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Original Article

The investigation of related factors for vancomycin resistant enterococcus colonization of inpatients at internal medicine service

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Abstract

Aim: Enterococci are located in the intestinal flora of animals and humans and have become a major cause of healthcare-associated infections over the years. In this study, related factors were investigated for the isolation of vancomycin-resistant enterococci (VRE) from rectal swab specimens of patients admitted to the internal medicine service.

Material and Methods: TRectal swab samples were obtained from 316 patients. VITEK-2 (bioMérieux, Marcy l'Etoile, France) automated system was used for identification of enterococci. Vancomycin susceptibility was studied by Kirby-Bauer disc diffusion method. Resistant strains were confirmed by vancomycin E-test (bioMerieux).

Results: VRE was growth in 70 (22.2%) of 316 patients included in the study. According to the univariate analysis results which comparing patients who were colonized with VRE to the control group; These were found, the duration of hospitalization for VRE colonized patients was significantly longer, the usage of glycopeptide and metronidazole increased the VRE colonization and VRE colonized patients were found to have more parenteral feeding. It was determined that hemoglobin, thyroxine and albumin values of patients colonized with VRE were lower. According to the logistic regression analysis, patients with VRE colonization had a higher rate of history in the intensive care unit and higher gamma glutamyl transferase value.

Conclusion: It was determined that the hospitalization history in intensive care unit is a risk factor for VRE colonization and especially in patients transported from intensive care unit. Patients colonized with VRE have been found to have higher GGT values and new research on this topic is considered to be needed.

Keywords: Colonization; internal medicine; risk factor; vancomycin resistant enterococcus

INTRODUCTION

Enterococci in the intestinal flora of humans and animals have become one of the most common causes of healthcare-associated infections over the years due to its natural resistance to some antibiotics and also it can develop resistance to some antibiotics (1, 2). Resistance to cephalosporins, aztreonam and macrolides is chromosomally encoded (2). Resistance to glycopeptides, high levels of aminoglycosides and to quinolone group is a later-acquired resistance (2).

Vancomycin-resistant enterococci (VRE) were first reported in 1986 and subsequently reported in many parts of the world (3). In our country, it was isolated for the first time in 1998 (4). VRE can remain colonized for years in the intestinal flora, which constitutes an important reservoir (2). The disease can be transmitted through faeces, urine and serum, it can be transmitted from person to person by direct contact because it can stay alive for weeks on dry surfaces. It has not shown to be contaminated by air (2).

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VRE has two clinically frightening aspects. First; the treatment options of infected patients are very few; Second, this resistance gene is likely to cross over to other Gram-positive microorganisms such as Staphylococcus aureus (S. aureus) (5).

Intensive care units (ICU) in hospitals are a source for many resistant microorganisms. While VRE colonization in healthy individuals is below 1%, this rate can be up to 27.4% in patients who admitted to ICU (3). It has been reported that 31.4% of pediatric hematology-oncology patients and 41.5% of the hematology clinic's ICU, have VRE colonization (2, 6). According to our literature review, there are no studies that evaluating the risks of VRE colonization in internal medicine clinics. However, immunosuppressive patients are frequently followed in internal medicine clinics and colonized and / or infected patients with VRE, can be transfered from ICU. In this study, it was aimed to investigate the factors related to VRE colonization from rectal swab specimens of patients hospitalized in our internal medicine clinic.

MATERIAL and METHODS

In this study, 316 patients who were hospitalized in Internal Medicine Clinic between January 2014 and April 2014 were included in the study. The ethics committee approval was taken from the Haydarpasa Numune Training and Research Hospital Ethics Committee. (HNEAH-KAEK2017 / KK / 13).

