Methicillin, Vancomycin and Multidrug-Resistance Among Staphylococcus Aureus

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Abstracts: Introduction: The difficult therapeutic problem of multidrug-resistant Staphylococcus aureus (MDRSA) is just one example of the diminishing efficacy of antimicrobial agents for the treatment of bacterial infections. The present study was undertaken to determine the prevalence of Methicillin, Vancomycin and multidrug-resistance of Staphylococcus aureus. Methodology: The study included 312 non-duplicate Staphylococcus aureus which were isolated from various clinical specimens. The isolates were tested for Methicillin resistance by Oxacillin disc diffusion, Cefoxitin disc diffusion and Oxacillin screen agar. They were also tested for vancomycin resistance by Vancomycin screen agar, agar dilution technique and E strip technique. The antibiogram was determined by Kirby Bauer Disc Diffusion Method. Results: Oxacillin screen agar technique was found to be more sensitive than Oxacillin disc diffusion method for detection of MRSA. Prevalence of MRSA in our study was found to be 36.54 %. All MRSA isolates were found to have increased resistance to all antibiotics as compared to MSSA isolates. No VISA and VRSA were found by any of the three methods. Prevalence of MDRSA in our set up was found to be 51.28%. **Conclusion-** In the Hospitals where resources are constrained, Cefoxitin disc diffusion method and Vancomycin screen agar can be used as screening of MRSA and VRSA strains respectively. [Kulkarni VL NJIRM 2017; 8(3):68-74]

Key Words: Staphylococcus aureus, MRSA, VRSA, MDRSA

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Introduction: Staphylococcus aureus, a Gram positive bacterium from Micrococcaceae family has been recognized as an important cause of human disease for more than 100 years.[1] It is perhaps the pathogen of greatest concern because of its intrinsic virulence, its ability to cause a diverse array of life threatening infections, its capacity to adapt to different environmental conditions and its nasal carriage which accounts for possible re-infection and also spread.[2]

Methicillin resistant Staphylococcus aureus (MRSA) has been reported with increasing frequency worldwide.[3] Life threatening sepsis, endocarditis, postoperative wound infections, skin & soft tissue infections and osteomyelitis caused by MRSA have been reported since 1961 from various parts of the world.[4] These strains are not only resistant to routinely used antibiotics but also act as a reservoir for multidrug-resistance development. Once MRSA is introduced in hospital, it is difficult to eradicate and have differential ability to spread and cause major outbreaks.[5,6]

Currently, the treatment options for MRSA infections are mainly limited to very expensive drug like Vancomycin and Teicoplanin.[6] However due to frequent and inadvertent use of Vancomycin for the treatment of MRSA; resistance to these antibiotics is also increasing. Staphylococcus aureus with reduced susceptibility to Vancomycin and Vancomycin resistant Staphylococcus aureus (VRSA) have been reported from various parts of the world.[7,8,9,10]

The difficult therapeutic problem of multidrug-resistant Staphylococcus aureus (MDRSA) is just one example of the diminishing efficacy of antimicrobial agents for the treatment of bacterial infections.[2] Multidrug-resistance has become a major cause of nosocomial and community acquired infections.[1]

The resistance pattern of this organism can be detected in the laboratory by various methods like disc diffusion test, resistance agar screening test and minimum inhibitory concentration (MIC) method.[11] Among these MIC is the most accurate and specific method for antimicrobial resistance determination. Also accurate and prompt detection of Methicillin resistance in Staphylococcus aureus and subsequent detection of Vancomycin resistance in these MRSA strains is of utmost importance in managing these infections and preventing their spread.

The present study was undertaken to know the prevalence of Methicillin and Vancomycin resistance among various clinical isolates of Staphylococcus aureus, to evaluate various detection methods and to know the antibiogram of the isolates to the commonly used antibiotics.

