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Original Research Article

The study of reduced susceptibility of methicillin resistant *Staphylococcus aureus* to various antibiotics with special reference to glycopeptides in a tertiary care hospital in central India

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ABSTRACT

Background: *Staphylococcus aureus* has emerged over the past several decades as a leading cause of hospital-associated and community acquired infections. Methicillin resistant *S. aureus* (MRSA), which are often resistant to several classes of antibiotics, is the most common cause of nosocomial infections and pose a great threat to the world. Vancomycin is regarded as the first-line drug for treatment of MRSA but resistance to this drug is being reported now a day.
Methods: It was carried out for a period between January 2014 to June 2017 in the microbiology diagnostic laboratory. MRSA detection was performed by cefoxitin disk diffusion method. Screening for the vancomycin intermediate and the vancomycin resistant *S. aureus* (VISA and VRSA respectively) was carried out by using vancomycin screen. MIC (minimum inhibitory concentration) of vancomycin was tested by agar dilution method and E strip on all MRSA isolates.
Results: A total of 287 *S. aureus* clinical isolates were included in the study. All MRSA were inoculated on vancomycin screen agar. Visible growth was present in 8 isolates. Five (3.73%) MRSA isolates with MIC of 4 were termed VISA (vancomycin intermediate *S. aureus*) by agar dilution method. Six isolates had the MIC of 4 and were termed as VISA.
Conclusions: As disc diffusion method is not recommended by CLSI for *S. aureus*, vancomycin screen agar and MIC determination by either of the methods viz. agar dilution or E test can be used.

Keywords: *Staphylococcus aureus*, Methicillin resistant *S. aureus*, Vancomycin intermediate *S. aureus*, Minimum inhibitory concentration

INTRODUCTION

Staphylococcus aureus continues to be a dangerous pathogen for both community-acquired as well as hospital-associated infections.[1] Methicillin resistant *S. aureus* (MRSA) is now endemic in India. The prolonged hospital stay, indiscriminate use of antibiotics, lack of awareness, receipt of antibiotics before coming to the hospital etc. are the possible predisposing factors of MRSA emergence.[2] Vancomycin, a glycopeptide is the drug of choice for the therapy of infections due to MRSA, but increase in vancomycin use has led to the emergence of two types of glycopeptides resistant *S. aureus*.

The first one, vancomycin Intermediate *S. aureus* (VISA) is due to thickened and poorly cross linked cell wall. The second type, vancomycin resistant *S. aureus* (VRSA) is

due to acquisition from enterococcus species of the vanA operon resulting in high level resistance. Since 2002, there are increasing numbers of reports of emergence of VISA and VRSA.[3] In India well documented reports of VISA and VRSA are few.

Aim

To study the antimicrobial susceptibility of *S. aureus* isolates obtained from various clinical specimens against various antibiotics with special reference to glycopeptides with agar dilution method and E strip.

METHODS

The present study is a hospital based cross sectional study. It was carried out for a period between January 2014 to June 2017 in the microbiology diagnostic laboratory of a tertiary care hospital (Government Medical College, Nagpur). The study was approved by the institutional ethical committee.

Sample size was calculated by the statistician using standard guidelines, as per the public service of creative research systems survey software.

Staphylococcus aureus isolates obtained from various clinical specimens like blood, pus, wound swabs, pleural/ascetic/synovial fluid, aspirates, sputum, ear swabs, urine received in microbiology diagnostic laboratory for the microbiological investigations were selected for the study.

The quality control and rejection criteria for the inappropriate specimen were followed as per the standard guidelines.[4]

Specimens were processed within 2 hours of collection by the standard microbiological technique.[4]

Specimens showing pus cells with gram positive cocci in clusters in primary smear were given special attention.

Sheep blood agar and MacConkey's medium were used for inoculation of all specimens. The plates were then incubated at 35 ± 2^0 Celsius for 18-24 hours in aerobic atmosphere.[4]

Gram positive cocci uniform in size, appearing characteristically in groups mostly, but also seen singly and in pairs were further identified by the scheme described for the identification of the gram positive cocci arranged in clusters using following tests like catalase test, modified oxidase test, furazolidone susceptibility test, coagulase test (slide and tube coagulase), mannitol sugar fermentation test .[4]

Antimicrobial susceptibility testing was performed as per the CLSI guidelines (2017) by modified Kirby Bauer method.[5,6]

Antibiotic discs

Commercially available antibiotic discs (Hi-media laboratories Pvt. Ltd. Mumbai) with proper diameter and potency were used. All the strains were tested for their sensitivity to antimicrobial drugs using recommended CLSI guidelines (2017) combined with institutional antibiotic policy and hospital formulary practices for the purpose of reporting to the clinician.[5]

MRSA detection

In this study, MRSA detection was performed by cefoxitin disk diffusion method.