Rectal swab samples were taken every three days during hospitalization and at initial hospital admission, and the samples were delivered to the laboratory within half an hour. Enterococcal agar containing 6 µg / ml vancomycin (Oxoid, UK) was used as a selective medium in bacteriological studies for VRE. Conventional methods and VITEK-2 (bioMérieux, Marcy l'Etoile, France) automated systems were used to identify the growing colonies. Vancomycin susceptibility was investigated by Kirby-Bauer disc diffusion method. Vancomycin-resistant strains were confirmed by the E-test (bioMerieux) method. Vancomycin susceptibility results have been evaluated in accordance with the CLSI recommendations (7).

Patients with the previously known VRE colonization and hospitalization of less than one day was accepted as a criterion of exclusion. The control group was screened for VRE colonization and was selected randomly among the patients who found negative and hospitalized in same period in internal medicine clinic.

Clinical and laboratory findings, treatment and follow-up results of the patients were evaluated retrospectively. Comorbid diseases, drug use, hospitalization history in the ICU in last six months, nutritional patterns, hemogram and various biochemical values of patients were investigated by using discharge files, epicrises recorded in hospital's information-technologies system and nurse records.

Descriptive statistics are used for continuous variables (mean, standard deviation, median, minimum, maximum). Student t test was used to compare two continuous variables that were independent and normally distributed. Mann Whitney U test was used to compare two independent and non-normally distributed variables. Chi-square or Fisher Exact tests were used to examine the relationship between categorical variables. Statistical significance level was determined as $p < 0,05$.

Analyzes were performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013) program. Variables that found to be significant in univariate analysis were analyzed by logistic regression analysis according to presence / absence of VRE. "Enter" method was used in the logistic regression. The model was significant ($p < 0.001$) and the model fit (Hosmer-Lemeshow Test $p = 0.714$) was found to be good.

RESULTS

After the exclusion criteria were applied, 316 patients were included in our study. 70 of these (22.2%) were found to have VRE in rectal swab cultures. All of the grown VRE strains were identified as E. feacium. Forty-six patients (14.6%) without having VRE, were selected randomly as control group and there was no difference between them in terms of age and gender. It was found that VRE colonization occurred after an average of 8.7 ±6.2 days in patients in our service. The mean hospitalization days of patients with vancomycin-resistant enterococcal colonization was 13.5 ± 10.7, and the mean hospitalization days was 8.8 ± 7.4 in patients without rectal VRE colonization. The duration of hospitalization for VRE colonized patients was significantly longer ($p < 0.05$).

When antibiotics which were used before VRE isolation, were compared with univariate analysis; glycopeptide and metronidazole were found to be associated with VRE colonization and VRE colonization was found to be statistically more frequent in patients with acute renal failure or Alzheimer's disease. It was also found that non-colonized patients had more enteral feeding and fewer hospitalizations in ICU in last six months (Table 1).

When colonized and non-colonized patient groups with VRE compared, hemoglobin, thyroxine (T4) and albumin values were found to be lower in the group of patients with VRE colonization. According to the logistic regression analysis; In the group with VRE colonization, it was determined that the hospitalization history in ICU was higher and the gamma glutamyl transferase (GGT) value was higher (Table 2). The VRE colonization increases 6.63 times in the patients with history of hospitalization in ICU in last six months. As GGT value increase one point, VRE colonization increases 1.01 times (Table 3). None of the patients were infected with VRE.

Table 1. Evaluation of patients according to comorbid factors and their medical history

