

## INDUCIBLE CLINDAMYCIN RESISTANCE IN STAPHYLOCOCCUS AUREUS IN A TERTIARY CARE HOSPITAL

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**Abstract**

**Background:** Staphylococcus aureus is a one of the most common pyogenic organism causing infections in humans. With increasing incidence of methicillin resistant Staphylococcus aureus [MRSA], treatment options are also limited. Clindamycin could be used for the treatment of MRSA. Inducible Clindamycin resistance can lead to treatment failure. The aim is to find out prevalence of inducible clindamycin resistance by disk approximation test [D test]. **Materials and Methods:** Out of 204 isolates of Staphylococcus aureus were tested for inducible Clindamycin resistance by D test. **Result:** A total of 204 clinical isolates of Staphylococcus aureus. Among the S.aureus 45(22%) were MRSA ,159 [77.94%] were MSSA. Among the MRSA 17 [37.77%] were iMLS<sub>B</sub>, among the MSSA 15 [9.43%] were iMLS<sub>B</sub>. **Conclusion:** Inducible clindamycin detection by simple D test,helps to avoid therapeutic failure with clindamycin.

## INTRODUCTION

Staphylococcus aureus is one of the most common organisms causing infections in humans worldwide.<sup>[1]</sup> Staphylococcus aureus infections are treated by various antibiotics. Clindamycin is one of the potent antibiotics commonly used in the community and hospital acquired Staphylococcal infections. Clindamycin with its excellent pharmacokinetic properties, is a common choice to treat soft tissue and skin infections.<sup>[1,2,3]</sup> It can be utilized for outpatient as well as in patient, because of its excellent tissue absorption.<sup>[4]</sup>

Macrolide, lincosamide, streptogramin [MLS<sub>B</sub>] antibiotics are commonly used in treatment of Staphylococcal infections. However widespread usage of MLS<sub>B</sub> antibiotics, has led to an increase resistance to these antibiotics.<sup>[5,6]</sup> Increasing prevalence of methicillin resistance in Staphylococcus aureus is quite common. Clindamycin is the one of the drug used for MRSA infections. But if there exist an inducible clindamycin resistance in Staphylococcus aureus, the therapeutical use of clindamycin is limited.<sup>[7]</sup>

Macrolide and lincosamide resistance are mainly due to one of these three mechanisms.<sup>[8]</sup>

**Target site modification:** Ribosomal mutation or methylation which prevents binding of antibiotics to its ribosomal target. This is the most prevalent mechanism of resistance to Macrolides and Lincosamides encoded by erm genes.

**Efflux of antibiotic:** Encoded by msr A gene.

**Drug inactivation:** Encoded by lnu gene.

Modification of ribosomal target which confers broad spectrum resistance to Macrolides and lincosamides is encoded by a variety of erm genes [Erythromycin ribosome methylase]. Erm A and ermC are typical Staphylococcal genes. This mechanism can be constitutive [cMLS<sub>B</sub>], always producing the rRNA methylase or inducible [iMLS<sub>B</sub>] that is producing methylase only in the presence of an inductor.<sup>[2]</sup> It has been demonstrated that clindamycin treatment in patient with inducible [iMLS<sub>B</sub>] may lead to therapeutic failure.<sup>[9]</sup> The best way to detect such a strains is a Disc approximation test or D test.<sup>[10]</sup> High prevalence of clindamycin resistance of Staphylococcus aureus may impact the empirical therapy.<sup>[11]</sup> Frequencies of different resistance phenotypes vary by geographical regions, hospital, patient group, bacterial strains.<sup>[12]</sup>

## MATERIALS AND METHODS

This study included 204 non duplicate isolates of Staphylococcus aureus isolated from pus, wound, blood, urine, sputum, throat swab, ear swab, vaginal swab. The isolates were identified using conventional method and their susceptibility testing was performed by Kirby-Bauer disc diffusion method on Muller –Hinton agar [Himedia labs, Mumbai] plate as per CLSI guidelines.<sup>[13]</sup>

Methicillin resistance was determined by the disk diffusion method using 30 microgram cefoxitin disc. All the isolates were tested for erythromycin

resistance and inducible clindamycin resistance by D-test method on Muller-Hinton agar plate.

