Journal of Molecular Science

Journal of Molecular Science
Volume 35 Issue 3, Year of Publication 2025, Page 576-586
DoI-10.004687/1000-9035.2025.079

Journal of Molecular Science
www.jmolecularsci.com ISSN:1000-9035

Enterococcus Species in Clinical Settings: Review on Virulence, Antibiotic Resistance, and Management Strategies

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Article Information
Received: 05-09-2025
Revised: 12-09-2025
Accepted: 24-09-2025
Published: 02-10-2025

Keywords
Enterococcal infection, virulence factors, antimicrobial resistance, Healthcare

ABSTRACT

Enterococci are gram-positive cocci that naturally inhabit the human gastrointestinal tract caused by enterococci include urinary tract infections, intra-abdominal infections, wound infections, bacteraemia, infective endocarditis, and meningitis. Several key virulence factors (VFs) contribute to their pathogenicity, including cytolysin (Cyl), aggregation substance (Asa), hyaluronidase (Hyl), enterococcal surface protein (Esp), and gelatinase (Gel). These virulence factors allow enterococci to thrive in healthcare environments, increasing their resilience and adaptability. Furthermore, enterococci present a significant therapeutic challenge due to their intrinsic resistance to multiple antibiotics and their ability to rapidly acquire new resistance mechanisms. Of particular concern are the increasing rates of vancomycin resistance and the emergence of linezolid-resistant enterococci. This review aims to highlight the clinical importance of enterococcal infections, explore their virulence factors, and examine the mechanisms underlying their antibiotic resistance.

INTRODUCTION:

Enterococci are generally commensals of the gastrointestinal tract, typically exhibiting low pathogenicity. However, they can cause invasive infections with significant morbidity and mortality, particularly in hospitalized patients with underlying health conditions, those undergoing invasive procedures, or immunocompromised individuals (García-Solache and Rice, 2019). Notably, enterococci are one of the significant pathogens in the ESKAPE group of multidrug-resistant organisms (Santajit and Indrawattana, 2016). The genus *Enterococcus* currently comprises approximately 58 species, with *E. faecalis* and *E. faecium* being the most prominent and widespread. *Enterococcus faecalis* is most commonly associated with community-acquired infections, while *Enterococcus faecium* is more frequently linked to healthcare-associated infections (Zhang et al., 2017). In addition to these, lesser-known species, often referred to collectively as "non-faecium non-faecalis enterococci," are increasingly recognized as emerging pathogens contributing to bloodstream and endovascular infections in humans. Notable among these are *E. avium, E. durans, E. caccae, E. gallinarum, E. raffinosus, E. casseliflavus, E. hirae, E. dispar*, and several others (Monticelli et al., 2018).

Enterococci possess a range of virulence factors that enhance their ability to cause infections(Haghi et al., 2019). Unlike other gram-positive cocci, enterococci exhibit intrinsic resistance to beta-lactams (especially cephalosporins), clindamycin, and low concentrations of aminoglycosides. Additionally, their highly adaptable genome enables them to rapidly acquire resistance to other antibiotics, including high-level resistance to aminoglycosides and vancomycin. This resistance arises either through genetic mutations or the horizontal transfer of resistance genes (García-

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Solache et al., 2019). The rising prevalence of vancomycin-resistant enterococci (VRE) in clinical settings has become a global concern, with these pathogens now classified as high-priority threats by the World Health Organization (Markwart et al., 2019)

Linezolid remains highly effective against VRE, but the emergence of linezolid resistance has resulted in severe clinical consequences, complicating treatment strategies, infection control measures, and contributing to a significant economic burden (Iqbal et al., 2024). This review explores the pathogenesis of enterococcal infections, their virulence factors, and the underlying mechanisms of antibiotic resistance.

