

Colonization With Vancomycin-Resistant Enterococci and Risk for Bloodstream Infection Among Patients With Malignancy: A Systematic Review and Meta-Analysis

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Background. Vancomycin-resistant enterococci (VRE) cause severe infections among patients with malignancy, and these infections are usually preceded by gastrointestinal colonization.

Methods. We searched the PubMed and EMBASE databases (up to May 26, 2016) to identify studies that reported data on VRE gastrointestinal colonization among patients with solid or hematologic malignancy.

Results. Thirty-four studies, reporting data on 8391 patients with malignancy, were included in our analysis. The pooled prevalence of VRE colonization in this population was 20% (95% confidence interval [CI], 14%–26%). Among patients with hematologic malignancy, 24% (95% CI, 16%–34%) were colonized with VRE, whereas no studies reported data solely on patients with solid malignancy. Patients with acute leukemia were at higher risk for VRE colonization (risk ratio [RR] = 1.95; 95% CI, 1.17–3.26). Vancomycin use or hospitalization within 3 months were associated with increased colonization risk (RR = 1.92, 95% CI = 1.06–3.45 and RR = 4.68, 95% CI = 1.66–13.21, respectively). Among the different geographic regions, VRE colonization rate was 21% in North America (95% CI, 13%–31%), 20% in Europe (95% CI, 9%–34%), 23% in Asia (95% CI, 13%–38%), and 4% in Oceania (95% CI, 2%–6%). More importantly, colonized patients were 24.15 (95% CI, 10.27–56.79) times more likely to develop a bloodstream infection due to VRE than noncolonized patients.

Conclusions. A substantial VRE colonization burden exists among patients with malignancy, and colonization greatly increases the risk for subsequent VRE bloodstream infection. Adherence to antimicrobial stewardship is needed, and a re-evaluation of the use of vancomycin as empiric therapy in this patient population may be warranted.

Keywords. bloodstream infection; cancer; colonization; malignancy; VRE.

Enterococci are part of the normal flora of the gastrointestinal tract and one of the most important causes of nosocomial infections [1]. Vancomycin-resistant enterococci (VRE) were first reported in 1986 [2] and have since evolved into a major cause of healthcare-associated infections, and their prevalence in the United States is reportedly increasing [3–5]. Vancomycin-resistant enterococci bloodstream infections (BSIs), in particular, have been associated with prolonged hospital stay, higher healthcare costs, and inferior clinical outcomes, compared with vancomycin-susceptible enterococcal BSIs [6, 7]. Cancer patients, as well as hematopoietic stem cell transplant recipients, are particularly susceptible to VRE BSIs, which are in turn associated with increased mortality in this patient population [8, 9].

It is interesting to note that VRE infections are closely related to, and usually preceded by, VRE colonization [10, 11]. In patients with malignancy, mucosal compromise due to chemotherapy allows translocation of these pathogens into the bloodstream [12, 13]. Thus, regular screening of these patients for VRE carriage has been proposed for limiting the clinical impact of these resistant microbes [1]. However, there is a relative paucity of aggregate data concerning the prevalence and importance of VRE colonization in this population. Thus, we performed a systematic review and meta-analysis to estimate the VRE colonization burden in these patients and assess its effect on the development of subsequent VRE BSIs.

METHODS

This systematic review and meta-analysis was performed according to the PRISMA guidelines [14].

Data Sources and Searches

We performed a systematic search of the PubMed and EMBASE databases for studies that reported VRE colonization rates among patients with solid or hematologic malignancy. We used the term (VRE or GRE or vancomycin-resistant OR glycopeptide-resistant) AND (tumor OR cancer OR carcinoma OR

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sarcoma OR neoplasia OR malignancy OR leukemia OR leukaemia OR lymphoma OR oncolog* OR hematolog* OR haematolog* OR neutropen*) AND (prevalence or colonization or colonisation OR carriage OR epidemiology OR rectal OR fecal OR faecal OR stool). Each database was examined separately, and our last day of access was May 26, 2016. Three authors (M. A., A. G., and K. T.) independently screened titles and abstracts to identify relevant studies, which were then accessed in full text. Duplicates were removed before study selection, and discrepancies were resolved by consensus. We also supplemented our search by screening the reference lists of all eligible studies and relevant reviews. Our analysis included published literature, whereas abstracts from conference proceedings were excluded. A restriction for English language was imposed.

Study Selection

Studies were considered eligible for inclusion in our analysis if they reported extractable data on VRE gastrointestinal colonization in patients with solid or hematologic malignancy. Both inpatient and outpatient populations were included. As colonization, we defined the isolation of VRE, by culture or polymerase chain reaction, from a rectal or fecal sample from patients without evidence of gastrointestinal infection. Included studies should clearly differentiate between VRE infection and colonization and state the timing of sample collection. In addition, they should state the number of collected isolates per subject, to avoid duplicate samples. In studies that included decolonization interventions, only data from the preintervention period were included in our analysis.

Outcomes of Interest

Our primary outcome of interest was the prevalence rate of VRE gastrointestinal colonization in patients with solid or hematologic malignancies. This rate was calculated by dividing the number of patients that had a positive VRE rectal or fecal sample, by the total number of screened patients. As secondary outcome, we estimated the risk of subsequent VRE BSI development among colonized and noncolonized patients. Furthermore, we calculated VRE colonization rates among different patient subgroups, and we examined the temporal trend of VRE colonization.

The individual data from each study were extracted by 3 authors (M. A., A. G., and K. T.). We used the Newcastle-Ottawa scale (NOS) to assess the methodological quality of the included studies [15]. The NOS utilizes a “star”-based system to evaluate studies on 3 categories: selection of appropriate patient population, comparability between different studied cohorts (when applicable), and ascertainment of the outcome of interest [15]. Some NOS fields did not apply to our analysis, specifically “selection of the non-exposed cohort,” “demonstration that the outcome of interest was not present at the start of the study,” and “comparability between cohorts”; consequently, each study could receive a maximum of 5 stars. Studies that received 4 or 5 stars (out of 5 maximum) were considered to be of high quality.

