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Antibiotic Resistance Patterns and Susceptibility Profiles of Enterococcus Species in Clinical Isolates

Eman Selem[1], Heba Abdallah[2] , Eman Tohamya [1] and Nabawy Elnabawy[1]
[1]Faculty of Science, Zagazig University, Zagazig, Egypt
[2] Faculty of Medical Veterinary, Zagazig University, Egypt

Correspondig author: nabawy.mostafa7@gmail.com

ABSTRACT: Enterococci, particularly *Enterococcus faecalis* and *Enterococcus faecium*, are significant nosocomial pathogens due to their intrinsic antibiotic resistance and ability to acquire resistance genes. This study assesses the antibacterial efficiency of widely used antibiotics against Enterococcus species, focusing on resistance patterns and susceptibility profiles. Special emphasis is placed on vancomycin-resistant enterococci (VRE), which pose a critical concern due to limited therapeutic options. The findings reveal high levels of resistance to first-line antibiotics, highlighting the role of intrinsic and acquired resistance mechanisms. Despite this, certain antibiotics demonstrate promising efficacy, offering potential therapeutic avenues for managing enterococcal infections. The results underscore the urgent need for robust antibiotic stewardship programs and continuous surveillance of resistance patterns to inform clinical decisions and guide empirical therapy.

Keywords- Enterococci- Antibiotic resistance- Vancomycin- Susceptibility - Nosocomial infections

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1. Introduction

Enterococci, members of the Gram-positive cocci family, are significant constituents of the human gut microbiota and are frequently encountered in the environment [1]. Despite their commensal nature, enterococci, particularly *Enterococcus faecalis* and *Enterococcus faecium*, have emerged as major opportunistic pathogens, causing various infections, including urinary tract infections, bacteremia, endocarditis, and intra-abdominal infections [2].

The clinical relevance of enterococci lies in their intrinsic resistance to several antibiotics, including cephalosporins and low-level aminoglycosides, and their ability to acquire resistance genes [3]. Of particular concern is the emergence of vancomycin-resistant enterococci (VRE), which were first reported in the 1980s and have since become prevalent in hospital settings [4]. VRE infections are associated with increased morbidity, mortality, and healthcare costs due to the limited therapeutic options available [5].

Enterococci exhibit a wide range of resistance mechanisms, such as modification of target sites (e.g., alterations in D-Ala-D-Ala to D-Ala-D-Lac in the case of vancomycin resistance), efflux pumps, and biofilm formation [6; 7]. These adaptations not only complicate treatment but also facilitate the spread of resistance genes to other bacterial species, further exacerbating the problem [8].

Given the rising prevalence of multidrug-resistant enterococci, it is imperative to evaluate the efficacy of existing antibiotics and identify reliable therapeutic options. Several studies have highlighted the effectiveness of newer agents, such as linezolid and daptomycin, against

enterococcal infections, even in cases of vancomycin resistance [9; 10]. However, variations in susceptibility patterns necessitate region-specific studies to guide clinical decision-making [4].

Enterococci, particularly *E. faecalis* and *E. faecium*, have emerged as significant nosocomial pathogens due to their intrinsic resistance to several antibiotics and their ability to acquire additional resistance genes. These bacteria are well-adapted to the hospital environment, where they cause a range of infections, including bacteremia, endocarditis, and urinary tract infections [11].

Intrinsic resistance mechanisms in enterococci include low-affinity penicillin-binding proteins, which reduce the efficacy of β-lactam antibiotics, and aminoglycoside-modifying enzymes, leading to low-level aminoglycoside resistance [11]. These bacteria also utilize efflux pumps and biofilm formation to evade antibiotic action, further complicating treatment [12].

One of the most concerning developments is the acquisition of vancomycin resistance genes, such as vanA and vanB, which have led to the widespread emergence of vancomycin-resistant enterococci (VRE). VRE infections are associated with higher morbidity and mortality rates due to the limited number of effective therapeutic options [12]. To address the increasing prevalence of multidrug-resistant enterococci, novel therapeutic strategies are under investigation. Recent studies have explored the potential of phage therapy, which utilizes bacteriophages to target and lyse resistant bacterial cells. Although promising, phage therapy presents challenges, including phage specificity and the possibility of bacterial resistance to phages [13].

