Evaluating Initial Empiric Therapy for Neutropenic Fever in Vancomycin-Resistant Enterococcus-Colonized Patients

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Abstract

Objectives: Vancomycin-resistant enterococcus infections impact mortality in oncology patients. Given the low rate of vancomycin-resistant enterococcus bacteremia, low virulence of vancomycin-resistant enterococcus, and advent of rapid diagnostic systems, vancomycin-resistant enterococcus-directed empiric therapy in vancomycin-resistant enterococcus-colonized patients with neutropenic fever may be unnecessary, promoting increased antimicrobial resistance, drug-related toxicity, and cost.

Methods: Vancomycin-resistant enterococcus-colonized adults admitted for hematopoietic stem cell transplantation or induction therapy for acute leukemia/myeloid sarcoma with neutropenic fever were stratified by vancomycin-resistant enterococcus bacteremia development and empiric vancomycin-resistant enterococcus-directed antimicrobial strategy for first neutropenic fever (Empiric Therapy vs. non-Empiric Therapy). Primary endpoints included vancomycin-resistant enterococcus-related, in-hospital, and 100-day mortality rates. Secondary outcomes included vancomycin-resistant enterococcus bacteremia incidence for first neutropenic fever and the entire hospitalization, length of stay, Clostridioides difficile infection rate, and duration and cost of vancomycin-resistant enterococcus-directed therapy.

Results: During first neutropenic fever, 3 of 70 eligible patients (4%) developed vancomycin-resistant enterococcus bacteremia. Although all 3 (100%) were non-Empiric Therapy, no mortality (0%) occurred. Of 67 patients not developing vancomycin-resistant enterococcus bacteremia, 42 (63%) received Empiric Therapy and 25 (37%) non-Empiric Therapy. Empiric Therapy had significantly greater median duration (3 days vs. 0 days; P<.001) and cost ($1604 vs. $0; P<.001) of vancomycin-resistant enterococcus-directed therapy but demonstrated no significant differences in clinical outcomes.

Conclusion: Available data suggest Empiric Therapy may offer no clinical benefit to this population, regardless of whether vancomycin-resistant enterococcus is identified in blood culture or no pathogen is found. Such an approach may only expose the majority of patients to unnecessary vancomycin-resistant enterococcus-directed therapy and drug-related toxicities while increasing institutional drug and monitoring costs. Even in the few patients developing vancomycin-resistant enterococcus bacteremia, waiting until the organism is identified in culture to start directed therapy likely makes no difference in mortality. This lack of benefit warrants consideration to potentially omit empiric vancomycin-resistant enterococcus-directed therapy in first neutropenic fever in many of these patients.

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Introduction

VRE infections have a substantial impact on morbidity and mortality in malignant hematology and HSCT patients. VRE bacteremias are difficult to treat in those with NPF and are an independent risk factor for mortality.[1-4] Preventing VRE infections in such patients is challenging due to prolonged hospitalization and antimicrobial administration, both of which are frequently required as part of their disease management.[5,6] The administration of immunosuppressive medications, prolonged neutropenia, disruption of mucosal barriers, and placement of indwelling central venous catheters further complicates the issue.[7]

VRE colonization greatly increases the risk for subsequent occurrence of invasive disease during the general post-HSCT period (up to day +35).[8,9] As a result, screening for VRE colonization is one method commonly employed to identify patients at risk for infection with the organism. While the current IDSA and NCCN guidelines have no definitive recommendations for screening, the practice is heavily implemented in our facility's institutional policies.[8,10] All malignant hematology and HSCT patients are screened for VRE using a rectal swab on admission and weekly while neutropenic. However, in VRE-colonized malignant hematology and HSCT patients, the link between colonization and subsequent infection during the first NPF episode (in addition to the optimal treatment strategy) has rarely been explored in the literature and remains uncertain.

Our review aimed to evaluate rates of VRE bacteremia with first NPF in VRE-colonized malignant hematology and HSCT patients and assess whether adding VRE-directed agents to initial NPF therapy impacted clinical outcomes.