Cefoxitin disk diffusion testing

All the *S. aureus* isolates were subjected to cefoxitin disk diffusion test using a 30 µg disk. A 0.5 McFarland standard suspension of the isolate was prepared and lawn culture done on Mueller–Hinton agar plates with 4% NaCl.

Plates were incubated at 37^0 C for 18 hour and zone diameters were measured.[7,8]

Table 1: Cefoxitin disk diffusion test.

Interpretive criteria (mm) for cefoxitin disk diffusion test		
	Susceptible	Resistant
S. aureus	≥22	≤21

Testing vancomycin susceptibility

Screening for the vancomycin intermediate and the vancomycin resistant *S. aureus* (VISA and VRSA respectively) was carried out by using vancomycin screen agar (MHA with 6µg/ml vancomycin, Hi Media, USA). All the plates were incubated at 35^0 C for 24-48 hours.[5,9]

Vancomycin screen agar plate method

In-house vancomycin screen agar plate was prepared by addition of 6 mg/l vancomycin to brain heart infusion (BHI) agar. Inoculum suspension was prepared by transferring colonies from overnight growth on nutrient agar plate to sterile saline to produce a suspension that matches the turbidity of a 0.5 McFarland standard. A 10 µl inoculum of a 0.5 McFarland suspension was spotted on the agar using a micropipette (final concentration=10^6 CFU/ml) and was incubated for 24 h at 35 °C in ambient air. Any visible growth indicated the vancomycin resistance. In addition, *S. aureus* ATCC 29213 was used as control strain.[5,10]

MIC of vancomycin was performed by agar dilution method and E strip method.

Agar dilution method to determine MIC of vancomycin

Based on the results of disc diffusion test, *S. aureus* isolates showing resistance to cefoxitin disc were selected for MIC testing. All the isolates were tested for determination of MIC for vancomycin by agar dilution method.[11,12]

Pure drug was procured from Hi media with code no CMS217.

Reading of results

The MIC of organism under testing was determined by the lowest concentration of antibiotic at which there is no visible growth.

- MIC of ≤2– susceptible (VSSA)
- MIC of 4 µg/ml–8 µg/ml- intermediate (VISA)
- ≥16 µg/ml– resistance VRSA

E–test method to determine MIC of vancomycin[7]

All isolates of MRSA were tested for minimum inhibitory concentration to vancomycin by E- test strips (Hi-media laboratories Pvt. Ltd. Mumbai).

0.5 McFarland standard suspension of the isolate was prepared and lawn culture done on Mueller–Hinton agar plates. After ensuring that the agar surface was completely dry, using the applicator, E-test strip was held and its bottom edge was placed against the inoculated agar surface. Plates were incubated at 37° C for 24 hours.

RESULTS

A total of 287 *S. aureus* clinical isolates were included in the study.

Table 2: Detection of MRSA by cefoxitin (30ug) disk using Kirby Bauer method (n=287).

Cefoxitin (30ug) disk diffusion	Resistant (%)
MRSA	134 (46.68)
MSSA	153 (53.31)
Total (n)	287 (100)

In this study MRSA was found to be 46.78% and methicillin sensitive *S. aureus* (MSSA) was found to be 53.31%.

The below table shows antibiotic sensitivity pattern of MRSA to various antibiotics. All the isolates were sensitive to linezolid. Amikacin and cotrimoxazole showed a sensitivity of 26.11%. Tetracycline had sensitivity of 15.67%. There was total 100% resistance to penicillin G and nitrofurantoin.

Table 3: Antibiotic sensitivity pattern of various antibiotics to all MRSA isolates (n=134).

S. no	Antibiotic	Sensitive no (%)	Resistant no (%)
1	**Penicillin G**	0 (0)	134 (100)
2	**Cotrimoxazole**	35 (26.11)	99 (73.88)
3	**Chloramphenicol**	15 (11.19)	119 (88.80)
4	**Ciprofloxacin**	10 (7.46)	124 (92.53)
5	**Ofloxacin**	6 (4.47)	128 (95.52)
6	**Gentamicin**	11 (8.20)	123 (91.79)
7	**Amikacin**	35 (26.11)	99 (73.88)
8	**Tetracycline**	21 (15.67)	113 (84.32)
9	**Erythromycin**	15 (11.19)	119 (88.88)
10	***Nitrofurantoin (tested against only 9 MRSA in urine)**	0 (0)	9 (100)
11	**Linezolid**	134 (100)	0 (0)

*For urine samples only.

