Original Article

The Study Of Invitro Susceptibility Of Vancomycin, Fosfomycin And Nitrofurantoin Among Urinary Isolates Of Enterococci

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Abstract

Background and objective: *Enterococcus* species are a common nosocomial pathogen thatare gaining resistance to multiple drugs. The present study aims to determine the prevalenceof Vancomycin resistant enterococci and susceptibility pattern of urinary isolates of Enterococci against different antimicrobials and special emphasis on urinary antimicrobial nitrofurantoin and Fosfomycin.

Materials and Methods: In the present study, a total of 80 isolates of Enterococci were isolated from urine sample. The antibiotic susceptibility testing was determined for antimicrobials byKirby-Bauer disc diffusion method. The results were interpreted according to CLSI guidelines, comparative evaluation of vancomycin susceptibility was done by disc diffusion and automated VITEK2 system.

Results: 42 isolates were identified as *E. faecalis* and 38 isolates were identified as *E. faecium* by VITEK 2. 95% of the Enterococcal strains were sensitive to Fosfomycin and 65% were sensitive to nitrofurantoin. Among 80 enterococcal isolates, 10 isolates were identified asVancomycin-resistant Enterococci (VRE) by both VITEK2 and disc diffusion. All VRE isolates were found to be sensitive to Fosfomycin and 50% of VRE isolates showed to be sensitive to nitrofurantoin.

Conclusion: Our study showed that Fosfomycin had a good invitro activity for both Enterococci and VRE when compared to Nitrofurantoin and other drugs. Vancomycin susceptibility detected by VITEK 2 and by disk diffusion showed good (100%) categorical agreement.

Keywords: Vancomycin resistant Enterococci, Fosfomycin, nitrofurantoin, disc-diffusion, VITEK 2.

INTRODUCTION

Enterococci are gram-positive cocci that form a part of normal enteric flora in humans and animals, they are ubiquitous in nature and are present in soil, water, plants, in some food products and as probiotics. Among the Enterococcal species *Enterococcus faecalis* and *Enterococcus faecium* are preponderantly isolated from most of the clinical samples. Less frequently isolated species are *E. gallinarum, E. casseliflavus, E. durans, E. avium* and *E. raffinosus*[1]. Enterococci affects almost all systems in the human body & are known to cause urinary tract infections more commonly like cystitis, urethritis, pyelonephritis, prostatitis and also commonest agent to cause bacteremia , mitral valve endocarditis in intravenous drug abusers, intra-abdominal, pelvic , soft tissue infections, late-onset neonatal sepsis , meningitis and infection on burn surfaces[2].

Enterococci express intrinsic resistance to cephalosporins, and clindamycin, aminoglycosides at lower levels[3]. There is an increasing trend of acquired resistance to High level aminoglycosides, vancomycin, chloramphenicol, erythromycin, tetracycline, and fluoroquinolones. Among these acquiring resistance to multiple antimicrobials glycopeptide resistance as posed a major risk specially to hospitalized patients resulting in the outbreaks which in turn results in rise in mortality and morbidity along with burdening of the patients with increased hospital cost. About 60-70% mortality is seen in patients suffering with vancomycin resistant enterococcal bacteraemia infections thus being directly accountable for half of the deaths in hospital[4]. Apart from existing as dominant nosocomial pathogen enterococci are the second commonest pathogen causing UTI both health care associated and community acquired infection posing a challenge to treating Physician[5].

Emerging drug resistance in enterococci narrows down the availability of treatment option for infections caused by these organisms ensuring the resume of interest of usage of older antimicrobials like Nitrofurantoin and Fosfomycin[6]. Nitrofurantoin is advocated as primary choice of treatment for uncomplicated cystitis and pyelonephritis in women by IDSA (Infectious disease society of America[7]. Likewise, Fosfomycin is a recommended antimicrobial for treating uncomplicated UTI[8]. Unfortunately, there has been paucity in data regarding the effectiveness of nitrofurantoin and

fosfomycin against enterococcal strains that are multi drug
Resistant[9]. However, vancomycin susceptibility data on vancomycin- resistant strains are also restricted and there is dearth of data regarding comparative studies of susceptibility of VRE strains to other antimicrobials used for treatment of UTI[10]. In view of this current scenario, it calls for a dier need of knowledge regarding the antimicrobial profile of enterococci causing UTI with special significance on antimicrobial activity of nitrofurantoin and fosfomycin against urinary isolates of enterococci which are vancomycin resistant. And to compare the laboratory methods used for detecting the vancomycin resistance by disk diffusion method and MIC of vancomycin by VITEK 2 and to know the agreement between the two method that is disk diffusion, MIC detection by VITEK-2.

