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ORIGINAL ARTICLE

Detection of inducible and constitutive clindamycin resistance among *Staphylococcus aureus* isolates in a tertiary care hospital, Eastern India

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ABSTRACT

Introduction: Clindamycin is an excellent drug for skin and soft tissue *Staphylococcus aureus* infections, but resistance mediated by inducible macrolide-lincosamide-streptogramin B ($iMLS_B$) phenotype leads to *in vivo* therapeutic failure even though they may be *in vitro* susceptible in Kirby–Bauer disk diffusion method. **Objective:** The study was aimed to detect the prevalence of $iMLS_B$ phenotype among *S. aureus* isolates by double disk approximation test (*D*-test) in a tertiary care hospital, Eastern India. **Materials and Methods:** A total of 209 consecutive *S. aureus* isolates were identified by conventional methods and subjected to antimicrobial susceptibility testing by Kirby–Bauer disk diffusion method. Erythromycin-resistant isolates were tested for *D*-test. **Results:** From 1282 clinical specimens, 209 nonrepeated *S. aureus* isolates were obtained. Majority of isolates 129 (61.7%) were methicillin-resistant *S. aureus* (MRSA). There was statistically significant difference between outpatients 60.1% and inpatients 39.9% ($P < 0.0001$). From 209 *S. aureus* isolates, 46 (22%) were *D*-test positive ($iMLS_B$ phenotype), 41 (19.6%) were *D*-test negative (methicillin sensitive [MS] phenotype), and 37 (17.7%) were constitutively resistant (constitutive macrolide-lincosamide-streptogramin B phenotype). The incidence of inducible, constitutive, and MS phenotype was higher in MRSA isolates compared to MS *S. aureus* (MSSA). The constitutive clindamycin resistance difference between MSSA and MRSA isolates were found to be statistically significant ($P = 0.0086$). **Conclusion:** The study revealed 22% of *S. aureus* isolates were inducible clindamycin resistant, which could be easily misidentified as clindamycin susceptible in Kirby–Bauer disk diffusion method. Therefore, clinical microbiology laboratory should routinely perform *D*-test in all clinically isolated *S. aureus* to guide clinicians for the appropriate use of clindamycin.

Key words: Constitutive macrolide-lincosamide-streptogramin B phenotype, *D*-test, inducible macrolide-lincosamide-streptogramin B phenotype, methicillin-resistant *Staphylococcus aureus*, sensitive methicillin phenotype, methicillin-sensitive *Staphylococcus aureus*, *Staphylococcus aureus*

INTRODUCTION

Staphylococcus aureus is one of the most common Gram-positive pyogenic bacteria responsible for variety of diseases that range in severity from mild skin soft tissue infections to life-threatening conditions such as endocarditis, pneumonia, and sepsis.[1] In the scenario of increasing methicillin-resistant *S. aureus* (MRSA) infections, the macrolide-lincosamide-streptogramin B (MLS_B) group of antibiotics which are structurally

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different with a same mechanism of action serves as one good alternative.[2] These antibiotics inhibit bacterial protein synthesis in susceptible organisms by reversibly binding to the 23 S ribosomal ribonucleic acid (rRNA) receptor 50 S ribosomal subunit.[3] Among these, clindamycin is the preferred agent due to its excellent pharmacokinetic properties, available in both intravenous and oral formulations with 90% oral bioavailability, less costly, good tissue penetration, and accumulation in deep abscesses, not impeded by high bacterial burden at infection sites and may be able to inhibit production of certain toxins and virulence factors in Staphylococci.[4,5] However, indiscriminate use of MLS_B group of antibiotics has led to an increase in resistance among Staphylococcal isolates.[6]

