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The change of antibiotic resistance rates over the years in *Enterococcus* spp. isolated from clinical specimens

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ABSTRACT

Aims: The aim of this study was to retrospectively evaluate the change in antibiotic resistance rates of *Enterococcus* species isolated from various clinical samples of outpatients and inpatients in our hospital over the years.

Methods: Between January 2018 and December 2021, various clinical samples sent to Tekirdağ Namık Kemal University Hospital Microbiology Laboratory from outpatients, inpatients and intensive care patients were retrospectively examined. The samples were inoculated on 5% sheep blood agar, chocolate agar and EMB agar media according to their types and incubated at 37°C. The blood cultures were performed by BACTEC 1280 System (Becton Dickinson, MA, USA). Bacterial identification and antimicrobial sensitivity tests were made using conventional methods and automated systems.

Results: A total of 417 *Enterococcus* strains were isolated in our laboratory at four years and included in the study. Of the 417 isolates, 204 (48.9%) were isolated from male patients and 213 (51.1%) from female patients. The mean age of the patients was 57.79±22.9 years (0-96 years). It was determined that 36.9% of the isolates belonged to outpatients, 33.4% to inpatients and 29.7% to intensive care unit patients. Of the 122 enterococci isolates identified as species, 49.2% were typed as *Enterococcus faecalis* (*E. faecalis*) and 40.2% as *Enterococcus faecium* (*E. faecium*). Of the 417 isolates, 60.4% were isolated from urine samples, 24.2% from blood samples, and 8.9% from wound samples. Considering the total antibiotic resistance rates; ampicillin was 34.9%, ciprofloxacin was 46.4%, vancomycin was 8.4%, tigecline was 3.2%, high-level gentamicin was 49.0%. Linezolid and nitrofurantoin resistance were not detected. Ampicillin and vancomycin resistance rates were determined to have a statistically significant increase within four years. Ampicillin, ciprofloxacin, vancomycin and high-level gentamicin resistance rates were found to be significantly higher in isolates obtained from inpatients and intensive care patients compared to enterococcal isolates obtained from outpatients.

Conclusion: In our study, it was determined that antibiotic resistance in enterococcal isolates, which are the causative agents of infection in our hospital, increased over the years. In this way, determining the change in antibiotic resistance rates is beneficial in determining appropriate antibiotic use policies. It is thought that conducting surveillance studies on antibiotic resistance periodically and taking new measures according to changing antibiotic resistance rates will be beneficial in terms of treatment.

Keywords: *Enterococcus*, antibiotic resistance, vancomycin, vancomycin resistant enterococci (VRE)

INTRODUCTION

Enterococci are gram-positive cocci that are found as single, pairs or short chains as one of the main elements of the microbiota in the mouth and vagina, especially in the gastrointestinal tract of humans and all other land animals.[1,2]

Enterococci cause various community and hospital-acquired infections such as urinary tract infection, bacteremia, neonatal sepsis, endocarditis, intra-abdominal and pelvic infections, wound and tissue infections, meningitis, hospital-acquired pneumonia. The ability of enterococci to transfer resistance and virulence genes, the colonization ability of the bacteria, widespread or incorrect antibiotic use, invasive applications like catheters, serious diseases of the patients or long-term hospital stays cause an increase in the incidence of hospital-acquired enterococcal infections. Enterococci have increased the importance of infecting patients with impaired host defenses, increasing resistance to antibiotics used in treatment, and causing serious and high-mortality infections. In recent years, the clinical importance of enterococci has increased with the increase in resistance to antibiotics, including vancomycin.[3-7]

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Antibiotic resistance is one of the most important health problems of today, and it is very important for each hospital to regularly monitor their own antibiotic resistance surveillance and to determine antibiotic restriction programs accordingly.[8]

In this study, we aimed to analyze retrospectively the change in antibiotic resistance rates of *Enterococcus* species isolated from various clinical samples of outpatients and inpatients in our hospital over the years.