Aims and Objectives:

Aim: To determine the prevalence of Methicillin, Vancomycin and multidrug-resistance among Staphylococcus aureus (S. aureus)

Objectives:

1. To find out the prevalence of Methicillin Resistant Staphylococcus aureus (MRSA)
2. To determine the prevalence of Vancomycin Intermediate Staphylococcus aureus (VISA) and Vancomycin Resistant Staphylococcus aureus (VRSA)
3. To evaluate various phenotypic methods for detection of MRSA & VRSA

Methods: The present study was carried out in the department of Microbiology at a tertiary care hospital. The study included a total of 312 non-duplicate Staphylococcus aureus which were isolated from various clinical specimens.

Study design: Prospective study

Ethical clearance from institutional ethical committee was obtained.

Inclusion criteria:

a) Specimen from both indoor as well as outdoor patients of all age groups and both sexes
b) Staphylococcus aureus isolated from various clinical specimen

Exclusion criteria: Species other than Staphylococcus aureus were excluded.

A history was taken with reference to name, age and sex. Clinical history was recorded on a predesigned proforma. The specimens were collected using strict aseptic precautions and immediately transported to the laboratory. All the specimens received were processed further for identification by standard microbiological procedures.[12,13]

Smears were prepared from specimens and Gram staining was done. It was examined under the oil immersion lens to see the presence of bacteria and to study their morphology. The samples were inoculated onto nutrient agar, blood agar and MacConkey agar plates. All plates were incubated aerobically at 37˚C and observed for growth after 18-24 hours.

Isolates of Staphylococcus aureus were identified on the basis of colony characteristics on nutrient agar and blood agar. Smears were prepared from the colonies and Gram stain was done. Cluster forming Gram positive cocci were further confirmed as S. aureus by catalase, coagulase test, fermentation of mannitol and battery of biochemical tests.

Antimicrobial susceptibility testing was done by Kirby-Bauer disc diffusion method on Mueller-Hinton agar as per CLSI guidelines.[14]

Detection of MRSA :

1.Oxacillin disc diffusion method:[14] MRSA isolates were identified by Kirby-Bauer disc diffusion method using Oxacillin disc 1µg (HiMedia, Mumbai). A 0.5 McFarland standard suspension of the isolate was prepared and lawn culture was done on Mueller-Hinton agar. Oxacillin disc was placed on the medium with the help of sterile forcep. Plates were incubated at 35˚ for 24 hours. Zones were interpreted as per CLSI guidelines.

2.Cefoxitin disc diffusion method:[14] All the isolates were subjected to Cefoxitin disc diffusion test using a 30 µg disc. A 0.5 McFarland standard suspension of the isolate was made and lawn culture done on MHA plate. Plates were incubated at 35^0 C for 24 hours and the diameter of zone of inhibition was measured. An inhibition zone diameter of ≤ 21 mm was reported as Cefoxitin resistant and ≥22 mm was considered as Cefoxitin sensitive.[14]

3.Oxacillin screen agar method: [14] Mueller-Hinton agar (MHA) plates containing 4% NaCl and 6 µg/ml of Oxacillin were prepared. (HiMedia, Mumbai) Plates were inoculated with 10 µL of 0.5 McFarland suspension of the isolate by streaking in one quadrant and incubated at 35^0 C for 24 h. Plates were observed carefully in transmitted light for any growth. Any growth after 24 hours was considered as Oxacillin resistant.

Detection of Vancomycin resistance:

1.Vancomycin screen agar method:[14,15] BHI agar (Hi-Media, India) screen plates containing 6 µg/ml Vancomycin were prepared. A 0.5 McFarland standard suspension was prepared by selecting colonies from overnight growth. The final concentration of 10^5 to 10^6 CFU per spot was prepared by adding sterile saline to the bacterial suspension. These suspensions were

inoculated onto BHI screen agar plates and were incubated for 24 hrs at 35°C in ambient air. Any visible growth indicated the Vancomycin resistance.[14]

2.Determination of MIC by agar dilution method:[14,16,17] Bacterial suspension was prepared from overnight cultures on blood agar and its turbidity was adjusted to be equivalent to that of a 0.5 McFarland standard. This suspension was inoculated onto Mueller-Hinton agar containing serial dilutions of Vancomycin (2 µg/ml, 4 µg/ml, 8 µg/ml, 16 µg/ml, 32 µg/ml). Plates were incubated at 37˚C for 24 hours. Any visible growth on agar plate indicated Vancomycin resistance.