Materials and Methods

This study was approved by the IRB of the University of South Florida (Pro00028221) and the Moffitt Cancer Center Scientific Review Committee (Protocol MCC 18920). It was the determination of the IRB that the study qualified for expedited review in addition to a waiver of the requirements for the informed consent/signed authorization process. It consisted of a retrospective review of VRE-colonized malignant hematology and HSCT patients who developed NPF from August 31, 2012 through October 4, 2020 at our tertiary care cancer institution.

Patients' clinical data were retrieved from the institution's electronic medical record system. All VRE-colonized patients ≥18 years of age who received intensive induction therapy for acute lymphoblastic leukemia, acute myeloid leukemia, or myeloid sarcoma or underwent HSCT and developed NPF [ANC < 500 cells/mm^3 or expected ANC < 500 cells/mm^3 over the next 48 hours in combination with a single oral temperature $\geq 38.3°C$

(101°F) or 38°C (100.4°F) or equivalent sustained over 1 hour] at the institution were eligible for inclusion in the study.[8] Criteria for inclusion and exclusion were slightly tightened from a prior analysis to provide a more accurate, clear, and clinically applicable assessment of the study's main focus (first NPF episode).[11] First NPF episode was chosen for evaluation of VRE-directed agent utilization because the authors felt that it would provide the most direct and clear answer to the main question at hand (necessity of such therapy empirically in NPF) with the least amount of influence from outside factors. Subsequent NPF episodes and hospitalizations would be confounded by several other variables that could greatly impact the use of VRE-directed therapy and results of the analysis (prior chemotherapy and antimicrobial exposure, hospitalizations, infections, current antimicrobial use, therapy-related adverse events or comorbidities, and more), detracting from the primary question at hand. Additional factors that could potentially cloud the study's outcomes were taken into consideration. Patients were excluded if they had a prior history of HSCT or CAR-T therapy, while admissions for haploidentical HSCT, cord blood HSCT, or CAR-T therapy were omitted given the relatively high propensity of frequent non-infectious fevers and other conflicting variables associated with those treatments. Except for one patient who received liposomal daunorubicin and cytarabine induction in the ambulatory setting and was subsequently admitted for monitoring prior to first NPF, all participants received their therapy in the hospital and remained inpatient afterward. Malignant hematology patients could have received prior therapy as long as the encounter assessed for data collection was their first intensive induction regimen. Those admitted to receive intensive re-induction or who underwent a second course of intensive induction during the same stay as their first were excluded. The main goal of the study was to evaluate the first incidence in which VRE-colonized patients developed NPF. As such, patients who had no positive VRE screens throughout the admission or whose VRE screen resulted positive after first NPF were excluded, as was any data related to VRE-directed therapy started for subsequent NPF episodes or hospitalizations. Given the review's aim to evaluate the role of VRE-directed therapy in patients with NPF who were managed in accordance with related IDSA and NCCN guidelines, any subjects who had broad-spectrum antimicrobial therapy started in a manner inconsistent with such recommendations for first NPF (e.g., not started on appropriate agent such as antipseudomonal β-lactam, therapy not initiated for true NPF, etc.) were left out of the study (the only exception being VRE-directed therapy given in a prophylactic manner leading into first NPF or empirically for first NPF as these practices were the main focus of the analysis).[8,10] The latter part of the review's time range occurred during the SARS-CoV-2 pandemic. Given the

increased mortality associated with the infection in oncology patients, any patients testing positive for SARS-CoV-2 were excluded to avoid biased comparisons to prior subjects in the study who received care before the pandemic started.[12]

Patients included in the study were stratified by VRE bacteremia development and empiric antimicrobial strategy. In the patients who developed VRE bacteremia with first NPF, ET involved starting VRE-directed therapy in an empiric fashion within 12 hours of NPF onset. Twelve hours was selected as a cutoff to more accurately capture the medical team's intent to start empiric VRE-directed therapy, accounting for any delays that may have occurred in getting such therapy started (e.g., delay in communication or drug delivery, NPF occurring during shift change, waiting to consult with the Infectious Diseases team on the case, etc.). nET consisted of situations where VRE-directed therapy was started after 12 hours or initiated as directed therapy for an identified pathogen. In those who did not develop VRE bacteremia, the definitions were slightly modified to see if foregoing empiric VRE-directed therapy in VRE-colonized patients (initiating the agents only if VRE was identified in blood culture) would be a viable strategy. The ET group contained patients who received VRE-directed therapy in a prophylactic manner leading into first NPF or empirically with first NPF, while nET patients were given no therapy meeting those criteria during the initial NPF episode. Primary endpoints included VRE-related, in-hospital, and 100-day mortality rates. Secondary outcomes included VRE bacteremia incidence for first NPF and the entire hospitalization, length of stay, Clostridioides difficile infection rate, and duration and cost of VRE-directed therapy.

