flora

RESEARCH ARTICLE/KLİNİK ÇALIŞMA

FLORA 2024;29(2):280-288 • doi: 10.5578/flora.2024021037

Comprehensive Comparative Analysis of *Enterococcus faecalis* versus *Enterococcus faecium* Strains Isolated from Clinical Samples: A Retrospective Observational Study

Klinik Örneklerden İzole Edilen *Enterococcus faecalis* ve *Enterococcus faecium* Suşlarının Kapsamlı Karşılaştırmalı Analizi: Retrospektif Gözlemsel Çalışma

Dilek BULUT[1](İD), Hanife Nur KARAKOÇ PARLAYAN[2](İD), İrfan ŞENCAN[1](İD)

[1] Clinic of Infectious Disease and Clinical Microbiology, Ankara Etlik State Hospital, Ankara, Türkiye
[2] Department of Infectious Disease and Clinical Microbiology, Karadeniz Technical University Faculty of Medicine, Trabzon, Türkiye

Cite this article as: *Bulut D, Karakoç Parlayan HN, Şencan İ. Comprehensive comparative analysis of Enterococcus faecalis versus Enterococcus faecium strains isolated from clinical samples: A retrospective observational study. FLORA 2024;29(2):280-288.*

ABSTRACT

Introduction: *Enterococci, common human pathogens, are widespread in the body and environment. Indeed, Enterococcus faecalis and Enterococcus faecium are significant human pathogens, contributing to the rising incidence of nosocomial infections. This study aims to compare their occurrence and mortality in diagnosed infections, demonstrating predictive value when strain typing is not feasible, and contributing to empirical treatment literature.*

Materials and Methods: *This study was conducted retrospectively on cases diagnosed and treated with healthcare-associated infections between 2015 and 2022 at a tertiary healthcare institution. The cases were categorized into bacteremia, urinary tract infections, pneumonia, and surgical site infections groups. Demographic, clinical, and laboratory characteristics of the cases, as well as the development/follow-up periods of the infections and mortality rates, were compared among the groups. Species identification was confirmed using conventional methods, VITEK® 2 Compact (bioMérieux, Marcy l'Etoile, France), and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, Bremen, Germany). Data analysis was performed using SPSS Software Version 23, and p< 0.05 was considered significant.*

Results: *Based on the data from the infectious diseases committee, a total of 4713 cases were followed up with a diagnosis of healthcare-associated infections. Among these cases, 528 (11.2%) were infected with Enterococcus spp. In Enterococcus infections, the causative agent was identified as E. faecalis in 290 cases (54.9%), E. faecium in 210 cases (39.8%), and other Enterococcus spp. in 28 cases (5.3%). Vancomycin resistance was assessed in 523 Enterococcus isolates, and resistance was detected in 26 cases (5%). The average age of the cases is 65.5 ± 17.8 years, with 49.1% of the included samples belonging to females. The prevalence of E. faecalis and E. faecium did not differ significantly based on gender and age (p= 0.709, p= 0.683). Around 54.5% of Enterococcus infections occurred before 2019 (p= 0.29), with the most common infections observed in the intensive care unit (ICU) (64.4%) and presenting as bloodstream infections (61.6%). The mean onset of infection was 25.3 ± 31.7 days. Upon analyzing the responsible microorganisms, no significant difference was found between E. faecalis and E. faecium (p> 0.05). Examining the risk factors for Enterococcus infections, it was observed that E. faecium was more frequently found in patients undergoing hemodialysis (p= 0.031).*

Received/Geliş Tarihi: 03/12/2023 - Accepted/Kabul Ediliş Tarihi: 05/03/2024

©Copyright 2024 by Flora. Available on-line at www.floradergisi.org.

Licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.

Available Online Date: 25.06.2024

Conclusion: *In our study, we analyzed E. faecalis and E. faecium isolates, finding shared characteristics. Enterococcus is linked to extended hospital stays and bloodstream infections. Hemodialysis patients face higher E. faecalis infection rates. Treating both pathogens empirically is crucial, considering the low vancomycin resistance.*

Key Words: *Enterococcus; Healthcare-associated infection; Mortality*

ÖZ

Klinik Örneklerden İzole Edilen *Enterococcus faecalis* ve *Enterococcus faecium* Suşlarının Kapsamlı Karşılaştırmalı Analizi: Retrospektif Gözlemsel Çalışma

Dilek BULUT[1], Hanife Nur KARAKOÇ PARLAYAN[2], İrfan ŞENCAN[1]

[1] Ankara Etlik Şehir Hastanesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği, Ankara, Türkiye
[2] Karadeniz Teknik Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Trabzon, Türkiye

