CONCISE COMMUNICATION

Unintended Consequences of Pretransplant Vancomycin-Resistant Enterococcus Screening on Antimicrobial Stewardship Among Allogeneic Hematopoietic Cell Transplant Recipients

Erica J. Stohs, MD, MPH;[1,2] Trenton MacAllister, MPH, MS;[2] Steven A. Pergam, MD, MPH;[1,2] Elizabeth M. Krantz, MS;[2] Rupali Jain, PharmD;[1,3] Ania Sweet, PharmD;[3] Catherine Liu, MD[1,2]

We examined vancomycin-resistant enterococci (VRE)-directed antimicrobial use and VRE bacteremia in a cohort of allogeneic hematopoietic cell transplantation patients from a center where VRE screening is standard prior to transplant. In this cohort, VRE bacteremia (VREB) was infrequent. In patients without VREB, colonized patients received VRE therapy more often than noncolonized patients.

Infect Control Hosp Epidemiol 2018;39:730–733

Screening for vancomycin-resistant enterococci (VRE) is commonly performed prior to hematopoietic cell transplantation (HCT), although its role in the prevention of healthcare-associated transmission is debated. Also, VRE colonization has been associated with an increased risk of VRE bacteremia (VREB)[1] and mortality in HCT recipients.[2] It is unclear whether this is a causal relationship or, as some studies suggest, VRE represents a marker of underlying comorbidities and poor overall clinical status.[2–4]

Guidelines for the management of febrile neutropenia suggest modification of initial empiric therapy to consider including a VRE-active agent based on history of prior colonization or high institutional prevalence.[5] One study found that empiric linezolid use in persistently febrile VRE-colonized hematology and HCT patients had no mortality benefit.[4] The emergence of daptomycin-nonsusceptible[6] and linezolid-resistant[7] VRE highlights the need for judicious use of these agents. Data examining the impact of VRE colonization on use of empiric VRE therapy in the HCT population are limited. We sought to determine the effect of pretransplant VRE colonization status on the use of VRE therapy among allogeneic HCT patients.

METHODS

We performed a retrospective cohort analysis of patients ≥18 years old who received their first allogeneic HCT at the Fred Hutchinson Cancer Research Center (FHCRC)/Seattle Cancer Care Alliance between September 1, 2007, and August 31, 2016. We recorded dates and times of VRE colonization, VRE bacteremia, and utilization of available antimicrobial agents with in vitro activity against VRE that achieved sufficient serum concentrations for treatment of bacteremia (linezolid, daptomycin, and quinupristin/dalfopristin) within the first 100 days posttransplant. Colonization status was determined from CHROMagar (Becton Dickinson, Franklin Lakes, NJ) identification of VRE on rectal or stool swabs obtained 1 week prior to transplant and weekly thereafter. Because duration of colonization is often prolonged among HCT recipients,[8] if any swab was positive for VRE prior to transplant, the patient was considered colonized. We defined VRE as any *Enterococcus* species with resistant or intermediate susceptibility to vancomycin. Patients colonized post-HCT and those with VRE-positive surveillance blood cultures, defined as blood cultures obtained in the outpatient setting while patients were asymptomatic, were excluded from analysis.

Primary analyses were performed among patients without VREB for whom the primary outcome was receipt of VRE therapy within 100 days posttransplant and the main exposure was pretransplant VRE colonization. Secondary outcomes included duration of and indications for therapy. Variables were compared using Mann-Whitney U tests.

For the subgroup of patients who developed VREB, we recorded time from blood culture collection to initiation of VRE therapy for suspected bacteremia or sepsis. Empiric VRE therapy was defined as the receipt of VRE therapy within 24 hours of blood culture collection and was the main exposure variable for secondary analyses. Outcomes included duration of bacteremia, intensive care unit (ICU) transfer within 72 hours, and 30-day mortality. Duration of bacteremia was the time from initial positive VRE blood culture to the first negative culture without any VRE-positive cultures in the subsequent 30 days or death, whichever came first. Death was treated as a competing risk for clearance of bacteremia. Median, 25th, and 75th percentiles of duration of VREB were estimated using cumulative incidence curves; groups were compared using competing risks regression. Binary outcomes were compared using the Fisher exact test and exact logistic regression. All models included unadjusted models and bivariable models adjusting for pretransplant assessment of mortality (PAM) scores.[9] Overall survival was estimated using Kaplan-Meier methodology. The FHCRC Institutional Review Board approved this study.

