Original Article

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Microbiology Section

Prevalence of Inducible Clindamycin Resistance in *Staphylococcus*: A Study from a Rural Teaching Tertiary Care Hospital in Southern Haryana

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ABSTRACT

Introduction: Clindamycin is the most commonly prescribed Macrolides, Lincosamides and Streptogramin-B (MLSB) antibiotics to treat staphylococcal infections. It has excellent pharmacokinetic properties. *Staphylococcus* species shows either constitutive (MLSBc) or inducible (MLSBi) clindamycin resistance. Routine D-test recommended by Clinical Laboratory and Standard Institute (CLSI) can detect MLSBi phenotype and prevent treatment failure.

Aim: To identify inducible clindamycin resistance in Staphylococci in a rural teaching Tertiary Care Hospital.

Materials and Methods: It was a prospective, cross-sectional study. The clinical samples were cultured on blood agar and MacConkey agar. *Staphylococcus* isolates were identified based on their colony characteristics, gram stain and standard biochemical test. Antimicrobial susceptibility test was performed by Kirby Bauer's disc diffusion method. To detect Methicillin resistance Cefoxitin disc (30 µg) was used. The isolates that were Erythromycin resistant and Clindamycin sensitive were further subjected to D test. CLSI 2019 guidelines were followed for performing the tests and its interpretation. Epi-info (version 7.2.3.1) Centre for Disease Control and Prevention (CDC), Atlanta, Georgia was used to analyse the data and interpretation of the results.

Results: Total 150 Staphylococci were isolated from different samples. *Staphylococcus aureus* were 70% and Coagulase negative *Staphylococcus* (CoNS) were 30%. Pus was the most common specimen from which 43% Staphylococci was isolated. Sensitivity to vancomycin and linezolid were 100%. *Staphylococcus aureus* (38%) and CoNS (33%) were Methicillin resistant. Overall (63%) of *staphylococcus* isolates were resistant to erythromycin. The different susceptibility patterns to clindamycin in both *Staphylococcus aureus* and CoNS were noted. MLSBc phenotype was most prevalent (37.3%) followed by MS (13.4%) and MLSBi (12%) among erythromycin resistant *Staphylococcus* isolate. Sensitive (S) phenotype was detected in 56 (37%). MLSBi was more frequent in Methicillin Resistant *Staphylococcus aureus* (MRSA) (23%) and MRCoNS (27%) than in MSSA (5%) and MSCoNS (7%).

Conclusion: D-test should be performed routinely to avoid false susceptible results leading to treatment failure.

Keywords: Disc approximation test, Inducible macrolides, Lincosamides, Macrolides, Streptogramin-B

INTRODUCTION

Staphylococcus aureus and CoNS are causative agents for wide spectrum of infections. It causes minor skin and soft tissue infections to life threatening conditions such as endocarditis, pneumonia and septicaemia [1,2]. The emergence of drug resistance among Staphylococci is of great concern. Increased incidence of Methicillin resistance among Staphylococci is a growing problem and they are commonly reported as Multi-Drug Resistant (MDR) microorganisms [3,4]. These microorganisms are resistant to at least one antimicrobial agent in three or more antimicrobial class or they are Methicillin resistant [5].

There has been renewed interest in MLSB group of antibiotics for management of Staphylococcal infections as some studies have reported resistance to newer drugs like vancomycin, linezolid and daptomycin [6,7]. The MLSB antibiotics are structurally unrelated; however, they have similar antimicrobial action. They inhibit bacterial protein synthesis by binding to 23s rRNA, which is a part of large ribosomal subunit [3]. Clindamycin is the most commonly used MLSB antibiotic in the treatment of staphylococcal infections particularly methicillin resistant isolates due to its excellent pharmacokinetic properties [8].

