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Role and efficacy of vancomycin-ceftriaxone combination for the treatment of serious Gram-positive bacterial infections at tertiary care centre

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Abstract

Introduction: Infections caused by Gram positive bacteria is the most common worldwide infection and the pattern of antimicrobial susceptibility varies widely in different geographical regions depending on the antibiotic policies and uses (CLSI 2018) vancomycin in combination with ceftriaxone given to the patients who suffer from the Gram positive bacterial infection.

Material and Methods: This study was prospective and conducted at department of Microbiology, Baba Raghav Das Medical College, Gorakhpur in eastern Uttar Pradesh. A total 258 clinical specimens collected aseptically, which were further cultured on Sheep blood agar, MacConkey agar and nutrient broth. Antibiotic sensitivity was tested using Kirby-Bauer disk diffusion method on Muller-Hinton agar as per standard CLSI guidelines (2018).

Results: There were 258 clinical specimens cultured, in which male/female ratio was 1.15:1. Among 258 specimens, 121 (46.89%) were identified to be culture positive in which 70 (58%) found Gram negative bacilli followed by 41 (34%) Gram positive *cocci* and 10 (8%) were *Candida* spp. All GPC isolates were tested for sensitivity and efficacy in between vancomycin-ceftriaxone (CVA) combination, vancomycin co-resistance with other antibiotics. Out of 41 isolated GPCs, 25 (60.97%) were confirmed as *Staphylococcus aureus*, 6(14.63%) reported as *CoNS*, 08(19.51%) *streptococcus* spp. and 2(04.87%) belongs to *Enterococcus* spp. CVA was found 100% sensitive in compared with vancomycin (80.5%).

Conclusion: Vancomycin resistance among Gram-positive isolates is an emerging health problem therefore the combination of ceftriaxone-vancomycin is recommended for the treatment of various infections (bacteremia, septicaemia and meningitis etc.) when untreated causing severe life-threatening infections in human.

Keywords: CVA (ceftriaxone-vancomycin), GPC (Gram-positive cocci), VA (vancomycin), FDC (Fixed-dose-combination).

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1. Introduction

Gram positive bacterial pathogens are responsible for healthcare associated infections as well as community acquired infections. The infections cause by Gram positive bacteria are skin infections, upper and lower respiratory tract infections, blood stream infections and endocarditis, surgical site infections, bone and joint infections, central nervous system infections, urinary tract infections and intestinal infections etc.

Central venous catheters and other artificial devices the most common site for Gram positive infections, mostly caused by coagulase-negative Staphylococcus (CoNS) [1].

Vancomycin is the current treatment of choice for patients who have serious Gram-positive infections. Some Gram positive organisms are resistant to vancomycin and are called Vancomycin resistant *staphylococcus aureus* (VRSA) [2]. Antimicrobial resistance among Gram-positive organisms has been increasing slowly and gradually during the past several decades [3]. Vancomycin is combined with other antibiotics for the treatment of serious Gram positive bacterial infections [4]. Vancomycin in combination with

ceftriaxone can be given to the patients who suffer from the Gram positive bacterial infection. Vancomycin is a glycopeptide antibiotic and ceftriaxone is a 3rd generation of cephalosporins. Ceftriaxone has shown high efficacy in a wide range of serious Gram positive bacterial infections but in last two decades ceftriaxone resistance has been gradually increasing in Gram positive bacteria [5,8]. Ceftriaxone has demonstrated a broad spectrum of bactericidal antimicrobial activity against Gram positive and Gram-negative bacteria[5].

