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Comparisons of Enterococcus Species Isolated From Patients Diagnosed With COVID-19 and Their Antibacterial Susceptibility With The One-Year Period Before The Pandemic

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ABSTRACT

In our study, the enterococci species isolated before the pandemic (BP) and the enterococci isolated from COVID-19 patients during the pandemic period (DP) and antibiotic susceptibility results were retrospectively analyzed. In these two periods, it was aimed to investigate the effects of antibiotics preferred for treatment on susceptibility status. The isolation and antibiotic susceptibilities of enterococci were defined by conventional methods and an automatized system (VITEK 2). The antibiotic susceptibilities have been evaluated according to EUCAST. The amount of antibiotic use in our hospital during these periods was obtained from pharmacy data. For the BP period 221 (7%) enterococci strains were included, and for the DP period, 146 (5.9%) enterococcus species that have been isolated only from COVID-19 patients have been included in the study. In both periods, the most frequently isolated enterococcus species is *E.faecalis*. In DP, the susceptibilities for ampicillin, ciprofloxacin, linezolid, high-level streptomycin (HLS), teicoplanin, and vancomycin have increased when compared to BP. High-level gentamycin (HLG) and tigecycline susceptibilities have decreased in DP when compared to BP.

It was observed that the increase in antibiotic use was reflected in the susceptibility rates. In the DP period, it was observed that ampicillin, vancomycin, teicoplanin, and ciprofloxacin were consumed less for the treatment, and accordingly, there was an increase in the sensitivity of these antibiotics. It was determined that the increase in the consumption of aminoglycoside, tetracycline, and tigecycline caused to decrease in the susceptibility of gentamicin and tigecycline. It was concluded that strategies for rational antibiotic prescribing to COVID-19 patients should be considered in order to prevent the negative effects of inappropriate antibiotic use from reaching levels that cannot be compensated for after the ongoing pandemic.

Keywords: Enterococci, COVID-19, pandemic, antibacterial susceptibility, antibiotic consumption

Introduction

Enterococci, which are gram-positive facultative anaerobic bacteria that inhabit the gastrointestinal microbiota of humans and animals, are important hospital-acquired infectious agents. Despite there being numerous species of enterococcus, the most commonly found species in humans are *Enterococcus faecalis* and *Enterococcus faecium* (1).

Enterococci with antibiotic resistance have an important place among nosocomial pathogens. There are difficulties in the design of treatment protocols for patients due to the acquired antibiotic resistance of enterococci alongside species-specific natural resistance. In the last few years, there have been reports of increasing resistance of enterococcus species, specifically against high-level aminoglycosides, beta-lactams, and glycopeptides (2). It is thought that the

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COVID-19 pandemic contributes to this increasing resistance profile. Various studies conducted in Germany, Italy, and the USA have reported increases and epidemics in infections caused by multidrug-resistant bacteria during the COVID-19 pandemic (3,4). Enterococci develop resistance to many antimicrobials thanks to genetic changes. Revealing these resistance rates could be a guide in the precautions against the rapid spread of infections and treatment approaches (5).

Epidemiological studies have shown a direct relationship between antibiotic consumption and the emergence and spread of resistant bacterial strains. Therefore, antibiotics should be prescribed and used appropriately (6). Early treatment with appropriate and rational antimicrobials has been shown to reduce morbidity and mortality in bacterial infections (7). Also, there are studies reporting that a positive effect of appropriate empiric treatment on patient prognosis (8). In this context, it was aimed to reveal the change in enterococcal species isolated before the pandemic (BP) and the enterococcal species isolated from COVID-19 patients during the pandemic period (DP) and to reveal the reflection of antibiotic preferences in these periods on antibiotic susceptibility of enterococcal species, in our study.

Materials and Methods

In our study, enterococci strains and antibacterial susceptibilities isolated from patients treated in the COVID-19 services and COVID-19 ICU in DP (1 March 2020 - 1 March 2021) and enterococci strains isolated in BP (1 March 2019-29 February 2020), and antibacterial susceptibilities were compared retrospectively. Enterococci strains isolated from patients with positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) test result with oropharyngeal and nasopharyngeal swabs or negative RT-PCR test and diagnosed with COVID-19 by clinical, thoracic computed tomography (CT) and other laboratory findings were included in this study. The amount of antibiotic use in our hospital during these periods was obtained from pharmacy data.

