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Distribution of Macrolide-Lincosamide-Streptogramin B Antibiotics Resistance Genes in Clinical Isolates of Staphylococci

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ABSTRACT

Background: *Staphylococci* are posing threat due to increasing trend of antimicrobial resistance particularly methicillin. Macrolide lincosamide streptogramin B (MLS_B) family of antibiotics is commonly used to treat such infections. This study was aimed to determine the prevalence of inducible clindamycin resistance and observation of erm and msr genes among Staphylococci isolated from tertiary care hospital of Nepal during July 2017 to March 2018.

Methods: *Staphylococci* from different clinical specimens were identified and antibiotic susceptibility profile was assessed following Kirby Bauer disc diffusion method. The double disc diffusion or D-zone test as outlined in CLSI document M100-S24 was performed to examine inducible clindamycin resistant isolates. Multiplex PCR was performed for detection of erm and msr gene in isolates using specific primers for ermA, ermB, ermC, msrA and msrB genes.

Results: Of the 60 *Staphylococci* isolates, 39 (65%) were *S. aureus* and 21 (35%) were coagulase negative *Staphylococci* (CNS) with 25 (64%) and 15 (71%) representing methicillin resistant *S. aureus* and CNS respectively. Constitutive and inducible MLS_B phenotype was observed among 24 (40%) and 14 (23%) isolates respectively by D test. The most prevalent resistant gene was ermC (37%) followed by msrB (12%), ermB (10%) and msrA (10%). None of the isolates were found to possess ermA gene.

Conclusions: The presence of constitutive and inducible MLS_B as well as resistant genes among *Staphylococci* necessitates detection of such isolates to minimize treatment failure. The result from this study may help elucidate the predominant resistant characteristics in clinical Staphylococci isolated from tertiary care hospital of Nepal.

Keywords: D test; erm gene; MLS_B; msr gene; staphylococci.

INTRODUCTION

Staphylococci are the emerging problem due to their increasing resistance to several antibiotics.[1,2] Marolides, lincosamides and streptogramin B (MLS_B) antibiotics are now preferred in the treatment of staphylococcal infections due to rise in methicillin resistance, as an alternative to patient allergic to penicillin and for excellent pharmacokinetic properties. Although MLS_B antibiotics are structurally distinct, the mode of action is similar because they inhibit protein synthesis by binding to the 50S subunit (23S rRNA) of bacterial ribosome. However, widespread use of MLS_B antibiotics has caused an increase in the number of strains resistant to it.[3-6]

Involvement of different genes for resistance to MLS_B antibiotics have been described. The active efflux mechanism encoded by msr gene making isolates resistant to erythromycin and sensitive to clindamycin both in vitro and in vivo but typically resistant to clindamycin during therapy. The most common resistance mechanism is target site modification by methylation or mutation in the 23S rRNA, mediated by erm genes (ermA, ermB, ermC and ermF). The predominant genes responsible for resistance to MLS_B antibiotics are ermA and ermC. These are expressed either constitutively ($cMLS_B$) or inducibly ($iMLS_B$).[5,6]

In routine laboratory, detecting inducible clindamycin resistance is difficult, as in vitro they appear resistant to erythromycin and sensitive to clindamycin when placed adjacent to each other. In such cases, in vivo treatment of patients with clindamycin can lead to emergence of resistant mutants to $cMLS_B$ from $iMLS_B$ causing treatment

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failure.

Clinical and Laboratory Standard Institute (CLSI) developed a reliable phenotypic method, the double disk diffusion test (D-test) to screen $iMLS_B$ resistant isolates.[7-10] In Nepal, reports on prevalence of inducible clindamycin resistance among clinical Staphylococci is described only phenotypically using D test[11,12] but detection of involved genes is scanty.

This study was conducted to determine the frequency of inducible clindamycin resistance phenotypically using D test and genotypically using PCR to confirm the presence of erm and msr genes.

METHODS

A hospital based cross-sectional clinical study was conducted in the Pathology Department of the B & B Hospital, Gwarko, Lalitpur from July 2017 to March 2018. All samples received in the laboratory from both gender and all age group patients attending B & B hospital were included in the study. Furthermore, the genetic analysis of the selected bacterial isolates was carried out in Interpid Nepal, Thapathali, Kathmandu. The clinical specimens used in this study were received for routine diagnostic process in the Clinical Microbiology Laboratory. Ethical clearance was taken from the IRC (Institutional Review Committee) of the hospital before the study was conducted.