3.MIC determination by Epsilometer (E) test: (source-Hi-Media) The E test strips are coated with Vancomycin in a concentration gradient manner, capable of showing MICs in the range of 0.016-256 µg/ml, on testing against test organism. Vancomycin MIC determined by agar dilution method was rechecked by E-test. E test was performed on all isolates according to the manufacturer's instructions (Hi Media, Mumbai) and Interpretation of Vancomycin MIC was done according to CLSI guidelines.

Statistical Methods: The data obtained was analyzed by applying appropriate statistics wherever needed.

Result: During study period, a total of 312 isolates of S. aureus were obtained from various clinical samples.

Table-1: Detection of MRSA by various phenotypic methods

Method	No. of MRSA (%)	No. of MSSA (%)	Total
Cefoxitin disc diffusion	114 (36.54)	198 (63.46)	312 (100%)
Oxacillin screen agar	111 (35.58)	201 (64.42)	312 (100%)
Oxacillin disc diffusion	109 (34.94)	203 (65.06)	312 (100%)

Out of 312 Staphylococcus aureus isolates, 114 (36.54%) were found to be Methicillin resistant by Cefoxitin disc diffusion method, 111 (35.58%) by Oxacillin screen agar and 109 (34.94%) by the Oxacillin disc diffusion method. Considering Cefoxitin disc diffusion method as best predictor of Methicillin resistance in Staphylococcus aureus, sensitivity of Oxacillin screen agar was 97.37 % and that of Oxacillin disc diffusion method was 95.61% while the specificity of both methods was 100 %.

Table-2: Comparison between antibiotic resistance pattern of MSSA and MRSA

Antibiotics	Total	MSSA n=198	MRSA n=114	P value*
Penicillin G	296 (94.87)	182 (91.92)	114 (100)	<0.05
Amoxicillin/Clavulanic acid	149 (47.76)	35 (17.68)	114 (100)	<0.05
Gentamicin	81 (25.96)	28 (14.14)	53 (46.49)	<0.05
Amikacin	85 (27.24)	31 (15.66)	54 (47.37)	<0.05
Netilmicin	0 (0)	0 (0)	0 (0)	-
Erythromycin	163 (52.24)	65 (32.83)	98 (85.96)	<0.05
Clindamycin	97 (31.09)	32 (16.16)	65 (57.02)	<0.05
Ciprofloxacin	150 (48.08)	58 (29.29)	92 (80.70)	<0.05
Nitrofurantoin	25 (8.01)	12 (6.06)	13 (11.40)	<0.05
Tetracycline	100 (32.05)	61(30.81)	39 (34.21)	<0.05
Trimethoprim/Sulfamethoxazole	226 (72.44)	118 (59.60)	108 (94.74)	<0.05
Linezolid	0 (0)	0 (0)	0 (0)	-
Teicoplanin	(0)	0 (0)	(0)	-

(*Two proportion Z test)

All MRSA isolates were found to have increased resistance to all antibiotics tested as compared to MSSA isolates and the difference was statistically significant. (p value < 0.05) All MSSA as well MRSA isolates were 100 % sensitive to Netilmicin, Linezolid and Teicoplanin.

Table-3: Detection of Vancomycin resistance by various phenotypic methods

Method	VISA	VRSA	VSSA	Total
Vancomycin screen agar	Nil	Nil	312	312
Agar dilution	Nil	Nil	312	312
Epsilometer test (E- test)	Nil	Nil	312	312

Among 312 Staphylococcus aureus isolates, no VISA and VRSA were found by any of the three methods. (Vancomycin screen agar, Vancomycin agar dilution method and E- test) Considering MIC determination of vancomycin by agar dilution method as gold standard, Vancomycin screen agar method showed 100% specificity and 100% negative predictive value.