Giriş: *Enterokoklar insan vücudunda, ağız boşluğu, gastrointestinal sistem ve vajen florasında ayrıca çevrede yaygın olarak bulunan patojenlerdir. Enterococcus türleri arasında, iki ana tür (Enterococcus faecalis ve Enterococcus faecium) insanlar için özellikle patojeniktir. Son yıllarda, dünya genelinde nozokomiyal infeksiyonların sık nedenlerinden biri haline gelmiştir ve hastalar için büyük bir tehdit oluşturmaktadır. Bu çalışmanın amacı, infeksiyon tanısı konan ve yatırılarak takip edilen hastalarda E. faecalis ve E. faecium izolatının görülme sıklığını ve mortalite oranlarını karşılaştırmak, etken tiplendirilmesi yapılamayan durumlarda etkenin tahmin edilebilirliğini ortaya koymak, ampirik tedavi kullanımında literatüre katkı sağlamaktır.*

Materyal ve Metod: *Bu çalışma üçüncü basamak sağlık kuruluşunda 2015-2022 yılları arasında sağlık bakımı ilişkili infeksiyon tanısıyla takip ve tedavi edilen olgularda retrospektif olarak yapılmıştır. Olgular bakteremi, üriner infeksiyon, pnömoni ve cerrahi alan infeksiyonları olarak gruplandırılmıştır. Olguların demografik, klinik, laboratuvar özellikleri, infeksiyon gelişme/takip süreleri ve mortalite oranları gruplar arasında karşılaştırılmıştır. Tür tanımlaması, konvansiyonel yöntemler, VITEK® 2 Compact (bioMérieux, Marcy l'Etoile, Fransa) ve matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, Bremen, Almanya) ile yapılmıştır. Veri analizi, SPSS Software Version 23 kullanılarak yapılmış, p< 0.05 anlamlı kabul edilmiştir.*

Bulgular: *İnfeksiyon hastalıkları komitesi verilerine göre 4713 vaka sağlık ilişkili infeksiyon tanısıyla takip edilmiştir. Bu vakaların 528 (%11.2)'i Enterococcus spp. ile infekte vakalardır. Enterokok infeksiyonlarının 290 (%54.9)'ında etken E. faecalis, 210 (%39.8)'unda E. faecium, 28 (%5.3)'inde Enterococcus spp.'dir. Enterococcus türlerinin 523'ünde vankomisin direnci bakılmış, 26 (%5)'sında direnç saptanmıştır. Dahil edilen örneklerin %49.1'i kadınlara ait olup, vakaların ortalama yaşı 65.5 ± 17.8'dir. E. faecalis ve E. faecium üreme sıklığının cinsiyet ve yaştan etkilenmediği saptanmıştır (p= 0.709, p= 0.683). Enterokok infeksiyonlarının %54.5'i 2019 öncesi döneme aittir (p= 0.29), en sık infeksiyon yoğun bakım ünitesinde meydana gelmiştir (%64.4) ve kan dolaşımı infeksiyonu ile karşımıza çıkmıştır (%61.6). Ortalama infeksiyon gelişme süresi 25.3 ± 31.7 gündür. Sorumlu mikroorganizmalar incelendiğinde E. faecalis ve E. faecium arasında anlamlı fark bulunmamıştır (p> 0.05). İki mikroorganizmanın mortalite oranları benzerdir (p= 0.315). Enterokok infeksiyonları risk faktörleri incelendiğinde hemodiyaliz yapılan hastalarda E. faecium'un daha yüksek görüldüğü saptanmıştır (p= 0.031).*

Sonuç: *Çalışmamızda E. faecalis ve faecium üremelerinin sıklığı, prezentasyonu ve risk faktörleri incelenmiş, iki mikroorganizmanın benzer özelliklerde karşımıza çıktığı görülmüştür. Elde edilen veriler, enterokok üremelerinin en sık uzamış yatış öyküsü olan vakalarda ve kan dolaşımı infeksiyonlarında karşımıza çıktığını desteklemektedir. Ampirik tedavide iki etkeni kapsayacak tedavi başlamak gerektiğini ve vankomisin direnci düşüklüğünün dikkate alınması gerektiğini düşünmekteyiz.*

Anahtar Kelimeler: *Enterococcus; Sağlık bakımı ilişkili infeksiyon; Mortalite*

INTRODUCTION

Enterococci are common pathogens found in the human body, inhabiting regions such as the oral cavity, gastrointestinal system, and vaginal flora. They are also widely present in the environment. Enterococci are considered significant endogenous pathogens that can lead to infections, particularly in hospital and community settings. Despite the presence of various species, *Enterococcus faecalis* and *Enterococcus faecium* are frequently identified as pathogenic agents in humans. In recent years, it has become one of the common causes of nosocomial infections worldwide. Among healthcare-associated infections, it ranks among

