

## Vancomycin-resistant enterococci colonization and bacteremia in patients with hematological malignancies

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### Abstract

**Introduction:** We retrospectively evaluated the rates of vancomycin-resistant enterococci (VRE) colonization and VRE-related infections in patients with hematological malignancies.

**Methodology:** All patients in the hematology department of the Ministry of Health Okmeydanı Training and Research Hospital, an 800-bed tertiary hospital in Istanbul, Turkey, older than 14 years of age and who developed febrile neutropenia during chemotherapy for hematological cancers between November 2010 and November 2012 were evaluated in this retrospective observational study.

**Results:** A total of 282 neutropenic episodes in 126 patients who met the inclusion criteria were analyzed. The mean patient age was 51.73 ± 14.4 years (range: 17–82 years), and 66 cases occurred in male patients. The mean Multinational Association for Supportive Care in Cancer score of patients with hematological malignancies was 17.18 ± 8.27. Fifty (39.68%) patients were colonized with VRE, and the mean number of VRE colonization days per patient was 34.27 ± 13.12 days. Only two patients developed VRE bacteremia: a male patient with non-Hodgkin's lymphoma who survived the infection, and a female patient with acute myeloid leukemia who died from VRE bacteremia.

**Conclusions:** Patients with hematological malignancies accompanied by VRE colonization should be expected to develop VRE- or vancomycin-sensitive enterococci-related bacteremia under certain conditions, which include the development of severe mucositis, invasive procedures, and the use of intensive broad-spectrum antibiotics, even if infection control measures are implemented properly.

**Key words:** hematological patients; vancomycin-resistant enterococci; bacteremia; colonization.

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### Introduction

Enterococci are part of the normal flora of humans and vertebrates. They can survive under adverse conditions in various environments such as soil, water, food, and on medical devices [1]. In animals, enterococci are found in the gastrointestinal tract, in oropharyngeal secretions, and on the skin [1]. These bacteria can cause nosocomial infections in vulnerable patients colonized with vancomycin-resistant enterococci (VRE) or exposed to contaminated tools or medical personnel [2]. Advanced age, severity of illness, inter-institutional transfer, prolonged hospital stay, gastrointestinal surgery, transplantation, exposure to medical devices—especially central venous catheters—and strong exposure to broad-spectrum antimicrobial drugs are risk factors for VRE colonization and infection [3]. VRE are also important nosocomial pathogens in patients with hematological

malignancies [4]. Patients with hematological malignancies during remission-induction chemotherapy who undergo an allogeneic hematopoietic stem cell transplant with prior conditioning chemotherapy are at risk of infection with colonizing and opportunistic microorganisms [5]. Only mucositis and increasing mucositis are reported to be independent risk factors for VRE-related blood stream infection (BSI) [6]. Enterococcal bacteremia is the third or fourth most common cause of nosocomial bacteremia, depending on the region, and its rates are increasing worldwide [5].

This study retrospectively evaluated VRE colonization and VRE-related infections in patients with hematological malignancies.

## Methodology

### *Study population*

All patients in the hematology department older than 14 years of age who developed febrile neutropenia during chemotherapy for hematological cancers between November 2010 and November 2012 were evaluated in this retrospective observational study. This study was approved by the ethics committee of Health Okmeydanı Training and Research Hospital. Patients were included if they had experienced at least one neutropenic episode due to chemotherapy in the hematology ward. Patients were excluded if they were treated for other hematological diseases (*e.g.*, anemia, idiopathic or immune thrombocytopenic purpura, etc.) or had not been screened by rectal swab culture for VRE colonization while in the hematology ward.

### *Prevention of drug-resistant infections*

The hematology department of the Ministry of Health Okmeydanı Training and Research Hospital is an 800-bed tertiary hospital in İstanbul, Turkey that is equipped with 23 beds in single, double, and quadruple rooms without high-efficiency particulate air filters. Patients and their attendants reside in the same room and share three toilets in the hematology ward. A weekly one-hour instructional program regarding drug-resistant microorganisms and preventative measures was taught to patients and their attendants by a nurse and doctor in the hematology ward. The instructional program promoted the use of alcohol-based hand disinfectant after contact with materials and areas that have been contaminated or are likely contaminated. Patients colonized with VRE underwent cohorting. Healthcare workers were required to use gloves when entering rooms as well as gloves and a gown when contact with body fluids was anticipated. Hospital floors were cleaned daily with a sodium hypochlorite solution (1,000 ppm). The use of glycopeptide and anti-anaerobic antibiotics was restricted according to the 2002 Clinical Practice Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer of the Infectious Diseases Society of America (2010 update) and the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group guidelines [7-9]. All procedures were strictly implemented without any additional interventions.

