Trends in incidence of vancomycin-resistant Enterococcus colonization and bacteremia among allogeneic hematopoietic cell transplant recipients at a large cancer center

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Abstract

Trends in incidence of vancomycin-resistant Enterococcus colonization and bacteremia among allogeneic hematopoietic cell transplant recipients at a large cancer center

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Background: Vancomycin-resistant Enterococcus (VRE) are important hospital-acquired pathogens among hematopoietic cell transplant (HCT) recipients. We examined the incidence and outcomes of patients with VRE colonization and bacteremia (VREB) over a ten-year period at a center that routinely screens and uses barrier precautions for VRE.

Methods: Adults receiving their first allogeneic HCT at our center between September 2007 and August 2016 were eligible for inclusion. Patients who were positive either by standardized pre-HCT stool/rectal screening or at any point two years prior to HCT were considered VRE colonized. Patients with acquired VRE were those with positive VRE cultures only post-HCT. Colonization and 100-day post-HCT VREB incidence rates were compared over time using linear regression. Cox proportional hazards models were constructed to assess the relationship between 100-day mortality and: a) pre-HCT colonization, and b) the number of days with sequential VREB cultures. Pre-transplant Assessment of Mortality (PAM) scores were calculated to allow adjustment for underlying disease severity.

Results: Of 1,492 eligible HCT recipients, 203 (14%) were colonized with VRE pre-HCT; an additional 90 (6.0%) acquired VRE colonization post-HCT. Forty-two patients (2.8%) developed VREB, the majority among those colonized with VRE (32 [76%] vs. 10 [24%] non-colonized). The cumulative incidence of VREB for the cohort was 2.9 per 10,000 patient-days. Over the study period, there were no significant changes in VRE colonization or VREB (p-values>0.1). Those with multiple days with positive VRE blood cultures had higher mortality than those with one positive culture (HR 3.23; 95%CI: 0.88, 11.8). Patients

with pre-HCT colonization had an increased risk of death compared to non-colonized patients in an unadjusted model (HR 2.1: 95%CI: 1.4, 3.2) and after adjustment by PAM score (HR = 2.2; 95%CI: 1.5, 3.3). Patients with higher PAM scores and VRE colonization pre-HCT had higher mortality than non-colonized patients with high PAM scores.

Conclusion: Despite nearly 15% of patients with pre-HCT colonization in our cohort, VREB was an infrequent post-HCT complication. We identified a subgroup of patients at high risk of VREB who may be targeted for VRE-specific measures. Studies examining the impact of antimicrobial stewardship programs are needed to inform infection prevention interventions.

Introduction

Hematopoietic cell transplant (HCT) recipients experience significant morbidity and mortality due to bloodstream infections, which occur in 20-40% of transplant patients.[1–3] Vancomycin-resistant enterococci (VRE) began to emerge in 1991, and recent reports suggest VRE is one of the leading causes of bacteremia in this population.[4–6] VRE has become a common hospital-acquired infection and gastrointestinal (GI) tract colonization rates are between 5 and 61% among HCT patients; GI colonization is strongly associated with VRE bacteremia (VREB).[4, 5, 7–9] Common risk factors for colonization include previous use of vancomycin, recent hospitalization, use of indwelling catheters, and immunosuppression, all of which are common among HCT recipients.[10] VRE colonization, both pre- and post-transplant, and VRE bacteremia (VREB) in the post-transplant period are associated with increased mortality.[7, 11–13]

Several infection prevention (IP) interventions have been developed to reduce the burden of VRE in this population. The Centers for Disease Control and Prevention guidelines for preventing VRE in healthcare settings recommend implementation of one or more of the following: active surveillance for GI colonization, contact precautions for colonized or infected patients, and standard environmental cleaning with effective disinfectant; the combination of interventions and duration of contact precautions decisions are up to individual centers.[14] Several cancer centers have limited the use of or discontinued routine isolation of colonized patients with no evidence of increasing VRE incidence,[15, 16] while others experienced a dramatic rise in VRE after discontinuing isolation practices.[17] Data regarding more recent changes in practice, including daily chlorhexidine wipes and enhanced room disinfection standards (activated hydrogen peroxide, UV disinfection), in HCT populations are limited.[18–20]

Reports have suggested that VRE is less virulent than other bacteria and that underlying disease and/or other complications may be responsible for the increased mortality associated with bacteremia.[5, 21] Several studies have accounted for disease severity and age in their analysis but few studies have been done to assess the impact of duration of bacteremia on mortality. To better understand IP interventions effects on VREB this study examines changes in incidence of VRE colonization and bacteremia over the past decade, investigates the association between colonization, number of sequential positive blood cultures and mortality, and describes patterns for additional drug resistance which have emerged among VRE isolates at a large cancer center.

Methods

Study population

All adult (>18 years of age) patients receiving an allogenic HCT between September 1st, 2007 and August 31st, 2016 at Seattle Cancer Care Alliance / Fred Hutchinson Cancer Research Center (FHCRC) were eligible for inclusion. For those patients who had undergone multiple transplants, only the first transplant at the center was included in these analyses. Those HCT recipients who were never screened for VRE or only screened post-HCT were excluded from the primary analysis. The study was approved by the FHCRC Institutional Review Board.

VRE-specific infection prevention practices

HCT recipients at the center undergo an initial VRE GI screening prior to transplantation as part of local standard practice guidelines. To identify VRE positive patients, HCT recipients undergo a rectal swab or swab from stool in the pre-transplant period, and post-transplant inpatients undergo weekly VRE rectal or stool swabs. All swabs are plated on CHROMagar™ to identify VRE colonization. Local infection prevention policies were modified from SHEA Guidelines,[22] where patients with VRE are placed into contact precautions for the duration of care at the center regardless follow-up screening results. As part of a center-wide effort to decrease overall blood stream infections, daily chlorohexidine gluconate (CHG) bathing was initiated in beginning in January 2010. Inpatients and outpatients are instructed to perform daily bathing with 2% CHG impregnated wipes (Sage® Products). Beginning in 2014, UV disinfection (Xenex™) was added to terminal cleaning for inpatient rooms occupied by HCT recipients with a multi-drug resistant infections.