The MLS_B resistant phenotype in *S. aureus* can be either constitutive MLS_B ($cMLS_B$) or inducible MLS_B ($iMLS_B$). Staphylococci that express ribosomal methylases (*erm*) genes may exhibit *in vitro* resistance to erythromycin, clindamycin, and other drugs of MLS_B group. This resistance is referred to as the $cMLS_B$ phenotype. However, in some Staphylococci, those express *erm* genes require an inducing agent to synthesize methylase for clindamycin resistance. This type of is referred to as $iMLS_B$ phenotype. These organisms are resistant to erythromycin and falsely susceptible to clindamycin *in vitro*.[7] This type of inducible clindamycin resistance cannot be detected by standard Kirby–Bauer disk diffusion method, broth micro dilution testing, automated susceptibility testing devices, or Epsilometer test.[8] Thus, falsely susceptible clindamycin will lose its effectiveness *in vivo* and thereby increase the chance of therapeutic failures.[9]

The double disk approximation test (*D*-test) that involves the placement of an erythromycin disk in proximity to the disk containing clindamycin. As the erythromycin diffuses through the agar, the resistance to the clindamycin is induced, resulting in a flattening or blunting of the clindamycin zone of inhibition adjacent to the erythromycin disk, giving a "*S*" shape to the zone. The Clinical and Laboratory Standards Institute (CLSI) recommends *D*-test, which is a phenotypic screening method for inducible clindamycin resistance.[10] Therefore, all erythromycin resistant *S. aureus* should be tested for inducible clindamycin resistance to prevent clindamycin treatment failures and to report prevalence resistant phenotypes which varies widely. The present study was aimed to determine the constitutive and inducible clindamycin resistance in *S. aureus* isolated from various clinical specimens at a tertiary care hospital in Odisha state, Eastern India.

MATERIALS AND METHODS

Study design, sample collection, and identification of *Staphylococcus aureus*

The prospective study was carried out from September 2013 to August 2014 in the Department of Microbiology at a Tertiary Care Hospital, Odisha state, Eastern India. A total of 1282 clinical specimens were collected, i.e., pus and wound swab, blood, urine, sputum, aspirates, and body fluids from patients with active infections. These specimens were collected from both hospitalized, i.e., surgical, medical, and Intensive Care Units and outpatients. From 1282 clinical specimens, 209 consecutive, nonrepeat *S. aureus* isolates were obtained. These isolates were confirmed as *S. aureus* isolates by conventional catalase, tube and slide coagulase, and DNAse test.[11] Patients from whom *S. aureus* was isolated in the absence of clinical disease suggesting colonization were not included in this study.

Antimicrobial susceptibility testing

All *S. aureus* isolates were subjected to antimicrobial susceptibility testing using Kirby–Bauer disk diffusion method on Mueller-Hinton agar (MHA) plates. Methicillin resistance was determined by disk diffusion method using 30 μg cefoxitin disks. The results were interpreted according to CLSI guidelines. The quality control of erythromycin, clindamycin, and cefoxitin disks were performed with *S. aureus* ATCC 25923 strains. All culture media, antibiotic disks, biochemical reagents, and control strains were procured from Hi Media Labs. Pvt. Ltd., Mumbai, India.

Double disk approximation test (*D*-test)

The isolates that were resistant to erythromycin were tested for inducible clindamycin resistance by double disk approximation test (*D*-test) as per CLSI guidelines. In this test, a 0.5 McFarland's standard suspension of *S. aureus* was prepared and plated onto MHA plate. An erythromycin disk (15 μg) and clindamycin (2 μg) were placed 15 mm apart edge-to-edge on MHA plate.[12] Plates were analyzed after 18 h of incubation at 35°C. Interpretation of zone of inhibition is indicated in [Table 1].

Different phenotypes were detected when erythromycin (15 μg) and clindamycin (2 μg) disks were placed next to each other in MHA plates.

