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THE STUDY OF INDUCIBLE AND CONSTITUTIVE CLINDAMYCIN RESISTANCE IN *STAPHYLOCOCCUS AUREUS* ISOLATES FROM CLINICAL SAMPLES IN A TERIARY CARE HOSPITAL IN CENTRAL INDIA.

Microbiology

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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), is the most common cause of nosocomial infections and pose a great threat to the world. Macrolide, lincosamide and streptogramin B (MLSB) antibiotics are commonly used in treatment of staphylococcal infections. Widespread use of MLSB antibiotics has led to an increase in resistance to these antibiotics especially clindamycin, amongst staphylococcal strains.

Material and methods: Study was carried for a period between January 2014 to June 2017 in the Microbiology Diagnostic Laboratory . MRSA detection was performed by cefoxitin disk diffusion method.

All *Staphylococcus aureus* isolates were tested for the inducible clindamycin resistance (MLS_Bi), Constitutive Clindamycin resistance (MLS_Bc) and MS phenotype by Double-disk diffusion test (D-zone test).

Results: A total of 287 *Staphylococcus aureus* clinical isolates were included in the study.

MRSA was found to be 46.68% of all samples.

Inducible Clindamycin resistance (MLS_Bi) was seen in 40.29% of MRSA,15.03% of MSSA ,and 26.82% of total *S. aureus isolates.* Constitutive Clindamycin resistance (MLS_Bc) was seen in 28.35% of MRSA samples, 15.68% of MSSA and 21.60% of total *S. aureus isolates.* MS Phenotype was seen in 20.14% of MRSA, 9.80% of MSSA and 14.63% of all *S. aureus isolates.*

Conclusions: Higher prevalence of iMLS_B phenotype in MRSA infections compared to MSSA infections suggests that clindamycin therapy for MSSA infections is successful in many circumstances while it may lead to treatment failure for MRSA infections.

KEYWORDS

Staphylococcus aureus, Methicillin resistant S. *aureus* (MRSA), inducible clindamycin resistance (MLS_Bi), Constitutive Clindamycin resistance (MLS_Bc), MS phenotype

Introduction

Staphylococcus aureus has been a plague of mankind since the dawn of history.[1]

Methicillin resistant *Staphylococcus aureus* (MRSA) strains were initially described in 1961 and emerged in the last decade as one of the most important nosocomial pathogens.[2] Infected and colonized patients provide the primary reservoir of infection and transmission of MRSA is mainly through hospital staff.

Macrolide, lincosamide and streptogramin B (MLSB) antibiotics are commonly used in treatment of staphylococcal infections. Injudicious use of antibiotics has led to an increase in resistance to all anti-staphylococcal antibiotics especially clindamycin.[3]

Clindamycin resistance in *staphylococcus* is of 2 types-Constitutive and Inducible.The most common mechanism for such resistance is target site modification mediated by *erm* genes, which can be expressed either constitutively (constitutive MLS_B phenotype) or inducibly (inducible MLS_Bphenotype).[4]

Strains with inducible resistance to clindamycin are difficult to detect in the routine laboratory as they appear erythromycin-resistant and clindamycin sensitive *in vitro* when not placed adjacent to each other. In such cases, therapy with clindamycin in patients may select constitutive *erm* mutants leading to clinical therapeutic failure.[4]

Aim

To study the *Staphylococcus aureus* isolates for the inducible clindamycin resistance (MLS_Bi), Constitutive Clindamycin resistance (MLS_Bc) and MS phenotype by Double-disk diffusion test (D-zone test).

Material and methods

The present study was 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. The study was approved by the Institutional Ethical Committee.

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

Isolation

Specimens showing pus cells with Gram positive cocci in clusters in primary smear were given special attention. The Sheep blood agar and Mac Conkey's medium were used for inoculation of all specimens. The plates were then incubated at 35 ± 2^0Celsius for 18 - 24 hours in aerobic atmosphere.[5]

Identification of genus staphylococcus

After the plates were examined, any colony showing morphology suggestive of Staphylococcus, showing beta-haemolysis / no haemolysis, butyrous in consistency on blood agar plates were studied by Gram stain.

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.[5]Catalase test, Modified Oxidase test,Furazolidone susceptibility test , Coagulase test(slide and tube coagulase), Mannitol sugar fermentation test[5].

Antimicrobial susceptibility testing was performed as per the CLSI guidelines (2016) by modified Kirby Bauer method.[6,7]

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)[8] combined with institutional antibiotic policy and hospital formulary practices for the purpose of reporting to the clinician.

MRSA detection (Methicillin Resistant *S. aureus*)

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

Cefoxitin disk diffusion testing[9,10]

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.