Fixed dose combination of ceftriaxone and vancomycin is used in (2:1) ratio as vancomycin binds to the terminal D-alanyl-D-alanine moieties of the N-acetyl muramic acid/N-acetyl glucosamine peptides, subsequently prevents the action of penicillin binding proteins and stops peptidoglycan growth but in case of resistant bacteria (*S. aureus*) the last D-alanyl moiety is replaced by D-lactate, which makes bacteria less permeable to vancomycin. To overcome this, ceftriaxone plus vancomycin formulation is used in 2:1 w/w ratio as ceftriaxone bind irreversibly with these proteins and thus inhibit the transpeptidation step of peptidoglycan synthesis to stop bacterial cell wall growth. Ceftriaxone-induced fragility in the peptidoglycan layer increases the penetrability of the vancomycin and restores (to some extent) its affinity towards the exposed D-alanine moieties [6].

2. Materials and methods

This study was performed at department of Microbiology, BRD Medical College Gorakhpur which is a tertiary care referral Centre in eastern U.P. Anon-duplicate, non-repeat successively and good quality 258 clinical sample were collected from different ward/ outpatient departments (OPD)/ inpatient department (IPD) of Nehru hospital associated with BRD Medical College Gorakhpur, U.P.

2.1 Specimen:

A total of 258specimens were included in this study. The different samples were; urine, pus, blood, cerebrospinal fluid (CSF), endotracheal tube (ET), pleural fluid, vaginal swab, throat swab and peritoneal fluid. Samples were collected aseptically and transported as soon as possible for bacteriological examination.

2.2 Inclusion criteria:

All type of clinical specimens received at the laboratory were checked for labeling such as patient name, client registration number, date, time and quality of specimen.

2.3 Exclusion criteria:

Unlabeled and inappropriate/ leaked samples were rejected.

2.4 Specimen processing:

All the samples were collected and processed by maintaining universal precautions. Samples were transported to the laboratory within two hours and processed immediately or refrigerated at 4°C to 8°C. Simultaneously all the samples were kept in peptone broth for 24-48 hours and tested for turbidity in broth. All the samples were processed on blood agar, chocolate agar and MacConkey agar plates for pus, vaginal swab, endotracheal tube (ET tube), pleural fluid, vaginal swab, throat swab, peritoneal fluid and urine samples were inoculated on cysteine lactose electrolyte deficient agar (CLED) and incubated in aerobic conditions at 37°C for 24-48 hours. Identification of isolated microorganisms were done on the basis of colony characteristics, Gram staining and battery of different biochemical tests as per the standard protocol at species level[7,8].

2.5 Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was done on Mueller-Hinton agar (Hi media, India) using standard disk diffusion (Kirby Bauer's) technique. This test and interpretation of result was done according to Clinical and Laboratory Standards Institute (CLSI) guidelines[8].

The antimicrobial agents tested were gentamicin (10mcg), cefotaxime (30mcg), vancomycin (30mcg), amoxycillin-clavulanic acid (20/10mcg), ciprofloxacin (5 mcg), imipenem (10mcg), nitrofurantoin (300mcg), vancomycin (30mcg), tetracycline (30mcg), doxycycline (30mcg), co-trimoxazole (25mcg), fosfomycin (200mcg), ofloxacin (5mcg), azithromycin (15mcg), oleandomycin (15mcg) (Himedia, India) and ceftriaxone-vancomycin (1.5 g / 3.0 mcg Venus Remedies Limited)[8].

2.5.1 Determination of multidrug resistance in bacterial isolates

The isolates were defined as multidrug resistant if they were resistant to two or more than two class of antibiotics tested or microorganisms which showed resistance to at least one antibiotic among three or more antimicrobial categories[8,9]

2.5.2 Detection of methicillin resistance in *Staphylococcus aureus*

Staphylococcus spp. was further screened for methicillin resistance by using 30 µg cefoxitin disc by modified Kirby Bauer disc diffusion method as per the CLSI guideline[12]. If the zone diameter less than 21mm, then it was considered methicillin resistant *S. aureus* (MRSA) and methicillin resistant CoNS (MR-CoNS) if zone is less than 24mm[9].

2.5.3 Quality control:

Reference strains of *S. aureus* (ATCC 25923) and *Enterococcus faecalis* (ATCC 29212) were used as control reference strains for identification and drug susceptibility testing) [8, 9].