A total of 312 *Staphylococci* were isolated from various clinical specimens like pus, wound swab, blood, urine, sputum, tissues and various tips (catheter tip, suction tip, drain tip, double J (DJ) stent, tracheal tip, endotracheal tip). The isolates were identified as Staphylococcal strain on the basis of colony morphology on Nutrient agar, Blood agar and Mannitol salt agar, Gram's stain, and different biochemical tests. The slide and tube coagulase test were used to differentiate S. aureus and CNS.[13]

The antimicrobial susceptibility test (AST) of all isolates was performed by modified Kirby Bauer disc diffusion technique.[10] Cefoxitin disc was used to detect methicillin resistance. *S. aureus* ATCC 25923 was used as control strain in each AST assay along with the test strains[10].

The double disc diffusion or D-zone test as outlined in CLSI document M100-S24 (2015) was performed to examine inducible clindamycin resistance among the erythromycin resistant isolates. Briefly, the bacterial isolates were diluted to 0.5 McFarland standard and spread over Mueller Hinton agar (MHA) plate, on which erythromycin (15 µg) disc and clindamycin (2 µg) disc were placed 15-26 mm edge to edge apart and incubated at 35 °C for 16-18 hours in aerobic condition.

Clindamycin resistance was detected as $iMLS_B$ phenotype if isolates are resistant to erythromycin (zone size ≤13 mm) while sensitive to clindamycin (zone size ≥21 mm) with a D-shaped zone of inhibition. Similarly, the isolates show $cMLS_B$ phenotype if resistant to both erythromycin and clindamycin (zone size ≤14 mm) and MS phenotype when resistant to erythromycin and susceptible to clindamycin without D-zone.[10]

Multiplex PCR was performed for detection of erm and msr genes in isolates using specific primers for ermA, ermB, ermC, msrA and msrB genes (Table 1). Each PCR was performed in a final volume of 15 µL consisting of 3µL of master mix, 0.3 µL of each ermA, ermB, ermC, msrA, and msrB forward and reverse primers respectively, 10.4 µL RNase free water and 1 µL of extracted DNA. DNA was amplified on a MJ Research PTC-225 Gradient Thermal Cycler, and DNA amplification was carried out with following parameters: preheating at 94°C for 10 min, 35 cycles of amplification with denaturation at 94°C for 30s, annealing at 53°C for 30s, and extension at 72°C for 60s, followed by a termination at 72°C for 10 min. The PCR product was analyzed in 2% agarose gel stained with ethidium bromide dye using standard molecular weight markers (100 kb DNA ladder; Solis Biodyne, Estonia). [12]

Table 1. Primers used in the study.[14,15]

Target gene	Primer sequence	bp
ermA	5′-GTTCAAGAACAATCAATACAGAG-3′	421
	5′-GGATCAGGAAAAGGACATTTTAC-3′	
ermB	5′-CGTTTACGAAATTGGAACAGGTAAAGGGC-3′	359
	5′-GAATCGAGACTTGAGTGTGC-3′	
ermC	5′-GCTAATATTGTTTAAATCGTCAATTCC-3′	572
	5′-GGATCAGGAAAAGGACATTTTAC-3′	
msrA	5′-GGCACAATAAGAGTGTTTAAAGG-3′	940
	5′-AAGTTATATCATGAATAGATTGTCCTGTT-3′	
msrB	5′-TATGATATCCATAATAATTATCCAATC-3′	595
	5′-AAGTTATATCATGAATAGATTGTCCTGTT-3′	

All data collected were analyzed using SPSS 17.0 and Chi-square test was used for analyzing categorical variables where $P < 0.05$ was considered significant.

RESULTS

Among 312 Staphylococcal isolates, 60 isolates were found to be erythromycin resistant comprising of 39

(65%) *S. aureus* and 21 (35%) CNS. *Staphylococci* were isolated more frequently from wound/pus (46, 77%) followed by urine (9, 15%), blood (3, 5%) and tips (2, 3%).

