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ORIGINAL ARTICLE

Incidence of vancomycin-resistant enterococci (VRE) infection in high-risk febrile neutropenic patients colonized with VRE

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Abstract
Purpose This study seeks to determine the incidence of vancomycin-resistant enterococci (VRE) infection in high-risk neutropenic fever patients colonized with VRE and to determine patient characteristics associated with VRE infection.
Methods We conducted a retrospective, single-center, unmatched case-control study. Fifty-three VRE-colonized, high-risk patients with neutropenic fever were identified between January 2006 and February 2009. The two most common diagnoses/conditions included acute myeloid leukemia and hematopoietic stem cell transplantation. Data collected included days of neutropenia, days of fever, demographic data, culture results, and antimicrobial therapy.
Results Twenty of the 53 patients (38%) with VRE colonization developed a VRE infection. The most common VRE infections were bacteremias (26%). The presence of neutropenia lasting longer than 7 days was associated with the development of VRE infection in this high-risk population colonized with VRE. The timeframe to develop VRE infection varied from 1 day to 2 weeks.
Conclusion For patients colonized with VRE, approximately 38% of high-risk neutropenic patients developed a VRE infection. This is the first study to specifically evaluate the incidence of VRE infections in febrile neutropenic patients colonized with VRE. Future research into the use and efficacy of empiric VRE coverage is needed.

Keywords Vancomycin-resistant enterococci (VRE) · Febrile neutropenia · Daptomycin · Linezolid

Abbreviations

FN	febrile neutropenia
VRE	vancomycin-resistant enterococci
HSCT	hematopoietic stem cell transplantation
BSI	blood stream infection
ANC	absolute neutrophil count

Broad-spectrum antibiotics are indicated for any febrile neutropenic patient as fever may indicate an ongoing infection. Often no source of infection is identified; even so, broad-spectrum antibiotics should be continued until the absolute neutrophil count (ANC) is greater than 500 cells/mm^3. The Infectious Diseases Society of America (IDSA) guidelines recommend vancomycin as part of initial antimicrobial therapy for patients with neutropenic fever for certain scenarios: (1) suspected catheter-related infection, (2) colonization with beta-lactam-resistant pneumococci or methicillin-resistant *Staphylococcus aureus* (MRSA) organisms, (3) gram-positive blood cultures awaiting susceptibility testing or identification, (4) hypotension or signs of sepsis,

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(5) severe mucositis from chemotherapy, and (6) a history of fluoroquinolone prophylaxis in afebrile patients [1]. The National Comprehensive Cancer Network (NCCN) guidelines make similar recommendations [2]. The NCCN guidelines expand the criteria for empiric vancomycin use to include patients receiving trimethoprim–sulfamethoxazole prophylaxis and/or patients with soft tissue infections. The NCCN recommends newer gram-positive antimicrobials (linezolid, daptomycin, and quinupristin/dalfopristin) be used only in documented infections from vancomycin-resistant organisms.

Neither the IDSA nor the NCCN guidelines comment on empiric therapy in patients colonized with vancomycin-resistant organisms. Thus, a treatment dilemma exists. Should vancomycin be used if febrile neutropenic are patients colonized with vancomycin-resistant organisms?

Vancomycin-resistance has been shown to be a predictor of mortality in patients with enterococcal bloodstream infection (BSI) [3, 4]. A smaller, single-center study demonstrated increased mortality, though not statistically significant, in neutropenic patients with vancomycin-resistance enterococcal (VRE) BSI [5].

A previous report from our institution documented a 4% incidence of VRE blood stream infections (BSI) in hospitalized (excluding those on an obstetrics or a gynecology service) patients colonized with VRE [6]. However, our clinical experience on the hematology service suggests a higher incidence in neutropenic patients with hematological malignancies. To date, three single-institution studies have been published concerning the incidence of VRE infection in neutropenic patients colonized with VRE.

Zaas and colleagues assessed the incidence of VRE BSI in all cancer patients colonized with VRE at the Johns Hopkins Hospital oncology center from 1997 to 2000 [7]. This population included patients with solid tumors, leukemias, lymphomas, and hematopoietic stem cell transplant (HSCT) recipients. The incidence of febrile neutropenia was not evaluated. Most of these patients were bone marrow transplant recipients (46%) or had hematological malignancies (46%). A total of 24 of 155 (13.4%) VRE-colonized patients developed VRE BSI. Multivariate analysis revealed vancomycin use, diabetes, gastrointestinal procedures, and acute kidney injury to be associated with the development of VRE BSI (Fig. 1).

