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Inducible Clindamycin Resistance in *Staphylococcus Aureus*: A Study from Western India

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Abstract: **The resistance to antimicrobial agents among Staphylococci is an increasing problem. The resistance to macrolide can be mediated by *msr a* gene coding for efflux mechanism or via *erm* gene encoding for enzymes that confer inducible or constitutive resistance to macrolide, lincosamide and Type B streptogramin. The present study was aimed to find out the percentage of *Staphylococcus aureus* having inducible clindamycin resistance (iMLS $_B$) in our geographic area using D-test.**

Keywords: **inducible clindamycin resistance (iMLS $_B$), Methicillin resistant Staphylococcus aureus (MRSA), Methicillin sensitive Staphylococcus aureus (MSSA), D-test.**

I. INTRODUCTION

The macrolide - lincosamide - streptogramin B family of antibiotics is commonly used in treatment of staphylococcal infections.[1] Erythromycin (a macrolide) and clindamycin (a lincosamide) represent two distinct classes of antimicrobial agents that act by binding to the 50s ribosomal subunit of bacteria to inhibit its protein synthesis. Macrolide resistance in *Staphylococcus aureus* is by diverse mechanisms. Macrolide resistance may be constitutive (MLSBc) or inducible (MLSBi). Among MLSBi strains, an inducer promotes production of methylase by *erm* genes and subsequent methylation of the 23S ribosome, thus making the strain fully resistant to the lincosamides (e.g., clindamycin) and group B streptogramins. Phenotypically, these MLSBi strains appear to be resistant to erythromycin and susceptible to clindamycin on routine antibiotic susceptibility testing. Inducible resistance can be expressed during a double-disk diffusion test (D test),[2] in which an erythromycin disk will induce clindamycin resistance. Therapeutic failure caused by MLSB inducible resistance is being more commonly reported.[1]

II. AIM

The present study was aimed to find out the percentage of Staphylococcus aureus having inducible clindamycin resistance (iMLS(B)) in our geographic area using D-test. Also, we tried to ascertain the relationship between Methicillin-resistant Staphylococcus aureus (MRSA) and inducible clindamycin resistance**.**

III. MATERIALS AND METHODS

Total 17,185 specimens like pus, wound swab, blood, endotracheal aspirate, body fluids, urine, stool etc coming to the laboratory were received in the Microbiology Laboratory, Government medical college, Aurangabad , Maharashtra, India, during October 2010 to October 2012. The samples were processed as per standard procedures.[3] Direct smear of each specimen (except blood) was stained with Gram's stain and findings noted. Each sample was cultured on Blood agar, MacConkey's agar aerobically, overnight at 37^0C. Colony morphology & Gram stain smear of the colonies was observed. Organisms having following colony characters were considered to be suggestive of *Staphylococcus* sp.: Blood agar colony – small (1-3mm in diameter), circular, white to golden yellow in colour, smooth, low convex, glistening, opaque

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with or without β haemolysis. These colonies from blood agar were picked for Gram's staining. Gram staining was done by using Huckers modification[4] to observe gram positive cocci approximately of 1µm diameter in size, arranged in clusters. Colonies suggestive of staphylococci were subjected to slide catalase and tube coagulase test. Positive catalase and coagulase test were considered as Staphylococcus aureus.[3]

A total of 1258 Staphylococcus aureus isolates from various clinical samples were subjected to Kirby Bauer disk diffusion method using cefoxitin 30µg along with routine antimicrobials including D-test. [4]

IV. RESULTS

Among 1258 Staphylococcus aureus strains, 357 (28.37%) were found to be MRSA and among MRSA isolates 129 were D-test positive. Also, MRSA isolates showed both higher inducible resistance and constitutive resistance to clindamycin as compared to Methicillin-sensitive Staphylococcus aureus (MSSA). All isolates of Staphylococcus aureus showed 100% sensitivity to vancomycin and linezolid.

Table: 1 Comparison of MLSBi & MLSBc resistance in MSSA & MRSA

	MSSA	**MRSA**	Total
MLSBi	167 (52.51%)	129 (71.27%)	296
MLSBc	151	52	203
	318	181	499

$\chi 2=16.81$, df=1, p=0.00004124

IV. DISCUSSION

Clindamycin (lincosamide group) is considered a useful alternate drug in penicillin-allergic patients in the treatment of skin and soft tissue infections. The good oral absorption of clindamycin makes it an attractive option for use in outpatients or as follow-up treatment after intravenous therapy (de-escalation). [1] Clinically, bacterial strains exhibiting MLSBi have a high rate of spontaneous mutation to constitutive resistance, which could be selected by use of clindamycin.[2]

Clinically, bacterial strains exhibiting MLSBi have a high rate of spontaneous mutation to constitutive resistance, which could be selected by use of clindamycin.[2] In such situation there is clinical failure during therapy. Therapeutic failure caused by MLSB inducible resistance is being more commonly reported.[1]

In our study inducible MLSB resistance was found to be 52.51% in MSSA, whereas in MRSA it was 71.27%. We found inducible MLSB resistance was higher than constitutive resistance in both MSSA & MRSA. Similar findings are reported by others with MLSBi phenotype ranging from 30 to 70%.[1,5,6,7]

Use of D test in a routine laboratory will enable us in guiding clinicians about judicious use of clindamycin. Clindamycin is not a suitable drug for D test positive isolates while it can definitively prove to be a drug of choice in case of D test negative isolates. The D-test is an easy, sensitive, and reliable means for detection of MLSBi strains in a clinical laboratory setting without specialized testing facilities.It is important for laboratories to be aware of the local prevalence of MLSBi isolates.[8]

V. CONCLUSION

The prevalence of MLSBi may change over time with the emergence of strains with different sensitivity patterns, so periodic surveys should be performed if testing is not a routine.[8] In hospital like ours where inducible MLSB strains was found more than 50% in both MSSA & MRSA, we recommend to perform D-test routinely. Inducible clindamycin resistance as noted by a positive D test should be reported as resistant. A comment should be added that ―this isolate is presumed to be resistant based on detection of inducible resistance. Clindamycin may still be effective in some patients.[4] Empirical outpatient treatment options for staphylococcal infections have become more limited as concerns about the prevalence of MRSA have increased.[9] Clindamycin should be kept as a reserve drug and be usually advocated in severe MRSA infections depending upon the antimicrobial susceptibility results.

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