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Impact of Empiric Treatment for Vancomycin-Resistant *Enterococcus* in Colonized Patients Early after Allogeneic Hematopoietic Stem Cell Transplantation

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A B S T R A C T

In recent years, vancomycin-resistant *Enterococcus* (VRE) colonization is being increasingly encountered in transplant recipients, and VRE has become one of the leading causes of bacteremia early after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Data are sparse on the effect of empiric VRE therapy for febrile, neutropenic allo-HSCT recipients colonized with VRE. All allo-HSCT recipients aged ≥18 years who developed VRE bacteremia (VREB) between 2005 and 2014 were identified and categorized as to whether they received empiric or directed VRE therapy. There were 434 (33%) VRE-colonized and 872 (67%) non-VRE-colonized patients during the study period, and 172 of the 434 (40%) VRE-colonized patients received empiric therapy. There was no significant difference in incidence of VREB among colonized patients who did or did not receive empiric therapy (28 of 172 [16%] vs 55 of 262 [21%]; $P = .22$). There were 95 patients with VREB, of which the majority (83 of 95; 87%) was known to be VRE-colonized. Of the 95 VREB episodes, 29 (31%) were treated with empiric VRE therapy, whereas 66 (69%) were treated with directed therapy. No significant differences in clinical outcomes, including median duration of bacteremia (2 days vs 2 days; $P = .39$), recurrent VREB (3 of 29 [10%] vs 5 of 66 [8%]; $P = .65$), 30-day all-cause mortality (1 of 29 [3%] vs 4 of 66 [6%]; $P = .62$), or VRE-attributable mortality (1 of 29 [3%] vs 1 of 66 [2%]; $P = .55$), were observed between the empiric therapy and directed therapy groups. Kaplan-Meier curve analysis showed no significant difference in survival at 30 days in allo-HSCT recipients with VREB who received empiric therapy and those who received directed therapy (97% vs 94%; $P = .62$). Based on our data, we recommend against empiric use of VRE-active agents for fever and neutropenia in VRE-colonized patients undergoing allo-HSCT.

INTRODUCTION

Vancomycin-resistant *Enterococcus* (VRE) is now a common problem among allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients and is the leading cause of nosocomial bloodstream infections (BSIs) at some centers, especially in the early post-transplantation period [1,2]. Gastrointestinal colonization with VRE is a strong predictor of BSIs in this population [3–5]. The progression to VRE bacteremia (VREB) early post-transplantation has been reported to occur in 11% to 34% of VRE-colonized patients [4–7]. Although VRE is often considered an organism of limited virulence, some data suggest that VREB may be associated with severe presentations (eg, septic shock) in allo-HSCT recipients [1].

Although the American Society for Blood and Marrow Transplantation, Infectious Diseases Society of America (IDSA), and Society for Healthcare Epidemiology of America do not recommend routine screening for VRE, such screening may be reasonable based on local epidemiology and/or evidence of ongoing transmission in a HSCT unit [8]. A natural question that follows is how to optimally manage VRE-colonized patients during the course of transplantation. The 2010 IDSA guideline states that modification to initial empiric therapy for fever and neutropenia may be considered for patients at risk for infection with antibiotic-resistant organisms, including VRE, particularly in patients in unstable condition or with positive blood culture results suspicious for resistant bacteria [9]. Whether such a practice would improve clinical outcomes is

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unclear, given the lack of prospective studies to date. In a recent retrospective report, investigators from Brazil found that empiric use of linezolid in VRE-colonized allo-HSCT recipients did not change in-hospital mortality [10].

At our center, linezolid was used for empiric therapy for VRE in combination with piperacillin-tazobactam (or, if penicillin-allergic, cefepime) for fever in VRE-colonized neutropenic allo-HSCT recipients between June 2006 and January 2011. We conducted a review of all adult allo-HSCT recipients who experienced preengraftment VREB between January 1, 2005, and December 31, 2014, to compare all-cause mortality at 30 days between patients who received empiric VRE therapy and those who received directed VRE therapy.

