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Prevalence of High Level Aminoglycoside Resistance and Vancomycin Resistance in Enterococcal Isolates at A Tertiary Care Hospital

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ABSTRACT

Background and Aim: Vancomycin resistant Enterococci (VRE) and high level aminoglycoside resistant (HLAR) Enterococci have complicated the available treatment modalities for Enterococci worldwide. The existing study was planned to evaluate the occurrence of HLAR and VRE strains in a tertiary care center in India and to study the association of HLAR with vancomycin sensitive Enterococci (VSE) and VRE.

Materials and Methods: A total of 50 enterococcal isolates from various clinical specimens were incorporated in the study. Speciation was done on the basis of standard biochemical tests. HLAR was tested by the disc diffusion method using 150µg gentamicin disc and 200 µg streptomycin discs. Vancomycin susceptibility patterns were reported using vancomycin disc and agar dilution methods.

Results & Conclusion: Pus samples comprised of the majority for the isolation of enterococcal strains (40%). 54% isolated strains were HLGR, 32% were HLSR and 14% isolates were positive for both HLGR and HLSR. 61.7% of *Enterococcus faecium* isolates demonstrated resistance for high-level gentamicin (HLGR) and 43.75% *Enterococcus faecalis* isolates were resistant to high-level streptomycin (HLSR). When VRE was compared to VSE, the rate of HLSR was detected to be 4.64% in VRE, while it was 32.55% in VSE; the rate of HLGR was noted to be 11.62% in VRE and it was 41.87% in VSE. The association of HLGR with HLSR (HLAR) was 2.32% in VRE and 13.95% in VSE strains. Enterococci strains are showing an increase in their antimicrobial resistance patterns. The increment of such strains in health care settings has to be reserved and controlled to avert complicated infections.

Keywords: Aminoglycoside, Enterococci, HLAR, Vancomycin, Vancomycin resistant Enterococci

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1. Introduction

For more than a century Enterococci have been acknowledged as potential human pathogens, but the latest studies and data reiterate the fact that these organisms are up-and-coming as prominent causes of nosocomial infections. The capability to acquire antibiotic resistance markers and dissemination in hospital set-ups makes the management of certain enterococcal infections more complicated in gravely sick patients. They can cause urinary tract infections, genital tract infections, and even endocarditis due to factors like colonization and resistance to multitude of drugs used for their treatment (1). Enterococci are also known to attain and transmit resistant genes easily which is responsible for emergence of high level aminoglycoside resistance (HLAR) strains, vancomycin resistant Enterococci (VRE) strains, and beta lactamase producing strains. In fact, commonly used antibiotics like aminoglycosides, cephalosporins,

aztreonam and semisynthetic penicillins have lost their therapeutic capacities for these organisms because of these resistance mechanisms **(2)**.

Aminoglycoside resistance in Enterococci can be attributed to two main mechanisms the first being moderate level resistance in which the permeability to aminoglycosides is low scale and the modality of synergism with cell wall active agents has been applied to counter this. The beta-lactam antibiotics amply disorganize the cell wall after which the aminoglycosides can enter the cell and target the ribosomes. If the organism attains resistance determinants for aminoglycoside or cell wall active agents (lactams, glycopeptides) this synergism operational for the combination therapy of Enterococci is lost **(1)**. The second mechanism is high level resistance or ribosomally mediated resistance wherein inhibitory enzymes like acetyl transferase and adenyl transferase are formed **(3)**. Adenyl transferase mediates resistance to streptomycin whereas gentamicin resistance is encoded by acetyl transferase. Resistance to gentamycin is a potent indicator of resistance to other aminoglycosides except streptomycin while streptomycin resistance is the sole indicator of resistance to streptomycin alone.

