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# 10-year trends in vancomycin-resistant enterococci among allogeneic hematopoietic cell transplant recipients☆

Trenton J MacAllister[a,b], Erica Stohs[a,c], Catherine Liu[a,c,d,e], Andrew Bryan[f], Estella Whimbey[c], Amanda Phipps[g,h,1], Steven A Pergam[a,b,c,e,1,*]

[a] Vaccine & Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
[b] Infection Prevention, Seattle Cancer Care Alliance, Seattle, WA, USA
[c] Department of Medicine, University of Washington, Seattle, WA, USA
[d] Antimicrobial Stewardship and Outpatient Parenteral Antimicrobial Therapy Programs, Seattle Cancer Care Alliance, Seattle, WA, USA
[e] Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
[f] Department of Laboratory Medicine, University of Washington, Seattle, WA, USA
[g] Department of Epidemiology, University of Washington, Seattle, WA, USA
[h] Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

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SUMMARY

*Objectives:* We examined VRE colonization, bacteremia (VREB) incidence and outcomes within 100 days of allogeneic hematopoietic cell transplantation (HCT).
*Methods:* HCT recipients screened for VRE were assessed, and colonization and VREB incidence compared over time using linear regression. Cox proportional hazards models were constructed to assess the relationship between mortality, pre-HCT colonization, and underlying disease.
*Results:* Of 1492 HCT recipients, 204 (14%) patients were colonized pre-HCT, while 90 (6%) acquired colonization post-HCT. Forty-two patients (2.8%) developed VREB within 100 days post-HCT; the majority, 32 (76%), were previously colonized. The cumulative incidence of VREB was 2.9 per 10,000 patient-days. Over the study period there were no significant changes in incidence of VRE colonization or VREB despite a number of interventions ($p > 0.1$). Patients with pre-HCT colonization had increased mortality compared to non-colonized patients (HR 2.1; 95% CI: 1.5, 3.3).
*Conclusions:* We found a low burden of VRE at our center with no significant changes observed over a 10-year study period. VRE, while responsible for substantial resource consumption from routine screening and isolation, was an infrequent cause of bacteremia.


## Introduction

Hematopoietic cell transplant (HCT) recipients experience significant morbidity and mortality due to bloodstream infections, which occur in 10–40% of transplant patients.[1–4] 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.[5–7] VRE has become a common hospital-acquired infection and gastrointestinal (GI) tract colonization varies between 28 and 61% among HCT recipients; GI colonization is strongly associated with VRE bacteremia (VREB).[5,6,8–10] 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.[11] VRE colonization, both pre- and post-transplant, and VREB in the post-transplant period are associated with increased mortality.[12–14]

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 managing multidrug-resistant organisms suggest the following interventions for prevention of VRE: active surveillance for GI colonization, contact precautions for colonized or infected patients, and standard environmental cleaning with an effective disinfectant; however,

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* Corresponding author at: Vaccine & Infectious Disease Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave., North, E4-100, Seattle, WA 98109, USA.

*E-mail addresses:* tjm37@uw.edu (T.J. MacAllister), estohs@fredhutch.org (E. Stohs), Catherine.liu@fredhutch.org (C. Liu), andrewbb@uw.edu (A. Bryan), ewhimbey@uw.edu (E. Whimbey), aiphipps@uw.edu (A. Phipps), spergam@fredhutch.org, spergam@fhcrc.org (S.A. Pergam).

[1] Contributed equally.

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they acknowledge that controversy exists regarding the optimal control strategies and recommend that interventions to prevent VRE transmission should be individualized to each facility based on assessments of their local disease burden.[15] Screening and isolation procedures vary between centers and several cancer centers have limited the use of or discontinued routine isolation of colonized patients. Studies have shown no evidence of increasing VRE incidence,[16,17] while others experienced a dramatic rise in VRE after discontinuing isolation practices.[18] Data regarding more recent changes in practice, including daily chlorhexidine wipes and enhanced room disinfection standards (e.g. activated hydrogen peroxide, UV disinfection), in HCT populations are limited.[19–21]

Underlying disease and/or other complications may be responsible for the increased mortality associated with VREB.[6,22,23] Several studies have accounted for factors such as disease severity and age in their analyses, but methods for pre-transplant mortality risk assessments, have not been extensively studied in relation to the occurrence of VRE colonization, bacteremia and overall mortality. To better understand the burden of VRE among HCT recipients and the impact of IP interventions at our Center, this study examines changes in the incidence of VRE colonization, bacteremia and mortality outcomes over the past decade.

## Methods

### *Study population*

All adults (>18 years of age) receiving an allogeneic HCT between September 1st, 2007 and August 31st, 2016 at Seattle Cancer Care Alliance/Fred Hutchinson Cancer Research Center (FHCRC) were eligible for inclusion. Our Center performs approximately 250 adult allogeneic HCTs, annually. 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, experienced pre-HCT VREB, or only screened post-HCT were excluded from the primary analysis. The study was approved by the FHCRC Institutional Review Board.

### *Center-wide infection prevention practices*

HCT recipients at the Center are screened for VRE prior to transplantation as part of local standard practice guidelines. To identify VRE colonized 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™ VRE to identify presumptive VRE. Screening is strictly used to inform local infection prevention policies, modified from SHEA Guidelines,[24] where patients with VRE are placed into contact precautions for the duration of care at the Center regardless of follow up screening results. As part of a Center-wide effort to decrease overall blood stream infections, daily chlorhexidine 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, Ultraviolet (UV) disinfection (Xenex™) was added to terminal cleaning for inpatient rooms occupied by HCT recipients with multi-drug resistant infections. All inpatients are admitted to single rooms with individual bathrooms on dedicated transplant units, and all patients in the intensive care unit (ICU) are admitted to cancer specific ICUs.

### *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 complete 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 resistant or with intermediate susceptibility to vancomycin based on Clinical and Laboratory Standards Institute (CLSI) standards. VRE colonization was defined by detection of VRE from stool/rectal screening or urinary detection during the pre-transplant screen or at any point prior to HCT. Patients found to be either colonized after initial negative results, those that developed VREB with prior negative stool screening or those who had any VRE detected from urinary cultures were considered to have acquired VRE during the post-transplant period. VRE colonization start date was defined as the day of detection at any point in the pre-transplant period, while acquired VRE colonization date was defined at the time point during the initial 100 day post-transplant period following detection of colonization.

VRE 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), microbroth dilution (Sensititre®), and/or E-test. Starting in 2015, the Verigene® Gram positive blood culture test (Luminex Corp.) was used for early identification of *Enterococcus faecium* and *Enterococcus faecalis* and to detect *vanA* and *vanB* gene targets; all isolates subsequently underwent standard identification and phenotypic susceptibility testing. All rectal/stool, urinary, and blood cultures were performed at the University of Washington Clinical Microbiology Laboratory.

An enterococcal isolate obtained from blood more than 30 days from the last positive blood culture or those with differing antimicrobial resistance profiles based on CLSI standards were considered a secondary bacteremia episode; only first bacteremia episodes were included in survival analyses. 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 h increments. We used the Pre-transplant Assessment of Mortality (PAM) score[25] to assess pre-transplant risk and graft-vs-host disease (GVHD) was categorized according to the NIH classification system.[26] 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.[27] 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.[28] The change in outcomes (VRE colonization or bacteremia) in the month following intervention implementation was defined as the level change. The percent change in slopes before and after intervention implementation was defined as the rate change. The post-intervention (-CHG or -UV disinfection) trend was the slope after the intervention was initiated.

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