METHODS

The study was carried out with the permission of Tekirdağ Namık Kemal University Non-interventional Clinical Researches Ethics Committee (Date: 26.04.2022, Decision No: 2022.51.04.01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Bacteria Isolation

Between January 2018 and December 2021, various clinical specimens (urine, blood, wound, respiratory, sterile body fluids, catheter, vaginal secretion samples) sent to the microbiology laboratory of Tekirdağ Namık Kemal University Hospital from outpatients, inpatients and intensive care patients were retrospectively analyzed. Clinical specimens were inoculated on 5% sheep blood agar (Oxoid, UK), chocolate agar (Oxoid, UK) and EMB agar (Oxoid, UK) media. Peritoneal and wound samples were incubated for 72 hours, CSF samples for 120 hours and other samples for 24-48 hours at 37°C. Blood cultures were followed in the BACTEC (Becton Dickinson, USA) automated blood culture system. Isolates were isolated by conventional methods (colony morphology, Gram stain, catalase, PYR) and automated bacterial identification system (VITEK2, bioMérieux, France/2018-2019 ve BD Phoenix 100, Becton Dickinson, USA/2020-2021). The first isolate was evaluated in repeated samples from the same patient.

Antibiotic Susceptibility Test

Enterococcal strains isolated from clinical samples were tested for antibiotic susceptibility by Kirby-Bauer disc diffusion and automated system (VITEK2, bioMérieux, France/2018-2019 and BD Phoenix 100, Becton Dickinson, USA/2020-2021) using European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards.[9] Ampicillin, nitrofurantoin and ciprofloxacin were reported for uncomplicated UTIs only. Also nitrofurantoin was evaluated only in *E. faecalis* strains according to EUCAST criteria. Isolates with vancomycin resistance in both methods were confirmed by gradient test (Liofilchem, Italy). Internal quality control for disk diffusion method is made once in a month and external quality control three periods in a year (*E. faecalis* ATCC 29212 strain used).

Statistical Analysis

IBM SPSS Statistics for Windows Version 22.0 (Statistical Package for the Social Sciences, IBM Corp, Armonk, NY, USA) package program was used for statistical analysis of the obtained data. Quantitative and categorical results were expressed as numbers and percentages. Chi-square test was used to compare and evaluate different groups of variables, and a p value of 0.05 or less was considered statistically significant.

RESULTS

A total of 417 enterococci strains were isolated in our laboratory in a four-year period and included in the study. Of the 417 isolates, 204 (48.9%) were isolated from male patients and 213 (51.1%) from female patients. The mean age of the patients was 57.79±22.9 years (0-96 years).

The distribution of enterococci isolates according to the clinics (outpatient, inpatient and intensive care unit) and years of isolation is given in **Table 1**. It was determined that 36.9% of the isolates belonged to outpatients, 33.4% to inpatients and 29.7% to intensive care unit patients.

Species identification was made for only 122 isolates out of 417 isolates included in the study. Of the isolates identified to species, 49.2% were *Enterococcus faecalis* (60/122), 40.2% were *Enterococcus faecium* (49/122), 3.3% were *Enterococcus durans* (4/122), 2.5% were *Enterococcus casseliflavus* (3/122), 1.6% were *Enterococcus raffinosus* (2/122), 2.5% were *Enterococcus gallinarum* (3/122) and 0.8% was *Enterococcus avium* (1/122). *E. faecalis* was the most frequently isolated one, followed by *E. faecium*.