The blood culture bottles that have arrived in our lab were evaluated using the BACTEC 9120 (Becton-Dickinson Diagnostic Instrument Systems, USA) automated system. The samples that gave a "positive warning" in the blood culture bottles as well as other samples were seeded in 5% sheep blood agar and eosin methylene blue agar (EMB). After 18-24 hours of incubation at 37 ^{0}C, enterococcus species have been identified using conventional methods, Gram staining, catalase test, PYR test (L-pyrrolidinyl-β-naphthylamide), growth at 6.5% NaCl containing medium, and VITEK 2 automatized system (BioMérieux, France). The antibiotic sensitivities of enterococcus species have been evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria (9). High-level gentamycin (HLG) and high-level streptomycin (HLS) resistance were determined as positive and negative. The resistance status of isolates identified as vancomycin- and teicoplanin-resistant in the VITEK 2 automatized system were confirmed by studying MIC values with E-test (BioMérieux, France).

The study's findings were analyzed using Statistical Package for Social Science for Windows (SPSS) 24.0 package program. Frequency and percentage distribution analysis was utilized in determining the patients' sex, enterococcus species, and antibiotic sensitivity distributions. Patients' ages were indicated as mean and standard deviation. The Chi-square test of independence was used to investigate whether there were statistically significant changes in enterococcus species and their antibiotic sensitivities between the BP and DP period. Independent samples t-test was used to statistically investigate age differences of patients from whom enterococci were isolated between the two time periods. The results were considered statistically significant within the 99% ($p<0.001$) and 95% ($p<0.05$) confidence interval.

This study has been approved by the Firat University Ethics Committee (Decision No:09-31, Date: 16.09.2021) and is in line with the principles of the Helsinki Declaration.

Results

It has been delivered 15.632 samples to our laboratory in one year in the BP period. Enterococcus species have been identified in 221 (7%) of the samples that showed growth. In DP, it has been delivered a total of 12.671 samples to our laboratory. Enterococcus species have been identified in 278 (11.23%) of the samples that showed growth. For the DP period, 146 (5.9%) enterococcus species isolated only from COVID-19 patients have been included in the study.

There were no significant differences in patients' sex distribution for samples from which

Table 1. Distribution of Clinical Samples According To Services and Intensive Care Units

	BP n (%)	DP n (%)
*ICU	169(76,5)	95(65,1)
SERVICES	52(23,5)	51(34,9)
TOTAL	221	146
	p=0.017	

BP: Before pandemic, **DP**: During pandemic, ***ICU:** Intensive care units

Table 2. Antibiotic Susceptibility Rates of Enterococci, According To Pre-Pandemic Period and During The Pandemic Period.

	E. durans/hirae		*E. faecalis*		*E. faecium*		
	BP=53 %	DP=14 %	BP=107 %	DP=81 %	BP=47 %	DP=43 %	p
Ampicillin	37.7	71.4	44.9	58.0	48.9	51.2	0.027
Ciprofloxacin	11.3	28.6	17.8	43.2	8.5	46.5	0.007
*HLG	17.0	7.1	8.4	0	12.8	2,3	0.039
Linezolid	96.2	100	88.8	95.1	87.2	95.3	0.0001
**HLS	1.90	14.30	0	0	2.1	4,8	0.0001
Vancomycin	81.1	85.7	78.5	88.9	78.7	88.4	0.0001
Teicoplanin	86.8	92.9	88.8	91.4	89.4	93	0.0001
Tigecycline	100	99.7	99.7	99.2	99.5	99.2	0.042

E: Enterococcus, ***HLG:**High-level gentamycin, ****HLS:** High-level streptomycin, **BP:** Before pandemic, **DP**: During pandemic

enterococcus species have been isolated between the BP and DP periods (p=0.006). In the one-year BP period, 141 (66.2%) of the patients from whom enterococci were isolated were female whereas 80 (33.8%) were male. In the DP period, 72 (51.9%) of the patients from whom enterococci were isolated were female whereas 74 (48.1%) were male.

There were significant differences in the mean ages of patients from whom enterococci were isolated in the BP and DP periods (p=0.002). The mean age of patients from whom enterococci were isolated in the one-year BP period was 71.01±23.54, whereas the mean age was 62.34±23.68 in the DP period. For the samples from which enterococci were isolated in the BP and DP periods, a significant change in the distribution of samples coming from the service and intensive care units were observed. (p=0.017). The rate of samples coming from the ICUs was 76.5% in the BP period and it was 65.1% in the DP period. The rate of samples coming from the services was 23.5% in the BP period while it was 34.9% in the DP period (Table 1).