Demographic information obtained included gender, age, height, weight, BMI, and BSA. Other baseline information collected included ECOG Performance Status, KPS Scale, and Sorror Comorbidity Index (for HSCT patients) obtained up to 1 month before or 1 week into admission, in addition to inpatient service unit (malignant hematology, HSCT) and the acquisition of a positive VRE screen on admission. If a patient's VRE screen was not positive initially, the number of days from hospital admission to VRE conversion was recorded. Agents for VRE-directed therapy (linezolid or daptomycin) that were given in a prophylactic manner leading into first NPF or empirically for first NPF and their respective length were reported, as were Clostridioides difficile infection rate after initiation of VRE-directed therapy or broad-spectrum therapy for first NPF while in the hospital and as an outpatient through 90 days post-discharge. Other variables assessed included time to initiation of VRE-directed therapy after first NPF and qSOFA score at first NPF incidence. The component of qSOFA measuring altered mental status (GCS) was not frequently available. To utilize a consistent measure for all patients, we substituted any mention of altered mentation from the subjective and objective assessments of providers' daily progress notes, reviewing nursing notes if further clarification was needed. To assess the likelihood of developing VRE bacteremia throughout hospitalization, total NPF occurrences were documented for all patients—each meeting the previously stated criteria for NPF and concluding with a period of defervescence [absence of an oral temperature of $\geq$ 38°C (100.4 F) or equivalent for at least 48 consecutive hours]. Administration or omittance of VRE-directed therapy was not assessed at subsequent NPF occurrences due to the possibility and presence of several confounding variables mentioned earlier. To avoid confounding the data, the NPF occurrence count for patients with VRE bacteremia was stopped after the NPF on which the infection developed. VRE bacteremia incidence, NPF occurrence that VRE bacteremia developed on, NPF occurrences per patient, length of stay, and VRE-related, in-hospital, and 100-day mortality were also recorded.

A descriptive statistical analysis was conducted to assess patients' demographic characteristics. Median or mean values and ranges are provided for continuous and ordinal variables, and patient numbers and percentages are shown for nominal variables. Primary and secondary outcome data along with patient characteristics were analyzed using IBM SPSS Statistics Version 26. The Shapiro–Wilk test was used to determine normality where applicable. Unpaired t-tests or Mann–Whitney U-tests were conducted for continuous and ordinal variables, while $\chi 2$ tests or the Fisher's exact test were employed for nominal variables. P<.05 was considered statistically significant.

To provide an accurate picture of the potential cost of empiric VRE-directed therapy for first NPF, only doses that were given in a prophylactic manner leading into or empirically for that episode were included in the pharmacoeconomic analysis. Doses that were part of therapy for subsequent NPF episodes (unless they were a continuation from the initial prophylactic or empiric course) or potentially directed at a known pathogen were omitted. Cost estimates were based on the upper end of each agent's generic product AWP range at the time of data analysis to adequately illustrate potential institutional savings. Every qualifying dose of a VRE-directed agent administered was summed together to arrive at a total amount of drug per patient. The selected AWP was then applied to this total to project cost of VRE-directed therapy.

Results

Seventy VRE-colonized patients met assessment criteria during the study period. Fifteen (21%) received intensive induction chemotherapy on the malignant hematology service, while the remaining 55 (79%) underwent HSCT. Overall, 3 of 70 subjects (4%) developed VRE bacteremia during first NPF, with 2 (67%) of those coming on the malignant hematology service. From a population standpoint, 2 of 15 (13%) malignant hematology patients developed VRE bacteremia during first NPF, while 1 of 55 (2%) HSCT patients acquired the infection during that episode (Table 1).