Widespread use of MLSB has led to macrolide resistance in *Staphylococcus*. This may be due to activation of efflux pump encoded by *msrA* gene. Second mechanism of resistance is controlled by a variety of *erm* genes expressing enzymes that confer constitutive or inducible resistance to MLSB agents. The third mechanism of drug modification is mediated by *lnu(A)* gene which code for lincosamide nucleotidyl transferases, with resistance to lincosamides only but not to the other groups [9]. r-RNA methylase is always produced in constitutive resistance, where as in inducible, an inducing agent is required for methylase production. Erythromycin is an effective inducer than clindamycin. Invitro, isolates of *Staphylococcus aureus* with constitutive resistance shows resistance to both clindamycin and erythromycin whereas the isolates those with inducible resistance shows resistance to only erythromycin and sensitivity to clindamycin [9,10].

Routine antimicrobial susceptibility tests can detect constitutive resistance but unable to detect inducible resistance. The CLSI has recommended the Erythromycin Clindamycin disc approximation test (D-zone test) to detect the inducible clindamycin resistance [1,2,8]. Rate of clindamycin resistance varies from place to place, so a local data is important to guide empirical treatment. Nuh in Haryana is one of the most remote and backward districts of India due to poor health and education infrastructure. The majority of population lives in villages [11]. Therefore, this study was planned with the aim to identify inducible clindamycin resistance in Staphylococci at rural teaching tertiary care hospital.

MATERIALS AND METHODS

Study design and setting: This was a prospective, cross-sectional study done in Department of Microbiology, SHKM GMC, Nalhar, Haryana, India from March 2019 to August 2019. All consecutive *Staphylococcus* isolated during this period were included in this study. There was no direct involvement of living subjects and study was done on *Staphylococcus* isolates from samples received in the laboratory and processed. Hence, consent and Institutional Ethical Committee (IEC) approval was not obtained.

Procedure: All samples received were cultured on Blood and MacConkey agar and incubated at 37°C for 18-24 hours. Staphylococcal isolates were identified by a battery of standard biochemical tests. Antimicrobial susceptibility testing was performed by Kirby-Bauer's disc-diffusion method on Muller Hinton Agar. Cefoxitin (30 µg) disc was used to detect Methicillin resistance. The isolates that were erythromycin resistant and clindamycin sensitive were further subjected to D test [12]. The erythromycin disc (15 µg) was placed 15 mm apart, edge to edge from the clindamycin disc (2 µg) on the inoculated Muller Hinton Agar plate and was incubated at 37°C for 18-24 hours. After incubation, the plates were examined to detect any flattening or blunting of the shape of the clindamycin zone. CLSI 2019 guidelines were followed for performing the tests and its interpretation [12]. All the media and antibiotic discs used were of Hi-media. *Staphylococcus aureus* ATCC 25923 was used for quality control.

Different phenotypes observed and interpreted were [1,9,12]:

Sensitive (S) phenotype: Inhibition of growth around Erythromycin (zone size ≥23 mm) and Clindamycin (zone size ≥21 mm). Sensitive to both E and CD.

Constitutive MLSB phenotype (MLSBc): Presence of growth around Erythromycin (zone size ≤13 mm) and Clindamycin (zone size ≤14 mm). Resistant to both E and CD.

Inducible MLSB phenotype (MLSBi): Presence of growth around Erythromycin (zone size ≤13 mm) and clearance around clindamycin (zone size ≥21 mm), giving D shaped zone of inhibition around clindamycin with flattening towards erythromycin disc (D test positive).