Various hospital outbreaks have been caused by VRE worldwide and this has dramatically augmented in past few years, for the reason that widespread injudicious and irrational use of antibiotics is being practiced allowing the dissemination of these strains **(4)**. This research work was intended to determine the antibiotic susceptibility patterns of Enterococci isolated from diverse clinical specimens with particular emphasis on aminoglycoside and vancomycin. The acquaintance of HLAR strains can help the clinicians to make prudent decisions for the use of antibiotics such as cell wall inhibitor plus aminoglycosides during the commencement of treatment evading the needless use of reserve antibiotics.

2. Materials and Methods

A six month study from November 2020 to April 2021 was planned and structured in the department of Microbiology & Immunology at a tertiary care institute. Fifty *Enterococcus* isolates from various clinical specimens including blood, body fluids (pleural, Peritoneal), CSF, pus, urine, semen, vaginal swab, and throat swab that were sent to the laboratory for culture and sensitivity were included in the study. Without delay the samples were processed post their collection and standard methods of identification were incorporated for the identification of *Enterococcus* isolates i.e. Gram staining, colony morphology, catalase test, bile solubility, growth in sodium chloride, bile esculin test, and sugar fermentation tests. M100 Clinical and Laboratory Standards Institute 2021 document was referred to analyze the antibiotic susceptibility patterns of enterococcal isolates and for the performance of screening and confirmatory tests used to distinguish particular resistance mechanisms like Penicillin resistance, HLAR and vancomycin resistance **(5)**.

Disc diffusion method was used for detecting the high level aminoglycoside resistance, if present, in the enterococcal isolates **(5)**. In disc diffusion method, high level gentamicin (120 μg) (Himedia, India) and streptomycin (300 μg) discs (Himedia, India) were placed on Mueller –Hinton agar (Himedia, India) medium. The incubation temperature and time of plates was 37ºC for 24 hours and after incubation measurement for the zone of inhibition diameter was done. Observation of no zone or a zone ≤ 6mm implied resistance, inconclusive (7–9 mm) and a zone of diameter ≥ 10mm implied susceptible pattern. A Resistant phenotype meant that the aminoglycoside shows non-synergism with cell wall–active agent (e.g., ampicillin, penicillin, and vancomycin) whereas susceptible indicates synergism with the cell wall inhibitors. Quality control of the test was performed by incorporating *Enterococcus faecalis* ATCC 29212 (susceptible) and *Enterococcus faecalis* ATCC 51299 (resistant). If disk diffusion result was inconclusive, verification of the result was done by agar dilution method. An inhibition zone of 7-9 mm was corroborated by the agar dilution method using brain heart infusion agar (BHI) containing gentamicin 500µg /ml as recommended by CLSI guidelines **(5)**. Spot inoculation of 10µl of the 0.5 McFarland suspension bacterial suspension was done on the agar and subject to aerobic incubation at 35±2ºC for a period of 24 hours. Streptomycin 1000 µg/ml was also tested likewise and the incubation was carried out for 24-48 hours. Re-incubation was done if susceptibility was obseved at 24 hours. The interpretation was taken as resistant with > 1 colony seen on screening agar **(5)**.

Vancomycin susceptibility/resistance patterns were reported using vancomycin disc (30µg) (Himedia, India); ≥17millimeter (mm) as sensitive, 15-16 mm intermediate and ≤ 14 mm as resistant. However agar dilution method using BHI agar was also done as per Clinical Laboratory standard institute (CLSI) guidelines. *Enterococcus faecalis* ATCC 29212 served as the negative control (susceptible) and *Enterococcus faecalis* ATCC 51299 as the positive control (resistant). Presence of >1 colony indicated presumptive vancomycin resistance. Interpretive criteria were defined as per CLSI: ≤ 4 sensitive, 8-16 intermediate and ≥ 32 as resistant **(5)**.

Microsoft excel was used for data study and analysis. The data extracted was subject to descriptive

statistical analyses and descriptive values, which were then recruited as numbers along with percentage frequencies. Independent variables were compared by means of t-test and chi-square test and a value of P <0.05 was considered as statistically significant.