2.5.4 Epsilometer test for MIC testing

Epsilometer test was done for Gram positive cocci for testing of vancomycin, teicoplanin and ceftriaxone. It is MIC determination paper strip test which is coated with two different antibiotics on a single strip in a different concentration gradient manner[8].

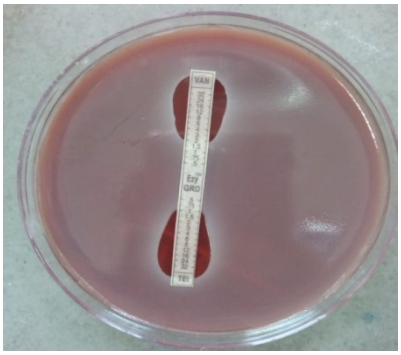

Figure 1: MIC test of vancomycin, teicoplanin by E-test

2.6 Ethical issue

Study was approved from institutional ethical committee as per institutional ethical guidelines after getting proper patient consent.

3. Result

In this study, patients suffering from various bacterial infections were included in our study. Out of 258 clinical samples, 121(46.89%) were culture positive in which 70 (57.85%) Gram-negative bacilli (GNB), 10 (8.26%) *candida* spp. and 41 (33.88%) Gram-positive cocci were isolated. Out of 121 positive samples, 41 (33.88%) Gram positive cocci (GPC) were isolated Among 41 Gram-positive cocci isolates 25(60.97%) were *Staphylococcus aureus*, 6 (14.63%) were *CoNS,* 08 (19.51%) *Streptococcus spp.* and *Enterococcus* spp. 2 (04.87%) isolated as shown in table 1 and figure 2.

Table 1: Distribution of micro-organisms in clinical samples

S.N	Type of samples	Number of samples	Positive culture (n)	GNB/GNCB/ GNC	Candida	GPC	Distribution of GPC
1	**Urine**	**94(36.43%)**	**47**	**31**	**4**	**11**	*S.aureus*=4
							Streptococcus spp.=2
							CoNS=3
							Enterococcus spp. =2
2	**Pus**	**81(31.39%)**	**39**	**28**	**3**	**10**	*S.aureus*=5
							Streptococcus spp.=3
							CoNS=2
							Enterococcus spp. =0
3	**Blood**	**32(12.40%)**	**12**	**4**	**2**	**6**	*S.aureus*=4
							Streptococcus spp.=1
							CoNS=1
							Enterococcus spp. =0
4	**C.S.F.**	**19(7.36%)**	**8**	**3**	**0**	**5**	*S.aureus*=5
							Streptococcus spp.= 0
							CoNS=0
							Enterococcus spp. =0
5	**Pleural fluid**	**12(4.65)**	**5**	**1**	**0**	**4**	*S.aureus*=3
							Streptococcus spp.=1
							CoNS=0
							Enterococcus spp. =0
6	**E.T**	**7(2.71%)**	**3**		**0**	**2**	*S.aureus*=2
							Streptococcus spp.=0
							CoNS=0
							Enterococcus spp. =0
7	**Vaginal swab**	**5(1.93%)**	**4**	**2**	**1**	**1**	*S.aureus*=1
							Streptococcus spp.=0
							CoNS=0
							Enterococcus spp. =0
8	**Throat swab**	**5(1.93%)**	**2**	**1**	**0**	**1**	*S.aureus*=0
							Streptococcus spp.=1
							CoNS=0
							Enterococcus spp. =0
9	**Peritoneal fluid**	**3(1.16%)**	**1**	**0**	**0**	**1**	*S.aureus*=1
							Streptococcus spp.=0
							CoNS=0
							Enterococcus spp. =0
	Total	**258**	**121(46.89%)**	**70(27.13%)**	**10(3.87%)**	**41(15.89%)**	*S.aureus*=25(60.97%
							Streptococcus spp. =8(19.51%)
							CoNS=6(14.63%)
							Enterococcus spp.=2(4.87%)

