)

Data are presented in median (interquartile range) or in absolute number (percentage). Because some patients had ICU-acquired bacteremia caused by multiple pathogens, the total number of bacteremia is more than the total number of patients in this study.

Abbreviation: ICU, intensive care unit.

[a] Among gram-negative rods, *Pseudomonas aeruginosa* (n = 10) and *Escherichia coli* (n = 9) were the most frequently isolated pathogens.

in patients with polymicrobial vs enterococcal bacteremia, respectively ($P = .53$).

Risk-Adjusted Mortality

Associations between enterococcal bacteremia, ICU discharge, and ICU death are listed in Table 3 and Supplementary Table 1. After adjustment for imbalances in patient characteristics at baseline, accounting for the time-dependent nature of the exposure, and including ICU discharge as a competing risk for mortality, ICU-acquired enterococcal bacteremia was associated with an increased overall risk of death in the ICU (SHR, 5.29; 95% CI, 3.51–7.96). After further adjustment for potentially remaining confounders by accounting for the evolution of disease severity prior to bacteremia onset using a marginal structural model analysis, an association with mortality remained (adjusted SHR, 2.68; 95% CI, 1.44–4.98). Cause-specific analyses showed that this was the combined result of both (a trend to) a reduced rate of ICU discharge (adjusted CSHR, 0.83; 95% CI, .62–1.08) and (a trend to) an increased daily risk of death (adjusted CSHR, 1.10; 95% CI, .61–1.98).

Comparative Analysis of Enterococci vs CoNS

Forty-four of 76 episodes (58%) of enterococcal ICU-acquired bacteremia were considered catheter related, as were 76 of 122 (62%) episodes of CoNS bacteremia events. In patients with CRBSI, the rate of replacement or removal of indwelling catheters was similar during episodes caused by enterococci and CoNS (Table 4). However, patients with CRBSI caused by enterococci more frequently received targeted antimicrobial treatment, with a trend for longer durations. The risk of ICU death was similar in patients with CRBSI due to enterococci and CoNS, both by crude analysis (observed mortality, 43% vs 37%; $P = .49$; CSHR, 1.32; 95% CI, .73–2.40) as well as in multivariable-adjusted analyses (SHR, 0.91; 95% CI, .49–1.67). The cumulative incidence of recurrent bacteremia was 14% and 17% for CRBSIs caused by enterococci and CoNS, respectively ($P = .62$).

Comparative Analysis of CRBSI vs non-CRBSI

Enterococcal bacteremia due to CRBSI appeared to be associated with lower case fatality than enterococcal bacteremia due to other causes (crude mortality, 43% vs 53%; $P = .39$), although this difference did not reach statistical significance. After extensive correction for time-dependent confounding and competing events, comparable effect estimates were found in both subgroups (Supplementary Tables 2 and 3).

Population-Attributable Mortality

The cumulative incidence of death in the observed cohort (n = 3080) and the mortality that would be expected if all episodes of enterococcal bacteremia could be prevented are shown in Figure 2. The population-attributable fraction of mortality associated with ICU-acquired enterococcal bacteremia was 4.9% (95% CI, 2.9%–6.9%) by day 90 (Supplementary Figure 1), which translates to a population-attributable risk of 0.8% (95% CI, .4%–1.1%).

Table 2. Patient Characteristics at the Day of Intensive Care Unit–Acquired Bacteremia

