



# VANCOMYCIN-RESISTANT *ENTEROCOCCUS FAECIUM* COLONIZATION AND *CLOSTRIDIUM DIFFICILE* INFECTION IN A HEMATOLOGIC PATIENT

Ivana Goić-Barišić<sup>1,2</sup>, Marina Radić<sup>1,2</sup>, Anita Novak<sup>1,2</sup>, Žana Rubić<sup>1,2</sup>,  
Nataša Boban<sup>2,3</sup>, Boris Lukšić<sup>2,4</sup> and Marija Tonkić<sup>1,2</sup>

<sup>1</sup>Department of Clinical Microbiology, Split University Hospital Centre, Split, Croatia;

<sup>2</sup>University of Split School of Medicine, Split, Croatia;

<sup>3</sup>Department of Clinical Epidemiology, Split University Hospital Centre, Split, Croatia;

<sup>4</sup>Department of Infectious Diseases, Split University Hospital Centre, Split, Croatia

**SUMMARY** – Vancomycin-resistant enterococci (VRE), especially *Enterococcus faecium*, have emerged as significant nosocomial pathogens and patients with impaired host defenses are at a particular risk of VRE infection. The most common occurrence is asymptomatic colonization of the gastrointestinal tract that can persist for a long time and serve as a reservoir for transmission of VRE to other patients. We present a case of a patient who was diagnosed with acute myelogenous leukemia and suffered from bone marrow aplasia following induction therapy. The patient received prolonged broad-spectrum antimicrobial therapy. During hospital stay, the patient developed *Clostridium difficile* infection (CDI) and was found to be colonized with a strain of *Enterococcus faecium* resistant to vancomycin during therapy for CDI. This case also highlights the role of risk factors that could contribute to development of resistance, particularly CDI. Early detection of VRE colonization or infection is a crucial component in hospital program designed to prevent transmission of nosocomial infections. Surveillance cultures of such patients should be mandatory.

**Key words:** *Acute myelogenous leukemia; Clostridium difficile; Enterococcus faecium; Vancomycin-resistant enterococcus*

## Introduction

Enterococci resistant to vancomycin have emerged as the leading cause of nosocomial infections worldwide. In an effort to prevent the spread of vancomycin resistance, Centers for Disease Control and Prevention have recommended periodical culture surveys of stool and rectal swabs, depending on the risk population and hospital units involved<sup>1</sup>. Therefore, this screening has been found to be effective in detecting vancomycin-resistant enterococci (VRE)<sup>2,3</sup>. However,

the widespread use of glycopeptides in hospitals has led to the emergence of VRE, which account for approximately 30% of all enterococcal infections, with the majority of VRE isolates (>90%) being *Enterococcus (E.) faecium*<sup>4</sup>. Some investigators have reported the overall prevalence of VRE in Europe to range from 1.5% to 8.6%<sup>5,6</sup>. In the United States, the prevalence of VRE on admission to an intensive care unit has been reported to range from 12% to 43%<sup>7</sup>. The reported rates of VRE colonization in hospitalized patients vary, ranging from 1.5% to 32%<sup>5,6,8</sup>. The risk factors for nosocomial VRE colonization or infection include advanced age, prolonged hospital stay, interhospital transfer, prolonged duration of antibiotic treatment (especially with vancomycin and cephalosporins), different surgical procedures and presence of immuno-

Correspondence to: Marina Radić, MD, Department of Clinical Microbiology, Split University Hospital Centre, Spinčićeva 1, HR-21000 Split, Croatia

E-mail: [radicmarina14@googlemail.com](mailto:radicmarina14@googlemail.com)

Received November 9, 2015, accepted September 20, 2016

compromised state<sup>9,10</sup>. Patients with *Clostridium difficile* infection (CDI) are considered to be at a greater risk of becoming colonized with VRE, probably because of the common risk factors involved<sup>11</sup>. CDI is also common in hematologic patients, with the incidence rate ranging from 4.8% to 9% in patients with acute myelogenous leukemia, from 4.9% to 7.5% in patients undergoing autologous and from 14% to 30.4% in those undergoing allogeneic hematopoietic stem cell transplantation (HSCT)<sup>12-15</sup>.

This report presents a case of a patient with acute myelogenous leukemia following induction therapy, whose surveillance rectal and throat swabs yielded *E. faecium* resistant to vancomycin, *VanA* phenotype.

