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# Antibiotic susceptibility pattern of *Enterococcus* isolates in a five year period at a tertiary care hospital

## Üçüncü basamak bir hastanede beş yıllık bir sürede izole edilen *Enterococcus* izolatlarında antibiyotik duyarlılık profili

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**Abstract**

Aim: Enterococci are present as a part of the normal gut flora which can cause many community- and hospital-acquired infections. It is essential to determine the antibiotic resistance profile in treatment of Enterococcus spp. In this study we aimed to determine the sub-species of Enterococcus spp and their antibiotic resistance profiles isolated from a tertiary hospital in a five-year period.

Methods: The antibiotic resistance profiles of 2995 Enterococcus spp isolated from various clinical specimens of patients between January 2014 and December 2018 were reviewed in this retrospective cohort study.

Results: Ampicillin resistance was very low (5.6%) in *E. faecalis*, but it was very high in *E. faecium (91.8%)*. High level gentamycin, high level streptomycin and levofloxacin resistances were very high in all Enterococcus species and especially in *E. faecium*. Linezolid, tigecycline or daptomycin resistance was not determined in any Enterococcus isolates. Nitrofurantoin resistance (61.9%) and parenteral penicillin resistance (82.4%) were also very high in *E. faecium* isolates. Teicoplanin resistance was very low in *E. faecalis (1.5%)* isolates but approximately half (44.9%) of the *E. faecium* isolates were resistant to Teicoplanin. Vancomycin resistance was determined in 1.5% of *E. faecalis* isolates and in 45.5% of *E. faecium isolates.*

Conclusion: In conclusion, we determined high resistance rates to many antibiotics in both *E. faecalis* and *E. faecium* isolates. Tigecyclin, linezolid and daptomycin resistance was not determined in any Enterococcus isolates. Vancomycin resistance was determined in 1.5% of *E. faecalis* isolates and in 45.5% of *E. faecium* isolates. This high rate of vancomycin resistance should be taken into account and studies should be conducted to eliminate this resistance.

**Keywords:** *Enterococcus faecalis*, *Enterococcus faecium*, Enterecoccus antibiotic resistance, Enterococcal infection

**Öz**

Amaç: Enterokoklar, normal bağırsak florasının bir üyesi olup, birçok toplum- ve hastane- kökenli enfeksiyona neden olabilmektedirler. Enterococcus spp. tedavisinde antibiyotik direnç profilinin belirlenmesi son derece önemlidir. Bu çalışmanın amacı, beş yıllık bir süre içerisinde üçüncü basamak bir hastaneden izole edilen Enterococcus spp. alt tiplerini ve antibiyotik direnç profillerini belirlemektir.

Yöntemler: Ocak 2014-Aralık 2018 tarihleri arasında çeşitli klinik örneklerden izole edilen 2995 Enterococcus spp. nin antibiyotik direnç profilleri bu retrospektif kohort çalışmada incelendi.

Bulgular: *E. faecalis* 'te ampisilin direnci çok düşük (%5,6) iken *E. faecium* 'da (%91,8) çok yüksekti. Yüksek düzey gentamisin, yüksek düzey streptomisin ve levofloksasin dirençleri tüm Enterococcus türlerinde ve özellikle *E. faecium* 'da çok yüksekdi. Enterococcus izolatlarında linezolid, tigesiklin veya daptomisin direnci saptanmadı. *E. faecium* izolatlarında nitrofurantoin (%61,9) ve parenteral penisilin direnci (%82,4) de yüksekti. *E. faecalis*'te (%1,5) teicoplanin direnci çok düşüktü, ancak *E. faecium* izolatlarının yaklaşık yarısı (%44,9) teicoplanine dirençliydi. Vankomisin direnci, *E. faecalis* izolatlarının %1,5'inde, ancak *E. faecium* izolatlarının %45.5'inde belirlenmiştir.

Sonuç: Sonuç olarak, hem *E. faecalis* hem de *E. faecium* izolatlarında birçok antibiyotiğe yüksek direnç oranları belirledik. Enteroccus izolatlarında tigesiklin, linezolid ve daptomisin direnci yoktu. Vankomisin direnci, *E. faecalis* izolatlarının %1,5'inde, ancak *E. faecium* izolatlarının %45,5'inde belirlenmiştir. Bu yüksek vankomisin direnci oranı göz önünde bulundurularak bu direnci ortadan kaldırmak için çalışmalar yapılmalıdır.