the top three most prevalent microorganisms, and it is estimated to be responsible for 25-50% of mortality in hospitalized patients, which poses a significant threat to patients[1-3]. The probable source of infections is usually endogenous, and enterococcal infections can be challenging to treat due to their intrinsic resistance to certain antibiotics[4-5]. They could be the causative agents of urinary tract infections, skin and soft tissue infections, endocarditis, and bacteremia. *E. faecalis* has been described as the most frequently isolated species from clinical samples and the most common species causing human infections. On the other hand, *E. faecium*, an important contributor to healthcare-associated infections, has shown an increasing incidence, particularly among patients with bacteremia. It has been associated with higher mortality rates and a higher frequency of accompanying comorbid conditions. Furthermore, *E. faecium* is known to be more resistant to antimicrobial agents compared to *E. faecalis*[6-8]. Moreover, the emergence of acquired resistance to β-lactam antibiotics and the development of vancomycin resistance have made the treatment of *E. faecium* infections increasingly challenging, and in some cases, even impossible[9-11]. Although existing scientific literature has explored the prevalence and role of *E. faecalis* and *E. faecium* strains in healthcare-associated infections, there is a noticeable gap in the literature regarding a comprehensive analysis of the clinical implications of the differences between these *Enterococcus* species. Our research endeavors to fill this void, aiming to contribute to the identification of rapid and effective empirical treatment options based on clinical presentations. By characterizing the distribution variations and clinical presentations of these agents, our research seeks to facilitate the initiation of appropriate empirical antibiotic therapy.

The primary endpoint of the study was the time to discharge from the hospital or death. The primary objective of this study was to compare the frequency of occurrence and mortality rates of *E. faecalis* and *E. faecium* isolates in patients diagnosed with infections and followed during their hospitalization. Secondly, the study aimed to compare the distribution and changes in infections over the years in intensive care units (ICUs) and clinics. Furthermore, demonstrating the predominance of the pathogen in cases where the etiology cannot be identified contributes to the empirical treatment approach and adds to the existing literature.

MATERIALS and METHODS

The study was conducted as a cross-sectional retrospective observational study in a 770-bed training and research hospital between January 1, 2015, and December 31, 2021. The study included adult patients aged 18 and over who were diagnosed with healthcare-associated infections based on surveillance conducted during their hospital stays in both intensive care units (ICUs) and clinics. Our institution comprises seven intensive care units (anesthesiology and reanimation, cardiovascular surgery, neurosurgery, general surgery, coronary, internal medicine, neurology ICU) and 16 clinics (internal medicine, hematology, oncology, nephrology, gastroenterology, infectious diseases, cardiology, pulmonology, dermatology, neurology, physical medicine and rehabilitation, neurosurgery, general surgery, urology, cardiovascular surgery, orthopedics). All patients with positive culture results for *E. faecalis* or *E. faecium* identified by the clinical microbiology laboratory were included in the study. The study included patients: 1) aged ≥18, 2) with cultures positive for *E. faecalis* or *E. faecium*, and 3) who were under inpatient follow-up. Excluded from the study were patients: 1) aged <18, 2) whose species identification was not determined, and 3) who presented as outpatients.

The demographic, clinical, and microbiological data of the included patients were obtained from the hospital's electronic medical record system and the infection control committee's records. Data collected included age, gender, number of hospital days before infection in hospital-acquired cases, presence of a high-risk source, presence of polymicrobial and clinically significant cultures, presence of invasive procedures, steroid use, hemodialysis, and predisposing factors. The results have been presented following the STROBE guidelines. Throughout the study period, if a patient had multiple episodes of *E. faecalis* or *E. faecium* infection, only the first episode was considered for evaluation. Additionally,

the mortality rates of enterococcal infections were analyzed, and the potential impact of *E. faecium* on mortality was assessed. Samples were inoculated into 5% sheep blood Columbia agar (bioMérieux, France) and incubated at 37 °C overnight in the Clinical Microbiology Laboratory. Species identification was confirmed using conventional methods, VITEK® 2 Compact (bioMérieux, Marcy l'Etoile, France), and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, Bremen, Germany).

Statistical Analysis

The results were presented as numbers (n) and percentages (%) for categorical variables and as mean ± standard deviation for continuous variables. Continuous variables were compared using independent samples t-tests. Non-normally distributed data were presented as median and interquartile range (IQR), and compared using the Wilcoxon rank-sum test. For comparisons between percentages of categorical variables, the Chi-square test or Fisher's exact test was utilized. Two-tailed $p< 0.05$ were considered statistically significant. Data analysis was performed using SPSS software version 23 (IBM Corp., Armonk, N.Y., USA).

RESULTS

During the study period, a total of 4713 cases were followed with a diagnosis of healthcare-associated infections according to the data from the infectious diseases committee. Among these cases, 528 (11.2%) were infected with *Enterococcus* spp. *E. faecalis* was identified as the causative agent in 290 cases (54.9%), *E. faecium* in 210 cases (39.8%), and *Enterococcus* spp. in 28 cases (5.3%). The distribution of *E. faecium* and *E. faecalis* isolates according to infections is presented in Table 1. Of the samples included in the study, 259 (49.1%) were females, and 269 (50.9%) were males. The average age of the cases was 65.5 ± 17.8 years (range, 18-88 years). It was determined that the frequency of *E. faecalis* and *E. faecium* isolations was not influenced by gender or age ($p= 0.709$, $p= 0.683$).