This study aims to assess the antibacterial effects of commonly used antibiotics, including TE (tetracycline), CIP (ciprofloxacin), LEV (levofloxacin), NOR (Norfloxacin), GAT (Gatifloxacin), F (Nitrofurantoin 300 mg), AM (ampicillin), P (penicillin), RA (Rifampin), C-30 (chloramphenicol), VA (vancomycin), E (erythromycin), NOR (Norfloxacin), and DO (doxycycline) on clinical isolates of Enterococcus species [14]. By analyzing susceptibility profiles and resistance mechanisms, this work seeks to provide insights into effective treatment strategies for managing enterococcal infections and mitigating the spread of antimicrobial resistance.

2. Materials and Methods

2.1. Bacterial Strains

Clinical isolates of *E. faecalis* and *E. faecium* were collected from the Central Laboratory at the Faculty of Medicine, Zagazig University Hospitals, Egypt, during the period from February 2021 to March 2022 [15]. Samples were collected and transported according to [16] under aseptic conditions quickly without delay within two hours to the Bacteriology Laboratory at the Faculty of Science, Zagazig University, where the study was carried out. The purified cultures of bacterial isolates were identified after investigating morphological and biochemical cultural characters according to standard clinical laboratory methods reported and recommended by Bergey's Manual of Determinative Bacteriology [17].

*2.2.*Microscopic Examination

To differentiate between Gram-positive, Gram-negative, spore-forming, and non-spore-forming bacteria, Gram staining was used [18]. Films were prepared from a pure culture of the isolated bacteria, stained with Gram's stain, and examined under a microscope for Gram-positive cocci. Enterococci appeared as short to long chains [18].

*2.3.*Biochemical and Cultural Identification

A positive catalase reaction was identified by the continuous formation of bubbles when hydrogen peroxide was added to bacterial colonies [19]. The identification of Enterococcus isolates was further confirmed by their growth in 6.5% NaCl broth [17]. The

culture media used included Enterococcosel Agar, HiCrome, E. faecium Agar, MacConkey's No. 2 Agar, and CLED agar [17].

*2.4.***Disc Diffusion Agar Method**

Antibiotic susceptibility testing for the selected bacteria was carried out using the disc diffusion technique according to [20]. The procedure involved inoculating pure colonies of each tested organism into 5 ml of sterile nutrient broth and incubating them at 37°C for 24 h. Then, 0.1 ml of bacterial suspension was spread using sterile swabs on Mueller-Hinton agar plates. The density of the bacterial suspension was visually equivalent (O.D.) to that of standard barium sulfate (0.5 McFarland), which was prepared by adding 0.05 ml barium chloride + 9.95 ml sulfuric acid, as described by [21]. McFarland turbidity standard (barium sulfate) was used as a reference for preparing bacterial suspensions of approximately standard concentration [22]. Antibiotic discs were applied to the surface of the plates at constant distances. The plates were incubated at 37°C for 24 h. At the end of the incubation period, zones of inhibition were measured in millimeters (mm). The entire diameter of the zone, including the diameter of the disc, was measured. The endpoint of the reading was taken as complete inhibition of growth visible to the naked eye [20].

*2.5.***Statistical Analysis**

Data were analyzed using ANOVA to compare the efficacy of different antibiotics [23].

3. Results and discussion

3.1. **Screening and Isolation of Enterococcus Isolates**

Urine and stool samples were collected from 50 patients admitted to Zagazig University Hospitals, Egypt. A total of 22 isolates were identified as Enterococcus species using preliminary Gram staining, which revealed Gram-positive cocci or coccobacilli arranged in pairs and short chains. Biochemical testing further confirmed these isolates as Enterococcus, as all were catalase-negative and able to grow in nutrient broth supplemented with 6.5% NaCl (Fig. 1) [24]. These findings align with established diagnostic criteria for enterococci, emphasizing the importance of comprehensive biochemical profiling in clinical microbiology [25].