### *Diagnosis of febrile neutropenia*

Febrile neutropenia was defined as an oral temperature  $> 38.3^{\circ}\text{C}$  or two consecutive readings  $> 38.0^{\circ}\text{C}$  for two hours and an absolute neutrophil count  $< 0.5 \times 10^9/\text{L}$  or a count expected to fall below  $0.5 \times 10^9/\text{L}$  [7]. Collected data included patient demographics and diagnoses, episode data, clinical presentation, laboratory findings, clinical therapy, microbiological data, interventions, invasive procedures, and outcomes. The treatment protocol for febrile neutropenia in the hospital was based on the aforementioned guidelines [7-9]. Blood samples drawn from a vein or catheter were inoculated into BactAlert 3D bottles (bioMérieux, Marcy-l'Etoile, France). Additional samples including urine, sputum, wound, conjunctive, abscess, and catheter samples were inoculated onto 5% sheep blood agar, chocolate agar, and MacConkey agar (Salubris Inc., İstanbul, Turkey). Identification and susceptibility testing were performed using an automated broth microdilution method (Vitek 2, bioMérieux, Marcy-l'Etoile, France), and confirmations were made by the Etest method (AB BIODISK, Solna, Sweden). The breakpoints defined by the Clinical and Laboratory Standards Institute (2008) were used. VRE colonization was detected by inoculating bile esculin azide agar plates containing  $6 \mu\text{g}/\text{mL}$  vancomycin (Becton, Dickinson and Company, Sparks, MD, USA) with rectal swabs. Plates were then incubated aerobically in 5%–10%  $\text{CO}_2$  at  $35^{\circ}\text{C}$ – $37^{\circ}\text{C}$  for up to 48 hours to confirm a negative result. Samples were collected from patients at two-week intervals.

### *VRE-related outcomes*

The number of colonization days with VRE was calculated as the number of days with positive rectal swab cultures. The colonization period was considered to have ended when two rectal swab cultures taken two weeks apart were negative in addition to a lack of clinical or radiologic findings associated with VRE [10]. Strains isolated from cultures determined by infectious diseases specialists or medical microbiologists to be contaminated were excluded from analysis. Patients with VRE bacteremia were treated with linezolid  $2 \times 600 \text{ mg}/\text{day}$  for at least 14 days. Patients with vancomycin-sensitive enterococci (VSE) were treated with ampicillin/sulbactam 8–12 g/day plus gentamycin 160–240 mg/day for at least 14 days. A positive response to treatment was defined as defervescence 48–72 hours after the initiation of antimicrobial therapy as well as improvements in vital signs and clinical symptoms associated with infection,

including improvement in arterial blood gas values, radiological improvement, negative urine culture for urinary tract infection, and recovery of signs and symptoms related to other infections. The primary outcome of this study was the VRE infection rate for patients colonized with VRE during the neutropenic phase. The secondary outcome was the mortality rate due to VRE-related infection.

### Statistical analysis

Continuous variables are expressed as mean  $\pm$  standard deviation and range. Overall mortality associated with febrile neutropenia was defined as death within 30 days of neutropenia development. Crude 30-day mortality rates were calculated as the proportion of study patients who died within 30 days of developing neutropenia.

### Results

During the study period, 15 of the 141 patients admitted to the hematology ward were excluded. Therefore, 282 neutropenic episodes in 126 patients during the two-year study period were retrospectively analyzed. The mean patient age was  $51.73 \pm 14.4$  years (range: 17–82 years), and 66 cases occurred in male patients. The Multinational Association for Supportive Care in Cancer score was  $17.18 \pm 8.27$  in patients with hematological malignancies (Table 1). Fifty (39.68%) patients were colonized with VRE; the mean number of VRE colonization days per patient was  $34.27 \pm 13.12$  days.