Cases were categorized into pre-2019 and post-2019 groups for the investigation of the impact of the COVID-19 disease on *Enterococcus* infections. *Enterococcus* infections (54.5%) were observed in the pre-2019 period, and there was no significant difference in the frequency of *Enterococcus* infections between the pre-2019 and post-2019 periods ($p= 0.29$). While *Enterococcus* infections were observed in internal medicine clinics at a rate of 20.3% and in surgical clinics at a rate of 15.2%, the most frequent occurrence of infection was in intensive care units (ICUs) at a rate of 64.4% ($p< 0.001$), mainly presenting as bloodstream infections (61.6%). The frequency of *E. faecalis* and *E. faecium* isolations was similar in both the intensive care units and hospital wards, and it was determined that being admitted to the ICU did not have an enhancing effect on either type ($p= 0.809$). The presentation of infections is provided in Table 1. Although *E. faecalis* and *E. faecium* isolations are most commonly encountered in bloodstream infections, no statistically significant difference was found between infection types and *Enterococcus* subtypes ($p> 0.05$).

The average hospital stay for patients was 45.8 ± 46.2 days (range= 5-389), and the average time to infection development was 25.3 ± 31.7 days (range= 1-321). When comparing the responsible microorganisms, there was no significant difference observed between *E. faecalis* and *E. faecium* in terms of time to infection development and duration of hospital stay ($p= 0.968$, $p= 0.345$). The in-hospital mortality rate of patients infected with *Enterococcus* was 54.7% in our study. The mortality rates for the two microorganisms were 54.2% for *E. faecalis* and 56.7% for *E. faecium*, with no statistically significant difference between them ($p= 0.315$).

Risk factors for *Enterococcus* infections were examined, revealing that *E. faecium* was more frequently observed in patients undergoing hemodialysis ($p= 0.031$). There was no statistically significant difference in terms of surgical history, presence of a central venous catheter, urinary catheterization, history of total parenteral nutrition (TPN), and steroid usage between patients with cultures positive for *E. faecalis* and *E. faecium* (Table 1). In 120 patients (22.7%), additional bacteria

Table 1. Distribution of *E. faecium* and *E. faecalis* isolates by infection type, with demographic data, risk factors, and mortality rates

	E. faecalis	*E. faecium*	Total (n/%)	p
Age (SD)	65.71 (17.38)	65.66 (17.95)	65.53 (17.77)	0.683
Gender				0.709
Female	143 (49.3)	100 (47.6)	259 (49.1)	
Male	147 (50.7)	110 (52.4)	269 (50.9)	
Time of Infection				0.29
Before 2019	165 (56.9)	106 (50.5)	288 (54.5)	
2019 and beyond	125 (43.1)	104 (49.5)	240 (45.5)	
From the Clinic				0.455
Internal	56 (19.3)	46 (21.9)	107 (20.3)	
Surgical	48 (16.6)	28 (13.3)	80 (15.2)	
Intensive care unit	186 (64.1)	135 (64.3)	340 (64.4)	
Type of Infection				<0.05
Catheter-related urinary tract infection	53 (18.3)	37 (17.6)	96 (18.2)	
Urinary tract infection	12 (4.1)	7 (3.3)	19 (3.6)	
Catheter-related bloodstream infection	88 (30.3)	87 (41.4)	184 (34.8)	
Primary bloodstream infection	80 (27.6)	53 (25.2)	139 (26.3)	
Ventilator-associated pneumonia	6 (2.1)	5 (2.4)	11 (2.1)	
Pneumonia	20 (6.9)	7 (3.3)	28 (5.3)	
Surgical site infection	31 (10.7)	14 (6.7)	51 (9.7)	
Mean hospitalization (days) mean (SD)	48.17 (51.05)	42.15 (40.58)	45.79 (46.23)	0.345
Day of enterococcal infection onset (mean) (SD)	25.46 (33.5)	24.9 (29.91)	25.28 (31.69)	0.968
Intensive Care Unit History				0.809
Negative	104 (35.9)	74 (35.2)	187 (35.5)	
Positive	186 (64.1)	135 (64.3)	340 (64.4)	
Mortality				0.315
Negative	104 (38.1)	74 (36.8)	191 (38.3)	
Positive	148 (54.2)	114 (56.7)	273 (54.7)	
Unknown (Dispatched)	38 (7.7)	22 (6.5)	65 (7)	
Risk Factors				
Intubation	104 (19.7)	73 (13.8)	185 (35)	0.756
Operation history	27 (9.3)	13 (6.2)	44 (8.3)	0.21
Central venous catheter	132 (45.5)	101 (48.1)	243 (46)	0.568
Presence of co-infection	69 (23.8)	44 (21)	120 (22.7)	0.579
Hemodialysis	6 (2.1)	12 (5.7)	18 (3.6)	0.031
Presence of bloodstream infection	168 (57.9)	140 (66.7)	323 (61.2)	0.099
Urinary catheter	171 (59)	129 (61.4)	315 (59.7)	0.579
Total parenteral nutrition	17 (5.9)	12 (5.7)	31 (5.9)	0.944
Steroid usage	45 (15.5)	21 (10)	69 (13.1)	0.072
Vancomycin resistance	7 (2.4)	16 (7.6)	26 (5)	0.25
Presence of *Enterococcus* spp. infection at hospital admission	7 (2.4)	5 (2.3)	12 (2.3)	1