Data Synthesis and Analysis

We performed a random effects meta-analysis to estimate the pooled prevalence and the 95% confidence intervals (CIs), using the DerSimonian and Laird approach [16]. We used the Freeman-Tukey methodology to stabilize the variance of the raw proportions [17]. Between-study heterogeneity was assessed with the tau-squared (τ^2) statistic [18], and the presence of small study effect was examined with the Egger’s test [19]. Studies were grouped by geographical continent. To calculate the time trend of VRE colonization, we transformed the model coefficients into rates, and then we plotted these rates against the midyear of each respective study along with the observed prevalence rates. If the study midyear could not be extracted, we assumed that it occurred 2 years before the publication year.

We also performed meta-regression analyses to compare different patient subgroups and thus control for potential sources of confounding and heterogeneity. We explored the effect of covariates on VRE colonization rates through univariate random effects meta-regression using Knapp and Hartung modification [20]. In addition, we examined the effect of VRE colonization on subsequent VRE BSI development. The pooled relative risk for VRE BSI between colonized and noncolonized patients was calculated using random effects meta-analysis and was reported as unadjusted risk ratio (RR) estimates and 95% CIs. Furthermore, to evaluate in greater depth the effect of VRE colonization on subsequent VRE BSI development, we performed a diagnostic accuracy meta-analysis. We used the bivariate random-effects model, which accounts for correlation between studies, to determine the logit-transformed sensitivity and specificity and their respective 95% CI [21]. In addition, we calculated the positive likelihood ratio (LR+), negative likelihood ratio (LR-), and diagnostic odds ratio, along with their respective 95% CI, pertaining to VRE colonization and its predictive value for subsequent VRE BSI. We used the Stata version 13 software package (StataCorp, College Station, TX) to perform the statistical analysis, and the statistical significance threshold was set at 0.05.

RESULTS

The initial database search yielded 1157 articles. After removal of 234 duplicates, 923 articles were screened by title and abstract reading and 192 were identified as potentially relevant and accessed in full text. From these 192 reports, 74 were excluded because they did not contain VRE colonization data, 41 did not provide the total number of patients screened, 20 did not contain extractable data on patients with malignancy, 13 reported data only on isolates without relation to patients, 6 were reviews, and 4 concerned outbreaks. At the end, 34 studies were considered eligible for inclusion in our analysis [22–40, Supplementary References 41–55]. All eligible studies were awarded 4 or 5 stars in the NOS, and they were thus considered of high quality and included in our analysis (Supplementary

Table 1), and no additional eligible studies were identified by searching through the reference lists of the included studies. The individual characteristics of these studies are provided in Table 1, and the review process is showcased in the PRISMA flowchart (Figure 1).

The 34 studies included in our analysis provided data on 8391 patients with solid or hematologic malignancy and reported data on the years 1989–2014 [22–40, Supplementary References 41–55]. Nine studies were retrospective [22, 23, 25, 27, 28, 36, 38, 39, Supplementary Reference 42], whereas 25 studies were prospective [24, 26, 29–35, 37, 40, Supplementary References 41, 43–55]. Thirty studies were conducted on inpatients [22–34, 36–39, Supplementary References 42–48, 50–55], 3 studies included both inpatients and outpatients [35, 40, Supplementary Reference 41], and 1 study included solely outpatients (Supplementary Reference 49).

The majority of the studies were performed in North America (16 studies in the United States [22–32, 34–38], and 1 in Canada [33]). Among the remaining studies, 10 were performed in Europe (2 in the United Kingdom [Supplementary References 47, 48]), 2 in Germany [Supplementary References 46, 54], and 1 each in Greece [Supplementary Reference 44], Serbia [Supplementary Reference 45], Ireland [Supplementary Reference 49], Netherlands [Supplementary Reference 50], Spain [Supplementary Reference 51], and France [Supplementary Reference 55]), 5 in Asia (3 in Turkey [39, Supplementary References 42, 43], 1 in India [40], and 1 in Iran [Supplementary Reference 41]), and 2 in Oceania (both in Australia [Supplementary References 52, 53]). Twenty-two studies included adult patients [22–28, 30, 31, 33, 34, 36, 38, 39, Supplementary References 44–47, 51–53, 55], 11 studies included pediatric patients [29, 32, 35, 37, 40, Supplementary References 41–43, 48, 49, 54], and 1 study reported data for both (Supplementary Reference 50).

Overall, the pooled prevalence of VRE gastrointestinal colonization among patients with malignancy was 20% (95% CI, 14%–26%; $\tau^2 = 0.18$; Egger's Test [ET] = 1.72, $P_{ET} = 0.04$) (Figure 2). Moreover, a diagnosis of acute leukemia was associated with a 1.95-times greater risk of VRE colonization (95% CI, 1.17–3.26), based on 4 studies on 410 patients [27, 29, 38, Supplementary Reference 45].

Stratifying by continent, the VRE colonization rate was 21% in North America (95% CI, 13%–31%; ET = 1.72, $P_{ET} = 0.14$), 20% in Europe (95% CI, 9%–34%); ET = 2.03, $P_{ET} = 0.37$), 23% in Asia (95% CI, 13%–38%; ET=3.90, $P_{ET} = 0.109$), and 4% in Oceania (95% CI, 2%–6%). In the ensuing univariate meta-regression analysis, these differences did not reach statistical significance (coefficient = 0.15, $P = .14$), except when we compared Oceania with the rest of the world. In this case, despite the small number of studies from Oceania (Supplementary References 52, 53), the difference in colonization rates approached statistical significance (coefficient = -0.55 , $P = .06$). We also detected

a 1.3% annual increase in the reported VRE colonization rate, although this increase was not statistically significant ($P = .176$) (Supplementary Figure 1).