Data collection

Study data were extracted from a prospectively collected database that includes information on demographic, transplant, and clinical data of HCT recipients. Allogeneic HCT recipients are cared for at the center for a minimum of 100 days post-transplant, ensuring thorough data collection over this time period. Additional clinical outcome data and antibiotic susceptibility profiles were collected through electronic medical record review.

Definitions

The primary outcome of interest was VREB during the first 100 days post-HCT, and was defined as a blood culture positive for any enterococcal species with resistance or intermediate susceptibility to vancomycin. VRE colonization was defined by detection of VRE from stool or rectal screening during the pre-transplant screen or at any point prior to HCT. Patients found to be either colonized after initial negative results, or those that developed VREB with prior negative stool screening were considered to have acquired VRE during the post-transplant period. VRE colonization start date was defined as the day of detection in the pre-transplant period, while acquired VRE colonization date was defined at the time point during the post-transplant period following detection of colonization.

Vancomycin-susceptible enterococci (VSE) were defined as isolation of any enterococcal species from blood cultures that were sensitive to vancomycin based on Clinical and Laboratory Standards Institute (CLSI) guidelines. In addition, isolates displaying additional resistance or intermediate susceptibility to other enterococcal-specific antibiotics (linezolid, daptomycin, quinupristin-dalfopristin, gentamicin, and/or streptomycin) were also captured during data review. Standard sensitivity panels were completed using Kirby-Bauer (KB) methods, except for daptomycin and linezolid where sensitivities were identified using E-test methods. Starting in 2016, the Verigene® gram positive blood culture test (Luminex Corp.) was used to identify blood culture isolates and assess sensitivity patterns; KB and E-test methods were used to confirm initial results. All screening stool tests and blood cultures were completed at the University of Washington Microbiology Clinical Laboratory.

An enterococcal isolate obtained more than 30 days from the last positive blood culture or those with differing antimicrobial resistance profiles were considered secondary bacteremia events; only primary bacteremia events were included in survival analyses. Polymicrobial bacteremia was defined as isolation of two or more bacterial species from the same blood culture. Persistent bacteremia was defined as the identification of positive VRE samples >1 day, and total period of persistence was defined as the time from the first positive blood culture to the last positive blood culture in 24 hour increments. We used the Pre-transplant Assessment of Mortality (PAM) score[23] to assess pre-transplant risk and graft-vs-host disease (GVHD) was categorized according to the NIH classification system.[24] Isolation-days were defined as the time from initial VRE detection, whether via rectal/stool screening or blood cultures, to 100-days post-HCT or death, whichever came first.

Statistical analysis

To estimate trends in incidence of VRE colonization and bacteremia, data were aggregated into monthly time intervals. Each HCT recipient contributed person-time from transplant to 100 days post-HCT or death, whichever came first. Trajectories of incidence rates over time were compared in the pre- and post-intervention periods using an interrupted time series analysis by comparing the slopes of a linear regression model.[25] This allowed for evaluation of the secular trend, immediate changes after intervention implementation (e.g. CHG bathing), and the long-term effect of the intervention.[26]

The 100-day all-cause mortality was compared between one and multiple VRE positive blood cultures using log-rank and Kaplan-Meier tests. A Cox proportional hazards model was constructed to determine the relationship between the number of sequential VRE positive blood cultures and mortality. Time at risk began the day of first post-transplant VRE blood culture isolation for each case. Censoring occurred at 100 days post-HCT, death, or relapse, whichever occurred first. The number of VRE positive blood cultures was dichotomized (one vs. multiple) for the analysis; this exposure was incorporated into the model as time-varying such that patients could contribute time-at-risk with one positive culture until the time of a subsequent positive culture. In addition to an unadjusted model, a model adjusting for PAM score was also performed. For the purposes of the VREB analysis PAM score was dichotomized into (low [<24], and mid/high [≥24]). The 100-day all-cause mortality was compared for pre-HCT VRE colonization vs. never colonized using PAM categories of <17, 17-23, 24-30, and >30 with time at risk beginning at day of transplant. All categorical variables were compared using Chi-square or Fisher exact tests and continuous variables were compared using Student's t-tests or Mann-Whitney U test. All p-values of 0.05 were considered statistically significant. Risk factors were assessed using logistic regression. All statistical analyses were conducted using Stata version 14 (StataCorp; College Station, TX).

Results

Over the study period 1,617 patients received a first allogeneic HCT at our center, with 1,492 (92.3%) meeting the inclusion criteria (**Figure 1**). There were 362, 737, and 393 patients receiving HCT in the pre-CHG, pre-UV, and post-intervention phases, respectively. Demographics and transplant characteristics of these patients are presented in **Table 1**. There were 203 (13.6%) and 90 (6.0%) patients found to be pre-

HCT and post-HCT colonized, respectively. There were 42 (2.8%) VREB events in this cohort. Among the VREB cases, 32 (76%) occurred in patients who were colonized prior to VREB. One patient had a secondary bacteremia event 67 days after initial VRE blood culture. All VREB isolates were *E. faecuim* except for two that were not speciated. There were 24 patients (1.6% of total cohort) which had VRE isolates with additional antibiotic resistance profiles. Additional laboratory characteristics of the VREB cases are presented in **Table 2**. Overall, patients colonized and those with VREB accounted for 36,182 isolation-days over the study period, with 25,138 isolation-days amassed post-HCT.