3. Results & Discussion

Fifty strains of *Enterococcus spp*. were isolated over a period of six months from different clinical specimens. Pus samples yielded a maximum of 20 (40%) strains, followed by urine 15 (30%) and blood 9 (18%). The rest of the strains were isolated from peritoneal fluid and Bronchoalveolar lavage (BAL); 4(8%) and 2 (4%), respectively. The maximum number of isolates were those having high-level gentamicin (HLGR) (54%), whereas the isolates with high-level streptomycin resistance (HLSR) comprised 32% of the isolates. Of the isolates, 14% were positive for both HLGR and HLSR (Table 1). Of *Enterococcus faecium* isolates, 61.7% were HLGR, and 43.75% of *Enterococcus faecalis* isolates were HLSR (Table 2). maximum majority of the pus samples demonstrated HLGR (41.5%) with blood and urine samples showing 12% of this resistance pattern. HLSR was as well more frequent in pus samples (12%) with 10% similar resistance morphology shown by urine samples (Table 3), while 70% of isolates were sensitive (zone diameter >17 mm) to vancomycin and 8% isolates showed Intermediate (zone diameter 15-16 mm) and 22% isolates showed resistance to vancomycin. The agar dilution method revealed that 74% of isolates with a vancomycin MIC < 4 µg/mL and 12% isolates with MIC ≥ 32 µg/mL are therefore resistant. 25% vancomycin resistance (maximum) was detected in isolates from pus samples (Table 4).

Table 1. Distribution of high-level gentamicin and high-level streptomycin resistance among the Enterococcal isolates (n=50)

HLAR	No. of Isolates (%)
HLGR	27 (54%)
HLSR	16 (32%)
HLGR+HLSR	7 (14%)

HLAR- High level aminoglycoside resistance, HLGR-High level gentamicin resistance, HLSR-High level streptomycin resistance

Table 2. High-level aminoglycoside resistance among *E. faecalis* and *E. faecium* (n=50)

Enterococcal species	Total Isolates No (%)	HLGR No (%)	HLSR No (%)	Resistant to both HLGR And HLSR No (%)
E. faecalis	16(32%)	6(37.5%)	7(43.75%)	2(12.5)
E. faecium	34(68%)	21(61.7%)	9(26.4)	5(14.7)

HLGR-High level gentamicin resistance, HLSR-High level streptomycin resistance

Table 3. The pattern of High-level Aminoglycoside resistance in *Enterococcus* spp. from various clinical specimens (n=50)

Clinical Specimen	HLGR		HLSR	
	No.	%	No.	%
Pus	11	22%	6	12%
Urine	6	12%	5	10%
Blood	6	12%	2	4%
Peritoneal fluid	3	6%	1	2%
BAL	0	0%	0	0%
Total	26	52%	16	32%

HLGR-High level gentamicin resistance, HLSR-High level streptomycin resistance

Table 4. Vancomycin Susceptibility among isolates of *Enterococcus* by using disc diffusion and agar dilution methods.

Disc Diffusion Method (n=50)			Agar dilution method (n=50)						
Disc Content (30 µg)			MIC (µg/mL)						
>17**(S)*** mm	15-16**(I)**# mm	<14**(R)**** mm	0.5	1	2	4	8	16	32
35 (70%)	4 (8%)	11 (22%)	3 (6%)	12 (24%)	20 (40%)	2 (4%)	2 (4%)	5 (10%)	6 (12%)

*S- Sensitive, **-Resistant, #-Intermediate

When VRE was compared to VSE, the rate of HLSR was detected to be 4.64% in VRE, while it was 32.55% in VSE; the rate of HLGR was noted to be 11.62% in VRE, and it was 41.87% in VSE. The association of HLGR with HLSR, namely high-level aminoglycoside resistance (HLAR), was 2.32% in VRE, and 13.95% in VSE strains, respectively (Table 5).

Table 5. High-level aminoglycoside resistance rate between VRE and VSE (n=43).