They were interpreted as follows:

- Methicillin-sensitive (MS) phenotype: Isolates resistant to erythromycin but sensitive to with a circular zone of inhibition around clindamycin (*D*-test negative). The organism is interpreted as clindamycin sensitive [Figure 1]
- $iMLS_B$ phenotype: Isolates resistant to erythromycin but

sensitive to clindamycin showing flattening of the zone of inhibition around clindamycin producing a "*D*" shaped blunting toward erythromycin disk (*D*-test positive). The organism is interpreted as clindamycin resistant [Figure 2]

- $cMLS_B$ phenotype: Isolates resistant to both erythromycin and clindamycin with no or small zone of inhibition around clindamycin.

Statistical analysis

GraphPad Inc. statistical software (2236 Avenida de la Playa La Jolla, CA 92037, USA) was used for calculation of *P* value using Fisher's exact test. Statistical significance was defined when $P < 0.05$.

RESULTS

A total of 209 nonrepeated *S. aureus* isolates were obtained from 1282 clinical specimens such as pus and wound swabs, blood, urine, sputum, aspirates, and body fluids which were collected from 770 (60.1%) outpatients and 512 (39.9%) hospitalized patients. Maximum *S. aureus* isolates were detected from pus and wound swabs 53.1%, followed by urine 18.6%, aspirates 12%, and blood 11.5%. From 209 *S. aureus* isolates, 129 (61.7%) were MRSA and rest 80 (39.3%) were MS *S. aureus* (MSSA). Highest number of MRSA was detected from pus and wound swabs 34.4%, followed by urine 10.5% [Table 2]. Majority of *S. aureus* isolates 149 (71.3%) were obtained from hospitalized patients and rest 60 (28.7%) were from outpatients. There was statistically significant difference in *S. aureus,* and MRSA isolates obtained between outpatients and hospitalized patients ($P < 0.0001$).

Table 1: Interpretation of zones of inhibition and *D*-test results in *Staphylococcus aureus*

Drug	Sensitive (S) in mm	Intermediate (I) in mm	Resistant (R) in mm
Cefoxitin (30 µg)	≥22	-	≤21
Erythromycin (15 µg)	≥23	14-22	≤13
Clindamycin (2 µg)	≥21	15-20	≤14
Cefoxitin and *D*-test results			
Cefoxitin-R		MRSA	
Cefoxitin-S		MSSA	
Erythromycin-R, clindamycin-R		$cMLS_B$ phenotype	
Erythromycin-R, clindamycin-S (circular zone)		MS phenotype	
Erythromycin-R, clindamycin-S (flat zone)		$iMLS_B$ phenotype	

According to CLSI guidelines 2010 performance standard for antimicrobial disk susceptibility tests mm- Millimetre, R- resistant, S- sensitive, *D*-test: Double disk approximation test, $iMLS_B$: Inducible macrolide-lincosamide-streptogramin B, MS: Methicillin-sensitive, $cMLS_B$: Constitutive macrolide-lincosamide-streptogramin B, MRSA: Methicillin-resistant *Staphylococcus aureus*, MSSA: Methicillin-sensitive *Staphylococcus aureus*, CLSI: Clinical and Laboratory Standards Institute

All 209 *S. aureus* isolates were subjected to antimicrobial susceptibility testing. One hundred twenty-four (59.3%) were found to be resistant to erythromycin. The resistant erythromycin isolates were tested for *D*-test. The result of the *D*-test revealed that 37 (7 MSSA, 30 MRSA) isolates were resistant to both erythromycin and clindamycin indicating $cMLS_B$ phenotype. Forty-one (12 MSSA, 29 MRSA) isolates were *D*-test negative, indicating MS phenotype. These isolates were truly susceptible to clindamycin. Rest 46 (14 MSSA, 32 MRSA) isolates were *D*-test positive, indicating $iMLS_B$ phenotype [Table 3]. These isolates were actually resistant to clindamycin which would have been easily missed and reported as clindamycin susceptible in regular Kirby–Bauer disk diffusion susceptibility testing. The study also showed that higher percentage MRSA isolates were both constitutive and inducible clindamycin resistant in comparison to MSSA.

