Emergence of VRE and their antimicrobial sensitivity pattern in a tertiary care teaching hospital

Narinder Kaur[1]
Uma Chaudhary[1]
Ritu Aggarwal[1]
Kiran Bala[1]

Abstract
During the last few years enterococci have emerged as an important cause of nosocomial and community acquired infection. They have acquired resistance to commonly used antibiotics including glycopeptides posing challenge to therapeutic options. The aim of this study was to investigate the prevalence and sensitivity of VRE to newer drugs. A total of 250 strains of E. faecalis were isolated using conventional scheme of Facklam and Collins. High level aminoglycoside resistance (HLAR) was detected by disc diffusion method using 120 μg gentamicin disc and confirmed by agar dilution screen method. Screening for vancomycin resistance was done by disc diffusion and the agar screen method, and was further confirmed by broth dilution method for minimum inhibitory concentration (MIC). The strains which were resistant to vancomycin were further tested for sensitivity to newer and commonly available antibiotics. Maximum number of enterococcal isolates were recovered from urine (32.8%) followed by blood (25.6%) and pus (18.4%). Penicillin (83.6%) and cotrimoxazole (77.9%) were found to be least effective drugs against the E. faecalis whereas; cefuroxime (76.8%) and vancomycin (98%) were most effective drugs in vitro. About two percent isolates of enterococci were resistant to vancomycin. All the VRE isolates were sensitive to quinupristin/dalfopristin. Linezolid and chloramphenicols were the two other in vitro effective drugs with 80% sensitive isolates. MIC of all the VRE isolates was found to be in range of 64-512μg/mL. So, quinupristin/dalfopristin can be used for infections caused by VRE. Continuous surveillance is necessary to detect early outbreak, and spread of VRE.

Keywords: *VRE – HLAR – Quinpristin/Dalfopristin.*

INTRODUCTION

Recently Enterococcus spp. has emerged as an important nosocomial and community acquired pathogen. These organisms can cause endocarditis, bacteremia, meningitis and urinary tract infections[1]*. Enterococci are indigenous flora of intestinal tract, oral cavity and genitourinary tract of humans and animals*[2]*. Risk factors for developing enterococcal infections are prolonged hospitalization especially in intensive care units (ICUs), surgical procedures, following transplants, immmunocompromised status, breakdown of normal physical barriers and neurosurgical procedures*[3]*. Enterococcus faecalis (E.faecalis) is the most common isolate being associated with 80-90% of human enterococcal infections. E.faecium ranks second and is isolated from 10-15% of infections. Other enterococcal species including E.avium, E.casseliflavus, E.cecorum, E.durans,*

[1] Sharma University of Health Sciences – Rohtak.

Correspondência para / Correspondence to:
Narinder Kaur.
H.No.717, Sector-1
ROHTAK (Haryana) INDIA
PIN 124001
Phone: +91-9812523230.
E-mail:drritu252@yahoo.com

E.gallinarum, E.hirae, E.raffinosus, E.malodoratus, E.dispar and E.mundtii are infrequently isolated from human infections[4]. These organisms survive in the hospital environment, due to their intrinsic resistance to many antimicrobial agents including aminoglycosides, clindamycin, antistaphylococcal penicillins, cephalosporins and most fluoroquinolones. They have acquired resistance to high level aminoglycosides, high level penicillin, chloramphenicol, tetracycline and glycopeptides either by mutation or receipt of foreign genetic material through the transfer of plasmids or transposons[5,6].

Vancomycin resistant enterococci VRE isolates were first reported from England in 1988[7]. Since then similar strains are being detected worldwide including India[8-11]. But still there is paucity of information on VRE in our country. VRE infections are especially aggressive and have been associated with mortality rate approaching 60% to 70%. They are now second leading cause of nosocomial infections in the US and their prevalence is increasing[12]. Although no currently available antimicrobial agent can eradicate VRE colonization, several treatment options exist for VRE infections, these options are quinupristin/ dalfopristin, tigecycline, linezolid, daptomycin, nitrofurantoin and semisynthetic glycopeptides like mannopeptimycins and dalbavancin[13].