All 3 patients (100%) who developed VRE bacteremia during first NPF fell into the nET group. Despite a median time to initiation of VRE-directed therapy of 22 hours after NPF onset, no VRE-related (0%), in-hospital (0%), or 100-day mortality (0%) was observed (Table 2).

Table 1. VRE Bacteremia and NPF Data for Overall Population (N = 70).

Variable	Malignant hematology (N = 15)	HSCT (N = 55)	Overall population (N = 70)
VRE bacteremia incidence			
First NPF, N (%)	2(13)	1(2)	3(4)
Entire hospitalization, N (%)	4 (27)	2(4)	6(9)
NPF occurrences[a]			
Entire hospitalization, N	28	66	94
NPF that VRE bacteremia developed on, N[b]	2(1-3)	2(1-3)	2(1-3)
Combined data[a]			
VRE bacteremia/NPF occurrence during hospitalization, N/N (%)	4/28(14)	2/66(3)	6/94(6)

[a]NPF occurrences and combined data – NPF occurrence count for patients developing VRE bacteremia was cutoff after the NPF during which they developed VRE bacteremia.
[b]Median values and ranges are provided for labeled variable.

Table 2. VRE-Colonized Patients Developing VRE Bacteremia with First NPF (N = 3).

Variable	Patients (N=3)
Height, cm[a]	177 (164-183)
Weight, kg[a]	99 (82-106)
BSA, m^{2a}	2.29 (2.24-2.93)
BMI, kg/m^{2a}	30.5 (29.6-33.9)
Age, years[a]	65 (43-73)
Male, N (%)	3 (100)
ECOG performance status[b,c]	2(1-3)
KPS scale[b,c]	65 (50-80)
Sorror comorbidity index[b]	5(5)
VRE screen positive on admission, N (%)	1 (33)
If negative, time to VRE positive screen, days[a]	8(5-10)
Inpatient service unit, N (%)	
Malignant hematology	2 (67)
HSCT	1 (33)
nET group, N (%)	3 (100)
Agent for VRE-directed therapy first NPF, N (%)[d]	
Daptomycin	2 (67)
Linezolid	2 (67)
Time to VRE-directed therapy Post-NPF onset, hr[a]	22 (20-73)
qSOFA score[b]	2 (0-2)
Length of stay, days[a]	31 (20-32)
Clostridioides difficile infection, N (%)	
In-hospital[e]	0 (0)
Through 90-day post-discharge	0 (0)
Mortality, N (%)	
VRE-related	0 (0)
Overall in-hospital	0 (0)
Overall 100-day	0 (0)

[a]Median values and ranges are provided for labeled variables.
[b]Mean values and ranges are provided for labeled variables.
[c]Data point not available for all applicable patients. Number of patients with assessable data (%): ECOG – 2/3 (67%), KPS – 2/3 (67%).
[d]One patient received both daptomycin and linezolid.
[e]Clostridioides difficile infection rate after initiation of VRE-directed therapy or broad-spectrum therapy for first NPF while in the hospital.

Table 3. VRE-Colonized Patients Not Developing VRE Bacteremia (N=67).