Morphology Characterization:
Enterococci are typically oxidase- and catalase-negative, with high salt tolerance and the ability to withstand 40% bile and hydrolyze esculin. These bacteria thrive in temperatures ranging from 10 to 45°C, with optimal growth occurring at 35 to 37°C. Remarkably, enterococci can endure exposure to 60°C for up to 30 minutes, a feature that distinguishes them from genera like *Streptococcus* (Foulquié Moreno et al., 2006). Both *E. faecalis* and *E. faecium* can grow across a pH range of 4.6 to 9.9. Due to their cation homeostasis and ability to thrive in 6.5% NaCl, *E. faecalis* is thought to be resistant to desiccation, salt, metals, and fluctuating pH levels.

While enterococci can grow within a temperature range of 10 to 45°C, most species grow best at temperatures between 35 and 37°C. When cultured on horse blood agar, enterococci may exhibit alpha, beta, or no hemolysis. Colonies typically measure between 1 and 2 mm and appear moist. They can be isolated using selective media containing esculin, tetrazolium, bile salts, and antibiotics. Clinically significant enterococcal species grow efficiently on these media. Common diagnostic techniques include the pyrrolidonyl arylamidase.

Table 1: Key phenotypic characteristics of *Enterococcus* species

Species	Yellow pigment	Motility	Arginine	Arabinose	Sorbose	Mannose
E.faecalis	Negative	Negative	Positive	Negative	Negative	Positive
E.faecium	Negative	Negative	Positive	Positive	Negative	Positive
E.gallinarium	Negative	Positive	Positive	Positive	Negative	Positive
E.casseliflavus	Positive	Positive	Positive	Positive	Negative	Positive
E.avium	Negative	Negative	Negative	Positive	Positive	Positive
E.durans	Negative	Negative	Positive	Negative	Negative	Negative
E.raffinosus	Negative	Negative	Negative	Positive	Positive	Positive

(Teixeira LM,1997)

Mechanism of Pathogenesis:
Once enterococci colonize the intestinal tract, they can multiply and spread to other infection-prone areas. The likelihood of infection is closely associated with the bacterial load in the intestinal reservoir—higher bacterial numbers increase the chances of contaminating vulnerable sites with sufficient bacteria to overwhelm host defenses (Taur et al., 2012; Weinstock et al., 2007) Infection occurs when enterococci bypass the host's immune barriers, multiplying faster than the body can clear them. This leads to tissue damage, either directly through toxin production or indirectly through inflammation-induced tissue injury (Garsin et al., 2014).

Colonization of Gastrointestinal Tracts.
Enterococci are important members of the healthy human gut microbiota (Eckburg et al., 2005). In hospitalized patients undergoing antibiotic therapy targeting gram-negative bacteria, the gut microbiota becomes disrupted. Early research provides valuable insights into how Vancomycin-Resistant Enterococci (VRE) can become dominant in the gut following antibiotic exposure. These studies reveal that lipopolysaccharide and flagellin from gram-negative bacteria trigger the synthesis of REGIIIγ by Paneth cells via interactions with Toll-like receptors. REGIIIγ, a C-type lectin encoded by the Reg3G gene, inhibits gram-positive bacteria, including VRE (Brandl et al., 2008). Typically, the depletion of gram-negative bacteria due to antibiotic treatment halts the production of REGIIIγ, creating an environment that may favor the overgrowth of VRE. This highlights the important role of intestinal microbiota in regulating colonization by multidrug-resistant organisms.(Kinnebrew et al., 2010)

Virulence Factors:
The development of enterococcal infections is mediated by virulence factors that enable adherence, colonization, and tissue invasion, while also affecting immune responses and producing enzymes and toxins that exacerbate infection severity.