Table 4: Vancomycin screen agar for screening MRSA for reduced susceptibility to vancomycin.

MRSA isolates inoculated	Number of isolates showing visible growth
n=134	8

All MRSA were inoculated on vancomycin screen agar. We found 8 isolates that had shown visible growth.

Table 5: Vancomycin MIC among MRSA isolates by agar dilution method (n=134).

S. no	Vancomycin MIC	MRSA (%)
1	0.5	10 (7.46)
2	1	40 (29.85)
3	2	79 (58.95)
4	4	5 (3.73)
5	8	Nil
6	≥16	Nil

The above table shows the vancomycin MIC among MRSA isolates by agar dilution method.

Five (3.73%) MRSA isolates with MIC of 4 were termed VISA. None of the isolates had MIC of ≥8.

Table 6: Vancomycin MIC among MRSA isolates by E test (n=134).

S. no	Vancomycin MIC	MRSA (%)
1	≤1	42 (31.34)
2	1.5	4 (2.98)
3	2	77 (57.46)
4	3	5 (3.73)
5	4	6 (4.47)
6	≥6	NIL

The above table shows Vancomycin MIC among MRSA isolates by E test.

Six isolates have the MIC of 4 and were termed as VISA. None of the isolates had the MIC of ≥6.

Table 7: Comparison of MIC of vancomycin by agar dilution method and E strip.

S. no	MIC of vancomycin	Agar dilution	E strip
1	≤1	50	42
2	≤2	79	81
3	≤4	5	11
4	>4	Nil	Nil

In this table, we found 50 isolates who had MIC of ≤1 by agar dilution method (10 isolates with MIC of 0.5 and 40 isolates with MIC of 1) and 42 isolates by E test.

There were 79 isolates with MIC 2 by agar dilution method and 81 isolates which had MIC ≤2 (77 isolates had MIC of 2 and 4 had MIC of 1.5) by E test.

Five isolates had MIC of 4 by agar dilution method and 11 isolates had MIC of ≤4 (6 isolates had MIC of 4 and 5 isolates had MIC of 3) by E test.

In the present study, a total of 6 VISA were isolated by E test (MIC 4). Their antibiotic susceptibility pattern is shown below.

Table 8: Antibiotic susceptibility pattern of 6 VISA strains.

S. no	Antibiotics	VISA 1	VISA 2	VISA 3	VISA 4	VISA 5	VISA 6
1	Penicillin G	R	R	R	R	R	R
2	Cotrimoxazole	S	R	R	R	R	R
3	Gentamicin	R	R	R	R	R	R
4	Ciprofloxacin	R	R	R	R	R	R
5	Ofloxacin	R	R	R	R	R	R
6	Tetracycline	R	R	R	R	R	R
7	Chloramphenicol	R	R	R	R	R	R
8	Erythromycin	R	R	R	R	R	R
9	Clindamycin	R	R	R	R	R	R
10	Pristinamycin	R	R	R	R	S	S
11	Linezolid	S	S	S	S	S	S

Table 9: Characterisation of 6 VISA samples.

No.	Age (in years)	Ward	Clinical specimen	Diagnosis
VISA1	39	Neurology ward	Blood	Septicaemia
VISA 2	54	ICU	Pus	Cerebral abscess
VISA 3	2	Paediatric ward	Blood	PUO (pyrexia of unknown origin)
VISA 4	29	Surgery ward	Pus	Breast abscess
VISA 5	62	Orthopaedic ward	Pus	Osteomyelitis
VISA 6	50	Surgery	Pus	Intra-abdominal abscess

All the isolates were susceptible to linezolid. VISA 1 was susceptible to linezolid and cotrimoxazole. VISA 2, VISA 3 and VISA 4 isolates were susceptible to only linezolid. VISA 5 and VISA 6 were susceptible to linezolid and pristinamycin both.

Among the 6 isolates, four were resistant to pristinamycin.