RESULTS

Figure 1 illustrates the numbers of patients with VREB, VRE colonization, and receipt of VRE therapy among 1,394 HCT patients analyzed. Of 1,372 patients who did not develop VREB, 67 (5%) received VRE therapy within 100 days posttransplant. Of those who did not develop VREB, VRE-colonized patients were more likely to receive VRE therapy than noncolonized patients (32 of 180 (18%) vs 35 of 1,192 (3%); $P < .001$). The median durations of VRE therapy were 3 days in the colonized group and

https://doi.org/10.1017/ice.2018.43 Published online by Cambridge University Press

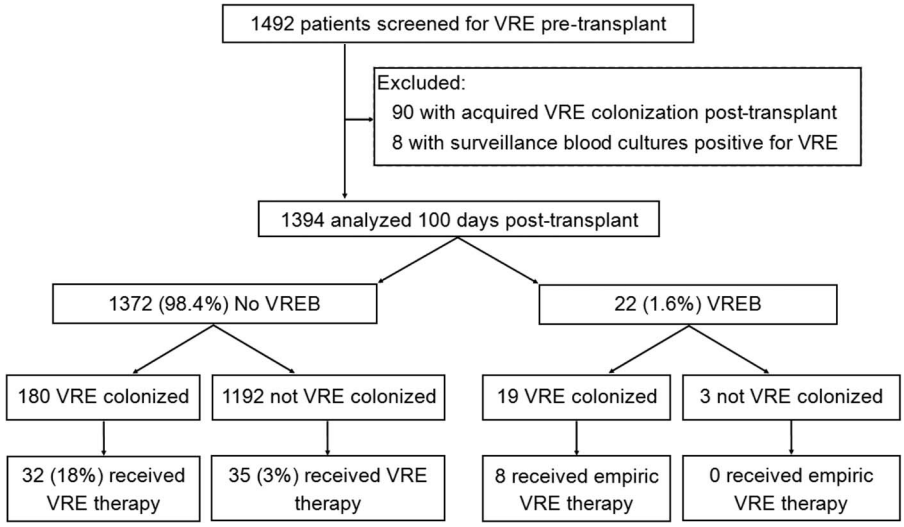

FIGURE 1. Flow diagram.

2 days in the noncolonized group ($P = .84$). Indications for VRE therapy are listed in Supplemental Table 1.

Overall, 22 patients (1.6%) developed VREB; 19 cases (86%) occurred among those colonized prior to transplantation. Furthermore, 8 patients (36%), all known to be colonized pretransplant, received empiric VRE therapy to which all isolates were susceptible (Table 1). The VREB patients who received empiric therapy were more likely to be transferred to the ICU within 72 hours of blood culture collection (71% vs 0; $P = .003$). There were no significant differences in median duration of bacteremia ($P = .21$) or 30-day mortality ($P = .99$). Overall survival was also similar between patients who did and did not receive empiric therapy (Supplemental Figure 1). Among 12 blood culture isolates with daptomycin minimum inhibitory concentration (MIC) data, 4 had an MIC > 4 μg/mL, 4 had an MIC of 4 μg/mL, and 4 had an MIC < 4 μg/mL. Also, 1 isolate had a linezolid MIC of 8 μg/mL.

DISCUSSION

In the absence of VREB, HCT patients who were colonized with VRE prior to transplantation were more likely to receive VRE therapy than noncolonized patients. Among the subgroup of patients with VREB, there were no significant differences in duration of bacteremia or 30-day mortality regardless of whether they received empiric therapy.

Controversy continues regarding the value of timely initiation of VRE therapy in patients with VRE bacteremia.[4,10] Some suggest using colonization status,[10] while others propose prediction scores to help guide use of empiric VRE therapy.[11] Some question the virulence of VRE in the HCT population and suggest that it is a surrogate marker of the severity of patients' underlying disease and complications.[2,3] While empiric linezolid use in VRE-colonized HCT patients did not confer survival benefit, persistence of neutropenia and GVHD were associated with increased mortality.[4] In another study of HCT recipients, VREB did not impact post-HCT survival and delayed initiation of daptomycin or linezolid did not affect duration of bacteremia.[12] Outcomes from our small cohort of VREB appear congruent with these studies, suggesting limited benefit of empiric VRE therapy.

Our analyses also identified important stewardship opportunities targeting use of VRE therapy. The use of VRE therapy among VRE-colonized non-VREB patients demonstrated a potential consequence of VRE screening. In addition, daptomycin use as an alternative to vancomycin for red man syndrome highlighted a need for educational feedback to prescribers. Increasing utilization of rapid molecular diagnostics may also help limit overuse.

This study has some limitations inherent to retrospective analyses. First, the period analyzed was subject to changes in clinical practice, which may have confounded our results. Lab-reported daptomycin MIC values were not routinely available until the latter third of the study period, limiting evaluation of trends in daptomycin susceptibility. The implementation of Verigene (Nanosphere, Northbrook, IL) at the end of our study period may influence future use of VRE therapy. Our study was not powered to detect differences in outcomes among patients who did and did not receive empiric therapy for VREB. Finally, our low VRE colonization and bacteremia rates may not be generalizable to other centers.