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Table: 2: Virulence Factors of Enterococci: Description and Functions

Virulence Factor	Description	Function	References
Enzymes and Secreted Toxins			
Aggregation Substance (Agg)	Encoded by *asa1*, this pheromone-responsive surface protein is essential for cell-to-cell contact during conjugation and eukaryotic cell adhesion	Facilitates bacterial aggregation, plasmid transfer, and enhances attachment to extracellular matrix proteins and epithelial cells, including renal and intestinal cells.	(Hällgren et al., 2009);(Cariolato et al., 2008) (Afonina et al., 2018)
Gelatinase (GelE)	Extracellular metalloprotease containing zinc.	Degrades host molecules like collagen, fibrinogen, and complement proteins C3 and C3a, facilitating bacterial migration, dissemination, and colonization. Also aids in biofilm development and activates autolysin to clear misfolded proteins.	(Qin et al., 2001) (Upadhyaya et al., 2009; Waters et al., 2003)
Cytolysin (cylR1, cylR2, cylLL, cylLS, cylM, cylB, cylA, cylI)	Operon encoding exotoxin with bacteriocin activity against Gram-positive bacteria.	Contributes to bloodstream invasion by lysing host cells. The operon is regulated by cylR1 and cylR2, with immunity provided by cylI.	(Medeiros et al., 2014);(Gaspar et al., 2009);(Singh et al., 2002)
Serine Protease (SprE)	Glutamyl endopeptidase I encoded by the sprE gene.	Plays a major role in the degradation of casein and biofilm formation. Contributes to pathogenesis, especially in peritonitis.	(Ali et al., 2022);(Yue et al., 2022); (Sifri et al., 2002)
Hyaluronidase (Hyl)	Synthesized by the hyl gene in *E. faecium*.	Hyaluronidase plays a crucial role in both nasopharyngeal colonization and exacerbating pneumonia Degrades mucopolysaccharides in connective tissues, enhancing bacterial invasiveness and facilitating toxin dissemination. Known as 'the spreading factor.'	(Abou-Rass and Bogen, 1998); (Sunde et al., 2002)
Secreted Antigen (SagA)	75 kDa protein specific to *E. faecium*.	Binds to extracellular matrix proteins and aids in biofilm formation. Antibodies against SagA show opsonic killing activity, making it a potential vaccine candidate.	(Paganelli et al., 2015); (Kropec et al., 2011)
Cell Surface Associated Virulence Factors:			
Capsular polysaccharides (Cps), wall teichoic acid (WTA), and lipoteichoic acid (LTA)	Capsular polysaccharides (Cps) Cell wall teichoic acid (WTA) Lipoteichoic acid (LTA).	Biofilm formation and immune evasion Protects against complement-mediated neutrophil killing, Modified by D-alanine ligase (dlt operon), enhances biofilms and antimicrobial resistance.	(Weidenmaier and Peschel, 2008)
MSCRAMMs Microbial surface component recognizing adhesive matrix molecules (Ace, Acm, Scm)	Microbial surface components that recognize and adhere to extracellular matrix molecules.	Ace (*E. faecalis*), Acm, and Scm (*E. faecium*) facilitate adherence to collagen and other substances like dentin and laminin.	(Rich et al., 1999; (Nallapareddy et al., 2003); (Kowalski et al., 2006)
Enterococcal Surface Protein (Esp)	Cell wall-associated protein that aids in adhesion and immune evasion.	Critical for biofilm formation and persistence of urinary tract infections	(Shankar et al., 1999);(Shankar et al., 2001)

Enterococcal Infections:

Enterococci causes a range of infections in both community and hospital settings. In the community, they are commonly associated with urinary tract infections, wound infections, and endocarditis. In hospitals, especially among immunocompromised patients or those undergoing invasive procedures, they can lead to more severe infections like intra-abdominal infections bacteremia and septicemia. The increased prevalence of antibiotic-resistant strains in hospitals further complicates treatment and poses significant challenges to healthcare providers. Enterococci, especially *Enterococcus faecalis* and *Enterococcus faecium*, are notable for their ability to acquire resistance to multiple antibiotics, including vancomycin, making them a significant concern for public health. (Kristich CJ, et al., 2014)

Urinary Tract Infections (UTIs): Enterococci cause a wide range of infections; however, they are specifically known to cause urinary tract infections (UTIs), often in patients with indwelling catheters or other medical devices. Virulence factors such as ace, ebpC, esp, and msrA aid in the formation of biofilms that aids bacterial adhesion to catheters and tissues, resulting in chronic, treatment-resistant infection; they can also lead to complicated UTIs like pyelonephritis, perinephric abscesses, and chronic prostatitis, all of which may serve as foci for bacteremia Complicated UTIs are associated with diabetes mellitus, pregnancy, indwelling urinary catheters and devices, immunocompromised state,

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neurogenic bladder, urinary obstruction, and nephrolithiasis. (Bhonchal Bhardwaj, 2020).