Interpretive Criteria (in mm) for Cefoxitin Disk Diffusion Test		
	Susceptible	Resistant
Staph. Aureus	≥ 22	≤ 21

INDUCIBLE CLINDAMYCIN RESISTANCE: D-zone test

All *Staphylococcus aureus* isolates were tested for the inducible clindamycin resistance by Double-disk diffusion test (D-zone test). Clindamycin disk (2 µg) was placed at the distance of 15 mm from the erythromycin disk (15 µg) on the Mueller Hinton agar plate inoculated with the test organism. Plates were analyzed after 18 - 24 hrs incubation.[10,11]

Reading and Interpretation:

Flattening of the zone (D shaped) of clindamycin disk towards the side facing the erythromycin disk indicated positive D-zone test i.e. presence of inducible clindamycin resistance. Growth of the organism till the edge of both the discs was taken as constitutive clindamycin resistance. Staphylococcal isolates exhibiting resistance to erythromycin (zone size ≤ 13 mm) while sensitive to clindamycin (zone size ≥ 21 mm) and giving circular zone of inhibition around clindamycin was taken as MS phenotype.[11]

Observations and results

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

Table no 1: Distribution of *Staphylococcus aureus* according to various clinical specimens (n=287)

Sr. No	Clinical Specimen	No. of *S. aureus* isolated. (%)
1	**Pus / wound swabs**	158(55.05%)
2	**Blood**	35(12.19%)
3	**Urine**	27(9.40%)
4	**Sputum**	25(8.71%)
5	**High vaginal swab**	19(6.62%)
6	**Fluids**	10(3.48%)
7	**Tracheal aspirate**	8(2.78%)
8	**Corneal scraping**	3(1.04%)
9	**CSF**	2(0.69%)
	Total	287(100%)

The above table shows the distribution of *Staphylococcus aureus* according to various clinical specimens. The maximum samples were isolated from pus/wound swabs (55.05%) followed by blood which constituted 12.19%, then urine samples (9.40%) and sputum (8.71%).The minimum number of isolates were from CSF samples which constituted 0.69% of all samples.

Table 2: Speciality wise distribution of *Staphylococcus aureus* (n=287)

Sr. No	Ward	No. of *S. aureus (%)*
1	**Surgery wards**	102(35.54%)
2	**Medicine wards**	39(13.58%)
3	**Orthopaedic wards**	38(13.24%)
4	**Obstetrics and Gynaecology wards**	36(12.54%)
5	**ICU**	25(8.71%)
6	**Paediatric wards**	24(8.36%)
7	**ENT wards**	10(3.48%)
8	**OPD(Out patient Department)**	13(4.52%)
	Total	287(100%)

The above table shows speciality-wise distribution of *S. aureus* isolates in the tertiary care hospital. The maximum number of isolates were from surgery wards (35.54%), followed by medicine wards (13.58%) and orthopaedic wards (13.24%). ICU constituted 8.71% of all samples.IPD(In Patient Department) constituted 95.5% and OPD (Out Patient Department) constituted 4.52%. The least isolates of *S. aureus* were from ENT wards (3.48%).

Table no 3: Antimicrobial susceptibility pattern of *S. aureus* by disk diffusion method (n=287)

Sr. No	Antibiotics	Sensitive no (%)	Resistant no(%)
1	**Penicillin G**	23(8.01%)	264(91.98%)
2	**Cotrimoxazole**	170(59.23%)	117(40.76%)
3	**Chloramphenicol**	146(50.87%)	141(49.12%)
4	**Ciprofloxacin**	84(29.26%)	203(70.73%)
5	**Ofloxacin**	115 (40.06%)	172(59.93%)
6	**Gentamicin**	101(35.19%)	186(64.80%)
7	**Amikacin**	175(60.97%)	112(39.02%)
8	**Tetracycline**	126(43.90%)	161(56.09%)
9	**Erythromycin**	106(37.28%)	181(63.06%)
10	***Nitrofurantoin (out of 27 urine samples)**	9(33.33%)	18(66.66%)
11	**Linezolid**	287(100%)	0(0%)

*for urine samples only.

The above table describes the antibiotic susceptibility pattern of *S. aureus* isolates. All the isolates were sensitive to linezolid. Amikacin showed a sensitivity of 60.97% followed by cotrimoxazole (59.23%), and chloramphenicol (50.87%). Nitrofurantoin was tested only against urinary isolates which showed 33.33% sensitivity to *S. aureus* .Least sensitivity was seen to penicillin (8.01%).

Table 4: Detection of Methicillin resistant *S. aureus* (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%)

Table 5: Comparison of different types of MLS_B resistance among *S. aureus* on D-zone test.