Antibiotic susceptibility testing of 10 clinically relevant antibiotics was performed for 60 erythromycin resistant isolates. The isolates were found resistant to Fluoroquinolone group of antibiotics, 70% isolates showing resistant to ofloxacin and ciprofloxacin. However, most of the isolates were susceptible to linezolid (88.3%) (Table 2). Similarly, 56% *Staphylococci* were resistant to methicillin representing 42% *S. aureus* and 25% CNS (Table 3).

In this study, almost all isolates of *Staphylococci* presented MLS_B resistant phenotypes. In fact, $cMLS_B$ resistant phenotype was the most common and highest (40%) followed by MS_B (37%) and $iMLS_B$ (23%) phenotypes. In this study, 8 (13.3%) *S. aureus* isolates were $iMLS_B$, 12 (20%) $cMLS_B$ and 19 (31.7%) were of MS phenotypes. The distribution of inducible clindamycin resistance was more among methicillin resistant than methicillin sensitive isolates as detected by D test (Table 3).

According to our findings, the ermC gene was the most prevalent among Staphylococci isolates (22, 37%) followed by ermB among 6 (10%) isolates while ermA gene was not detected. Among 39 *S. aureus*, ermC and ermB was detected in 14 (36%) and 2 (5%) respectively. Similarly, among 21 CNS isolates, the presence of ermC and ermB was observed in 8 (38%) and 4 (19%) respectively (Table 4, Figure 1). In this study, 6 (10%) isolates were detected with the presence of msrA and 7 (12%) with msrB genes. Similarly, msrA and msrB were detected among 1 (2.6%) and 2 (5.1%) *S. aureus* whereas both msrA and msrB genes were detected in 5 (23.8%) CNS isolates (Table 4, Figure 1).

The erm genes were detected in 5 isolates showing $cMLS_B$, 12 isolates showing $iMLS_B$ and 2 isolates with MS phenotype. Similarly, ermB gene was detected 3 isolates showing $cMLS_B$, 2 isolates showing $iMLS_B$ and a single isolate with MS phenotype. None of the isolates with MLS_B resistance were detected with ermA gene (Table 4).

Table 2. Antibiotic susceptibility pattern of isolates.

Class	Antibiotics	Potency	Resistant		Sensitive	
			N	%	N	%
Aminoglycosides	Amikacin	30 mcg	31	51.7	29	48.3
	Gentamycin	10 mcg	31	51.7	29	48.3
Cephalosporins	Cefoxitin	30 mcg	40	55.7	20	33.3
Fluoroquinolones	Ciprofloxacin	5 mcg	42	70	18	30
	Ofloxacin	5 mcg	42	70	18	30
Lincosamides	Clindamycin	2 mcg	38	63.3	22	36.7
Macrolides	Erythromycin	15 mcg	60	100	-	-
	Azithromycin	15 mcg	41	68.3	19	31.7
Oxazolidones	Linezolid	30 mcg	7	11.7	53	88.3
Others	Chloramphenicol	30 mcg	15	25	45	75

N = Total observed value; % = Percentage

Table 3. Susceptibility to erythromycin and clindamycin among Staphylococci isolates.

Phenotype	MRSA N (%)	MSSA N (%)	MRCNS N (%)	MSCNS N (%)	Total N (%)
E-R, CD-R (constitutive MLS_B)	3 (12.0%)	5 (35.7%)	12 (80.0%)	4 (66.7%)	24 (40.0%)
E-R, CD-S (inducible MLS_B, D-positive)	11 (44.0%)	1 (7.1%)	2 (13.3%)	-	14 (23.3%)
E-R, CD-S (MS, D-negative)	11 (44.0%)	8 (57.1%)	1 (6.7%)	2 (33.3%)	22 (36.7%)
Total	25 (41.7%)	14 (23.3%)	15 (25%)	6 (10.0%)	60 (100%)

E-R=erythromycin resistant, CD-R=clindamycin resistant, CD-S=clindamycin sensitive, MLS_B = macrolide lincosamide streptogramin B

Table 4. Distribution of resistant genes among the isolates.