Variable	ET (N = 42)	nET (N=25)	P value
Height, cm[a]	170 (152-192)	170 (160-188)	.280
Weight, kg[a]	82 (45-160)	88 (54-139)	.464
BSA, m^{2}[a]	1.98 (1.42-2.69)	2.05 (1.57-2.66)	.291
BMI, kg/m^{2}[a]	29.7 (17.3-60.6)	30.2 (20.4-52.2)	.707
Age, years[a]	60 (20-73)	58 (27-73)	.775
Male, N (%)	23 (55)	14 (56)	.921
ECOG performance status[b,c]	.91 (0-3)	1.06 (0-3)	.565
KPS scale[b,c]	84.87 (60-100)	81.6 (70-90)	.120
Sorror comorbidity index[b,c]	3 (0-8)	3.6 (1-9)	.255
VRE screen positive on admission, N (%)	29 (69)	17 (68)	.929
If negative, time to VRE positive screen, days[a]	7 (4-14)	9 (4-10)	.841
Inpatient service unit, N (%)			
Malignant hematology	10 (24)	3 (12)	.342
HSCT	32 (76)	22 (88)	.342
Agent for VRE-directed therapy first NPF, N (%)			
Daptomycin	37 (88)	0 (0)	<.001
Linezolid	5 (12)	0 (0)	.149
Time to VRE-directed therapy post-NPF onset, hr[a,c]	2 (0-141)	N/A	N/A
Length of VRE-directed therapy, days[a]	3 (1-30)	0 (0)	<.001
Cost of VRE-directed therapy ($/patient)[a,d]	1604 (366-28065)	0 (0)	<.001
qSOFA score[b]	.88 (0-3)	.92 (0-3)	.563
Length of stay, days[a]	25 (15-50)	23 (13-78)	.160
Clostridioides difficile infection, N (%)			
In-hospital[e]	2 (5)	1 (4)	1.000
Through 90-day post-discharge	4 (11)	0 (0)	.288
Mortality, N (%)			
VRE-related	0 (0)	0 (0)	N/A
Overall in-hospital	5 (12)	2 (8)	.704
Overall 100-day	6 (14)	5 (20)	.734

[a]Median values and ranges are provided for labeled variables.
[b]Mean values and ranges are provided for labeled variables.
[c]Data point not available for all applicable patients. Number of patients with assessable data in ET and nET therapy groups (%): ECOG Performance Status Score—32/42 (76%) and 18/25 (72%); KPS Score—39/42 (93%) and 25/25 (100%); Sorror Comorbidity Index Score (HSCT patients only)—31/32 (97%) and 21/22 (95%); Time to VRE-Directed Therapy Post-NPF Onset—39/42 (93%; 3 patients in ET group were on VRE-directed therapy as prophylaxis leading into first NPF; no patients in nET group got VRE-directed therapy with first NPF).
[d]Cost based on upper end of generic product AWP range at time of data collection.
[e]Clostridioides difficile infection rate after initiation of VRE-directed therapy or broad-spectrum therapy for first NPF while in the hospital.
Characteristics were assessed via a descriptive statistical analysis. Median or mean values and ranges are provided for continuous and ordinal variables. Patient numbers and percentages are shown for nominal variables. The Shapiro–Wilk test was used to determine normality where applicable. Unpaired t-tests or Mann–Whitney U-tests were conducted for continuous and ordinal variables, while χ^2 tests or the Fisher's exact test were employed for nominal variables. P < 0.05 was considered statistically significant.

Sixty-seven patients did not develop VRE bacteremia during first NPF. Forty-two (63%) of these patients received ET while 25 (37%) did not, belonging instead to the nET group. Data with respect to patient characteristics, performance status, in-patient service unit, VRE screen positivity on admission, median time to conversion to VRE screen positivity, and qSOFA score at NPF onset were similar between the two groups (Table 3). With respect to the primary endpoints, no patients in the ET (0%) or nET (0%) groups experienced VRE-related morality (P=N/A). There were no statistically significant differences between ET and nET groups when assessing in-hospital (12% vs. 8%; P=.704) or 100-day mortality (14%

vs. 20%; P=.734). Patients in the ET group had a significantly longer median duration of VRE-directed therapy leading into or for first NPF (3 days vs 0 days, P<.001). The 183 total days of VRE-directed therapy administered in this setting to the ET group resulted in an estimated $115,856 being spent on those drugs alone. The median cost of such therapy per patient for the ET group was significantly higher than that of their nET counterparts ($1604 vs. $0; P<.001). There were no significant differences between groups in any secondary clinical outcomes for the hospitalization course, including length of stay and occurrence of Clostridioides difficile-associated infection after initiation of VRE-directed therapy or broad-spectrum therapy

for first NPF while in the hospital and as an outpatient through 90 days post-discharge (Table 3).

Three of 67 patients (4%) who did not develop VRE bacteremia during first NPF had the infection occur during a subsequent NPF event. Of the entire population, 6 of 70 subjects (9%) developed VRE bacteremia at any point in time, with the infection occurring on a median second NPF episode. Malignant hematology patients accounted for 4 (67%) of all VRE bacteremias. Among all patients there were 94 distinct qualifying episodes of NPF throughout the hospitalization course, meaning a VRE bacteremia occurred in 6% of NPF events. From a population perspective, malignant hematology patients developed 4 VRE bacteremias in 28 occurrences of NPF (14%), while HSCT patients had 2 VRE bacteremias in 66 NPF episodes (3%) (Table 1).