**Anahtar kelimeler:** *Enterococcus faecalis*, *Enterococcus faecium*, Enterecoccus antibiyotik direnci, Enterokok enfeksiyonu

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## Introduction

Enterococci are present as a part of the normal gut flora and can cause many community- and hospital-acquired infections, including bloodstream infections, endocarditis, meningitis, and urinary tract infections [1]. Enterococcal infections are important since they may contribute to patient mortality, increased length of hospital stay and higher healthcare costs. *Enterococcus faecalis* and *Enterococcus faecium* are the most common enterococcal species. Especially *E. faecium* has emerged as an important multidrug-resistant nosocomial pathogen [2,3]. Unfortunately, Enterococci are intrinsically resistant to many antimicrobials and easily acquire the high-level drug resistance via horizontal gene transfer. Resistant Enterococci species, especially vancomycin resistant enterococci may cause difficulties in treatment [4,5]. In that aspect, it is essential for every hospital to determine their antibiotic profile in treatment of Enterococcus spp.

In this study we aimed to determine the sub-species of Enterococcus spp and their antibiotic resistance profiles isolated from a tertiary hospital in a five-year period.

## Materials and methods

This study was performed in Health Sciences University Okmeydanı Education and Research Hospital, Medical Microbiology Department. The antibiotic resistance profiles of 2995 Enterococcus spp isolated from various clinical specimens of patients between January 2014 and December 2018 were retrospectively reviewed. Among patients with reproduction in more than one sample, only one strain was included in the study. Repeated samples were excluded from the study and different samples of the same patient were not included in determining susceptibility rates. Demographic features of the infected patients were also investigated.

Blood cultures were assayed on a fully automated blood culture device, BACTEC 9240 (Becton Dickinson, Diagnostic Instrument System, Sparks, USA). The passage of the detected vials in the automated blood culture device to the Macconkey, chocolate and 5% sheep blood agar was performed. Cultures of urine, tissue-abscess, tracheal aspirate, catheter tip, sterile fluids were evaluated according to the material and using standard microbiological techniques in accordance with the procedure [6].

Colonies thought to be effective, especially for inpatients, were identified at the species level by the Phoenix ™ - 100 (Becton Dickinson, Diagnostic Instrument System, Sparks, USA) automated system and antibiotic susceptibilities were studied. Isolated colonies from an outpatient group, Gram positive cocci with positive colony morphology on blood agar, having negative catalase test, forming blackness on bile esculin medium, growing on medium containing 6.5% NaCl and positive for pyrrolidonyl arylamidase (PYR-Oxoid) test were defined as Enterococcus spc. Antibiotic susceptibilities of isolated enterococci were determined by Kirby-Bauer disc diffusion method. Antibiotic susceptibilities were evaluated in accordance with the recommendations of the Clinical and Laboratory Standards Institute (CLSI) [7] in January 2014-December 2015, and of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [6] in January 2016- December 2018. The study was approved by Okmeydanı Training and Research Hospital ethics committee (Date: 27.8.2019; Number:1415)

**Statistical analysis**

Statistical analyses were performed with SPSS 19.0 (IBM Company, Chicago, IL) software. The conformity of the parameters to the normal distribution was evaluated by Kolmogorow-Smirnov test. Descriptive statistics (number, percentage, mean and median) were performed. Comparison of descriptive data between groups was performed with cross tables and chi square test. One-way ANOVA test was used to compare the antibiotic resistance rates of different enterococcus spp. Results with *P*-value <0.05 were considered statistically significant.

## Results

A total of 2995 Enterococcus spp were investigated. The mean age of the study participants was 52.45 (28.67) (median age: 62, range: 1-100) years. Among the patients, 1427 (47.6%) were male and 1568 (52.4%) were female. Enterococcus spp were isolated from 1250 (41.7%) patients who were admitted from the outpatient clinics while remaining 1745 (58.3%) were isolated from the hospitalized patients. The subgroups of isolated Enterococcus spp are summarized in Table 1. *E. faecalis* and *E. faecium* were significantly more common in hospitalized patients ($P<0.001$) while Enterococcus spp were significantly more common in out-patient admissions.