Results were presented as mean ± standard deviation or count (n) and percentages (%). According to distribution Student t-test or Mann-Whitney U test was performed. Chi-square test (or Fisher's exact) was applied for categorical variables. $p < 0.05$ results were statistically significant.

were isolated alongside *Enterococcus* cultures. Additional growth was present in 23.8% of cases for *E. faecalis* and 21% for *E. faecium*, with no statistically significant difference between two groups (p= 0.579).

Vancomycin resistant (VR) was assessed in 523 *Enterococcus* isolates, and resistance was detected in 26 cases (5%). *E. faecalis* was identified in 7 (2.4%) cases, while *E. faecium* was identified in 16 (7.6%) cases; however, no statistically significant difference was observed between two groups (p= 0.250).

DISCUSSION

In recent years, enterococci have emerged as pathogens causing both hospital-acquired and community-acquired infections, posing challenges for clinicians[3,4,10]. Enterococcal infections have increased in the past few decades, leading to a rise in antibiotic-resistant enterococci and healthcare-associated infections[11,12]. This study is significant in contributing to local and national data on antimicrobial usage by describing the local epidemiological data of enterococcal isolates.

In our study, 11.2% of the patients diagnosed with healthcare-associated infections were infected with *Enterococcus* spp. Although *E. faecium* is isolated less frequently compared to *E. faecalis*, it demonstrates a higher resistance rate to multiple antimicrobial agents[1,13]. Studies have shown an increasing prevalence of enterococcal infections, particularly with *E. faecium* isolates[8,14,15].

Consistent with our study, the causative agent was identified as *E. faecalis* in 54.9% of the observed enterococcal infections, while it was *E. faecium* in 39.8%. When comparing the periods before and after 2019, there was no overall increase in enterococcal infections; however, there was an increase in the proportion of *E. faecium* among enterococcal isolates. Nevertheless, this increase was not statistically significant.

In the literature, *E. faecium* has been reported to account for 5-10% of *Enterococcus* infections[16]. In a multicenter study conducted by Simonsen and colleagues, although a similar percentage (4.1%) was found among samples isolated from outpatient cases, a higher rate of *E. faecium* (22.1%) was detected among hospitalized patients. They also indicated that *E. faecium* constituted 31.4% of bloodstream isolates and 14.1% of other samples[15]. The emergence of *E. faecium* bloodstream infections has been suggested to be a result of the diversity of hospitalized patient populations and the variety of antimicrobial agents used[16]. In our study, although *E. faecium* was frequently isolated from bloodstream infections, consistent with the literature, this difference was not statistically significant.

In a study conducted by Protonotariou and colleagues in Greece involving 2123 enterococcal isolates, they reported that out of 1498 isolates, 70.6% were *E. faecalis* and 29.4% were *E. faecium*. They noted that these proportions had increased over the years. The majority of isolates were obtained from urinary tract infections (37.2%), followed by bloodstream infections (21.5%) and skin and soft tissue infections (19.7%)[17]. In another study, it has been indicated that there might be an increase in the frequency of *E. faecalis* infections associated with urinary system abnormalities[18,19]. *Enterococcus* infections were most commonly observed as bloodstream infections in our study. The isolation of *E. faecalis* was more frequently observed in urinary tract samples, although no statistically significant difference was detected.

McBride et al. examined the local epidemiology and risk factors of *E. faecalis* and *E. faecium* bacteremia in their study[20]. They found that *E. faecalis* was dominant, with an average age of 62 ± 17.9 among patients. They also observed that *E. faecium* infections were more common in younger patients and were not influenced by gender (p= 0.0013). This study also highlighted that the genitourinary system was the most common source of enterococcal bacteremia. The 30-day mortality rate was 25% (52/205), and it was noted that *E. faecium* bacteremia had a higher frequency of antimicrobial resistance and increased mortality (p= 0.0124). In our study, out of the included samples, 259 (49.1%) belonged to females, and 269 (50.9%) belonged to males. The mean age of the cases was 65.5 ± 17.8 years. The frequency of *E. faecalis* and *E. faecium* isolations was found not to be influenced

by gender and age (p= 0.709, p= 0.683). While nearly half of the bloodstream culture isolates were reported to be polymicrobial, our study found this rate to be 22.7%. The average length of hospital stay was also similar.

