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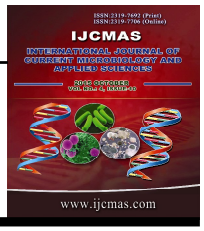

Original Research Article

Detection of inducible Clindamycin Resistance among *Staphylococcal* isolates from Various Clinical Specimens in a Tertiary Care Institute in North West Region of Rajasthan, India

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A B S T R A C T

The emergence of resistance to most antimicrobial agent in staphylococci indicates the need for new effective agents in the treatment of staphylococcal infection. Clindamycin is considered to be one safe, effective and less costly agent. One important issue in clindamycin treatment is the risk of clinical failure during therapy. Therapeutic failure caused by macrolide - lincosamine -streptogramin-B (MLSB) inducible resistance is being more commonly reported. The present study was aimed to detect inducible clindamycin resistance among *Staphylococcal* isolates and to study the relationship between clindamycin and methicillin resistance. A total number of 500 *Staphylococcal* strains were isolated from clinical specimens and methicillin resistance were detected by the routine antibiotic susceptibility testing methods including the oxacillin disk method, the Cefoxitin disc diffusion test and the results were interpreted as per the CLSI guidelines. The clinical isolates of erythromycin-resistant (ER-R), clindamycin susceptible Staphylococci (CL-S) were examined for inducible clindamycin resistance (ICR) by D-test. Strains which produced ICR showed flattening of the clindamycin disczone which was adjacent to the erythromycin disc. 93 (18.66%) isolates showed inducible clindamycin resistance, 60 (12%) showed constitutive resistance while remaining 100 (20%) showed MS phenotype. Inducible and constitutive resistances were found to be higher in MRSA as compared to MSSA (30.66%, 17.33% and 15.82%, 5.03% respectively). Given the high rate of inducible resistance to clindamycin in the staphylococcal isolates, the test for inducible resistance to clindamycin should be included in the routine antibiotic susceptibility tests, as it will help in guiding the therapy.

Keywords

Resistance, Inducible, Methicillin, Clindamycin

Introduction

Staphylococcus aureus and coagulase negative Staphylococcus (CNS) infection have become common among both hospitalized and non hospitalized patients. The emergence of resistance to antimicrobial agents among Staphylococci is an increasing problem (Pal *et al.,* 2010).

Emergence of methicillin resistant *Staphylococcus aureus* (MRSA) has left us

with very few therapeutic alternatives to treat Staphylococcal infections. The macrolide-lincosamide–streptogramin B (MLS_B) family of antibiotic serves one such alternative with clindamycin being the preferred agent in MLS_B group for treating *Staphylococcal* infection (Gade *et al.*, 2012). Widespread use of macrolide-lincosamide – streptogramin B (MLS_B) antibiotics, has led to an increase in a number of Staphylococci acquiring cross-resistance toMLS antibiotics. Cross-resistance to MLS antibiotic (MLS resistance) in staphylococci is attributable to one of the two mechanisms:

First is an active efflux, due to energy-dependent pump, which expels antimicrobial agents from the bacterial cell. Efflux mechanism is encoded by *mrs (A)* gene and confers resistance to macrolides and type B streptogramin, but clindamycin remains active (MS_Bresistance).

Second mechanism is modification of the drug-binding site on the bacterial ribosome, mediated by ribosomal methylases, which leads to the reduced binding of MLS antibiotics. Ribosomal methylases are encoded by *erm* genes (*erm (A)* or *erm (C)* in staphylococci) and results in resistance to macrolides, lincosamides and type B streptogramin (MLS_B resistance).

Phenotypic expression of this resistance can be inducible ($iMLS_B$ resistance phenotype) and constitutive ($cMLS_B$ resistance phenotype). In inducible expression, the bacteria produce inactive methylase mRNA that is unable to translate in to ribosomal methylase, but becomes active only in the presence of a strong inducer, such as erythromycin. By contrast, in constitutive expression, active methylase mRNA is produced in continuity, and in the absence of an inducer. In vitro, Staphylococcal isolates with $cMLS_B$ phenotypes are resistant to all MLS_B antibiotics, whereas those with $iMLS_B$ phenotypes demonstrate resistance to macrolides, while appearing susceptible to lincosamides and type B streptogramin (Aleksandra *et al.*, 2014).

Strains with inducible resistance to clindamycin are difficult to detect in the routine laboratory as they appear erythromycin resistant and clindamycin sensitive in vitro when not placed adjacent to each other. In such cases, in vivo therapy with clindamycin may select constitutive *erm* mutants leading to clinical therapeutic failure (Gade *et al.*, 2013).

The Clinical Laboratory Standards Institute (CLSI) has recommended the erythromycin clindamycin disc approximation test (D–zone test) to detect the inducible clindamycin resistance. Published data of inducible clindamycin resistance among pathogen Staphylococcal isolates in North West region of Rajasthan was missing. Because of that, the present study was aimed to find out the percentage of *Staphylococcal* isolates having inducible clindamycin resistance in our geographic area using D-test as per CLSI guidelines (Gade *et al.*, 2013) and to record the current trend in regard to the prevalence and distribution of inducible clindamycin resistance among *Staphylococcus aureus* and coagulase-negative Staphylococci [CNS] in North west region of Rajasthan (Aleksandra *et al.*, 2014).