## Case Report

In March 2015, a 48-year-old female patient was admitted for the first time to the Department of Hematology because of fever and spontaneous gingival bleeding. During the previous year, she was taking antibiotic treatment several times due to recurrent urinary tract infection (UTI). Two weeks before this admission, she was treated with peroral cefuroxime because of suspected pyelonephritis. After finishing the antibiotic treatment prescribed, laboratory findings showed leukocytosis ( $39.3 \times 10^9/L$ ) and thrombocytopenia ( $82 \times 10^9/L$ ) with blasts detected in peripheral blood (17%), so she was hospitalized for further treatment.

On day 2 of her hospital stay, urine culture yielded *Klebsiella pneumoniae*  $>10^5$  colony forming units (CFU/mL), with a significantly lowered leukocyte count after treatment for UTI. However, further clinical findings revealed acute myelogenous leukemia, with no chromosome 16 inversion detected by fluorescent *in situ* hybridization technique. Following induction therapy, the patient suffered from bone marrow aplasia accompanied by febrility and increase in C-reactive protein level (256.7 mg/L). Due to development of fever in granulocytopenia, and based on the clinical picture, duration and degree of granulocytopenia, monotherapy with a beta-lactam with activity against *Pseudomonas aeruginosa* was first started, combined with other gram-negative and gram-positive agents, for suspicion of possible infection caused by resistant gram-negative or gram-positive bacteria. Therefore, further therapy included piperacillin/tazobactam (3x4.5 g i.v. daily for 4 days), meropenem (3x1 g i.v. daily for 17 days), then

amikacin (2x500 mg i.v. daily for 8 days), vancomycin (2x1 g i.v. daily for 10 days) and imipenem (3x1 g i.v. daily for 10 days). As our patient was at a high risk of developing fungal infection, empirical antifungal therapy with amphotericin B was also administered. The patient became afebrile from day 30. After 40 days of hospital stay, the patient was discharged with no prophylactic antibiotic therapy.

One week after discharge, in April, the patient was readmitted to the Department of Hematology for further chemotherapy. From that time on, she was clinically stable, afebrile, with periods of bone marrow aplasia, so multiple transfusions of red blood cells and platelets were administered. On day 7, she started having profuse watery diarrhea, up to 10 times, which was clinically indicative of *Clostridium (C.) difficile* infection, and a stool sample was taken and sent for detection of *C. difficile* toxin. On the same day, after *C. difficile* toxin was detected, peroral treatment with vancomycin was initiated at a dose of 2.5 mL 4 times a day for 10 days.

The patient had negative surveillance cultures upon admission (initial screening). However, in order to exclude possible colonization with multidrug-resistant hospital pathogens, surveillance cultures should be taken on at least three consecutive occasions, one week or more apart<sup>16</sup>. Therefore, another surveillance throat swab was obtained on day 10 and yielded *E. faecium* resistant to vancomycin. On day 15 of admission, she became febrile (38.4 °C), so blood culture was taken and *Klebsiella pneumoniae* was grown. At that time, meropenem was added to therapy at a dose of 1 g i.v. every 8 hours. Surveillance rectal swab was taken on day 19 for detection of multidrug-resistant hospital pathogens (vancomycin-resistant enterococci, VRE; multidrug-resistant *Acinetobacter baumannii*, MRAB; carbapenem-resistant *Enterobacteriaceae*, CRE; extended spectrum beta-lactamase producing gram-negative bacilli, ESBL) and *E. faecium* resistant to vancomycin was isolated.

The strain was sent to Dr Fran Mihaljević University Hospital for Infectious Diseases in Zagreb, and polymerase chain reaction (PCR) assay confirmed the *VanA* phenotype of vancomycin resistance.

## Microbiology

Rectal swab was inoculated on CHROMagar VRE plate, a chromogenic medium for detection of *VanA*/

*VanB* phenotype of vancomycin resistance in *Enterococci* (CHROMagar, Paris, France). On the first day of subculture at 37 °C, pink to mauve colonies were revealed (after 24 h). The grown isolate was confirmed as *E. faecium* using automated Vitek 2 System (bioMérieux, Marcy-l'Étoile, France).

Throat swab was inoculated on blood agar and shiny,  $\gamma$  (gamma)-hemolytic colonies were observed after 24 hours of incubation with further identification being identical as described above.