METHODS

This study was reviewed and approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center, a 473-bed tertiary care cancer center in New York City. All adults aged ≥18 years who underwent allo-HSCT and developed VREB between January 1, 2005, and December 31, 2014, were identified and categorized as receiving empiric or directed VRE therapy. Data were collected from institutional transplantation, pharmacy, and infection control databases, as well as microbiology records. Abstracted data included demographics, underlying cancer diagnosis, comorbidities (eg, type 2 diabetes, chronic renal insufficiency), conditioning regimen, transplant type, donor type, VRE screening results, and reason for intensive care unit (ICU) transfer. The reason for ICU transfer was evaluated to determine whether the critical illness was due in part to VREB. Clinical variables within 24 hours of blood culture collection, including fever (≥38.1°C), hypotension (<90/50 mmHg), alteration in mental status, presence of moderate to severe mucositis [11], and signs of central venous catheter infection (eg, focal redness at the catheter insertion site), were recorded as well. The primary outcome was all-cause mortality at 30 days after the incident VRE blood culture in the 2 groups. Secondary outcomes included the time to clearance of VREB, recurrence of VREB, and VRE-attributable mortality.

VRE Surveillance

During the study period, patients admitted for allo-HSCT underwent rectal swab screening for VRE colonization initially by culture on BBL Campy CVA agar (BD, Sparks, MD) (from January 2005 to June 2013) and then by a commercial polymerase chain reaction system that targets the *vanA* gene (from July 2013 onward) [12]. Screening was obtained on admission to the transplantation unit and then weekly until discharge throughout the study period. All VRE-colonized and/or -infected patients were placed on contact barrier precautions.

Laboratory Methods

For blood culture specimens, if gram-positive cocci in pairs and chains were detected on the Gram stain, further identification with catalase, the pyrrolidonyl arylamidase test, vancomycin disc susceptibility, and the MicroScan Positive ID 2 panel (Beckman Coulter, Brea, CA) was performed until September 2014, when matrix-assisted laser desorption ionization-time of flight mass spectrometry (Vitek MS; bioMérieux, St. Louis, MO) was implemented. Sensitivities were measured using the MicroScan POS MIC 34 panel (Beckman Coulter).

Antibiotic Management

Since 2006, we have administered intravenous (IV) vancomycin prophylaxis, alone or with a fluoroquinolone (FQ), during the preengraftment period to prevent viridans streptococcal bacteremia [2,13]. Antibiotic prophylaxis is started 2 days before stem cell infusion (day-2). FQ prophylaxis is continued until neutrophil engraftment or onset of fever and neutropenia, whichever comes first. Vancomycin prophylaxis is continued until day +7, after which continuation of vancomycin is at the discretion of the treating physician as necessary for the management of fever and neutropenia or treatment of a documented infection.

Between June 2006 and January 2011, VRE-colonized, febrile, neutropenic patients were switched from IV vancomycin with or without FQ prophylaxis to empiric IV linezolid 600 mg every 12 hours in combination with IV piperacillin/tazobactam 4.5 g every 6 hours (or, if penicillin-allergic, IV cefepime 2 g every 8 hours). Empiric linezolid was continued until blood cultures were negative for 48 hours, at which point the linezolid was stopped or switched back to IV vancomycin. Sporadic use of linezolid as empiric VRE therapy was observed before June 2006 or after January 2011 at the discretion of the primary team; these cases were included in this analysis. Linezolid was the recommended VRE-active agent to be used for empiric intent based on local susceptibilities; daptomycin was used only rarely [3].