In a study by Kayoko Hayakawa and colleagues, they compared VR *E. faecium* and VR *E. faecalis* bacteremias[21]. They found that bacteremia due to VR *E. faecalis* was associated with diabetes, heart valve diseases, peripheral vascular disease, the presence of permanent devices, chronic hemodialysis treatment, and longer hospital stays. Additionally, bacteremia caused by VR *E. faecalis* was more frequently associated with surgical and invasive procedures compared to VR *E. faecium*. They noted that there were no significant differences in gender and age between the two groups.

Noskin and colleagues, have indicated that healthcare-associated infections, malignancy, neutropenia, chronic kidney failure, corticosteroid usage, and broad-spectrum antibiotic usage increase the risk of *E. faecium* infections[8]. In our study, *E. faecium* infections were found to be more frequent in patients undergoing hemodialysis. However, among other risk factors, no statistically significant difference was observed in terms of the frequency of *E. faecium* infections. These differences could stem from variations in the resistance patterns of these isolates and the diversity of antimicrobial agents previously used by the patients.

When the two strains are examined in terms of antibiotic resistance rates, studies suggest that *E. faecium* isolates have higher resistance rates to antibiotics compared to *E. faecalis* isolates, indicating a more pathogenic nature[8,22,23]. According to reports, *E. faecalis* isolates possess a higher frequency of virulence genes compared to *E. faecium* isolates. Studies also indicate that *E. faecalis* isolates are more commonly associated with biofilm production[18]. The biofilm structure protects bacteria from many antimicrobials and disinfectants, making treatment more challenging[23,24]. In our study, biofilm production and virulence genes were not compared.

McBride reported 69.0% amoxicillin resistance in *E. faecium* isolates, while VR was not detected[20]. Vancomycin resistance was first described in enterococci in 1988[25]. In a study conducted by Baylan et al. in our country, VR was not observed in *E. faecalis* isolates, but it was observed at a rate of 25.8% in *E. faecium* isolated[26]. In another study, vancomycin and teicoplanin resistance was found to be 8.2%, with no resistance detected in *E. faecalis* isolates.

In a meta-analysis conducted by Shiadeh and colleagues, it was determined that antimicrobial resistance in bloodstream infections caused by *E. faecium* is significantly higher compared to *E. faecalis*[27]. High resistance levels to ampicillin, vancomycin, and high-level aminoglycosides were found in pathogenic types of *E. faecium*. This situation complicates the treatment of *E. faecium* infections and has become a serious issue requiring more sensitive treatment strategies. In our study, the VR was determined to be 5%. Vancomycin-resistant enterococci (VRE) have emerged as a growing clinical concern worldwide. VRE bacteremia has been linked to a higher specific mortality rate compared to vancomycin-susceptible enterococcal bacteremia[28,29].

Noskin and colleagues statistically determined significantly higher mortality rates in patients infected with *E. faecium* compared to those infected with *E. faecalis* (50% vs. 11%; p= 0.001)[8]. de Perio and colleagues noted in their study that bloodstream infections caused by *E. faecium* were associated with higher mortality rates, while infections caused by non-*E. faecalis* and non-*E. faecium* species were not significantly linked to severe disease or mortality[30]. On the other hand, Hayakawa, detected higher rates of in-hospital mortality associated with VR *E. faecalis* bacteremia in their study[21]. In our study, higher mortality rates were observed in *E. faecium* infections compared to *E. faecalis* infections, although the difference was not statistically significant. When bacteremia was analysed as a subgroup, no statistically significant difference in terms of mortality was observed (p= 0.332). This may be due to the limited patient population and the relatively low number of patients with vancomycin resistance.

High mortality rates could be attributed to the severity of underlying diseases, virulence

mechanisms, antibiotic resistance, or the interaction of these factors. Identifying these factors should be elucidated through multivariate analyses with larger patient numbers, utilizing these risk factors.

Our study has some limitations. Firstly, being a single-center study may limit its generalizability to the entire country. Additionally, due to the retrospective nature of the study, some data such as patients' clinical conditions at the time of infection, prior antibiotic usage, hospitalizations, patients' antimicrobial use, resistance profiles of the samples, presence of bacterial colonization before infection in patients, could not be included.

CONCLUSION

In conclusion, the emergence of hospital-associated infections caused by *Enterococcus*, coupled with the rise of resistant strains, has elevated the severity of *Enterococcus* infections to that of other nosocomial pathogens. This study explored the frequency, presentation, and risk factors of *E. faecalis* and *E. faecium* isolations from human sources, revealing that these two microorganisms share similar characteristics. While endorsing the prevalence of *Enterococcus* isolations in cases with prolonged hospital stays and bloodstream infections, the study also suggests a potentially higher occurrence of *E. faecium* among hemodialysis patients and shows no significant difference in mortality rates.