Enterococcus spp were isolated from different tissues and body fluids. The most commonly infected body fluid was urine (Table 2). Distribution of main Enterococcus subtypes in main tissues and body fluids infected are summarized in Table 3. In urine the most commonly isolated subtype was *E. faecalis* and in rectal swabs the main subtype was *E. faecium.* The most commonly isolated subtypes in some different wards are summarized in Table 4. Most common isolates were obtained from the intensive care unit and the most common subtype isolated in intensive care unit was *E. faecium.*

The resistance rates of Enterococcus spp to different antimicrobiotics are summarized in Table 5. Ampicillin resistance was very low in E. *faecalis*, but it was very high in *E. faecium*. Ciprofloxacin, High level Gentamycin, High level Streptomycin and Levofloxacine resistances were very high in all Enterococcus species, and especially in *E. faecium*. All *Enterococcus* isolates were susceptible to Linezolid, Tigecycline and Daptomycin. Nitrofurantoin resistance and parenteral penicillin resistance was also very high in *E. faecium* isolates. Teicoplanin resistance was very low in *E. faecalis* isolates but approximately half of the *E. faecium* isolates were resistant to Teicoplanin. There were significant differences between Enterococcus species regarding antibiotic resistance rates (Table 5). Vancomycin resistance was determined in 1.5% of *E. faecalis* isolates but in 45.5% of *E. faecium* isolate. Among Vancomycin resistant isolates, 175 (4 *E. faecalis* and 171 *E. faecium* isolates) were obtained from rectal swabs. Since rectal isolates are regarded as colonization, we should ignore those isolates. In that aspect, Vancomycin resistance was determined in 1.1% of *E. faecalis* isolates but in 30.4% of *E. faecium* isolates.

We also investigated the distribution of Enterococcus species in time and we determined that there was a significant

increase in *E. faecalis* isolates compared with *E. faecium* isolates, in time. In general, female patients were slightly higher when distribution of genders of patients infected with Enterococcus species is evaluated (Figure 2).

Vancomycin resistance rates of different Enterococcus spp in time is summarized in Figure 3. Regarding these findings, Vancomycin resistance rates in *E. fecalis* and *E.spc* were very low in time without significant alterations. However we determined very high Vancomycin resistance rates in *E. faecium* which showed a significant decrease in last 2 years.

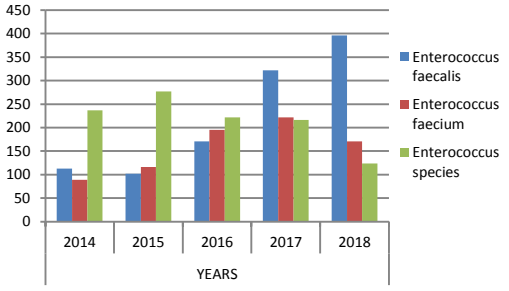


Figure 1: Distribution of Enterococcus species in time

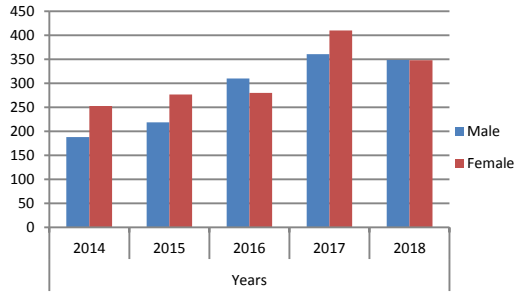


Figure 2: Distribution of gender of patients infected with Enterococcus species in time

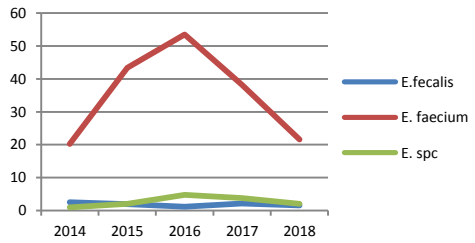


Figure 3: Vancomycin resistance rates of different Enterococcus spp in time

Table 1: The subgroups of isolated Enterococcus spp

| Subgroups | In-patient | Out-patient | Number of isolates (%) |
|---|---|---|---|
| Enterococcus faecalis | 648 | 456 | 1104 (36.8) |
| Enterococcus spp | 337 | 739 | 1076 (35.9) |
| Enterococcus faecium | 750 | 43 | 793 (26.5) |
| Enterococcus casseliflavus/gallinarum | 4 | 10 | 14 (0.46) |
| Enterococcus raffinosus | 5 | 1 | 6 (0.21) |
| Enterococcus durans | 1 | 1 | 2 (0.07) |

Table 2: Different tissues and body fluids from which Enterococcus spp were isolated

| | Number of isolates (%) |
|---|---|
| Urine | 2331 (77.8) |
| Blood | 366 (12.2) |
| Rectal swab | 182 (6.1) |
| Wound swab | 58 (1.9) |
| Catheter | 13 (0.4) |
| Abscess | 11 (0.37) |
| Tissue | 11 (0.37) |
| Peritoneal fluid | 8 (0.26) |
| Cerebrospinal fluid | 8 (0.26) |
| Throat swab | 4 (0.13) |
| Sputum | 1 (0.03) |
| Tracheal aspirate | 1 (0.03) |
| Urethral effluent | 1 (0.03) |