Twenty-three studies provided colonization data on 6739 adult patients [22–28, 30, 31, 33, 34, 36, 38, 39, Supplementary References 44–47, 50–53, 55], whereas 12 studies provided data on 1652 pediatric patients [29, 32, 35, 37, 40, Supplementary References 41–43, 48–50, 54], with 1 study providing data for both adult and pediatric populations [50]. Among both groups, the VRE colonization rate was 19% (95% CI, 12%–27% and 11%–28%, respectively), and thus age did not independently predict the colonization rate (coefficient = 0.00, $P = .99$). In addition, 19 studies reported colonization data on 4485 patients with hematologic malignancies, and the pooled prevalence in this population was 24% (95% CI, 16%–34%) [22–29, 31, 32, 36, 38, 39, Supplementary References 41, 45, 47, 50, 51, 55]. This patient population included 2338 patients with leukemia, 814 patients with lymphoma, 169 patients with multiple myeloma, 89 patients with myelodysplastic syndrome, and 1075 patients with nonspecified hematologic malignancy [22–29, 31, 32, 36, 38, 39, Supplementary References 41, 45, 47, 50, 51, 55]. The rest of the included studies did not sufficiently differentiate between patients with solid and hematologic malignancies to allow for a dedicated analysis.

Four studies on 451 patients reported data on antibiotic use among colonized and noncolonized patient, within the previous 6 months [30, 32, Supplementary References 41, 45]. Based on these studies, recent antibiotic use was associated with a 1.41 times greater risk of VRE colonization that did not reach statistical significance (95% CI, .89–2.23). Notably, based on data from 3 studies on 380 patients [30, 32, Supplementary Reference 41], patients that had received vancomycin in the previous 3 months were significantly more likely to be VRE carriers (RR = 1.92; 95% CI, 1.06–3.45). It is unfortunate that the aforementioned studies did not differentiate between intravenous and oral administration of vancomycin for *Clostridium difficile* infection. In addition, based on 2 studies on 227 patients [30, 32], hospitalization during the most previous 3 months was also associated with a greater VRE colonization risk (RR = 4.68; 95% CI, 1.66–13.21).

Regarding the relation of VRE colonization to subsequent VRE BSI, 13 studies on 5096 patients reported extractable data on VRE BSI development in colonized and noncolonized patients [22–25, 27, 28, 34, 38, 39, Supplementary References 42, 46–48]. From these studies, 5 studies followed up patients until discharge from the hospital or death [23, 34, 39, Supplementary References 46, 47], whereas 8 studies reported data concerning a set period of time after detection of colonization [22, 24, 25, 27, 28, 38, Supplementary References 42, 48]. The median period of observation was 5 weeks, based on available data from 10 studies [22–25, 27, 28, 38, 39, Supplementary References 42, 48], and the maximum reported observation period

Table 1. Summarized Data of Included Studies^a

Author Study Midyear	Country (State)	Screened	Colonized (%)	Setting	Screening Policy	Sample	Isolation Method
North America							
Ford [23] 2010	USA (UT)	508	224 (44.1%)	Adults with hematologic malignancy undergoing autologous and allogeneic HSCT	At admission and weekly thereafter	F	Culture
Ford [22] 2009	USA (UT)	214	82 (38.3%)	Adults with newly diagnosed acute leukemia	At admission and weekly thereafter	F	Culture
Taur [24] 2010	USA (NY)	94	35 (37.2%)	Adults with hematologic malignancy undergoing allogeneic HSCT	At admission and during hospitalization	F	PCR
Kamboj [25] 2009	USA (NY)	247	68 (27.5%)	Adults with hematologic malignancy before allogeneic HSCT	At admission and weekly thereafter	R	Culture
Calderwood [26] 2004	USA (IL)	416	134 (32.2%)	Adults with hematologic malignancy undergoing autologous and allogeneic HSCT	At admission and weekly thereafter	R	Culture
Weinstock [27] 2005	USA (NY)	92	37 (40.2%)	Adults with hematologic malignancy before allogeneic HSCT	At admission and during hospitalization	F	Culture
Matar [28] 2001	USA (TX)	2115	99 (4.7%)	Adults with hematologic malignancy and HSCT recipients	At admission and weekly thereafter for 3 consecutive weeks	F	Culture
Tsiatis [29] 2001	USA (TN)	48	12 (25%)	Children with solid and hematologic malignancy undergoing HSCT	At admission and weekly thereafter	F	Culture
Suntharam [30] 1999	USA (IL)	155	11 (7.1%)	Adults with solid and hematologic malignancy at a hematology/oncology unit, noncolonized at admission	Weekly during hospitalization	R	Culture
Shaikh [31] 1997	USA (TX)	39	4 (10.3%)	Adults with leukemia	At admission and weekly thereafter	R	Culture
Henning [32] 1994	USA (NY)	73	19 (26%)	Children with solid or hematologic malignancy	At admission and every 2 weeks thereafter	F	Culture
Montecalvo [34] 1994	USA (NY)	306	86 (28.1%)	Adults with solid and hematologic malignancy at an oncology unit	At admission and weekly thereafter	R	Culture
Rubin [35] 1991	USA (NY)	26	4 (15.4%)	Pediatric oncology inpatients and outpatients	Weekly screening (inpatients) and point-prevalence screening (outpatients)	R	Culture
Levitt [36] 2006	USA (FL)	312	98 (31.4%)	Adults with AML admitted for chemotherapy or allogeneic HSCT	At admission	R	Culture
Song [37] 2013	USA (DC)	44	3 (6.8%)	Children hospitalized at a pediatric oncology and HSCT unit	Point-prevalence screening among inpatients	R	Culture/PCR
Zirakzadeh [38] 2001	USA (MN)	205	22 (10.7%)	Adults with hematologic malignancy undergoing allogeneic HSCT	Prior to HSCT	R/F	Culture/PCR
Embil [33] 1995	Canada	30	0 (0%)	Children hospitalized at a pediatric oncology and HSCT unit	After 72 h of hospitalization	R/F	Culture
Asia							
Gedik [39] 2011	Turkey	126	50 (39.7%)	Adults with hematologic malignancy and febrile neutropenia	During hospitalization	R	Culture
Thacker [40] 2014	India	618	65 (10.5%)	Pediatric cancer patients	Within 7 days of registration as either inpatient or outpatient	R (outpatients)/ F (inpatients)	Culture
Nateghian [41] 2008	Iran	130	33 (25.4%)	Pediatric ALL patients	Point-prevalence screening at inpatients and outpatients	F	Culture/PCR
Akturk [42] 2012	Turkey	229	72 (31.4%)	Children with solid and hematologic malignancy admitted at a hematology/oncology unit	At admission and weekly thereafter	R	Culture