		VRE(-)	VRE(+)	p
Glycopeptide use	Yes	6 (13%)	22 (31.4%)	0.027*
	No	40 (87%)	48 (68.6%)	
Metronidazole use	Yes	0	9 (12.9%)	0.011*
	No	46 (100%)	61 (87.1%)	
Beta lactam use	Yes	31 (67.4%)	50 (71.4%)	0.683*
	No	15 (32.6%)	20 (28.6%)	
Clarithromycin use	Yes	7 (15.2%)	12 (17.1%)	1.00*
	No	39 (84.8%)	58 (82.9%)	
Quinolone use	Yes	1 (2.2%)	5 (7.1%)	0.400*
	No	45 (97.8%)	65 (92.9%)	
Acute Renal Failure	Yes	7 (15.2%)	25 (35.7%)	0.019*
	No	39 (84.8%)	45 (64.3%)	
Alzheimer's / SVE	Yes	0	10 (14.3%)	0.026*
	No	46 (100%)	60 (85.7%)	
Congestive Heart Failure	Yes	14 (30.4%)	17 (24.3%)	0.523*
	No	32 (69.6%)	53 (75.7%)	
COPD	Yes	7 (15.2%)	10 (14.3%)	1.00*
	No	39 (84.8%)	60 (85.7%)	
Malignancy	Yes	6 (13%)	8 (11.4%)	0.780*
	No	40 (87%)	62 (88.6%)	
Diabetes Mellitus	Yes	20 (43.5%)	27 (38.6%)	0.369*
	No	26	43 (61.4%)	
Chronic Renal Failure	Yes	18 (39.1%)	24 (34.3%)	0.368*
	No	28 (60.9%)	46 (65.7%)	
Immunosuppression	Yes	2 (4.3%)	2 (2.9%)	0.661
	No	44 (95.7%)	66 (94.3%)	
Hemodialysis	Yes	9 (19.6%)	15 (21.4%)	1.00*
	No	37 (80.4%)	55 (78.6%)	
Hepatitis	Hepatitis B+	1 (2.2%)	2 (3.2%)	0.289*
	Hepatitis C+	1 (2.2%)	1 (1.6%)	
	Negative	43 (95.6%)	59 (95.2%)	
Enteral		43 (93.5%)	55 (78.5%)	0.013*
Enteral + Parenteral		1 (2.2%)	13 (18.6%)	
Parenteral		2 (4.3%)	2 (2.9%)	
Intensive Care Story	Yes	3 (6.5%)	15 (21.4%)	0.036*
	No	43 (93.5%)	55 (78.6%)	

*Fisher'sExact p, SVE: Cerebro-vascular event, COPD: Chronic Obstructive Pulmonary Disease

Table 2. Evaluation of patients according to their biochemical parameters

	VRE	n	Average	Median	Standard deviation	p
Hemoglobin	Negative	46	12.7	10.7	13.9	0.040*
	Positive	69	10	10.1	2.1	
T4	Negative	44	1.2	1.2	0.3	0.047**
	Positive	48	1.1	1.1	0.3	
Albumin	Negative	45	2.7	2.8	0.6	0.047**
	Positive	62	2.4	2.5	0.6	
GGT	Negative	44	35.9	21.5	39.8	<0.05**
	Positive	65	66.3	33	95.9	
WBC	Negative	46	8.362.4	7.530	3.264	0.167**
	Positive	70	10478	9.395	6.509	
Neutrophils	Negative	46	5.852.9	5.280	2.864.6	0.193**
	Positive	70	7.723	6.460	5.863.6	
Lymphocytes	Negative	46	1.608.8	1.590	763.8	0.321**
	Positive	70	1.844	1.340	1.905.3	
Platelets	Negative	46	244.499	231.000	109.341	0.666**
	Positive	70	257.254	249.000	121.870	
Glucose	Negative	45	136	119	62.7	0.456**
	Positive	70	135.5	109.5	82.8	
HBA1c	Negative	16	15.8	6.3	32.2	0.907**
	Positive	26	8.2	6.5	3.9	
Total Protein	Negative	46	6.5	6.4	1.6	0.668**
	Positive	69	6.4	6.4	1.3	
ALT	Negative	46	83.2	15	213.9	0.948**
	Positive	70	37.9	15.5	101.4	
AST	Negative	46	88.2	19.5	240.1	0.362**
	Positive	69	38.8	21	42.3	
LDH	Negative	43	303.6	223	267	0.063**
	Positive	63	328.6	285	243.6	
ALP	Negative	43	94.4	81	51.3	0.419**
	Positive	62	101.5	89	58.1	
Amylase	Negative	45	61.4	62	28.5	0.248**
	Positive	62	57.8	44.5	35.1	
BUN	Negative	44	42.9	34.5	30.6	0.737**
	Positive	69	39.6	30	28	
Creatinine	Negative	46	2.4	1.4	2.4	0.821**
	Positive	70	2.5	1.3	2.5	
Uricacid	Negative	43	6.3	5.2	3.2	0.354**
	Positive	66	6.7	6	3.2	
TSH	Negative	45	1.6	1.5	1.5	0.481**
	Positive	56	1.9	1.2	3.8	
T3	Negative	40	1.8	1.7	0.5	0.739**
	Positive	54	1.8	1.7	0.5	
Iron	Negative	38	50.9	37	44.9	0.339**
	Positive	54	45.3	35.5	40.7	
TIBC	Negative	38	190.3	162.5	93.1	0.902**
	Positive	54	192.8	170	92.9	
Ferritin	Negative	41	1.924.3	138	6.958	0.588**
	Positive	64	508.9	250	708.2	
Triglycerides	Negative	40	153.7	116.5	147.4	0.549**
	Positive	62	179.5	121	199.8	
Cholesterol	Negative	40	163.4	153	50.3	0.414**
	Positive	60	152.9	152.5	46.8	
HDL	Negative	42	34.7	34.5	14	0.377**
	Positive	58	31.1	31.5	13.6	