In conclusion, our findings suggest potential unintended consequences of VRE screening in our HCT population. Furthermore, VRE colonized status was associated with increased use of VRE-directed therapy in non-VRE bacteremic HCT patients. Among patients with VREB, there were no differences in duration of bacteremia or 30-day mortality, whether or not they received empiric VRE therapy.

https://doi.org/10.1017/ice.2018.43 Published online by Cambridge University Press

TABLE 1. Characteristics and Outcomes for 22 Vancomycin-Resistant Enterococcus (VRE) Bacteremia Patients by Receipt of Empiric VRE Therapy[a]

Characteristic[b]	Empiric Therapy (n = 8)	No Empiric Therapy (n = 14)
Age, y, median (IQR)	42.2 (31.4–48.5)	42.0 (25.8–53.6)
Male, no. (%)	2 (25)	9 (64.3)
Race/Ethnicity, no. (%)		
White	4 (50)	8 (61.5)
Black	…	2 (15.4)
Hispanic	2 (25)	…
Asian/Pacific Islander	…	2 (15.4)
Other	2 (25)	1 (7.1)
Unknown	…	1
Stem cell source, no. (%)		
Bone marrow	…	2 (14.3)
Peripheral stem cell	5 (62.5)	5 (35.7)
Cord	3 (37.5)	7 (50.0)
Conditioning regimen, no. (%)		
Myeloablative	5 (62.5)	11 (78.6)
Nonmyeloablative	3 (37.5)	3 (21.4)
Underlying disease, no. (%)		
Acute myelogenous leukemia	3 (37.5)	7 (50)
Myelodysplastic syndromes	…	1 (7.1)
Acute lymphocytic leukemia	4 (50)	5 (35.7)
Non-Hodgkin's lymphoma	…	1 (7.1)
Immune deficiency disorder	1 (12.5)	…
Disease status, no. (%)		
Relapse	1 (14.3)	2 (15.4)
Remission	6 (85.7)	11 (84.6)
Unknown	1	1
GVHD, no. (%)[c]	…	2 (14.3)
PAM score, median (IQR)[d]	24.0 (19.8–25.3)	23.5 (22.0–29.8)
VREB day post-HCT, median (IQR)	7 (5.5–11.5)	12 (11–19)
Absolute neutrophil count, median (IQR)	0 (0–0)	0 (0–0)
Hours to initiation of VRE therapy, median (IQR)	19.0 (16.1–21.5)	41.3 (28.9–43.5)
Daptomycin dose in mg/kg, median (IQR)[e]	6.0 (5.7–7.9)	5.7 (5.0–5.8)
Outcomes		
Median days of bacteremia (IQR)	4.0 (2.0–6.5)	4.9 (2.6–41.9)*
Transfer to ICU within 72 h of 1st positive VRE blood culture, no. (%)[f]	5 (71)	0 (0)**
Deaths within 30 d of 1st positive VRE blood culture, no. (%)	2 (25)	4 (29)***

NOTE. HCT, hematopoietic stem cell transplant; IQR, interquartile range; GVHD, graft versus host disease; PAM, pretransplant assessment of mortality; VREB, VRE bacteremia.

[a]Percentages are computed among nonmissing values.

[b]Status at time of transplant unless otherwise specified.

[c]By date of first positive VRE blood culture.

[d]Pretransplant assessment of mortality score predicts survival after allogeneic HCT by integrating the following variables: patient age, disease risk, donor relationship, human leukocyte antigen matching, type of conditioning regimen, and measures of pulmonary, renal, and hepatic comorbidities.

[e]Dose information provided for the 3 patients who received daptomycin in the VRE empiric therapy group and 13 patients who received daptomycin in the no VRE empiric therapy group.

[f]Only evaluated among 17 patients who were not already in the ICU at the time of first positive blood culture.

*$P = .14$ (unadjusted), 0.21 (adjusted for PAM score).

**$P = .003$ (unadjusted), n/a (adjusted for PAM score).

***$P = .99$ (unadjusted and adjusted for PAM score).

https://doi.org/10.1017/ice.2018.43 Published online by Cambridge University Press

Antimicrobial stewardship implications should be considered when determining VRE screening and isolation policies in centers performing HCT.

ACKNOWLEDGMENTS

Financial support: No financial support was provided relevant to this study.

Potential conflicts of interest: S.A.P. has served as a consultant for and has participated in clinical trials with Chimerix and Merck & Co. All other authors report no conflicts of interest.

Affiliations: 1. Division of Allergy and Infectious Diseases, University of Washington, Seattle, Washington; 2. Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington; 3. Department of Pharmacy, University of Washington, Seattle, Washington.

Address correspondence to Erica Stohs, MD MPH, 1100 Fairview Ave, North, E4-100, Seattle, WA 98109 (estohs@fredhutch.org).

PREVIOUS PRESENTATION. Portions of this work were presented at IDWeek on October 6, 2017, in San Diego, California.

Received December 5, 2017; accepted February 4, 2018; electronically published March 28, 2018

 0899-823X/2018/3906-0016. DOI: 10.1017/ice.2018.43

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2018.43

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