Table 3: Distribution of main Enterococcus subtypes in main tissues and body fluids infected

| | *E. faecalis* n=1104 | *Enterococcus spc* n=1076 | *E. faecium* n=793 | Total |
|---|---|---|---|---|
| Urine | 845 | 1030 | 438 | 2313 |
| Blood | 192 | 21 | 150 | 363 |
| Rectal swab | 5 | 0 | 177 | 182 |
| Wound swab | 32 | 16 | 9 | 57 |

Table 4: Distribution of main Enterococcus subtypes in some wards

| | *E .faecalis* n=1104 | *Enterococcus spc* n=1076 | *E. faecium* n=793 | Total |
|---|---|---|---|---|
| Intensive care unit | 241 | 125 | 385 | 751 |
| Internal medicine | 215 | 117 | 142 | 474 |
| Pediatrics | 16 | 17 | 47 | 80 |
| Hematology | 15 | 13 | 44 | 72 |
| Urology | 30 | 12 | 17 | 59 |

Table 5: Antibiotic resistance rates

| | *E. faecalis* n=1104 (%) | *Enterococcus spc* n=1076 (%) | *E. faecium* n=793 (%) | *P*-value |
|---|---|---|---|---|
| Ampicillin | 62/1093 (5.6) | 275/1072 (25.6) | 729/794 (91.8) | 0.01 |
| Ciprofloxacin | 365 /769 (47.5) | 531/1067 (49.7) | 284/371 (76.5) | 0.01 |
| Fosfomycin | 0 /48 | 259 /992 (26.1) | 6/45 (13.3) | 0.01 |
| High level gentamycin | 493/1103 (44.7) | 359/1055 (34.0) | 481/790 (60.8) | 0.09 |
| Levofloxacin | 449/953 (47.1) | 490/ 1065 (46.0) | 437 /563 (77.6) | 0.02 |
| Linezolid | 0/1103 | 0/1077 | 0 /785 | |
| Daptomycin | 0/212 | 0/4 | 0 /220 | |
| Nitrofurantoin | 46 /950 (4.8) | 100/1019 (9.8) | 161 /260 (61.9) | 0.01 |
| Penicillin (parenteral) | 67 /258 (25.9) | 158 /1008 (15.7) | 215 /261 (82.4) | 0.01 |
| Quinupristin/Dalfopristin | 175/213 (82.1) | 12 /639 (1.8) | 1 /4 (25.0) | 0.01 |
| High level streptomycin | 446 /885 (50.4) | 13 /59 (22.0) | 433/584 (74.1) | 0.01 |
| Teicoplanin | 17 / 1098 (1.5) | 56/1073 (5.2) | 355 /790 (44.9) | 0.01 |
| Tigecycline | 0 /881 | 0/58 | 0/580 | |
| Vancomycin | 17/1092 (1.5) | 48/1073 (4.4) | 360/791 (45.5) | 0.01 |

## Discussion

In this study we analyzed the antimicrobial resistance in 2995 Enterococcus isolates and we determined that approximately half of the E. *faecalis* isolates were resistant to ciprofloxacin, gentamycin, levofloxacin and streptomycin while approximately 80% of *E. faecalis* isolates were resistant to Quinupristin/Dalfopristin. On the other hand, among *E. faecium* isolates, more than 90% were resistant to ampicillin, approximately 75% were resistant to ciprofloxacin, levofloxacin, and streptomycin, and 60% were resistant to gentamycin and nitrofurantoin and approximately half of the isolates were resistant to teicoplanin. Tigecyclin, linezolid and daptomycin resistance was not determined in any Enteroccus isolates. Vancomycin resistance was determined in 1.1% of *E. faecalis* isolates but in 30.4% of *E. faecium* isolates. Moreover, we also determined that, there was a significant increase in *E. faecalis* isolates compared with *E. faecium* isolates, in time.