Resistant genotype	No. of isolates with phenotype						Total	
	$cMLS_B$		$iMLS_B$		MLS_B			
	S. aureus	CNS	*S. aureus*	CNS	*S. aureus*	CNS	*S. aureus*	CNS
ermA	0	0	0	0	0	0	0	0
ermB	0	3	1	1	1	0	2	4
ermC	3	5	10	2	1	1	14	8
msrA	1	5	0	0	0	0	1	5
msrB	1	5	0	0	1	0	2	5
ermB+ermC	0	1	1	1	0	0	1	2
ermB+msrA+msrB	0	1	0	0	0	0	0	1
ermB+ermB+msrA+msrB	0	1	0	0	0	0	0	1
msrA+msrB	1	3	0	0	0	0	1	3
No gene	4	7	2	0	16	2	22	9

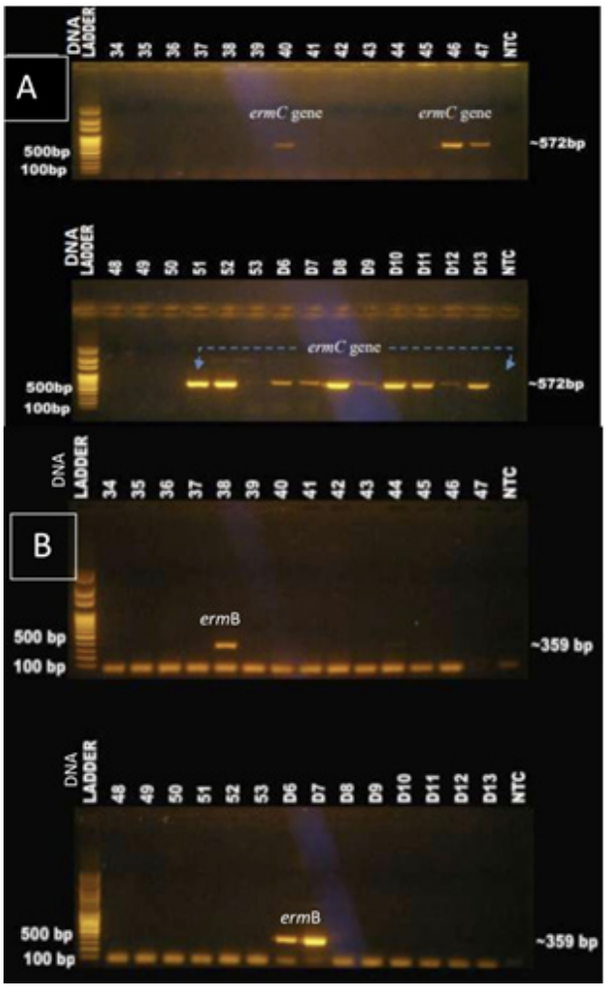

Figure 1. Occurrence of ermC gene (A) and ermB gene (B) in Staphylococcal isolates

34 - 53 = Staphylococcal isolates; D6 - D13 = D test positive Staphylococcal isolates; NTC = Negative template control

