Vancomycin-resistant enterococci colonization in patients with hematological malignancies: screening and its cost-effectiveness

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Abstract:

Background and objective: We evaluated the rates of vancomycin-resistant enterococci (VRE) colonization and VRE-related bacteremia in patients with hematological malignancies in terms of routine screening culture and its cost-effectiveness.

Materials and Methods: All patients of the hematology department who were older than 14 years of age and who developed at least one febrile neutropenia episode during chemotherapy for hematological cancers between November 2010 and November 2012 were evaluated retrospectively.

Results: We retrospectively analyzed 282 febrile episodes in 126 neutropenic patients during a two-year study period. The study included 65 cases in the first study-year and 78 cases in the second study-year. The numbers of colonization days and colonized patient were748 days of colonization in 29 patients (44%) in the first study-year and 547 colonization days in 21 patients (26%) in the second study-year, respectively. Routine screening culture for VRE cost $4516,4 (427 cultures) in the first study-year, $5082,7 (504 cultures) in the second study-year depending on the number of patients and their length of stay.

Conclusion: In line with our study results, routine screening of hematological patients for VRE colonization is not cost-effective. Routine surveillance culture for VRE should be considered with respect to the conditions of health care setting.

Keywords: Hematological patients, febrile neutropenia, vancomycin-resistant enterococci, vancomycin-sensitive enterococci, bacteremia, colonization.

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Introduction

Enterococci are part of the normal flora of humans and vertebrate animals. They can survive under difficult conditions and varied environments, such as in soil, water, and food and on medical devices[1]. Enterococci are found in the gastrointestinal tract, in oropharyngeal secretions, and on the skin[1]. Vancomycin-resistant enterococci (VRE) can persist on dry surfaces for days to months, contributing to the spread of VRE among patients[2]. These bacteria can cause nosocomial infections in vulnerable patients who are colonized with VRE or exposed to contaminated tools or medical staff[3]. Advanced age, severity of illness, inter- institutional transfer of the patient, prolonged hospital stay, gastrointestinal surgery, transplantation, exposure to medical devices, especially central venous catheters, and heavy exposure to broad-spectrum antimicrobial drugs are risk factors for colonization and infection with VRE[4]. In addition, contact with contaminated health care workers, patients, attendants, environmental surfaces and equipment promotes VRE colonization[5]. Colonization of the rectum with VRE was reported to be a more important predictor than colonization of other regions[6]. VRE is also an important nosocomial pathogen in hematological patients[7]. Patients who have hematological malignancies during remission-induction chemotherapy and undergo allogeneic hematopoietic stem cell transplantation with prior conditioning chemotherapy are at risk of infection with colonizing and opportunistic microorganisms[8]. Only mucositis and increasing mucositis have been reported as independent risk factors for VRE-related bloodstream infection (BSI)[9]. Enterococcal bacteremia is the third or fourth

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most common cause of nosocomial bacteremia, with increasing rates worldwide[8].
In this study, we retrospectively evaluated the rates of vancomycin-resistant enterococci (VRE) colonization and VRE-related bacteremia in patients with hematological malignancies in terms of routine screening culture and its cost-effectiveness.

Material and Methods

Study population: All patients in the hematology department who were older than 14 years of age and developed febrile neutropenia (FN) during chemotherapy for hematological cancers between November 2010 and November 2012 were evaluated in this retrospective study. The study period was divided into two periods: the "first study-year" was from November 2010 to November 2011, and the "second study-year" was from November 2011 to November 2012. Due to the fact that some patients were treated in the first and second study- years, the total number of patients differs from the sum of the number of patients in the first and second study-years. This study was approved by the local ethics committee. Patients were included if they had experienced at least one neutropenic episode due to chemotherapy in the hematology ward. Meanwhile, patients were excluded if they were treated for other hematological diseases (e.g., anemia, idiopathic or immune thrombocytopenic purpura, etc.).