Definitions

Standard consensus definitions for fever, neutropenia, and sepsis were used [9,14]. Neutrophil engraftment was defined as 3 consecutive days with an absolute neutrophil count >500 cells/mm^3. Empiric treatment for VRE referred to initiation of linezolid (or, rarely, IV daptomycin 6 mg/kg daily) with fever in a VRE-colonized neutropenic patient in the absence of known positive blood culture(s) for VRE. Directed VRE therapy referred to initiation of a VRE-active agent when gram-positive cocci in pairs and chains were visualized on Gram stain from 1 or more positive blood cultures in a VRE-colonized, febrile, neutropenic patient. Antibiotic therapy was modified based on final identification and sensitivities of the organism. Only VREB occurring before neutrophil engraftment was considered for this study. VREB was attributed to a gastrointestinal source following the National Health Safety Network's mucosal barrier injury criteria [15]. Persistent VREB occurred if the patient had positive blood cultures for >3 calendar days. Mortality was attributed to VREB if the patient did not clear VRE at the time of death and/or never recovered from sepsis.

Statistical Analysis

Characteristics of patients with VREB who received empiric VRE therapy and those who received directed VRE therapy were compared using the χ^2 or Fisher exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. Stepwise multiple logistic regression analysis was used to calculate odds ratios in multivariate analyses. All variables from univariate analysis were entered into the model if $P < .30$ and were retained in the final model if $P < .10$. Overall survival probabilities were estimated using the Kaplan-Meier method. The log-rank test was used in time-to-event analyses. A *P* value <.05 was considered statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

VRE Colonization and Bacteremia

During the study period (January 1, 2005, to December 31, 2014), a total of 1306 adult allo-HSCTs were performed at Memorial Sloan Kettering Cancer Center; 71 patients underwent 2 transplantations. The cohort included 434 (33%) VRE-colonized patients and 872 (67%) non-VRE-colonized patients. VREB occurred in 83 of the 434 (19%) VRE-colonized patients, compared with only 12 of 872 (1%) non-VRE-colonized patients. All 12 of these latter patients had undergone VRE screening by culture.

Approximately 40% (172 of 434) of the VRE-colonized patients received empiric VRE therapy (Figure 1). There was no significant difference in incidence of VREB among colonized patients who received empiric therapy and those who did not (28 of 172 [16%] versus 55 of 262 [21%]; $P = .22$). Of 172 recipients of empiric VRE therapy, 139 (81%) received it between June 2006 and January 2011 when this practice was standard

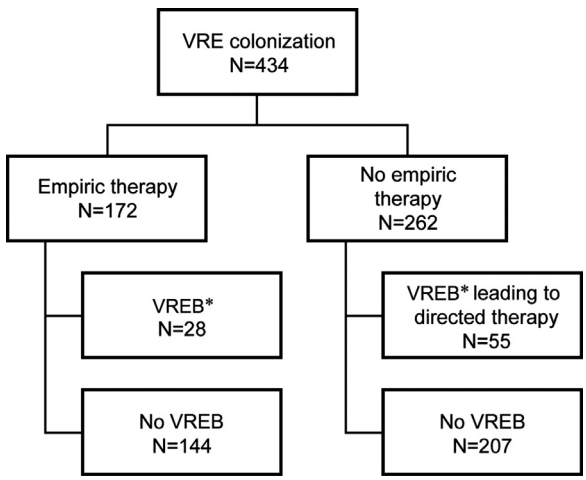

Figure 1. Patient flowchart. *Twelve of 872 non-VRE-colonized patients had VREB, of whom 1 received empiric therapy and 11 received directed therapy.

of care. Linezolid was the primary agent used in empiric VRE therapy (164 of 173; 95%).

A total of 95 allo-HSCT recipients had preengraftment VREB, of whom 83 (87%) were tested and found to have VRE colonization. Of the 95 VREB episodes, 29 (31%) were treated with empiric VRE therapy, and the other 66 (69%) were treated with directed VRE therapy. Most of the patients in the empiric VRE treatment group (25 of 29; 86%) developed VREB on the same day as the initiation of linezolid.

Demographic and Clinical Characteristics of Patients with VREB

The median age of patients with VREB was 59 years (range, 20 to 70 years) (Table 1). Fifty-nine patients (62%) were men. The majority of patients with VREB had acute leukemia or myelodysplastic syndrome (83 of 95; 87%). There were no significant between-group differences in age, sex, underlying malignancy, conditioning regimen, transplant type, previous VREB, gastrointestinal or central venous catheter source, hypotension, altered mental status, or ICU transfer (Table 1). The empiric VRE therapy group was more likely to have a matched related donor, diabetes, chronic renal insufficiency, and fever (Table 1).