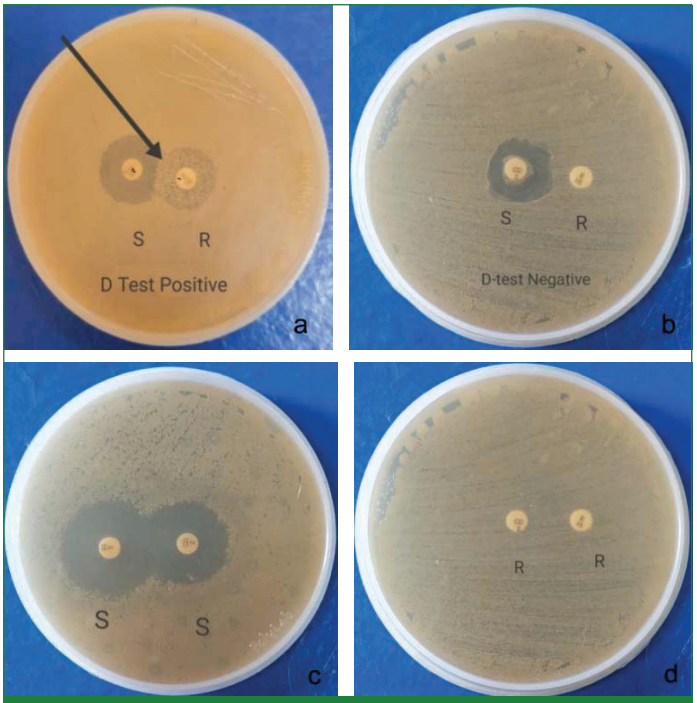
MS phenotype: Presence of growth around erythromycin (zone size ≤13 mm) and inhibition of growth around clindamycin (zone size ≥21 mm) and giving circular zone of clearance around clindamycin (D test negative) [Table/Fig-1].

STATISTICAL ANALYSIS

The data were entered in spread sheet. The data were analysed using epi-info (version 7.2.3.1) CDC, Atlanta, Georgia. Univariate analysis were summarised using numbers and percentages. Bivariate analysis was done using Chi-square statistics. Statistically significant association was set with p-value <0.05.

RESULTS

Among the 150 isolates studied, 92 (61%) were isolated from males and 58 (39%) from females. Staphylococcal isolates were most commonly isolated in the age group 21-40 years (67, 45%), followed by 0-20 year (47, 31%), 41-60 years (25, 17%) and >60 years (11, 7%). Among the 150 isolates, 105 (70%) were *Staphylococcus* aureus and 45 (30%) were CoNS. Pus was the most common specimen from which 64 (43%) Staphylococci were isolated, followed by blood 42 (28%), urine 36 (24%) and others (Body fluid, endotracheal tube tip, catheter tip) 8 (5%). Forty (38%) out of 105 *Staphlococcus aureus* and 15 (33%) out of 45 CoNS were Methicillin resistant [Table/Fig-2]. Sensitivity to vancomycin and linezolid were 100%. Seventy nine percent *Staphylococcus* aureus and 71% of CoNS were sensitive to gentamicin. Ciprofloxacin resistance was seen in 78% of *Staphylococcus aureus* and 66% of CoNS. Amoxyclav was 47% sensitive to *Staphylococcus aureus* and 42% sensitive to CoNS. Penicillin showed 4% sensitivity to both. Erythromycin resistance was detected in 60% *Staphylococcus aureus* isolates and 69% of CoNS. Overall, 94 (63%) of Staphylococcal isolates were resistant to erythromycin.



[Table/Fig-1]: Different phenotypes of staphylococcal isolates; a) MLSBi-inducible clindamycin resistance (E=Resistant CD=Sensitive with positive D test; b) MS-(E=Resistant and CD=Sensitive); c) S-(E=Sensitive and CD=Sensitive); d) MLSBc-constitutive clindamycin resistance (E=Resistant and CD=Resistant. E-Erythromycin; CD-Clindamycin).

Sample source	Total no of samples	MRSA	MSSA	MRCoNS	MSCoNS
Pus	64 (43%)	25	33	2	4
Blood	42 (28%)	8	20	4	10
Urine	36 (24%)	4	12	6	14
Body fluid	4 (3%)	1	0	1	2
ET tip*	2 (1%)	2	0	0	0
Catheter tip	2 (1%)	0	0	2	0
Total	150	40/105 (38%)	65/105 (62%)	15/45 (33%)	30/45 (67%)

[Table/Fig-2]: *Staphylococcus* isolated from specimen and their methicillin susceptibility.
*ET tip: Endotracheal tube tip

The frequency of susceptibility pattern to erythromycin as well as different patterns of susceptibility to clindamycin in both *Staphylococcus aureus* and CoNS was noted [Table/Fig-3]. The inducible clindamycin resistance (D-test positive) was more commonly seen in MRSA and CoNS (MRCoNS) that is 23% and 27% as compared to 5% and 7% among Methicillin sensitive *Staphylococcus aureus* (MSSA) and CoNS (MSCoNS) [Table/Fig-4].