Table 1. Continued

Author Study Midyear	Country (State)	Screened	Colonized (%)	Setting	Screening Policy	Sample	Isolation Method
Devrim [43] 2012	Turkey	120	24 (20%)	Children with solid and hematologic malignancy admitted at a hematology/oncology unit	During hospitalization	R	Culture/PCR
Europe							
Papadimitriou-Olivgeris [44] 2011	Greece	68	19 (27.9%)	Adults with solid and hematologic malignancy admitted to the ICU	At admission to the ICU	R	Culture/PCR
Mioljevic [45] 2011	Serbia	70	32 (45.7%)	Adults with hematologic malignancy admitted to the ICU	At admission to the ICU and during hospitalization	R/F	Culture
Liss [46] 2009	Germany	513	51 (9.9%)	Adults with solid tumors or hematologic malignancies at a hematology/oncology unit	Within 72 h of admission	F	Culture
Bradley [47] 1996	UK	293	120 (41%)	Adults with hematologic malignancy and HSCT recipients	Weekly during hospitalization	F	Culture
Gray [48] 1998	UK	154	59 (38.3%)	Pediatric hematology/oncology unit	During hospitalization	F	Culture
Nourse [49] 1997	Ireland	137	4 (2.9%)	Pediatric outpatients with solid or hematologic malignancy	Point-prevalence screening	F	Culture
Guiot [50] 1989	Netherlands	95	9 (9.5%)	Children and adults with hematologic malignancy	At admission and weekly thereafter	F	Culture
Rinaudo [51] 2007	Spain	220	0 (0%)	Adults with solid and hematologic malignancy admitted to the ICU	At admission to the ICU	R	Culture
Schuster [54] 1996	Germany	48	24 (50%)	Pediatric inpatients at an oncology unit	During hospitalization	F	Culture
Plessis [55] 1993	France	132	14 (10.6%)	Adults with hematologic malignancy and neutropenia	Weekly during hospitalization	F	Culture
Oceania							
Bass [52] 2010	Australia	229	18 (7.9%)	Adult inpatients at a hematology/oncology unit, noncolonized at admission	Weekly during hospitalization	R	PCR
Padiglione [53] 1998	Australia	285	4 (1.4%)	Adult inpatients at a hematology/oncology unit	Weekly during hospitalization	R	Culture

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; F, fecal sample; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; PCR, polymerase chain reaction; R, rectal sample.

*References 41–72 are located in the Supplementary Material.

was 52 weeks [28]. Overall, 13% (95% CI, 8%–19%) of colonized patients with malignancy developed a BSI due to VRE. Colonized patients were 24.15 (95% CI, 10.27–56.79; $\tau^2 = 1.12$; $ET = 1.27$, $P_{ET} = 0.129$) times more likely to develop a BSI due to VRE than noncolonized patients (Figure 3). The sensitivity and specificity of VRE colonization as a predictive tool for subsequent VRE BSI were 0.94 (95% CI, .83–.98) and 0.78 (95% CI, .69–.85), respectively. In addition, LR+ and LR– were calculated as 4.36 (95% CI, 3.01–6.30) and 0.07 (95% CI, .02–.24), respectively, and the diagnostic odds ratio (DOR) was 60.68 (95% CI, 16.31–225.78).

DISCUSSION

Bloodstream infections due to VRE constitute a major cause of morbidity and mortality in patients with solid and hematologic malignancy [1, 6, 7] and are usually preceded by colonization of the gastrointestinal tract [10, 11]. However, there are limited aggregate data concerning the prevalence of VRE

colonization, associated risk factors, and the impact of colonization on subsequent VRE-related BSIs in this patient population. In our analysis, we found that 20% of patients with malignancy were colonized with VRE and the prevalence was higher among patients with acute leukemia. Vancomycin use and hospitalization within the previous 3 months were associated with increased colonization rates. In addition, VRE-colonized patients were 24 times more likely to develop a BSI due to VRE compared with noncolonized patients, with up to 13% of colonized patients developing such an infection over an approximate median period of observation of 5 weeks.

The considerable VRE colonization burden noted in patients with malignancy can be attributed to multiple factors. Antimicrobial agents are frequently administered in these patients, both for therapeutic and prophylactic purposes (Supplementary Reference 56). In our analysis, we found that previous use of vancomycin was associated with a 2-fold greater risk of VRE carriage. Vancomycin exerts selective pressure to enterococci and also interferes with the intestinal microbiome,

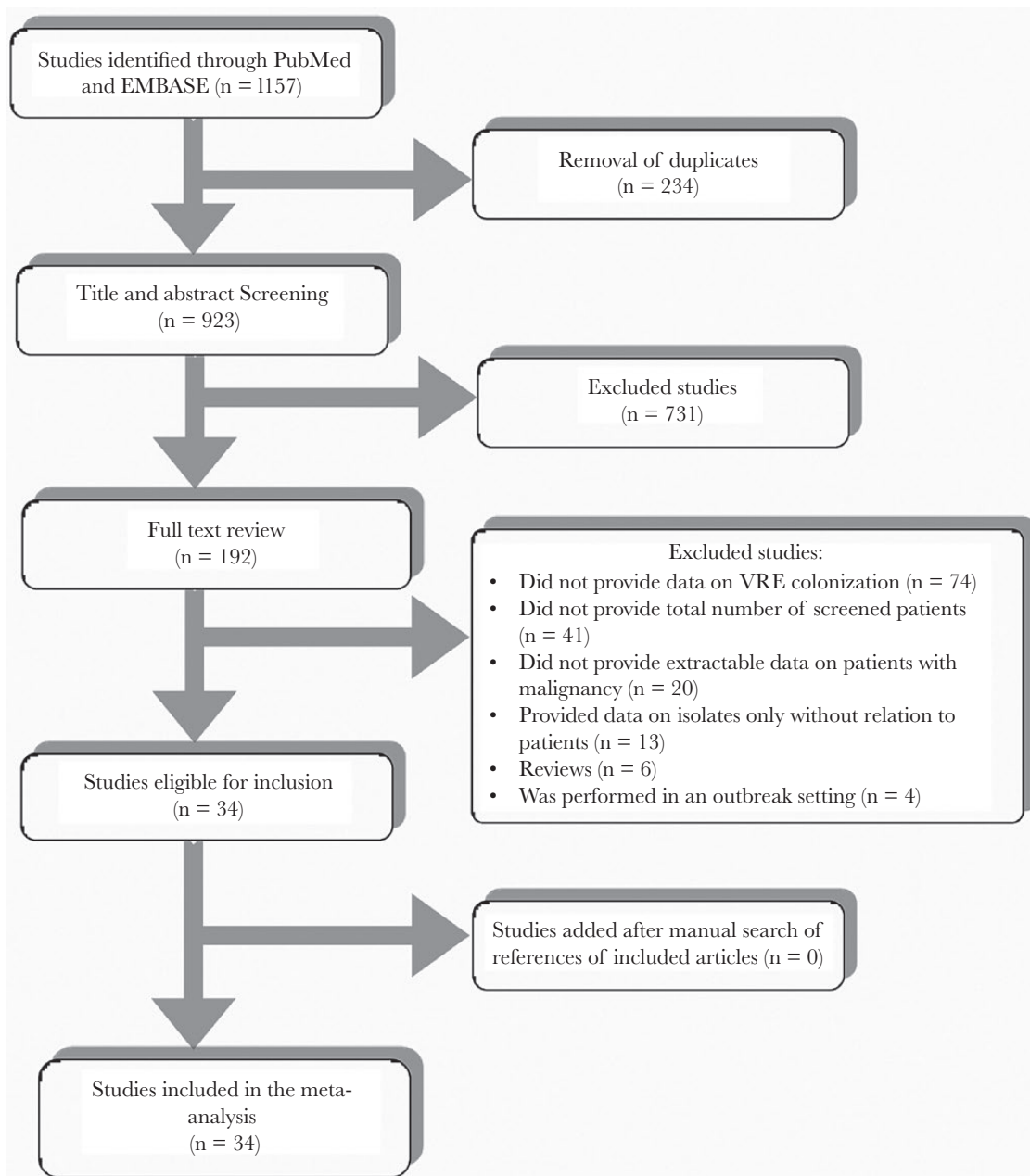


Figure 1. PRISMA flow diagram. VRE, vancomycin-resistant enterococci.

allowing VRE to predominate [1, Supplementary Reference 57]. This finding is especially concerning because high rates of inappropriate vancomycin use are reported in patients with febrile neutropenia (Supplementary Reference 58), despite the fact that addition of empiric Gram-positive coverage in this setting has not been associated with significant clinical benefit (Supplementary References 59–61).

In addition, frequent contact with healthcare facilities, also common among patients with malignancies, predisposes to VRE colonization [6, Supplementary Reference 62]. In our analysis, hospitalization within the previous 3 months was associated with a 2-fold increase in the risk of VRE

colonization. Vancomycin-resistant enterococci have been isolated from virtually every object within patient rooms, and their ubiquitous presence, combined with their high survivability on dry surfaces, causes high VRE transmission rates within healthcare facilities [11, Supplementary Reference 62]. Moreover, immunosuppression and the presence of indwelling vascular and urinary catheters, which are commonly encountered in cancer patients, are well recognized risk factors for VRE colonization [6, 8, Supplementary References 63, 64]. Notably, our finding that acute leukemia is associated with a 2-fold increased risk for VRE colonization may reflect the high incidence of the aforementioned

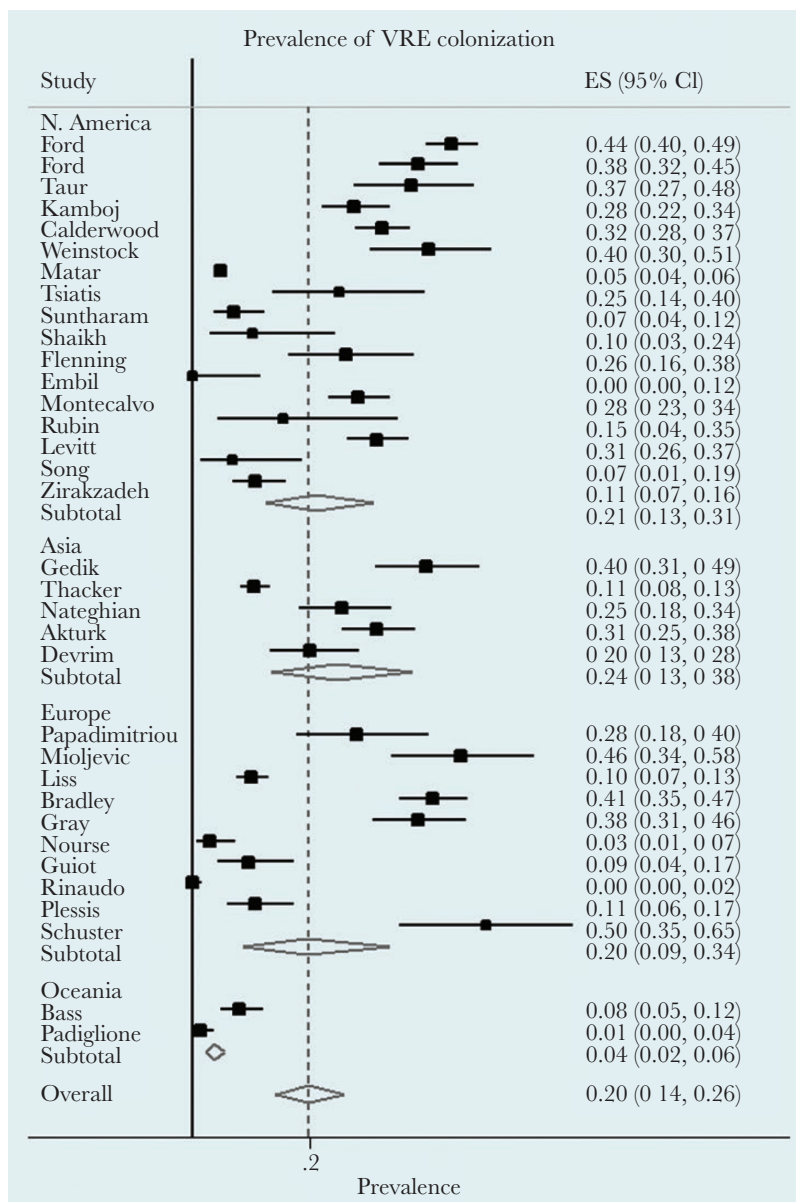


Figure 2. Forest plot of included studies. Prevalence of vancomycin-resistant enterococci (VRE) colonization among patients with malignancy, stratified by continent. CI, confidence interval; ES, estimated prevalence.

risk factors for VRE colonization in these patients (Supplementary References 65, 66).

Concerning the geographic variation of our results, the rates of VRE colonization in North America, Europe, and Asia did not differ significantly from each other. A lower VRE prevalence was detected in Oceania; however, our analysis was underpowered to detect a significant difference, because only 2 studies from Oceania were identified (Supplementary References 52, 53). Our findings are in accordance with previously published studies examining global VRE rates in other high-risk patient populations, which report limited geographic variability in VRE carriage rates (Supplementary References 67, 68), and contradict the belief that VRE colonization is limited to certain geographic areas.

The importance of the substantial VRE colonization burden noted in our analysis is primarily underscored by the fact that VRE colonization is usually the first step in the development of BSIs with VRE [10, 11]. In our analysis, we found that colonized patients face a 24-fold greater risk to develop a BSI due to VRE than noncolonized patients, with approximately 1 in 8 colonized patients developing such an infection. In patients with malignancy, chemotherapy regimens and poor functional status can both lead to a damaged intestinal mucosa, thus allowing VRE translocation into the bloodstream [12, 13]. In addition, neutropenia further increases the risk for BSI among colonized patients due to inadequate clearance of circulating pathogens [12, Supplementary Reference 69]. In turn, VRE BSIs in patients

Prior Colonization as Risk Factor for Bloodstream Infection

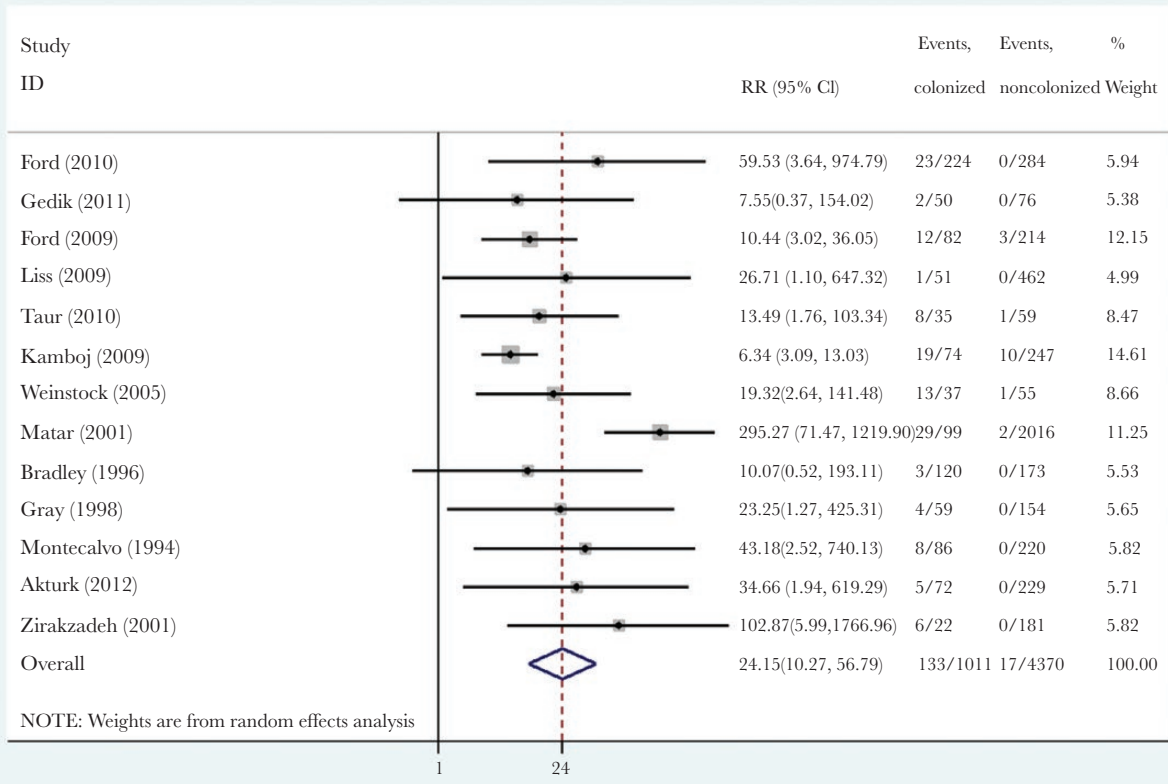


Figure 3. Forest plot of included studies. Relative risk (RR) estimates of bloodstream infection with vancomycin-resistant enterococci among colonized and noncolonized patients. CI, confidence interval; ID, identification.

with malignancy are associated with delayed administration of appropriate antibiotic therapy, prolonged hospitalization, and high mortality [8–10, Supplementary Reference 70].

Of note, our results show a higher rate of VRE colonization among patients with malignancies than the respective rates in similar meta-analyses performed in other high-risk populations, such as ICU patients and solid-organ transplant recipients (9% and 12%, respectively) (Supplementary References 67, 68). The higher colonization burden noted in patients with malignancy may reflect a higher cumulation of risk factors for VRE colonization in this particular patient population, such as antibiotic consumption and frequent hospitalizations (Supplementary References 56, 62). The reported VRE colonization rates in patients with malignancy and the observed link between colonization and infection have prompted evaluations on the role of active VRE screening in hematology/oncology units. Thus far, this practice is still under debate, and there are only a few studies examining its effectiveness that report conflicting results [1, Supplementary Reference 71].

Our findings have several clinical ramifications, which should be formally explored in future studies. In light of the significant association between vancomycin and VRE carriage, as noted in our analysis and in the literature [1, 7, Supplementary

Reference 57], addition of vancomycin to empiric therapy regimens in this patient population may need to be re-evaluated. In addition, VRE coverage in VRE-colonized patients with bacteremia should be considered for patients at high risk for VRE translocation, such as those with mucositis or neutropenia (Supplementary References 69, 72). Furthermore, given the relative scarcity of data, the cost-effectiveness of active VRE screening should be investigated further, so that appropriate conclusions may be reached regarding its benefit.

Regarding study limitations, the included studies did not contain adequate data to allow calculation of separate prevalence rates across different time-points during hospitalization, such as admission or discharge. In addition, our secondary analysis on VRE colonization risk factors was based on a relatively small number of studies, which might limit the precision of our secondary estimate, and the data provided do not allow for a multivariate analysis to address potential confounding. Furthermore, the included studies did not contain sufficient extractable data on patients with solid malignancy to allow calculation of the colonization prevalence in this specific population. Moreover, data were not available concerning the presence of central lines in patients that developed BSIs caused by VRE, compared with the patients that did not. Lastly, among the included studies,

there was an alarming lack of data from Africa, East Asia, and South America regarding patients with malignancy. Thus, further studies from these regions are needed to delineate further the global colonization burden in patients with malignancy.

CONCLUSIONS

In conclusion, patients with malignancy, and especially those with acute leukemia, represent a high-risk population for colonization with VRE. Patients with recent vancomycin use or recent hospitalization are especially at risk. More importantly, VRE colonization in this patient population is associated with a considerable increase in the risk of VRE BSIs. In light of the above findings, re-evaluation of the use of vancomycin as empiric therapy in this population should be considered, and adherence to antimicrobial stewardship is warranted to diminish further VRE dissemination. Furthermore, this colonization rate and the associated significantly increased BSI risk should be taken into account when evaluating screening programs and infection control measures in this patient population.

Supplementary Data

Supplementary material is available at *Open Forum Infectious Diseases* online.