Outcomes

There were no significant differences in 30-day all-cause mortality, median duration of VREB, recurrent VREB, and mortality attributable to VREB between the empiric and directed VRE treatment groups (Table 2). We then analyzed factors to examine their association with mortality via logistic regression. Previous VREB, hypotension, and persistent VREB were associated with 30-day mortality, whereas age, sex, conditioning regimen, transplant type, donor type, diabetes, fever, altered mental status, and empiric VRE treatment were not associated with 30-day all-cause mortality on univariate analysis (Table 3). None of the associations remained significant on multivariate analysis (Table 3). Kaplan-Meier curve analysis showed no significant difference in survival at 30 days between the 2 groups of allo-HSCT recipients (Figure 2).

Table 1
Comparison of Demographic Data and Other Clinical Characteristics in Patients with VREB Who Received Empiric versus Directed VRE Therapy

Characteristic	Empiric Therapy (N = 29)	Directed Therapy (N = 66)	*P* Value
Age, yr, median (range)	58 (26-69)	59 (20-70)	
Male sex, n (%)	22 (76)	37 (56)	.11
Underlying malignancy, n (%)			
Acute leukemia	24 (83)	49 (74)	.46
Chronic leukemia	0 (0)	3 (5)	
Lymphoma	2 (7)	2 (3)	
Other*	3 (10)	12 (18)	
Conditioning regimen, n (%)			
Myeloablative	15 (52)	38 (57)	.76
Reduced intensity	14 (48)	27 (41)	
Nonmyeloablative	0 (0)	1 (2)	
Transplant type, n (%)			
Conventional	3 (10)	12 (18)	.68
Cord	3 (10)	8 (12)	
T cell depletion	23 (80)	46 (70)	
Donor type, n (%)			
Matched related	15 (52)	17 (25)	.01
Matched unrelated	11 (38)	23 (35)	
Mismatched related	0 (0)	1 (2)	
Mismatched unrelated	3 (10)	25 (38)	
Diabetes, n (%)	11 (38)	12 (18)	.04
Chronic renal insufficiency, n (%)	5 (17)	3 (5)	.05
Previous VREB, n (%)	4 (14)	4 (6)	.24
Fever ≥38.1°C, n (%)	28 (97)	39 (59)	<.001
Hypotension (<90/50 mmHg), n (%)	0 (0)	6 (9)	.17
Altered mental status, n (%)	2 (7)	8 (12)	.72
ICU transfer due to VREB, n (%)	1 (3)	11 (17)	.10
Gastrointestinal source, n (%)	22 (76)	51 (77)	.88
Central venous catheter source, n (%)	7 (24)	15 (23)	.88

* Myelodysplastic syndrome (n = 10), myeloproliferative disorder (n = 1), multiple myeloma (n = 3), T cell leukemia/lymphoma (n = 1).

Table 2
Comparison of Outcomes after Empiric versus Directed VRE Therapy for VREB

Outcome	Empiric Therapy (N = 29)	Directed Therapy (N = 66)	*P* Value
Duration of VREB, days, median (range)	2 (1-9)	2 (1-19)	.39
Recurrent VREB, n (%)	3 (10)	5 (8)	.65
Attributable mortality, n (%)	1 (3)	1 (2)	.55
30-day all-cause mortality, n (%)	1 (3)	4 (6)	.62
60-day all-cause mortality, n (%)	4 (14)	8 (12)	.84

DISCUSSION

Our data derived from a large retrospective cohort of >1300 allo-HSCT recipients with a high prevalence of VRE colonization (33%) at the time of transplantation fail to demonstrate any clinical benefit of empiric therapy among colonized patients. Gram-positive bacteria remain dominant causes of preengraftment bloodstream infections in allo-HSCT [16,17], and multidrug-resistant pathogens, including VRE, are frequently isolated [1,2]. At our institution, VRE is the leading cause of preengraftment BSI in allo-HSCT recipients [2], and VRE invasion of the bloodstream has been shown to be preceded by its predominance in the gastrointestinal tract [18,19].