Table 1. Distribution of Enterococci isolates by isolated clinics and years (n/%)

Clinics	Years								Total	
	2018		2019		2020		2021			
	n	%	n	%	n	%	n	%	n	%
Outpatient clinics	42	44.7	29	38.7	27	28.1	56	36.8	154	36.9
Inpatient clinics	33	35.1	22	29.3	34	35.4	50	32.9	139	33.4
Intensive care unit	19	20.2	24	32.0	35	36.5	46	30.3	124	29.7
Total	94	100	75	100	96	100	152	100	417	100

417 isolates were isolated from patients treated in 44 different clinics. Isolates were mostly obtained from intensive care unit patients with 29.5% and urology clinic patients with 24.5% (nephrology 7.4%, pediatrics 6.0%, oncology 5.0%, surgery 3.8%, infectious diseases 3.8%, orthopedics 3.4%, hematology 3.1%, internal medicine 2.2% and others clinics 11.2%). When the distribution of *E. faecalis* and *E. faecium* isolated from clinics was analyzed, both species were isolated mostly from intensive care unit patients with a rate of 51.7% and 49%, respectively.

Isolates were mostly isolated from urine, blood and wound samples, respectively. Of 417 isolates, 253 (60.4%) were isolated from urine samples, 101 (24.2%) from blood samples and 37 (8.9%) from wound samples. The remaining 26 isolates were isolated from sputum, cerebrospinal fluid (CSF), throat, drainage, catheter, peritoneal fluid, respiratory secretion and vaginal samples (Table 2). Of the species identified isolates, both *E. faecalis* and *E. faecium* were highest in blood, urine and wound samples, respectively.

In our study all isolates were analyzed for resistance rate without species discrimination and the highest resistance rates were high-level gentamicin resistance with 49.0% (39.5%in *E. faecalis*, 89.5% in *E. faecium*) and ciprofloxacin resistance with 46.4% (42.9% in *E. faecalis*, 93.3% in *E. faecium*). Ampicillin resistance rate was 34.9% (12.5% in *E. faecalis*, 93.3% in *E. faecium*) , vancomycin was 8.4% (3.4% in *E. faecalis*, 30.4% in *E. faecium*). Vancomycin resistance was detected in 2 of 59 *E. faecalis* (intensive care unit) isolates and 14 of 46 *E. faecium* (8 inpatient clinics, 6 intensive care unit) isolates and confirmed by gradient test. While resistance was detected against tigecycline at the rate of 3.2% in all 417 isolates, no resistance was detected in *E. faecium* and *E. faecalis* isolates. Linezolid resistance (0%) was not detected in the isolates (Table 3).

Table 3: Antibiotic resistance rates of Enterococci isolates (%)

Antibiotics	*Enterococcus* spp. (n=417)	*E. faecalis* (n=60)	*E. faecium* (n=49)
AMP	34.9	12.5	93.3
CIP	46.4	42.9	93.3
VAN	8.4	3.4	30.4
LZD	0.0	0.0	0.0
TIGE	3.2	0.0	0.0
GEN	49.0	39.5	89.5
NIT	-	0.0	-

AMP: Ampicillin, CIP: Ciprofloxacin, VAN: Vancomycin, LZD: Linezolid, TIGE: Tigecycline, GEN: High-level gentamicin, NIT: Nitrofurantoin

The distribution of antibiotic resistance rates among outpatient clinic, inpatient clinic and intensive care unit patients from whom enterococcal isolates were isolated was analyzed and ampicillin, ciprofloxacin, vancomycin and high-level gentamicin resistance rates of isolates obtained from inpatients and intensive care unit patients were statistically significantly higher than enterococcal isolates obtained from outpatients (p<0,05) (Table 4).

Table 4. Antibiotic resistance rates according to the clinic where Enterococci isolates are isolated (%)

Antibiotics	Total	Outpatient clinics	Inpatient clinics	Intensive care	p
AMP	34.9	14.1	66.7	47.5	0.000*
CIP	46.4	30.1	69.1	67.6	0.000*
VAN	8.4	2.0	11.9	12.5	0.002*
LZD	0.0	0.0	0.0	0.0	-
TIGE	3.2	0.0	3.0	4.0	0.759
GEN	49.0	9.1	54.5	50.0	0.020*
NIT	0.0	0.0	0.0	0.0	-