The rates of enterococci isolated from blood and wound cultures decreased while growth in urine culture increased in the DP period when compared to the BP period. In both BP (75.6%) and DP (81.5%) periods, enterococcus species were isolated mostly from urine culture samples. However, these differences were not statistically significant (p=0.538) (Figure 1).

There was no significant difference between the rates of enterococci in the samples with growth in BP and DP periods (p=0.085). The 7% of samples with growth showed enterococci in the BP period, while this rate dropped down to 5.9% in the DP period.

There was a significant difference between BP and DP periods in terms of enterococcus species (p=0.019). *E. faecalis* was isolated at 48.4% in the BP period and 55.5% in the DP period. *E. faecium* was isolated at 21.3% in the BP period and 29.5% in the DP period. In both periods, the most commonly isolated enterococcus species was *E. faecalis. E. durans/hirae* was isolated at 24% in the BP period and 9.6% in the DP period. In the DP period, there was a significant decrease in the isolation rates of *E. casseliflavus*, *E. durans/hirae,* and *E. gallinarum* species (Figure 2).

When compared to the BP period, the antibiotic susceptibilities of enterococcus species against to ampicillin, ciprofloxacin, linezolid, HLS, teicoplanin, and vancomycin increased in the DP

Table 3. Antibiotic Consumption in BP and DP in Our Hospital

	BP n(%)	DP (n)(%)	TOTAL
Ampicillin (500 mg)	7.333 (19.3%)	5.341 (16.4%)	12.674
Ciprofloxacin (500 mg)	5.213 (13.7%)	3.911 (12%)	9.124
Ciprofloxacin (200 mg)	5.055 (13.3%)	2.006 (6.2%)	7.061
Aminoglycoside (500 mg)	1.563 (4.1%)	1.873 (5.7%)	3.436
Linezolid (600 mg)	2.461 (6.5%)	4.200 (12.9%)	6.661
Vancomycin (1 gr)	8.400 (22.1%)	8.298 (25.5%)	16.698
Teicoplanin (1 gr)	2.947 (7.8%)	1.210 (3.7%)	4.157
Tigecycline (50 mg)	4.621 (12.1%)	5.535 (17%)	10.156
Tetracycline (500 mg)	80 (0.2%)	90 (0.3%)	170
TOTAL	38.018 (100%)	32.565 (100%) p<0.001	70.583

BP: Before Pandemic**, DP:** During Pandemic

period. The susceptibilities against HLG and tigecycline decreased significantly in the DP period when compared to the BP period. The changes observed in susceptibility rates against all antibiotics were statistically significant (p<0.05) (Table 2).

Isolates of *E. avium* showed 100% resistance against ciprofloxacin, HLG, and HLS antibiotics in the DP period. *E. casseliflavus* isolates showed 100% resistance against to ciprofloxacin in the BP period, and against to ciprofloxacin and gentamycin in the DP period. Moreover, susceptibilities against to ampicillin, HLS, teicoplanin, and vancomycin increased in the DP period. While isolates of *E. gallinarum* showed 100% resistance against to ciprofloxacin and HLG in the BP period, they did not show susceptibility against to gentamycin in the DP period. The differences between the two time periods could not be statistically analyzed due to the insufficient numbers of *E. avium, E. casseliflavus,* and *E. gallinarum* isolates.

In the DP period, the sensitivity of *E. durans/hirae* isolates against to ampicillin, ciprofloxacin, vancomycin, and teicoplanin increased significantly while HLG and tigecycline susceptibilities decreased (p<0.05).

In the DP period, the susceptibilities of *E. faecalis* isolates against to ampicillin, ciprofloxacin, linezolid, vancomycin, and teicoplanin increased significantly while HLG and tigecycline susceptibilities decreased. There was a significant increase in the susceptibilities of *E. faecium* isolates against to ciprofloxacin, vancomycin, and teicoplanin in the DP period, while HLG and tigecycline susceptibilities decreased (p<0.05).

According to the data obtained from the pharmacy of our hospital, a decrease was observed in the consumption of ampicillin, ciprofloxacin, vancomycin, and teicoplanin. In contrast, increased consumption of aminoglycosides, tigecyclines, and tetracyclines was observed (p<0.001) (Table 3).