DISCUSSION

Antimicrobial resistance in *S. aureus* has become an ever-increasing problem among both outpatients and inpatients of health care facilities. Clindamycin, a

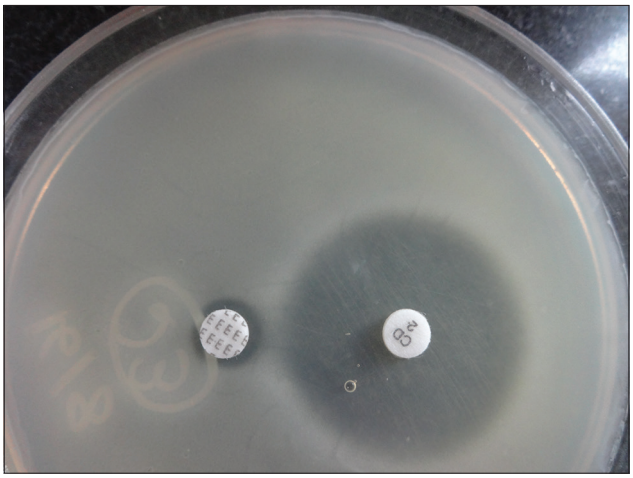

Figure 1: Methicillin-sensitive phenotype (*D*-test negative)

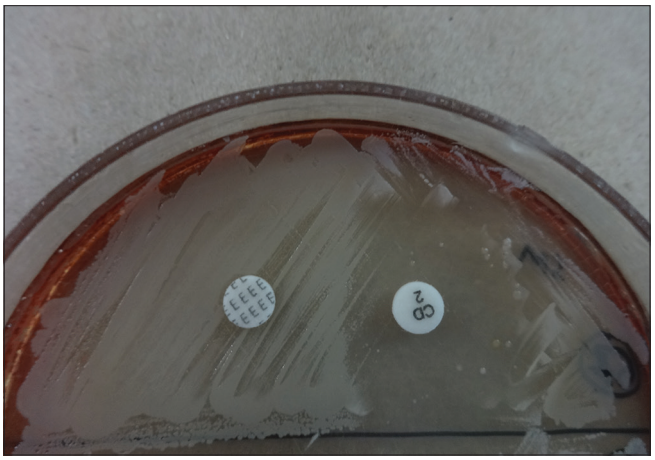

Figure 2: Inducible macrolide-lincosamide-streptogramin B phenotype (*D*-test positive)

Table 2: Distribution of clinical specimens according to their origin and methicillin susceptibility

Type of specimen	*Staphylococcus aureus* (%)				Total (%)
	MSSA		MRSA		
	OPD	IPD	OPD	IPD	
Urine	6	11	7	15	39 (18.6)
Wound swab/pus	13	26	23	49	111 (53.1)
Blood	3	6	3	12	24 (11.5)
Sputum	1	3	1	5	10 (4.8)
Body fluids/aspirates	2	9	1	13	25 (12)
Total (%)	25 (12)	55 (26.3)	35 (16.7)	94 (45)	209 (100)

MSSA: Methicillin-sensitive *Staphylococcus aureus*, MRSA: Methicillin-resistant *Staphylococcus aureus*, OPD: Outpatient department, IPD: Inpatient department

Table 3: Results of the *D*-test

Distribution according to inducible clindamycin resistant phenotype (D-test positive) of MSSA and MRSA isolates			
	D-test positive, *n* (%)	D-test negative, *n* (%)	*P*
MSSA (*n*=80)	14 (17.5)	66 (82.5)	0.2340 (not significant)
MRSA (*n*=129)	32 (24.8)	97 (75.2)	
Total	46 (22)	163 (78)	
Distribution according to constitutive clindamycin resistant phenotype of MSSA and MRSA isolates			
	Constitutively resistant, *n* (%)	Not resistant, *n* (%)	*P*
MSSA (*n*=80)	7 (8.7)	73 (91.3)	0.0086 (significant)
MRSA (*n*=129)	30 (23.3)	99 (76.7)	
Total	37 (17.7)	172 (82.3)	
Distribution according to MS phenotype of MSSA and MRSA isolates			
	Isolates showed MS phenotype, *n* (%)	Not showed MS phenotype	*P*
MSSA (*n*=80)	12 (15)	68 (85)	0.2127 (not significant)
MRSA (*n*=129)	29 (22.5)	100 (77.5)	
Total	41 (19.6)	168 (80.4)	