The aim of the present study was to investigate the prevalence of VRE at our centre and to know the sensitivity of VRE to other commonly available and newer antibiotics. This study can serve a futuristic approach in formulating the antibiotic policy as well as in infection control practices.

MATERIALS AND METHODS

The present retrospective study was carried out in Microbiology department, during March 2005 to March 2006. A total of 1976 clinical samples comprising of urine, pus, blood, CSF, other body fluids, stool, sputum and throat swab were received in microbiology laboratory during the study period. All the samples were immediately inoculated on the plate of blood agar and Mac-Conkey agar. From all clinical samples 250 strains of E. faecalis were isolated. The isolates were identified by colony morphology, Gram stain, catalase reaction, growth on bile esculin agar and tolerance to 6.5% NaCl[14]. Species identification was done using conventional scheme of Facklam and Collins[15]. The susceptibility testing to various antibiotics was done by Kirby-Bauer disc diffusion method [16]. The following panel of antimicrobials (Hi-Media Disc in μg) were tested:penicillin(10μg), tetracycline(10μg),erythromycin(5μg), cefazolin(30μg),cotrimoxazole(25μg), cefuroxime(30μg),amikacin(30μg), clindamycin(2μg), nitrofurantoin(50μg), gentamicin(120μg)and vancomycin(30μg). High level aminoglycoside resistance (HLAR) was detected by disc diffusion method using 120μg gentamicin disc and confirmed by agar dilution screen method, 10^6 Colony forming unit (CFU) of the test strain was inoculated on to brain heart infusion(BHI) agar plate containing 500μg/mL of gentamicin and incubated at 37^0 C for 24 h, the presence of more than one colony or a haze of growth denoted resistance[16]. Screening for vancomycin resistance was done by disc diffusion and the agar screen method. BHI agar supplemented with 6μg of vancomycin per mL was inoculated with 10^6 CFU of the test strain and interpreted after 24 h as for HLAR and was further confirmed by broth dilution method for minimum inhibitory concentration (MIC)[16]. The strains which were resistant to vancomycin were further tested for sensitivity to tiecoplanin(30μg), linezolid(30μg), quinupristin/ dalfopristin (15μg), cloramphenicol(30μg), rifampin(5μg), ampicillin+sulbactam(10/10μg) and doxycycline(30μg). E. faecalis ATCC 29212 was included as control.

RESULTS

Out of 1976 specimens received in the laboratory 250 strains of E.faecalis were recovered. Maximum number of isolates were recovered from urine (32.8%) followed by blood(25.6%), pus(18.4%), stool(16%), sputum(5.2%) and CSF and other body fluids (2%) (Table 1). Maximum number of isolates were from indoor patients (66.8%) (Table 2). Among the indoor patients 28.1% isolates were from medical ICU, followed by neonatal ICU(17.9%), medicine ward(17.3%), surgical

Table 1 - Distribution of E.faecalis in clinical samples in various age group.

Age group (years)	*Urine (n=82)**	*Blood (n=64)**	*Pus and pus swabs (n=46)**	*Sputum and throat swabs (n=13)**	*Stool (n=40)**	*CSF and other body fluid (n=5)**	*Total number of enterococci**
0-1	*0 (0)*	*30 (46.8)*	*2 (4.3)*	*0 (0)*	*2 (5)*	*1 (20)*	***35 (14)***
2-10	*0 (0)*	*9 (14.0)*	*5 (10.8)*	*1 (7.6)*	*2 (5)*	*1 (20)*	***18 (7.2)***
11-20	*7 (8.5)*	*9 (14.0)*	*13 (28.2)*	*1 (7.6)*	*4 (10)*	*0 (0)*	***34 (13.6)***
21-30	*37 (45.1)*	*8 (12.5)*	*9 (19.5)*	*3 (23.0)*	*7 (17.5)*	*2 (40)*	***66 (26.4)***
31-40	*14 (17.07)*	*2 (3.1)*	*6 (13.04)*	*3 (23.0)*	*8 (20)*	*1 (20)*	***34 (13.6)***
41-50	*9 (10.9)*	*2 (3.1)*	*7 (19.5)*	*2 (15.3)*	*7 (17.3)*	*0 (0)*	***27 (10.8)***
51-60	*5 (6.09)*	*3 (4.6)*	*3 (6.5)*	*2 (15.3)*	*6 (15)*	*0 (0)*	***19 (7.6)***
>60	*10 (12.1)*	*1 (1.5)*	*1 (2.1)*	*1 (7.6)*	*4 (10)*	*0 (0)*	***17 (6.8)***
Total	*82 (32.8)*	*64 (25.6)*	*46 (18.4)*	*13 (5.2)*	*40 (16)*	*5 (2)*	***250***

** N(%).*

Table 2 - Distribution of enterococci according to outdoor and indoor patients.