Discussion

E. faecalis and *E. faecium* are the most prominent resistant enterococcus types **(**10). The use of wide-spectrum antibiotics, prolonged hospitalization, and other underlying diseases increase the colonization of resistant enterococcus species, which facilitates the occurrence of infection. The increase in resistant enterococcus isolates have been shown to cause bad prognosis in COVID-19 patients (11). Palanisamy et al. (12) have determined that enterococcus isolates are relatively more in bloodstream infections in the DP period and that most of these (81.8%) are resistant to multidrug. In Italy, in 78 of critical COVID-19 patients who developed bloodstream infections after admission to the ICU, *E. faecalis* was identified as the cause of infection in 18% (13). A study reported that most of the ICU-related infections in 60 of hospitalized COVID-19 patients were caused by *E. faecalis* and *E. faecium* isolates (14). In our study, it was observed that the majority of species isolated from COVID-19 patients consisted of *E. faecalis* (55.5%) and *E. faecium* (29.5%). A significant increase in these isolates in the DP period was observed compared to the BP period. These results support the

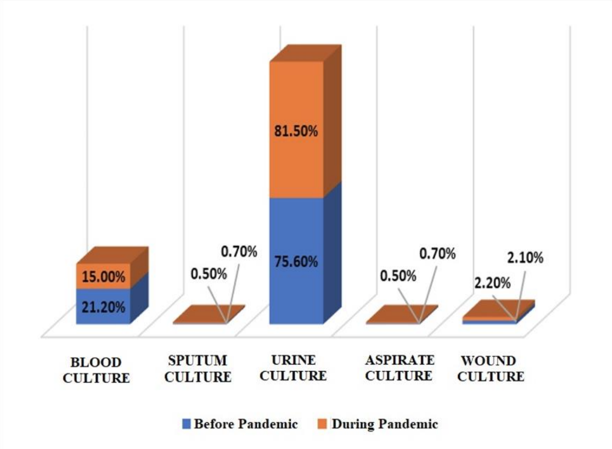

Fig.1. Distribution of Enterococci Isolated From Samples With Growth Before and During The Pandemic, According To Clinical Samples

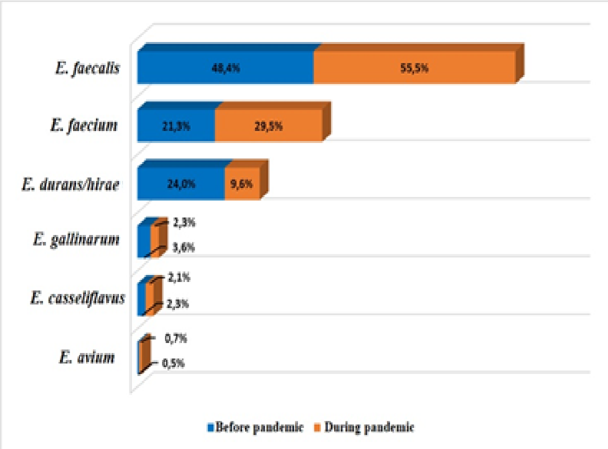

Fig.2. Distribution of Enterococci Isolated From Samples With Growth Before and During The Pandemic, According To Species

knowledge that secondary infections increase in relation to COVID-19.

In the studies conducted, the distribution of enterococci in our country, *E. faecalis* 51.6% (15), 52% (16), 62.7% (17), *E. faecium* 46.4% (15), 48% (16), 37.2% (17) reported as. Etiz et al. (15) have reported enterococcus species other than *E. faecalis* and *E. faecium* as *E. gallinarum* 0.3%, *E. durans* 0.3%, *E. hirae* 0.1%, and *E. avium* 0.9%. In our study, the distributions in the DP period were determined as 55.5% for *E. faecalis*, 29.5% for *E. faecium*, 2.7% for *E. gallinarum*, 9.6% for *E. durans/ hirae*, 0.7% for *E. avium*, and 2.1% for *E. casseliflavus*. The BP period distributions were 48.4% for *E. faecalis*, 21.3% for *E. faecium*, 3.6% for *E. gallinarum*, 24% for *E. durans/ hirae*, 0.5% for *E. avium*, and 2.3% for *E. casseliflavus*.