Antimicrobial susceptibility testing was first done using Kirby-Bauer disk-diffusion method and confirmed by determining minimum inhibitory concentration (MIC) values using Vitek 2 automated method. The strain was shown to be resistant to ampicillin (MIC  $\geq 32$   $\mu\text{g/mL}$ ), vancomycin (MIC  $\geq 32$   $\mu\text{g/mL}$ ) and teicoplanin (MIC  $\geq 32$   $\mu\text{g/mL}$ ), but susceptible to linezolid (MIC 2  $\mu\text{g/mL}$ ) and tigecycline (MIC  $\leq 0.12$   $\mu\text{g/mL}$ ), having a *VanA* specific phenotype of vancomycin resistance confirmed by PCR assay.

Stool sample was tested according to two-step algorithm guidelines of the European Society of Clinical Microbiology and Infectious Disease and a toxigenic strain of *C. difficile* was detected using a confirmatory molecular test<sup>17</sup>.

## Discussion

Enterococci resistant to vancomycin were first detected in England in 1988<sup>18</sup>. VRE, especially *E. faecium*, is a significant nosocomial pathogen and presents a serious threat to immunocompromised patients. Compared to strains of *E. faecalis*, *E. faecium* displays a higher degree of resistance to multiple antibiotics, including ampicillin, gentamicin, ciprofloxacin, vancomycin and teicoplanin<sup>19</sup>. Therefore, it is important to identify the enterococcal strain to the species level. Enterococci belong to the fourth most common nosocomial pathogens in intensive care units, with VRE accounting for 28.5% of enterococcal isolates<sup>20</sup>. Invasive VRE infections have been associated with high morbidity and mortality rates<sup>21,22</sup>. Studies found crude mortality rates to range from 17% to 100%, with a mortality rate of 73% in patients with hematologic malignancies<sup>23-25</sup>. There are studies showing VRE infection to be a strong predictor of mortality in liver transplant patients, with a mortality rate of 46% in liver transplant recipients with VRE bacteremia<sup>26,27</sup>. It

has been suggested that VRE infections and colonization may be a reflection of a complicated medical course, and those patients have therefore been at a higher risk of dying, which could contribute to high mortality rates. Asymptomatic VRE colonization is of particular interest as it can persist for a long period and serve as a reservoir for transmission of VRE or present a source of possible infection. Thus, it is important to perform active surveillance (screening) of patients, especially those in intensive care units and hemato-oncology wards<sup>9,10</sup>. Many studies also showed correlation between VRE colonization and treatment with certain antimicrobial agents such as metronidazole, second- and third-generation cephalosporins, aminoglycosides and vancomycin<sup>28,29</sup>.

In our case, the patient was on a prolonged broad-spectrum antimicrobial therapy during her first hospitalization (meropenem, piperacillin/tazobactam, then amikacin, vancomycin and imipenem/cilastatin), which was continued with meropenem and vancomycin during second hospitalization. She was also immunosuppressed because of her hematologic disease, which has been identified as an independent risk factor for acquiring VRE<sup>30</sup>. Developing diarrhea in our patient could have also increased the likelihood of colonization with VRE, as proposed in a study by Falk *et al.*<sup>31</sup>. Prolonged hospital stay could have also contributed in our case. Due to bone marrow aplasia, she was isolated in a hematologic sterile unit. All the risk factors mentioned could have triggered the development of resistance, especially prolonged therapy with vancomycin, which is more likely to promote colonization and transmission of VRE by selection pressure. As the *E. faecium* strain resistant to vancomycin was isolated from surveillance throat and rectal swabs, with no clinical and laboratory markers of infection, we detected gastrointestinal VRE colonization. Most VRE colonized patients remain colonized for a long period. Montecalvo *et al.* showed a 7-week persistence of gastrointestinal VRE colonization in adult patients hospitalized on oncology ward<sup>32</sup>.

There are studies that indicate a correlation between *C. difficile* infection and gastrointestinal VRE colonization, possibly because of the common risk factors including prolonged broad-spectrum antimicrobial therapy, extended hospital stay and underlying immunocompromised state<sup>10</sup>. In this way, *C. difficile* infection could be a possible predictor for developing

VRE associated infection or colonization due to similar patient risk profile<sup>33,34</sup>. Our patient had both *C. difficile* infection and VRE colonization, which could be explained by the risk factors mentioned above.

