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Review ARTICLE

Enterococci: An Evolving Threat of Multidrug Resistance and Linezolid Resistance in the Clinical Era

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Abstract:

Background: Enterococcus species, formerly seen as harmless gut flora, have developed into an increasing health threat in the healthcare environment due to their ability to develop resistance to multiple antibiotics. Now, they are among the most common etiological agents of nosocomial infections, particularly in patients who are vulnerable and immunocompromised. This review aims to critically review the taxonomy, virulence factors, and antimicrobial resistance mechanisms of *Enterococcus* species, with a special focus on linezolid resistance, based on literature from the past decade to support better clinical management and infection control strategies.

Conclusion: Linezolid-resistant Enterococcus species have emerged as significant clinical threats due to their adaptability, diverse resistance mechanisms, and remarkable ability to spread in healthcare settings. Tackling this challenge requires rapid diagnostics, strict infection control measures, and responsible antibiotic use. Continued research, innovation, and global collaboration are essential to develop new treatment options and to prevent the further spread of resistance.

Keywords: Enterococci; Multidrug Resistance; Linezolid Resistance.

INTRODUCTION

Enterococci are among the Gram-positive who are naturally established in the intestines of humans and animals. Long considered harmless commensals of the human gut, *Enterococcus faecalis* and *Enterococcus faecium* were historically assumed to have limited clinical significance. However, with the growing recognition of their role in healthcare-associated infections (HAIs) worldwide, these organisms have increasingly gained prominence as formidable nosocomial pathogens [1]. Clinically important *Enterococcus* species, predominantly *Enterococcus faecalis* and *Enterococcus faecium*, have emerged as important pathogens in a wide variety of infections, including but not limited to urinary tract infections, bacteremia, endocarditis, and intra-abdominal infections [2,3]. Their great ability to survive in extreme environments and persisting in different aspects within the hospitals makes these two bacteria formidable opponents in the clinical setting [4].

Fast acquiring antimicrobial resistance, which includes high level aminoglycosides, beta-lactams and glycopeptides such as vancomycin, which is one of the most alarmingly growing characteristics of *Enterococcus spp*. [5]. The emergence of *Enterococcus* strains resistant to vancomycin, commonly referred to as VRE, posed a global challenge in the treatment of their infections especially among immunocompromised and critically-ill patients [6]. The increasing inability to treat those infections presents a true challenge for surgeons or critical care specialist because of narrow

therapeutic options, Linezolid, an oxazolidinone, is the main drug against multidrug-resistant enterococcal infections [7]. There are increasing reports on resistance to Linezolid attributed to the action of such mobile genetic elements as optrA, poxtA, and cfr that make this antibiotic questionable concerning its long-term efficacy [8].

This review aims to critically review the taxonomy, virulence factors, and antimicrobial resistance mechanisms of *Enterococcus* species, with a special focus on linezolid resistance, based on literature from the past decade to support better clinical management and infection control strategies.

Taxonomy and Classification of Enterococcus Species

Enterococcus is a genus of bacteria belonging to the phylum Firmicutes and the class Bacilli. These are Gram-positive, facultative anaerobic organisms. Historically, through its introduction as a group D streptococcus, it was later classified as an independent genus due to molecular taxonomy advances such as 16S rRNA sequencing in 1984. The key reason has been genetic and phenotypic traits differentiating Enterococcus from streptococci for setting apart [9].

More than 50 species of Enterococcus have been characterized at present, of which only a few, such as *E. faecalis* and E. faecium, assume considerable clinical importance as they are almost always isolated from human infections. Others, like *E. gallinarum, E. casseliflavus, and E. durans*, are sometimes involved in infections but are not considered seriously pathogenic. The classification is primarily phenotypically based involving biochemical reactions and molecular techniques including whole-genome sequencing [10].

Enterococci are ubiquitous species in nature and usually found in the gastrointestinal tracts of human beings and animals, besides which, they may also be found in water, soil, plants, and food. Their ability to withstand harsh environmental conditions — including high salt concentrations, extreme pH levels, and a wide range of temperatures — facilitates their adaptation to diverse ecological niches [11]. It is this robustness toward environments and variability in genetics that has enabled Enterococcus to adapt into opportunistic pathogens in the hospital where they particularly become troublesome due to developing antibiotic resistance [12].

Morphology and Physiology of *Enterococcus* Species

Enterococci are cocci that are typically oval or spherical and form pairs or short chains. They are gram-positive, non-spore-forming, and lack a capsule. However, some of them may have surface-associated polysaccharides that help evade immunity. This enables them to tolerate some survival conditions for extreme temperatures - growing up to 45 degrees Celsius - as well as high salt concentrations which are 6.5% NaCl and wide ranges of pH (4.5-10.0) making them hardy under environmental and clinical conditions similar to those mentioned above [13].