The changing epidemiology of *Enterococcus* infections necessitates intensified and continuous efforts in hospital infection control. Understanding the reasons behind the frequency of *Enterococcus* infections and potential future trends requires further research. Initiating empirical treatment covering both pathogens is crucial, and it is important to take into account the relatively low prevalence of vancomycin resistance.

ETHICS COMMITTEE APPROVAL

This study was approved by the Ankara Etlik City Hospital Ethics Committee 1 (Decision no: 2023-500, Date: 06.09.2023).

CONFLICT of INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: HNKP, DB

Analysis/Interpretation: HNKP, DB

Data Collection or Processing: DB

Writing: All of authors

Review and Correction: İŞ, HNKP

Final Approval: All of authors

REFERENCES

1. *Deshpande LM, Fritsche TR, Moet GJ, Biedenbach DJ, Jones RN. Antimicrobial resistance and molecular epidemiology of vancomycin-resistant enterococci from North America and Europe: A report from the SENTRY antimicrobial surveillance program. Diagn Microbiol Infect Dis 2007;58:163-70. https://doi.org/10.1016/j.diagmicrobio.2006.12.022*
2. *Reik R, Tenover FC, Klein E, McDonald LC. The burden of vancomycin-resistant enterococcal infections in US hospitals, 2003 to 2004. Diagn Microbiol Infect Dis 2008;62:81-5. https://doi.org/10.1016/j.diagmicrobio.2008.04.013*
3. *Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: Analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39:309-17. https://doi.org/10.1086/421946*
4. *Murray BE. New aspects of antimicrobial resistance and the resulting therapeutic dilemmas. J Infect Dis 1991;163: 1184-94. https://doi.org/10.1093/infdis/163.6.1185*
5. *Spera RV Jr, Farber BF. Multidrug-resistant Enterococcus faecium: An untreatable nosocomial pathogen. Drugs 1994;48:678-88. https://doi.org/10.2165/00003495-199448050-00003*
6. *Teixeira LM, Siqueira Carvalho MDG, Facklam RR. Enterococcus, pp. Murray PR, Baron EJ, Jorgensen JH, Landry ML, Pfaller MA (eds), Manual of Clinical Microbiology. 9th ed. ASM Press, Washington DC; 2007:430-42.*
7. *Paganelli FL, Huebner J, Singh KV, Zhang X, van Schaik W, Wobser D, et al. Genome-wide screening identifies phosphotransferase system permease BepA to be involved in Enterococcusfaecium endocarditis and biofilm formation. J Infect Dis 2016;214:189-95. https://doi.org/10.1093/infdis/jiw108*
8. *Noskin GA, Peterson LR, Warren JR. Enterococcus faecium and Enterococcus faecalis bacteremia: Acquisition and outcome. Clin Infect Dis 1995;20:296-301. https://doi.org/10.1093/clinids/20.2.296*
9. *Shay DK, Maloney SA, Montecalvo M, Banerjee S, Wormser GP, Arduino MJ, et al. Epidemiology and mortality risk of vancomycin-resistant enterococcal bloodstream infections. J Infect Dis 1995;172:993-1000. https://doi.org/10.1093/infdis/172.4.993*
10. *Schaberg DR, Culver DH, Gayes RP. Major trends in the microbial etiology of nosocomial infection. Am J Med 1991;91;72-6. https://doi.org/10.1016/0002-9343(91)90346-Y*