Characteristic	Enterococcus (n = 76)	Coagulase-Negative Staphylococcus (n = 122)	*Staphylococcus aureus* (n = 10)	Gram-Negative Rod (n = 41)	Candida Species (n = 17)
Clinical characteristics:					
Day of ICU admission	10 (7–18)	12 (7–21)	12 (4–35)	12 (8–24)	8 (6–13)
Sequential organ failure assessment score from the previous day	10 (6–13)	7 (4–10)	5 (4–9)	8 (4–12)	12 (10–15)
Use of renal replacement therapy	29 (38)	25 (20)	2 (20)	13 (32)	10 (59)
Use of mechanical ventilation	66 (87)	109 (89)	10 (100)	36 (88)	15 (88)
Immunosuppression[a]	33 (43)	38 (31)	2 (20)	16 (39)	12 (71)
Presence of intravascular or orthopedic foreign bodies	31 (41)	27 (22)	0 (0)	15 (37)	4 (24)
Indwelling catheters:					
Arterial	70 (92)	113 (93)	8 (80)	38 (93)	17 (100)
Pulmonary artery	4 (5)	3 (2)	0 (0)	1 (2)	0 (0)
Short-term CVC (non-RRT)	52 (68)	79 (65)	4 (40)	28 (68)	16 (94)
RRT	26 (34)	30 (25)	1 (10)	14 (34)	12 (71)
Long-term CVC	2 (3)	3 (2)	0 (0)	1 (2)	1 (6)
Other type	2 (3)	8 (7)	0 (0)	0 (0)	1 (6)
Prior antibiotic exposure during ICU stay:					
Vancomycin	3 (4)	7 (6)	0 (0)	8 (20)	3 (18)
Gentamycin	2 (3)	1 (1)	0 (0)	0 (0)	0 (0)
Amoxicillin	1 (1)	4 (3)	0 (0)	5 (12)	2 (12)
Flucloxacillin/clindamycin	7 (9)	5 (4)	0 (0)	1 (2)	3 (18)
Cephalosporin	12 (16)	16 (13)	0 (0)	4 (10)	4 (24)
Most likely source of bacteremia:					
Catheter infection	44 (58)	76 (62)	4 (40)	11 (27)	11 (65)
Abdominal	16 (21)	6 (5)	0 (0)	8 (20)	1 (6)
Pulmonary	2 (3)	0 (0)	4 (40)	11 (27)	0 (0)
Urinary tract	0 (0)	0 (0)	0 (0)	3 (7)	0 (0)
Endocarditis	2 (3)	0 (0)	2 (20)	1 (2)	0 (0)
Wound	2 (3)	4 (3)	0 (0)	2 (5)	1 (6)
Other	2 (3)	10 (8)	1 (10)	1 (2)	0 (0)
Unknown	15 (20)	36 (30)	1 (10)	7 (17)	6 (35)
Contamination	2 (3)	20 (16)	1 (10)	0 (0)	0 (0)
Severity of bacteremia:					
High bacterial load[b]	55 (72)	72 (59)	8 (80)	35 (83)	11 (65)
Bacteremia recurrence[c]	11 (14)	20 (16)	1 (10)	5 (12)	5 (29)

Some bacteremia cases were allocated to 2 likely sources of infection. Data are presented in median (interquartile range) or in absolute number (percentage).

Abbreviations: CVC, central venous catheter; ICU, intensive care unit; RRT, renal replacement therapy.

[a] Immunosuppression was defined as solid organ transplantation, stem cell transplantation or chemo-radiotherapy during current hospital admission, neutropenia (absolute neutrophil count $<1.0 \times 10^9$/L) or corticosteroid use (hydrocortisone >100 mg or equivalent) at the time of bacteremia.

[b] High bacterial load was presumed if more than 50% of blood culture bottles obtained on the first day of the bacteremia episode showed growth for the indicated pathogen.

[c] Bacteremia recurrence was defined by the presence of 1 or more consecutive blood cultures (obtained more than 3 days after the first positive sample) showing growth for the same pathogen.

DISCUSSION

In the present study, ICU-acquired enterococcal bacteremia occurred at a rate of 3.0 events per 1000 days at risk. These events presented with a peak incidence approximately 10 days after ICU admission and occurred in the most severely ill and in those with chronic illnesses. As a result, comorbidities and time-dependent bias largely accounted for the high crude ICU case fatality rates that were observed in patients with enterococcal bacteremia. However, despite the use of advanced

Table 3. Associations Between Enterococcal Bacteremia and Clinical Outcome

Cox Proportional Model	ICU Discharge CSHR (95% CI)	ICU Mortality CSHR (95% CI)	ICU Mortality SHR (95% CI)
Crude model with adjustment for: time-varying onset of bacteremia	0.51 (0.40–0.66)	2.27 (1.63–3.16)	7.99 (5.63–11.32)
Multivariable model with adjustment for: time-varying onset of bacteremia and baseline covariables[a]	0.57 (0.44–0.74)	1.70 (1.14–2.52)	5.29 (3.51–7.96)
Multivariable model with adjustment for: time-varying onset of bacteremia, baseline covariables[a], and evolution of disease prior to onset of bacteremia[b]	0.83 (0.62–1.08)	1.10 (0.61–1.98)	2.68 (1.44–4.98)

Data are presented as hazard ratios with 95% confidence intervals. The cause-specific hazard ratio estimates the direct effect of enterococcal bacteremia on clinical outcome (ie, discharge alive or death). The subdistribution hazard ratio is a summary measure of both separate cause-specific hazards and estimates the overall risk of dying from enterococcal bacteremia while taking into account the competing event of discharge alive.