Enterococci are facultative anaerobes i.e. survive both aerobically and anaerobically. Fermentation is their means of metabolizing carbohydrates, with the lactic acid produced as the major end product. This is the condition categorized under the lactic acid bacteria category. Like most of the other lactic acid bacteria, these can incorporate several substrates in energy metabolism and have the ability to tolerate oxidative stress [14].

The Enterococcus cell wall structure has peptidoglycan, teichoic acids, and lipoteichoic acids, which add rigidity and osmotic pressure resistance to them. The membranes contain cardiolipin, believed to be important for mechanisms of antibiotic resistance. All these structures contribute not just to survival levels but also to interactions between the bacterial cell and antimicrobial agent [15].

Thus, adaptability is a major feature amongst the Enterococcus species. They can thrive when there is a limit in available nutrients and have

proven this to last for even long time periods on dry surfaces, a fact that makes them quite easy to transmit in healthcare locations. Their metabolic flexibility even puts them in positions allowing colonization of a variety of niches in the human body and external environments, which helps in defining their double role as commensals as well as opportunist pathogens [16].

Virulence Factors and Pathogenicity of *Enterococcus* Species

Enterococcus species possess a broad arsenal of virulence factors that facilitate their transition from commensals to opportunistic pathogens, particularly in hospitalized or immunocompromised patients. These factors can be grouped into phenotypic and genotypic traits, as well as secreted virulence molecules, including enzymes and toxins that mediate adhesion, colonization, immune evasion, tissue invasion, and biofilm formation [17].

1. Phenotypic and Genotypic Virulence Traits

One of the hallmark traits of pathogenic *Enterococcus* species is the expression of surface-associated adhesins. These include aggregation substance (AS), enterococcal surface protein (Esp), and collagen-binding proteins such as Ace (*E. faecalis*) and Acm (*E. faecium*). These proteins promote adhesion to host tissues, medical devices, and epithelial surfaces, facilitating colonization and the development of biofilms [17,18].

The presence of the esp gene has been particularly associated with increased virulence and persistence in hospital settings, especially in urinary tract infections and endocarditis. These genes are often carried on mobile genetic elements such as plasmids and transposons, promoting horizontal gene transfer and enhancing the adaptive capacity of the organism [19].

2. Secreted Virulence Molecules

a. Toxins

Cytolysin is a pore-forming exotoxin produced by some strains of *E. faecalis*. It exhibits both hemolytic and bacteriocin-like activity, capable of lysing erythrocytes and competing bacterial species. Importantly, cytolysin can also damage host immune cells, promoting immune evasion and persistence in host tissues [19,20].

b. Enzymes

Pathogenic enterococci secrete various enzymes that play a critical role in their virulence and ability to sustain chronic infections. Among these, gelatinase is a notable enzyme that degrades host proteins such as collagen and gelatin, thereby facilitating tissue invasion and contributing to the breakdown of structural barriers. In addition, enterococci produce serine proteases, which are involved in the degradation of host tissues and can disrupt normal immune functions. These enzymes collectively enhance bacterial dissemination within the host and modulate the host's inflammatory responses, promoting a microenvironment that supports persistent infection and evasion of immune surveillance [20].

3. Biofilm Formation

Biofilm production is a major virulence mechanism in *Enterococcus* species. Surface adhesins, especially Esp and AS, facilitate initial attachment to surfaces such as catheters and prosthetic valves. The mature biofilm matrix provides a physical barrier that protects embedded bacteria from antibiotics and host immune responses [18,19].

Biofilm-forming strains are strongly associated with persistent and recurrent infections, especially in device-related cases such as catheter-associated urinary tract infections, prosthetic valve endocarditis, and intra-abdominal infections. In these settings, antibiotic penetration is limited, often necessitating combined antimicrobial therapy and device removal [19].

4. Interaction with the Host Immune System

Enterococcus species possess remarkable mechanisms to evade or modulate host immune responses, enabling them to persist in hostile environments and contribute to chronic

infections. One key strategy involves their resistance to phagocytosis and host-derived antimicrobial peptides, which allows them to survive and proliferate despite innate immune defenses. Additionally, certain virulence factors such as cytolysin can directly suppress immune cell activity, further impairing the host's ability to mount an effective response [21].

The formation of biofilms adds another layer of protection, as the biofilm matrix shields bacterial cells from immune detection and clearance. Moreover, some enterococcal strains are capable of disrupting host immune signaling pathways, facilitating their persistence within inflamed or damaged tissues. These immune evasion strategies are particularly concerning in critically ill or immunocompromised patients, where enterococci often exploit weakened defenses to establish long-standing infections [21].