AMP: Ampicillin, CIP: Ciprofloxacin, VAN: Vancomycin, LZD: Linezolid, TIGE: Tigecycline, GEN: High-level gentamicin, NIT: Nitrofurantoin (only for *E. faecalis*)
*p<0,05

Table 2. Distribution of Enterococci isolates according to the samples and years of isolation (n/%)

Samples	Years								Total	
	2018		2019		2020		2021			
	n	%	n	%	n	%	n	%	n	%
Urine	61	64.9	49	65.3	53	55.2	90	59.3	253	60.4
Blood	17	18.1	24	32.0	25	26.0	35	23.0	101	24.2
Wound	10	10.6	2	2.7	11	11.5	14	9.2	37	8.9
Peritoneal fluid	1	1.1	0	0.0	0	0.0	6	3.9	7	1.7
Sputum	2	2.1	0	0.0	1	1.0	2	1.3	5	1.2
Respiratory secretion	2	2.1	0	0.0	2	2.1	1	0.7	5	1.2
Vaginal secretion	1	1.1	0	0.0	0	0.0	4	2.6	5	1.2
CSF	0	0.0	0	0.0	1	1.0	0	0.0	1	0.2
Throat	0	0.0	0	0.0	1	1.0	0	0.0	1	0.2
Drainer	0	0.0	0	0.0	1	1.0	0	0.0	1	0.2
Catheter	0	0.0	0	0.0	1	1.0	0	0.0	1	0.2
Total	94	100	75	100	96	100	152	100	417	100

*CSF: Cerebrospinal fluid

The change in antibiotic resistance rates of 417 isolates over the years was analyzed and it was observed that the resistance rates to ampicillin, ciprofloxacin, vancomycin and high-level gentamicin detected in 2018 decreased in 2019 and increased again in 2020 and 2021. The increase in resistance to ampicillin and vancomycin continued in 2021 and was found to be statistically significant ($p<0.05$) (Table 5).

Table 5. Antibiotic resistance rates of Enterococci isolates over the years (%)

Antibiotics	Year				p
	2018	2019	2020	2021	
AMP	26.2	24.5	49.1	38.2	0.004*
CIP	41.0	39.6	48.1	53.5	0.244
VAN	11.0	2.7	11.9	12.5	0.002*
LZD	0.0	0.0	0.0	0.0	-
TIGE	0.0	0.0	2.5	8.2	0.111
GEN	65.2	36.4	46.3	49.3	0.268
NIT	0.0	0.0	0.0	0.0	-

AMP: Ampicillin, CIP: Ciprofloxacin, VAN: Vancomycin, LZD: Linezolid, TIGE: Tigecycline, GEN: High-level gentamicin, NIT: Nitrofurantoin (only for *E. faecalis*)
*p<0,05

DISCUSSION

Enterococci, which are among the human flora elements, cause many clinical manifestations in both outpatients and inpatients, especially urinary system infections. They are considered to be one of the most common causes of nosocomial infections, especially due to their colonization ability and their ability to develop resistance to antibiotics used in treatment. In the literature, they are also reported as common pathogens in wound and bloodstream infections.[10-15] Mataj et al.[16] investigated the prevalence of the microorganisms isolated from blood cultures for a ten-year period and found that *Enterococcus* spp. isolation rates has increased between the first and the last five-year period. In our study, it was determined that 63.1% of the isolates belonged to inpatients. Also, most of the isolates were isolated from urine samples with a rate of 60.4%, followed by blood samples with 24.2% and wound samples with 8.9%, and this order did not change over the years. This result suggests that *Enterococcus* species may be an important cause of bacteremia in addition to urinary tract infections in our hospital.