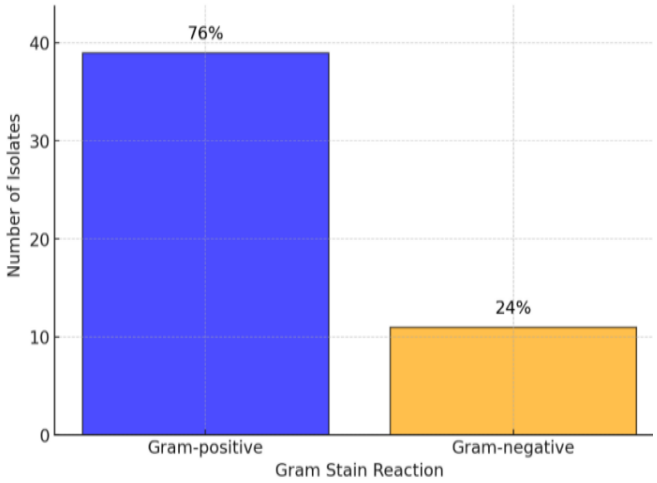

Fig (1) Gram stain-based categorization, confirming the dominance of Gram-positive isolates.

Table (1): Biochemical tests for identification of Enterococcus species

Biochemical tests	*Enterococcus faecalis*	*Enterococcus faecium*	*Streptococcus pyogenes*
Catalase	-	-	-
Oxidase	+	+	+
Haemolysis (5% SBA)	-	-	β
Growth at 6.5 % salt	+	+	-
Growth at 10 °C	+	+	-
Growth at 45 °C	V	+	V
Esculin hydrolysis	+	+	V
Arginine dihydrolase	+	+	+
Hippurate hydrolysis	+	V	-
Sugar fermentation:Lactose	+	+	+
Mannitol	+	+	-
Arabinose	-	+	-
Ribose	+	+	-
Sorbitol	+	-	-
Raffinose	-	V	-

This table summarizes the results of various biochemical tests used to differentiate and identify *Enterococcus faecalis*, *Enterococcus faecium*, and Streptococcus based on their metabolic and growth characteristics.

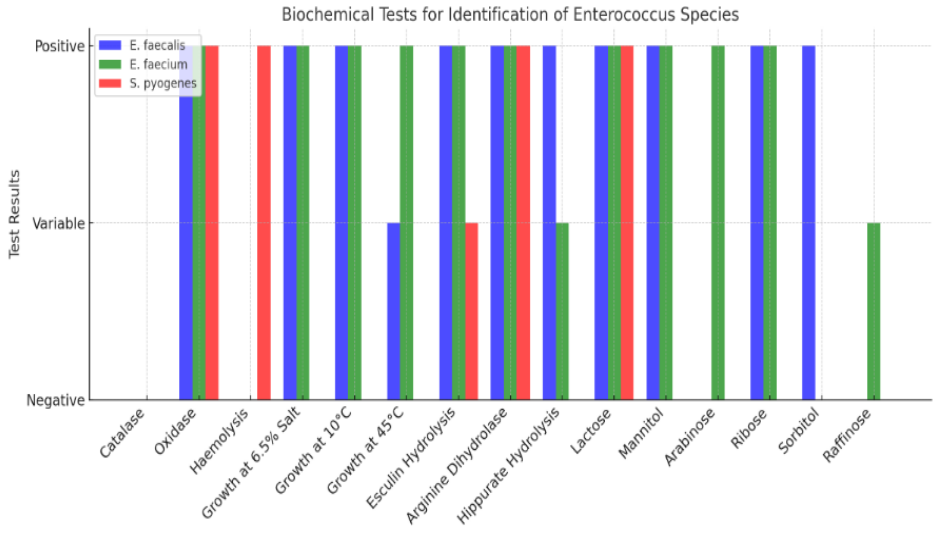

Fig (2)biochemical test results for Enterococcus faecalis, Enterococcus faecium, and Streptococcus pyogenes.