LDL	Negative	42	98.5	90.5	36.8	0.551**
	Positive	53	99.9	103	34.6	
VLDL	Negative	38	25.2	23	12.8	0.380**
	Positive	53	28.7	24	16.3	
Vitamin B12	Negative	45	682	468	534	0.149**
	Positive	66	609.1	403	582	
Folate	Negative	37	7	5.6	4.5	0.717**
	Positive	58	6.9	5.1	4.7	
Potassium	Negative	46	4.2	4.1	0.6	0.219**
	Positive	70	4.1	4	0.7	
Sodium	Negative	46	135.7	135.5	5.4	0.271**
	Positive	68	136.7	137	5.2	
Calcium	Negative	46	8.5	8.7	0.9	0.769**
	Positive	70	8.5	8.4	0.8	
Chlorine	Negative	45	101.9	101	7.3	0.457**
	Positive	69	102.7	102	5.5	
Magnesium	Negative	45	47.3	2	303	0.327**
	Positive	69	9.1	1.9	59.8	
Phosphorus	Negative	45	3.8	3.5	1.4	0.428**
	Positive	68	3.8	3.4	1.7	
Sedimentation	Negative	43	43.1	32	31.4	0.067**
	Positive	55	57.2	61	34.4	

*Student t, **Mann-Whitney U p, ALP. Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma glutamyl transferase, HDL: High-density lipoprotein, LDH: Lactate dehydrogenase, LDL: Low-density lipoprotein, TIBK: Total iron binding capacity, TSH: Thyroid stimulating hormone, T3: Triiodothyronine, T4: Thyroxine, VLDL: Very low density lipoprotein, WBC: White blood cell

Table 3. Logistic regression analysis results of variables that found significant with univariate analysis

	Significance	OR	95% CI Lower limit	95% CI Upper limit
Intensive Care Story	0.046	6.632	1.031	42.655
GGT	0.028	1.016	1.002	1.03
Length of stay	0.064	1.119	0.993	1.261
Hemoglobin	0.809	0.99	0.916	1.071
T4	0.125	0.116	0.007	1.819
Albumin	0.197	2.312	0.646	8.27
Glycopeptideuse	0.751	1.388	0.183	10.536
Metronidazoleuse	0.998	3110220058	0	-
Alzheimer's / SVE	1	5.407	0	-
Enteral / Parenteral	0.177	0.169	0.013	2.239
Acute renal failure	0.421	1.866	0.408	8.527
Constant	0.999	79182302.7		

CI: Confidence interval,GGT: Gama glutamil transferaz, OR: Odds Ratio, SVE: Serobro – vascular event, T4: Thyroxine

DISCUSSION

It is known that VRE is an important cause of nosocomial infection and that the rate of E. faecium in these infections is increasing (8). E. faecium is reported to have higher resistance to antimicrobial than E. faecalis (9, 10). Also in our study, VRE strains in our hospital, determined as E. faecium.