Risk factors for VREB are summarized in **Table 3**. VREB cases were younger, more likely to have a stem cell source other than peripheral blood (PBSC), VRE colonization pre-HCT, gut GVHD grade 2 or higher, higher PAM scores, and longer inpatient stays pre-HCT. After multivariate analysis, age and length of inpatient stays pre-HCT were no longer significantly associated with VREB. The multivariate model found patients with VREB were 9.09 (95%CI: 4.74, 17.5) times more likely to be pre-HCT VRE colonized than non-VREB patients. After controlling for stem cell source, colonization status, gut GVHD, and length of inpatient stay pre-HCT, the odds of VREB are 7% higher for every one unit increase in PAM scores (95%CI: 1.00, 1.13).

Time series analysis

Pre-HCT colonization over the ten-year study period remained constant (-0.012%; 95%CI: -0.069, 0.046). Before CHG bathing began, pre-HCT colonization was increasing by 0.5% monthly (95%CI: 0.16, 0.84). In the month following implementation of CHG bathing, we observed a 15.2% reduction in pre-HCT colonization (95%CI: -23.0, -7.4). The rates of colonization dropped by 56.7%, although not statistically significant (p-value=0.2). After UV disinfection began, there were no significant immediate (-6.3%; 95%CI: -15.4, 2.8) or long-term (-150%; 95%CI: -340, 30) changes in VRE colonization. The post-UV disinfection rate in colonization was -0.11% monthly (-0.52, 0.30).

The overall incidence of VREB was 2.9 per 10,000 patient-days (95%CI: 2.0, 4.1). There were neither significant overall changes in the incidence of VREB over the study period (p-value=0.43), nor a change (-0.098; 95%CI: -0.22, 0.020) in VREB incidence during the post-CHG bathing period. Following the introduction of UV disinfection, a similar finding was observed (-0.19; 95%CI: -0.50, 0.13). The coefficients of the interrupted time series analysis are displayed in **Table 4**.

Survival analysis

Patients colonized with VRE pre-transplant experienced higher mortality compared to non-colonized patients (7.8% vs. 15.8%; p<0.001). VRE colonization pre-transplant was associated with 2.1 times higher risk of death compared to non-colonized patients in an unadjusted model (95%CI: 1.4, 3.2). After PAM score adjustment, this association persisted (HR = 2.2; 95%CI: 1.5, 3.3) (**Figure 3**). The association between pre-transplant colonization and mortality differed by PAM score category (**Figure 4)**. Pre-transplant VRE colonization was associated with 2.46 (95%CI: 1.32, 4.59) and 3.39 (95%CI: 1.39, 8.27) times higher risk of death compared to non-colonized patients, for PAM scores of 17-23 and >30, respectively.

VREB cases with multiple positive VRE blood cultures had higher mortality than patients with only one positive VRE blood culture (45% vs. 25%; p=0.2), although this did not reach significance (**Figure 5**). In an unadjusted Cox proportional hazards model, multiple positive VRE blood cultures were associated with higher mortality than a single positive VRE blood culture (HR = 3.23; 95%CI: 0.88, 11.8). After adjustment for PAM scores (<24 vs. ≥24), multiple VRE positive blood cultures were associated with 2.5 times higher risk of death (95%CI: 0.65, 9.5) compared to a single positive VRE blood culture. While patients with multiple positive blood cultures were slightly more likely to be transplanted in the first half of the study period and have higher PAM scores, these did not reach significance (data not shown). We did not identify any other significant risk factors for the development of multiple VRE positive blood cultures.

Discussion

Pre-transplant VRE colonization was found in 14% of HCT recipients, and 2.8% developed VREB during the first 100 days post-HCT. When including those that developed post-HCT colonization, the cumulative incidence of VRE colonization at day 100 was 19.6% (n=293). Of the pre-HCT colonized patients, 15.8% developed VREB within 100 days post-HCT. Despite implementation of CHG bathing and terminal UV disinfection we did not observe a decrease in VRE colonization or bacteremia over the ten-year period. In addition to common risk factors for VREB, pre-HCT VRE colonization and PAM scores were also associated with bacteremia in our cohort. We found that HCT recipients were more likely to die if they had pre-HCT VRE colonization which was associated with double the risk of death in the post-HCT period.

Our data demonstrate a lower prevalence of VRE colonization than what others have reported in similar allogeneic HCT populations, where pre-transplant rates vary between 27.5 and 53.9%.[4, 5, 9, 27] Our rates appear to align more closely with older studies which have reported less VRE colonization.[8, 13] A recent meta-analysis estimated the prevalence of VRE colonization in North America to be 21% (95%CI: 13, 31%) in patients with malignancies.[10] Similarly, rates of VREB vary between studies, likely reflecting both differences in transplant management, antibiotic use, colonization rates at baseline, and on length of follow-up post-transplant.[4, 5, 9, 13, 27] Our VREB rates compare to a recent study that reported 100-day VREB of 6.5% among allogeneic HCT recipients,[11] however rates of up to 19% have been reported by others.[28] Differences between our study and other prior reports, may because when calculating rates of VRE colonization and bacteremia estimates we only included first allogeneic HCT at our center. Additionally, these lower rates could be related to differences in vancomycin/other antibiotic use, geographic location, and infection control policies.