The biochemical characteristics of the isolated *Enterococcus faecalis*, *Enterococcus faecium*, and Streptococcus pyogenes are summarized in Table 1. These tests differentiate the species based on metabolic and growth traits, such as hemolysis patterns, esculin hydrolysis, sugar fermentation profiles, and arginine dihydrolase activity. Notably:

- Both *E. faecalis* and *E. faecium* exhibited gamma hemolysis on 5% sheep blood agar, while *S. pyogenes* demonstrated beta hemolysis.

- The ability to grow at extreme temperatures (10°C and 45°C) distinguished *Enterococcus species* from *S. pyogenes*.
- Differential sugar fermentation patterns, including sorbitol and arabinose utilization, allowed for precise identification of *E. faecalis* and *E. faecium* [26].

3.2. **Susceptibility test of different antibiotic drugs against selected bacterial isolates.**

olated Susceptibility testing of different antibiotic drugs was performed on the is Enterococcus strains to evaluate their resistance profiles. The results are presented in Tables 3 .and 4, highlighting significant trends in antibiotic resistance among the isolates

and penicillin (P) showed ,(Among the antibiotics tested, ampicillin (AM), nitrofurantoin (F the highest sensitivity rates, with 17, 17, and 16 isolates classified as sensitive, respectively. In contrast, tetracycline (TE), ciprofloxacin (CIP), and levofloxacin (LEV) exhibited high sistant isolates, respectively. These observations resistance rates, with 14, 13, and 12 re underscore the growing challenge posed by antimicrobial resistance (AMR) and highlight the need for prudent antibiotic use.[27]

E, F, P, and Isolate 6E: Shows resistance to most antibiotics, with sensitivity to only T Do. This suggests significant drug resistance. Isolate 7B: Almost entirely resistant, except for .F, AM, and RA, with some intermediate results. It poses a significant challenge for treatment

cs tested, but resistant to TE. This isolate Isolate D4: Generally sensitive to most antibioti .[might be more manageable, though some antibiotics are ineffective [28

Table (3): Antibiotic potency and interpretative criteria

Antibiotic	**Antibiotic code**	**Potency µg**	**Susceptible (S) (mm)**	**Intermediate (I) (mm)**	**Resistant (R) (mm)**
Tetracycline	TE	30µg	≥ 19		<14
Levofloxacin	LEV	5µg	≥ 17		≤ 13
Chloramphenicol	C	30µg	≥ 18	-	12
Nitrofurantoin	F	300µg	≥ 17		≤ 14
Doxycycline	Do	30 µg	≥ 16		≤ 12
Vancomycin	VA	30 µg	≥ 17	-	≤ 14
Ciprofloxacin	CIP	5 µg	≥ 21		≤ 15
Rifampin	RA	30 µg	≥ 20		≤ 16
Norfloxacin	NOR	10 µg	≥ 17		<12
Gatifloxacin	GAT	5 µg	≥ 18		≤ 14
Ampicillin	AM	10 µg	≥ 17		≤ 16
Erythromycin	E	15	≥ 23		≤ 13
Penicillin G	P	10 µg	≥ 15		≤ 14

Table 4. Antibiogram of selected bacterial isolates against different antibiotics drugs:

Bacterial isolate code	Diameter of Inhibition Zone (mm) of different antibiotics														Total		
	TE	LEV	E	C	F	Do	VA	CIP	RA	NOR		GAT	AM	P	R	I	S
6E	21 (S)	13 (R)	15 (I)	12 (R)	20 (S)	20 (S)	14 (R)	15 (R)	15 ®	12 (R)		18 (R)	16 (R)	15 (S)	8	1	4
7B	6 (R)	6 (R)	6 (R)	6 (R)	20)S)	11 (R)	15 (I)	6 (R)	20 (S)	6 (R)		6 (R)	20 (S)	13 (R)	9	1	3
D4	14 (R)	19 (S)	20 (I)	20 (S)	20 (S)	16 (S)	17 (S)	16 (I)	20 (S)	14 (I)		20 (S)	18 (S)	17 (S)	1	3	9
10F	6 (R)	6 (R)	6 (R)	8 (R)	19 (S)	9 (R)	15 (I)	6 (R)	20 (S)	6 (R)		6 (R)	18 (S)	18 (S)	8	1	4
9F	12 R	6 (R)	6 R	20 S	20 S	14 I	16 I	6 R	17 I	6 (R)		6 (R)	18 S	18 S	6	3	4
13F	4 R	8 (R)	6 R	6 (R)	22 (S)	14 I	15 (I)	6 R	19 I	6 (R)		9 (R)	20 S	22 S	7	3	3
15E	9 (R)	6 (R)	6 R	15 I	22 S	12 (R)	16 I	6 (R)	23 S	6 (R)		6 (R)	19 S	14 (R)	8	2	3
15F	21 (S)	17 S	18 I	20 S	21 (S)	22 S	11 R	17 (I)	16 (R)	15 I		18 S	20 S	22 S	6	-	4
7B	6 (R	16 I	20 I	17 I	18 (S)	15 I	16 (I)	15 R	16 (R)	15 I)		16 I	17 S	18 S	3	7	3
D3	15 I	15 I	26 S	25 (S)	23 S	6 R	20 (S)	14 R)	20 S	13 I		20 S	25 S	22 S	6	-	4
11D	12 R	19 S	6 R	22 S	23 S	14 I	16 I	16 I	18 I	16 I		23 S	22 S	18 S	2	5	6

2C	**19 S**	**15 R**	**15 I**	**9 (R)**	**20 (S)**	**6 R**	**6 R**	**13 (R)**	**16 (R**	**6 (R)**		**6 R**	**18 S**	**16 S**	**8**	**1**	**4**
8c	**12 R**	**6 (R)**	**6 R**	**6 (R)**	**18 (S)**	**15 I**	**16 I**	**6 R**	**16 (R)**	**6 (R)**		**6 R**	**18 S**	**16 R**	**9**	**2**	**2**
5B	**6 R**	**6 R**	**6 R**	**6 R**	**19 S**	**9 R**	**15 I**	**6 R**	**20 S**	**6 R**		**6 R**	**20 S**	**19 S**	**8**	**1**	**4**
13C	**14 R**	**16 I**	**19 I**	**20 S**	**20 S**	**16 S**	**16 I**	**17 I**	**16 R**	**15 I**		**20 S**	**23 S**	**20 S**	**2**	**5**	**6**
10D	**8 R**	**10 R**	**19 I**	**8 R**	**19 S**	**12 R**	**14 R**	**17 I**	**21 S**	**12 R**		**12 R**	**15 R**	**20 S**	**8**	**2**	**3**
3E	**30 S**	**19 S**	**20 I**	**18 S**	**20 S**	**23 S**	**18 S**	**19 I**	**18 I**	**14 I**		**19 S**	**23 S**	**20 S**	**-**	**4**	**9**
7f	**6 R**	**6 R**	**6 R**	**12 R**	**15 I**	**13 I**	**20 S**	**6 R**	**21 S**	**6 R**		**9 R**	**18 S**	**17 S**	**7**	**2**	**4**
7c	**7 R**	**6 R**	**6 R**	**9 R**	**15 I**	**10 R**	**15 I**	**6 R**	**19 S**	**6 R**		**12 R**	**19 S**	**18 S**	**8**	**2**	**3**

R: Resistance to antibiotic. S: Sensitive to antibiotic. I: Intermediate to antibiotic.