Discussion

To our knowledge, this is one of a select few published studies evaluating the necessity of empiric VRE-directed therapy in both malignant hematology and HSCT patients with first NPF, especially in regard to evaluating those patients as distinct groups and assessing the role of multiple agents (daptomycin and linezolid) in empiric VRE-directed therapy. While the concept is not entirely new, scant literature exists on limiting the utilization of empiric VRE-directed therapy in first NPF. Data on the practice of omitting the agents altogether until VRE is identified in blood culture is even harder to find. Our analysis examines these important issues and provides data that can impact the care of many malignant hematology and HSCT patients in a positive manner.

The current IDSA guidelines recommend the early addition of VRE-directed therapy for NPF in patients "at risk" for such an infection (including those colonized with the organism in a hospital with high rates of endemicity).[8] However as a B-III recommendation, it has "moderate evidence for support" and is "based on evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees." This lack of definitive high-quality evidence from even one well-designed clinical trial to support this recommendation brings its validity into question, to the extent that one group has recently released guidelines advising against the practice.[13]

Previously published studies support this concept. A retrospective analysis by Lisboa and colleagues in 100 VRE-colonized hematology and HSCT patients with NPF found that delaying administration of linezolid for at least 48 hours after onset of NPF did not impact patients' survival in a negative manner compared to giving the agent at NPF onset.[14] Another analysis by Bossaer and colleagues assessed 53 VRE-colonized high-risk hematology and HSCT patients who developed NPF and found that while 20 (38%) had a documented VRE infection at some point in time during the study, only 8 (15%) developed one within 3 days of starting empiric broad-spectrum antimicrobial therapy.[15] Kamboj and

colleagues retrospectively analyzed 484 VRE-colonized allogeneic HSCT recipients with NPF and found that empiric VRE-directed therapy (extensively linezolid) demonstrated no benefit on clinical outcomes or mortality.[16]

Our analysis confirms and expands on these findings by providing a more wide-ranging and representative sample of adult malignant hematology and HSCT patients (Lisboa et al included pediatric subjects, while Kamboj et al assessed only those undergoing allogeneic HSCT).[14,16] Instead of combining malignant hematology and HSCT patients into one group (Lisboa et al and Bossaer et al), our analysis separates them into distinct arms.[14,15] This is an important issue that needs to be thoroughly examined and addressed, as the groups have several significant differences that may produce contrasting results. Even a slight variance in VRE infection rates or other associated endpoints could demonstrate a divergence in the optimal management strategies of malignant hematology and HSCT patients, helping to identify certain patients in each group who may not need initial empiric VRE coverage. In contrast from prior studies in which linezolid was extensively used, our data also provides insight into both main agents comprising VRE-directed therapy (daptomycin and linezolid), with daptomycin being the predominant choice.[14,16] Other unique features of the analysis include the reporting of NPF episodes, which provides a better understanding of our population's true incidence of VRE bacteremia per NPF event and helps assess which NPF event VRE bacteremia is most likely to occur on, as well as the pharmacoeconomic analysis which demonstrates the potential financial benefit of omitting empiric VRE-directed therapy in first NPF.

A relatively small proportion of patients in our analysis developed VRE bacteremia during first NPF and throughout the hospitalization, with the incidence of each in the HSCT population being particularly low. Several items are important to note with this subgroup. While it is a small sample, these patients tended to be older (median age 65), obese (median BMI 30.5 kg/m^2), and have poor performance status (median ECOG Performance Status 2 and KPS Scale 65) and clinical measures (median qSOFA score 2). Despite these factors and the long period of time from first NPF onset to VRE-directed therapy initiation (median 22 hours), all subjects in the group were able to be treated adequately and did not experience any mortality related to VRE infection (or by any other measure for that matter). Of the remaining patients not developing VRE bacteremia with first NPF, those in the ET and nET groups possessed similar demographics, performance status, and qSOFA scores at NPF onset. Even without receiving any VRE-directed therapy for first NPF, patients in the nET group demonstrated no significant differences in clinical outcomes or mortality. This omittance of VRE-directed therapy allowed for significantly less associated cost and exposure to those agents.

