

Research Article

Linezolid resistant *Enterococci*: An Emerging Threat to Infection Control

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Abstract: Background: *Enterococci* cause healthcare-associated infections and can develop resistance to multiple antimicrobial agents. Linezolid is used to treat infections caused by multidrug-resistant and Vancomycin-resistant *Enterococci*. However, the emergence of linezolid-resistant *Enterococci* limits treatment options and complicates infection control and antimicrobial stewardship.

Objective: This study evaluated the prevalence of Linezolid resistant *Enterococci* isolated from various clinical samples at a tertiary care hospital in Karachi.

Materials and Methods: A retrospective analysis was conducted in the Microbiology laboratory of Liaquat National Hospital from 1st September 2021 – 31st December 2023 after taking approval from the Institutional Review Board & Ethical Review Committee (Ref: 1026-2024-LNH-ERC), dated: 4th April 2024. The study determined the prevalence of Linezolid resistant *Enterococci* in clinical samples. All consecutive samples from which Linezolid resistant *Enterococci* were isolated were included in the study. Duplicate samples from the same patient were excluded. Identification of the isolates was performed using standard Microbiological techniques. Antibiotic susceptibility testing used the Kirby–Bauer disk diffusion method, on Muller–Hinton agar (MHA) and Minimum inhibitory concentration (MIC) on Vitek 2 system. Susceptibilities were interpreted according to recommended CLSI (Clinical and Laboratory Standards institute) guidelines, M100, 32nd edition.

Results: During the study period a total of 2891 *Enterococcus species* were isolated from various clinical samples. Out of these twenty-four linezolid resistant *Enterococcus faecium* were isolated from fourteen male and ten female patients. Majority of the isolates were from urinary samples (n= 14), followed by blood (n=6), Pus (n=2) and one each from tissue and pleural fluid. In addition to being resistant to Linezolid all the isolates were also resistant to Vancomycin (VRE), Ampicillin, Amoxicillin + Clavulanate. The urinary isolates although being resistant to Linezolid and Vancomycin showed good sensitivity to Nitrofurantoin and Fosfomycin (85.7 % ,12 out of 14 were sensitive).

Conclusion: The emergence of linezolid – resistant *Enterococci* in clinical samples presents a significant threat to public health. Understanding the local burden is critical for guiding effective infection control and antibiotic stewardship strategies to preserve the efficacy of this vital therapeutic agent.

Keywords: *Enterococcus species*, Linezolid, Vancomycin resistance, Antimicrobial resistance, Nosocomial.

INTRODUCTION

Enterococci exist as ubiquitous microorganisms in the environment and gastrointestinal tract of humans and animals [1]. They are members of the family Enterococcaceae and are catalase negative facultative anaerobes. Under the microscope the *Enterococci* appear as gram positive cocci either singly or arranged in pairs [2]. The ability to form biofilm contributes to their virulence as it enhances antibiotic resistance and serves as a mechanism to evade phagocytosis [3].

In the hospital environment *Enterococci* cause a significant number of infections ranking second only to *Staphylococci* which are responsible for highest number of nosocomial infections worldwide [4]. They are capable of causing a variety of infections, such as urinary tract infections, bacteremia and endocarditis, attributed to their ability to colonize and resistance to multiple antibiotics [5]. Their intrinsic resistance to a number of antibiotics and the capacity to develop additional resistance through mutations or acquiring foreign genes via plasmids and transposons helps them survive in the hospital environment [6].

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Enterococcus species exhibits high level resistance against β -lactams, aminoglycosides and glycopeptides among which 'Vancomycin Resistant *Enterococci*' (VRE) are most prominent [7]. Emergence of 'Vancomycin Resistance *Enterococci*' (VRE), is a serious concern by not only presenting a challenge for the treating physicians but also having the ability to donate Vancomycin resistant gene to other organisms such as *Staphylococcus aureus* [8]. Isolation of VRE from intensive care patients with co morbidities further complicates the course of illness and limit the therapeutic options for patients [9]. Healthcare-associated infections (HAIs) related to VRE have been on the rise since the last decade and raise alarm for infection prevention departments to limit their spread [10].