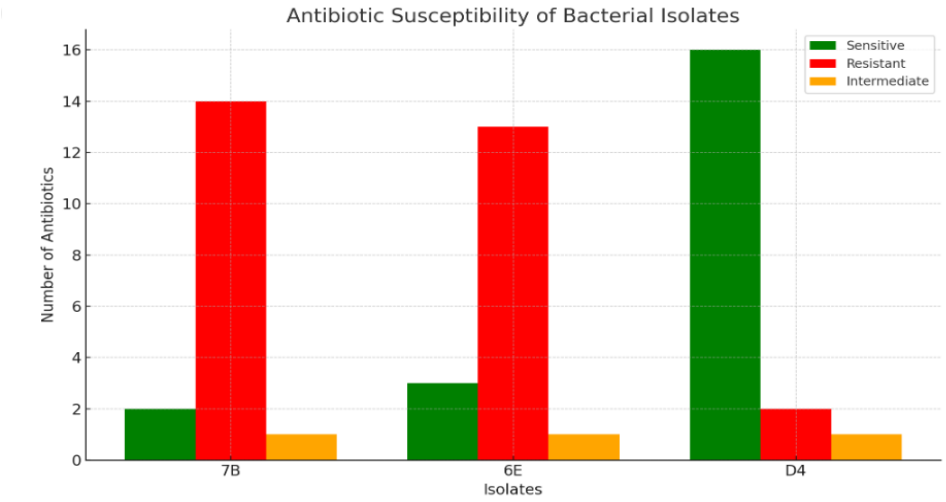

Fig (4): Resistance and sensitivity patterns for key isolates, highlighting MDR trends.

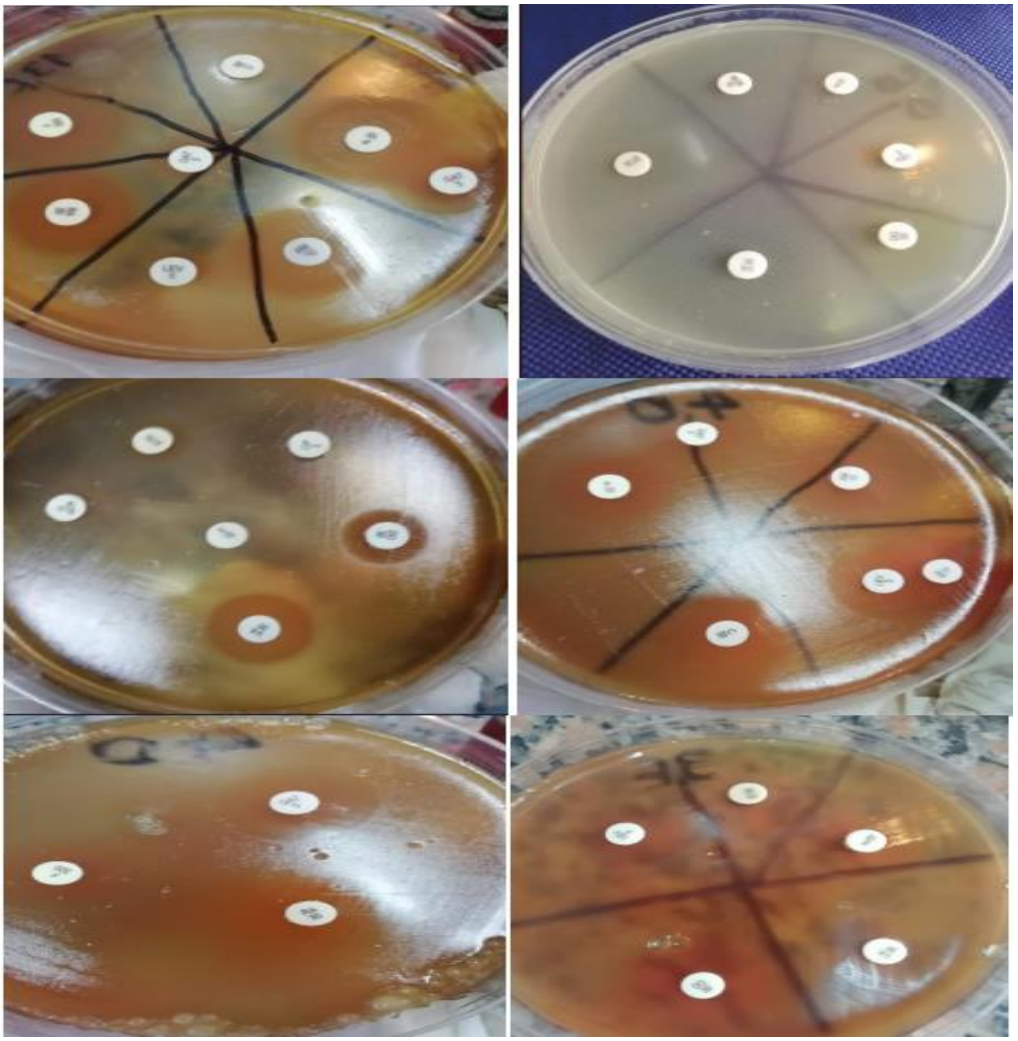

Fig (5): Antibiotic susceptibility test.