Table 9 shows the characterisation of 6 VISA isolates. Only one isolate was in paediatric age group (2 years). Rest of the isolates were from adult patients. Two isolates were from surgery ward. One isolate was from ICU and one each from neurology ward, paediatric and orthopaedic wards respectively. Out of the 6 VISA isolates, 4 were isolated from pus samples. One from breast abscess, one from cerebral abscess, one from osteomyelitis and one from intra-abdominal abscess. Two isolates were recovered from blood samples.

DISCUSSION

S. aureus is one of the most common causes of nosocomial infections, especially pneumonia, surgical site infections and blood stream infections. It continues to be a major cause of community acquired infections.[13]

MRSA

MRSA strains are important for their resistance to many other commonly used antibiotics and the emergence of resistance to vancomycin.[14] Therefore, it is very important to detect and study the antibiotic susceptibility pattern of MRSA to minimize the irrational use of

vancomycin when other antibiotics would cure an infection.

In the present study we detected 46.78% MRSA by cefoxitin disc by Kirby Bauer disc diffusion method (Table 2).

The resistance of MRSA to a wide range of antibacterials is well documented. Prevention of MRSA infections is very important as once introduced in a hospital, MRSA is very difficult to eradicate. Multiple, prolonged use of antibiotics and prolonged hospitalisation are important factors which make hospitals an ideal place for transmission and perpetuation of MRSA.[2]

Table 10: Percentage of MRSA strains reported from India.

S. no	Author	Year	% of MRSA
1	Shantala et al[15]	2011	54.8
2	Sharma et al[16]	2013	25.25
3	Kulkarni et al[17]	2014	70.33
4	Bouchiat et al[18]	2015	52.4
5	Present study	2017	46.78

Antimicrobial resistance pattern of MRSA on disk diffusion test

In the present study, all MRSA were resistant to penicllin and nitrofurantoin (used against urinary isolates only). Erythromycin had sensitivity of 11.19%, ciprofloxacin (7.46%), cotrimoxazole (26.11%) and amikacin (26.11%) gentamicin (8.20%) (Table 3).

Vancomycin screen agar

The development of antibiotic resistance in developing countries is related to the irrational antibiotic usage due to easy availability at drug store without prescriptions and injudicious use in hospitals. The emergence and spread of resistance to vancomycin is a threat to the already challenging therapy of MRSA.[19]

So a precautionary measure should be ensured before starting the patient on vancomycin. Clinicians should seek the help of clinical microbiologist to determine MIC of these strains so that VISA are not missed and emergence of VRSA can be prevented. Minimizing the antibiotic pressure is essential to control the emergence of resistant strains in hospital and community.

Currently CLSI recommends vancomycin screen agar (BHI agar containing 6 µg/ml vancomycin) method for the detection of VRSA and VISA.[5]

Staphylococci with reduced susceptibility to vancomycin were observed in this study. On vancomycin screen agar we found 8 (5.97%) isolates that had visible growth (Table 4).

According to Riederer et al from USA, since population analysis is not practical, screening for isolates with reduced susceptibility on vancomycin-supplemented BHI agars are a reliable alternative. They recommend BHI-with vancomycin for hVISA screening and for VISA detection.[20]

Satola et al from USA found 9 (6.42%) isolates positive by vancomycin screen agar approach which is similar to our study. They also concluded that it is an inexpensive and efficient way to test multiple clinical isolates on a daily basis.[21]

Liaqat et al from Pakistan found 5 MRSA isolates showed growth on vancomycin screen agar. They subjected them for agar dilution method and found them to be VISA isolates.[22]

Amongst the 8 isolates that that showed visible growth on vancomycin screen agar, 6 MRSA turned out to be VISA (5 by agar dilution method and 6 by E strip method). The remaining isolates could be hVISA which showed visible growth on the vancomycin screen agar. hVISA strains can also have a MIC range from 1.5-≥4.[23] We did not test these isolates further for hVISA because population analysis curve which is considered gold standard in the detection of it, as it is cumbersome and not very practicable.