Antibiotic Resistance in *Enterococcus* Species: Focus on Linezolid

Enterococcus species exhibit a complex resistance profile that includes both intrinsic resistance and acquired resistance mechanisms, making them particularly challenging to treat. Intrinsically, enterococci are resistant to several commonly used antibiotics such as low concentrations of aminoglycosides, cephalosporins, and clindamycin, due to inherent structural or functional features like low-affinity penicillin-binding proteins and limited permeability. Over time, these organisms have also developed acquired resistance through mutation and horizontal gene transfer, conferring high-level resistance to aminoglycosides, beta-lactams, vancomycin, and more recently, linezolid. The combination of intrinsic barriers and rapidly spreading acquired traits has contributed to the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Enterococcus* strains in clinical settings, raising significant concerns about treatment failures and infection control [22].

Emergence of Linezolid Resistance

Linezolid is a synthetic antibiotic belonging to the oxazolidinone class, introduced in the early 2000s as a last-resort agent against Gram-positive multidrug-resistant bacteria, including *Enterococcus* spp., methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci (VRE). Structurally, linezolid contains an oxazolidinone ring critical to its activity, and it exerts its antimicrobial effect by binding to the 50S ribosomal subunit, specifically the peptidyl transferase center of domain V in the 23S rRNA [22].

This action inhibits the initiation of protein synthesis, making it bacteriostatic against enterococci and other susceptible organisms. Linezolid was initially heralded for its low cross-resistance potential; however, with increasing clinical use, resistance began to emerge globally within a few years, driven by both chromosomal mutations and acquisition of transferable resistance genes. The spread of these mechanisms has since been documented in healthcare and community settings, raising concerns over the sustainability of linezolid as an effective therapeutic option [23].

Mechanisms of Linezolid Resistance in *Enterococcus* Species

Resistance to linezolid in *Enterococcus* species arises through two major mechanisms: chromosomal mutations and the horizontal acquisition of resistance genes mediated by mobile genetic elements [24-28].

1. Chromosomal Mutations

The earliest recognized mechanism involves point mutations in the 23S rRNA gene, particularly the G2576T mutation within domain V, which reduces the binding affinity of linezolid to its ribosomal target [28]. The degree of resistance correlates with the number of mutated 23S rRNA gene copies present in the bacterial genome. Additionally, mutations in ribosomal proteins L3 and L4, which contribute to the structural configuration of the ribosomal binding site, have been implicated in reduced susceptibility to linezolid [28].

2. Acquisition of resistance genes

The acquisition of mobile resistance genes such as *cfr*, *optrA*, and *poxtA*. These genes are often located on plasmids, facilitating their horizontal transfer across bacterial populations. The *cfr* gene encodes a methyltransferase that modifies adenine at position 2503 in the 23S rRNA, leading to resistance not only to oxazolidinones but also to phenicols, lincosamides, and streptogramins—a resistance pattern known as the PhLOPSA phenotype. In contrast, *optrA* and *poxtA* encode ATP-binding cassette F (ABC-F) ribosomal protection proteins that prevent oxazolidinones from binding by displacing them from the ribosome. These genes have been detected in both clinical and environmental isolates, often in conjunction with other resistance determinants, significantly contributing to multidrug resistance and therapeutic challenges [24].

Role of Mobile Genetic Elements

Several investigations have highlighted the critical role of insertion sequences (e.g., IS1216E) and transposons (e.g., Tn6674, Tn554-like elements) in the mobilization and spread of linezolid resistance genes [29-30]. These elements facilitate the integration, rearrangement, and horizontal transfer of resistance determinants within plasmids and chromosomes, enhancing adaptability and persistence of resistant strains in clinical, agricultural, and environmental settings [31]. The presence of such mobile elements accelerates the dissemination of resistance across the human–animal–environment interface, reinforcing the urgent need for comprehensive surveillance strategies [32].

Epidemiological Trends and Clinical Implications

While the global prevalence of linezolid-resistant *Enterococcus* spp. remains relatively low, there is a rising trend, particularly in healthcare settings with high linezolid usage. Molecular epidemiological studies have revealed clonal dissemination of resistant strains, as well as independent acquisition events via mobile genetic elements such as plasmids, insertion sequences, and transposons. Notably, the co-localization of optrA and poxtA with other resistance genes complicates treatment and highlights the need for integrated surveillance systems [25].

Colonized patients may remain asymptomatic carriers of linezolid-resistant enterococci, serving as silent reservoirs for nosocomial spread. Routine screening and molecular diagnostics, including PCR assays targeting resistance genes, are essential tools for early detection and infection control [26,27].