Matar and colleagues undertook a similar evaluation at the M.D. Anderson Cancer Center for the calendar year 2001 [8]. A total of 99 VRE-colonized patients with leukemia (56), lymphoma (11), and undergoing a HSCT (32) were evaluated. The incidence of febrile neutropenia was not evaluated. VRE BSI was documented in 29% of these patients. Bacteremia was found equally in patients with leukemia (30%), HSCT (28%), and lymphoma (27%), but risk factors for BSI were not assessed.

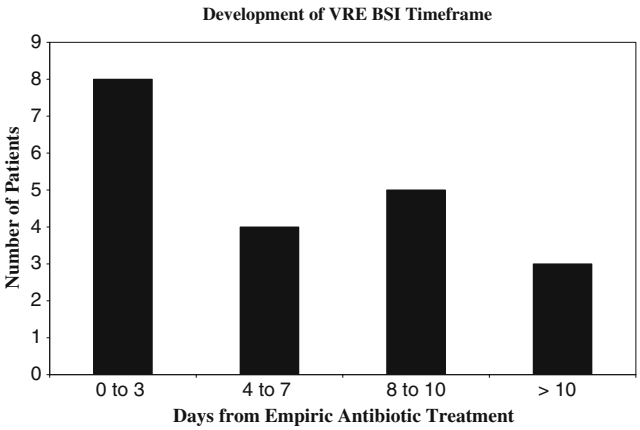

Fig. 1 Development of VRE BSI timeframe

Weinstock and colleagues examined VRE-colonized allogeneic HSCT patients during the first 35 days (+35) following transplant at the Memorial Sloan–Kettering Cancer Center [9]. Between August 2004 and February 2006, VRE BSI was documented in 13 (34.2%) of 37 patients colonized with VRE. Comparatively, one of 55 (1.8%) patients not colonized with VRE developed VRE BSI. The authors stated "no other demographic, disease, or treatment-related factors" increased the risk for VRE bacteremia, but did not provide details on the possible risk factors examined. Of the 14 patients developing VRE bacteremia, ten were treated with sequential daptomcyin and linezolid and four were treated with only linezolid. Daptomycin was given as a 6 mg/kg/day in all cases except when adjusted for renal dysfunction. VRE infection was the direct cause of death in two (14.3%) and a contributor to death in three (21.4%). Microbiological failure occurred in four (28.5%). Given the high incidence of VRE infection and associated mortality in allogeneic HSCT patients colonized with VRE, the authors suggest empiric VRE therapy with linezolid or daptomycin for 48 h.

The results of these retrospective studies raise questions concerning the empiric coverage of VRE in colonized patients. Is vancomycin use for the aforementioned conditions the best care in VRE-colonized patients? Alternative agents to vancomycin have limitations. Daptomycin is inactivated in pulmonary surfactant and thus not effective in treating pneumonia [10]. Linezolid is associated with reversible myelosuppression, most notably thrombocytopenia. This is especially evident after prolonged courses of treatment (≥14 days) and represents a barrier to its use in neutropenic patients [11].

The efficacy of empiric VRE coverage in febrile neutropenia with daptomycin or linezolid has yet to be studied in a randomized clinical trial, but the activity of these drugs against VRE infections has been described in neutropenic patients [12–15].

Table 1 VRE-colonized patient demographics

	All (n=53)	VRE Infection (n=20)	No VRE Infection (n=33)	p value
Age (mean, years)	51	50	52	
Gender				
Male	28	8 (40%)	20 (61%)	0.17
Female	25	12 (60%)	13 (39%)	
Malignancy				
AML	30	10 (50%)	20 (61%)	0.35
ALL	5	3 (15%)	2 (6%)	
CML	4	3 (15%)	1 (3%)	
Biphenotypic leukemia	2	1 (5%)	1 (3%)	
MDS	1	1 (5%)	0 (0%)	
DLBCL	5	1 (5%)	4 (12%)	
Burkitt lymphoma	2	1 (5%)	1 (3%)	
Hodgkin's lymphoma	1	0 (0%)	1 (3%)	
Multiple myeloma	3	0 (0%)	3 (9%)	
Transplant status				
Allogeneic	11	5 (25%)	6 (18%)	0.49
Autologous	10	2 (10%)	8 (24%)	
None	32	13 (65%)	19 (58%)	