MATERIALS AND METHODS

This is a laboratory-based prospective study carried out between March 2022 and May 2022 in Department of Microbiology, J.S.S. Medical College and Hospital, Mysore. Urine samples received routinely in the laboratory for culture and sensitivity of all age groups and gender were included in this study. Repeated urine samples from same patients were not included in this study. A total 80 enterococcal strains were isolated from the urine samples. Urine samples were inoculated onto the uri-chrome agar medium, and after inoculation plates were incubated aerobically in the incubator for 24 hours at 37º C. After 24 hours of incubation, plates were analysed, those which yielded tiny blue colonies with significant colony count of more than 10^5 in correlation with urine microscopy with inflammatory cells were considered, and were further processed by VITEK- 2. Antimicrobial sensitivity of isolates which were identified as *E. faecalis* and *E. faecium* by VITEK- 2 was noted.

Antimicrobial susceptibility testing

The inoculum was prepared by emulsifying the colonies in saline and was matched to 0.5 McFarland standard. Sterile cotton swabs were dipped, and lawn culture was made on Muller- Hinton Agar (MHA) medium. Antibiotic disc Vancomycin (30 µg), Fosfomycin (200 µg), Nitrofurantoin (300 µg) was placed and incubated at 37º C for 24 hours. After 24 hours, the zone diameters were noted. The interpretation was made according to CLSI-2022 guidelines and categorized as susceptible, intermediate, and resistant.

RESULTS

80 enterococcal strains were isolated from the urine samples received in the microbiology laboratory, which were non-duplicate samples. Out of these 42 (52.50%) were identified as *E. faecalis*, 38 (47.50%) as *E. faecium* by VITEK2. Among 80 urinary isolates of Enterococci 57% of Enterococci species was isolated from male patients and 43% from females. The study population was divided into four age categories ranging from 0-15 years of age, 16-27 years, 28-55years, 56 years and above. Out of which 21.21% of Enterococci were isolated from 0-15 years of age, 13.63% from 16-27 years, 40.92% from 28-55 years, 24.24% from 50 and above years of age group. Maximum number of Enterococci were isolated from the age group of 28-55 years and minimum number were isolated from 16-17 years of age group. The age-wise distribution of the Enterococcal isolates is given in **Table 1.** Among 42 *E. faecalis* isolates 4 were resistant to vancomycin and among 38 *E. faecium, 6* were resistant to Vancomycin, which was detected by both VITEK2 and Kirby- Bauer disk diffusion method is shown in **Table 2.** Among 80 urinary isolates of Enterococci maximum number of Enterococci species showed resistance to Tetracycline (92%), followed by Erythromycin (88.76%), Ciprofloxacin (87.5 %), levofloxacin (82.5%),High level gentamycin (55%) , Tigecycline(48.75%) and Penicillin (41.25%). All strains were sensitive to Linezolid. Antimicrobial Susceptibility profile of Enterococcus species detected by VITEK2 is depicted in **Table 3.** 36 (87.80%) isolates of *E. faecalis* showed to be sensitive to Nitrofurantoin, 1(2.45%) isolate showed intermediate and 3 (9.75%) isolates showed to be resistant to Nitrofurantoin. Similarly, 16 (41.02%) isolates of *E. faecium* showed to be sensitive to Nitrofurantoin, 5 (12.82%) isolates showed intermediate and 18 (46.15%) showed to be resistant to Nitrofurantoin. The susceptibility pattern for nitrofurantoin is shown in **Table 4.** 39 (95.12%) isolates of *E. faecalis* showed to be sensitive to Fosfomycin, 1 (2.43%) isolate showed intermediate and 1 (2.43%) isolate of *E. faecalis* showed to be resistant to Fosfomycin. Similarly, 37 (94.87%) isolates of *E. faecium* showed to be sensitive to Fosfomycin, 1 (2.56%) isolate showed intermediate and 1 (2.56%)isolate showed to be resistant to Fosfomycin. Susceptibility pattern to Fosfomycin is represented in **Table 5**. Antimicrobial activity of Nitrofurantoin and Fosfomycin against VRE strains is depicted in **Table 6**. Among the 80 Enterococcal species, 10 isolates (4 *E. faecalis* and 6 *E. faecium*) showed to be resistant to vancomycin which was detected by both VITEK 2 and disc diffusion methods. Hence, both the methods had a good categorically agreement. Comparison of detection methods for vancomycin resistance in Enterococci by Vitek2 and disk diffusion is represented in **Table 6.**

