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Risk of vancomycin-resistant enterococci bloodstream infection among patients colonized with vancomycin-resistant enterococci



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ABSTRACT

Background: Vancomycin-resistant enterococci colonization has been reported to increase the risk of developing infections, including bloodstream infections.

Aim: In this study, we aimed to share our experience with the vancomycin-resistant enterococci bloodstream infections following gastrointestinal vancomycin-resistant enterococci colonization in pediatric population during a period of 18 months.

Method: A retrospective cohort of children admitted to a 400-bed tertiary teaching hospital in Izmir, Turkey whose vancomycin-resistant enterococci colonization was newly detected during routine surveillances for gastrointestinal vancomycin-resistant enterococci colonization during the period of January 2009 and December 2012 were included in this study. All vancomycin-resistant enterococci isolates found within 18 months after initial detection were evaluated for evidence of infection.

Findings: Two hundred and sixteen patients with vancomycin-resistant enterococci were included in the study. Vancomycin-resistant enterococci colonization was detected in 136 patients (62.3%) while they were hospitalized at intensive care units; while the remaining majority (33.0%) were hospitalized at hematology-oncology department. Vancomycin-resistant enterococci bacteremia was present only in three (1.55%) patients. All these patients were immunosuppressed due to human immunodeficiency virus (one patient) and intensive chemotherapy (two patients).

Conclusion: In conclusion, our study found that 1.55% of vancomycin-resistant enterococci colonized children had developed vancomycin-resistant enterococci bloodstream infection among the pediatric intensive care unit and hematology/oncology patients; according to our findings, we suggest that immunosuppression is the key point for developing vancomycin-resistant enterococci bloodstream infections.

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Introduction

The emergence and spread of vancomycin-resistant enterococci (VRE) as a nosocomial pathogen represent a major health problem since its first isolation in the United Kingdom and in France.^{1,2} Recent articles reported a double digit number of hospitalizations for VRE infections between 2003 and 2006.³

Colonization is the key point for VRE infections. Infections generally follow VRE colonization mostly in gastrointestinal tract.⁴ VRE colonization was reported to increase a patient's risk of developing infections, such as bloodstream infections (BSIs).^{5,6} Another study reported a 5- to 10-fold increased risk of infection once a patient was colonized with VRE.⁷ The VRE infection rates were highest in hematologic-oncologic patients, organ transplant recipients and patients in intensive care units while it is reported to be nearly zero in immunocompetent patients. However, studies including children with VRE infections following gastrointestinal VRE colonization were rare and most data were adopted from adult studies.^{5,6,8-11}

In this study, we report our experience with the VRE bloodstream infections following gastrointestinal VRE colorizations for an 18-month period.

Materials and methods

This retrospective study was conducted in Dr. Behçet Uz Children's Hospital, a 400-bed tertiary teaching hospital in Izmir, Turkey, between January 2009 and December 2012. Patients with newly detected VRE colonization during routine surveillances for gastrointestinal VRE colonization were included in this study.

In our center, rectal sample screening for VRE was performed at admission and weekly in all intensive care units (ICUs); hematology-oncology department and neonatal intensive care unit using conventional cultures and molecular diagnostic techniques. The "red flag" precautions for patients with VRE colonization were also performed and strict infection control policies as part of patient management were applied in our center.

Using the VRE colonized patients cohort, we observed all the patients during 18 months after initial detection using in-patient and outpatient medical records at the same institution. The patients' age, gender, service where patient was hospitalized, re-hospitalization, episodes of bacteremia, and

isolated microorganism were recorded. Medical records were reviewed to identify the body site that had been colonized or infected when the initial VRE-positive culture sample was obtained and whether the detection represented colonization or infection on the basis of the Centers for Disease Control and Prevention criteria.¹²

All VRE isolates found within 18 months after initial detection were evaluated for evidence of discrete infection. Two trained reviewers separately verified whether infections represented distinct and unrelated events. Subsequent infections were described according to the infection site and days since initial detection. We determined the proportion of patients who subsequently developed VRE infection within the study cohort. The investigators obtained further information about the patients' complaints by calling the patients' family.