Enterococci are highly adapted bacteria of GI tract in a variety of insects and other hosts which utilize organic matter colonized by antibiotic resistant or antibiotic producing microorganisms. The antibiotic treated hospital patients provide them with an opportunity to colonize and evolve as pathogens [11]. Hospital-adapted *Enterococci* strains carry over 25% mobile elements, and the loss of CRISPR protection enhances the expression and transfer of resistance and virulent traits [12]. The injudicious use of antibiotics such as Cephalosporin, Aminoglycosides and Vancomycin leads to the development of resistance. A high gastrointestinal concentration of antibiotics with poor activity against *Enterococci* promotes resistant strains [13]. Linezolid is the only drug of choice that remains to treat such infections [14].

Linezolid was approved as the first oxazolidinone to treat infections caused by multidrug resistant (MDR) gram positive bacteria. It inhibits bacterial protein synthesis by binding in the V domain of the 23S rRNA component of the 50S ribosomal subunit [15]. In the absence of effective therapeutic options, Linezolid is a crucial last line antibiotic for managing severe VRE pneumonia as well as complicated skin and soft tissue infections [16].

Resistance to linezolid in *Enterococci* can occur as a result of G2576T or G2505A mutations in the 23S rRNA gene, or mutations in genes encoding ribosomal proteins L3/L4. However, resistance can also develop following acquisition of the resistance genes: *cfr*, *cfr* (B), *cfr* (D), *optrA*, and *poxA* located on plasmids and transposons which can lead to horizontal transfer of resistance [17]. Linezolid resistance was identified in *E. faecalis* and *E. faecium*, which are the two *Enterococcal species* most commonly isolated from patients with HAIs [18]. Emer-

gence of Linezolid resistant *Enterococci* have been reported globally with cases from India and Pakistan [19-21].

The objective of this study was to evaluate the prevalence of Linezolid resistant *Enterococci* isolated from clinical samples presenting at Liaquat National Hospital, Karachi. Knowledge of our local burden of Linezolid-resistant *Enterococci* emphasizes the need to implement strategies to preserve this last resort antibiotic.

MATERIALS AND METHODS

A retrospective analysis was conducted in the Microbiology laboratory of Liaquat National Hospital from 1st September 2021 – 31st December 2023, to determine the prevalence of Linezolid resistant *Enterococci* (LRE) in clinical samples.

Approval for the study was obtained from the Institutional Review Board & Ethical Review Committee (Ref: 1026-2024-LNH-ERC), dated 4th April 2024.

All consecutive samples from which Linezolid resistant *Enterococci* were isolated were included in the study. Duplicate samples from the same patient were excluded. Identification of the isolates was performed using standard Microbiological techniques. The bile-esculin test was used for the identification of *Enterococci* if catalase-negative, Gram-Positive cocci were isolated [22]. Kirby-Bauer disk diffusion method on Muller-Hinton agar (MHA) was used for antibiotic sensitivity testing as recommended by CLSI M100, (Clinical and Laboratory Standards institute). Bacterial identification and antibiotic sensitivity was also confirmed by Vitek 2 (BioMerieux, France). Susceptibilities were interpreted according to CLSI M100, 32nd edition [23]. The laboratory findings and basic demographics of patients were recorded for analysis.

STATISTICAL ANALYSIS

Data entry and analysis was done on statistical package for social sciences (SPSS) version 25. Frequencies were calculated for categorical variables and were presented as percentages.

RESULTS

During the study period, 2891 *Enterococcus species* were recovered from various clinical specimen. A total of twenty-four (0.83 %) were resistant to linezolid and

all were identified as *Enterococcus faecium*. Fourteen of the isolates were from male and ten from female patients. Majority of the isolates were from urinary samples (n=14), followed by blood (n=6), Pus (n=2) and one each from tissue and pleural fluid as shown in Table 1. According to the year wise trend, there was a consistent isolation of linezolid resistant *Enterococci* during the study period as shown in Fig. (1). The antibiotic susceptibility results show that all the Linezolid resistant *Enterococcus faecium* (LRE) also exhibited resistance to Vancomycin, Ampicillin, Amoxicillin + Clavulanate. Table 2 shows the susceptibility rates of the various antibiotics tested. Urinary isolates although being resistant to the antibiotics tested showed 85.7% sensitivity to Nitrofurantoin & Fosfomycin (12 out of 14 were sensitive).