The unnecessary use of VRE-directed therapy can have several negative consequences. Daptomycin and linezolid have many potential toxicities (myopathy/rhabdomyolysis and myelosuppression) which can be troubling in this population

and may require extensive monitoring of laboratory parameters (creatine phosphokinase) or medication profiles (concomitant agents contributing to serotonin syndrome), complicating patient care and draining resources that could be better utilized elsewhere.[17,18] Overuse of the agents can drive the development of resistant Enterococcus isolates, increase the risk of Clostridioides difficile-associated infection, and negatively impact the patient and institution financially.[17-23] These same concerns may also apply to other VRE-directed therapies that are utilized less commonly (quinupristin-dalfopristin and tigecycline).[22-26] While early de-escalation strategies are becoming more commonplace, some practitioners may not be willing to stop VRE-directed therapy that has been initiated as quickly as current guidelines recommend (even if no infectious pathogen is detected). Extended use in such situations can further exacerbate these problems and prove detrimental to patient outcomes.

These factors lend credence to the thought that not all VRE-colonized patients may require immediate empiric VRE-directed therapy at first NPF onset. Our study indicates that there appears to be a low risk of VRE bacteremia in our patient population (particularly in HSCT patients) and little chance of VRE-related mortality in those who end up developing the infection, even if VRE-directed therapy is omitted for several hours after first NPF onset. The advent of rapid diagnostics such as multiplex polymerase chain reaction now allow for detection of VRE isolates within one hour of positive blood culture result, meaning providers could potentially wait until culture positivity and VRE identification before initiating directed therapy without fear of worse outcomes. The data from patients not developing VRE bacteremia with first NPF further this idea. Adding VRE-directed empiric therapy at first NPF onset showed no beneficial impact on clinical outcomes or mortality but did increase patients' exposure to many of the negative consequences of the agents mentioned above. It brought significant financial ramifications into play in the nET patients who did not develop VRE bacteremia (drug cost alone for what ended up being unnecessary empiric VRE-directed therapy was a median of $1604 per patient, not to mention the additional staffing, laboratory, and other medical expenses required to monitor for and manage potential toxicities of those agents). If the overall risk of VRE bacteremia is low, the pathogen can be detected rapidly and directed treatment initiated promptly in the few patients it does infect, and clinical outcomes and mortality are not impacted by waiting to initiate VRE-directed therapy until the organism is identified, it is reasonable to consider that uniformly starting VRE-directed empiric therapy immediately at first NPF for all VRE-colonized malignant hematology and HSCT patients may be unnecessary and perhaps detrimental to these populations and the institutions that serve them.