Although gram-positive organisms are now among the most common bacteria causing infection early after transplantation and chemotherapy, empiric use of vancomycin has shown no clinical benefit or difference in all-cause mortality, leading to the conclusion that vancomycin can be safely deferred until the documentation of an infection that warrants its use [20,21]. For VRE infections, the empiric administration of gram-positive agents, such as linezolid, daptomycin, quinupristin-dalfopristin, and tigecycline, in patients with known VRE colonization undergoing induction chemotherapy for acute leukemia or allo-HSCT has not been prospectively evaluated in clinical studies. It has been reasoned that the results of VRE surveillance can potentially guide antimicrobial therapy for fever and neutropenia; however, the benefit of empirically initiating VRE-active therapy while awaiting blood culture results must be carefully weighed against the potential harm from this approach [1,22]. The most recent iteration of the IDSA practice guideline for use of antimicrobial agents in high-risk febrile patients with neutropenia recommends considering the early use of VRE-active agents in areas of high endemicity [9].

In the present study, the majority of VRE-colonized patients (137 of 172; 81%) received empiric therapy in accordance with institutional guidelines in effect between June 2006 and January 2011. Our findings show no clinical benefit from the use of linezolid as empiric treatment in VRE-colonized, febrile, neutropenic patients early after HSCT. Specifically, there were no significant differences in the median duration of VREB, recurrent VREB, VRE-attributable mortality, or 30- or 60-day all-cause mortality between patients with VREB who received empiric therapy and those who did not receive empiric therapy. When we examined factors affecting 30-day all-cause mortality, empiric VRE therapy was not significant in either univariate or multivariate analysis. In another study, Lisboa

Table 3
Univariate and Multivariate Regression Analysis for Predictors of 30-Day All-Cause Mortality in Allogeneic HSCT Recipients with VREB

Variable	Predictors of 30-Day All-Cause Mortality			
	Univariate OR (95% CI)	*P* Value	Multivariate OR (95% CI)	*P* Value
Age	1.06 (.95-1.17)	.31		
Male sex	.39 (.06-2.43)	.31		
Conditioning regimen				
Myeloablative	Reference			
Reduced intensity	2.01 (.32-12.65)	.97		
Nonmyeloablative	NA			
Transplant type				
Conventional	Reference			
Cord	1.45 (.17-12.23)	.12		
T cell depletion	.10 (.01-1.13)	.03		
Donor type				
Matched related	Reference			
Matched unrelated	NA			
Mismatched related	NA			
Mismatched unrelated	5.17 (.54-49.27)	.94		
Diabetes	2.19 (.34-13.99)	.41		
Previous VREB	9.33 (1.30-67.03)	.03	9.38 (.8-110.54)	.08
Fever ≥38.1°C	.61 (.01-3.86)	.60		
Hypotension (<90/50 mmHg)	14.33 (1.84-111.44)	.01	11.34 (.9-142.76)	.06
Altered mental status	2.25 (.23-22.38)	.49		
Empiric VRE therapy	.55 (.06-5.18)	.60		
Persistent VREB >48 h	11.65 (1.24-109.66)	.03	9.44 (.88-101.33)	.08

NA indicates not applicable.

et al [10] considered linezolid on a case-by-case basis in VRE-colonized patients with persistent fever after 48 hours of broad-spectrum gram-negative coverage and a glycopeptide antibiotic. They also found no impact of this practice on mortality, which instead appeared to be associated with other factors, such as persistence of neutropenia.