	Phenotypes			
	MLSBc (E-R, CD-R)	MLSBi (E-R, CD-S. D-test-positive)	MS (E-R, CD-S. D-test-negative)	S (E-S, CD-S)
S.aureus	35 (33.3%)	12 (11.4%)	16 (15.2%)	42 (40%)
CoNS	21 (46.7%)	6 (13.3%)	4 (8.9%)	14 (31.1%)
Total	56 (37%)	18 (12%)	20 (13.4%)	56 (37%)

[Table/Fig-3]: Phenotypes of staphylococcal isolates.

DISCUSSION

The present study was done in a remote, rural, most underdeveloped district of Haryana in India. There is an emergence of Methicillin resistant staphylococcal infections. Clindamycin is a good option which should be used judiciously for infections caused by Methicillin resistant Staphylococci. Clindamycin is preferred for outpatient therapy and changeover after intravenous antibiotics as it has

Methicillin susceptibility	D-test (18)		Total	Chi-square value	p-value
	Positive	Negative			
MRSA	9 (23%)	31(77%)	40	7.8245	0.005
MSSA	3 (5%)	62 (95%)	65		
MRCoNS	4 (27%)	11 (73%)	15	3.46	0.062
MSCoNS	2 (7%)	28 (93%)	30		

[Table/Fig-4]: Pattern of inducible clindamycin resistance in staphylococci with respect to methicillin susceptibility.

good oral bioavailability. D-test recognises iMLSB phenotype which cannot be done by using routine susceptibility test methods. It is important to identify iMLSB phenotype and to prevent treatment failure [1,2,8,12,13].

Staphylococcus was isolated most commonly from pus 64 (43%) in the present study. Juyal D et al., from Uttarakhand also isolated *Staphylococcus* from pus specimen (46.3%). Similarly, Mohanasoundaram KM from Tamil Nadu and Jangla MS et al., from Maharashtra reported pus as most common source that is 35% and 29% respectively. Ciraj AM et al., from Karnataka reported urine (50%) was the most common source of staphylococcal isolates [1,3,8,14].

As per ICMR 2018 report, the prevalence of MRSA in India was 23.8%-52.8% [15]. In the present study, the prevalence of MRSA is 38%. This was similar to the findings of Mohanasoundaram KM (39%), Singh T et al., from Madhya Pradesh (38%) and Shetty J et al., from Uttar Pradesh (37%) [3,13,16]. Lower prevalence of Methicillin resistance in *Staphylococcus aureus* was observed by Juyal D et al., and Ciraj AM et al., that is 13% and 17%, respectively [1,8].

As per ICMR 2018 report, resistance in CoNS was upto 72.1% [15]. The present study observed 33% Methicillin resistance among CoNS. Juyal D et al., reported MRCoNS 28% whereas Ciraj AM et al., reported MRCoNS in only 4% [1,8]. Some other studies have reported higher prevalence of MRCoNS ranging from 50%-68.67% [2,17,18]. All the isolates were sensitive to vancomycin and linezolid whereas only 4% of them showed sensitivity to penicillin. Present study detected erythromycin resistance in 60% *Staphylococcus aureus* isolates and 69% of CoNS. This was higher than that observed in previous studies [1,3,4,8].

