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

Gedik Habip¹, Şimşek Funda¹, Kantürk Arzu¹, Yıldırımkan Taner¹, Arıca Deniz², Aydın Demet², Yokuş Osman², Demirel Naciye²

1. Department of Infectious Diseases and Clinical Microbiology, Ministry of Health Okmeydani Training and Research Hospital, Istanbul
2. Department of Hematology, Ministry of Health Okmeydani Training and Research Hospital, Istanbul

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 were 748 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.

DOI: http://dx.doi.org/10.4314/ahs.v14i4.18

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 devices¹. Enterococci are found in the gastrointestinal tract, in oropharyngeal secretions, and on the skin¹. Vancomycin-resistant enterococci (VRE) can persist on dry surfaces for days to months, contributing to the spread of VRE among patients². These bacteria can cause nosocomial infections in vulnerable patients who are colonized with VRE or exposed to contaminated tools or medical staff³. 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 VRE³. In addition, contact with contaminated health care workers, patients, attendants, environmental surfaces and equipment promotes VRE colonization⁴. Colonization of the rectum with VRE was reported to be a more important predictor than colonization of other regions⁶. VRE is also an important nosocomial pathogen in hematological patients⁵. 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 microorganisms⁸. 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

Corresponding author
Gedik Habip
Department of Infectious Diseases and Clinical Microbiology, Ministry of Health Okmeydani Training and Research Hospital, Istanbul
Phone: +90 505 336 27 70
E-mail: habipgedik@yahoo.com
most common cause of nosocomial bacteremia, with increasing rates worldwide. In this study, we retrospectively evaluated the rates of vancomycin-resistant enterococci (VRE) colonization and VRE-related bacteremia in patients with hematologic 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 hematologic 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 hematologic 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 preventive 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. 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. 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 and an absolute neutrophil count <0.5 x 10^9/L or a count expected to fall below 0.5 x 10^9/L. 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. 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 (Vitek 2, 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. 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 linezolid (2400 mg/day) for at least 14 days.

Patients with VSE were treated with ampicillin-sulbactam (8-12 gr/day) plus gentamicin (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, radiologic 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 neutropenia developed febrile neutropenia (FN) during chemotherapy between November 2010 and 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 hematologic diseases (e.g., anemia, idiopathic or immune thrombocytopenic purpura, etc.).

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

<table>
<thead>
<tr>
<th>Hematologic Malignancies</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myelogenous leukemia</td>
<td>17(13)</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>22(17)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>7(6)</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>5(4)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>3(2)</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>4(3)</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>3(2)</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>2(2)</td>
</tr>
<tr>
<td>Plasma cell leukemia</td>
<td>2(2)</td>
</tr>
<tr>
<td>Multiple myeloma with Waldenström’s lymphoma</td>
<td>1(1)</td>
</tr>
<tr>
<td>Total</td>
<td>126(100)</td>
</tr>
</tbody>
</table>

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 MASCSC score was 17.18 ± 8.27 in patients with hematologic malignancies (Table 1).

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 the price that had been billed to the Republic of Turkey Social Security Institution per culture on the U.S. dollar exchange rate.
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, and colonized patients were 748 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 pneumo-

Enterococcus faecium was isolated from broncho-alve-
lary 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 bacteremia developed in a male patient who recovered from infection under sal-

The vancomycin-resistant enterococcal species isolated from VRE- colonized patients were Enterococcus faecium (81%), multiple myeloma (n=1), chronic myeloid leukaemia (n=1) in the first study-year and ALL (n=1), ALL (n=4), non-Hodgkin lymphoma (n=1) in the first 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-

**Discussion**

Routine screening culture for VRE costed more than $4500 per year, although a few cases with VRE related bacteremia were observed. Although the benefits of surveillance cultures as being a part of infection control measures have been reported in the studies, cost-

**Vancocycin-sensitive E. faecium was isolated from the patient with bacteruria. The hematological malignancies in the patients with VSE-related bacteremia and bacteruria 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-

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 ad-

In line with our study results, routine screening of ha-

The number of cases with VRE-related bacteremia in-

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

References: