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Evaluation of Vancomycin-Resistant Enterococcus Isolates in Pediatric Clinic: An Experience From A Teaching and Research Hospital

Pediyatri Kliniğinde Vankomisine Dirençli Enterokok İzolatlarının Değerlendirilmesi: Bir Eğitim ve Araştırma Hastanesi Deneyimi

Sibel Tuğçe Aygün[1](İD), Emre Aygün[1](İD), Çiğdem Arabacı[2](İD), Adem Karbuz[3](İD)

[1] *Clinic of Pediatric Health and Diseases, Okmeydanı Training and Research Hospital, İstanbul, Türkiye*
[2] *Clinic of Medical Microbiology, Okmeydanı Training and Research Hospital, İstanbul, Türkiye*
[3] *Clinic of Pediatric Infectious Diseases, Okmeydanı Training and Research Hospital, İstanbul, Türkiye*

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Abstract

Objective: Infections due to vancomycin-resistant enterococci (VRE) have recently raised concern as an important ailment especially amongst children. This study aimed to evaluate the clinical characteristics and risk factors of cases with VRE isolation in our hospital›s pediatric clinic.

Material and Methods: We retrospectively analyzed patients under 18 years of age with VRE isolation in our hospital's pediatric clinic between January 2014 and June 2022. Patients' demographic characteristics, admission diagnoses, risk factors, antibiotic use history, clinical courses, and laboratory findings were evaluated.

Results: Of the 103 patients included in the study, 54.4% were male, with a mean age of 14.29 ± 34.41 months. Of the patients, 61.2% were treated in the pediatric intensive care unit, while 20.4% were in the neonatal intensive care unit. The most common admission diagnoses were respiratory failure (30.2%), sepsis (13.0%), and congenital heart disease (9.5%). Among the risk factors, total parenteral nutrition (27.2%), catheter presence (22.3%), and tracheostomy (10.7%) were prominent. Of the patients, 86.4% had a history of antibiotic use during hospitalization. Of the isolated strains, 97.1% were identified as *Enterococcus faecium*. Of the isolates, 95.15% were evaluated as colonization and 4.85% as infection. Mortality rate was determined to be 8.8%.

Conclusion: VRE colonization is more frequently observed in intensive care patients and those with prolonged hospitalization. The classification of risk factors followed by the proper infection control measures is

Öz

Giriş: Vankomisine dirençli enterokoklara (VRE) bağlı enfeksiyonlar son zamanlarda özellikle çocuklar arasında önemli bir hastalık olarak endişe yaratmaktadır. Bu çalışma, hastanemizin pediyatri kliniğinde VRE izolasyonu olan vakaların klinik özelliklerini ve risk faktörlerini değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Ocak 2014 ile Haziran 2022 arasında hastanemizin pediyatri kliniğinde VRE izolasyonu yapılan 18 yaş altı hastaları geriye dönük olarak inceledik. Hastaların demografik özellikleri, kabul tanıları, risk faktörleri, antibiyotik kullanım öyküsü, klinik seyirleri ve laboratuvar bulguları değerlendirildi.

Bulgular: Çalışmaya dahil edilen 103 hastanın %54.4'ü erkekti ve ortalama yaş 14.29 ± 34.41 aydı. Hastaların %61.2'si pediyatrik yoğun bakım ünitesinde, %20.4'ü ise neonatal yoğun bakım ünitesinde tedavi edilmiştir. En yaygın kabul tanıları solunum yetmezliği (%30.2), sepsis (%13.0) ve konjenital kalp hastalığı (%9.5) idi. Risk faktörleri arasında toplam parenteral beslenme (%27.2), kateter varlığı (%22.3) ve trakeostomi (%10.7) öne çıkmıştır. Hastaların %86.4'ünün hastanede yattıkları süre boyunca antibiyotik kullanım öyküsü vardı. İzole edilen suşların %97.1'i *Enterococcus faecium* olarak tanımlandı. İzolatların %95.15'i kolonizasyon, %4.85'i ise enfeksiyon olarak değerlendirilmiştir. Mortalite oranı %8.8 olarak belirlenmiştir.

Sonuç: Vankomisine dirençli enterokoklar kolonizasyonu, yoğun bakım hastalarında ve uzun süre hastanede yatan hastalarda daha sık

Correspondence Address/Yazışma Adresi

Sibel Tuğçe Aygün

Clinic of Pediatric Health and Diseases,
Okmeydanı Training and Research Hospital
İstanbul, Türkiye

E-mail: sibeltugceaygun@gmail.com

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important in the prevention of hospital acquired infections which are VRE associated.

Keywords: Vancomycin-resistant enterococcus, pediatric infections, antibiotic resistance, intensive care

görülmektedir. Risk faktörlerinin sınıflandırılması ve ardından uygun enfeksiyon kontrol önlemlerinin alınması, VRE ile ilişkili hastane kaynaklı enfeksiyonların önlenmesinde önemlidir.

Anahtar Kelimeler: Vankomisine dirençli enterokok, pediyatrik enfeksiyonlar, antibiyotik direnci, yoğun bakım

Introduction

Enterococci are resilient, gram-positiv cocci that commonly inhabit the gastrointestinal tracts of virtually all terrestrial animals, including humans. While they are natural members of the microbiota, they can cause serious opportunistic infections, particularly in hospitalized patients treated with broad-spectrum antibiotics who experience disrupted intestinal microbiota. Although enterococci have been recognized as human pathogens for over a century, they have gained prominence in recent years as leading causes of healthcare-associated infections.

Enterococci, which are facultative anaerobic gram-positive cocci, can cause various infections despite typically being commensal organisms in the human gastrointestinal system (1). Vancomycin-resistant enterococci (VRE) exist within the normal flora of humans and animals but can be responsible for severe infections. Of the 19 identified enterococcal species, two are particularly pathogenic to humans: *Enterococcus faecalis* accounts for 80-90% of infections, while *Enterococcus faecium* is responsible for 5-15%. Enterococci represent the third most common cause of community-acquired urinary tract infections and the second most frequent cause of hospital-acquired urinary tract infections. They also cause intra-abdominal and pelvic infections, sepsis, surgical site infections, bacteremia, endocarditis, and meningitis (2). In hospitalized children, enterococcal infections remain a significant cause of morbidity and mortality.

The ability of enterococci to acquire antibiotic resistance makes the treatment of ear infections more problematic (3). It is becoming an increasingly common concern for clinicians to deal with antimicrobial resistance which in the case of VRE, is most difficult. The situation is further complicated when patients diagnosed with enterococcal infections are children, making management harder and in most cases increasing the duration of their hospitalization. Enterococci represent the third most prevalent type of hospital pathogen in the United States. While VRE prevalence in Europe remains lower than in the United States, it continues to rise steadily (4,5). A comprehensive meta-analysis from Türkiye revealed a significant rise in vancomycin-resistant *Enterococcus* spp., with resistance rates increasing to 6.5% during 2012-2016, highlighting a growing trend since initial reports of 0% in 2004 (6).

There is a lack of literature that focuses on demographic characteristics, patterns of colonization and infection, and risk factors of being VRE positive among the pediatric population. This study aimed to explore the frequency with which VRE is detected, the demographic attributes of the patients, the relationship between the length of hospital stay and VRE positivity, sites of isolation, VRE positivity risk factors, history of antibiotic therapy in the last three months, need for treatment, treatment response when given, relationship between VRE and prognosis, and the effect of the COVID-19 pandemic on the proportion of VRE-positive children being treated at our hospital's clinic of pediatric health and diseases between January 2014 to June 2022.

Materials and Methods

This research was designed as a retrospective, cross-sectional, and descriptive study. Ethics approval was obtained from the Ethics Committee with decision number E-48670771-514.99 dated July 04, 2022. The study encompassed patients who were hospitalized in the Pediatric Health and Diseases Clinic of our hospital between January 2014 and June 2022 and were found positive for VRE. The research population included all eligible patients admitted to the clinic during this period, without employing any specific sampling method.

Depending on age and clinical context, urine samples were obtained via suprapubic aspiration in neonates, and through transurethral catheterization in infants and children. These standardized sampling methods were applied to minimize contamination risk and ensure diagnostic accuracy.

Inclusion criteria comprised patients under 18 years of age, hospitalization during the specified period, detection of VRE positivity primarily in rectal swab samples and other sites, and accessibility of patient file data. Conversely, patients aged 18 years and above, those with vancomycin-sensitive enterococcal growth, and cases with inaccessible patient files were excluded from the study.

Data were retrospectively collected from the hospital's electronic data system (Panates) and Infection Control Committee records. For each patient, demographic information such as age, sex, and admission date was recorded, along with clinical data including primary admission diagnosis, underlying conditions, risk factors, length of stay, and treatment unit. Microbiological data encompassed VRE detection time, isolated species, colonization or infection status, and information regarding treatment and prognosis. Additionally, patients' antibiotic use history, necessity for linezolid treatment, VRE negativization status, and clinical outcomes were evaluated in detail.

SPSS 22.0 (IBM Corp., Armonk, NY, USA) statistical analysis software was utilized for data analysis. Descriptive statistics included frequencies and percentages for categorical variables and means and standard deviations for continuous variables. Kolmogorov-Smirnov test assessed normality distribution, with parametric tests applied for normally distributed variables and non-parametric tests for non-normally distributed variables. Statistical significance was set at $p< 0.05$.

The study was conducted in accordance with the Declaration of Helsinki principles, and patient data were processed anonymously to maintain confidentiality. Due to the retrospective nature of the study, individual patient consent was not required. Considering similar studies in the literature, this detailed methodological approach aims to enhance the scientific validity and comparability of the study.

Results

A notable increasing trend was observed in the annual distribution of VRE infections in the pediatric clinic. A significant spike in cases was recorded particularly in 2021, accounting for 37.9% of all cases. Seasonal analysis revealed the highest case rate in spring months (32.0%), followed by autumn (26.2%) and winter (22.3%), with summer showing a relatively lower rate (19.4%). These data suggest the need for strengthened infection control measures, particularly during periods of increased case density (Figure 1).

Analysis of age and length of stay revealed that the mean age of patients was 14.29 ± 34.41 months, and the mean length of hospitalization was 35.40 ± 61.26 days. Analysis of treatment units showed VRE cases were distributed as follows: 61.2% in the pediatric intensive care unit (PICU), 20.4% in the neonatal intensive care unit (NICU), and 18.4% in the pediatric ward. Regarding previous hospitalization history, 69.9% of patients had prior hospital admissions, with 35.9% having one previous admission and 34.0% having multiple admissions. Most previous hospitalizations occurred in the NICU (49.0%) (Table 1).

In the assessment of risk factors and clinical characteristics, 38.8% of the patients presented with at least one risk factor. The most prevalent risk factors included total parenteral nutrition (TPN) (27.2%), catheter presence (22.3%), and tracheostomy (10.7%). Since patients often had more than one risk factor simultaneously, the percentages listed for individual factors may exceed the overall proportion of patients with any risk factor. Similarly, 57.3% of patients had underlying comorbidities, with neurogenic diseases (29.6%) and congenital heart diseases (9.3%) being predominant. Multiple comorbidities were present in several patients, leading to cumulative percentages above 100% (Table 2).

A detailed examination of antibiotic usage profiles revealed a high rate of antibiotic administration during hospitalization (86.4%). In the preceding three months, 54% of the patients had received antibiotics, 34.3% had not, and

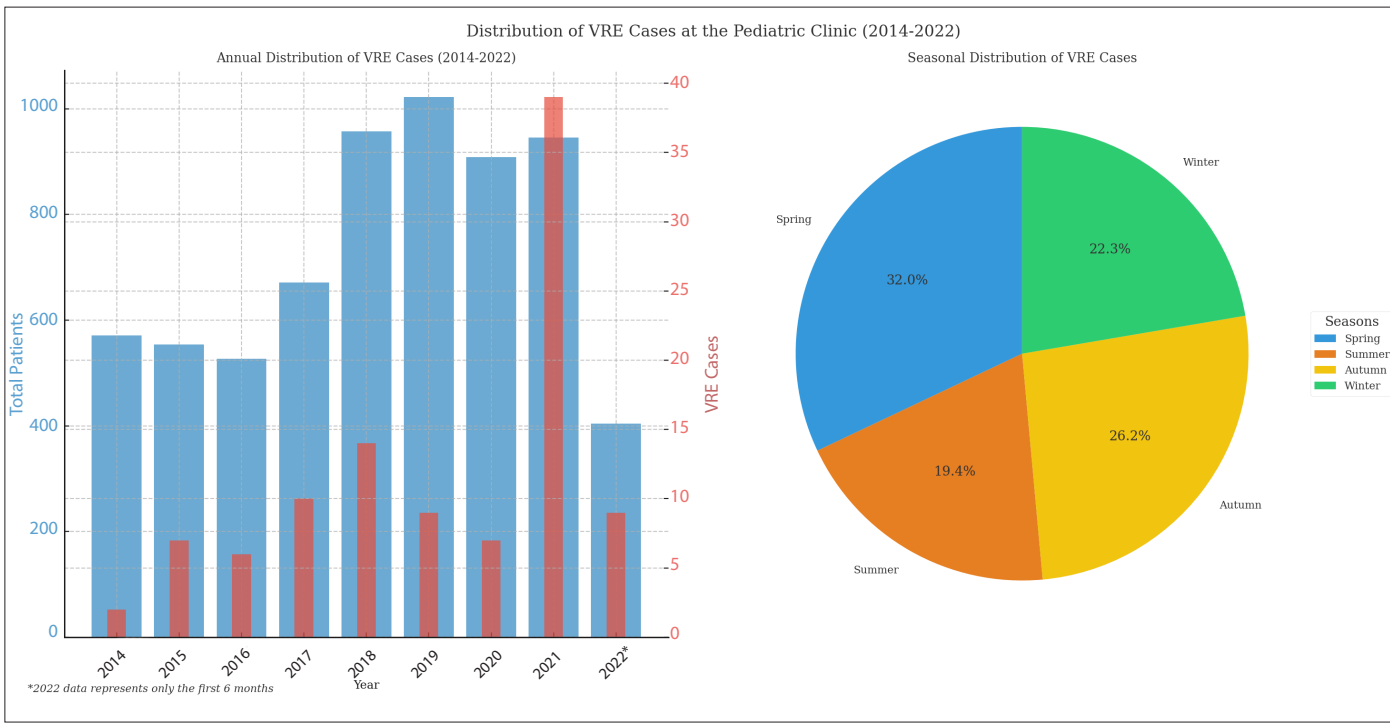

Figure 1. Distribution of VRE cases at the pediatric clinic (2014-2022).

Table 1. Temporal characteristics and patient admission status (n= 103)

Characteristic	n (%) or mean ± SD	Test Statistic	p
Age (months)	14.29 ± 34.41	-	-
Length of stay (days)	35.40 ± 61.26	-	-
Unit of admission		χ^2= 34.786	<0.001
PICU	63 (61.2)		
NICU	21 (20.4)		
Pediatric ward	19 (18.4)		
Seasonal distribution		F= 3.86†	0.023
Spring	33 (32.0)		
Summer	20 (19.4)		
Autumn	27 (26.2)		
Winter	23 (22.3)		
Previous admission history		χ^2= 16.243	<0.001
No admission history	31 (30.1)		
With admission history	72 (69.9)		
Single admission	37 (35.9)		
Multiple admissions	35 (34.0)		
Previous admission location‡		χ^2= 42.157	<0.001
Ward	27 (26.0)		
NICU	51 (49.0)		
PICU	13 (12.5)		
Surgical Ward	13 (12.5)		

†Cosinor analysis F-value, ‡Some patients have a history of admission to multiple units.
SD: Standard deviation, PICU: Pediatric intensive care unit, NICU: Neonatal intensive care unit.

Table 2. Clinical characteristics and risk factors (n= 103)

Characteristic	n (%)	Test Statistic	p	OR (95% CI)†
Risk factors				
No risk factor	63 (61.2)	χ^2= 5.282	0.022	1.0 (Baseline)
With risk factor (n= 40)	40 (38.8)			
Catheter	23 (22.3)	χ^2= 8.746	0.003	2.84 (1.42-5.68)
Immunodeficiency	8 (7.8)	χ^2= 4.235	0.040	1.96 (1.03-3.74)
VP shunt	9 (8.7)	χ^2= 3.892	0.048	1.78 (0.98-3.22)
Tracheostomy	11 (10.7)	χ^2= 5.167	0.023	2.12 (1.15-3.91)
TPN	28 (27.2)	χ^2= 7.453	0.006	2.46 (1.32-4.58)
Antibiotic use (last three months)	89 (86.4)	χ^2= 8.924	0.003	2.98 (1.56-5.72)
Comorbidities				
No comorbidity	44 (42.7)	χ^2= 4.893	0.027	1.0 (Baseline)
With comorbidity (n= 59)	59 (57.3)			
Hematologic disease	3 (2.8)	χ^2= 3.241	0.072	1.54 (0.82-2.89)
Neurologic disease	32 (29.6)	χ^2= 9.867	0.002	2.93 (1.58-5.44)
Gastrointestinal disease	3 (2.8)	χ^2= 3.156	0.076	1.48 (0.78-2.82)
CHD	10 (9.3)	χ^2= 4.782	0.029	1.92 (1.07-3.45)
Renal disease	4 (3.7)	χ^2= 3.567	0.059	1.67 (0.89-3.12)
Malignancy	4 (3.7)	χ^2= 3.892	0.049	1.82 (1.01-3.28)
Other	3 (2.8)	χ^2= 3.211	0.074	1.49 (0.81-2.85)

†Patients could present with more than one risk factor or comorbidity; therefore, the sum of percentages exceeds 100%.
OR: Odds Ratio, CI: Confidence interval, VP: Ventriculoperitoneal, TPN: Total parenteral nutrition, CHD: Congenital heart disease.

Table 3. Antibiotic usage (n= 89)

Antibiotic	During Admission n (%)	Last 3 Months n (%)	Test Statistic†	p	OR (95% CI)‡
Usage status					
No antibiotics	14 (13.6)	47 (34.3)	χ^2= 12.867	<0.001	1.0 (Baseline)
Antibiotics used	89 (86.4)	40 (54.0)	χ^2= 15.234	<0.001	2.86 (1.64-4.98)
Unknown	-	16 (11.7)	-	-	-
Antibiotics used	**(n= 89)**	**(n= 40)**			
Penicillin group	59 (66.3)	29 (72.5)	χ^2= 8.932	0.003	2.34 (1.42-3.86)
Cephalosporin group	55 (61.7)	14 (35)	χ^2= 10.467	0.001	2.58 (1.54-4.32)
Carbapenem group	26 (29.2)	4 (10)	χ^2= 7.893	0.005	2.12 (1.28-3.52)
Oxazolidinones	4 (4.5)	-	-	-	-
AG	27 (30.3)	16 (40)	χ^2= 3.245	0.072	1.46 (0.88-2.42)
Macrolide group	19 (21.3)	3 (7.5)	χ^2= 5.678	0.017	1.92 (1.14-3.24)
Nitroimidazoles	4 (4.5)	-	-	-	-
GP	35 (39.3)	7 (17.5)	χ^2= 8.234	0.004	2.28 (1.36-3.82)
Quinolone group	7 (7.9)	1 (2.5)	χ^2= 3.892	0.049	1.76 (1.01-3.06)
Sulfonamide group	2 (2.2)	-	-	-	-
PMB	4 (4.5)	-	-	-	-

Percentages may exceed 100% because some patients received more than one class of antibiotics during hospitalization or in the last three months.
‡McNemar's test and chi-square test were used.
OR: Odds Ratio, CI: Confidence interval, AG: Aminoglycosides, GP: Glycopeptides, PMB: Polymyxin B.

11.7% had unknown usage status. Among antibiotic classes, penicillins were most frequently used (66.3% of antibiotic-exposed patients), followed by cephalosporins (61.7%) and glycopeptides (39.3%). Aminoglycosides, carbapenems, and macrolides were used at rates of 30.3%, 29.2%, and 21.3%, respectively. Less frequently used antibiotics included quinolones (7.9%), oxazolidinones (4.5%), nitroimidazoles (4.5%), polymyxin B (4.5%), and sulfonamides (2.2%). Since several patients received more than one antibiotic class simultaneously or sequentially, percentages exceeded 100% and represent overlapping exposures. Statistical analysis showed that broad-spectrum antibiotic use was significantly associated with increased risk of VRE colonization (Table 3).

Microbial and clinical characteristics analysis of VRE strains showed *E. faecium* predominance (97.1%), with *E. faecalis* detected at a considerably lower rate (2.9%). Rectal swabs showed positivity in all patients (100%), while additional positive cultures were found in urine (15.5%), blood (1.0%), and both blood and catheter cultures (1.0%). Clinically, vast majority of the cases (95.1%) were classified as colonization, with only 4.9% (five patients) developing confirmed infections. Among these, two had urinary tract infections confirmed by urine culture, one had bloodstream infection with a positive blood culture, and one had both blood and catheter culture positivity. An additional patient received linezolid empirically for clinical sepsis during PICU admission, despite having no positive microbiologic cultures; this patient was classified as colonized with empirical treatment.

Linezolid was administered to five patients (4.9%); four of these were treated for microbiologically confirmed infections (urinary tract or bloodstream), and one for clinical suspicion without culture positivity. The overall mortality rate was 8.8% (nine patients), with 33.3% directly attributed to VRE infection, 44.4% associated with multiple contributing factors including VRE, and 22.2% due to non-VRE causes. Among the deceased patients, septicemia and acute respiratory failure were equally prevalent (44.4% each), while multi-organ failure accounted for 11.2%. Regarding VRE clearance status, 54.4% achieved documented decolonization, 8.7% could not be assessed due to in-hospital death, and 36.9% were lost to follow-up (Table 4).

A subgroup analysis comparing colonized (n= 98) and infected (n= 5) VRE-positive patients was performed to assess differences in demographic and clinical characteristics. Infected patients had higher rates of PICU admission (80.0% vs. 59.2%), TPN use (60.0% vs. 25.5%), central venous catheter presence (80.0% vs. 20.4%), and tracheostomy (40.0% vs. 9.2%). Moreover, congenital heart disease and mortality were significantly more common in the infected group. Statistically significant differences were observed particularly for central catheter presence (p= 0.003) and mortality (p= 0.001). These findings are summarized in Table 5.

Table 4. VRE characteristics and clinical outcomes (n= 103)

Characteristic	n (%)	Test Statistic	p	OR (95% CI)†
VRE species				
E. faecium	100 (97.1)	χ^2= 89.456	<0.001	32.4 (10.2-102.8)
E. faecalis	3 (2.9)			1.0 (Baseline)
Isolation and growth sites				
Rectal swab	103 (100.0)	-	-	-
Urine	16 (15.5)	χ^2= 6.782	0.009	2.34 (1.28-4.26)
Blood	1 (1.0)	Fisher exact	0.214	1.86 (0.76-4.52)
Blood and catheter	1 (1.0)	Fisher exact	0.214	1.86 (0.76-4.52)
Clinical status and infections				
Colonization	98 (95.15)	χ^2= 82.345	<0.001	1.0 (Baseline)
Infection	5 (4.85)			3.86 (1.92-7.74)
UTI	2 (1.94)	Fisher exact	0.048	2.46 (1.24-4.88)
Bloodstream infection (blood culture)	1 (0.97)	Fisher exact	0.214	1.86 (0.76-4.52)
Bloodstream + catheter culture	1 (0.97)	Fisher exact	0.214	1.86 (0.76-4.52)
Clinical sepsis without positive cultures (linezolid use, treated empirically)	1 (0.97)	Fisher exact	0.214	1.86 (0.76-4.52)
Treatment and outcomes				
Linezolid treatment				
Treated	5 (4.85)	Fisher exact	0.042	2.34 (1.28-4.28)
Treated for confirmed infection	4 (3.9%)	Fisher exact	0.045	2.52 (1.26-5.04)
Treated for colonization with clinical suspicion	1 (0.97)	Fisher exact	0.214	1.86 (0.76-4.52)
VRE status in deceased patients				
Associated with VRE infection	3 (33.3)	Fisher exact	0.042	2.34 (1.28-4.28)
Co-occurrence with other factors	4 (44.4)			3.24 (1.76-5.96)
Non-VRE-related causes	2 (22.2)			2.86 (1.42-5.76)
Causes of death				
Septicemia	4 (44.4)			3.24 (1.76-5.96)
Acute respiratory failure	4 (44.4)			3.24 (1.76-5.96)
Multiorgan failure	1 (11.2)			2.86 (1.42-5.76)
VRE clearance				
Cleared	56 (54.4)	χ^2= 18.234	<0.001	1.0 (Baseline)
Not assessed due to death	9 (8.7)			2.86 (1.54-5.32)
Lost to follow-up	38 (36.9)			1.92 (1.14-3.24)

One patient who received linezolid treatment had no microbiologic confirmation of infection (no growth in blood, urine, or catheter cultures) and was treated empirically for clinical sepsis. This patient was classified as colonized rather than infected.

†OR: Odds Ratio, CI: Confidence interval, VRE: Vancomycin-resistant enterococcus, UTI: Urinary tract infection.

Discussion

The purpose of this study was to examine the clinical characteristics, risk factors, and prognostic features of vancomycin-resistant enterococcal colonization and infections in the patients of our hospital's pediatric clinic for more than eight years. We comprehensively examined the demographic characteristics, clinical courses, and treatment responses of included pediatric patients. Interesting correlations emerged between the colonization of VRE more evident among intensive care unit patients and different risk factors as well as conversion rates of the infections. The increase in cases during the pandemic period, antibiotic usage patterns, and the impact of underlying diseases on VRE colonization were among significant results. Our data reaffirms the importance

Table 5. Comparison between colonized and infected VRE-positive patients (n= 103)

Characteristic	Colonized (n= 98)	Infected (n= 5)	Test Statistic	p/OR (95% CI)†
Mean age (months)	13.9 ± 34.0	18.2 ± 36.7	t= 0.378	p= 0.707
Length of stay (days)	33.1 ± 60.4	62.4 ± 68.5	t= 1.205	p= 0.232
PICU admission	58 (59.2%)	4 (80.0%)	χ^2= 0.939	p= 0.333
TPN use	25 (25.5%)	3 (60.0%)	χ^2= 2.846	p= 0.092
Central catheter	20 (20.4%)	4 (80.0%)	χ^2= 8.571	p= 0.003/4.44 (1.21-16.25)
Tracheostomy	9 (9.2%)	2 (40.0%)	χ^2= 5.167	p= 0.023/2.12 (1.15-3.91)
Neurologic disease	28 (28.6%)	2 (40.0%)	χ^2= 0.321	p= 0.571
CHD	8 (8.2%)	2 (40.0%)	χ^2= 6.231	p= 0.013/3.42 (1.18-9.97)
Broad-spectrum antibiotics	82 (83.7%)	5 (100.0%)	-	-
Mortality	6 (6.1%)	3 (60.0%)	χ^2= 11.476	p= 0.001/5.67 (1.74-18.49)

†OR: Odds Ratio, CI: Confidence interval, PICU: Pediatric intensive care unit, TPN: Total parenteral nutrition, CHD: Congenital heart disease.

of VRE surveillance in hospital infection control while emphasizing the necessity of early identification of risk factors and implementation of appropriate measures.

In our research, we observed a balanced sex distribution (54.4% male, 45.6% female). This result supports previous findings that sex typically has no significant effect on VRE colonization and infection in pediatric patients (7,8). The mean age of 14.29 months emphasizes the potential increased risk of infection during critical periods. Previous studies have shown that children in this age group are more susceptible to infections due to their immature immune systems (7).

The notable increase observed in 2021 (37.9%) suggests that the COVID-19 pandemic's effects on infection control measures may have led to fluctuations in VRE rates (9). Increased antibiotic use during the pandemic period, access to broad-spectrum antibiotics, and changes in hospital density are cited as potential contributing factors (10,11). Particularly, increased patient density in intensive care units and stricter or inadequate implementation of infection control protocols may increase VRE colonization rates (8,12).

In the literature, the pandemic's impacts on infection control measures and antibiotic use have been frequently emphasized. For instance, the use of broad-spectrum antibiotics, particularly "watch" and "reserve" class drugs, has been reported to increase colonization risk of resistant microorganisms (13). Additionally, hospital density and patient transfers are noted as significant factors in the spread of resistant bacteria like VRE (14,15). In this context, the importance of strict implementation of infection control measures, especially in critical age groups, is once again highlighted.

Finally, strategic interventions such hygienic methods and appropriate antibiotic usage can help to lessen the two phenomena of colonization and infection rates (7). Consistency in implementing infection control measures during the pandemic period is crucial for preventing future VRE fluctuations (9).

Our study found VRE colonization rates of 61.2% in the PICU and 20.4% in the NICU. These high rates in intensive care units are in parallel to literature findings indicating that prolonged antibiotic use, mechanical ventilation requirements, and previous hospitalizations increase colonization risk (10,12). Seasonal factors' impact on VRE colonization has been associated with fluctuations in infection control measures and hospital density in the literature. However, the effect of seasonal changes on VRE rates requires further research (10). The high rate of previous hospitalization history (69.9%) aligns with previous study findings. The literature repeatedly emphasizes that previous hospitalizations and transfers are significant risk factors for the spread of resistant bacteria like VRE (10,12). These results emphasize the need to strengthen infection control strategies by focusing on factors such as transferred patient management and hospital density.

Our study identified risk factors associated with VRE colonization as TPN use (27.2%), intravascular catheter presence (22.3%), neurogenic diseases (29.6%), and congenital heart diseases (9.3%). The literature indicates that TPN use and long-term catheterization significantly increase infection risk (16). The effect of neurogenic diseases on VRE colonization is also supported in literature (17). Additionally, congenital heart diseases are noted to increase infection risk, particularly in the first six months post-surgery (18,19). Such data suggestion that the strategy for preventing VRE infections should stress on the minimization of the TPN use, improvement of catheter care standards, and strengthening surveillance of at-risk categories of patients.

The problems associated with VRE colonization at the time of admission were recorded in VRE colonized subjects were respiratory failure at 30.2%, sepsis 13.0%, and congenital heart

disease 9.5%. The literature reports these diagnoses among the primary factors increasing infection risk (15). A study by Wang and Xia has indicated that mechanical ventilation duration and invasive procedures in pediatric intensive care units are significant risk factors for VRE infections (15). Sepsis has been identified as a crucial factor that may increase VRE colonization following systemic spread of infection (15). Abera et al. have demonstrated that prolonged hospitalization history and invasive interventions increase VRE risk in pediatric patients (14). Children with congenital heart disease, particularly in the post-surgical period, have been reported to be more susceptible to infective endocarditis and VRE colonization. This suggests that infection control strategies should focus more intensively on this high-risk group (18,19). These findings emphasize the need to optimize infection control programs and enhance preventive measures, particularly in managing pediatric intensive care patients undergoing invasive procedures.

Our study identified a high rate of antibiotic use during hospitalization (86.4%), with penicillins (24.4%) and cephalosporins (22.7%) being the most frequently used antibiotics, and an antibiotic use rate of 54.0% in the previous three months. The literature reports that broad-spectrum antibiotics and prolonged use increase the risk of colonization by resistant bacteria such as VRE (13). For instance, Sulis et al. have demonstrated that broad-spectrum antibiotics, particularly the "watch" and "reserve" groups in the AWaRe classification, have a stronger association with multi-resistant organism colonization (13). The rate of antibiotic use in the previous three months is supported by literature indicating that exposure to broad-spectrum antibiotics in pediatric patients contributes to resistance development. Verma et al. have noted that antibiotic use plays a significant role in resistant microorganism colonization among pediatric liver transplant patients (11). Increasing levels of bacteria with resistance mechanisms are reported as a consequence of the use of penicillins and cephalosporins. Nikmanesh et al. have stated that antibiotic resistance is common among enterococcal species, and excessive use of beta-lactam antibiotics such as cephalosporins in pediatric patients may increase VRE rates (20). These findings emphasize the necessity of optimizing antibiotic use and developing strategies to prevent resistant organisms. Raising education and awareness of antimicrobial drugs as well as their appropriate prescription of antibiotics is important in controls resistance development.

In our study, we observed that *E. faecium* was the dominant species in pediatric VRE cases (97.1%), with a urine culture growth rate of 15.5%, colonization being far more prevalent (95.15%) than infection, and a mortality rate of 8.8%. Literature indicates that *E. faecium*, particularly vancomycin-resistant strains, is associated with higher mortality rates and is more aggressive compared to *E. faecalis* (21). The distinction between colonization and infection plays a crucial role in infection diagnosis. Karandikar et al. emphasized that mortality associated with VRE infections in pediatric cancer patients was higher compared to colonized carriers (22). The VRE clinical management protocols should incorporate more effective epidemiologic containment measures and therapeutical strategies against infections caused by this pathogen, considering the current high mortality indexes in patients and form of *E. faecium*. Shirvani et al. associated the increase in resistant Enterococcus species in intensive care patients with hospital stay duration and antibiotic resistance (23).

Among the 103 patients with VRE in our study, infection developed in 5 (4.85%). The distribution of these infections revealed urinary tract infection in 2 (1.94%) patients, catheter-related bloodstream infection in 2 (1.94%) patients, and bacteremia in 1 (0.97%) patient. Linezolid treatment was administered to five patients: four with microbiologically confirmed infections (two urinary tract infections and two bloodstream infections), and one patient who received empirical treatment for clinical sepsis despite having no microbiologic confirmation. This case was classified as colonized with empirical therapy. Examining the microorganism distribution in infected patients, *E. faecium* was isolated in all cases. Among the 9 (8.8% mortality) deceased patients, 3 (33.3%) deaths were directly attributed to confirmed VRE infection. Four (44.4%) deaths occurred in patients with VRE colonization alongside other critical conditions, and 2 (22.2%) were unrelated to VRE. Importantly, one colonized patient who received empirical linezolid therapy (without culture-proven infection) was not included in the infection-attributed mortality group. Clinical evaluation of these patients revealed that all were monitored in intensive care units, with underlying conditions including neurogenic disease in two patients, congenital heart disease in two patients, and malignancy in one patient. Regarding risk factors, all infected patients had a history of broad-spectrum antibiotic use, with four having central venous catheters, three using TPN, and two having tracheostomy. These findings align with the clinical characteristics and mortality rates of pediatric VRE infections reported in Karandikar et al.'s study (22). Additionally, Sutcu et al.'s study examining risk factors for VRE infections in critical pediatric patients supports our findings (7). Similarly, Wang et al. emphasized the importance of underlying diseases in pediatric patients developing VRE infections in intensive care units (17).

Analyzing the annual distribution of VRE-positive cases in our study, the most notable increase occurred in 2021, reaching 37.9% VRE positivity, significantly higher compared to other years (ranging from 0.35% to 1.49% between 2014-2020). Several factors may be responsible for the remarkable growth experienced: increased hospitalizations during

the COVID-19 pandemic, increased bed occupancy rates particularly in intensive care units, and increased antibiotic use due to concerns about secondary bacterial infections in viral pneumonia treatment. The literature also reports studies indicating increased risk of bloodstream infections from opportunistic pathogens, particularly enterococci, in SARS-CoV-2 infected patients during the COVID-19 pandemic (24). This is attributed to disruption of the intestinal barrier caused by viral replication and increased antibiotic use. The increase in antimicrobial use to combat secondary bacterial infections during the pandemic led to increased antibiotic resistance (25). Literature provides data on increased reports of highly resistant Enterococcus strains, including VRE, and increases in enterococcal populations (26). In light of these data, we believe the significant VRE increase observed in 2021 directly reflects the pandemic process.

The analysis of the evolution of VRE colonization and infection over time throughout this study is one of the strengths with particular emphasis put under the pandemic period and the rise that was witnessed during these times. However, the results are limited in their generalizability due to the retrospective nature of the study and data being collected from a single center. Furthermore, distinguishing between colonization and true infection can be clinically challenging in critically ill pediatric patients, especially when empirical treatments such as linezolid are initiated before culture confirmation. Future studies should evaluate these findings in multicenter, prospective settings with larger patient cohorts, particularly to assess the long-term effects of the post-pandemic period and the effectiveness of implemented infection control measures. Considering the data presented, this study also sheds light on how antimicrobial stewardship strategies and prescription control programs may influence resistance trends and clinical outcomes.

Conclusion

Based on the study's findings, it can be concluded that patients staying for longer hospitalization periods and those in the pediatric clinic of the hospital's intensive care units had a greater tendency to be colonized or infected with VRE. Key risk factors include use of broad-spectrum antibiotics, invasive procedures, presence of chronic diseases and prolonged hospitalization so on. The notably higher colonization rate compared to infection in our study and the increased numbers of cases observed particularly in 2021 emphasize the importance of infection control measures and surveillance studies. In this regard, it is necessary to implement more efficiently preventive measures such as restricting the use of antibiotics, increasing compliance with hand hygiene, careful observing of high-risk patients and regular surveillance cultures. As well, organizing continuous education programs for the health care staff and tailoring infection control policies to current recommendations are also important in the control of VRE-associated hospital infections.

Ethics Committe Approval: This study has been approved by the Clinical Research Ethics Committee of İstanbul Prof. Dr. Cemil Taşçıoğlu City Hospital (Decision no: E-48670771-514.99, Date: 04.07.2022).

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