We did not observe a significant correlation between the implementation of CHG bathing or UV disinfection and a reduction in either VRE colonization or VREB. Although there were month to month variations, due to the low frequency of events it was not possible to attribute any changes directly to any intervention. A recent study used an interrupted time series analysis to determine the impact of CHG bathing on VRE colonization and bacteremia among HCT recipients. The authors reported a significant post-CHG reduction in both colonization and bacteremia.[20] In contrast to our study, the authors followed patients for 1-year post-HCT and included both allogeneic and autologous HCT recipients. Another study involving 13 European ICUs found that initiation of CHG bathing as part of a prevention bundle did not reduce acquisition of VRE.[29] However, the authors noted a gradual decrease in overall multidrug-resistant organism acquisition during the implementation phase suggesting improvements in hand hygiene may be more beneficial over time. The UV disinfection portion of the analysis is somewhat limited as it has been more recently implemented. Our data are however, are consistent with studies which suggest that UV disinfection had limited to no effect on VRE-related events.[30, 31]

The utility of active surveillance for all HCT recipients has been questioned[15, 16, 32] particularly since accumulating evidence has demonstrated that contact isolation is associated with adverse events.[33–35] As active surveillance identifies more patients requiring contact isolation, such policies

much be considered when implementing routine screening.[32] An evaluation of 9 studies examining the association of infection prevention measures found contact isolation had no significant impact on reducing VRE acquisiton.[36] In response to these findings, several centers have limited the use of or discontinued active surveillance and/or contact isolation for VRE colonized high-risk populations. Some institutions observed significant increases in VRE after the discontinuation of these practices while others reported no changes in VRE rates, further adding to the confusion about choosing whether to implement routine surveillance.[15–17]

The American Society for Blood and Marrow Transplantation guidelines recommend utilizing VRE rectal swabs to identify colonized patients if evidence of ongoing VRE transmission is present.[37] These recommendations and infrequency of VRE at our center, call into question the utility of routine screening. For example, a large cancer center in the US with similar VRE rates to those reported in this study does not actively screen or isolate VRE colonized patients, suggesting no benefit of routine screening.[11] While the risk of VREB among colonized patients is increased, active screening did not identify 10, or 24%, of all patients whom developed VREB prior to any positive rectal/stool screening. Furthermore, over 30% of all colonized patients developed VRE colonization post-transplant in our cohort despite early screening and isolation. These data suggest targeted VRE screening and discontinuation of contact isolation may have little impact on non-outbreak VRE situations.

Treatment of VRE infections is challenging due to the limited number of effective available therapies. Several reports exist in the literature suggesting the emergence of resistance to these last line therapies.[38–40] A recent report from Germany found that up to 27% of HCT recipients colonized or infected with VRE had an isolate with resistance to linezolid,[41] which is of particular concern as it is the one orally bioavailable drug that targets VRE.[42] However, the literature on additional drug resistance among VRE isolates remains limited to case series with small sample sizes.[38, 39, 41] We identified a large number of VRE with daptomycin resistance at our center (14.3% of initial blood culture isolates), although rates of up to 27% have been reported at other centers.[43] Antimicrobial stewardship programs are increasingly being recognized as an important and cost effective measure to control rates of VRE.[44, 45] A study examining trends after relaxation of active surveillance and isolation precautions, observed an increase in VRE incidence but concluded that antimicrobial stewardship may be more important than the

discontinued infection prevention measures.[17] As vancomycin use has been established as a significant risk factor for VRE colonization, it is plausible that knowledge of colonization status may influence treatment during febrile neutropenia leading to inappropriate antibiotic therapy.

Unfortunately, VRE colonization was as an independent risk factor for mortality in our data, as has been previously described by other studies.[46, 47] In our cohort, colonized patients with high PAM scores had significantly higher mortality than non-colonized patients with high PAM scores. The association was the strongest among patients with PAM scores above 30 (HR = 3.39 95%CI: 1.39, 8.27).

Risk factors for VREB have been well established in prior studies,[5, 11, 12] including underlying disease severity.[21, 27, 48] Interestingly, although VREB patients were younger than non-VREB controls, this was not significant after multivariate analysis. Pre-HCT colonization was the strongest predictor of subsequent bacteremia, consistent with previous findings.[10, 12, 27] We found that PAM scores are an independent predictor of VREB, and suggest HCT recipients with risk factors for post-transplant mortality may benefit from targeted VRE surveillance and other IP interventions.

The extent of VREB-attributable mortality has also remained controversial.[7, 12, 48] Although not statistically significant, we found that patients with multiple days of positive cultures were more likely to die than patients with a single positive culture. After accounting for PAM scores, we found that mortality was most prominent among HCT recipients with multiple positive cultures and higher PAM scores. We did not detect any significant risk factors for developing multiple positive blood cultures, however receiving HCT in the first half of the study or having higher PAM scores warrant further investigation and possibly reflect recent improvements in HCT care.[49]

Our study has several limitations. First, because this was a retrospective study we were unable to attribute any changes in colonization or VREB directly to the implemented system-wide interventions. Data on unmeasured confounders such as antibiotic consumption (pre- and post-transplant), prior hospitalization, changes in transplant practices and other organisms causing bloodstream infections were not collected for this study and may have contributed to VRE colonization and bacteremia. Furthermore, the small number of VREB events limited our ability to fit an appropriate model to analyze the ten-year trends. This study was done at a single center and may not be applicable to other institutions as the burden of VRE has been shown to vary dramatically.[4, 5, 28, 50] We did not collect antibiotic susceptibility

information on VRE isolates from rectal or stool screenings and were thus unable to estimate additional drug resistance carriage among VRE colonized patients.

In conclusion, we found a low burden of VRE at our center with no significant changes observed over time. We identified a subgroup of patients at high risk of VREB who may be targeted for VRE-specific interventions. Despite causing bacteremia in only 2.8% of first allogeneic HCT recipients, VRE is responsible for substantial resource consumption due to routine screening and isolation. Further studies examining the effectiveness of antimicrobial stewardship on reducing VRE colonization and bacteremia are needed.