Enterococcus species can be isolated from particularly urinary tract infections, bloodstream infections, infective endocarditis, intraabdominal infections, pelvic infections, tissue, and wound site infections, burn infections, foreign body infections, rarely nervous system infections, ear infections, and eye infections (18). In reported studies, enterococcus species are most commonly isolated from urine cultures (19,20,21). Similarly, enterococcus species were isolated, most commonly from urine cultures in our study as well.

Enterococcus species show resistance at different rates to ampicillin, a group A antibiotic in enterococcus isolates, according to the EUCAST criteria. Ampicillin is more effective in *E. faecalis* isolates compared to the *E. faecium* isolates (22). In a study by Yenişehirli et al. (19), ampicillin (0%) resistance was reported in community-acquired *E. faecalis* isolates isolated from urine culture samples, while ampicillin (8.7%) resistance was reported in hospital-acquired isolates. In addition, they reported ampicillin resistance in the community- and hospital-acquired *E. faecium* isolates as 100%. In a study by Alkan-Çeviker et al. (23), ampicillin resistance of 94% in E. faecium and 14.6% in *E. faecalis* isolated from blood cultures were determined. In a study by Çelik et al., ampicillin resistance was reported as 3.6% in *E. faecalis* and 87.6% in *E. faecium* (24). In our study, sensitivity for ampicillin in *E. faecalis* isolates was 58% in the DP period and 44.9% in the BP period, respectively; and it was 51.2% in the DP period and 48.9% in the BP period respectively in *E. faecium* isolates. According to these results, our ampicillin resistance rates were found to be higher in *E. faecalis* isolates and lower in *E. faecium* isolates when compared with Çelik et al.'s (24) study. But, there was a significant increase in susceptibility to ampicillin between the BP and DP periods. The use of narrow-spectrum antibiotics like ampicillin decreased in the DP period. We think that this leads to an increase in susceptibility.

The studies conducted in our country report high resistance rates to the quinolones that are especially used in urinary tract infections. The resistance rates of enterococ isolates were reported in different studies as follows, *E. faecalis*:34.3% (20), 37.5% (21), 45% (22) and *E. faecium*: 84.4% (20), 68.5% (21), 93% (22). In our study, sensitivity rates were established for *E. faecalis* isolates as 17.8% (BP) and 43,2% (DP); for *E. faecium* isolates as 8.5% (BP) and 46.5% (DP); and for *E. durans/hirae* isolates as 11.3% (BP) and 28.6% (DP). Similar to other studies, quinolone susceptibility rates were very low. However, an increase in quinolone susceptibility was found when BP and DP were compared. These data show that the susceptibility to quinolones is gradually increasing due to the decrease in their use in the empirical treatment of DP in our hospital.

In a study, it was reported that *E. faecium* isolates were resistant to ampicillin at 83.9%, HLG at 36.4%, HLS at 10.5%. It was also reported that *E. faecalis* isolates were resistant to ampicillin at 10.6%, HLG at 14.8%, HLS at 6.2% (25). In another study, it was reported that *E. faecium* isolates isolated from urine samples were susceptible to ampicillin at 38.8%, vancomycin at 100%, at teicoplanin 100%, ciprofloxacin at 75%, HLG at 0% and linezolid 100% (26). Yüksel et al's (27) study reported resistance rates for *E. gallinarum* isolates against ampicillin at 100%, penicillin at 100%, vancomycin at 100%, streptomycin at 67%, ciprofloxacin at 100%, and linezolid 0%. Our results are concurrent with these findings. Gök et al. (1) reported HLG resistance as 41.7% in *E. faecalis* isolates and 37.7% in *E. faecium* isolates. Also, HLS resistance was reported as 54.2% in *E. faecalis* isolates and 73.8% in *E. faecium* isolates. A study conducted with COVID-19 ICU patients showed antibiotic resistance in enterococcus isolates against to ampicillin at 81.8%, erythromycin at 90.9%, vancomycin and teicoplanin at 18.1%, ciprofloxacin at 81.8%, tigecycline at 0%, and linezolid 0% (12). In our study, high rates of HLG resistance were observed in all isolates enterococcus species. Specifically, *E. faecalis* isolates showed HLG (BP=8.4%, DP=0%) and HLS (BP=0%, DP=0%) sensitivity; *E. faecium* isolates showed HLG (BP=12.8%, DP=2.3%) and HLS (BP=2.1%, DP=4.8%) sensitivity; and *E. durans/hirae* isolates showed HLG (BP=17%, DP=7.1%) and HLS (BP=1.9%, DP=14.3%) sensitivity. The HLG susceptibilities decreased significantly between the two periods. This was thought to be due to increased aminoglycoside consumption in our hospital.