In the present study, the most common phenotype among erythromycin resistant staphylococcal isolate was MLSBc type 56 (37.3%), followed by MS 20 (13.3%) and MLSBi 18 (12%). Among erythromycin sensitive group, S phenotype was detected in 56 (37%). Pardo L et al., from Uruguay, Pereira JN et al., from Brazil and Sedaghat H et al., from Iran in their studies also observed MLSBc as predominant phenotype which is similar to the present study [19-21]. MS phenotype was most common isolate reported by Juyal D et al., Mohanasundarm KM, Ciraj AM et al., and in Punjab by Lyall KS et al., [1,3,4,8]. L phenotype was very rare in Staphylococci. It shows invitro susceptibility to clindamycin though the antibacterial activity is diminished [9,19].

In this study, inducible clindamycin resistance was observed in 12% of the isolates. This was similar to the findings of Ciraj AM et al., (13.1%), Juyal D et al., (12.1%) and Lim JA et al., from Korea (14.6%) [1,8,22]. The [Table/Fig-5] below shows the incidence of MLSBi reported by various authors in their studies from different regions [1-3,8,13,14,16,23,24].

It was also observed that MLSBi has higher prevalence in MRSA and MRCoNS that is 23% & 27% respectively and it was 5% &7% in MSSA and MSCoNS. This was significant finding in *Staphylococcus aureus* (p-value= 0.005). Juyal D et al., and Ciraj AM et al., also reported MLSBi in 19.4%, 38.5% of MRSA and 6.3%, 13% of MSSA, respectively. Among MRCoNS they reported that it was 15.7% and 0% and 20.8% and 7% in MSCoNS [1,8]. Mohanasoundaram KM in his study found MLSBi in 28% of MRSA, 11% of MSSA and 17% of CoNS [3]. Angel MR et al., also from Tamil Nadu observed it in

Author	Year	Place of study	Organism	MLSBi
Ciraj AM et al., [8]	2009	Karnataka	*Staphylococci* species	13.1%
Deotale V et al., [23]	2010	Maharastra	*Staphylococcus aureus*	14.5%
Mohanasoundaram KM et al., [3]	2011	Tamil Nadu	*Staphylococci* species	17.3%
Juyal D et al., [1]	2013	Uttarakhand	*Staphylococci* species	12.1%
Singh T et al., [13]	2016	Madhya Pradesh	*Staphylococcus aureus*	29.4%
Shetty J et al., [16]	2017	Uttar Pradesh	*Staphylococcus aureus*	16.9%
Bora P et al., [2]	2018	Chandigarh	CoNS	35.8%
Jangla MS et al., [14]	2019	Maharashtra	*Staphylococci* species	22.04%
Khan S et al., [24]	2018	Haryana	CoNS	18%
Current study	2019	Haryana	*Staphylococci* species	12%

[Table/Fig-5]: Inducible Clindamycin resistance reported from different geographical areas.

64% of MRSA and only 5% of MSSA whereas 10% of CoNS [25]. Khan S et al., from Haryana noted MLSBi in 19.2% of MRCoNS and 17.2% in MSCoNS [24].

The frequency of MLSBi ranges from 7%-94% [26,27]. This phenotype widely varies on the basis of geographical location, patient age, type of clinical specimen, hospital environment, bacterial species and antibiotic susceptibility profile of bacteria. The emergence of MDR in Staphylococci has left limited options to the clinicians and appropriate selection of antibiotics is not possible without relevant antibiotic susceptibility data. Hence, D test becomes significant. The inducible resistance may be missed by routine invitro susceptibility tests. D test is very simple, easy to perform and reliable method for detection of MLSBc and MLSBi resistance in resource limited setup. D test should be performed on all the staphylococcal isolates as a routine antimicrobial susceptibility testing. To avoid therapeutic failures clindamycin can be omitted in the patients with MLSBi phenotype infections.

Limitation(s)

The prevalence of genotypes determining the resistance of Staphylococci to MLSB group of antibiotics could not be done due to lack of infrastructure and financial funding.

CONCLUSION(S)

According to present study findings, considerable number of bacterial isolates in this rural hospital showed MLSBi pattern. As this type of resistance cannot be recognised in routine antimicrobial susceptibility tests so a simple test like D-test should be performed routinely to avoid false susceptible results leading to treatment failure.

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