Abbreviations: CI, confidence interval; CSHR, cause-specific hazard ratio; ICU, intensive care unit; SHR, subdistribution hazard ratio.

[a] Baseline covariables were age, sex, non-European ethnicity, prior ICU admission during the hospital stay, surgical reason for admission, Charlson comorbidity index, and acute physiology and chronic health evaluation IV score.

[b] To predict enterococcal bacteremia on each day we included the sequential organ failure assessment (SOFA) score, prior amoxicillin or vancomycin administration, and abdominal perforation or surgery as time-dependent covariables. For SOFA and amoxicillin/vancomycin administration, we explicitly used lagged daily values from 2 days before to avoid possible overadjustment as the scores measured within 24 hours before the onset of bacteremia may have been influenced by an insidious onset of bacteremia.

methodologies to adjust for potential confounding by disease severity prior to bacteremia onset, a significant independent association with mortality remained. From a population perspective, the excess mortality that could be attributed to enterococcal bacteremia in the ICU was low nonetheless (0.8% by day 90). This modest impact may have resulted from the relatively low incidence of these events, limited virulence of the bug, or both. In any respect, direct comparisons suggested that the virulence of enterococci and CoNS in a setting of CRBSI is similar.

The Infectious Diseases Society of America (IDSA) guidelines recommend that all catheters be removed and antimicrobial treatment be initiated for 7 to 14 days in cases of suspected CRBSI due to enterococci [7]. However, in the current setting, only 68% of indwelling catheters were pulled and just 82% of patients received appropriate antimicrobial treatment for a median duration of only 3 days. In part, this observation might be explained by a lenient attitude of attending clinicians regarding the presumed virulence of enterococci and the focus of infection. Abdominal infections were the second most frequent source of enterococcal bacteremia in our study. The joint IDSA and Surgical Infection Society guidelines currently recommend antibiotic treatment for 4 to 7 days in the presence of adequate source control and depending on clinical response [24]. In our study, appropriate systemic antibiotics were given for 6.5 (IQR, 3.5–8.5) days for enterococcal abdominal

Table 4. Intravascular Catheters and Antimicrobial Management in the Subgroup of Catheter-Related Bloodstream Infections

Clinical Management	Enterococci (n = 44)	Coagulase-Negative Staphylococci (n = 76)	*P* Value
Number (%) of indwelling catheters that were removed within 3 d	63/92 (68)	95/161 (59)	.14
Peripheral arterial catheter[a]	22/40 (53)	35/73 (48)	NA
Short-term central venous catheter (non-RRT catheter)[a]	28/36 (75)	36/52 (69)	NA
RRT catheter[a]	11/14 (73)	18/25 (66)	NA
Number (%) of (appropriate) antibiotic treatment against pathogen[b] within 3 d	36/44 (82)[c]	47/76 (62)	.02
Duration of antibiotic treatment[d]	3 (1–7)	2 (1–4)	.09

Data are presented in absolute number (percentage) unless otherwise specified.

Abbreviations: NA, not applicable; RRT, renal replacement therapy.

[a] Percentages were calculated for the 3 most frequent catheters. The denominators for each type of catheter and pathogen group were different.

[b] Appropriate treatment was defined as vancomycin for amoxicillin-resistant enterococci, vancomycin or amoxicillin for amoxicillin-sensitive enterococci, and vancomycin for coagulase-negative staphylococci.

[c] Appropriate treatment in the first 3 days after onset of bacteremia consisted of 92% vancomycin monotherapy, 3% amoxicillin monotherapy, and 5% vancomycin-amoxicillin switch therapy.

[d] Duration of antibiotic treatment was only calculated for patients for whom treatment was stopped before the last day in the intensive care unit (ICU; 92%) because registration of antibiotic treatment after ICU discharge was not performed. Thus, for 8% of cases, it remained uncertain whether antibiotic treatment was continued after ICU discharge.