A total of 931 rectal swab cultures were taken from all patients. The VRE species isolated from VRE-colonized patients were *Enterococcus faecium*

(81%) and *Enterococcus faecalis* (19%). Vancomycin-sensitive *E. faecium* was also isolated from wound (n = 1), urine (n = 1), and sputum (n = 1) cultures.

Among the 50 patients colonized with VRE, VRE bacteremia developed in two (4%) patients during a total of 1,295 colonization days, including a male patient with non-Hodgkin's lymphoma who survived the infection and a female patient with acute myeloid leukemia who died from VRE bacteremia. In addition to these two cases, VRE were isolated from bronchoalveolar lavage and blood cultures from a patient admitted with pneumonia and dyspnea from another hospital. All rectal swab cultures of this case collected during follow-up yielded normal flora bacteria. This patient was successfully treated with linezolid. In addition, VSE-related bacteremia (n = 6), bacteriuria (n = 2), sputum (n = 1), and wound (n = 1) were reported in nine patients. *E. faecalis* (n = 4) and *E. faecium* (n = 2) were isolated from patients with VRE-related bacteremia. Vancomycin-sensitive *E. faecalis* was isolated from a patient with bacteriuria. The hematological malignancies in the patients with VSE-related bacteremia and bacteriuria were acute myeloid leukemia (n = 3), acute lymphocytic leukemia (n = 1), multiple myeloma (n = 1), non-Hodgkin's lymphoma (n = 1), and hairy cell leukemia (n = 1). Two patients with VSE bacteremia died. Only two patients who had persistent fever accompanied by distinctive clinical findings (e.g., cough, pain in the anal region, and ulcerations of the oral mucosa) responded to linezolid treatment. Invasive procedures performed on patients colonized with VRE during follow-up included the placement of a chemotherapy port catheter and bone marrow biopsy. No cases of

**Table 1.** Distribution of hematologic malignancies in patients with febrile neutropenia

| Hematologic malignancies                             | n (%)            |
|--|------------------|
| Acute myeloblastic leukemia                          | 73 (58)          |
| Acute lymphocytic leukemia                           | 22 (17)          |
| Non-Hodgkin's lymphoma                               | 7 (5)            |
| Chronic lymphocytic leukemia                         | 5 (4)            |
| Multiple myeloma                                     | 5 (4)            |
| Hairy cell leukemia                                  | 4 (3)            |
| Aplastic anemia                                      | 3 (2)            |
| Chronic myeloid leukemia                             | 2 (2)            |
| Plasma cell leukemia                                 | 2 (2)            |
| Mantle cell lymphoma                                 | 2 (2)            |
| Chronic lymphocytic leukemia with Burkitt's lymphoma | 1 (1)            |
| <b>Total</b>   | <b>126 (100)</b> |

VRE-related bacteremia developed among patients who were not colonized with VRE.

The overall 30-day crude mortality rate among patients with hematological malignancies was 31.74% (40/126). The hematological malignancies of patients who died included acute myeloid leukemia (n = 32), acute lymphocytic leukemia (n = 9), multiple myeloma (n = 1), and non-Hodgkin's lymphoma (n = 1). Twenty-eight (22.22%) patients died from infections that included Gram-negative bacteremia (n = 5), candidemia (n = 5), VSE-related bacteremia (n = 3), methicillin-resistant *Staphylococcus aureus*-related bloodstream infections (n = 2), invasive fungal infections (n = 2), VRE-related bacteremia (n = 1), and severe vancomycin-sensitive *E. faecium*-related sepsis (n = 1).

## Discussion

The VRE colonization rate among all patients was approximately 40% despite the unfavorable conditions of our hematology ward. Unfavorable ward conditions such as shared toilets, housing attendants with patients, close contact between patients and attendants, frequent antibiotic use for infections, and immunosuppression likely caused the higher VRE colonization rates in the present study. This was in spite of the implementation of an infection control program for patients and attendants as well as the restriction of glycopeptide and anti-anaerobic antibiotics in our hematology ward.