As antibiotic sensitivity testing of *S. aureus* using vancomycin disc by Kirby Bauer disk diffusion method is not recommended by CLSI, we tested all MRSA isolates for MIC by agar dilution method and E strip. Both these methods are recommended by CLSI for determining MIC of *S. aureus.*

Vancomycin MIC by agar dilution

Drugs approved for the treatment of MRSA infections are vancomycin, linezolid, daptomycin, teicoplanin, quinupristine-dalfopristine and tigecycline. The glycopeptide vancomycin has been regarded as the drug of choice for the treatment of infections due to MRSA. Antibiotic sensitivity of vancomycin by disc diffusion method is not approved by CLSI. It recommends MIC determination by E test, agar dilution or broth microdilution method as gold standards (Table 4).[5]

In a study conducted Tiwari et al two (0.62%) *S. aureus* strains were found to be vancomycin resistant.[24]

A study conducted by Saha et al reported a pathogenic VRSA isolate (MIC ≥64 µg/ml) by PCR.[25]

A total of 5 VISA isolates were reported by Patrick et al in 2004 which is similar to our study.[26] Thati et al reported 16 (5.61%) VISA isolates and 7 (2.45%) VRSA in ICUs in Hyderabad by the agar dilution method and subjected them for PCR.[27]

Tandel et al compared MIC of *S. aureus* by agar dilution method and E test and reported 1 (1.88%) VISA by agar dilution method and 7 (13.20%) by E test. They concluded that automated systems, which used to perform susceptibility testing, do not provide a precise vancomycin MIC. The E test method is an alternative and feasible option for vancomycin testing since it is easy to perform and cost-effective for testing only one drug for one strain. Interpretation of results is also easy.[28]

They recommend using E test as a routine test for determining MIC because of the above mentioned reasons. Agar dilution test should be done on all those strains showing higher MIC (intermediate or resistant results) by E test. Routine use of agar dilution is cumbersome and labour intensive. Higher vancomycin MIC results provided by the E test appear to be more reliable in predicting vancomycin treatment responses.[28]

Chaudhari et al reported 2 VISA by agar dilution method and 4 VISA by E strip method. They concluded that E test was found equally sensitive as compared to agar dilution method in screening MRSA for vancomycin susceptibility. But agar dilution method is time consuming, cumbersome and so E test can be used as an alternative to agar dilution method.[29]

Vancomycin MIC among MRSA by E strip

In our study we found that 93.28% isolates of MRSA had MIC of ≤2. We isolated 6 VISA with MIC 4 by E test (Table 6).

Chaudhari et al reported 92.7% with MIC ≤2. They isolated 4 VISA with MIC 4 by E test and 2 VISA by agar dilution which is similar to our study.[29]

Prakash et al reported 69 (98%) MRSA with MIC 2 for vancomycin by E test which is also near to our study.[30]

Havaei et al from Iran isolated 5 (4.34%) VISA by E strip and then subjected to PCR analysis.[31]

Liaqat et al from Pakistan isolated 4 (8.16%) VISA by E strip and agar dilution. All the isolates showed growth on vancomycin screen agar.[32] Sancak et al from UK found 71 (40.6%) MRSA isolates with MIC 2 in vancomycin and 59.4% with MIC ≤1 by E test.[33]

There was good sensitivity, specificity and MIC correlation between MIC by E test against agar dilution method. Therefore any one of the tests can be used for MIC determination of vancomycin.

Characteristics of 6 VISA isolates and their sensitivity pattern

In our study we found 6 VISA isolates with MIC of 4. Out of these 6 VISA isolates, 4 were isolated from pus samples (one from breast abscess, one from cerebral abscess, one from osteomyelitis ,one from intra-abdominal abscess) and two from blood samples. All the VISA isolates were sensitive to linezolid. Out of these 6 VISA isolates, one was sensitive to cotrimoxazole along with linezolid. Two isolates were susceptible to both linezolid and pristinamycin. Four isolates out of these were resistant to pristinamycin (Table 7, 8, 9).

Havaei et al from Iran also reported 5 (4.34%) VISA isolates by E test and then subjected them for PCR. Out of these, one VISA was susceptible to cotrimoxazole. It was also from blood sample at neurology department which is similar to our study.[31]

In a study by Bhatawadekar et al, seven vancomycin and quinpristin-dalfopristin-resistant staphylococci were isolated from the blood samples of neonates and pediatric patients.[34]

In our study, one VISA isolate was susceptible to cotrimoxazole and isolated from blood sample from neurology department.

CONCLUSION

Vancomycin is considered the mainstay of therapy in multi-drug resistant MRSA infections and should be used judiciously. As disc diffusion method is not recommended by CLSI for *S. aureus*, vancomycin screen agar and MIC determination by either of the methods viz agar dilution or E test can be used. VISA and VRSA isolates recovered should be informed to clinicians for proper treatment of patients. Linezolid can be used as a good option for serious MRSA infections.

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