AML acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *CML* chronic myeloid leukemia, *MDS* myelodysplastic syndrome, *DLBCL* diffuse large B-cell lymphoma

Objectives

The primary objective of this study is to determine the incidence of VRE infection in high-risk neutropenic patients colonized with VRE. Secondary objectives include determining any patient or treatment-related variables that may predict the likelihood of VRE infection in this population.

Methods

A retrospective chart review was undertaken to assess the incidence of VRE infection in high-risk neutropenic patients colonized with VRE from January 1, 2006 to February 1, 2009. All patients were defined as high risk by MASCC criteria and admitted and treated inpatient at the Medical University of South Carolina (MUSC), which is a tertiary teaching facility in Charleston, South Carolina, [16]. In September of 2008, the hematology and oncology units were relocated to the newly built Ashley River Tower facility. Perianal swabs are obtained upon admission and weekly thereafter to screen for VRE colonization for all patients admitted to an MUSC facility. This study was approved by our institution's Investigational Review Board.

Patients

High-risk patients included those who had experienced an absolute neutrophil <500 cells/mm^3 and a diagnosis of acute leukemia, lymphoma, or undergoing an allogeneic or autologous HSCT. Febrile neutropenia is defined as a single temperature greater than 101°F in a patient with an absolute neutrophil count of <500 cells/mm^3 [1]. VRE colonization was determined by routine infection control perianal swabs performed weekly in all hospitalized patients. Patients were initially identified by ICD-9 codes for acute leukemia, lymphoma, or bone marrow transplant in addition to neutropenic fever. Electronic chart review was then performed on all patients. Patients less than 18 years of age and those without a positive VRE surveillance culture at the time were excluded. Additionally, patients were excluded if VRE colonization occurred after resolution of neutropenic fever. Only the first episode of neutropenic fever following VRE colonization was evaluated.

Data collected

Treatment-related data collected included sterile body site cultures including blood, surveillance cultures for VRE, white blood cell count, absolute neutrophil count, days of neutropenia, medications administered, and temperature. Demographic data collected included age, gender, malignancy, history of autologous or allogeneic HSCT, chemotherapy regimens/agents received, use of fluoroquinolone prophylaxis, presence of mucositis, and graft-versus-host disease (GVHD) of the gastrointestinal tract. Mucositis is defined as any mention of mucositis or initiation of analgesic for mucositis in the medical record. Antimicrobial use targeting gram-positive organisms (vancomycin, daptomycin, linezolid) were recorded in accordance with onset of

Table 2 Characteristics of infection

	VRE infection (n=20)	No VRE infection (n=33)	Odds ratio (95%CI)
All patients (n=53)			
Neutropenia >7 days	19 (95%)	22 (67%)	9.4 (1.1–80.5)
Neutropenia >14 days	11 (55%)	9 (27%)	3.3 (1.01–10.5)
Mucositis	8 (40%)	10 (30%)	1.5 (0.5–4.9)
Ciprofloxacin prophylaxis	17 (85%)	26 (79%)	1.53 (0.4–6.7)
Empiric vancomycin	16 (80%)	28 (85%)	0.7 (0.17–3.05)
Allogeneic HSCT (n=11)			p value
GVHD of the GI tract	2/5 (40%)	0/6 (0%)	0.18[a]

VRE vancomycin-resistant enterococci, *HSCT* hematopoietic stem cell transplant, *GVHD* graft-versus-host disease, *GI* gastrointestinal

[a] Fisher's exact test

fever (empiric treatment) or upon persistent fevers and positive cultures. Fever curves were analyzed to determine the time to defervescence after initial gram-positive antimicrobial use. Defervescence is defined as the absence of temperatures >101°F for 72 h. Patients not discharged upon neutrophil recovery (ANC >500 cells/mm^3) were evaluated until hospital discharge.