Samples (n=250)	*Outdoor N (%)*	*Indoor N (%)*
Urine (n=82)	*30 (36.5)*	*52 (63.4)*
Blood (n=64)	*23 (35.9)*	*41 (64.0)*
Pus and pus swabs (n=46)	*16 (34.7)*	*30 (65.2)*
Stool (n=40)	*8 (20)*	*32 (80)*
Sputum and throat swabs (n=13)	*6 (46.1)*	*7 (54.0)*
CSF and other body fluids (n=5)	*0 (0)*	*5 (100)*
Total	***83 (33.2)***	***167 (66.8)***

Table 3 - Prevalence of concomitant organisms along with enterococci in various clinical samples.

Organisms	*Urine (n=82)*	*Blood (n=64)*	*Pus & pus swabs (n=46)*	*Stool (n=40)*	*Sputum & throat swabs (n=13)*	*CSF & body fluid (n=5)*	*Total*
S. aureus	*5*	*4*	*2*	*3*	*1*	*0*	*15*
Escherichia coli	*13*	*1*	*3*	*17*	*0*	*0*	*24*
Klebsiella spp.	*5*	*1*	*1*	*1*	*1*	*0*	*9*
Enterobacter spp.	*2*	*1*	*2*	*0*	*1*	*0*	*6*
Citrobacter spp.	*2*	*1*	*2*	*0*	*0*	*0*	*5*
Acinetobacter spp.	*2*	*2*	*3*	*0*	*1*	*0*	*8*
Pseudomonas spp.	*2*	*1*	*12*	*0*	*0*	*1*	*16*
Total	***31 (37.8%)***	***11 (17.18%)***	***25 (54.3%)***	***11 (27.5%)***	***4 (30.7%)***	***1 (20%)***	***83 (33.2%)***

ward (14.3%), oncology (12.5%), obstetrics and gynecology (9.5%). The infection was polymicrobial in 33.2% of cases. Concomitant infection with Escherichia coli and Pseudomonas spp. was present in 24% and 16% cases respectively (Table 3).

Penicillin and cotrimoxazole were found to be least effective drugs against the E. faecalis whereas, cefuroxime and vancomycin were found to be the most effective drugs in-vitro (Table 4). About two percent isolates of enterococci were resistant to vancomycin.

Table 4 - Antimicrobial resistance of enterococci by disc diffusion test.

Age group (years)	*Urine (n=82)**	*Blood (n=64)**	*Pus and pus swabs (n=46)**	*Stool (n=40)**	*Sputum and throat swabs (n=13)**	*CSF and other body fluid (n=5)**	*Total number of enterococci**
Penicillin	*79 (96.3)*	*58 (90.6)*	*34 (73.9)*	*25 (62.5)*	*10 (76.9)*	*3 (60)*	***209 (83.6)***
Tetracycline	*not done*	*not done*	*18 (39.1)*	*32 (80)*	*5 (38.4)*	*not done*	***55 (55.5)***
Erythromycin	*62 (75.6)*	*32 (50)*	*31 (67.3)*	*29 (72.5)*	*8 (61.5)*	*5 (100)*	***167 (66.80)***
Cefazolin	*72 (8.78)*	*56 (78)*	*30 (65.2)*	*27 (67.5)*	*10 (76.9)*	*3 (60)*	***198 (79.2)***
Cotrimoxazole	*67 (81.7)*	*not done*	*38 (82.6)*	*25 (62.5)*	*11 (84.6)*	*not done*	***141 (77.9)***
Cefuroxime	*17 (20.7)*	*23 (35.9)*	*26 (56.5)*	*10 (25)*	*4 (30.7)*	*3 (60)*	***83 (33.2)***
Amikacin	*20 (24.3)*	*42 (65.6)*	*21 (45.6)*	*12 (30)*	*4 (30.7)*	*3 (60)*	***102 (40.8)***
Clindamycin	*23 (28)*	*47 (73.4)*	*21 (45.6)*	*8 (20)*	*5 (38.4)*	*3 (60)*	***107 (42.8)***
Nitrofurantoin	*69 (84.1)*	*not done*	*not done*	*not done*	*not done*	*not done*	***69 (84.1)***
Gentamicin (high synergy)	*not done (68.7)*	*44*	*not done*	*not done*	*not done (100)*	*5 (71.0)*	***49***
Vancomycin	*1 (0.4)*	*3 (1.2)*	*1 (0.4)*	*0 (0)*	*0 (0)*	*0 (0)*	***5 (2.0)***