Limitations of this study include its retrospective design; thus, the inability to control for all variables that may influence the primary endpoints. The Infectious Diseases service at our institution is a consult service that can make recommendations for the use of empiric VRE-directed therapy, but the final decision on antimicrobial selection rests with the attending oncologist and primary team. This was often the cause for the delayed initiation or unnecessary continuation of VRE-directed therapy in the ET group (or in the case of the nET patients who did not develop VRE bacteremia, foregoing the agents altogether). A few data points (ECOG Performance Status, KPS Scale, and Sorror Comorbidity Index) were not collected for all patients due to lack of provider recording at time of patient evaluation. However, a large enough proportion were collected to provide an adequate understanding that the baseline values were not significantly different between groups and that the few pieces of data that were omitted would have little impact on the study's outcomes. GCS was not used for the altered mental status segment of qSOFA scores (so few patients had GCS assessed that qSOFA comparisons between groups would not have been possible). Instead, presence of altered mentation on evaluation by providers was deemed to be an acceptable and consistent substitution that all patients had undergone. A relatively small number of patients in either group had signs of altered mentation. Even if utilizing GCS may have produced slightly different qSOFA scores, it would be in so few instances that the impact on overall score comparisons between groups would be negligible. As explained in the study methods, the authors felt the study's exclusion criteria were necessary to help overcome what was initially a heterogenous patient population with many confounding factors. The risk of leaving these issues unaddressed and failing to clearly and accurately assess the major question at hand far outweighed any potential biases that might have been introduced by selecting the criteria. They allowed for adequate assessment of VRE-directed empiric therapy in NPF without being clouded by a large amount of outside variables while still maintaining a fairly representative sample of these populations. The clarity these provided far outweighed any potential bias that may have been introduced. A few patients in the ET group who did not develop VRE bacteremia (3 of 42, 7%) received VRE-directed therapy leading into first NPF. These patients were still included as our analysis aimed to assess the general concept of any empiric VRE-directed therapy attached to first NPF, whether started prior and continued into the episode or initiated during the event itself. That subgroup of 3 patients was not large enough to impact or alter the ET group's data in a significant manner; hence, no sensitivity analysis excluding them was conducted. While comparable in size with some previously published studies that examined this area, our patient population is not large enough to adequately power our analysis and make a definitive declaration on the topic.[14,15] This study does not demonstrate the superiority of foregoing empiric VRE-directed therapy in VRE-colonized patients and initiating the agents only if VRE is identified in culture. It also does not suggest that this approach should be taken for all such patients at first NPF [there may be exceptions for select cases (for example, clinically unstable patients with severe sepsis) in which empiric VRE-directed therapy is a reasonable decision]. However, it

does help support the hypothesis that the clinical outcomes of such a strategy in many patients appear to be no worse than those associated with administering empiric VRE-directed therapy in all VRE-colonized patients at first NPF onset. And if clinical outcomes are not worse omitting VRE-directed empiric therapy, several evident areas of potential benefit await the patient and institution (less drug-related toxicity and monitoring requirements, antimicrobial resistance, and financial cost). The fact that the 3 patients who developed VRE bacteremia were classified as nET does not carry much significance for similar reasons. The main objective of the study was not to demonstrate whether ET was more effective in preventing VRE bacteremia (sample size was small and bacteremias could be due to chance; analysis was not powered for that determination). Instead our review set out to assess the rate of VRE bacteremia in this population (which was relatively low) and see whether similar outcomes and survival could be achieved with a nET approach (which appeared to be the case in those with and without development of VRE bacteremia). This opens the door to considering a nET strategy in many patients to potentially take advantage of the aforementioned benefits. Future prospective studies with larger sample sizes are needed to make any definitive conclusions regarding these issues.

Conclusion

Overall, our population of VRE-colonized malignant hematology and HSCT patients had a relatively low risk of developing VRE bacteremia with first NPF and during the entire hospitalization (particularly in HSCT recipients). Despite the delayed time to initiation of VRE-directed therapy in the few patients who developed VRE bacteremia with first NPF, no mortality was seen. In patients who did not develop VRE bacteremia with first NPF, the addition of VRE-directed agents in a prophylactic or empiric fashion made no difference in clinical outcomes. Such patients receiving ET had a significantly higher cost of VRE-directed therapy, in addition to a significantly increased exposure to those agents (and hence the resultant risks and complications associated with their use). Available data suggest ET may offer no clinical benefit to VRE-colonized patients in our review's population, regardless of whether VRE is identified in blood culture or no causative pathogen is found. This apparent lack of benefit brings traditional practice into question and warrants consideration to potentially omit VRE-directed therapy in first NPF in many of these patients to avoid the high cost and risks associated with such agents' utilization.

Appendix

List of abbreviations

ANC	absolute neutrophil count
AWP	average wholesale price
BMI	body mass index
BSA	body surface area
CAR-T	chimeric antigen receptor T-cell
ECOG	Eastern Cooperative Oncology Group
ET	empiric therapy
GCS	Glasgow Coma Scale
HSCT	hematopoietic stem cell transplantation
IDSA	Infectious Diseases Society of America
IRB	Institutional Review Board
KPS	Karnofsky Performance Status
NCCN	National Comprehensive Cancer Network
NPF	neutropenic fever
nET	non-Empiric therapy
qSOFA	quick Sepsis-related Organ Failure Assessment
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VRE	vancomycin-resistant enterococcus

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