Colonization rates with VRE were found between 4.7% and 38% in different studies (11-14). The data in our study are compatible with these studies. The difference in VRE colonization rates is due to infection control measures, antibiotic usage policy, awareness of health workers and VRE detection methods (3).

Some studies have found long-term hospitalization as a risk factor (3, 15). Prolonged hospital stay leads to increased antibiotic use and increased duration of contact with patient colonized with VRE (3). In accordance with other studies, in our study, it was determined that patients colonized with VRE were hospitalized for longer periods.

In a meta-analysis, the use of vancomycin was reported to increase the VRE colonization 4.5 times (16). Vancomycin treatment, especially for methicillin-resistant S. aureus

infections, has been shown to increase colonization and infection (2). There are some studies that take antimicrobial treatment from different antimicrobial groups as a risk factor (5, 17, 18). Also in our study, univariate analysis showed a significant difference in the use of vancomycin and metronidazole in patients with VRE colonization. Prolonged use of antimicrobial or cytotoxic drugs disrupts the intestinal mucosa and the immune system (19). Furthermore, the inhibition of VRE in the intestinal system by type C lectin has been shown in mouse studies even if limited. Antibiotics, inhibit C-type lectin and facilitate the VRE colonization (17).

In a previous study, chronic renal failure was found as a risk factor (5) but in our study, acute renal failure was associated with VRE colonization according to univariate analysis. It is not surprising that patients with Alzheimer's disease or "cerebrovascular events" are more colonized with VRE because they may have worse self-care. Furthermore, there are also studies that investigating whether comorbid diseases increase VRE colonization (20, 21).

Different results can be obtained from studies that made on nutritional forms. In one study, enteral feeding was found to be a risk factor for VRE colonization (22), whereas in other studies enteral feeding was found to be protective against VRE colonization (5,6). Parenteral nutrition is thought to increase the risk of VRE due to invasive procedures, prolongation of hospital stay and negative effects on intestinal flora (6). The univariate analysis results in our study are consistent with these results.

It has been shown in many studies that the treatment in ICU is a risk factor (23, 24). Our study was made in internal medicine service and does not contain any ICU patients. However, it has been determined that patients who colonized with VRE were more likely to be hospitalized in ICU at a significant level. In addition, according to logistic regression analysis, VRE colonization is increased 6.63 times in patients who have history of ICU hospitalization.

In our study, hemoglobin, T4 and albumin values were observed to be lower in patients colonized with VRE. In some studies, hemoglobin levels were found to be lower in patients with VRE colonization than in non-colonized patients (25, 26). Our study is also compatible with these studies. One study reported that the level of T4 was low in patients with poor nutritional status (27). The low level of T4, suggests that it may be a marker for severe conditions such as sepsis, as well as a marker for VRE colonization. In addition, no studies have been found in the literature investigating the relationship between VRE colonization and T4. Proteins such as albumin can be used as a marker of nutritional status (28). In our study, albumin levels were significantly lower in patients who are VRE positive. Univariate analysis of our study indicates that the low values of hemoglobin, T4 and albumin in VRE positive patients are compatible with each other and this suggesting that VRE colonization is more frequent in the patient with poor nutrition.