11. *Arias CA, Murray BE. The rise of the Enterococcus: Beyond vancomycin resistance. Nat Rev Microbiol 2012;10:266-78. https://doi.org/10.1038/nrmicro2761*
12. *Austin DJ, Bonten MJ, Weinstein RA, Slaughter S, Anderson RM. Vancomycin-resistant enterococci in intensive-care hospital settings: Transmission dynamics, persistence, and the impact of infection control programs. Proc Natl Acad Sci USA 1999;96:6908-13. https://doi.org/10.1073/pnas.96.12.6908*
13. *Sharifi Y, Hasani A, Ghotaslou R, Naghili B, Aghazadeh M, Milani M, et al. Virulence and antimicrobial resistance in enterococci isolated from urinary tract infections. Adv Pharm Bull 2013;3:197-201.*
14. *Routsi C, Platsouka E, Paniara O, Sotiropoulou C, Nanas S, Markaki V, et al. Enterococcal infections in a Greek intensive care unit: A 5-y study. Scand J Infect Dis 2000;32:275-80. https://doi.org/10.1080/00365540050165910*
15. *Simonsen GS, Småbrekke L, Monnet DL, Sørensen TL, Møller JK, Kristinsson KG, et al. Prevalence of resistance to ampicillin, gentamicin, and vancomycin in Enterococcus faecalis and Enterococcus faecium isolates from clinical specimens and use of antimicrobials in five Nordic hospitals. J Antimicrob Chemother 2003;51:323-31. https://doi.org/10.1093/jac/dkg052*
16. *Facklam RR, Sahm DF, Teixeira LM. Enterococcus. In Manual of Clinical Microbiology, 7th edn ASM Press, Washington, DC, USA 1999:297-305.*
17. *Protonotariou E, Dimitroulia E, Pournaras S, Pitiriga V, Sofianou D, Tsakris A. Trends in antimicrobial resistance of clinical isolates of Enterococcus faecalis and Enterococcus faecium in Greece between 2002 and 2007. J Hosp Infect 2010;75:225-7. https://doi.org/10.1016/j.jhin.2009.12.007*
18. *Strateva T, Atanasova D, Savov E, Petrova G, Mitov I. Incidence of virulence determinants in clinical Enterococcus faecalis and Enterococcus faecium isolates collected in Bulgaria. Braz J Infect Dis 2016;20:127-33. https://doi.org/10.1016/j.bjid.2015.11.011*
19. *Billington EO, Phang SH, Gregson DB, Pitout JDD, Ross T, Church DL, et al. Incidence, risk factors, and outcomes for Enterococcus spp. bloodstream infections: A population-based study. Int J Infect Dis 2014;26:76-82. https://doi.org/10.1016/j.ijid.2014.02.012*
20. *McBride SJ, Upton A, Roberts SA. Clinical characteristics and outcomes of patients with vancomycin-susceptible Enterococcus faecalis and Enterococcus faecium bacteremia--a five-year retrospective review. Eur J Clin Microbiol Infect Dis 2010;29:107-14. https://doi.org/10.1007/s10096-009-0830-5*
21. *Hayakawa K, Marchaim D, Martin ET, Tiwari N, Yousuf A, Sunkara B et al. Comparison of the clinical characteristics and outcomes associated with vancomycin-resistant Enterococcus faecalis and vancomycin-resistant E. faecium bacteremia. Antimicrob Agents Chemother 2012;56:2452-8. https://doi.org/10.1128/AAC.06299-11*
22. *Mete E, Kaleli İ, Cevahir N, Demir M, Akkaya Y, Kiriş Satılmış Ö. Enterokok türlerinin virülans faktörlerinin araştırılması. Mikrobiyol Bul 2017;51:101-14. https://doi.org/10.5578/mb.53992*
23. *Gök ŞM, Türk Dağı H, Kara F, Arslan U, Fındık D. Klinik örneklerden izole edilen Enterococcus faecium ve Enterococcus faecalis izolatlarının antibiyotik direnci ve virülans faktörlerinin araştırılması [Investigation of antibiotic resistance and virulence factors of Enterococcus faecium and Enterococcus faecalis Strains isolated from clinical samples]. Mikrobiyol Bul 2020;54:26-39. https://doi.org/10.5578/mb.68810*
24. *Soares RO, FediAC, Reiter KC, Caierao J, d'Azevedo PA. Correlation between biofilm formation and gelE, esp, and agg genes in Enterococcus spp. clinical isolates. Virulence 2014;5:634-7. https://doi.org/10.4161/viru.28998*
25. *Leclercq R, Derlot E, Duval J, Courvalin P. Plasmid-mediated resistance to vancomycin and teicoplanin in Enterococcus faecium. N Engl J Med 1988;319:157-61. https://doi.org/10.1056/NEJM198807213190307*
26. *Baylan O, Nazik H, Bektöre B, Çitil BE, Turan D, Öngen B, et alFa. Üriner enterokok izolatlarının antibiyotik direnciile virülans faktörleri arasındaki ilişki. Mikrobiyol Bul 2011;45:430-45.*
27. *Jabbari Shiadeh SM, Pormohammad A, Hashemi A, Lak P. Global prevalence of antibiotic resistance in blood-isolated Enterococcus faecalis and Enterococcus faecium: A systematic review and meta-analysis. Infect Drug Resist 2019;12:2713-25. https://doi.org/10.2147/IDR.S206084*
28. *DiazGranados CA, Zimmer SM, Klein M, Jernigan JA. Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal bloodstream infections: A meta-analysis. Clin Infect Dis 2005;41:327-33. https://doi.org/10.1086/430909*
29. *Bhavnani SM, Drake JA, Forrest A, Deinhart JA, Jones RN, Biedenbach DJ, et al. A nationwide, multicenter, case-control study comparing risk factors, treatment, and outcome for vancomycin-resistant and -susceptible enterococcal bacteremia. Diagn Microbiol Infect Dis 2000;36:145-58. https://doi.org/10.1016/S0732-8893(99)00136-4*
30. *Perio MA, Yarnold PR, Warren J, Noskin GA. Risk factors and outcomes associated with non-Enterococcus faecalis, non-Enterococcus faecium enterococcal bacteremia. Infect Control Hosp Epidemiol 2006;27:28-33. https://doi.org/10.1086/500000*

Address for Correspondence/Yazışma Adresi

Dr. Hanife Nur KARAKOÇ PARLAYAN

Department of Infectious Disease and Clinical Microbiology,
Karadeniz Technical University Faculty of Medicine, Trabzon, Türkiye

E-posta: nurkarakoc61@gmail.com