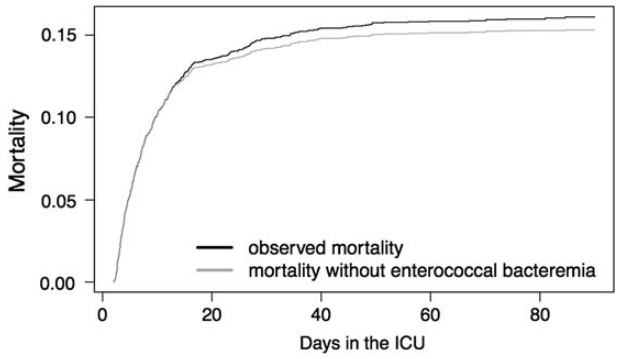

Figure 2. Observed intensive care unit (ICU) mortality vs expected ICU mortality without enterococcal bacteremia. This figure presents the observed ICU mortality in the patient cohort (black line) and the expected mortality if all ICU-acquired enterococcal bacteremia in the same ICU patient population had been prevented (light gray line). Thus, the light gray line represents mortality both in patients who never acquired enterococcal infection and in those who did acquire bacteremia but, in the (hypothetical) situation by which all exposure time to enterococcal bacteremia, would be annihilated.

infections. Although evidence regarding optimal duration of antibiotic treatment for enterococcal infections is lacking, it is conceivable that the increased risk of death that remained despite optimal adjustment for confounding was caused, in part, by clinical management that was insufficiently aggressive. Nonetheless, the observed case fatality rate in our study cohort was compatible with other reported mortality rates of bloodstream infections in the ICU, varying from 35% to 50% [8]. Furthermore, results from a recent metaanalysis suggest that antibiotic therapy for shorter periods than recommended by the IDSA guideline seem to be as effective as longer-duration therapy in achieving clinical cure, microbiologic cure, and survival in critically ill patients with bacteremia [25]. In particular, a large randomized controlled trial in patients with complicated intraabdominal infections recently showed that antibiotic therapy for a fixed duration of 4 days was as effective as traditional, longer treatment [26]. Nevertheless, we cannot exclude the possibility that some subgroups in our study population would have benefited from more prolonged antibiotic treatment.

Strengths of our study include the use of advanced methodologies to adjust for various sources of potential confounding. Moreover, because data were prospectively collected using validated protocols [13], the risk of information bias was minimized. Nonetheless, we cannot completely exclude the presence of residual confounding or bias, and some limitations with regard to the interpretation of our results must be considered. First, our study was performed in 2 centers in the Netherlands only and thus may not reflect ICU practice in all settings. As both hospitals used selective digestive decontamination protocols, the incidence of ICU-acquired bacteremia caused by gram-negative bacteria and *Candida* species is probably lower than in settings not using these strategies [27]. Yet, there is no evidence that these interventions influence either the incidences or outcomes of ICU-acquired bacteremia caused by enterococci and CoNS. Indeed, in a multicenter cluster randomized controlled trial in which selective digestive decontamination was compared with standard care, the incidence of ICU-acquired enterococcal bacteremia was similar in both groups [27]. Furthermore, the incidence that was observed in our study (ie, 76 episodes among 3080 patients, or 2.5%) lies well within the 0.9% to 5.4% range of previously documented occurrence rates for enterococcal bacteremia [17, 28, 29]. However, it is important to consider that our study exclusively focused on infections that were newly acquired in the ICU and that the total incidence of bacteremia events due to enterococci in an ICU setting (or in the hospital at large) may thus be higher. In fact, we observed 108 patients having at least a single blood culture growing enterococci during ICU admission; however, only 76 of these events were considered ICU-acquired based on the definitions used in our study. Second, as all cultured enterococci in our study were susceptible to vancomycin, our findings may not apply to settings with a high prevalence of infections caused by vancomycin-resistant enterococci. Third, it is plausible that some events that we considered to represent enterococcal bacteremia were, in fact, clinically irrelevant and should have been considered as merely contaminated blood draws. However, case fatality seemed to be increased in cases of higher bacterial loads, which underlines the clinical relevance of finding a blood culture positive for enterococci. Furthermore, from a clinical perspective, it is frequently very difficult to distinguish true infection from contamination, even in retrospect. Case fatality also appeared higher in polybacterial vs monobacterial bloodstream infections involving enterococci. Although interesting, it is important to stress that these findings are limited by small numbers of observations and that we did not perform multivariable modeling in these subgroups.

In conclusion, our findings show that ICU-acquired enterococcal bacteremia is independently associated with increased case fatality, although the population-attributable mortality of these infections remains low. The high crude mortality observed in cases of enterococcal bacteremia, in general, and in cases of non-CRBSI, in particular, can be largely explained by concomitant patient and disease characteristics, suggesting that these bloodstream infections may, for the most part, be markers of impending complications that carry a high risk of death in the ICU, rather than being causes of death out of their own. This hypothesis is supported by our observation that patients with CRBSI caused by enterococci had similar outcomes to those with CRBSI caused by CoNS, indicating that the virulence of enterococci in this setting is indeed low.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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