VRE detection: rectal swabs were directly inoculated onto a chromogenic agar plate (ChromID VRE agar bioMérieux, France) containing 8 mg of vancomycin ml⁻¹ and incubated at 36 °C aerobically for 72 h. Identification and antibiotic susceptibility tests were performed using the automated VITEK-2 system (bioMérieux, France) via Gram positive identification card, AST-P592, a supplementary E-test (bioMérieux, Durham, NC) and disk diffusion test according to the manufacturer's instructions. Van A and Van B resistance phenotypes were reported by the system on the basis of MIC values.

Statistical analysis was performed by using the Statistical Package for the Social Science (SPSS) software. Distribution of numeric variables was tested by both graphical methods and Shapiro-Wilk test. The difference between means of numeric variables was tested by Student's *t* test or Mann-Whitney *U* test, where appropriate. The difference between proportions was tested by Chi-Square or Fisher's exact test. *p* < 0.05 was considered statistically significant.

Results

Two hundred and sixteen patients with VRE colonization were included in the study. The median age of the patients was two months ranging from 14 days to 16 years. One hundred and forty patients were male (64.2%).

Colonization was detected in 136 patients (62.3%) while they were hospitalized at ICUs, and 71 patients (33.0%) were hospitalized at the hematology-oncology department.

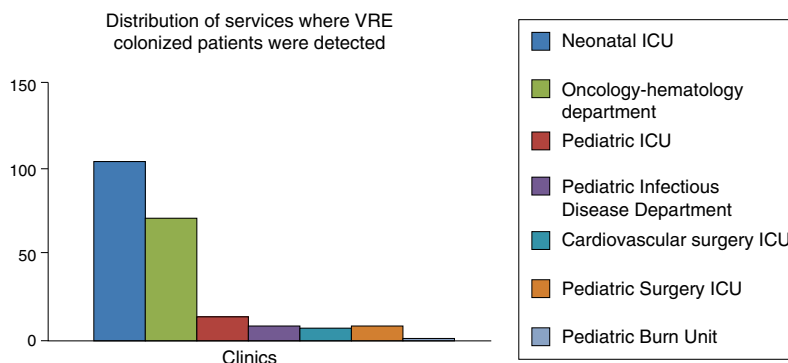


Fig. 1 – Distribution of the causative agents of bacteremia during the study period.

During the study period of 18 months, 17 VRE colonized patients identified in the first year of hospitalization and six patients who had been hospitalized in other centers for fever were not included in the analysis.

During the study period a total of 103 bacteria were isolated. Seventeen coagulase-negative staphylococci isolates were deemed to be contamination as they had been isolated only in one bottle of the culture sets. Among the 86 isolated microorganisms, the most isolated bacteria was coagulase-negative staphylococci (32.5%), followed by *Candida parapsilosis* (12.7%), *Escherichia coli* (11.6%) and *Klebsiella* species (9.3%) (Fig. 1). Out of the 193 colonized VRE patients, VRE bacteremia was present only in three (1.55%) patients.

The three patients who had VRE bacteremia episodes were a 4-month old girl who had perinatal human immunodeficiency virus (HIV) infection, a 6-year old boy who had been under intensive chemotherapy for acute myeloblastic leukemia, and a 7-year old girl under acute lymphoblastic leukemia.

Discussion

Enterococci were reported to be the third most common organism causing BSI in hospitalized children.^{13,14} However, in our clinical experience, we have witnessed few VRE associated BSI. This retrospective study was designed to review our experience with VRE associated BSI following VRE-colonized patients and to identify risk factors associated with VRE BSI infection.