Tables and Figures

Figure 1. Flow chart of inclusion criteria for the study population from Sept. 1, 2007 to August 31, 2016

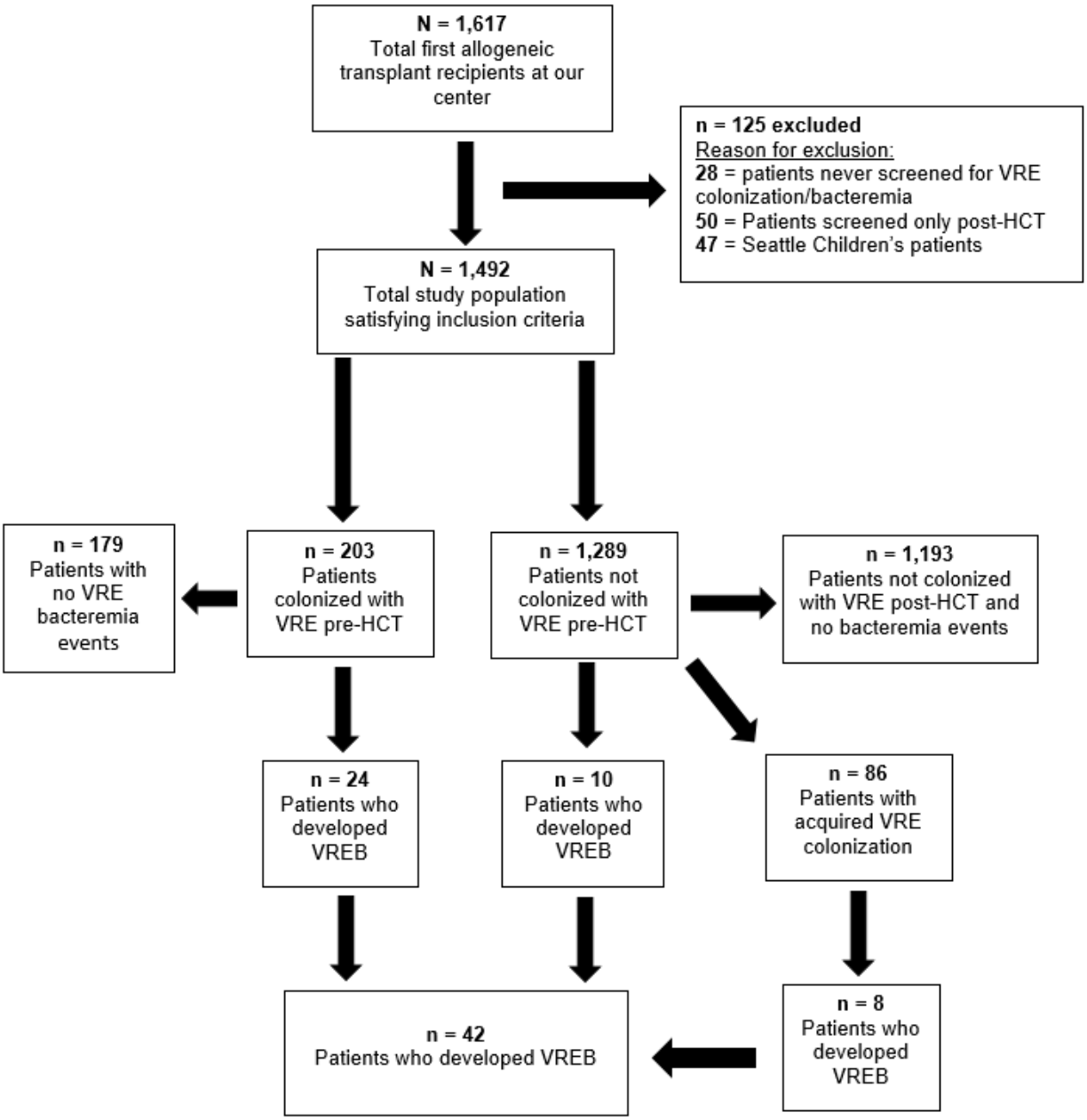


Table 1. Demographics and transplant characteristics of all adults undergoing their first allogenic HCT from Sept. 2007 to Aug. 2016

Variable	N=1,492 n (%)
Age (years) – median (IQR)	53.9 (41.7, 62.1)
Sex	
Male	865 (57.9)
Female	629 (42.1)
Race*	
White	1,147 (76.8)
Black	24 (1.6)
Hispanic	55 (3.7)
Asian/Pacific Islander	107 (7.2)
Native American	16 (1.1)
Other	65 (4.4)
Missing	80 (5.4)
Stem cell source	
BM	169 (11.3)
PBSC	1,155 (77.3)
Cord	166 (11.1)
BM + PBSC	4 (0.3)
Underlying disease*	
Acute myeloid leukemia	633 (42.4)
Myelodysplastic syndromes	374 (25.0)
Acute lymphoblastic leukemia	211 (14.1)
Chronic lymphocytic leukemia	77 (5.2)
Other	198 (13.2)
Disease status	
Relapse	223 (14.9)
Remission	829 (55.5)
Other/Unknown	442 (29.6)
CMV status	
Recipient positive	870 (58.2)
Donor positive	530 (35.4)
PAM scores*	
<17	385 (25.8)
17-23	705 (47.2)
24-30	275 (18.4)
>30	96 (6.4)
Pre-HCT outpatient days – median (IQR)	25 (21, 36)

*Numbers do not add due to missing

Figure 2. Trends in patients A) colonized with VRE pre-HCT and B) VREB incidence from September 2007 to August 2016