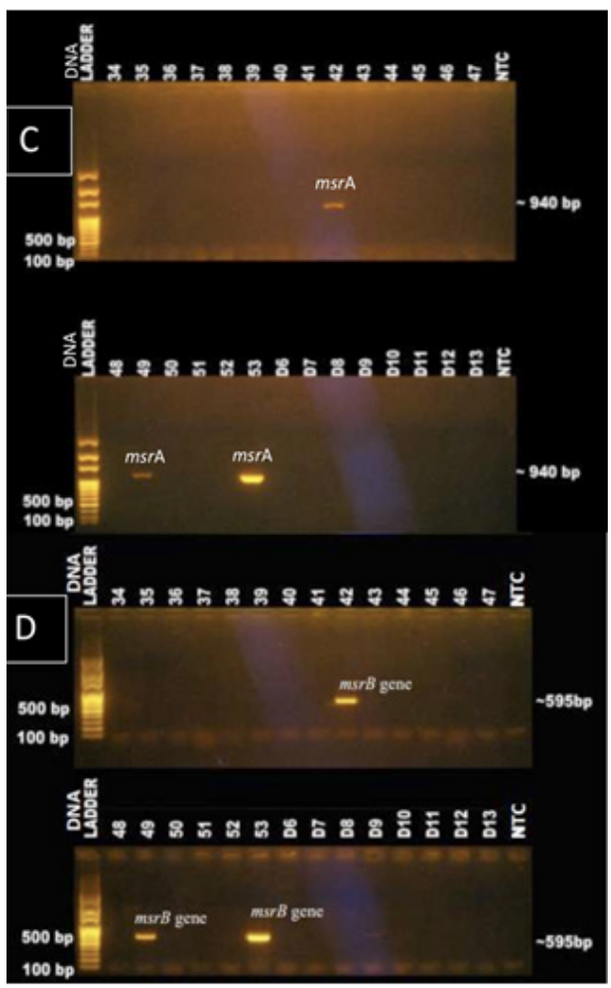

Figure 2. Occurrence of msrA gene (C) and msrB gene (D) in Staphylococcal isolates

34 - 53 = Staphylococcal isolates; D6 - D13 = D test positive Staphylococcal isolates; NTC = Negative template control

DISCUSSION

Staphylococci are responsible for a wide spectrum of diseases. Currently, the organism is posing a global threat due to high rate of antibiotic resistance. Antibiotic susceptibility testing of 10 clinically relevant antibiotics was performed for 60 erythromycin resistant isolates. The isolates were found resistant to Fluoroquinolone group of antibiotics, 70% isolates showing resistant to ofloxacin and ciprofloxacin. However, most of the isolates (88.3%) were susceptible to linezolid. Methicillin resistance was observed among 56% *Staphylococci* with 42% *S. aureus* and 25% CNS. This result is in accordance with the findings disseminated by other studies done in various regions of Nepal and of the world.[8,13,16-18] A marked variation has been observed in methicillin resistance isolated among different geographical regions as well as among hospitals of the same country. In Nepal, a relatively lower rate of MRSA and MRCNS (18% & 9%) was reported by Thapa and Sapkota.[17] Another report, however, showed alarmingly high MRSA prevalence of 75.5% and 69%.[19] Inappropriate use of antibiotics, improper infection control procedure in hospitals, increased use of medical implants may contribute to emerging methicillin resistant isolates.

Increasing frequency of MRSA and MRCNS infection and changing pattern in antibiotic resistance have sparked renewed interest in the use of MLS_B antibiotic. Particularly, clindamycin has become an excellent drug for Staphylococcal infection as an alternative to patients allergic to ß lactam antibiotics because of its low cost, low side effects and good tissue penetration.[8,15,20] Steward et al have described different phenotypes which include $iMLS_B$, $cMLS_B$, moderate sensitive (MS) and sensitive (S) among Staphylococcal isolates resistant to macrolide.[21] Macrolide resistant Staphylococcal isolates may have constitutive or inducible resistant to clindamycin which is difficult to detect in routine laboratory test if they are not placed adjacent to one another. During clindamycin therapy, these inducible phenotypes can gradually develop constitutively resistant mutants both in vitro and in vivo. Hence, detection of such resistant phenotypes is important to minimize treatment failure.[6] Since the $iMLS_B$ resistance mechanism is unrecognized by using standard susceptibility test methods and its prevalence varies according to geographic location, D-test becomes an imperative part of routine antimicrobial susceptibility test for all clinical isolates.[22]

In this study, almost all isolates of *Staphylococci* presented MLS_B resistant phenotypes. In fact, $cMLS_B$ resistant phenotype was the most common and highest (40%) followed by MS_B (37%) and $iMLS_B$ (23%) phenotypes. Varying prevalence rates of MLS_B resistance phenotype are reported by other studies.[14,16,22-24] Meanwhile $iMLS_B$ was found higher (44%) in MRSA whereas it was $cMLS_B$ (36%) in MSSA. Among 21 CNS isolates, $iMLS_B$, $cMLS_B$ and MS phenotype was detected in 2 (3.3%), 16 (26.7%) and 3 (5%) respectively. Constitutive resistance among CNS was observed in various studies as well.[13,24,25] $cMLS_B$ was detected among 80% MRCNS and 67% MSCNS while $iMLS_B$ was observed only among MRCNS (13.3%) and not in MSCNS. Variations in these results depend on factors like sample size, patient's age, geographical region, population studied, trends of antibiotic prescription, circulating clones and origin of isolates.[26]