Intra-abdominal Infections: These infections are common in ICU patients and can be the cause of significant morbidity and mortality, especially if they are not diagnosed and treated in a timely manner (Kajihara et al., 2015; Montravers et al., 2009);

Skin and Soft Tissue Infections (SSTIs): Enterococci cause diabetic foot ulcers and surgical site infections that are commonly polymicrobial, but can occasionally be caused by enterococci alone in chronic cases (Leong et al., 2018).

Bacteremia: Enterococci are a common cause of Gram-positive bacteremia, often from the gastrointestinal tract. The infection can be severe and associated with a high mortality rate, particularly in patients with comorbidities or those with invasive procedures (Kajihara et al., 2015) (Fiore et al., 2019; Le Jeune et al., 2010).

Infective Endocarditis: Among Enterococcus species, *E. faecalis* in particular, are one of the leading causes of infective endocarditis (Kajihara et al., 2015).
Other Infections: Enterococci can also cause rarer infections such as osteomyelitis, septic arthritis, meningitis, and pneumonia. Pneumonia is most common in immunocompromised individuals, particularly those receiving broad-spectrum antibiotics (Agudelo Higuita and Huycke, 2014a)

Treatment:
The treatment of enterococcal infections varies significantly depending on whether the strain is susceptible or resistant to common antibiotics. For susceptible strains, penicillin or ampicillin is the first-line treatment option, as it inhibits bacterial cell wall synthesis. In severe infections, combination therapy with aminoglycosides (gentamicin or streptomycin) may be employed to enhance the therapeutic effect, as the aminoglycosides penetrate the bacterial cell wall. Vancomycin is used in case of penicillin allergy or intolerance, although it is less effective against *E. faecalis* (Baddour et al., 2015) than penicillin. Infections caused by vancomycin-resistant enterococci (VRE) require alternative treatments, with linezolid being one of the primary options due to its ability to inhibit protein synthesis. Daptomycin is another key option, particularly for serious infections like bacteremia and endocarditis, as it disrupts bacterial cell membrane integrity (Said et al., 2025). Tigecycline may also be considered in multidrug-resistant cases. For high-level aminoglycoside-resistant enterococci (HLAR), combination therapy with a beta-lactam (such as penicillin) and other agents like linezolid or daptomycin is recommended (Hodel-Christian and Murray, 1991). In severe cases like enterococcal endocarditis, combination therapy with penicillin or ampicillin and an aminoglycoside is standard, while for VRE endocarditis, linezolid or daptomycin are preferred (Mir et al., 2011). In cases of nephrotoxicity concerns, especially when using vancomycin or aminoglycosides, careful dosing and monitoring of kidney function are crucial (Said et al., 2025). Thus, the treatment approach must be tailored to the resistance profile, with regular monitoring to avoid complications such as nephrotoxicity.

Enterococci are inherently resistant to widely used antibiotics; they exhibit reduced susceptibility to penicillin and ampicillin as well as high-level resistance to most cephalosporins and all semi-synthetic penicillins due to expression of low-affinity penicillin-binding proteins. Although many strains show some resistance to ampicillin, it is usually not strong enough to rule out its clinical use; in fact, ampicillin continues to be the preferred treatment for enterococcal infections that do not exhibit additional mechanisms of high-level resistance. Enterococci possess intrinsic resistance to clindamycin, conferred by the lsa gene product, although the exact mechanism remains unclear. Beyond this inherent resistance and tolerance, they are highly proficient at acquiring resistance to newly introduced antimicrobial agents. Notably, resistance to chloramphenicol, erythromycin, and tetracyclines emerged quickly.