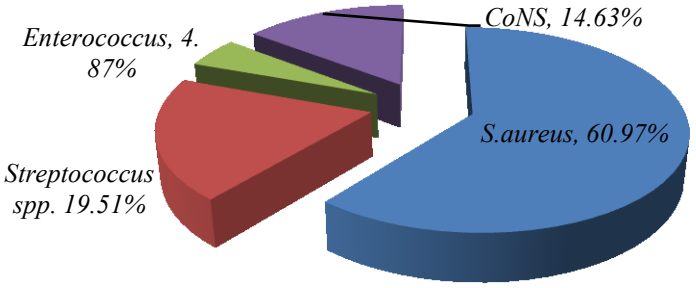

Figure 2: Distribution of Gram positive isolates among culture positive clinical samples

Distribution of Gram-positive cocci in various clinical samples including urine, pus, blood, CSF, body fluids and swabs seen in the table 2.

Table 2: Distribution of different Gram positive cocci in various clinical samples

S.N	Type of samples	Gram positive cocci			
		S.aureus (n=25)	*Streptococcus spp.* (n=8)	CoNS (n=6)	*Enterococcus spp.*(n=2)
1	Urine	4 (16%)	2(25%)	3(50%)	2(100%)
2	Pus	5(20%)	3(37.5%)	2(33.33%)	0
3	Blood	4(16%)	1(12.5%)	1(16.66%)	0
4	C.S.F.	5(20%)	0	0	0
5	Pleural fluid	3(12%)	1(12.5%)	0	0
6	ET aspirate	2(8%)	0	0	0
7	Vaginal swab	1(4%)	0	0	0
8	Throat swab	0	1(12.5%)	0	0
9	Peritoneal fluid	1(4%)	0	0	0

Vancomycin in combination with ceftriaxone (CVA) was found sensitive to all the Gram-positive isolates but vancomycin alone was found resistant invariably in different Gram-positive isolates as shown in table 3. High resistance to vancomycin was seen in *Enterococcus spp.* (100%). Antimicrobial sensitivity patterns for all the Gram-positive isolates were shown in table 4. Out of total isolates collected, 22 were male and 19 were female was found as shown in table 5.

Table 3: Antimicrobial sensitivity pattern for different Gram positive isolates

Name of Drugs	Antimicrobial sensitivity of other recommended antibiotics among different Gram positive cocci							
	***S. aureus* (25)**		***Streptococcus spp.* (8)**		***CoNS* (6)**		***Enterococcus spp.*(2)**	
	S	R	S	R	S	R	S	R
TE	**16**(64%)	**9**(36%)	0	**8**(100%)	0	**3**(100%)	**1**(50%)	**1**(50%)
C	**18**(72%)	**7**(28%)	0	**8**(100%)	0	**3**(100%)	0	**NA**
GEN	**15**(60%)	**10**(40%)	**2**(25%)	**6**(75%)	**4**(66.6%)	**2**(33.3%)	**1**(50%)	**1**(50%)
DO	**17**(68%)	**8**(32%)	0	**8**(100%)	**2**(33.3%)	**4**(66.6%0	**1**(50%)	**1**(50%)
COT	**4**(16%)	**21**(84%)	**3**(37.5%)	**5**(62.5%)	0	**6**(100%)	0	**2**(100%)
AZM	**3**(12%)	**22**(88%)	0	**8**(100%)	0	**6**(100%)	0	**NA**
OL	**5**(20%)	**20**(80%)	0	**8**(100%)	0	**6**(100%)	0	**NA**
CIP	**9**(36%)	**16**(64%)	0	**8**(100%)	0	**6**(100%)	0	**2**(100%)
NIT	**2**(8%)	**23**(92%)	**3**(37.5%)	**5**(62.5%)	**5**(66.6%)	**1**(33.3%)	**1**(50%)	**1**(50%)
CFM	**2**(8%)	**23**(92%)	0	**8**(100%)	0	**6**(100%)	0	**2**(100%)
OF	**10**(40%)	**15**(60%)	0	**8**(100%)	0	**6**(100%)	0	**2**(100%)
CTX	**1**(4%)	**24**(96%)	0	**8**(100%)	0	**6**(100%)	0	**2**(100%)
AMC	**2**(8%)	**23**(92%)	0	**8**(100%)	0	**6**(100%)	0	**2**(100%)
FO	0	**25**(100%)	**2**(25%)	**6**(75%)	0	**6**(100%)	0	**NA**
TEI	**10**(40%)	**15**(60%)	**4**(50%)	**4**(50%)	**1**(16.6%)	**5**(83.3%)	**1**(50%)	**1**(50%)
LZ	**18**(72%)	**7**(28%)	**5**(62%)	**3**(37.5%)	**4**(66.66%)	**2**(33.33%)	**2**(100%)	**0**
S = Sensitive, R = Resistant, NA= Not applicable								