Enterococci are associated with both community-acquired and nosocomial infections and their antibiotic resistance potential and multidrug resistant isolates poses an important therapeutic challenge [8]. Sattari et al. [9] reported that more than 92% of *E. faecium* isolates were resistant to ampicillin (92.5%), ciprofloxacin (96%), erythromycin (100%) and clindamycin (96%) while a high frequency of resistance to clindamycin (100%), erythromycin (98.5%) and ciprofloxacin (80.5%) was reported in *E. faecalis* isolates, with a less frequent resistance to ampicillin (7%) in a children's hospital. In a study from Korea, Liu et al. [10] reported the ampicillin and penicillin resistance in *E. faecalis* blood strains was as 0.6% and 26.3%, respectively. On the other hand, they reported that resistance to vancomycin (34.0%) and teicoplanin (18.8%) was more frequent in *E. faecium* strains. Mamtora et al. [11] reported that *Enterococcus* spp were highly susceptible to linezolid (96%), vancomycin (92%), and teicoplanin (93.3%) while being resistant to erythromycin and ciprofloxacin. Zallipour et al. [12] reported the highest antibiotic resistance rates against tetracycline (93.5%), erythromycin (87%), and ciprofloxacin (80%) in *E. faecalis* isolates. They did not determine any resistance to fosfomycin or linezolid. Our results were similar with the results of previous studies. In another study performed in our country, more than 80% of the enterococci were reported

to be resistant to tetracycline and erythromycin; but Vancomycin resistance was not defined in any of the 235 Enterococcus isolates obtained in an animal study [13]. In a literature review, *E. faecalis* was reported to have a high resistance rate against erythromycin (67% resistance), gentamicin (65%), trimethoprim/sulfamethoxazole (54%), ciprofloxacin (51%) and oxacillin (49%), whereas nitrofurantoin (4% resistance) and teicoplanin (9%) were the most active agents against this species. On the other hand, *E. faecium* isolates were reported to be mostly resistant against erythromycin (78%), norfloxacin (84%), imipenem (82%) and trimethoprim/sulfamethoxazole (81%), whereas linezolid with no resistance and nitrofurantoin (16%) were the most effective antibiotics [14]. Huang et al. [15] also reported greater resistance rates of *E. faecium* than *E. faecalis* as in our study. They also reported the resistance rates of *E. faecium* to ampicillin and quinolones were more than 80%. Besides, the authors reported that, linezolid resistance in *E. faecalis* increased from 1.6% in 2008 to 2.97% in 2016, and linezolid resistance was higher in *E. faecalis* than in *E. faecium.* However, in our study, we did not determine any linezolid resistance in *Enterococcus spp*.

Vancomycin is regarded as the main treatment option in resistant enterococci infections. However we determined the Vancomycin resistance as 1.1% in *E. faecalis* isolates, but as high as 30.4% in *E. faecium isolates.* An increasing prevalence of vancomycin resistant enterococci (VRE) has been reported in previous literature [16,17]. Zallipour et al. [12] reported that 22.8% of 232 *E. faecalis* isolates were vancomycin resistant (MIC $\geq$ 256 μg/ml). Linezolid is the main treatment option in patients with VRE. Although linezolid resistance was also reported previously, the rates are still very low [18,19]. We also did not determine any isolates resistant to linezolid. Our results were compatible with the previous literature regarding the resistance rates, except very high Vancomycin resistance rates in *E. faecium isolates*.

Another interesting finding of this study was a significant increase in *E. faecalis* isolates compared with *E. faecium* isolates, in time. Due to the lower resistance potential of *E. faecalis* isolates than *E. faecium* isolates, this increased prevalence may be favorable and should be investigated in further studies. Interestingly, we also determined a decrease in Vancomycin resistance rates in *E. faecium* isolates within the last 2 years. In previous literature, the majority of vancomycin-resistant *Enterococcus* isolates were also defined as *E. faecium* and the resistance rates were reaching more than 80% [20]. High Vancomycin resistance rates were associated with long hospital stays and extended use of antibiotics [21]. This decrease in Vancomycin resistance rates in recent years may be associated with an increased awareness of this condition by clinicians and precautions taken to decrease this resistance which should also be investigated in further studies.

The main power of this study was the high number of isolates included in the study. However, these results were obtained from a single center and we did not perform any resistance analyses at molecular or genetic level, which are the main limitations.

## Conclusion

We determined high resistance rates to many antibiotics in both *E. faecalis* and *E. faecium* isolates. Tigecyclin, linezolid and daptomycin resistance was not determined in any Enteroccus isolates. Vancomycin resistance was determined *in 1.1%* of *E. faecalis* isolates and in *30.4%* of *E. faecium* isolates. This high rate of vancomycin resistance should be taken into account and studies should be conducted to eliminate this resistance. However, we also determined a decrease in Vancomycin resistance in last two years in *E. faecium*, which should also be confirmed with prospective clinical studies.

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