Mechanism of Antibiotic resistance:
Antimicrobial agents are broadly classified based on their mechanisms of action. The major categories include: (1) agents that inhibit cell wall synthesis, (2) agents that disrupt or depolarize the cell membrane, (3) inhibitors of protein synthesis, (4) agents that interfere with nucleic acid synthesis, and (5) drugs that target essential bacterial metabolic pathways. Although these diverse mechanisms provide multiple avenues for combating bacterial infections, the effectiveness of antimicrobials has been increasingly compromised by the global rise in antibiotic resistance. This crisis is largely driven by the overuse of antimicrobials and inappropriate prescribing practices.

Bacteria employ four principal strategies to develop resistance against antimicrobial agents: (1) reduction in drug uptake, (2) alteration of the drug's target site, (3) enzymatic inactivation of the drug, and (4) active efflux of the drug via specialized efflux pumps (Chancey et al., 2012; Mahon et al., 2015).

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Table: 3: Mechanism of antimicrobial agent

Mode of action	Antimicrobial agents	Intrinsic resistance mechanism	Acquired resistance mechanism
Inhibit cell wall synthesis	Beta lactam (particularly cephalosporin)	Enterococci express low affinity PBPs (PBP4/5 production) Altered cell wall L d transpeptidase	Penicillin Binding protein (PBP 4/5point Mutation) Beta lactamase production (bla gene)
Drug efflux	Clindamycin	ABC Efflux pump – Lsa gene	-
Low cell permeability	Aminoglycosides	Low level aminoglycoside resistance synergism preserved Tobramycin and kanamycin resistance (EfmM)	High-level aminoglycoside resistance with MIC > 128,000 µg/ml High level gentamicin resistance (Aph(2)-Ib, Aph(2) Ic, Aph Id) High level streptomycin resistance (Ant (6) -Ia Ant (3)-Ia)
Inhibit cell wall synthesis	Vancomycin	D-Ala-D-Ala to D-Ala-D-Ser (Van c)	Synthesis of alternative cell wall (VanA, VanH, VanY, VanX, VanR, VanS) Transposon
Inhibit Protein synthesis	Linezolid	-	23s rRNA point mutation (G2576T, G2505A) Methylated RNA (cfr)

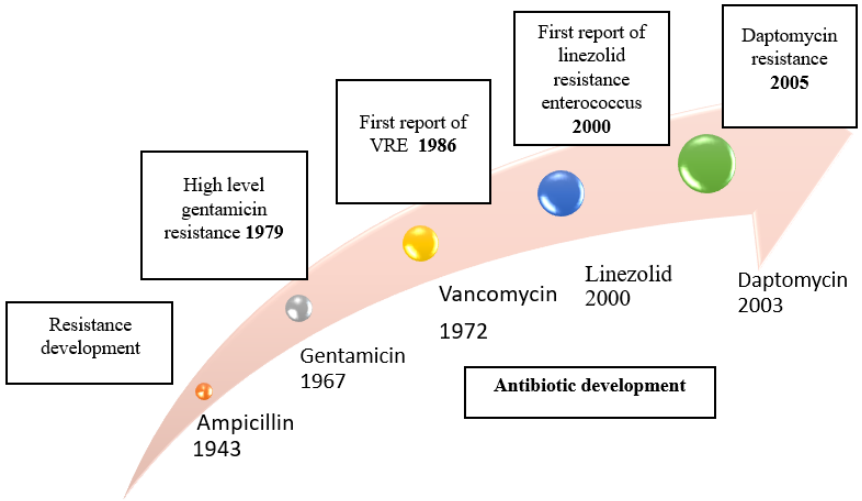

Figure: 1: Timeline for antibiotic resistance of Enterococcus
García-Solache et al., 2019

Beta-Lactams:
Mode of Action:
β-lactam antibiotics, including penicillin and ampicillin, inhibit enterococcal growth by targeting penicillin-binding proteins (PBPs), primarily D,D-transpeptidases involved in peptidoglycan cross-linking. Binding to PBPs disrupts cell wall synthesis and may trigger reactive oxygen species mediated bacterial death (Kohanski et al., 2007).