Results of some studies indicate the possibility of VRE screening by using stools sent for *C. difficile* toxin analysis, as the results are comparable to screening using separately taken stool specimens or rectal swabs<sup>11,35</sup>. This is also less invasive and might be less of a problem in neutropenic patients for whom rectal swabs are sometimes a concern<sup>35</sup>. However, all these promising results could potentially lead to in-hospital screening using stools sent for *C. difficile* toxin analysis as a reasonable surrogate for screening individual high-risk patients, with substantial cost savings<sup>35</sup>.

Although up to now six phenotypes of vancomycin resistance have been described in enterococci, the *VanA* and *VanB* phenotypes are clinically significant and mediated by transferable operons. The *VanA* phenotype is almost always plasmid-mediated, raising the possibility of horizontal transfer of resistance<sup>36</sup>.

By using measures of active screening of patients, we successfully detected VRE *VanA* phenotype in our institution, emphasizing their importance and continuous implementation, especially in high-risk patients. According to the last available data provided by the Croatian Committee for Antibiotic Resistance Surveillance in 2013 on the three-month follow-up (October 1 to December 31), 5% of *E. faecium* strains resistant to vancomycin were isolated<sup>37</sup>.

Performing special surveillance cultures of patients to detect gastrointestinal colonization should be considered as an essential component of successful VRE control programs. Obtaining periodic stool or rectal specimens from high-risk patients such as those in intensive care units, hematology-oncology wards or transplantation units should be mandatory. Surveillance cultures should be taken upon admission and twice weekly thereafter, and should be inoculated on appropriate selective media for detecting VRE<sup>16,38</sup>.

In conclusion, early detection of VRE colonization or infection is a crucial component of hospital program designed to prevent nosocomial infections. Quick information from microbiology laboratory is the first line of defense against the intrahospital spread of VRE. Prompt and correct identification of enterococci and detection of vancomycin resistance are essential in detection of VRE colonization or infection,

in order to avoid complex and costly procedures required when the problem is delayed.

Active screening accompanied by infection control measures is crucial in the prevention of VRE transmission. Rational use of antibiotics is also a helpful preventive measure against the development of antimicrobial resistance.

#### Acknowledgments

We are thankful to Dr. Dominik Lozić from the Department of Hematology, Split University Hospital Centre, for his contribution in providing patient data. We also thank Dr. Iva Butić from the Department of Clinical Microbiology, Dr Fran Mihaljević University Hospital for Infectious Diseases, Zagreb, for her generous assistance in molecular confirmation of the resistance phenotype.

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#### Sažetak

### KOLONIZACIJA VANKOMICIN REZISTENTNOM BAKTERIJOM *ENTEROCOCCUS FAECIUM* I *CLOSTRIDIUM DIFFICILE* INFEKCIJA U HEMATOLOŠKE BOLESNICE

I. Goić-Barišić, M. Radić, A. Novak, Ž. Rubić, N. Boban, B. Lukšić i M. Tonkić

Vankomicin-rezistentni enterokoki (VRE), naročito *Enterococcus faecium*, spadaju među najznačajnije bolničke patogene, pri čemu su naročito ugroženi bolesnici oslabljenog imunskog statusa. Pritom je najčešća pojava asimptomatske kolonizacije probavnog sustava koja može ustrajati duže vremena i biti rezervoar za širenje VRE na ostale bolesnike. Donosimo prikaz slučaja bolesnice s dijagnozom akutne mijelomonocitne leukemije praćene aplazijom koštane srži nakon indukcijske terapije. Bolesnica je liječena antibioticima širokog spektra. Tijekom hospitalizacije u bolesnice se razvila infekcija bakterijom *Clostridium difficile* (CDI) uz dokazanu kolonizaciju sojem *Enterococcus faecium* rezistentnog na vankomicin tijekom terapije zbog CDI. Također su prikazani čimbenici rizika koji su u navedenom slučaju mogli poslužiti kao potencijalni okidač za razvoj rezistencije, s osobitim naglaskom na CDI. Rano otkrivanje kolonizacije ili infekcije navedenim sojevima je iznimno značajan čimbenik bolničkog programa za prevenciju širenja bolničkih infekcija. Mikrobiološki nadzor uzimanjem nadzornih kultura mora biti obvezni dio protokola pri hospitalizaciji takvih bolesnika.

Ključne riječi: *Akutna mijelomonocitna leukemija; Clostridium difficile; Enterococcus faecium; Vankomicin-rezistentni enterokok*