3.2.1. **Tetracycline Resistance**

Tetracycline resistance was observed in 14 isolates, consistent with global reports of widespread tetracycline resistance due to its overuse in both medical and agricultural settings. Mechanistically, resistance is primarily mediated by efflux pumps (e.g., tet(A), tet(B)) and ribosomal protection proteins (e.g., tet(M), tet(O)), which prevent the antibiotic from inhibiting bacterial protein synthesis. This finding aligns with previous studies indicating that tetracycline resistance genes are often disseminated via horizontal gene transfer (HGT) on mobile genetic elements [29].

*3.2.2.***Ciprofloxacin and Levofloxacin Resistance**

Ciprofloxacin and levofloxacin resistance were prevalent, affecting 13 and 12 isolates, respectively. This resistance is likely driven by mutations in the quinolone resistance-determining regions (QRDRs) of gyrA and parC genes, as well as increased expression of efflux pumps. These mechanisms have been extensively documented in enterococci and other Gram-positive bacteria [30]. The high resistance rates to fluoroquinolones underscore the urgent need for their judicious use in clinical practice.

3.2.3. **Intermediate Susceptibility to Vancomycin and Erythromycin**

Intermediate susceptibility to vancomycin (VA) and erythromycin (E) was noted in 11 and 8 isolates, respectively. Intermediate resistance to vancomycin raises particular concern, as it is a last-resort drug for treating Gram-positive infections, including methicillin-resistant *Staphylococcus aureus* (MRSA). The vancomycin-intermediate phenotype (VISA) is often linked to mutations in regulatory genes like walRK and vraSR, leading to thickened cell walls

and reduced antibiotic binding affinity [31]. For erythromycin, intermediate resistance frequently results from ribosomal methylation mediated by erm genes or active efflux mediated by msr(A) genes [32].

3.2.4 **Doxycycline Susceptibility Profile**

Doxycycline demonstrated a nuanced susceptibility profile, with 8 resistant, 6 intermediate, and 5 susceptible isolates. Resistance mechanisms include efflux pumps and modifications to ribosomal target sites. Intermediate resistance may indicate a transitional stage toward full resistance, particularly if doxycycline is used indiscriminately. However, the presence of susceptible isolates suggests that doxycycline remains a viable treatment option for certain infections when guided by susceptibility testing [33].

3.3 **Multidrug Resistance (MDR)**

The detection of multidrug-resistant isolates across multiple antibiotic classes highlights the pressing issue of AMR in clinical settings. Resistance to multiple drugs often arises from the accumulation of resistance genes on mobile genetic elements, such as plasmids, transposons, and integrons, facilitating HGT among bacterial populations [34]. Notably, isolates 6E and 7B exhibited significant multidrug resistance, posing challenges for effective treatment.

3.4. **Implications and Future Directions**

The increasing prevalence of AMR necessitates a multifaceted approach to combat resistant pathogens. Strategies include:

1. Surveillance Systems: Implementing robust global surveillance networks, as advocated by the World Health Organization (WHO), to monitor resistance trends in both human and veterinary medicine [35].
2. Prudent Use of Antibiotics: Promoting rational prescribing practices to minimize selective pressure driving resistance development [36].
3. Combination Therapy: Exploring synergistic combinations of antibiotics, such as pairing doxycycline with beta-lactams or aminoglycosides, to enhance efficacy against resistant strains [37].
4. Novel Therapies: Developing alternative treatments, such as phage therapy and antimicrobial peptides, to address limitations of current antibiotics [38].

In conclusion, this study provides valuable insights into the resistance profiles of Enterococcus isolates, underscoring the critical need for continuous monitoring and evidence-based interventions to mitigate the threat of AMR. Future research should focus on identifying novel therapeutic targets and optimizing treatment strategies to preserve the effectiveness of existing antibiotics [39].

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