Prevention of drug-resistant infections: The hematology department was equipped with 23 beds in single, double and four-person rooms without high-efficiency particulate air filters. Patients and their attendants resided in the same room and used three shared toilets in the hematology ward. In both study periods, a weekly one-hour instructional program regarding drug-resistant microorganisms and preventative measures was administered to patients and their attendants by a nurse and a doctor in the hematology ward. The instructional program promoted the use of alcohol-based hand disinfectant after contact with materials and zones that were contaminated or likely to be contaminated. Patients who were colonized with VRE underwent cohorting. Healthcare workers were required to use gloves when entering the room and gloves and gown when contact with body fluids was anticipated. Hospital floors were cleaned daily with a 1000 parts per million (ppm) solution of sodium hypochlorite[10]. The use of glycopeptide and anti-anaerobic antibiotics were restricted according to the 2002 clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer, the 2010 update by the Infectious Diseases Society of America, 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 (EORTC/MSG) guidelines.[11-13] All procedures were strictly implemented during the first and second year periods without any additional interventions.

Diagnosis of FN: FN was defined as an oral temperature >38.3°C or two consecutive readings>38.0°C for 2 h and an absolute neutrophil count <0.5 × 10^9/L or a count expected to fall below 0.5 × 10^9/L.[11] Collected data included patient demographics and diagnoses, the episode data, clinical presentation and laboratory findings, clinical therapy, microbiological data, interventions, invasive procedures and outcomes. The treatment protocol for FN in our hospital was based on the aforementioned guidelines[11-13]. Blood samples drawn from a vein or a catheter were inoculated into BactAlert 3D bottles (bioMérieux, Marcy-L'Etoile, France). Additional samples, such as urine, sputum, wound, conjunctive, abscess, and catheter samples, were inoculated onto 5% sheep blood agar (Salubris Inc., Istanbul, Turkey), chocolate agar (Salubris Inc.) and MacConkey agar (Salubris Inc.). Identification and susceptibility testing were performed using an automated broth microdilution method (Vitek2, bioMérieux, Marcy-L'Etoile, France), and confirmations were made by the E test method (AB BIODISK, Solna, Sweden). The breakpoints defined by the Clinical and Laboratory Standards Institute (CLSI, 2008) were used. VRE colonization was detected by inoculation of rectal swabs onto a bile-esculin-azide agar plate containing 6 µg/ml of vancomycin (Becton, Dickinson and Company, Sparks, MD, USA). Plates were then incubated aerobically at 5 to 10% CO2 at 35 to 37°C for up to 48 hours (for confirmation of 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, which were taken at an interval of two weeks, were negative without clinical or radiologic findings associated with VRE[11]. Strains isolated from cultures that were defined as contaminated by infectious disease specialists or medical microbiologists were excluded from the study. Patients with VRE bacteremia were treated with linezolide (2x600 mg/day) for at least 14 days.

Patients with VSE were treated with ampicillin-sulbactam (8-12 gr/day) plus gentamycin (160-240 mg/day) for at least 14 days. A positive response to treatment was defined as defervescence in the 48-72 hours subsequent to initiation of antimicrobial therapy and improvements in vital signs and clinical symptoms associated with infection (e.g., 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 VRE infection rate for patients colonized with VRE during the neutropenic phase was the primary outcome of this study. The mortality rate due to VRE-related infection was the secondary outcome of this study.

Posaconazole (POS) was used for primary antifungal prophylaxis as given 200 mg per oral three times in a day with fat meal and acidic fruit juice during a period a time that neutrophil count decreased to below 1×10^9/L subsequent to chemotherapy until recovered to 1×10^9/L. Secondary antifungal prophylaxis was administered to patients who were treated with IPA diagnosed clinically or microbiologically developed subsequent to previous chemotherapy as voriconazole (VOR) 200 mg twice in a day per oral or POS 200 mg three times in a day during a period a time that neutrophil count decreased to below 1×10^9/L subsequent to chemotherapy until recovered to 1×10^9/L. If patient could not receive oral therapy, secondary antifungal prophylaxis was given intravenously. Antibiotic prophylaxis was administered to any patients.

Statistical analysis: Continuous variables were represented as the mean ± standard deviation and the range. Percentile values were represented without decimals. Overall mortality associated with febrile neutropenia was defined as death within 30 days of the development of neutropenia. Crude 30-day mortality rates were calculated as the proportion of study patients who died within 30 days of the development of neutropenia. The cost of screening cultures had been calculated as converting of the price that had been billed to the Republic of Turkey Social Security Institution per culture on the U.S. dollar exchange rate.