There is an increase in the vancomycin-resistant enterococci (VRE) due to the invasive interventions, misuse of antibiotics, poor hygiene conditions, and the effects of COVID-19 infection that have been prevalent in the last years. Vancomycin resistance shows differences across countries. While *E. faecalis*, these rates are 4.5% in America, 1% in Europe, 4% in southeast Asia, and 5% in eastern Mediterranean; for *E. faecium*, these rates are 10.5%, 6.5%, 6%, and 23.2%, respectively. (28). The spread of VRE to COVID-19 patients in the hospital environment has been shown by the full genome sequencing studies conducted in the Münster University Hospital in Germany. Researchers have identified clonally-related VRE isolates in ICU patients and peripheral samples and have shown that contaminated surfaces play a role in transmitting VRE to COVID-19 patients (3). In a study, it has been reported that vancomycin resistance in E. gallinarum isolates is 0.3%, in E. durans isolates is 0.3%, and in E. avium isolates is 0.9% (29). Çelik and colleagues (24) reported vancomycin resistance in *E. faecium* isolates as 3.3%. When compared to this study, the vancomycin resistance of the enterococcus isolates in our hospital is higher. However, the comparisons of BP and DP showed increases in susceptibility rather than vancomycin resistance. We contemplate that this was achieved by the top-end hygiene practices introduced in the DP period, active use of the laboratory, heavy and rigorous work by the infection control committee, surveillance practices, and correct use of antimicrobials based on restricted reporting of antibiotic susceptibility. In addition, we can say that it contributes to reducing vancomycin and teicoplanin consumption in DP. Gülmez and colleagues (30) reported vancomycin resistance in *E. faecium* as 7.8%, and in *E. faecalis* as 0.1%, which is in line with our findings. The resistance rates of *E. faecium* in this study are concurrent with our data.

E. faecium and *E. faecalis* isolates have been reported to have 100% susceptibility to linezolid, an oxazolidinone antibiotic used in VRE isolates. However, some studies show low levels of resistance (2%, 1.8%, 0.4% in *E. faecium*) (1). Bilgin et al. (21) have reported 6% linezolid resistance in *E. faecium* isolates. In our study, *E. faecalis* (BP=88.8%, DP=95.1%), *E. faecium* (BP=87.2%, DP=95.3%), and *E. durans/hirae* (BP=96.2%, DP=100%) isolates were found to be sensitive to linezolid. An increase in linezolid susceptibility was observed when BP and DP were compared. However, compared with the studies, it was determined that our susceptibility to linezolid was at lower levels due to the increase in linezolid consumption in our hospital.

Studies have reported resistance of 0.4% in *E. faecium* isolates and 0.3% in *E. faecalis* isolates against tigecycline, an antibiotic of the glycylcycline group used in VRE isolates (15). However, some studies did not report any tigecycline resistance (31). Our results showed lower rates of tigecycline susceptibility compared to other data obtained in our country. There was a significant decrease in the tigecycline susceptibility of *E. faecium*, *E. faecalis* and *E. durans/ hirae* between BP and DP periods. Based on our pharmacy data, we think that this decrease is due to the increase in the use of tetracycline and tigecycline.

Resistant enterococci are among the important community and hospital-acquired pathogens. Demonstrating the antibiotic resistance profile in enterococci is important in terms of controlling the spread of these microorganisms and new treatment approaches. In addition to species-specific natural resistance in enterococci, there are difficulties in establishing treatment protocols for patients due to acquired antibiotic resistance (2).

According to the data obtained from the pharmacy of our hospital, a decrease was found in the consumption of ampicillin, vancomycin, teicoplanin, and ciprofloxacin in DP. As a result of the decrease in the consumption of these antibiotics, a significant increase in their susceptibility was observed. However, there was an increase in the use of tetracycline and tigecycline. As a result of the increased consumption of these antibiotics in DP, a significant decrease in tigecycline susceptibility, that is, resistance was detected. Before starting antibiotic treatment, bacteriological culture and antibiotic susceptibility tests that will shed light on us must be performed, and consumption must be made within indications by adhering to restricted antibiotic notification rules. The post-pandemic long-term effects of inappropriate antibiotic use in COVID-19 patients need to be evaluated.

Conflict of Interest: The authors declare no conflict of interest.

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