It is reported that 80-90% of enterococcal infections are caused by *E. faecalis* and 5-10% by *E. faecium*, but in recent years, the incidence of *E. faecium* strains has increased in relation to its ability to resist more than one antibiotic, especially in inpatients.[10,17] In two studies conducted from samples of inpatients in Brazil and Italy, 82.2-87% of isolates were reported to be *E. faecalis* and 10.8-17.8% were reported to be *E. faecium* (18,19). In our country, Agus et al.[20] identified 77% of the isolates as *E. faecalis* and 23% as *E. faecium* in outpatients and inpatients. Celik et al.[21] identified 60.8% of the isolates as *E. faecalis* and 38.2% as *E. faecium* only in inpatients. In our study, only 122 isolates were identified at the species, 49.2% of them were typed as *E. faecalis* and 40.2% as *E. faecium*. Species identification of *Enterococcus* in our hospital is frequently made in samples of inpatients, and we think that this may cause the frequency of *E. faecium* to be detected a little higher than in other studies.

Studies on ampicillin, the first-line antimicrobial agent used in the treatment of enterococcal infections, have shown that ampicillin resistance rates have increased in recent years. Sig et al.[22] determined ampicillin resistance as 28.9% in *Enterococcus* spp., 2.4% in *E. faecalis* and 85.6% in *E. faecium*. Odemis et al.[17] found ampicillin resistance in 50% of *E. faecalis* and 94% of *E. faecium* in samples from inpatients in 2010-2015. Bilgin et al.[23] determined ampicillin resistance as 8.1% in *E. faecalis* and 95% in *E. faecium* in outpatient and inpatient samples in 2018. Simsek[24] reported ampicillin resistance as 31.9% in *Enterococcus* spp., 10.6% in *E. faecalis*, and 83.9% in *E. faecium* in samples from outpatients and inpatients in 2019. In our study, it was observed that the ampicillin resistance rates were consistent with the studies and showed a statistically significant increase over the years.

Ciprofloxacin is used in the treatment of urinary tract infections due to enterococci.[24] Etiz et al.[25] found ciprofloxacin resistance rate as 66.6% in *Enterococcus* spp., 42.5% in *E. faecalis* and 94.3% in *E. faecium* in a study including only enterococci isolates from urine samples. In our study, the ciprofloxacin resistance rate of 417 enterococcal isolates was 46.4%. It was determined that ciprofloxacin was the second antibiotic with the highest resistance rate in the study and that the resistance increased over the years, although not statistically significant. With these results, we believe that ciprofloxacin is not a suitable option for empirical treatment of enterococcal UTIs in our hospital.

Nitrofurantoin is an antibiotic that can be used in the treatment of urinary tract infections due to *E. faecalis* in accordance with EUCAST recommendations.[26] Yenisehirli et al.[27] reported nitrofurantoin resistance as 4.3% in *E. faecalis* isolates obtained from urine samples between 2011 and 2014. In our study, nitrofurantoin resistance was evaluated only in *E. faecalis* strains that isolated in urine samples, and no resistance was observed.

In different studies, high-level gentamicin resistance has been reported in the range of 39.4-52% in *Enterococcus* spp., 27-57.2% in *E. faecalis*, and 39.7-70% in *E. faecium*.[10,28-30] In our study, high-level gentamicin resistance was determined as 49% in total, 39.5% in *E. faecalis* and 89.5% in *E. faecium*. It can be said that the total

high-level gentamicin resistance rate and the resistance rate of *E. faecalis* isolates in our study are compatible with other studies, but the resistance rate of *E. faecium* isolates was found to be higher than other studies. In the evaluation of resistance rates, the clinic from which the sample was isolated (outpatient or inpatient) is a factor affecting the result. In our study, high-level gentamicin resistance was statistically significantly higher in inpatients compared to outpatients. The high resistance observed in *E. faecium* may be related to this.