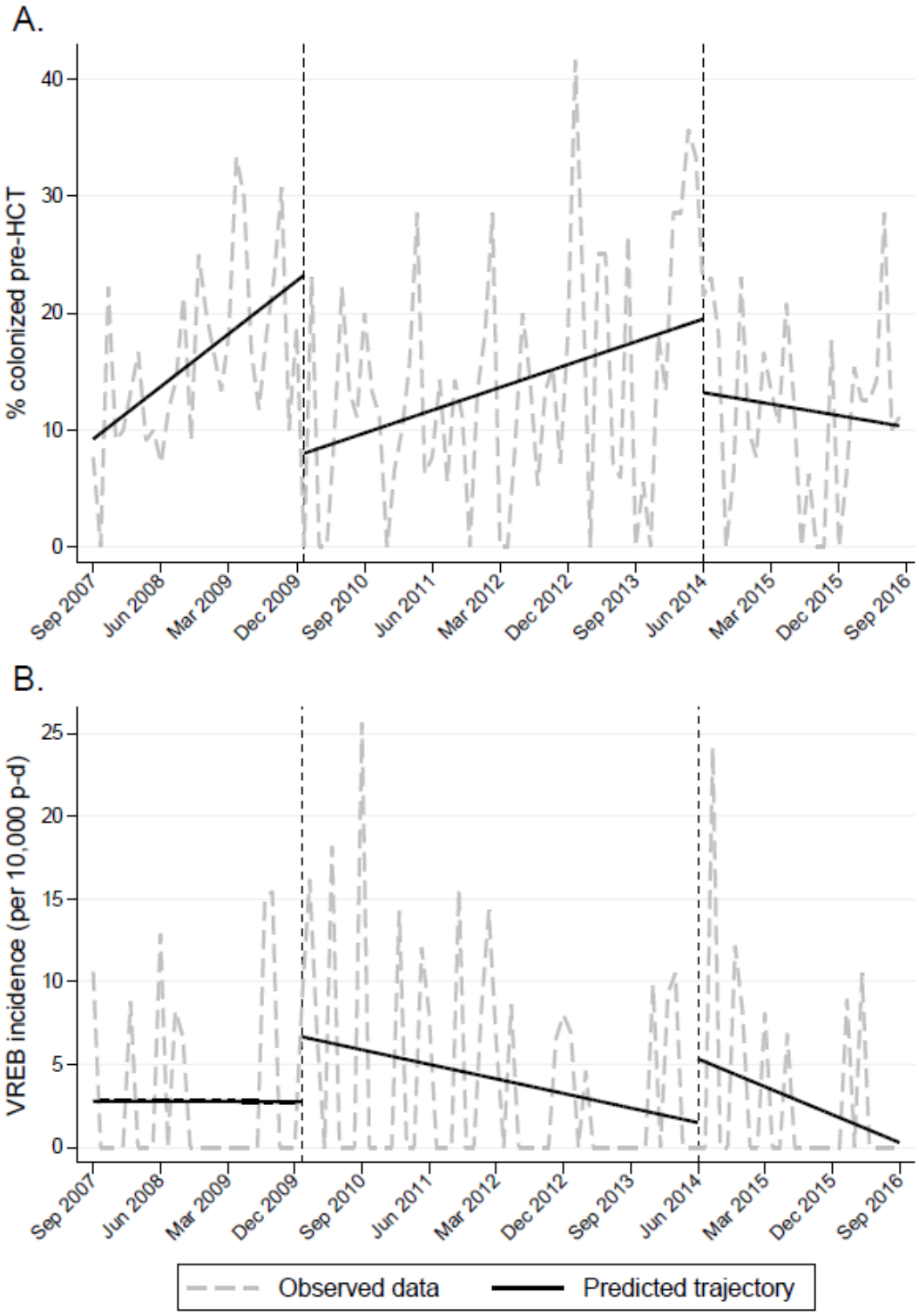


Figure 2. Interrupted time series analysis of A) VRE colonization pre-HCT and B) VREB post-HCT following implementation of CHG bathing (Jan 2010) and UV disinfection (June 2014).

Table 2. Laboratory characteristics of the 42 VREB patients

Variables	N = 42 n (%)
Polymicrobial infection	8 (19.0)
Initial drug-resistant isolates	
Daptomycin	6 (14.3)
Linezolid	1 (2.38)
Quinupristin/dalfopristin	2 (4.76)
Streptomycin†	16 (38.1)
Gentamycin†	5 (11.9)
Subsequent drug-resistant isolates	
Daptomycin	2 (4.76)
Linezolid	1 (2.38)
Quinupristin/dalfopristin	2 (4.76)
Streptomycin†	1 (2.38)
Gentamycin†	0 (0)
Colonization status	
Never	6 (14.3)
Pre-HCT	24 (57.1)
Post-HCT	12 (28.6)
Day of positive VRE blood culture – median (IQR)	16 (11, 48)
Number of positive blood cultures – median (IQR)	2 (1, 4)
Duration of positivity – median (IQR)	2 (1, 11)

†No synergy

Table 3. Risk factors for VREB among all HCT recipients

Variable	No VREB n = 1,450	VREB n = 42	P-value	Univariate analysis OR (95%CI)	Multivariate analysis OR (95%CI); P-value
Age (years) – median (IQR)	54 (42, 62)	46 (35, 56)	0.007	0.97 (0.95, 0.99)	0.98 (0.96, 1.01); 0.12
Female sex – n (%)	607 (41.9)	22 (52.4)	0.2	-	-
Transplant year ≥ 2012 – n (%)	787 (54.3)	18 (42.9)	0.1	-	-
PBSC – n (%)	1,136 (78.3)	22 (52.4)	0.001	0.30 (0.16, 0.56)	0.43 (0.21, 0.89); 0.022
Colonization pre-HCT – n (%)	179 (12.3)	24 (57.1)	0.001	9.47 (5.04, 17.8)	9.09 (4.74, 17.5); 0.001
PAM score – median (IQR)	20 (17, 24)	23 (19, 26)	0.005	1.08 (1.02, 1.13)	1.07 (1.00, 1.13); 0.042
Creatinine† – median (IQR)	0.8 (0.6, 1.0)	0.7 (0.6, 0.9)	0.5	-	-
Outpatient days pre-HCT – median (IQR)	25 (21, 36)	25.5 (21,36)	0.8	-	-
Inpatient days pre-HCT – median (IQR)	3 (1, 7)	7 (4, 8)	0.001	1.08 (1.01, 1.14)	1.05 (1.00, 1.11); 0.05