Double disc diffusion test was carried out as described in the CLSI recommendations. Erythromycin disc [15microgram] and Clindamycin [2microgram] were used for the disk approximation test, which were placed 15mm apart [edge to edge] in the same plate of MHA. Isolates with inducible clindamycin resistance showed flattening of inhibition zone [D-shaped] around clindamycin [iMLS<sub>B</sub>].<sup>[10,13]</sup>

The quality control for the erythromycin, clindamycin and cefoxitin [himedia labs] was performed with S.aureus 25923. The test allows for identification of four different phenotypes:

The iMLS<sub>B</sub>phenotype[inducible] – Resistant to erythromycin and susceptible to clindamycin with a D zone of inhibition around the clindamycin disc.

The MS<sub>B</sub> phenotype- Resistant to erythromycin and susceptible to clindamycin without D zone.

The constitutive MLS<sub>B</sub> phenotype- Resistant to both erythromycin and clindamycin.

The susceptible [S] phenotype – Sensitive to both clindamycin and erythromycin.<sup>[10,13]</sup>

**Statistical analysis:** This was a cross sectional study done in microbiology department, SMIMS, Kulasekhram, Tamilnadu, India from January 2022 to June 2022. All consecutive Staphylococcus aureus isolated in this period were included in this study. The study was done on Staphylococcus aureus isolated from clinical samples received in the central laboratory and there was no direct involvement of living subjects. Hence, consent and Institutional Ethical Committee (IEC) approval was not obtained. Data entry was done in Microsoft Excel 2010 and data analysis was done on SPSS software trial version 20.0. Descriptive statistics and chi-square tests were used for data analysis. Significant level was fixed at 5%,ie,p value <0.05 was considered statistically significant.

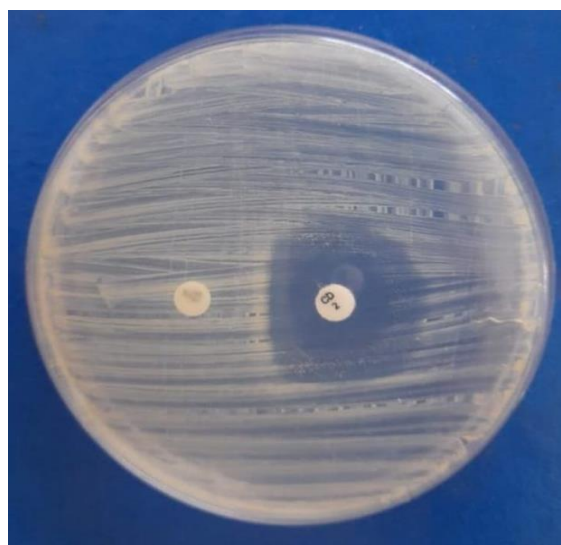
## RESULTS

Of the 204, Staphylococcus aureus, methicillin resistant Staphylococcus aureus were 45[22%], and Methicillin sensitive S.aureus were 159[77.94%] [Table1].

The inducible clindamycin resistance [iMLS<sub>B</sub>] among the S.aureus was found to be 32[15.68%] [Table3]. Among the MRSA, inducible clindamycin resistant was found to be 17[37.78%] and MSSA it was 15[9.43%], by D-test [Table 2] [Figure1]

Among the S.aureus constitutive MLS<sub>B</sub> phenotype was 16 [7.8%], inducible clindamycin resistance phenotype [iMLS<sub>B</sub>] observed to be 32 [15.68%] and MS phenotype was 92 [45%] [Table 3].