Variable	VRE(6)	VSE(37)	P value
GEN R-STREP R	1(2.32%)	6(13.95%)	0.977
GEN S- STREP S	0(0%)	11(25.58%)	-
GEN R-STREP S	4(9.30%)	12(27.90%)	0.10
GEN S- STREP R	1(2.32%)	8(18.6%)	0.78

*7 Enterococcal Isolates with Intermediate Vancomycin Resistance (8-16 µg/mL)

VRE-vancomycin resistant Enterococci, VSE- Vancomycin sensitive Enterococci, GEN- gentamicin, STREP- Streptomycin, R-Resistant, S - Sensitive

Most *Enterococcus faecalis* isolates were resistant to benzylpenicillin and levofloxacin (75%), followed by erythromycin (62.5%). Most of the *Enterococcus faecium* isolates depicted resistance to ciprofloxacin, levofloxacin, and erythromycin (82.3%), followed by benzylpenicillin (73.5%). Maximum sensitivity was shown by linezolid for both species; 62.5% in *Enterococcus fecalis* and 82.3 % in *Enterococcus faecium*.

Our research work shows that the isolation rate of *Enterococcus* was maximum in the age group of 51-60 (28%) followed by patients in the age group of 41-50 (24%). Out of 50 isolates of *Enterococcus* spp., the highest figure was detected in pus samples (40%) followed by urine (30%), and the least were isolated from BAL (4%). Our study is in concurrence with studies by Hemlatha G and Sreeja S, wherein 51% and 43% of enterococcal isolates were reported to be isolated from pus samples, followed by 44% and 31% from urine, respectively **(6, 7)**. This can be attributed to the fact that a good number of infections caused by enterococcal species are urinary tract infections; however, they can also cause intra-abdominal infections, pelvic abscesses, and post-surgery wound infections **(7)**.

The existing work shows that the percentage positivity of the isolates with high-level gentamicin resistance (54%) was higher in contrast to those with high-level streptomycin resistance (32%). High-level resistance to gentamycin and streptomycin was found in 14% of the isolates. Our findings are in concurrence with those of Randhawa VS *et al.* who have also reported high-level gentamycin resistance and high-level streptomycin resistance in 68% and 43% of isolates, respectively, whereas 43% of the reported isolates depicted both HLGR and HLSR patterns (2). Mendiratta and Shah have also reported HLGR in 37.5% and 53% of isolates, respectively, whereas 28.4% and 40% were reported to have HLSR, respectively **(8, 9)**. However, a report from Nagpur by Agarwal *et al.* revealed a high level of gentamycin resistance in 7.8% of enterococcal isolates, whereas resistance to streptomycin was seen in 24.7%. This may be attributed to the majority of treatment modalities concentrated more on streptomycin utilization than gentamycin **(10)**.

In this study, out of 50 samples, the maximum number of HLGR isolates were *Enterococcus faecium* (61.7%), and the majority of HLSR isolates were *Enterococcus faecalis* (43.75%). This is in consensus with a report by Shrihari N *et al.* wherein 66.67% of

Enterococcus faecium isolates were resistant to gentamicin, and 41.17% *Enterococcus faecalis* isolates confirmed high-level resistance to streptomycin **(11)**. These resistance patterns and multi-drug resistance may be transferred to other Gram-positive bacteria at the genetic level resulting in aggregates of resistant organisms, which would evade all possible modalities of effective antimicrobial treatment. Hence, deliberation on this potential threat is the need of the hour, and clinically significant enterococcal isolates ought to be evaluated for their antibiograms, in conjunction with HLAR for the judicious use of beta-lactam or glycopeptide antibiotic in amalgamation with an aminoglycoside **(12)**.

Our work shows that HLGR was more frequent in pus samples (22%) with blood (12%) and urine samples (12%) following. HLSR was also recurrent in pus samples (12%) with urine samples (10%) following subsequently. This is in contrast to a study by Mittal S wherein HLGR was preponderant in urine samples (41.5%), and 36% was reported in blood samples; however, high-level streptomycin resistance (HLSR) was more widespread in pus samples (52.6%) followed by blood samples (36%) **(1)**. This could be explained by the fact that 40% of the enterococcal isolates were isolated from pus samples, with 30% from urine samples following this.