†Baseline value pre-HCT

Table 4. Interrupted time series analysis for VRE colonization and VREB

	VRE colonization		VREB	
Coefficient	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Constant	8.7	3.7, 13.8	2.8	-1.1, 6.7
Rate pre-CHG	0.5	0.2, 0.8	-0.001	-0.3, 0.3
Level change post-CHG	-15.2	-23.0, -7.4	3.9	-2.4, 10.2
Rate change post-CHG	-0.3	-0.7, 0.1	-0.1	-0.4, 0.2
Level change post-UV	-6.3	-15.4, 2.8	3.8	-2.6, 10.3
Rate change post-UV	-0.3	-0.8, 0.1	-0.09	-0.4, 0.2
Post-CHG trend†	0.2	0.02, 0.4	-0.1	-0.2, 0.02
Post-UV trend†	-0.1	-0.5, 0.3	-0.2	-0.5, 0.1

†From intervention start to end of the study

Figure 3. Kaplan-Meier estimates for survival by pre-HCT colonization status

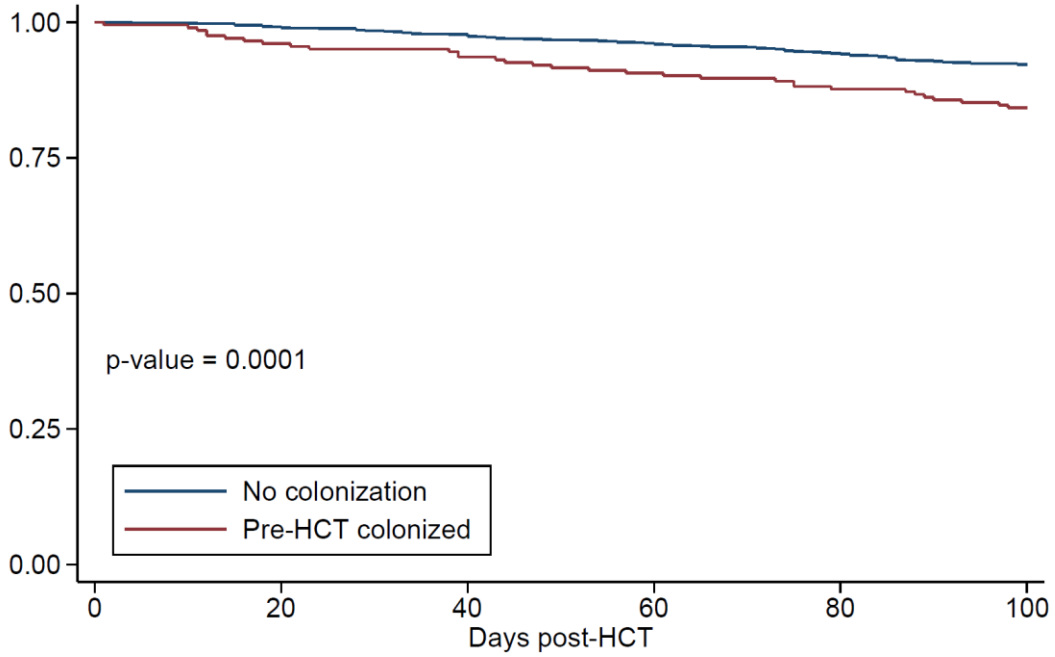


Figure 4. Kaplan-Meier estimates of the relationship between colonization status and 100-day mortality by PAM score categories.