In our study, GGT was found to be higher and logistic regression analysis showed that one unit increase of GGT increases the detection of VRE by 1.01 times. GGT has recently been suggested as an indicator of oxidative stress. In the case of oxidative stress, GGT may increase to compensate the decreasing glutathione (29-31). In our study, the higher GGT level in VRE colonized patients was attributed to the prooxidant property of GGT. Furthermore, patients with VRE colonization have higher prevalence of admission to the ICU and this suggests that previously used antibiotics and other chemicals may also cause GGT elevation in these patients. Because there is no article in the literature that investigates the relationship between VRE colonization and GGT, it is thought that more study is needed about this topic.

It is not a universal rule for VRE infection to follow colonization. However, the incidence of infection in colonized patients ranges between 0% to 45%, while in non-colonized this rate is 2% (3). It is pleasing that none of patients within our study had an infection that caused by enterococci.

CONCLUSION

Clonal analysis is often used in hospitals in the association of isolates causing epidemic. The lack of clonal analysis in isolated bacteria in our study is the limiting step for our study. The main goal should be prevention of spreading because there is no treatment for colonization and decolonisation is time-consuming (19). In order to prevent colonization with VRE, it is necessary to establish guidelines for informing both healthcare personnel and patients, to determine hospital infection control measures and to conduct active surveillance studies. It has also been reported that active surveillance practices reduce colonization and infection rates, increase awareness among staff, and reduce costs (6).

Competing interests: The authors declare that they have no competing interest.

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REFERENCES

1. Bayık SA, Mumcuoğlu İ, Kurşun Ş, et al. Clonal Analysis of Vancomycin-Resistant Enterocci Strains by rep-PCR Method. Turk Hij Tecr Biyol Derg 2016;73:1-8.
2. Mioljević V, Marković-Denić L, Vidović A, et al. Risk factors for vancomycin-resistant Enterococcus colonization in hematologic patients. Vojnosanit Pregl 2013;70:1109-16.