DISCUSSION

Enterococcus is gram-positive cocci in the water, soil, plants, but they are predominantly found in the lower gastrointestinal tract of humans and tend to colonize in them. *E. faecalis* and *E. faecium* are opportunistic human pathogens that have become particularly important etiological agents of nosocomial infections. A rapid increase in the incidence of hospital infections and their resistance towards the antibiotics, lead to increase in morbidity and mortality. In our study, out of 80 Enterococcal strains that were isolated from urine samples, 41 were *E. faecalis* and 39 were *E. faecium*. Among this, 10 urinary enterococcal isolates were vancomycin-resistant strains. These were in concordance with the study done by Mulla S et alentitled "prevalence of enterococci with higher resistance level in a tertiary care hospital". In this study among 99 enterococcal strains isolated, 69 strains were *E. faecalis* and 21 strains were *E. faecium.* 8%

enterococcal strains were vancomycin-resistant[12]. A similar study was done by Mary Beth et al entitled "in vitro susceptibility of vancomycin-resistant enterococci (VRE) to Fosfomycin". They reported that out of 75 enterococcal isolates, 23 strains were *E. faecalis* and 52 strains were *E. faecium*[13].

In our study, the greater number of *Enterococcus* species were isolated from the male population than female population. About 46 isolates (57.5%) of *Enterococcus* species were isolated from the male population, and 34 isolates (42.5%) of *Enterococcus* were isolated from the female population. This was in concordance with a study by Abamecha et al entitled "antimicrobial resistance profile of *Enterococcus* species isolated from intestinal tracts of hospitalized patients". Where male predominance was seen out of 150 population, 76 were male (50.7%) and 74 (49.3%) were females[14]. Similar findings were also noted in a study done by Johnstone, Jennie, et al. entitled "patient-and hospital-level predictors of vancomycin-resistant *Enterococcus* (VRE) bacteremia", where out of 217 population, 131 (60%) were male and 86 (40%) were females[15].

In our study, the total isolates which showed to be sensitive to Fosfomycin were 76 isolates (95%). Similarly, *a* study done by Gary E. Stein et al, reported 94% of sensitivity to Fosfomycin[16]. A similar study done by Sabharwal, et al entitled as "Fosfomycin: an alternative therapy for the treatment of UTI amidst escalating antimicrobial resistance". They reported that 20 isolates of *Enterococcus* species were isolated. All the isolates showed to be sensitive to Fosfomycin. Another similar study done by Bozkurt, O., et al. entitled the "comparative efficacy of single-dose Fosfomycin with ciprofloxacin in the treatment of urinary tract infection" fifty patients who were given Fosfomycin, had a clinical cure rate of 96% compared to the ciprofloxacin. A similar study was done by Sahni, Rani Diana, et al. entitled "Evaluation of Fosfomycin activity against uropathogens in a Fosfomycin-naive population in South India: aprospective study". They reported that out of 725 *Enterococcus* species isolates, 99% of the isolates showed to be sensitive to Fosfomycin.
In our study, the total isolates which showed to be sensitive to nitrofurantoin were 52 isolates (65%).
A study by Abamecha et al isolated 114 enterococcal isolates. Among 114 enterococcal isolates, 77 isolates (67.5%) showed to be sensitive to nitrofurantoin[14]. A study conducted by Butt T et al isolated 144 clinical isolates of *Enterococcus* species, where 127 of clinical isolates of *Enterococcus* were susceptible to nitrofurantoin.Another study by Akhter et al, isolated 52 enterococcal species. Out of 52enterococcal species, 44 isolates showed to be sensitive to nitrofurantoin[15]. A similar study done by Meena et al entitled "Revisiting nitrofurantoin for vancomycin resistant enterococci" where out of 70 *Enterococcus* species, 79% of the urinary isolates weresusceptible to nitrofurantoin[25]. Another study done by Wali et al in their study 24 *Enterococcus* species were isolated. 20 isolates(80%) of enterococcal species showed to be sensitive to nitrofurantoin[27]. A study Ali, Shamshad, et al, they isolated 100 *Enterococcus* species where 81isolates (81%) showed to be sensitive to nitrofurantoin[33]. The antimicrobial resistance shown by *Enterococcus* species is high and hence the treatment options of these organisms are limited and challenging especially for the vancomycin-resistant strains. In our study out of 80 *Enterococcus* species, 10 isolates (12.5%) were identified as vancomycin-resistant enterococcal species (VRE). A study by Goel, Varun et al entitled "Community-acquired enterococcal urinary tract infections and antibiotic resistance profile in North India" where they isolated 115 Enterococci isolates. Among them, 11.3% of the isolates showed to be vancomycin-resistance enterococci (VRE)[36]. A study done by Toner et al entitled "vancomycin-resistant enterococci in urine cultures", where they isolated 5528 *Enterococcus* species.