Table-4: Distribution of MIC at different concentration of Vancomycin drug by E- test

MIC range	No of isolates	Percentage
≥1.5 to 2	82	26.28
≥1 to <1.5	57	18.27
≥0.5 to <1	96	30.77
<0.5	77	24.68
Total	312	100

All S. aureus isolates showed MIC of Vancomycin within susceptible range (≤ 2µg/ml). Maximum number of isolates were having MIC less than 1 µg/ml.

Table 5: Association of MIC level of Vancomycin with Methicillin resistance

Vancomycin MIC range in µg/ml	No. of MSSA isolates	No. of MRSA isolates	P value
1-2	40	99	<0.05
<1	158	15	-
Total	198	114	-

Maximum number of MRSA isolates showed MIC to Vancomycin at upper limit of susceptibility range as compared to MSSA. This difference was found to be statistically significant with P value <0.05.

Table-6: Multidrug-resistance among Staphylococcus aureus

Type	Number of isolates	Percentage (%)
MDRSA*	160	51.28
Non MDRSA	152	48.72
Total	312	100

*MDRSA- Multidrug-resistant S. aureus.

A total 160 (51.28 %) S. aureus isolates were resistant to ≥ 1 antibiotic in ≥ 3 antimicrobial categories.

Discussion: In our study, a total of 312 isolates of Staphylococcus aureus were obtained from various clinical specimens and Methicillin, Vancomycin and multidrug-resistance was determined by using various phenotypic methods.

In the present study, we attempted to evaluate three phenotypic methods for detection of MRSA. MRSA detected by Cefoxitin disc diffusion, Oxacillin screen agar and Oxacillin disc diffusion methods were 36.54%, 35.58% and 34.94% respectively. Similar observation was made by Dhanalaxmi et al [18] who reported the rate of detection of MRSA by Cefoxitin disc diffusion, Oxacillin screen agar and Oxacillin disc diffusion method as 32%, 31.2% and 30.8% respectively. KB Anand et al[19] found that 64% of S. aureus isolates were Methicillin resistant by Cefoxitin disc diffusion method, 60% by Oxacillin screen agar and 56% by Oxacillin disc diffusion method.

One of the limitations of the present study was that, the detection of mecA or PBP 2a which is considered as the gold standard for detecting the MRSA strains was not done because of unavailability of molecular detection methods in our set up. As per CLSI recommendations, in the absence of availability of molecular techniques, the Cefoxitin disc is the best predictor of Methicillin resistance in S. aureus among the techniques tested.[14,20]

Among the screening methods which are used for MRSA detection, Cefoxitin disc diffusion method should be preferred over Oxacillin, because Cefoxitin is a potent inducer of the mecA gene, less affected by hyper production of penicillinases and requires no special medium or temperature as required for testing with Oxacillin.[18]

Prevalence of MRSA in our study was 36.54%. This rate is comparable with studies done by Sasirekha B et al[21] (27.45%), Dhanalaxmi et al[18] (32%) and Loveena Oberoi et al[22] (45.36%). Higher prevalence was noted by Verma S et al[23] (80.89%) and lower prevalence of MRSA was given by Tahnkiwale S et al[24] (19.56%). This discrepancy in the prevalence could be due to difference in the study design, population and geographical distribution.

The antibiotic sensitivity results showed that all MRSA isolates were significantly more resistant to all antibiotics tested than MSSA isolates. Similar findings were seen in the studies by Sasirekha B et al [21], Anupurba et al [25] and Anvikar et al[26]**.** The MRSA strains have tendency to accumulate additional unrelated resistance determinants and incorporate in their genome. This has led MRSA strains to become resistant to all commonly used antibiotics.[27]

VISA and VRSA isolates are not detected by disc diffusion method and automated methods did not accurately identify these strains. MIC determinations by broth or agar dilution methods are "gold standard" for detection of VISA and VRSA. The Center for Disease Control and Prevention (CDC) recommends that laboratories use MIC method plus screen agar for detection of VISA and VRSA because, disc diffusion method does not reliably detect and differentiate VISA and VRSA isolates.[14,15]

We evaluated three different phenotypic methods to identify Vancomycin resistance in S. aureus (Vancomycin screen agar, agar dilution method and E-test). VISA or VRSA were detected by Vancomycin screen agar and these finding were confirmed by agar dilution and E-test.