Statistical considerations

We examined associations between demographic and clinical data (described above) and infection and reported odds ratios with 95% confidence intervals. Fisher's exact test was used to estimate p values comparing categorical variables with small sample sizes (e.g., infection in allogeneic HSCT patients and GVHD).

Results

Patients

Fifty-three patients met the inclusion criteria, and their demographic information is outlined in Table 1. The mean and median lengths of neutropenia were 17 and 12 days, respectively. Patient demographics were similar between the case (VRE infection) and control groups (Table 2). With their first fever, the majority of patients received empiric vancomycin along with meropenem (Table 3). Four patients (7.5%) received empiric daptomycin with their first fever (Table 4).

VRE infection

Twenty patients (38%) developed a documented VRE infection. Fourteen patients (26%) had bacteremia, five (9%) had urinary tract infections of >100,000 colony-forming units, and one had an abscess. The 26% VRE BSI infection rate is significantly greater than a historical control group from our institution (p<0.0001) which found a 4% VRE BSI infection rate among all hospitalized patients not on an obstetrics or gynecology service [6]. Twelve patients developed VRE BSI (60%) within 7 days of starting empiric antibiotics (Fig. 1). Six patients expired during hospitalization, five of whom had developed VRE bacteremia. VRE bacteremia persisted for more than 7 days in three of these patients and likely contributed to death. Other likely contributing factors to death included GVHD (one patient), invasive fungal infection (one patient), and disease progression (three patients). VRE bacteremia was associated with death (OR=21.1; 95%CI 2.2–203.4).

Antibiotic use

The majority of patients (80%) were receiving ciprofloxacin prophylaxis prior to episodes of febrile neutropenia,

Table 3 Empiric antibiotic use with first fever

	VRE Infection (n=20)	No VRE infection (n=33)
Empiric gram + coverage		
Vancomycin	18 (90%)	29 (88%)
Daptomycin	1 (5%)	3 (9%)
Linezolid	0 (0%)	0 (0%)
None	1 (5%)	1 (3%)

VRE vancomycin-resistant enterococci

Table 4 Empiric VRE coverage

Pt	VRE Abx	Disease state	Neutropenia	Risk factor(s)	Outcome
1	dapto	30 yo M w/NHL undergoing auto HSCT	11 days	Enteric fistula; mucositis	Bacteremia cleared after 1 day of dapto; survived
2	dapto	69 yo F w/AML receiving AraC ± clofarabine	4		No VRE infection; survived
3	dapto	46 yo F w/BL receiving hyperCVAD-"a" cycle	8		No VRE infection; survived
4	dapto	69 yo M w/MM undergoing auto HSCT	12	Mucositis	No VRE infection; survived

VRE vancomycin-resistant enterococci, *Abx* antibiotic, *HSCT* hematopoietic stem cell transplant, *dapto* daptomycin

and the majority of the patients (89%) received empiric vancomycin with the patient's first fever (Table 4). One of those four who received empiric daptomycin developed bacteremia with VRE prior to receiving empiric daptomycin. All others receiving daptomycin remained free of VRE infection throughout their hospitalization, and all four of these patients receiving empiric VRE treatment with daptomycin survived (Table 4).

Empiric vancomycin use was not associated with an increase in VRE infections (OR=0.7; (95%CI 0.17–3.05; Table 3). Ten patients developed a VRE infection more than 7 days after empiric vancomycin. Three of these ten patients received daptomycin after empiric vancomycin. One patient was receiving daptomycin at the time of VRE infection, but the other two patients had daptomycin discontinued prior to development of a VRE infection.

Risk factors for VRE infection

Neutropenia lasting longer than 7 and 14 days, respectively, was associated with VRE infection (Table 2). Two of five (40%) allogeneic HSCT patients with VRE infection experienced GVHD of the gastrointestinal tract whereas none of the six without VRE infection had GVHD, but this result did not reach statistical significance (p=0.18). None of the other risk factors (i.e., mucositis, use of ciprofloxacin prophylaxis, nor the empiric use of vancomycin) were associated with developing a documented VRE infection (Table 2).

Discussion

VRE-colonized cancer patients who experience febrile neutropenia are at higher risk of developing a VRE infection compared to the general hospitalized population [6]. Unlike earlier studies, this review explored the incidence of VRE infection in patients with VRE colonization who developed neutropenic fever [7–9].