In our study, most patients with VRE colonization were neonates and pediatric hematology–oncology patients followed by patients in intensive care units. VRE colonization in Neonatal ICU (NICU) was reported more occasionally compared to the two wards above.^{15–19} In addition to the NICU, VRE colonization has been well-defined in pediatric hematology–oncology wards supporting our findings.^{20–22}

In our study, the rate of VRE BSI among colonized patients was 1.55%, which was lower than the majority of reports suggesting VRE BSI rates ranging from 0% to 45% among colonized individuals, depending on the population studied.^{9,10,23–32} Brennen et al.²³ reported that no VRE BSI was recorded in 36 colonized residents of a long-term care facility, supporting the variability of VRE BSI. In a study, including 52 patients with VRE colonization, two patients were reported to have VRE BSI.³⁰ A recent study from Taiwan reported only two patients with VRE BSI out of 47 patients who acquired VRE during their ICU stays.³¹

Adult patients are more likely to have more serious comorbid conditions reported to increase VRE colonization and infections.³² However, a previous study including 768 patients reported that only 31 (4.0%) of the patients had VRE BSI.³² Moreover, 13.4% of the adult patients with malignancies and VRE colonization were reported to develop VRE BSI suggesting that malignancy is an important risk factor for VRE-BSI.⁹ Comparing to these adult studies, children had shown the same pattern of adults but with a low rate of VRE BSI development.

Two of our hematology–oncology patients and one HIV infected child had significant degree of immunosuppression. Previous studies reporting higher rates of VRE BSI among

colonized solid organ transplant patients (6.3–11.5%),^{27–29} colonized patients with cancer (13.4–29.3%),^{9,24,25} colonized bone marrow transplant recipients (26.7–34.2%),^{31,32} and colonized patients (45%)³³ supported our findings. Immunosuppressed patients were reported to be a special risk group for severe VRE infections.^{11,34} Matar et al.²⁵ reported that, among 99 VRE-colonized patients with cancer, 29 (29.3%) developed VRE BSI, and the majority of these (71%) were neutropenic at the time they developed their infection. Zaas et al.⁹ reported that, among colonized cancer patients, diabetes mellitus, undergoing a gastrointestinal procedure, acute renal failure, and exposure to vancomycin were significant risk factors for developing VRE BSI.

Since hematology–oncology patients were found to have VRE associated BSI more intense precautions should be taken in these wards, as recommended by the Society for Healthcare Epidemiology of America³⁵ and by the Centers for Disease Control and Prevention in hematology–oncology guidelines.³⁶

This study is limited by its retrospective design and unavailability of subtyping VRE by pulsed-field gel electrophoresis. Since data regarding the risk of VRE BSI among children are limited our findings will be helpful in discriminating risk groups for developing VRE BSI.

In conclusion, our study found that 1.55% of VRE-colonized children had developed VRE BSI. According to our findings, Pediatric ICU and hematology/oncology patients are under higher risk for VRE colonization, and immunosuppression is the key point for developing VRE bloodstream infections.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Uttley AH, Collins CH, Naidoo J, George RC. Vancomycin-resistant enterococci. *Lancet*. 1988;1:57–8.
2. Leclercq R, Derlot E, Duval J, Courvalin P. Plasmid-mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*. *N Engl J Med*. 1988;319:157–61.
3. Schooneveld TV, Rupp ME. Control of Gram-positive multidrug-resistant pathogens. In: Lautenbach E, Woeltje KF, Malani PN, editors. *Practical healthcare epidemiology*, 3rd ed. Chicago, USA: The University of Chicago Press; 2010. p. 197–208.
4. Chavers LS, Moser SA, Benjamin WH, et al. Vancomycin-resistant enterococci: 15 years and counting. *J Hosp Infect*. 2003;53:159–71.
5. Montecalvo MA, Shay DK, Patel P, et al. Bloodstream infections with vancomycin-resistant enterococci. *Arch Intern Med*. 1996;156:1458–62.
6. Kuehnert MJ, Jernigan JA, Rimland D, Jarvis WR. Association between mucositis severity and vancomycin-resistant enterococcal bloodstream infection in hospitalized cancer patients. *Infect Control Hosp Epidemiol*. 1999;20:660–3.
7. Montecalvo MA, Shay DK, Gedris C, et al. A semiquantitative analysis of the fecal flora of patients with vancomycin-resistant enterococci: colonized patients pose an infection control risk. *Clin Infect Dis*. 1997;25:929–30.