Moreover, prior linezolid exposure, prolonged hospital stays, intensive care unit (ICU) admission, and underlying comorbidities are well-established risk factors for acquiring linezolid-resistant infections. Treatment options for these strains are limited and often require susceptibility-guided therapy using agents such as daptomycin or tigecycline, which may have limited efficacy in certain infection sites or patient populations [28].

Mobile linezolid resistance genes, such as optrA and poxtA, have been detected not only in clinical isolates but also in bacterial strains derived from animals, meat products, and environmental sources [30]. This phenomenon highlights the need for a One Health approach, recognizing that antimicrobial resistance (AMR) is an interconnected problem at the human–animal–environment interface [31,32].

In agricultural settings, extensive antibiotic use in livestock can select for resistant enterococcal strains, which may subsequently contaminate the food chain through meat, milk, and other animal products [33]. Furthermore, wastewater from farms and hospitals containing resistant bacteria or resistance genes can contaminate surface water, groundwater, and soil, creating environmental reservoirs [34]. These reservoirs can sustain and disseminate resistance traits across different bacterial populations within ecosystems.

Clinical Effects and Obstacles in the Treatment of Linezolid-resistant Enterococcus Infections

Linezolid-resistant strains of Enterococcus may be a problem in clinical outcomes, especially for immunocompromised persons or patients in an intensive care unit. Common infection types are bacteremia, urinary tract, surgical wound infection, and endocarditis, followed by increased morbidity, prolonged stays and health care costs [32].

One of the major clinical concerns associated with LRE infections is the management options that are limited. VRE normally limited therapeutic options, and with the development of the pathogen to linezolid, a last-resort drug, it gets worse. Daptomycin and tigecycline are used as alternatives to some extent; however, they are not as effective, and susceptibility testing is needed prior to administering. Moreover, these agents are not appropriate for most infections, particularly those involving the central nervous system or endovascular foci [33].

Apart from therapeutic constraints, LRE strains are commonly found to have patterns of multidrug resistance, leading to most instances of treatment being empirical. The delay in instituting the right treatment has been associated with poor clinical outcomes. To make things worse, there are cases in which LRE infections exist in patients having more than one comorbidity or a previous episode of continuous antibiotic therapy [34].

Treatment of LRE infections employs a combination of remedies, but evidence from the clinical arena is scant regarding whether any of these regimens have actual proven efficacies or not. Some hospitals have also used linezolid with other antimicrobials to prevent resistance formation but are largely based on in vitro synergy studies, not strong clinical trials [35].

For all these reasons, the growing tolerance of Enterococci to linezolid makes it very imperative for newer antimicrobials and better stewardship to be employed as part of enhanced infection control measures. Time is running short before the period arrives when enterococcal infections will be very difficult and often inefficient to treat [36].

Prevention and Control Strategies for Linezolid-Resistant *Enterococcus* Infections

Prevention of transmission of linezolid-resistant strains of Enterococcus has to be multi-strategic combining very strong infection control practices with an antimicrobial stewardship. Such strategies would include early detection of the colonised or infected individuals, strict application of hand hygiene, as well as isolation precautions to limit patient-to-patient transmission [37].

Routine screening among high-risk populations, particularly patients at ICUs, transplant units, and patients on antibiotics for an extended period, can assist in identifying carriers of Linezolid-Resistant Enterococci (LRE). Molecular tools like PCR assays of resistance genes (e.g., optrA, cfr, poxtA) have revolutionized the speed and quality of diagnosis making it possible to initiate containment measures in the nick of time [38].

Environmental decontamination all through proves to be equally vital since the Enterococci can survive for longer durations on inanimate surfaces. Enhanced cleaning protocols especially in areas housing patients found to be LRE infected are necessary to break the chain of transmission. Education and training of healthcare workers on current infection-control policies are still crucial [38].

Antimicrobial stewardship plays a pivotal role in minimizing the selective pressure that drives resistance. Judicious use of linezolid and other last-line agents should be guided by susceptibility testing and clinical need. Hospitals are encouraged to implement stewardship programs that monitor antibiotic consumption, promote de-escalation of therapy, and audit prescribing behaviors [38].

Ultimately, the successful prevention and control of LRE outbreaks hinge on coordinated efforts at institutional, national, and global

levels. Surveillance data should inform policy updates, and investments in rapid diagnostics, research, and development of new antimicrobials are necessary to stay ahead of evolving resistance threats [38].

Conclusion

Linezolid-resistant *Enterococcus* species have emerged as significant clinical threats due to their adaptability, resistance mechanisms, and ability to spread in healthcare settings. Tackling this challenge requires rapid diagnostics, strict infection control measures, and responsible antibiotic use. Continued research and global collaboration are essential to develop new treatment options and to prevent the further spread of resistance.

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