We describe an overall VRE infection rate of 38% and a BSI rate of 26%. These numbers are similar to other institutions. Previous single-center studies have demonstrated an incidence of VRE BSI ranging from 13% to 34% (Table 5) [7–9]. There appears to be a trend toward an increased incidence of VRE infections in VRE-colonized patients depending on the underlying disease (allogeneic HSCT > hematologic malignancy patients > oncologic malignancy patients (Table 5)). Three of the four studies presented here yielded VRE infection rates of approximately 33%. In our study, VRE bacteremia was associated with a fatal outcome. This association may have contributed to mortality, but may also be a surrogate marker for extremely sick patients as previously suggested [17]. Given the association of VRE bacteria and mortality, is it worth empirically covering VRE in neutropenic patients considering one of three will develop a VRE infection? Randomized clinical studies are clearly needed to answer that question definitively with regard to any reduction in mortality. Until those clinical

Table 5 Single institution VRE infection rates in VRE-colonized cancer patients

Reference	Patient population	*n*	VRE infection	Risk factors identified
Zaas AK, et al. 2002 [7]	Onc, Heme, HSCT	179	13.4% BSI	DM ARF GI procedures Vanc use >7 days
Matar MJ, et al. 2006 [8]	Heme, HSCT	99	29% BSI	Not evaluated
Weinstock DM, et al. 2007 [9]	Allo HSCT	92	34% BSI	
Bossaer JB, et al. [this study]	Heme, HSCT	53	38% infection 26% BSI	Neutropenia >7 days

DM diabetes mellitus, *ARF* acute renal failure, *Vanc* vancomycin, *GVHD* graft-versus-host disease, *GI* gastrointestinal, *BSI* blood stream infection, *BMT* bone marrow transplant, *VRE* vancomycin-resistant enterococcus)

trials are completed, clinicians should evaluate their patients' risk factors for VRE infections to make sound decisions.

In our patient population, only neutropenia lasting more than 7 days appeared to be associated with VRE infection. There was a trend toward risk of VRE infection in patients with GVHD of the GI tract. The strength of this association is difficult to interpret due to the wide confidence intervals (Table 2). A limitation of our study is the small size compared to previously similar studies [7–9]. Previous studies had also identified acute renal failure, diabetes, recent history of gastrointestinal procedures, and vancomycin use >7 days as potential risk factors for VRE infection in cancer patients colonized with VRE. Additionally, VRE infection appears to be more common in patients undergoing allogeneic HSCT who are VRE-colonized. Until randomized controlled trials provide the best answers to this clinical dilemma, utilizing our results as well as other studies, one can list characteristics of VRE-colonized patients associated with VRE infection in the setting of neutropenic fever:

- Allogeneic HSCT patients [9]
  - Especially those with GI GVHD
- Neutropenia >7 days
- Vancomycin use >7 days [7]
- Interruptions of gastrointestinal integrity (e.g., gastrointestinal procedures) [7]

To prevent VRE infections in this patient population, one could limit the use of vancomycin. Vancomycin use has been well established as a risk factor for the development of vancomycin-resistant organisms, including VRE [3, 6, 7]. The empiric use of vancomycin did not appear unsafe as VRE infection rates were similar between groups receiving or not receiving empiric vancomycin (80 versus 85%). Interestingly, more than 80% of our patients received ciprofloxacin prophylaxis. This practice has been shown to prevent episodes of neutropenic fever, but does not impact survival [18, 19]. With the concerns of antibiotic resistance, the routine use of fluoroquinolone prophylaxis remains controversial [1, 20, 21]. As the IDSA guidelines for neutropenic fever recommend considering vancomycin in neutropenic fever patients receiving prophylactic fluoroquinolones, it is not surprising how often vancomycin is used in our hospital. It is possible that widespread ciprofloxacin prophylaxis has led to an increase in vancomycin use which in turn has led to increase in vancomycin use resulting in an increase in VRE colonization and infection. Infection control measures to limit the development of VRE are critically important.

In conclusion, the incidence of VRE infection in febrile neutropenic cancer patients colonized with VRE appears to be approximately 38%. Randomized studies are needed to define the role and potential advantage of empiric VRE therapy.

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