OF=Ofloxacin; CIP= Ciprofloxacin;, GEN=Gentamicin; TE:- Tetracycline; LZ= Linezolid; TEI= Teicoplanin; AMC= Amoxycillin-clavulanic acid; FO= Fosfomycin; CTX= Cefotaxime; CFM= Cefepime; NIT= Nitrofurantoin; OL= Oleandomycin; AZM= Azithromycin; COT= Co-trimoxazole; DO= Doxycycline; C= Chloramphenicol.

In this study, among Gram-positive cocci, *S. aureus* was found as emerging multi drug resistant strain. The isolated bacteria showed wide differences in their susceptibility to the different recommended and tested antimicrobial agents. ***CoNS*** were found higher sensitivity to gentamicin **4**(66.6%), nitrofurantoin **5**(66.6%), and linezolid 4 (66.66%). In our study linezolid showed 100% sensitivity for *Enterococcus spp*. as shown in table 3.

All MRSA strains were invariably found high resistance to other multiple drugs and major cause of multi drug resistant bacterial infections among GPC.

Table-4: Sensitivity of CVA and VA in various organisms

Name of the Drug	Result of vancomycin alone and vancomycin–ceftriaxone combi disk among GPC							
	***S. aureus* (25)**		***Streptococcus spp.* (8)**		***Enterococcus spp.(2)***		***CoNS* (6)**	
	S	R	S	R	S	R	S	R
CVA	25(100%)	0	8(100%)	0	2(100%)	0	6(100%)	0
VA	22(88%)	3(12%)	6(75%)	2(25%)	0	2(100%)	5(83.3%)	1(16.6%)
S = Sensitive, R = Resistant								

In this study, CVA was found 100% sensitive as compared with vancomycin alone (80.5% sensitive). Vancomycin showed highest sensitivity in *S. aureus* 22 (88%) as compared with other GPC and the difference was statistically significant ($p<0.05$) as shown in table 4and figure 3