Among them, 542 isolates (9.8%)were vancomycin resistant enterococci (VRE)[43].
Antimicrobial resistance among *Enterococcus* species to a variety of drugs is increasing, limiting treatment options for these organisms' infections, particularly for vancomycin-resistant strains. In our study, total of 10 vancomycin resistant *Enterococcus* (VRE) was isolated. All of the VRE isolates were shown to be sensitive to Fosfomycin. Similarly, a study done by Asfia et al isolated 4 Vancomycin-resistance enterococci. All the VRE isolates showed to be sensitive to fosfomycin[16]. A similar study was done by Perri, Mary Beth, et al isolated 75 vancomycin-resistantenterococci. The results showed that 74 isolates (98.6%) of VRE were susceptible to Fosfomycin[30]. A similar study by Pogue, et al reported that 52 VRE were isolated. Among them 46isolates (90%) were found to be sensitive to Fosfomycin[44]. Fosfomycin resistance was not observed in any of the enterococcal isolates in our study. A study by Butcu et al reported that 2.3 percent of *Enterococcus* species showed to beresistant to Fosfomycin, but resistance to Fosfomycin among vancomycin-resistant enterococci strain was not observed. In this study, 50% of VRE isolates showed to be sensitive to nitrofurantoin. A similar study by Singh et al reported that among all the VRE isolates, 53.4% isolates showed to be sensitive to nitrofurantoin. In our study, 20% of VRE isolates showed to be resistant to nitrofurantoin. A study done by Meena et al entitled "Revisiting nitrofurantoin for vancomycin-resistant enterococci", isolated 26 VRE isolates. Among them, 6 (19.23%) isolates showed to be resistant to nitrofurantoin.

CONCLUSION

In the present study, the prevalence of VRE were 12.5% out of 80 urinary enterococcal isolates isolated from urine samples over a period of three months indicating the higher incidence of VRE. Regular surveillance and a strong infection management strategy must beimplemented. Vancomycin sensitivity testing was done by automated VITEK 2 and disk diffusion method, both methods when compared had a good categorical agreement that is 100% so detection of Vancomycinsusceptibility may be done by using disk diffusion method where VITEK2 availability is limited. Fosfomycin had agoodinvitro activity for both Enterococci and VRE when compared to Nitrofurantoin and other drugs, Fosfomycin is less expensive and available orally can be used as an alternative drug in treating the uncomplicated UTI .

Table - 1 Age Wise Distribution Of *Enterococcus* Species Isolated From Urine Sample

S.No	Age	Number	Percentage
1.	0-15	17	21.25%
2.	16-27	9	11.25%
3.	28-55	34	42.50%
4.	56 and above	20	25%

Table -2 VRE And Their Percentage Of Distribution

S.No	Isolates	VRE	Percentage
1.	***E. faecalis***	**4**	**5**
2.	***E. faecium***	**6**	**7.5**

Table 3: Antimicrobial Profile Of Enterococcal Urinary Isolates

ANTIBIOTICS	% SENSITIVE	% RESISTANT
Ampicillin	70	30
Benzyl penicillin	58.75	41.25
Ciprofloxacin	12.5	87.50
Erythromycin	11.25	88.75
High-level gentamycin	45	55
Levofloxacin	17.5	82.50
Linezolid	100	-
Teicoplanin	85	15
Tetracycline	8.75	91.25
Tigecycline	51.25	48.75

Table 4: Antimicrobial Activity Of Nitrofurantoin By Disc Diffusion Method

ISOLATES	SENSITIVE	INTERMEDIATE	RESISTANT
E. faecalis	36	1	4
E. faecium	16	5	18

Table 5: Antimicrobial Activity Of Fosfomycin By Disc Diffusion Method

ISOLATES	SENSITIVE	INTERMEDIATE	RESISTANT
E. faecalis	39	1	1
E. faecium	37	1	1

Table 6: Fosfomycin And Nitrofurantoin Activity Against Vancomycin-Resistant *E.Faecalis* And Vancomycin-Resistant *E. Faecium*

ANTIBIOTICS	VR *E. faecalis* (4)			VR *E. faecium* (6)		
	S	I	R	S	I	R
FOSFOMYCIN	4	-	-	6	-	-
NITROFURANTOIN	4	-	-	1	3	2

Table 7: The Comparison Of VRE Isolates With Disc Diffusion Results And VITEK 2

ISOLATES	VITEK 2	DISC-DIFFUSION
E. faecalis	4	4
E. faecium	6	6

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