8. Orloff SL, Busch AM, Olyaei AJ, et al. Vancomycin-resistant *Enterococcus* in liver transplant patients. *Am J Surg*. 1999;177:418-22.
9. Zaas AK, Song X, Tucker P, Perl TM. Risk factors for development of vancomycin-resistant enterococcal bloodstream infection in patients with cancer who are colonized with vancomycin-resistant enterococci. *Clin Infect Dis*. 2002;35:1139-46.
10. Kapur D, Dorsky D, Feingold JM, et al. Incidence and outcome of vancomycin-resistant enterococcal bacteremia following autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant*. 2000;25:147-52.
11. Bach PB, Malak SF, Jurcic J, et al. Impact of infection by vancomycin-resistant *Enterococcus* on survival and resource utilization for patients with leukemia. *Infect Control Hosp Epidemiol*. 2002;23:471-4.
12. Horan TC, Gaynes RP. Surveillance of nosocomial infections. In: Mayhall CG, editor. *Hospital epidemiology and infection control*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004. p. 1659-702.
13. Das I, Gray J. Enterococcal bacteremia in children: a review of seventy-five episodes in a pediatric hospital. *Pediatr Infect Dis J*. 1998;17:1154.
14. Grohskopf LA, Sinkowitz-Cochran RL, Garrett DO, et al. A national point-prevalence survey of pediatric intensive care unit-acquired infections in the United States. *J Pediatr*. 2002;140:432.
15. Lee WG, Ahn SH, Jung MK, Jin HY, Park IJ. Characterization of a vancomycin-resistant *Enterococcus faecium* outbreak caused by 2 genetically different clones at a neonatal intensive care unit. *Ann Lab Med*. 2012;32:82-6, <http://dx.doi.org/10.3343/alm.2012.32.1.82>.
16. Duchon J, Graham P, Della-Latta P, et al. Epidemiology of enterococci in a neonatal intensive care unit. *Infect Control Hosp Epidemiol*. 2008;29:374-6, <http://dx.doi.org/10.1086/533544>.
17. Hufnagel M, Liese C, Loescher C, et al. Enterococcal colonization of infants in a neonatal intensive care unit: associated predictors, risk factors and seasonal patterns. *BMC Infect Dis*. 2007;7:107.
18. Singh N, Léger MM, Campbell J, Short B, Campos JM. Control of vancomycin-resistant enterococci in the neonatal intensive care unit. *Infect Control Hosp Epidemiol*. 2005;26:646-9.
19. Nateghian A, Robinson JL, Arjmandi K, et al. Epidemiology of vancomycin-resistant enterococci in children with acute lymphoblastic leukemia at two referral centers in Tehran, Iran: a descriptive study. *Int J Infect Dis*. 2011;15:e332-5, <http://dx.doi.org/10.1016/j.ijid.2011.01.006>.
20. Taşdelen Fişgin N, Darka O, Fişgin T, Hepsert S, Coban AY, Elli M. Surveillance study of vancomycin resistant enterococci in pediatric haematology and oncology patients. *Mikrobiyol Bul*. 2006;40:245-50.
21. Yameen MA, Iram S, Mannan A, Khan SA, Akhtar N. Nasal and perirectal colonization of vancomycin sensitive and resistant enterococci in patients of paediatrics ICU (PICU) of tertiary health care facilities. *BMC Infect Dis*. 2013;13:156, <http://dx.doi.org/10.1186/1471-2334-13-156>.
22. Devrim I, Genel F, Atlihan F, Ozbek E, Gülfidan G. Risk factors for vancomycin-resistant enterococci colonization in infants in neonatal intensive care unit. *Am J Infect Control*. 2010;5:499-503.