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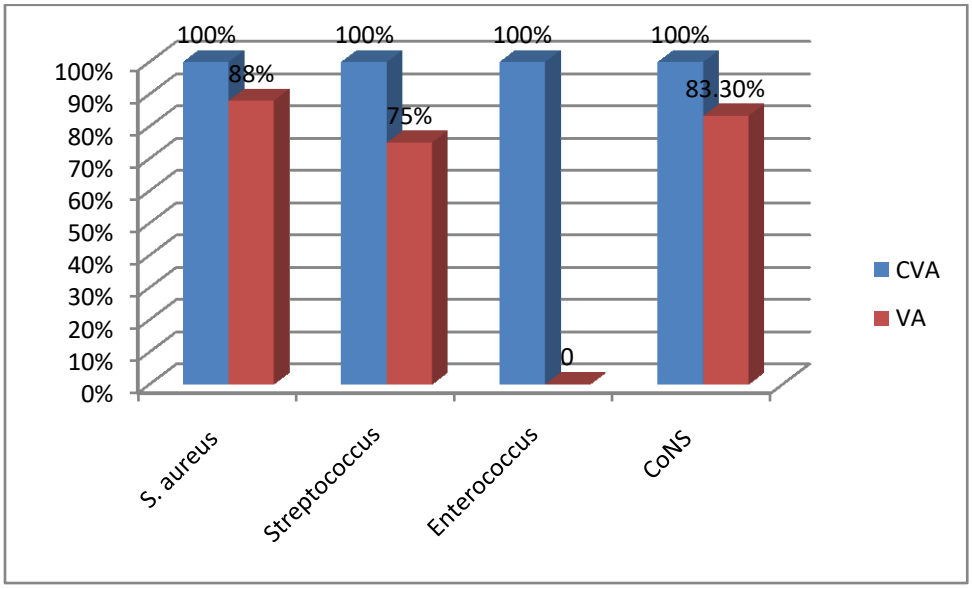

Figure 3: Sensitivity pattern of vancomycin and CVA in different GPC

Table 5: Resistance of CVA and VA in male and female patients in different age groups

Age	Gender		CVA (n=41)	VA (41)
	Male(n=22)	Female(n=19)		
0-20	12(54.54%)	8(42.10%)	0	2 (4.87%)
21-40	7(31.81%)	7(36.84%)	0	2 (4.87%)
41-60	3(13.63%)	3(15.78%)	0	3 (7.31%)
61-80	0	1(5.26%)	0	0

Among total 41 GPC isolates tested for antibiotic sensitivity, 22(53.65%) were male and 19(46.41%) were female. The incidence of Gram positive bacterial infection was high among the male than female.

The most common Gram positive microorganism isolated in 0-20 age-groups was 12 (54.54%) in male and 8 (42.10%) in female. Vancomycin was highly resistant in 41-60 age group but no resistance was found in CVA as shown in table 5.

4. Discussion

Antibiotic resistance issues are common among Gram-positive cocci pathogen, especially among staphylococci (mostly *Staphylococcus aureus* but also in *coagulase-negative staphylococci*) *streptococci*, and *enterococci*[10]. Vancomycin is a widely used glycopeptide antibiotic that is effective against most Gram-positive bacteria including *Staphylococcus spp.* and *Streptococcus spp.* It is commonly used for the treatment of methicillin-

resistant *coagulase-negative Staphylococcus*, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcal* infections[11].

Our findings demonstrated that out of 121 positive samples, 41 (33.88%) Gram positive cocci (GPC) were isolated, among which 25(60.97%) were *Staphylococcus aureus*, 6 (14.63%) were *CoNS,* 08 (19.51%) *Streptococcus spp.* and2 (04.87%) *Enterococcus spp*. Similar finding by Asghar *et al*., as they have reported 63.3% *S. aureus* isolates in all clinical isolates in Saudi Arabi [12] and also Iman *et al*. reported most common isolated among Gram-positive bacteria from all samples was *S. aureus* (38.30%) in Iran [13]. The same study group identified *S. aureus* as the most prevalent pathogenic bacteria isolated from 41 (19%) patients in India [14].

Staphylococcus aureus was the most common bacterial isolate among all clinical samples because causes a wide range/severity of infections in both community and in intensive care units. Humans are colonized by microorganism mainly in the nasopharynx and skin. *S. aureus* has the unique propensity to infect and destroy normal healthy tissue, causing skin and wound infections to severe life-threatening infection therefore infection cause by other Gram-positive bacteria including coagulase-negative *staphylococci, enterococci* and *streptococci* are less common but most important species of clinical interest [10,15-18].