Of all isolates tested ,31.4% were sensitive to both [Erythromycin and Clindamycin] [Table:3].



**Figure 1: D zone around Clindamycin indicates inducible Clindamycin resistance (MLS<sub>B</sub>i)**

**Table 1: Distribution pattern of MRSA and MSSA**

Organism	Number	Percentage (%)
MRSA	45	22%
MSSA	159	77.94%

MRSA- Methicillin resistant Staphylococcus aureus.

MSSA- Methicillin sensitive Staphylococcus aureus.

**Table 2: Susceptibility to ERY and CL in MRSA and MSSA clinical isolates**

Phenotype	MRSA (%)	MSSA (%)	χ <sup>2</sup> value	P value	Odds ratio	95% CI
E-S, CD-S	2 (4.44)	62 (38.99)	19.45	0.001*	0.073	0.017-0.311
E-R, CD-R	12 (26.67)	4 (2.51)	28.30	0.001*	14.09	4.27- 46.427
E-R, CD-SD test positive	17 (37.78)	15 (9.43)	18.196	0.001*	0.158	0.065- 0.389
E –R, CD-SD test negative	14 (31.11)	78 (49.06)				
Total	45	159	204			

E: Erythromycin; CD: clindamycin; S: Sensitive; R- Resistant; MRSA- Methicillin resistant Staphylococcus aureus; MSSA- Methicillin sensitive Staphylococcus aureus; CI-confidence intervals; \*very high statistical significance (p<0.01).

**Table 3: Distribution of phenotype pattern of all clinical isolates**

Phenotypes	Number of isolates	Percentage
Inducible Clindamycin resistance	32	15.68
Constitutive Clindamycin resistance	16	7.8
MS phenotype	92	45.09
ER=-S, CD-S	64	31.4

## DISCUSSION

Frequencies of different resistance phenotypes vary by geographical regions, hospital, patient group, bacterial strains and bacterial susceptibility pattern.<sup>[12]</sup>

In the present study the prevalence of the iMLS<sub>B</sub>, cMLS<sub>B</sub>, MS<sub>B</sub> resistance phenotype was 15.7%, 7.8%, 45.1% respectively.

In a study from Iran reports prevalence of iMLS<sub>B</sub>, cMLS<sub>B</sub>, MS<sub>B</sub> were 9.7%, 5.2%, 5.3% respectively.<sup>[2,14,15]</sup> A study from Punjab, India reported the prevalence pattern wherein of iMLS<sub>B</sub>, cMLS<sub>B</sub> and MS<sub>B</sub> phenotype were 20.7%, 18.40% and 20.13% respectively.<sup>[16]</sup> In Turkey Yilma et al reported a higher percentage of inducible clindamycin resistance in MRSA compared to MSSA [24.4%, 14.8%].<sup>[17]</sup> In my study also inducible clindamycin resistance is high in MRSA compared to MSSA (37.78%, 9.43% respectively), which was statistically significant ( $p < 0.01$ ,  $Z^2 = 18.196$ , Odds ratio- 0.158, CI -0.065-0.389). The high prevalence of clindamycin resistance may impact the empirical therapy and it leads to therapeutical failure for staphylococcus infections.<sup>[11]</sup> Such high resistance cases when studied genotypically shows the presence of erm A gene on the transposon TN554 with SCC mec.<sup>[18]</sup>

Performing D-test on a routine antibiotic susceptibility plate save time, material, man power as inducible resistance can be reported simultaneously along with other susceptibility results.<sup>[19]</sup>

### Limitations

Genotypic study not done for inducible clindamycin resistance phenotype due to lack of financial funding.

## CONCLUSION

Our study highlights high prevalence of inducible clindamycin resistance among Staphylococcus aureus, especially MRSA (37.78%). Hence it is mandatory to perform D-test on a routine antibiotic susceptibility plate for clinical isolates on the routine basis to avoid therapeutic failure with clindamycin.

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