3. Amberpet R, Sistla S, Parija SC, et al. Screening for intestinal colonization with vancomycin resistant enterococci and associated risk factors among patients admitted to an adult intensive care unit of a large teaching hospital. J Clin Diagn Res 2016;10:DC06.
4. Vural T, Sekercioglu AO, Ogunc D, et al. Vancomycin resistant enterococcus casseliflavus strain. ANKEM Derg 1998;12:1.
5. Papadimitriou-Olivgeris M, Drougka E, Fligou F, et al. Risk factors for enterococcal infection and colonization by vancomycin-resistant enterococci in critically ill patients. Infection 2014;42:1013-22.
6. Akturk H, Sutcu M, Somer A, et al. Results of Four-Year Rectal Vancomycin-Resistant Enterococci Surveillance in a Pediatric Hematology-Oncology Ward: From Colonization to Infection. Turk J Haematol 2016;33:244-7.
7. Wayne PA. Performance Standards for antimicrobial susceptibility testing, 23rd informational supplement. Clinical and Laboratory Standards Institute 2013;100:23.
8. Karakeçili F, Dalyan Cilo B, Cikman A, et al. Molecular epidemiological analysis of vancomycin-resistant enterococci. Nobel Med 2017;13:22-8.
9. Hanci H, Uyanik M, Gültekin E, et al. In-vitro Activity of Daptomycin Against Enterococcus strains Isolated from Blood Cultures. J Turk Microbiol Soc 2015;44:91-7.
10. Mete E, Kaleli I, Cevahir N, et al. Evaluation of virulence factors in enterococcus species. Mikrobiyol Bul 2017;51:101-14.
11. Ford CD, Lopansri BK, Haydoura S, et al. Frequency, risk factors, and outcomes of vancomycin-resistant Enterococcus colonization and infection in patients with newly diagnosed acute leukemia: different patterns in patients with acute myelogenous and acute lymphoblastic leukemia. Infect Control Hosp Epidemiol 2015;36:47-53.
12. Suntharam N, Lankford MG, Trick WE, et al. Risk factors for acquisition of vancomycin-resistant enterococci among hematology-oncology patients. Diagn Microbiol Infect Dis 2002;43:183-8.
13. Worth LJ, Thursky KA, Seymour JF, et al. Vancomycin-resistant Enterococcus faecium infection in patients with hematologic malignancy: patients with acute myeloid leukemia are at high-risk. Eur J Haematol 2007;79:226-33.
14. Dubberke ER, Hollands JM, Georgantopoulos P, et al. Vancomycin-resistant enterococcal bloodstream infections on a hematopoietic stem cell transplant unit: are the sick getting sicker? Bone Marrow Transplant 2006;38:813-9.
15. 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;7:47297.
16. Carmeli Y, Samore MH, Huskins C. The association between antecedent vancomycin treatment and hospital-acquired vancomycin-resistant enterococci: a meta-analysis. Arch Intern Med 1999;159:2461-8.
17. Almyroudis NG, Lesse AJ, Hahn T, et al. Molecular epidemiology and risk factors for colonization by vancomycin-resistant Enterococcus in patients with hematologic malignancies. Infect Control Hosp Epidemiol 2011;32:490-6.
18. Yoon YK, Lee SE, Lee J, et al. Risk factors for prolonged carriage of vancomycin-resistant Enterococcus faecium among patients in intensive care units: a case-control study. J Antimicrob Chemother 2011;66:1831-8.
19. Umit EG, Kuloglu F, Demir AM. Hypogammaglobulinemia and Poor Performance Status are Predisposing Factors for Vancomycin-Resistant Enterococcus Colonization in Patients with Hematological Malignancies. Turk J Haematol 2017;34:89-92.
20. Kim YJ, Kim SI, Kim YR, et al. Risk factors for vancomycin-resistant enterococci infection and mortality in colonized patients on intensive care unit admission. Am J Infect Control 2012;40:1018-9.
21. Batistao DW, Gontijo-Filho PP, Conceicao N, et al. Risk factors for vancomycin-resistant enterococci colonisation in critically ill patients. Mem Inst Oswaldo Cruz 2012;107:57-63.
22. Butler KM. Enterococcal infection in children. Semin Pediatr Infect Dis. 2006;17:128-39.
23. Sakka V, Tsiodras S, Galani L, et al. Risk-factors and predictors of mortality in patients colonised with vancomycin-resistant enterococci. Clin Microbiol Infect 2008;14:14-21.
24. Tacconelli E, Cataldo MA. Vancomycin-resistant enterococci (VRE): transmission and control. Int J Antimicrob Agents 2008;31:99-106.
25. Choi HK, Kim KH, Lee SH, et al. Risk factors for recurrence of Clostridium difficile infection: effect of vancomycin-resistant enterococci colonization. J Korean Med Sci 2011;26:859-64.
26. Kee SY, Park CW, Lee JE, et al. Healthcare-associated risk factors of vancomycin-resistant Enterococci colonization among outpatients undergoing hemodialysis. Jpn J Infect Dis 2012;65:57-60.
27. Martins VJ, Neves AP, Garcia MC, et al. Normal cortisol response to cold pressor test, but lower free thyroxine, after recovery from undernutrition. Br J Nutr 2016;115:14-23.
28. Rolandelli RH, Ullrich JR. Nutritional support in the frail elderly surgical patient. Surg Clin North Am 1994;74:79-92.
29. Whitfield J. Gamma glutamyl transferase. Crit Rev Clin Lab Sci 2001;38:263-355.
30. Jones DP, Carlson JL, Mody Jr VC, et al. Redox state of glutathione in human plasma. Free Radic Biol Med 2000;28:625-35.
31. Abdul-Rasheed OF, Al-Shamma GA, Zillo BH. Serum γ-glutamyltransferase as oxidative stress marker in pre-and postmenopausal Iraqi women. Oman Med J 2010;25:286.