The most common site of infection caused by Gram positive bacteria (n=41) was urine (26.82%) followed by wound/pus (24.39%) and blood (14.63%) and this is quite similar findings to Iman *et al*. and Asghar *et al.* in their study [12,13]. Out of 41 GPC isolates, 22 were male and 19 were female and male -female ratio was 1.15:1 and mean age of the patients was 12 years (range 0 to 20 years) which was quite different to Dilworth *et al*. and Khera *et al*. reported 35 years (20-70 years) in their study[10,17]. This may be because as we are having maximum case burden from pediatric patients as this particular geographical area is prone and epidemic for acute encephalitis syndrome.

Gram-positive bacterial infection continues to extract a huge toll worldwide because of its increasing infection rate as well as variable degree of antimicrobial resistance. Increasing resistance to β-lactams and macrolide antimicrobials among isolates of Streptococcus and Enterococcus [10,11]. Antibiotic resistance among the Gram-positive bacteria including *Staphylococcus aureus, Streptococcus spp*. and *Enterococcus spp*. were exponentially increasing and leads to global resistance challenges.

It was observed that antibiotic resistance among the Gram-positive bacteria especially *Staphylococcus* spp. (*S. aureus* and *CoNS*) were higher to fosfomycin(100%), amoxicillin-clavulanic acid (70.73%), co-trimoxazole (65.85%) and cephalosporins (73.17%). A lower degree of resistance was observed to teicoplanin (4.87%) and linezolid (7.31%) which was accordance to the Asghar el al. in their studies [12].

S. aureus was the most common Gram-positive cocci among clinical isolates and most of *S. Aureus* strain were *MRSA* reported 91% which was significantly higher ($p<0.05$) as compared to previous studies conducted in India [12,18,19] as because mostly cases were enrolled from intensive care units. *MRSA* strains were also shown high resistance in cephalosporin, macrolides and glycopeptide antibiotics among staphylococci. The prevalence of methicillin resistant *S. aureus* continues to increase in many areas of the world, there is evidence that the major drug for treating *MRSA* infections especially vancomycin, is losing effectiveness against microorganisms due to a number of genetic changes that ultimately lead to hetero-resistance or frank resistance to vancomycin[19,20].

In *Streptococcus spp.* also showed high resistant to ciprofloxacin, ceftriaxone and azithromycin reported 100% resistance simultaneously *Enterococcus spp*. strains were also reported 100% resistant to tetracycline, ciprofloxacin, ceftriaxone and vancomycin and low resistant was reported in teicoplanin and linezolid as compared to other studies reported much lower resistance pattern[18,19]. Our findings revealed the extensively high antibiotics resistance among Gram-positive bacteria being increasing and the reason may be rampant/uncontrolled use of higher antibiotics. Vancomycin-resistant *enterococci (VRE)* are also resistant to virtually all standard antimicrobials, although resistance to linezolid has also been reported in several studies[19,21].

In our study, GPC was 100% sensitive to vanco-plus (ceftriaxone-vancomycin) combination using standard disk diffusion test and we also found that occurrence of development of resistance under the influence of ceftriaxone-vancomycin was lesser than ceftriaxone and vancomycin alone [21]. In this study, patients suffering from serious respiratory tract disease, bronchitis, gastrointestinal tract infections, urinary tract infection, cellulites and meningitis were cured, suggesting that the combination of ceftriaxone-vancomycin fixed dose combination (FDC) exhibits wide antibacterial spectrum.

5. Conclusion

In conclusion, *S aureus* was the most common clinical isolates among Gram positive bacteria and most of *S. aureus* strain was *MRSA* which triggered the rise of multi drug resistant in Gram-positive cocci. The expansion of resistance to antimicrobial agents is currently the main concern of the medical community worldwide. Infections caused by drug resistant Gram-positive bacterial isolates

seem to be associated with increased morbidity and mortality in hospitals. Infection prevention and control measures should be established to reduce such healthcare–associated infections.

Vancomycin resistance among Gram-positive isolates is an emerging serious health problem therefore the combination of ceftriaxone-vancomycin is recommended for the treatment of various infections caused by drugs resistant Gram-positive cocci..

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