** N(%).*

Table 5 - Sensitivity of vancomycin resistant enterococci to other antibiotics.

Antibiotics	*Isolate*				
	1	*2*	*3*	*4*	*5*
Doxycycline	*S*	*S*	*R*	*S*	*R*
Quinupristin/dalfopristin	*S*	*S*	*S*	*S*	*S*
Chloramphenicol	*S*	*S*	*R*	*S*	*S*
Rifampin	*S*	*S*	*R*	*R*	*R*
Linezolid	*R*	*S*	*S*	*S*	*S*
Ampicillin + Sulbactam	*S*	*R*	*S*	*R*	*S*

S = Sensitive, R= Resistant.

VRE isolates were 100% sensitive to qinupristin/ dalfopristin, and 80% of the isolates were sensitive to linezolid and chloramphenicol (Table 5). MIC of all the five VRE isolates was found to be in range of 64-512µg/mL. We did not attempt any genotypic method to determine the phenotype of VRE but sensitivity to teicoplanin and MIC of vancomycin were suggestive of Van A and Van B phenotypes (Table 6).

DISCUSSION

Our study investigated the prevalence of VRE, HLAR and sensitivity of VRE to various antibiotics. The majority of isolates were from urine samples (32.8%) followed by blood (25.6%). Our findings are in concordance with the study of Mathur et al[10]. In our study maximum number of isolates

Table 6 - Characteristics of Vancomycin resistant enterococci.

Isolate No.	*Specimen*	*Vancomycin (30µg)*	*Teicoplanin (30µg)*	*Vancomycin agar screen dilution*	*MIC by broth micro-*	*Probable phenotype*
1.	*Blood*	*Resistant*	*Resistant*	*Resistant*	*128µg/mL*	*Van A*
2.	*Blood*	*Resistant*	*Resistant*	*Resistant*	*512µg/mL*	*Van A*
3.	*Blood*	*Resistant*	*Resistant*	*Resistant*	*512µg/mL*	*Van A*
4.	*Urine*	*Resistant*	*Sensitive*	*Resistant*	*64µg/mL*	*Van B*
5.	*Pus*	*Resistant*	*Sensitive*	*Resistant*	*256µg/mL*	*Van B*

(66.8%) were recovered from indoor patients. Whereas studies showed 84% and 97.8% isolation from admitted patients[17,18]. The enterococcal infection was polymicrobial in 33.2% cases in our study in contrast to other study that reported polymicrobial infection in 55% of cases[17].

A combination of penicillin and gentamicin had been the mainstay of treatment of enterococcal infections till now, but high level of resistance to aminoglycosides could nullify the efficacy of this combination. Therefore to distinguish these high level aminoglycoside resistant strains from simply intrinsic strains is of vital importance. In our study HLAR was seen in 71 % of isolates. HLAR strains have also been identified by various researchers[10,11,18]. This high level of HLAR at our centre leaves vancomycin as the only treatment available against such strains, but we isolated five E. faecalis strains from indoor patients that were resistant to vancomycin. Other studies done in the similar setting in North India, South India and Kuwait has reported VRE in 1%, 2.6%, 10% isolates respectively[10,19,20]. According to MIC values of vancomycin and sensitivity to teicoplanin they appeared to be Van A and Van B phenotypes. Risk factors for VRE include prolonged hospital stay, severe underlying disease, ICU stay, proximity to another patient with VRE, and treatment with antimicrobial drugs such as vancomycin, third-generation cephalosporins and some anti anaerobic drugs [7]. In our study all the VRE isolates were recovered from patients admitted to ICU. Three isolates were from blood and one each from urine and pus.