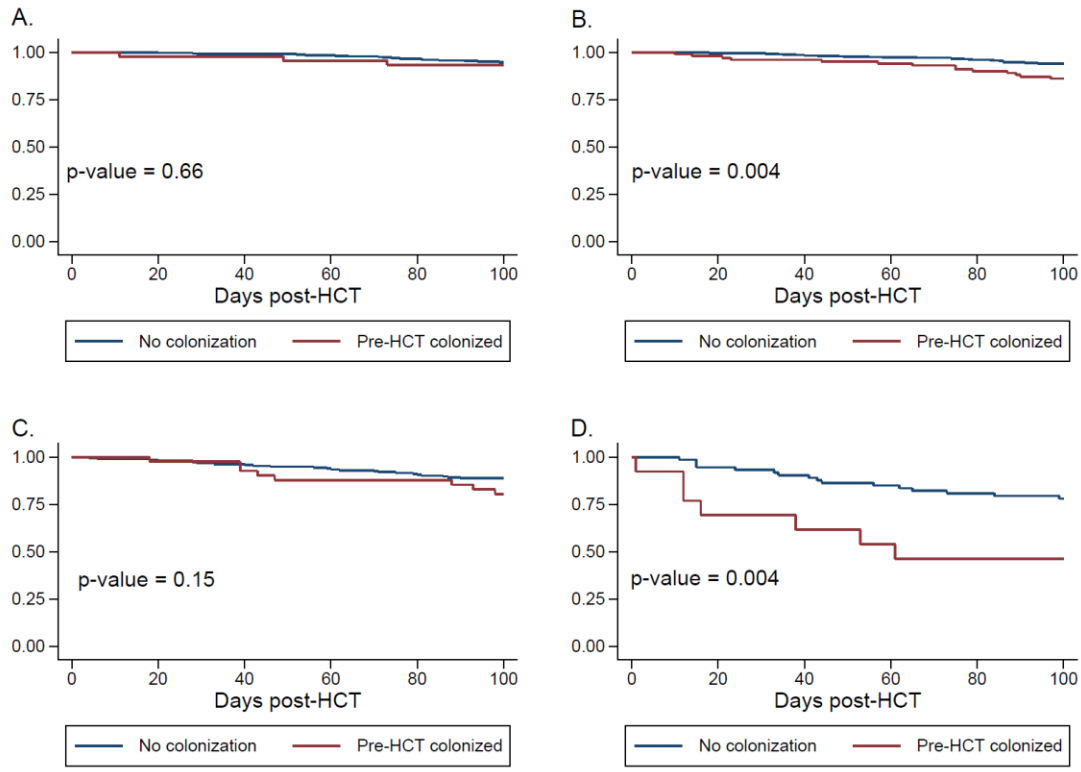
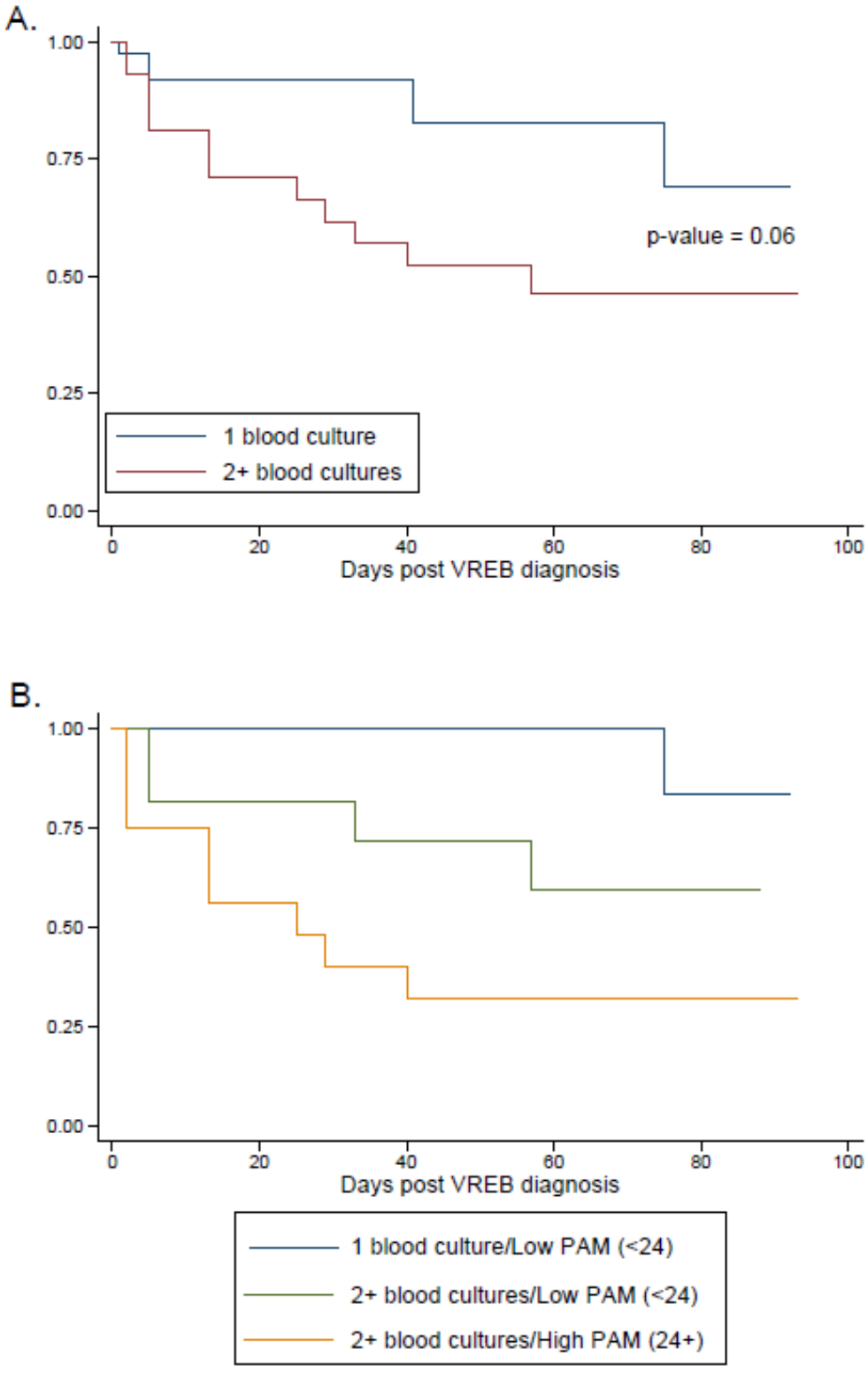


Figure 4. Kaplan-Meier Survival estimates of colonization status on mortality by A) PAM<17 (HR = 1.31; 95%CI: 0.39, 4.49), B) PAM: 17-23 (HR = 2.46;95%CI: 1.32, 4.59), C) PAM: 24-30 (HR = 1.79; 95%CI: 0.80, 3.98), and D) PAM > 30 (HR = 3.39; 95%CI: 1.39, 8.27)

Figure 5. Kaplan-Meier estimates for survival of A) multiple blood cultures vs. a single culture, and B) number of sequential blood cultures by PAM score categories



The category of one blood culture and PAM ≥ 24 was excluded due to the limited number of events

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