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Author contributions. Only the named authors participated in gathering the data and writing of the manuscript. M. A. and E. M. accept full responsibility for the conduct of the study, have access to the data, and have control of the decision to publish. M. A. had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. M. A. conceptualized and designed the study, participated in data collection, extraction and interpretation, performed the statistical analysis, prepared tables and figures, wrote and drafted the initial manuscript, drafted and approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. A. G. designed the study, participated in data collection, extraction and interpretation, prepared tables, wrote and drafted the initial manuscript, drafted and approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. D. N. designed the study, performed the statistical analysis, prepared figures, drafted and approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. K. T. designed the study, participated in data collection, extraction and interpretation, drafted and approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. M. E. F. designed the study, participated in data interpretation, drafted and approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. E. M. conceptualized and designed the study, interpreted the data, drafted, reviewed and approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Humphreys H. Controlling the spread of vancomycin-resistant enterococci. Is active screening worthwhile? *J Hosp Infect* **2014**; 88:191–8.
2. Uttley AH, Collins CH, Naidoo J, George RC. Vancomycin-resistant enterococci. *Lancet* **1988**; 1:57–8.
3. Ramsey AM, Zilberberg MD. Secular trends of hospitalization with vancomycin-resistant *Enterococcus* infection in the United States, 2000–2006. *Infect Control Hosp Epidemiol* **2009**; 30:184–6.
4. Zilberberg MD, Shorr AF, Kollef MH. Growth and geographic variation in hospitalizations with resistant infections, United States, 2000–2005. *Emerg Infect Dis* **2008**; 14:1756–8.
5. Centers for Disease Control and Prevention. Biggest Threats. Available at: http://www.cdc.gov/drugresistance/biggest_threats.html. Accessed 1 September 2016.
6. Salgado CD. The risk of developing a vancomycin-resistant *Enterococcus* bloodstream infection for colonized patients. *Am J Infect Control* **2008**; 36:S175.e5–8.
7. Chavers LS, Moser SA, Benjamin WH, et al. Vancomycin-resistant enterococci: 15 years and counting. *J Hosp Infect* **2003**; 53:159–71.
8. 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.
9. Vydra J, Shanley RM, George I, et al. Enterococcal bacteremia is associated with increased risk of mortality in recipients of allogeneic hematopoietic stem cell transplantation. *Clin Infect Dis* **2012**; 55:764–70.
10. Tavazde M, Rybicki L, Mossad S, et al. Risk factors for vancomycin-resistant *Enterococcus* bacteremia and its influence on survival after allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant* **2014**; 49:1310–6.
11. Zirakzadeh A, Patel R. Vancomycin-resistant enterococci: colonization, infection, detection, and treatment. *Mayo Clin Proc* **2006**; 81:529–36.
12. Peel T, Cheng AC, Spelman T, et al. Differing risk factors for vancomycin-resistant and vancomycin-sensitive enterococcal bacteraemia. *Clin Microbiol Infect* **2012**; 18:388–94.
13. Yoo JH, Lee DG, Choi SM, et al. Vancomycin-resistant enterococcal bacteremia in a hematology unit: molecular epidemiology and analysis of clinical course. *J Korean Med Sci* **2005**; 20:169–76.
14. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* **2015**; 162:777–84.
15. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2000. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 1 September 2016.
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* **1986**; 7:177–88.
17. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health* **2014**; 72:39.
18. Rucker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I in assessing heterogeneity may mislead. *BMC Med Res Methodol* **2008**; 8:79.
19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* **1997**; 315:629–34.
20. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med* **2002**; 21:1559–73.
21. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med* **2001**; 20:2865–84.
22. 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.
23. Ford CD, Lopansri BK, Gazdik MA, et al. The clinical impact of vancomycin-resistant *Enterococcus* colonization and bloodstream infection in patients undergoing autologous transplantation. *Transpl Infect Dis* **2015**; 17:688–94.
24. Taur Y, Xavier JB, Lipuma L, et al. Intestinal domination and the risk of bacteremia in patients undergoing allogeneic hematopoietic stem cell transplantation. *Clin Infect Dis* **2012**; 55:905–14.
25. Kamboj M, Chung D, Seo SK, et al. The changing epidemiology of vancomycin-resistant *Enterococcus* (VRE) bacteremia in allogeneic hematopoietic stem cell transplant (HSCT) recipients. *Biol Blood Marrow Transplant* **2010**; 16:1576–81.
26. Calderwood MS, Mauer A, Tolentino J, et al. Epidemiology of vancomycin-resistant enterococci among patients on an adult stem cell transplant unit: observations from an active surveillance program. *Infect Control Hosp Epidemiol* **2008**; 29:1019–25.

27. 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.
28. Matar MJ, Tarrand J, Raad I, Rolston KV. Colonization and infection with vancomycin-resistant *Enterococcus* among patients with cancer. *Am J Infect Control* **2006**; 34:534–6.
29. Tsiatis AC, Manes B, Calder C, et al. Incidence and clinical complications of vancomycin-resistant *Enterococcus* in pediatric stem cell transplant patients. *Bone Marrow Transplant* **2004**; 33:937–41.
30. 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.
31. Shaikh ZH, Osting CA, Hanna HA, et al. Effectiveness of a multifaceted infection control policy in reducing vancomycin usage and vancomycin-resistant enterococci at a tertiary care cancer centre. *J Hosp Infect* **2002**; 51:52–8.
32. Henning KJ, Delencastre H, Eagan J, et al. Vancomycin-resistant *Enterococcus faecium* on a pediatric oncology ward: duration of stool shedding and incidence of clinical infection. *Pediatr Infect Dis J* **1996**; 15:848–54.
33. Embil JM, Kabani A, Zhanel G, Nicolle LE. Low prevalence of gastrointestinal colonization with antimicrobial-resistant bacteria in high risk units in a Canadian tertiary care centre. *Can J Infect Dis* **1996**; 7:307–12.
34. Montecalvo MA, de Lencastre H, Carraher M, et al. Natural history of colonization with vancomycin-resistant *Enterococcus faecium*. *Infect Control Hosp Epidemiol* **1995**; 16:680–5.
35. Rubin LG, Tucci V, Cercenado E, et al. Vancomycin-resistant *Enterococcus faecium* in hospitalized children. *Infect Control Hosp Epidemiol* **1992**; 13:700–5.
36. Levitt LA, Yacoub AT, Khwaja SI, et al. Daptomycin prevention of vancomycin-resistant *Enterococcus* bacteremia in colonized patients with acute myelogenous leukemia. *Infect Dis Clin Pract (Baltim Md)* **2014**; 22:89–91.
37. Song X, Toal D, Walker T, et al. Multidrug-resistant organism colonization in a high-risk pediatric patient population. *Infect Control Hosp Epidemiol* **2016**; 37:614–6.
38. Zirakzadeh A, Gastineau DA, Mandrekar JN, et al. Vancomycin-resistant enterococcal colonization appears associated with increased mortality among allogeneic hematopoietic stem cell transplant recipients. *Bone Marrow Transplant* **2008**; 41:385–92.
39. Gedik H, Şimşek F, Kantürk A, et al. Vancomycin-resistant enterococci colonization in patients with hematological malignancies: screening and its cost-effectiveness. *Afr Health Sci* **2014**; 14:899–905.
40. Thacker N, Pereira N, Banavali SD, et al. Alarming prevalence of community-acquired multidrug-resistant organisms colonization in children with cancer and implications for therapy: A prospective study. *Indian J Cancer* **2014**; 51:442–6.