Intrinsic Resistance:
Enterococci exhibit natural resistance due to PBPs with low β-lactam affinity—PBP5 in *E. faecium* and PBP4 in *E. faecalis* (Sifaoui et al., 2001). *E. faecalis* can tolerate β-lactams by neutralizing reactive oxygen species via superoxide dismutase. Tolerance, first noted by Jawetz and Sonne, (1966) may be induced by pulsed penicillin exposure. Both *E. faecalis* and *E. faecium* are intrinsically resistant to cephalosporins, with resistance in *E. faecalis* mediated by PBP5, the CroRS system, IreK kinase, and MurAA enzyme (Kristich et al., 2014).

Acquired (Extrinsic) Resistance:
High-level ampicillin resistance (MIC ≥128 µg/mL) may result from point mutations—such as Met485→Ala and Ser466 insertion—rather than increased PBP expression (Jawetz and Sonne, 1966). In rare cases, resistance is independent of PBPs, involving bypass of D,D-transpeptidation through deletion of PBP5 (Mainardi et al., 2000).

β-Lactamase-Mediated Resistance:
Plasmid-mediated *bla* genes were first reported in *E. faecalis* in 1983. These β-lactamase-producing strains resist penicillin, ampicillin, and piperacillin but typically remain susceptible to imipenem and β-lactam/β-lactamase inhibitor combinations (Murray

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and Mederski-Samaroj, 1983).

Aminoglycoside:

Mode of Action:

Aminoglycosides bind to the A-site of 16S rRNA in the 30S ribosomal subunit, disrupting protein synthesis (Kotra et al., 2000).

Intrinsic Resistance:

Enterococci exhibit low-level intrinsic resistance to aminoglycosides (MIC: 4–256 µg/mL), largely due to limited drug uptake under facultative anaerobic conditions, which reduces electron transport activity. Synergistic bactericidal activity is achieved when combined with cell wall-active agents like ampicillin or vancomycin, which enhance aminoglycoside uptake. (Chow, 2000).

Acquired Resistance:

High-level aminoglycoside resistance (HLAR) arises from aminoglycoside-modifying enzymes. The aac(6')-Ie-apjh(2'')-Ia gene confers resistance to most aminoglycosides except streptomycin and abolishes synergism. Other resistance genes—aac(6')-Ii, aph(3')-IIIa, ant(4')-Ia, and aph(2'') variants (Ib, Ic, Id)—contribute to variable resistance patterns, with some retaining partial gentamicin synergy (Cattoir and Giard, 2014)

Clindamycin:

Enterococcus faecalis exhibits intrinsic resistance to clindamycin (a lincosamide), quinupristin (streptogramin B), and dalfopristin (streptogramin A), primarily due to the presence of the **lsa** gene. This gene, structurally related to ATP-binding cassette (ABC) efflux transporters, is believed to mediate resistance through active drug efflux (Singh et al., 2002).

Fluoroquinolones:

Quinolones exhibit limited efficacy against *Enterococcus* species. Their mechanism involves inhibition of DNA replication by targeting type II topoisomerases—DNA gyrase and topoisomerase IV—enzymes crucial for maintaining DNA supercoiling. Quinolone binding disrupts these enzymes, leading to lethal double-strand DNA breaks. Resistance commonly arises from mutations in the quinolone resistance-determining regions (QRDRs) of the genes encoding these targets, reducing drug binding affinity and permitting continued DNA replication despite drug presence. Such mutations have been identified in both clinical and laboratory-derived quinolone-resistant enterococcal strains (Kak et al., 2000).