The emergence of VRE at our centre is a cause for concern because of the limited therapeutic option for treating serious infections and because of their potential to transfer vancomycin resistance genes to other organisms such as methicillin-resistant Staphylococcus aureus. In our study all the VRE isolates were 100% sensitive to quinupristin/dalfopristin. Our results are similar to other study which suggested that quinupristin/ dalfopristin should be used for VRE[21]. Hence, we conclude that at our centre quinupristin-dsalfopristin can be considered a therapeutic alternative for infections caused by VRE.

In the present study although the prevalence of glycopeptides resistance was low among the isolates studied, their presence together with HLAR calls for regular surveillance of antimicrobial susceptibilities to detect emerging resistance and prevent the establishment and spread of multiple antibacterial resistance strains. Controlling the spread of vancomycin resistance has been the goal of Hospital Infection Control Practices Advisory Committee(HICPAC) who have worked in collaboration with Centers for Disease Control and Prevention (CDC) to formulate recommendations for preventing the spread of the resistant phenotypes. HICPAC listed four elements which must be addressed by hospital departments to achieve the prevention and control of vancomycin resistance. Firstly, to avoid colonization with VRE the prudent use of vancomycin by clinicians is crucial. Secondly, hospital staff must be educated in the problem and consequences of vancomycin resistance. Thirdly, resistant organisms must be identified and reported promptly. Finally, the appropriate infection control procedures must be implemented to prevent patient to patient spread of infection[22]. Absence of genotypic confirmation of VRE phenotypes limits the impact of our study. Still our data can be used for local therapeutic choices.

Aparecimento do enterococo resistente à vancomicina e sua sensibilidade antimicrobiana padrão em um hospital universitário

Resumo

Durante os últimos anos, os enterococos tem surgido como uma importante causa de infecção hospitalar e adquirida na comunidade. Esses agentes adquiriram resistência aos antibióticos comumente utilizados, incluindo glicopéptidos, gerando assim um desafio para os profissionais quanto às opções terapêuticas. O objetivo deste estudo foi investigar a prevalência e sensibilidade dos enterococos resistentes à vancomicina frente a novas drogas. Um total de 250 cepas de *E. faecalis* foram isoladas utilizando o sistema convencional de FACKLAM e Collins. Um alto nível de resistência a aminoglicosídicos foi detectado pelo método de difusão em disco, utilizando 120 μg de gentamicina e confirmado pelo método do teste de diluição em ágar. A detecção da resistência à vancomicina foi feita pelos métodos de difusão em disco e diluição em ágar, e foi posteriormente confirmada pelo método de diluição da concentração inibitória mínima. As cepas que eram resistentes à vancomicina foram novamente testadas para sensibilidade com os antibióticos mais novos e comumente disponíveis no mercado. O número máximo de enterococos isolados foram adquiridos da urina (32,8%), seguido pelo sangue (25,6%) e pus (18,4%). A penicilina (83,6%) e o cotrimoxazole (77,9%) foram os medicamentos menos eficazes contra o E. faecalis enquanto que a cefuroxima (76,8%) e a vancomicina (98%) foram as drogas mais eficazes *in vitro*. Cerca de dois por cento de enterococos resistentes à vancomicina foram isolados. Todos os eles foram sensíveis à quinupristina / dalfopristina. O cloramfenicol e a linezolida foram os dois outros medicamentos eficazes, *in vitro*, com 80% de sensibilidade. A concentração inibitória mínima de todos os enterococos resistentes à vancomicina isolados ficou entre 64-512μg/mL. Concluiu-se que a quinupristina / dalfopristina pode ser usada para as infecções causadas por enterococos resistentes à vancomicina. Contudo, a vigilância contínua é necessária para a detecção precoce de surto e disseminação de enterococos resistentes à vancomicina.

Palavras-chave: Enterococos Resistentes à Vancomicina – Alto Nível de Resistência a Aminoglicosídicos – Quinupristina/ Dalfopristina.

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