Results

We retrospectively analyzed 282 febrile episodes in 126 consecutive patients with neutropenia excluding 15 of 141 patients who were not eligible for study criteria during a two-year study period. The study included 65 cases in the first study-year and 78 cases in the second study- year. The mean patient age was 51.73 ± 14.4 years (range: 17–82 years), and 66 cases were male patients. The MASCC score was 17.18 ± 8.27 in patients with hematological malignancies (Table 1).

Table 1. Distribution of hematologic malignancies in patients with febrile neutropenia (n=126)

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)
Total	126 (100)

The vancomycin-resistant enterococcal species isolated from VRE- colonized patients were Enterococcus faecium (81%) and Enterococcus faecalis (19%). The mean number of VRE colonization days per patient was 34.27 ± 13.12 days. Among the 50 patients colonized with VRE, VRE bacteremia developed in 2 (4%) patients during a total of 1,295 colonization days in two study-years. The numbers of colonization day and colonized patients were748 days of colonization in 29 patients (44%) in the first study-year and 547 colonization days in 21 patients (26%) in the second study-year, respectively. During the first study-year, no cases of VRE bacteremia developed. Vancomycin-sensitive E. faecium was also isolated from wound (n=1), urine (n=1) and sputum (n=1) cultures. VRE bacteremia was observed in a patient who was admitted with pneumonia as being transferred from a hospital.

Enterococcus faecium was isolated from broncho-alveolar lavage and blood cultures, but rectal swab cultures yielded normal flora bacteria. That patient with VRE bacteremia was successfully treated with linezolid. In the second study-year, VRE bacteriemia developed in a male patient who recovered from infection under salvage chemotherapy due to non-Hodgkin's lymphoma and a female patient who died of VRE bacteremia under consolidation chemotherapy due to acute myeloid leukemia (AML). Enterococcus faecium was isolated from blood cultures of both cases. In addition, VSE-related bacteremia (n = 6), bacteriuria (n= 2), sputum (n = 1), and wound (n = 1) were observed in nine patients. Of those seven patients, four were male, and the median age was 44 years (range: 25-73). VSE-related bacteremia attacks were caused by E. faecalis (n = 4) and E. faecium (n = 2) in the patients receiving consolidation chemotherapy.

Vancomycin-sensitive E. faecalis was isolated from the patient with bacteriuria. The hematological malignancies in the patients with VSE-related bacteremia and bacteriuria were AML (n=3), acute lymphocytic leukemia (ALL) (n=1), multiple myeloma (MM) (n=1), non-Hodgkin's lymphoma (NHL) (n=1), and hairy cell leukemia (n=1), respectively. Two patients who had VSE- related bacteremia died. Only two patients who had persistent fever accompanied by distinctive clinical findings (e.g., cough, pain in the anal region, or ulcerations of the oral mucosa) responded to linezolid treatment. The placement of a chemotherapy port catheter and bone marrow biopsy were the invasive procedures that were performed on patients colonized with VRE during follow-up. No case of VRE-related bacteremia developed among patients who were not colonized with VRE.

A total of 2,574 rectal swab cultures was taken from all patients. Each VRE screening culture costed between $9.49 and $11.51 during the study period. Screening cultures for VRE costed between $9.49 (one culture) and $244.7 (25 cultures) per patient depending on length of stay. Routine screening culture for VRE costed $4516.7 (427 cultures) in the first study-year, $5082,7 (504 cultures) in the second study-year depending on the number of patients and their lengths of stay.

The overall 30-day crude mortality rates among patients with hematological malignancies were 35% (23/65) in the first study-year and 21% (17/78) in the second study-year. The hematological malignancies of patients who died included AML (n=16), acute lymphocytic leukemia (ALL, n=5), multiple myeloma (n=1), chronic myeloid leukemia (n=1) in the first study-year and AML (n=16), ALL (n=4), non-Hodgkin lymphoma (n=1) in the second study- year. The number of patients who died of infections was 17 (26%) in the first study-year, and 11 (14%) in the second study-year. Patients died of MRSA-related bloodstream infections (n=2), invasive fungal infection (n=6) and severe vancomycin-sensitive E. faecium-related sepsis(n=1) in the first study-year and Gram-negative bacteremia (n=5), VSE-related bacteremia (n=3), invasive fungal infection (n=2) and VRE-related bacteremia (n=1) in the second study-year.