Trimethoprim-Sulfamethoxazole:

Most bacteria depend on de novo folate synthesis for nucleic acid production, as they cannot import folate from their environment. The combination of trimethoprim and sulfamethoxazole inhibits two sequential steps in the tetrahydrofolate synthesis pathway, acting synergistically to suppress bacterial growth. However, *Enterococcus* species are unique in their ability to uptake exogenous folic acid, bypassing the targeted pathway and rendering the combination ineffective. Consequently, susceptibility testing of enterococci in folate-free media may show them as susceptible. Nevertheless, despite this in vitro susceptibility, trimethoprim-sulfamethoxazole fails to effectively treat serious infections caused by enterococci (Bushby and Hitchings, 1968; Grayson et al., 1990)

Vancomycin:

A rigid peptidoglycan layer, made up of lengthy chains of N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM), which is heavily cross-linked, reinforces the cell wall of bacteria. By binding to the D-alanyl D-alanine moiety, vancomycin inhibits the function of P-phospholipid carrier and glucosyltransferase (peptidoglycan synthase). NAM and NAG cannot assemble or polymerize as a result of this interference.

Mechanisms of Resistance:

1. **D-Ala-D-Lac–Mediated Resistance** *(VanA, VanB, VanD, VanF, VanM)*
   Resistance arises from substitution of D-Ala-D-Ala with **D-Ala-D-Lac** in Lipid II, eliminating a key hydrogen bond and reducing vancomycin binding affinity by 1,000-fold. This results in high-level resistance with MICs >64 µg/mL (Bugg et al., 1991).
2. **D-Ala-D-Ser–Mediated Resistance** *(VanC, VanE, VanG, VanL, VanN*
   Here, **D-Ala-D-Ser** replaces the terminal dipeptide, leading to low-level resistance. Vancomycin's binding affinity is reduced six-fold due to the bulkier hydroxymethyl group of serine compared to alanine (Reynolds, 1998)

Table: 4: Summarizes characteristics of different van gene

Van gene	Species	Resistance profile	Phenotypic Expression	Mobility
Van A	*E.faecium E.faecalis*	High for both vancomycin and teicoplanin	Inducible	Chromosome transferable
VanB	*E.faecalis E.faecium*	High-variable to vancomycin Susceptible to teicoplanin	Inducible	Chromosome transferable
Van C	*E. gallinarum E. casseliflavus*	Low to vancomycin	Constitutive Inducible	Chromosome
Van D	*E. faecium*	Low to high for both	Constitutive	Chromosome

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			Inducible	
Van E	*E. faecalis*	Low-moderate to vancomycin Susceptible to teicoplanin	Inducible	Chromosome
Van G	*E.faecalis*	Low to vancomycin & Susceptible to teicoplanin	Inducible	Chromosome
Van L	*E.faecalis*	Low to vancomycin susceptible to teicoplanin	Inducible	Chromosome
Van M	*E.faecium*	High for both	Inducible	Unknown
Van N	*E. faecium*	Low to vancomycin	Constitutive	Plasmid transferable

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Table: 5: Prevalence of Enterococcus species resistance to vancomycin in India

Author	Year	Place	E.faecalis	E.faecium	Sensitive to Vancomycin (%)	Resistant to Vancomycin (%)	Gene
(Das et al., 2022)	2022	India	76.9	16.9	83.1	16.9	Van A Van B
(Mohanty and Behera, 2022)	2022	Eastern India	60.4	28.8	92.8	7.2	Van A
(Sengupta et al., 2023)	2023	India	64.2	30.2	93.53	6.47	Van A Van C
(Rajan, 2023)	2023	South India	93.80	4.26	96.12	3.88	Van A Van B
(Bhavana et al., 2020)	2020	India	66.5	33.5	90.6	9.4	Gene not detected

Linezolid:

Mode of Action:

Linezolid, a synthetic oxazolidinone, inhibits bacterial protein synthesis by binding to the 23S rRNA of the 50S ribosomal subunit. This prevents formation of the initiation complex and impairs peptide chain elongation, thereby disrupting translation.(Diekema and Jones, 2000)