Phenotype Susceptibility pattern	MRSA (%) (n=134)	MSSA (%) (n=153)	Total (%) (n=287)
Inducible Clindamycin resistance (MLSBi) (ER-R, CL-S, D test +ve)	54(40.29%)	23(15.03%)	77(26.82%)
Constitutive Clindamycin resistance (MLSBc) (ER-R, CL-R)	38(28.35%)	24(15.68%)	62(21.60%)
MS Phenotype (ER-R, CL-S, D test -ve)	27(20.14%)	15(9.80%)	42(14.63%)
Susceptible to Erythromycin & Clindamycin (ER-S, CL-S)	15(11.19%)	91(59.47%)	106(36.93%)

ER - Erythromycin; CL - Clindamycin; S - sensitive; R – resistant

$p \leq 0.05$

The above table shows comparison of different types of MLS_B resistance among *S. aureus* on D-zone test .Inducible Clindamycin resistance (MLS_Bi) was seen in 40.29% of MRSA,15.03% of MSSA ,and 26.82% of total *S. aureus isolates.* Constitutive Clindamycin resistance (MLS_Bc) was seen in 28.35% of MRSA samples, 15.68% of MSSA and 21.60% of total *S. aureus isolates.* MS Phenotype was seen in 20.14% of MRSA, 9.80% of MSSA and 14.63% of all *S. aureus isolates.*

Statistical analysis of the above table was done by using chi-square test. The p value ≤ 0.05 was considered as statistically significant. We found that Inducible Clindamycin resistance, Constitutive Clindamycin resistance, MS Phenotype and both Erythromycin and Clindamycin sensitive between MRSA and MSSA isolates were statistically significant.($p \leq 0.05$)

Discussion

MRSA is now endemic in India. Its incidence varies from 25% in Western India to 50% in Southern India.[2] Early detection of MRSA and its susceptibility profile becomes important from treatment point of view because it leaves us with very few treatment options such as glycopeptides and linezolid.[12]

A total of 287 isolates of *S. aureus* were studied from different clinical specimens like pus, wound swabs, blood, body fluids, sputum, ear swabs, corneal scrappings, urine etc. These samples were processed using standard laboratory procedures.

Isolates were selected only when they were incriminated as a source of

infection. Majority of specimens / isolates in our study were from pyogenic lesions and *S .aureus* is an important cause of pyogenic lesions.

Distribution of *Staphylococcus aureus* according to various clinical specimens.

In the present study, the maximum number of *S. aures* were isolated from pus and wound swabs (55.05%) followed by blood which constituted 12.19%, then urine samples (9.40%) followed by sputum (8.71%),fluids (3%) and tracheal aspirate constituted 2.78%.The minimum number of isolates were from CSF samples which constituted 0.69% of all samples.(Table no 1)

Our study correlates with a study conducted by Bhat M P *et al* in 2015, where maximum *S. aures* isolates were isolated from pus and wound swabs (68%),followed by blood(11%), urine 4%,tracheal aspirate 3% and pleural fluid 1%.[12]

Similar findings were also reported by Bhatt CP *et al* (2014) where 67% isolates were pus, 4.5% were from sputum, 3.1% from fluids, 0.25% were from CSF.[13] Hence the fact that *S. aureus* causes wound infections is well documented.

Tiwari *et al* (2009)also reported 63.7% of *S. aures* from pus and wound swabs (63.7%), from blood 6.1%, from pleural/synovial fluid 4%, sputum/ throat swab 6%, urine 14% and CSF 1.8%.[14]

In the study of Mehndiratta *et al* (2001) lower number of *S. aureus* (39.65%) were isolated from pus.[15]

Speciality wise distribution of *Staphylococcus aureus.*

In the present study, 35.54% of *S. aureus* isolates were from surgical wards. (Table no 2).

A total of 95.5% of *S. aureus* isolates were obtained from in-patient departments (IPD) and (4.52%) isolates were from out-patient departments (OPD) (Table no 2). This correlates with the findings of Mallick and Basak (2010)[16]who reported 85.7% *S. aureus* strains from the IPDs and 2.5% from the OPDs.