Why empiric therapy has not been effective in improving survival is unclear. Several studies concluded that the poor outcomes seen in allo-HSCT recipients with VREB were not directly attributable to VRE [23–25]. VREB in and of itself may be simply an indicator of gut inflammation, such as toxicity from the conditioning regimen leading to mucositis or from graft-versus-host-disease, both of which are known to be associated with morbidity and mortality in allo-HSCT recipients [10,25,26]. Thus, a delay in VRE-active therapy might not have detrimental consequences, in contrast to BSIs due to gram-negative bacteria or *Candida* [27,28]. In the present study, empiric therapy was administered at a median of 2 hours after the incident blood culture, compared with a median of 24 hours in patients receiving directed therapy. This delay did not appear to convey clinically measurable differences in examined outcomes, however. The increasing adoption of rapid diagnostics (eg, peptide nucleic acid fluorescence in situ hybridization, matrix-assisted laser desorption ionization time-of-flight mass spectrometry, multiplexed nucleic acid amplification testing) by clinical microbiology laboratories may further make the empiric strategy superfluous, given that these technologies combined with antimicrobial stewardship intervention have been shown to decrease the time to initiation of appropriate therapy [29–31].

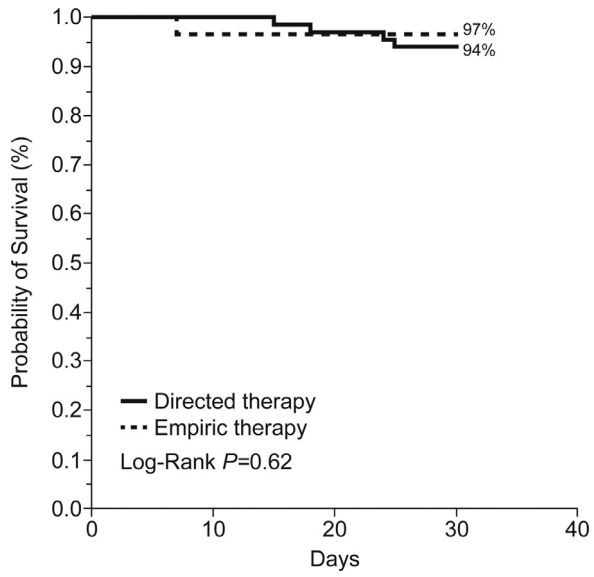

Figure 2. Kaplan-Meier curve of 30-day survival comparing allo-HSCT recipients with VREB who received empiric VRE therapy (n = 28) and those who received directed VRE therapy (n = 62).

Our study has several limitations. Because of its retrospective design, undetected biases might have been present that determined who did and who did not receive early VRE-active treatment. Because linezolid was by far the most frequently used VRE-active agent, our findings may be restricted to linezolid use and not applicable to other VRE-active agents. However, we and others have reported increasing enterococcal resistance to daptomycin, making the routine use of this agent problematic [3,32,33]. Consideration of quinupristin/dalfopristin or tigecycline for empiric therapy may be limited by such factors as side effect profile (eg, myalgias/arthralgias with quinupristin/dalfopristin, nausea/vomiting with tigecycline), tissue distribution versus serum distribution (eg, tigecycline), and safety (eg, tigecycline) [34,35]. Given the low 30-day mortality rates in both study arms, our sample size might have been insufficient to allow detection of differences.

Because our findings showed no benefit of empiric VRE therapy on clinical outcomes and mortality, we discontinued this practice at our center in early 2011. Instead, administration of VRE-active agents early after transplantation is contingent on the recovery of gram-positive cocci in pairs and chains

from blood cultures in allo-HSCT recipients known to be colonized with VRE. Similarly, the most recent guideline for the treatment of fever and neutropenia by the German Society of Hematology and Medical Oncology does not recommend the addition of linezolid to empiric first-line treatment in VRE-colonized patients [36].

In conclusion, empiric therapy did not impact the 30-day all-cause mortality, median duration of VREB, recurrent VREB, or VRE-attributable mortality in allo-HSCT recipients with preengraftment VREB. Based on our findings, we do not recommend empiric VRE therapy in colonized patients undergoing allo-HSCT with fever and neutropenia.

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