MSSA: Methicillin sensitive *Staphylococcus aureus*, MRSA: Methicillin resistant *Staphylococcus aureus*, MS: Methicillin sensitive, *D*-test: Double disk approximation test

lincosamide, has always been an attractive opinion for MSSA and MRSA skin and soft tissue infections. It is available in oral and parenteral formulations, 90% oral bioavailability, less costly in comparison to newer drugs, good tissue penetration and may be able to inhibit production of certain toxins and virulence factors in Staphylococci.[4,5] However, resistance to clindamycin is highly variable, and incidence of its resistant phenotypes varies by geographic regions and even between hospitals.[13] These isolates have a high rate of spontaneous mutation during the therapeutic process which would enable them to develop resistance to clindamycin.[14] Thus, the empirical treatment options against *S. aureus* infections have become more limited. Few studies have been performed that report the presence of both constitutive and inducible clindamycin resistance in Eastern India. Therefore, this study was undertaken to detect and report the presence of clindamycin-resistant phenotypes in a tertiary care hospital, Eastern India.

The prevalence of MRSA isolates among *S. aureus* was high (61.7%) in this study, which is similar to Sah *et al.* (61.4%), Mansouri and Sadeghi (56.8%), and Chudasama *et al.* (54.78%).[15-17] Lyall *et al.* had reported a very high percentage of MRSA (91.5%) in their study.[18] Between the mid-1970s and late-1990s, MRSA was considered a healthcare system-associated pathogen resistant to multiple drug classes in addition to β-lactam resistance. However, the emergence of community-associated MRSA in the past years among patients without obvious risk factors has shifted the management of Staphylococcal infections from various β-lactam first line antibiotics to MLS group of antibiotics.

In our study from 209 *S. aureus*, 124 (59.3%) isolates were resistant to erythromycin. All erythromycin resistants were subjected to *D*-test. A positive *D*-test indicates that there is existence of inducible clindamycin resistant phenotype. Our study revealed 46 (22%) of *S. aureus* isolates were *D*-test positive. In different studies, the inducible clindamycin ranged from 0% to 37.1% [Table 4].[7,12,15-27] It was observed that percentage of inducible clindamycin resistance was higher among MRSA (24.8%) compared to MSSA (7.5%). The difference between MSSA and MRSA isolates were not statistically significant ($P = 0.2340$). Most of the authors have reported higher inducible clindamycin-resistant isolates in MRSA compared to MSSA [Table 4]. On the contrary, Bottega *et al.* and Sasirekha *et al.* had shown a higher percentage of inducible resistance in MSSA compared to MRSA.[19,20] The different patterns of resistance observed in various studies are due to resistance varies by geographical regions, age groups, antibiotic prescription patterns, methicillin susceptibility, and even from hospital to hospital. This type of inducible clindamycin resistance can only be detected phenotypically by placing erythromycin and clindamycin disk adjacent to each other in MHA plate by disk diffusion method. Therefore, the *D*-test can minimize clindamycin treatment failures.