Similar to our finding, Dhanalakshmi T. A. et al [18] reported no VISA and VRSA by any of the method used. Tiwari HK et al [28] found 0.25 % of Staphylococcus aureus strains were Vancomycin resistant and 0.76% strains were Vancomycin intermediate resistant by both Vancomycin screen agar and agar dilution method. In a study done by Bandaru et al [1]**,** 6.79% isolates were found to be Vancomycin intermediate resistant by both (agar dilution method and E- test) and no Vancomycin resistant strain was reported.

Considering MIC determination of vancomycin by agar dilution method as gold standard, Vancomycin screen agar technique showed 100% specificity and 100% negative predictive value. Same finding were reported by Dhanalakshmi T. A. et al [18] while Timothy R. Walsh et al [32] reported 97% specificity for Vancomycin screen agar.

In our study, MIC of all S. aureus strains for Vancomycin were in the susceptible range of ≤2 µg/ml. Among the total, 139 showed MIC within the range 1-2 µg/ml and most of them were MRSA (71.22 %). Significant association was found between Methicillin resistance and higher MIC range for Vancomycin sensitivity. Similar observation was made by Sachin Kishore et al**.**[31] Some retrospective studies have independently found that MRSA strains with Vancomycin MIC at the upper limits of susceptibility (MIC 1-2 µg/ml) are associated with poor treatment outcomes in pneumonia and bacteremia.[31]

Emergence of resistance to multiple antimicrobial agents in pathogenic bacteria has become a significant public health threat as there are fewer, or even sometimes no, effective antimicrobial agents available for infections caused by these bacteria.

Multidrug-resistant Staphylococcus aureus is defined as resistance to ≥1 antibiotic in ≥3 antibiotic classes used for treating Staphylococcus aureus infection.[33] The burden of multidrug resistant staphylococcus aureus is increasing over time.

In the present study, prevalence of multidrug-resistant S. aureus was found to be 51.28 %. Onanuga A. et al [34] reported higher (71.7%) prevalence of multidrug-resistant S. aureus, while Ricardo Castillo Neyra et al [35]**,** Dhanalakshmi et al [18] & Rinsky et al[36] reported lower rate of 29.5%, 26.8% & 16 % respectively.

The developing countries like ours are presently characterized with inappropriate prescription, unethical dispensing and indiscriminate use of antibiotics. These factors are responsible for the development of numerous problems including the emergence of multidrug resistant bacteria, increased morbidity and mortality due to number of nosocomial infections and increased health care costs.

Conclusion: Antibiotics have traditionally been known as miracle drugs, but there is growing evidence that they are becoming overworked miracles. Although the development of antibiotic resistance may be inevitable, the rate at which it develops may be reduced by the rational use of antibiotics.

Irrational and inappropriate use of antibiotics is responsible for emergence of Methicillin, Vancomycin and multidrug-resistance in S. aureus. For early detection of such kind of resistance, Clinical Microbiology laboratory should use different phenotypic methods with high sensitivity and specificity. In the Hospitals where resources are

constrained, Cefoxitin disc diffusion method and Vancomycin screen agar can be used as screening of MRSA and VRSA strains respectively.

Vancomycin resistance has been considered as a worrisome threat to the already challenging therapy of MRSA and multidrug- resistant S. aureus. Before starting the patient on vancomycin, the clinicians should seek the help of clinical Microbiologist to determine the MIC of such strains so that emergence of Vancomycin resistance can be prevented. The E-test is an alternative and feasible option for rapid MIC testing since it is easy to perform and cost effective as compared to cumbersome and labor intensive agar dilution technique.

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