This is in contrast to the findings by Tiwari *et al* (2008) who reported 64.2% *S. aureus* strains from OPD.[17]

Methicillin resistant *S. aureus* (MRSA)

Methicillin-resistant *S. aureus* (MRSA) is a major nosocomial and community pathogen causing significant morbidity and mortality.[17] In addition to dire consequences of infections, MRSA strains are important for their resistance to many other commonly used antibiotics and the emergence of resistance to vancomycin, the drug that has been used to treat MRSA infections for more than three decades.[17] 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 no 4)

Jain *et al* (2014) reported 48.78% of *S. aureus* were MRSA which is similar to our study.[18]

Similarly Hanumanthappa *et al* (2003) reported 43% MRSA and Arora *et al* (2010) reported 46% of MRSA.[19,20]

The resistance of MRSA to a wide range of anti-bacterials is well documented.MRSA spreads rapidly by hands of medical personnel. Multiple, prolonged use of antibiotics and prolonged hospitalisation are important factors which make hospitals an ideal place for transmission and perpetuation of MRSA.[21]

Table No 6- Percentage of MRSA strains reported from India

S.No	Author	Year	% of MRSA
6	Pai *et al* [22]	2010	29.1%
7	Shantala *et al* [23]	2011	54.8%
8	Sharma et al [24]	2013	25.25%
9	Kulkarni *et al*[25]	2014	70.33%
10	Bouchiat et al [26]	2015	52.4%
11	**Present study**	2015	46.78%

Macrolides & Lincosamides:

Clindamycin is one of the most commonly used antibiotics for *S. aureus* infections. Accurate susceptibility data are important for appropriate therapy decisions. However, false in vitro susceptibility results may be obtained by the disk diffusion testing with erythromycin and clindamycin disk in nonadjacent positions. Hence, the routine testing of staphylococcal isolates for inducible clindamycin resistance was done as recommended by the CLSI guidelines 2010.[10]

Different types of MLS_B resistance on D-zone test

In this study, it was found that both the inducible and constitutive clindamycin resistance were seen in significantly higher proportion among MRSA as compared to methicillin susceptible *S. aureus* (MSSA) isolates.(Table no 5).

Similar findings were made by Mallick *et al* (2009) & Deotale *et al* (2010).[27,28]

In the present study inducible clindamycin resistance was present in 40.29% isolates of MRSA and 15.03% isolates of MSSA. Similarly constitutive clindamycin resistance was present in 28.35% isolates of MRSA as compared to 15.68% of MSSA.

Table No - 7Various studies with Inducible clindamycin resistance and Constitutive clindamycin resistance.

S. No.	Author	Year	MLS_Bi	MLS_Bc
1	Angel *et al* [29]	2008	64.0%	0%
2	Deotale *et al* [28]	2010	27.6%	7.3%
3	Shantala *et al* [23]	2011	32.5%	15.07%
4	Mohanasoundaram *et al* [30]	2011	28.0%	19.0%
5	Patil *et al* [31]	2013	36.95%	8.69%
6	Mallikarjuna Reddy *et al*[32]	2014	46.34%	35.8%
7	Tyagi *et al*[33]	2015	20.27%	18.40%
8	**Present Study**	2015	26.82%	24.04%

According to Kader *et al (2005)* from Saudi Arabia, 43% of MRSA isolates demonstrated Inducible clindamycin resistance and 28.9% of total isolates which is similar to our study.[34]

Yilmaz *et al (2007)* from Turkey found inducible resistance in 14.8% in MSSA which is also similar to the present study.[35]

A study by Levin *et al* (2005) from USA reported Inducible Clindamycin resistance (MLS_Bi) in 27.5% of all isolates which is also near to our study.[36]

In a study by Juyal *et al* in 2013, 33.6% isolates demonstrated Inducible Clindamycin resistance (MLS_Bi). Among the MLSBi phenotypes, 13.3% isolates were MRSA and 28.9% were MSSA.[37]

Ciraj *et al* (2009) also reported similar results that is 38.4% of the total MRSA and 12.9% of the total MSSA.[38]

Patil *et al* (2013) reported Inducible clindamycin resistance of 36.95% in MRSA.[31]

Kumar *et al* (2012), reported constitutive clindamycin resistance in 23.0% of all isolates and MS phenotype of 16.9% which also correlates to our study.[39]

Gadepalli *et al* (2006) reported 26.5% isolates were found to exhibit the constitutive, 21% the inducible MLSB resistance phenotype and 12% the MS phenotype which is near to our study.[40]

In our study, MS Phenotype was seen in 20.14% of MRSA, 9.80% of MSSA and 14.63% of all *S. aureus isolates.*

In a study by Deotale *et al* (2010) MS phenotype was seen in 24.3% of MRSA and 14.17% of total isolates which is similar to our study.[28]

According to Sasirekha *et al*(2014), MS phenotype was seen in 13.07% of MSSA and 18.95% of total isolates which is also similar to our study.[41]

Conclusions

In the light of the restricted range of antibiotics available for the treatment of MRSA infections and the known limitations of

vancomycin, clindamycin should be considered for the management of serious soft-tissue infections with MRSA that are sensitive to clindamycin.

Higher prevalence of $iMLS_B$ phenotype in MRSA infections compared to MSSA infections suggests that clindamycin therapy for MSSA infections is successful in many circumstances while it may lead to treatment failure for MRSA infections.

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