The disc diffusion method showed that 22% of isolates were resistant to vancomycin. However, using the agar dilution method, only 12% of isolates were resistant, i.e., MIC > 32 µg/mL. The discrepancy shown by the two methods can be explained by the fact that 10% of the isolates resistant to the disc diffusion method were established to have intermediate sensitivity to vancomycin by the agar dilution method. Mittal S and Yaqoob S have also reported 9% and 7% vancomycin resistance by the disc diffusion method in the enterococcal isolates **(1, 13)**. Verma D and Yangzom T have reported 12% and 13.7% of isolates to be resistant to vancomycin by agar dilution method, respectively **(14, 15)**. VRE is continually being reported globally; the occurrence and predominance are changeable concerning the geographical location. VRE is recognized to spread spread in the hospital milieu via unhygienic hands and infected surfaces **(4)**.

In our work, when VRE was compared to VSE, the rate of HLSR was detected to be 4.64% in VRE, HLGR was 11.62%, while HLAR was 2.32% in VRE strains. This is in disagreement with a study by Baldir G et al wherein HLAR was found to be significantly higher in VRE strains (78%) than in VSE strains (36%) **(3)**. In another study by Verma D, although VRE isolates depicted high-level aminoglycoside resistance 1.5 times more than VSE isolates, a statistical association of this difference could not be proven **(14)**. However, this research work may be ascribed to the reason that only one out of six VRE showed HLAR (2.32%), and the data is therefore not adequate to reach any conclusion. However, it may be emphasized that the clinical significance of HLAR in VRE isolates is to a large extent higher than in other strains because glycopeptide antibiotics and aminoglycosides cannot work synergistically in this setting. Such strains may propagate in a health care setting and consequently the role of screening of enterococcal isolates with high level gentamycin and streptomycin resistance holds significance.

The maximum sensitivity was shown by linezolid for both species; *E. fecalis* (62.5%) and *Enterococcus faecium* (82.3 %). Linezolid can be an appropriate therapeutic option in such cases **(12)**. Also, the permutation of vancomycin and linezolid can be an opposite alternative in infections with co-infection of VRE and HLAR strains **(16)**. Further research is required to provide evidence for the relevance of this combination.

14% of the total isolates were confirmed to have HLAR with a resistant prototype to both gentamycin and streptomycin. In contrast, the remaining 86% were established as HLGR or HLSR, which points to a high frequency of HLAR in our environmental setting. Albeit only 6 (12%) of the enterococcal strains were resistant to vancomycin, nonetheless preponderance of the isolates 22 (44%) with increased MIC values (2-4 µg/ml) for vancomycin was observed in the existing study. All these 6 VRE isolates demonstrated HLAR with no susceptibility pattern to any aminoglycoside, paving an insight into the potential augmentation of HLAR with an ascent in MIC values of vancomycin as has been seen in our study that isolates with steeper MIC values are increasing and in times to come may be predisposed to become resistant with a parallel increase of HLAR strains.

4. Conclusion

Multiple drug-resistant Enterococci pose a grave concern in hospital settings, leading to therapeutic failure in patients. As a significant number of clinical Enterococci were positive for both HLGR and HLSR, there is a need to treat infections with high-level aminoglycoside resistance in optimal dosage and duration. It is, therefore, imperative for laboratories to endow with precise antimicrobial resistance phenotypes for Enterococci so that efficient remedies and measures for infection control can be initiated. Also, drugs like vancomycin and daptomycin should be judicious, and linezolid-like antibiotics should be administered when enterococcal infections are proved by culture.

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Nil.

Ethics Statement

The study protocol was approved by the Ethical Committee Shri Guru Ram Rai Institute of Medical and Health Sciences.

Conflict of Interest

The authors declare no conflict of interest.

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