23. Brennen C, Wagener MM, Muder RR. Vancomycin-resistant *Enterococcus faecium* in a long-term care facility. *J Am Geriatr Soc*. 1998;46:157-60.
24. Roghmann MC, McCarter RJ Jr, Brewrink J, et al. Clostridium difficile infection is a risk factor for bacteremia due to vancomycin-resistant enterococci (VRE) in VRE-colonized patients with acute leukemia. *Clin Infect Dis*. 1997;25:1056-9.
25. Matar MJ, Tarrand J, Raad I, Rolston KVI. Colonization and infection with vancomycin-resistant *Enterococcus* among patients with cancer. *Am J Infect Control*. 2006;34:534-6.
26. Weinstock DM, Conlon M, Iovino C, et al. Colonization, bloodstream infection, and mortality caused by vancomycin-resistant *Enterococcus* early after allogeneic hematopoietic stem cell transplant. *Biol Blood Marrow Transplant*. 2007;13:615-21.
27. Patel R, Allen SL, Manahan JH, et al. Natural history of vancomycin-resistant enterococcal colonization in liver and kidney transplant recipients. *Liver Transpl*. 2001;7:27-31.
28. Bakir M, Bova JL, Newell KA, Millis JM, Buell JF, Arnow PM. Epidemiology and clinical consequences of vancomycin-resistant enterococci in liver transplant patients. *Transplantation*. 2001;72:1032-7.
29. McNeil SA, Malani PN, Chenoweth CE, et al. Vancomycin-resistant enterococcal colonization and infection in liver transplant candidates and recipients: a prospective surveillance study. *Clin Infect Dis*. 2006;42:195-203.
30. Se YB, Chun HJ, Yi HJ, Kim DW, Ko Y, Oh SJ. Incidence and risk factors of infection caused by vancomycin-resistant enterococcus colonization in neurosurgical intensive care unit patients. *J Korean Neurosurg Soc*. 2009;46:123-9.
31. Pan SC, Wang JT, Chen YC, et al. Incidence of and risk factors for infection or colonization of vancomycin-resistant enterococci in patients in the intensive care unit. *PLoS ONE*. 2012;7:e47297, <http://dx.doi.org/10.1371/journal.pone.0047297>.
32. Olivier CN, Blake RK, Steed LL, Salgado CD. Risk of vancomycin-resistant *Enterococcus* (VRE) bloodstream infection among patients colonized with VRE. *Infect Control Hosp Epidemiol*. 2008;29:404-9.
33. Hendrix CW, Hammond JM, Swoboda SM, et al. Surveillance strategies and impact of vancomycin-resistant enterococcal colonization and infection in critically ill patients. *Ann Surg*. 2001;233:259-65, <http://dx.doi.org/10.1097/0000658-200102000-00016>. PubMed: 11176133.
34. Diaz Granados CA, Jernigan JA. Impact of vancomycin resistance on mortality among patients with neutropenia and enterococcal bloodstream infection. *J Infect Dis*. 2005;191:588-95.
35. LeDell K, Muto CA, Jarvis WR, et al. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of *Staphylococcus aureus* and *Enterococcus*. *Infect Control Hosp Epidemiol*. 2003;24:639-41.
36. Siegel JD, Rhinehart E, Jackson M, Chiarello L, The Healthcare Infection Control Practices Advisory Committee, Management of Multi-drug-Resistant Organisms in Healthcare Settings. Center for Disease Control and Prevention; 2006. Available from: <http://www.cdc.gov/ncidod/dhqp/pdf/ar/mdroGuideline2006.pdf> [accessed 31.10.07].