Discussion

Routine screening culture for VRE costed more than $4500 per year, although a few cases with VRE related bacteriemia were observed. Although the benefits of surveillance cultures as being a part of infection control measures have been reported in the studies, cost-effectiveness of routine VRE screening cultures in the hematological patients who are vulnerable to opportunistic infections have not been evaluated yet. Infection control measures provide more saving than routine surveillance cultures[14]. However, screening culture for VRE is recommended for patients/residents who are at increased risk for VRE, such as previously being colonized or infected with VRE, being transferred from hospital with VRE outbreak or high VRE colonization or infection rates on admission. If a patient or resident has been a roommate or has been in physical contact with the unidentified patient or resident subsequently found to have VRE, at least two specimens should be taken on different days with one taken a minimum of seven days following the last exposure to VRE[14]. There is no evidence about the benefits of screening staff for VRE[14]. Infection control strategies, including surveillance cultures supplies ($4,137) were reported to cost $116,515 for one year.

The savings associated with fewer VRE BSI ($123,081), fewer patients with VRE colonization ($2,755), and reductions in antimicrobial use ($179,997) were reported to total $305,833. Ranges of costs and savings were estimated for enhanced infection control strategies were $97,939 to $148,883 for costs and $271,531 to $421,461 in savings[15]. And also stool specimens were reported to be more effective than rectal swabs[16].

There is no study regarding the cost-effectiveness of routine VRE surveillance culture as well. Unfavorable ward conditions, such as shared toilets, housing of attendants with patients, close contact between patients and their attendants, frequent antibiotic use for infections, and immunosuppression, were likely to be important risk factors in terms of higher VRE colonization rates in the first study-year. Reduced VRE colonization rates in the second year were likely to be related to increase compliance of patients and their attendants in the second year. VRE colonization increases in patients with hematological malignancies under certain conditions, including immunosuppression, serious comorbid conditions (e.g., diabetes, renal failure, and high APACHE score), increased lenghth of 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[10, 17].

Patients whose rectal swab cultures yield VRE should be considered positive until three consecutive negative cultures are obtained with at least one-week intervals, according to the hospital infection control practices advisory committee (HICPAC) guidelines[18]. However, this approach does not guarantee complete eradication of VRE[18]. Infection control measures and instruction of patients and their attendants can decrease colonization rates in the ward and contamination of the environment.

The number of cases with VRE-related bacteremia increased while VRE colonization rates were decreasing in the second year of the study. This confounding result can be explained by risk factors, 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. It has also been reported that VRE-related bacteremia has a close relationship between severity of the patient's illness and the pathogenicity of the bacteria[6].

Subsequent to induction or consolidation chemotherapy impairing mucosal barriers, pathogenic microorganisms can invade the intravascular compartment through the damaged mucosa. Mucositis and increasing mucositis were reported to be independent risk factors for VRE-related bloodstream infection (BSI)[9]. BSI rates were reported from 0% to 34% in patients who are colonized with VRE. These rates are higher in patients with cancer and patients who received solid and bone marrow transplants. Among VRE-colonized patients, 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 Clostridium difficile infection were reported to be risk factors for VRE-related BSI[19, 20]. VRE-related bacteremia should be considered in case persistent fever and worsening clinical signs and symptoms occur during febrile neutropenia episode of patient colonized with VRE.

Active VRE therapy should be initiated in these cases. Since mortality rates were found to be 2.5 times higher in patients colonized with VRE than in patients colonized with VSE[21, 22]. Moreover, less frequent invasive procedures, including the placement of chemotherapy port catheters and bone marrow biopsies are likely to be related to lower rates of VRE-related bacteremia as found in our study[23]. Endocarditis or intestinal lesions should be examined in case of persistent VRE- or VSE-related bacteremia. Vancomycin resistance, comorbidity and severity of illness decrease achievement rates[20, 21].

In line with our study results, routine screening of hematological patients for VRE colonization is not cost-effective. Routine surveillance culture for VRE should be considered with respect to the conditions of health care setting. VRE colonization precedes VRE- or VSE-related bacteremia if certain conditions, including the development of severe mucositis, the administration

of invasive procedures, and the use of intensive broad-spectrum antibiotics exist in patient colonized with VRE.

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