Table 1. Demographic Characteristics of Patients and Sample Source.

Characteristics	Number of Patients (n=24)
Age	
0 – 49	11 (45.83 %)
≥ 50 years	13 (54.1 %)
Gender	
Male	14 (58.3%)
Female	10 (41.6 %)
Patient Location	
In-patient	22 (91.66%)
Out-patient	2 (8.3 %)
Sample source	
Urine	14 (58.3 %)
Blood	6 (25 %)
Pus	2 (8.3%)
Tissue	1 (4.1 %)
Pleural fluid	1 (4.1 %)

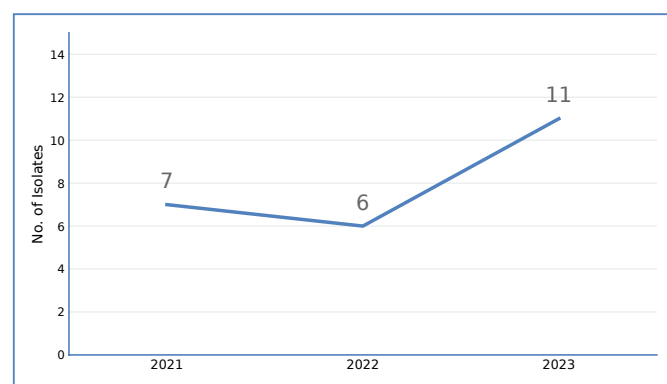


Fig. (1) Trend of Linezolid-Resistance over the Study Period.

Table 2. Antibiotics Susceptibility of Linezolid resistant *Enterococci* (n= 24).

Antibiotics	Resistant	Sensitive
AMP	24 (100%)	0
AMC	24 (100%)	0
VAN	24 (100%)	0
LZD	24 (100%)	0
E	10 (100 %)	0
OT*	11 (78.5%)	3 (21.4%)
CIP*	13 (92 %)	1 (7.1%)
F*	2 (16.6 %)	12 (85.7 %)
FOS *	2 (16,6 %)	12 (85.7 %)

AMP: Ampicillin, AMC: Amoxicillin+ Clavulanate, VAN: Vancomycin, LZD: Linezolid, E: Erythromycin OT: Oxytetracycline, CIP: Ciprofloxacin, FOS: Fosfomycin, F: Nitrofurantoin, *tested on urine isolates only.

DISCUSSION

Linezolid is an effective therapeutic option for treating infections by Vancomycin resistant *Enterococci* (VRE). There are reports of Linezolid resistant *Enterococci* from multiple regions worldwide including Pakistan [24].

In this study we analyzed the emergence of Linezolid resistant *Enterococci* from patient samples presenting at Liaquat National hospital. The first Linezolid resistant *Enterococcus faecium* was isolated at our Hospital in September 2021 from the blood sample of a 67 years old male patient admitted in Nephrology ICU.

Studies have linked previous linezolid exposure to the development of linezolid resistant *Enterococci* [25]. In this study the Isolation of linezolid resistant *Enterococci* mainly from patients admitted in ICUs or on dialysis, suggests a possibility of prior Linezolid exposure. As it was a retrospective study, clinical histories were not fully available to confirm prior treatment with linezolid to be responsible for the development of resistance. The *Enterococci* included in the study showed resistance to Ampicillin, Tetracycline and Vancomycin in addition to Linezolid Although most studies report Linezolid resistant *Enterococci* (LRE) resistant to Vancomycin and other antimicrobial agents, however, *Enterococci* resistant to Linezolid but sensitive to Vancomycin have also been identified [20]. Linezolid is a WHO reserve antibiotic and is tested and reported in case of Vancomycin resistant *Enterococci* (VRE) only [26]. As this was a retrospective study, linezolid susceptibility had been tested and was available in the Vancomycin resistant isolates only. Therefore, linezolid resistance co-occurred with Vancomycin resistance.

Prolonged therapy with linezolid was considered a risk factor for developing resistance to the antibiotic. This has been contradicted by the reports of rapid development of resistance to Linezolid in *Enterococcus faecium* [27]. Genetically related strains of linezolid and Vancomycin resistant *Enterococci* have been identified in specimen obtained from patients not previously treated with Linezolid suggesting the possibility of nosocomial transmission via healthcare workers or fomites [28, 29].