Constitutive clindamycin resistance in our study was observed in 7 (8.7%) of MSSA and 30 (23.3%) of MRSA isolates, which is similar to Chudasama *et al.*[17] The constitutive clindamycin resistance difference between MSSA and MRSA isolates were found to be statistically significant ($P = 0.0086$). In different studies, the constitutive clindamycin resistance was reported varies from 1.77% to 52.3% [Table 4].[7,12,15-27]

Truly clindamycin-sensitive isolates, which exhibit MS phenotype, were present in 15% of MSSA and 22.5% of MRSA isolates in our study. This result is in close agreement with Sah *et al.*[15] In different studies, authors have reported the MS phenotype varies between 0.7% and 44.6%

Table 4: Distribution of inducible, constitutive and MS clindamycin resistant phenotypes in *Staphylococcus aureus* from various studies across the globe

Author and reference number	Place and year of study	Total number of *Staphylococcus aureus* studied	MSSA (%)			MRSA (%)		
			$iMLS_B$	$cMLS_B$	MS	$iMLS_B$	$cMLS_B$	MS
Sah *et al*.[15]	Bhairahawa, Nepal in 2015	140	0	9.3	14.8	14	12.8	19.8
Kumurya and Ado[21]	Kano, Nigeria in 2015	125	0	42.7	2.4	7	44.1	2.3
Bottega *et al*.[19]	Santa Maria, Brasil in 2014	140	5.8	3.6	0.7	2.1	14.3	0.7
Mansouri and Sadeghi[16]	Kemran, Iran in 2014	162	4.28	2.85	7.14	11.95	47.82	10.87
Seifi *et al*.[22]	Mashhad, Iran in 2012	211	4.88	7.3	9.76	20.45	52.3	15.91
Mokta *et al*.[23]	Shimla, India in 2015	350	9.32	13.43	6.71	28.04	29.26	13.41
Banik *et al*.[12]	Shillong, India in 2015	243	5.31	1.77	15.05	15.38	30	8.47
Phukan *et al*.[24]	Assam, India in 2015	215	5.5	3.6	12.8	7.5	16.9	6.3
Koppada *et al*.[25]	Vijayawada, India in 2015	164	12.1	4.8	20.7	8.5	12.8	13.4
Chudasama *et al*.[17]	Ahmedabad, India in 2014	230	15.38	9.61	16.34	32.53	15.07	25.39
Sasirekha *et al*.[20]	Bengaluru, India in 2014	153	8.49	7.84	13.07	0.65	5.22	5.88
Lyall *et al*.[18]	Ludhiana, India in 2013	593	34.61	7.5	46	33.2	22.1	44.6
Juyal *et al*.[7]	Garhwal Hills, India in 2013	239	6.3	12.5	24.5	19.4	29	38.7
Lall and Sahni[26]	Delhi, India in 2013	305	6	4.8	31.5	37.1	16.6	22.8
Kumar *et al*.[27]	Kolkata, India in 2012	195	11.8	11.8	17.6	8.5	12.8	13.4
Present study	Cuttack, India	209	17.5	8.7	15	24.8	23.2	22.5

MS: Methicillin-sensitive, $iMLS_B$: Inducible macrolide-lincosamide-streptogramin B, $cMLS_B$: Constitutive macrolide-lincosamide-streptogramin B, MSSA: Methicillin-sensitive *Staphylococcus aureus*, MRSA: Methicillin resistant *Staphylococcus aureus*

[Table 4].[7,12,15-27] This result implies that clindamycin can be safely and effectively instituted as a therapeutic option in this group of patients even in the presence of macrolide resistance.

CONCLUSION

Due to the emergence of resistance to antimicrobial agents among *S. aureus,* accurate antimicrobial susceptibility data is an essential factor in making appropriate therapeutic decisions. Overall, the inducible clindamycin-resistant isolates obtained in our study were 22%. If *D*-test would not have been performed, nearly one-fourth of inducible clindamycin resistant *S. aureus* could have been easily misidentified as clindamycin susceptible leading to therapeutic failure. Thus, simple and reliable *D*-test can be incorporated into routine Kirby–Bauer disk diffusion method in clinical microbiology laboratory. This enables the clinicians in judicious use of clindamycin, as clindamycin is not a suitable drug for *D*-test positive *S. aureus* isolates. Therefore, the clindamycin treatment failure could be minimized.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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