Studies on the prevalence of MLS_B resistance in Staphylococci using phenotypic method is available to some extent but to our knowledge data on responsible gene is not available. Resistance to MLS_B is mostly based on ribosomal target modification encoded by erm gene for enzyme methylase. The resistance mechanism is the methylation of 23S binding site to cause premature dissociation of the peptidyl tRNA from the ribosome halting further protein synthesis. In inducible resistance, the bacteria produce inactive mRNA that is unable to encode methylase. The mRNA becomes active only in the presence of a macrolide inducer. By contrast, in constitutive expression, active methylase mRNA is produced even in the absence of an inducer. The strains harbouring an inducible erm gene are resistant to the inducer but remain susceptible to non inducer macrolides and lincosamides. Mutations in the promoter region of erm allow production of methylase without an inducer.[3]

According our findings, the ermC gene was the most prevalent among *Staphylococci* isolates (22, 37%) followed by ermB among 6 (10%) isolates while ermA gene was not detected. Studies shows that MLS_B resistance is caused most often by ermC. The presence of erm genes varied in studies carried out by different researchers. The study carried out by Martineau et al. in Canada, ermA gene was detected among 20.9% S. aureus and 66% CNS.[27] Also, a multi-centre study in 24 European University hospitals, prevalence of ermA gene was higher than ermC and ermB genes among 851 S. aureus.[22] Lina et al showed 63.2% *S. aureus* positive for ermA gene and 44% CNS positive for ermC gene while ermB was positive only in 1% Staphylococci.[24] As opposed to these studies, our study did not detect any ermA gene. In *S. aureus*, constitutive resistance tends to be caused mostly by ermA and the inducible phenotype by ermC which corroborate with the phenotypic result as detected by D test of this study.

The strains with MS phenotype are resistant to macrolide and streptogramin but are susceptible to clindamycin. Such resistance is encoded by msr gene, either msrA or msrB.[3] Conferring active efflux of antibiotics such that intracellular concentration becomes low and ribosomes are free from the antibiotics. In this study, 6 (10%) isolates were detected with the presence of msrA and 7 (12%) with msrB genes. Export of macrolides is rarely seen in S. aureus but seems to be more frequent in CNS.[24]

The erm genes were detected in 5 isolates showing $cMLS_B$, 12 isolates showing $iMLS_B$ and 2 isolates with MS phenotype. Similarly, ermB gene was detected 3 isolates showing $cMLS_B$, 2 isolates showing $iMLS_B$ and a single isolate with MS phenotype. None of the isolates with MLS_B resistance were detected with ermA gene. This result is in accordance with the study carried out in Germany with 63% ermC showing constitutive resistance.[28] In contrast to situations reported by other studies, in which constitutive resistance tends to be caused by ermA and the inducible phenotype is caused by ermC.[9,24]

None of the erythromycin resistant isolates were encountered without any of the tested resistant mechanism. This is in contrast to other previous studies where unidentified resistance mechanism were observed among Staphylococcal isolates.[8,13] Additionally, resistant genes were not detected among phenotypically erythromycin susceptible isolates. Our findings show a correlation between the presence of specific genes or sets of genes and the phenotypic MLS_B resistance.

Due to limited resources, erm and msr gene were not detected among all the isolates and other resistant genes responsible for clindamycin resistant were also not studied.

CONCLUSIONS

Staphylococci, particularly MRSA, are posing a threat to clinical management of diseases. Clindamycin resistance in the form of iMLSB and cMLSB limits the therapeutic options for such methicillin resistant isolates. In this study, we tried detecting the presence of common resistant genes as erm and msr along with phenotypic method in clindamycin resistant clinical isolates. Constitutive and inducible MLS_B phenotype was observed among 40% and 23% isolates respectively by D test. The most prevalent resistant gene was ermC gene (37%) followed by msrB (12%), ermB (10%) and msrA (10%). Therefore, these resistance mechanisms should be identified that will help us in guiding the clinicians regarding the judicious use of clindamycin.

CONFLICT OF INTEREST

None declared.

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