Glycopeptides are among the most effective antibiotics in enterococcal infections. Vancomycin-resistant enterococci (VRE) were identified in 1986 and enterococcal strains resistant to these antibiotics have been observed in many countries.[31] In the reports of the European Antimicrobial Resistance Surveillance System published in 2019, it was reported that there was a significant increase in VRE rates in Europe and the vancomycin resistance rate of *E. faecium* isolates was 18.3%.[32] In the summary report of the National Healthcare Associated Infections Surveillance Network conducted in our country in 2019, the vancomycin resistance rate in *E. faecalis* was reported as 3.8% and 18.9% in *E. faecium*.[33] In the 2019 annual report published by the National Antimicrobial Resistance Surveillance System (UAMDSS), the vancomycin resistance rate was reported as 1% and 13% for *E. faecalis* and *E. faecium* isolates, respectively.[34] In recent studies conducted in our country, vancomycin resistance was detected between 4.5-16% in *Enterococcus* spp., 0-4% in *E. faecalis* and 8.2-23% in *E. faecium*.[10,29,35,36] In our study, vancomycin resistance was found to be 8.4% in all isolates, 3.4% in *E. faecalis* and 30.4% in *E. faecium* isolates. The resistance rates we found are higher than other studies. There could be several reasons for this. First of all, since species identification could not be made all of the *Enterococcus* spp., isolates innate resistant to vancomycin could not be excluded. In addition, the low number of *E. faecalis* and *E. faecium* isolates included in the study may be the reason for high resistance rates. Also, it is observed that the number of resistant isolates increased in 2020 and 2021. Therefore, we think that some precautions should be taken in terms of VRE infections in our hospital.

Linezolid is an important antimicrobial used for the treatment of VRE.[37] In the 2016 report published by the National Antimicrobial Resistance Surveillance System, it was reported that the linezolid resistance rate was 1% for *E. faecium* isolates, while no resistance was detected for *E. faecalis*.[30] In a study by Dadashi et al.[38] analyzing 114 studies conducted between 2000 and 2020, linezolid resistance was reported as 2.8%, 2.1% and 0.7% for *E. faecalis* and 0.9%, 1.8% and 3.4% for *E. faecium* in Asia, Europe and the Americas, respectively. In a 15-year meta-analysis from Turkey, the mean resistance rates to vancomycin and linezolid was reported to 1.0±2.2% and 1.9±2.6% in *E. faecalis* and 10.3±11.3% and 2.4±0% in *E. faecium*, respectively.[39] In our study, no linezolid-resistant isolates were detected. This is a good result for our hospital.

Tigecycline is a broad spectrum antibiotic with antimicrobial activity in gram positive and gram negative bacteria and is used in VRE infections.[38] In different studies, tigecycline resistance rate in *Enterococcus* spp. has been reported to be around 1%.[24,38] In our study, the rate of tigecycline resistance in enterococcal isolates was determined as 3.2%. The tigecycline resistance rate we obtained in our study was higher than other studies. This may be because more than 60% of the samples included in our study belonged to inpatients and intensive care unit patients. In addition, tigecycline resistance could not be studied with the reference method, the broth microdilution method, in our study. This may have caused our results to be higher than other studies.[40]

In our study, only 122 of the 417 isolates we isolated were identified as species, and 295 isolates were *Enterococcus* spp. was typed. This is the main limitation of our study. The retrospective design of the study and the inability to study tigecycline resistance with the broth microdilution method in line with EUCAST recommendations are other limitations.

CONCLUSION

In our study it was determined that enterococci can be an important infectious agent in our hospital, resistance rates have increased over a four-year period, and this increase is statistically significant for antibiotics that are important in the treatment of enterococcal infections such as ampicillin and vancomycin. Antibiotic resistance is one of the most important health problems of today, and isolates resistant to last-line antibiotics such as vancomycin pose a serious risk for public health. In this way, determining the change in antibiotic resistance rates is useful in determining the appropriate antibiotic use policies. It is thought that periodic surveillance studies on the basis of country, province, district and hospital regarding antibiotic resistances and taking new measures according to changing antibiotic resistance rates will be beneficial in terms of treatment selection and success.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Tekirdağ Namık Kemal University Non-interventional Clinical Researches Ethics Committee (Date: 26.04.2022, Decision No: 2022.51.04.01).

Informed Consent: Written informed consent was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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