VRE can persist on dry surfaces for days to months, facilitating their spread among patients [11]. In addition, contact with contaminated healthcare workers, patients, attendants, environmental surfaces, and equipment promotes VRE colonization [11]. VRE colonization develops in patients with hematological malignancies under certain conditions including immunosuppression, serious comorbid conditions (*e.g.*, diabetes, renal failure, and high Acute Physiology and Chronic Health Evaluation score), prolonged hospital stay, residence in a long-term care facility, proximity to another colonized or infected patient (including sharing a room), hospitalization in a room previously occupied by a patient colonized with VRE, invasive procedures, and administration of broad-spectrum antibiotics or vancomycin [12, 13]. Colonization of the rectum with VRE is reported to be a more important predictor than colonization of other regions [11]. Pathogenic microorganisms can invade the intravascular compartment via damaged mucosa after induction or consolidation chemotherapies that severely damage mucosal barriers. Only mucositis and

increasing mucositis are reported to be independent risk factors for VRE-related BSI [14]. Meanwhile, patients with diarrhea or *Clostridium difficile* infection have increased colonization and environmental contamination rates [6].

VRE colonization is reported to increase the risk for VRE bloodstream infections, although this remains controversial [15]. Comorbidities and other conditions such as prolonged use of intensive antimicrobial therapy, high-dose cancer chemotherapy, severe mucositis, gastrointestinal surgery, and the placement of invasive devices are more likely to promote the development of VRE-related BSI. In addition, VRE bacteremia is reported to be more strongly related to the severity of the patient's condition than to the pathogenicity of the bacteria [16]. Infection control measures and patient education can decrease colonization rates in the population as well as environmental contamination rates. The reported rates of BSI in patients colonized with VRE range from 0 to 34 percent; these rates are higher in patients with cancer and in those who have received solid and bone marrow transplants. Risk factors for VRE-related BSI in VRE-colonized patients include cancer or diabetes (relative risk [RR] = 3.91), gastrointestinal procedures (RR = 4.56), acute renal failure (RR = 3.1), exposure to vancomycin (RR = 1.95), infection of an additional site other than the blood (odds ratio = 3.9), and concurrent *C. difficile* infection [6,16].

Even if blood cultures are negative, episodes of VRE-related bacteremia should be considered in patients with neutropenia undergoing antimicrobial therapy and in those who present with persistent fever as well as worsening clinical signs and symptoms. Active VRE therapy should be initiated in such cases, because the mortality rate of patients colonized with VRE is 2.5 times higher than that of patients colonized with VSE [17,18]. According to the Hospital Infection Control Practices Advisory Committee guidelines, patients whose rectal swab cultures yield VRE should be considered positive until three consecutive negative cultures are obtained in at least one-week intervals [10]. However, this approach does not guarantee the eradication of VRE [19]. Patients admitted from other hospitals or intensive care units should be screened for VRE, because imported patients who are not identified as being colonized with VRE may promote the spread of VRE in the ward [10]. Patients with hematological malignancies are predisposed to enterococcal bacteremia because of neutropenia and the breakdown of mucosal barriers, which create a suitable entry point for endogenous microbial flora [10].

Persistent VRE- or VSE-related BSI is related to the presence of endocarditis or intestinal lesions. In the present study, one of the two patients (50%) with VRE-related BSI and two of the six patients (33%) with VSE-related BSI died. Furthermore, vancomycin resistance, comorbidity, and the severity of the patient's condition impede response to therapy [16,17]. Moreover, the low frequency of invasive procedures, including bone marrow biopsies and the placement of chemotherapy port catheters, is likely to be related to the low rates of VRE-related BSI observed among patients colonized with VRE in the present study.

## Conclusions

Infection control measures including active surveillance, isolation or cohorting of colonized and infected patients, strict adherence to appropriate infection control practices, favorable healthcare conditions, and antimicrobial stewardship may not only reduce the rates of VRE colonization, but also the rates of colonization of other antibiotic-resistant microorganisms. However, patients who have hematological malignancies accompanied by VRE colonization can be predicted to develop VRE- or VSE-related bacteremia under certain conditions, including the development of severe mucositis, administration of invasive procedures, and use of intensive broad-spectrum antibiotics, even if infection control measures are implemented properly.

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