Mechanisms of Resistance

1. **23S rRNA Mutations:**Point mutations in the 23S rRNA gene, particularly G2576T, G2447U, and G2504A, reduce linezolid binding and confer resistance in *Enterococcus faecalis* (LRE) (Bonilla et al., 2010). Mutations in ribosomal proteins L3 and L4 can also contribute to increased MICs.
2. **CfrGene:** The cfr gene encodes a methyltransferase that modifies the A2503 nucleotide in 23S rRNA by adding a methyl group at the C8 position, leading to cross-resistance to the PhLOPSA group: phenicols, lincosamides, oxazolidinones, pleuromutilins, and streptogramin A (Giessing et al., 2009). Initially chromosomal, cfr is now widely plasmid-borne and transferable. Variants such as cfr(B), cfr(C), and cfr(D) have also been detected in *Enterococcus* (Stojković et al., 2019).
3. **optrA Gene:** The optrA gene encodes an ABC-F family ATP-binding cassette protein that confers resistance via ribosomal protection, rather than efflux. It mediates resistance to oxazolidinones and phenicols, and is plasmid-borne, facilitating interspecies transfer (Almeida et al., 2020; Wang et al., 2015)

Table: 5: Prevalence of Linezolid resistant enterococcus

Author/ Publication year	Country	Linezolid resistant Enterococcus (%)
(Singh Naruka et al., 2019)	India	3.06
(Sami et al., 2020)	India	0.79
(Khanal et al., 2021)	India	0.82
(Wada et al., 2024)	India	14

Tigecycline:

Tigecycline, a last-resort glycylcycline antibiotic, is increasingly used due to the rising prevalence of vancomycin-resistant enterococci (VRE) (Hegstad et al., 2024). Although global resistance remains low (<1%), it is gradually spreading. *E. faecium* exhibits higher resistance (1%) than E. faecalis (0.3%). Regionally, resistance rates are highest in Europe (3.5%), followed by Asia (1.3%) and America (0.3%) (Dadashi et al., 2021). The primary resistance mechanisms include mutations in the ribosomal protein S10 (RpsJ) and upregulated activity of Tet(M) and Tet(L) efflux or protection systems (Bender et al., 2018).

Infection control:

Vancomycin-resistant enterococci (VRE) are effectively controlled in the healthcare setting by implementing a multifaceted approach: In acute care settings, VRE control relies on strict hand hygiene, use of barrier precautions, thorough disinfection of medical equipment, avoidance of shared medical devices, and isolation of patients infected with VRE. In long-term care facilities, standard precautions are generally followed, with emphasis on hygiene and proper disinfection practices, since complete isolation may not always be feasible. In hemodialysis units, prudent use of vancomycin is critical, along with early removal of vascular access lines to minimize the risk of colonization and transmission. In outpatient care, healthcare workers should be alerted when managing VRE-positive patients, especially those with a higher risk of

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spreading the organism. Finally, surveillance and clearance, as recommended by the Infection Control Advisory Committee (ICAC), involve active monitoring through weekly rectal swabs in high-risk patients identified by ward type, antibiotic exposure, or prolonged hospitalization. A patient is considered cleared only after three consecutive negative swabs taken at one-week intervals.(Agudelo Higuita and Huycke, 2014b).

CONCLUSION:

Enterococci have evolved multiple strategies that enable their persistence in hospital environments. This resilience is attributed to a combination of factors: (i) although they possess limited virulence factor diversity, the ones identified play a critical role in pathogenesis and survival under hostile conditions; (ii) their intrinsic resistance to a broad spectrum of antibiotics, coupled with high genetic plasticity; and (iii) their capacity to acquire resistance-related genetic elements. The rising incidence of vancomycin- and linezolid-resistant enterococci underscores the urgent need for comprehensive studies focusing on their resistance mechanisms and virulence-associated genes.

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