LIMITATIONS

This study did not perform molecular testing to discover the genetic relatedness of the isolated *Enterococcus* strains. A whole-genome sequencing study conducted in China identified multiple mechanisms of linezolid resistance in *Enterococcus* isolates, including the *optrA*, *poxtA*, and *cfr (D)* genes and chromosomal mutations, demonstrating the molecular diversity of linezolid resistance. In contrast to the findings in this study, the prevalent species was *Enterococcus faecalis* [30]. These data are further strengthened by Peykov *et al.*, which describe the global detection rate for linezolid-resistance *Enterococcus faecalis* to be double of linezolid-resistance *Enterococcus faecium* [31]. Conversely, a study in Copenhagen reports the prevalence of Linezolid resistant *Enterococcus faecium* in a tertiary care hospital setting, similar to this study [29].

RECOMMENDATIONS

Despite the limitations, the appearance of Linezolid resistance in clinical isolates is alarming and should be considered as a warning signal due to risk of nosocomial spread of Linezolid resistant *Enterococci*. In order to contain the spreading of *Enterococci* resistant to Linezolid within the hospital and community rational use of Linezolid & strict surveillance for early detection and containment of the resistant strains is required.

CONCLUSION

Emergence of Linezolid resistant *Enterococci* resistant to Linezolid in clinical samples presents a significant threat to public health. Lack of effective treatment options can lead to higher morbidity and mortality. Infections with LRE can lead to longer hospital stays and increased healthcare costs. These resistant bacteria can spread rapidly within healthcare settings, thus necessitating strict infection control measures to prevent their spread. Association of resistance with linezolid consumption empha-

sizes the need to implement strategies for rational use of Linezolid.

ABBREVIATIONS

MHA: Muller- Hinton Agar.

MIC: Minimum Inhibitory Concentration.

CLSI: Clinical and Laboratory Standards Institute.

VRE: Vancomycin Resistant *Enterococci*.

MDR: Multidrug Resistant.

LRE: Linezolid Resistant *Enterococci*.

SPSS: Statistical Package for Social Sciences.

AUTHORS' CONTRIBUTIONS

Sana Anwar: Conceptualization, study design, and critical review and revision of the manuscript.

Uzma Saad: Methodology, data analysis and interpretation, drafting the manuscript, and critical review and revision of the manuscript.

Sana Muslim: Methodology, data analysis and interpretation, and drafting the manuscript.

Shaheen Sharafat: Critical review and revision of the manuscript.

Fizza Faisal: Drafting the manuscript and critical review and revision of the manuscript.

All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declared None.

ETHICAL DECLARATIONS

Data Availability

The data supporting the findings of this study are not publicly available because they were obtained from hospital records and may be subject to institutional and privacy restrictions. Further inquiries regarding data access may be directed to the corresponding author, subject to applicable ethical, privacy, and institutional requirements.

Ethical Approval

This retrospective analysis was conducted in the Microbiology Laboratory of Liaquat National Hospital, Karachi, Pakistan, using data collected from 1st September 2021 to 31st December 2023. The study was approved by the Institutional Review Board and Ethical Review Committee (Ref. No. 1026-2024-LNH-ERC; approved 4th April 2024).

Consent to Participate

As this was a retrospective study based on anonymised hospital records, the requirement for individual informed consent was waived by the Institutional Review Board and Ethical Review Committee.

Consent for Publication

Not applicable. This article does not contain any individually identifiable patient information, images, or other material requiring consent for publication.

Declaration of Competing Interest

The authors declare that they have no known financial or non-financial competing interests that could have influenced the work reported in this study.

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Use of AI-Assisted Technology

The authors used Google Gemini, an artificial intelligence (AI)-assisted language tool, to assist with improving the language, grammar, readability, and formatting of the manuscript. The use of AI was limited to language-related assistance and did not involve data collection, data analysis, interpretation of results, or generation of scientific conclusions. The authors critically reviewed, revised, and approved all AI-assisted content and take full responsibility for the accuracy, integrity, originality, and final content of the manuscript.

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