Materials and Methods

The present study has been carried out in Bacteriology laboratory of Microbiology Department of Sardar Patel Medical College, Bikaner (Rajasthan) from September 2013 to September 2014 to detect inducible clindamycin resistance among Staphylococcal isolates from various clinical specimens from attached hospitals. Total

500 staphylococcal strainswere isolated from various clinical specimens such as urine, blood, wound swabs, pus, sputum and other respiratory tract specimens, body fluids, high vaginal swabs, ear swabs, stool etc. Received from patients attending various outpatient departments and admitted in wards at P.B.M. hospital and associate group of hospitals, were included in this study.

Inclusion criteria

All Staphylococci strains (non-repetitive) were collected from various specimens of patients attending outpatient departments and admitted in wards at P.B.M. hospital and associate group of hospitals. Specimens included are urine, blood, pus, wound swab, sputum and other respiratory tract specimen, high vaginal swab, stool, semen and CSF etc.

Exclusion criteria

Three different organisms with no predominating organism and repeated isolate from same patient were excluded from study.

Processing of specimens

The clinical isolates were processed immediately as follows-The samples were processed for the identification of organisms on the basis of conventional microbiological procedures including colony morphology, gram stain, catalase, slide coagulase, tube coagulase and mannitol fermentation (Pal *et al.*, 2010).

Antibiotic susceptibility testing

The isolates were tested for antimicrobial susceptibility on Mueller Hinton agar by Kirby Bauer disk diffusion method as per CLSI recommendation. A lawn culture was made on the surface of medium by a sterile cotton swab with an inoculum matched with 0.5 McFarland turbidity standard, prepared by suspending few colonies of test strain in0.9% sterile saline. Then the antimicrobial discs were applied on the inoculated agar surface with all sterile precautions, and the plates were incubated at 37°C overnight.

Staphylococcus aureus ATCC 25923 was used to check the potency of the disc. Following antibiotic discs (obtained fromHi-Media, Mumbai, India) were used for antimicrobial sensitivity testing:

Oxacillin (1µg), erythromycin (15µg), clindamycin (2µg), trimethoprim-sulfamethoxazole (25µg), vancomycin (30µg), ofloxacin (5µg), gentamycin (10µg), tetracyclin (30µg).

Methicillin resistance will be detected based on CLSI recommendation by using Oxacillin disc (1µg) and a cefoxitin disc (30µg) (CLSI M2-A7 2005).

Laboratory detection of MRSA

Disc Diffusion method with 1ug Oxacillin disc

The Kirby-Bauer method disc diffusion test is performed on Mueller Hinton agar. 0.5 McFarland suspension of isolates is made and streaked on the Mueller Hinton Agar. A 1 ug oxacillin disc is placed in the centre of the plate with sterile precautions. The plate was incubated at 35^0C for 24 hours.

Plates are observed carefully in transmitted light for any growth. *Staphylococcus aureus* ATCC 25923 and *Staphylococcus aureus* ATCC 43300 may be used as reference strains. If any colonies were observed within the zone diameter then it was reported as resistant strain.

Disc diffusion method with 30ug cefoxitin disc

The disc diffusion test is performed on Mueller Hinton Agar. 0.5 McFarland suspension of isolates is made and streaked on the Mueller Hinton Agar. A 30ug gfefoxitin disc is placed in the centre of the plate with sterile precautions. The plate is incubated at 35^0C for 24 hours. Plates are observed carefully in transmitted light for any growth. *Staphylococcus aureus* ATCC 25923 and *Staphylococcus aureus* ATCC 43300 may be used as reference strains.

The isolates that will be found to be erythromycin resistant will be further studied for inducible clindamycin resistance (CLSI M2-A7 2005, Ciraj *et al.*, 2009)

Laboratory detection of inducible clindamycin resistance by D test method

Those isolates which were erythromycin resistant were further subjected to 'D test' as per CLSI guidelines. 0.5 McFarland suspension was prepared in normal saline for each Isolates and Inoculated on Mueller Hinton agar plate.

Clindamycin 2µg and erythromycin15µg disks were placed 15mm apart edge to edge manually. Plates were incubated at 37^o C for 24 hours.

Following overnight incubation at 37^oC three different phenotype were appreciated and interpreted as follow

MS Phenotype- Staphylococcal isolates exhibiting to erythromycin (zone size ≤13mm) while sensitive to clindamycin (zone ≥21mm) and giving circular zone of inhibition around clindamycin was labelled as having this phenotype.

Inducible MLS_B phenotype-Staphylococcal isolates showing resistance to erythromycin (zone size ≤13mm) while being sensitive to clindamycin (zone size ≥21mm) and giving D shaped zone of inhibition around clindamycin with flattening towards erythromycin disc were labelled as having phenotype.

Constitutive MLS_B phenotype- This phenotype was labelled for those Staphylococcal isolates which showed resistance to both erythromycin (zone size ≤13mm) and clindamycin (zone size ≤14mm) with circular shape of zone of inhibition if any around clindamycin.

Quality control for erythromycin and clindamycin disc was performed with *Staphylococcus aureus* ATCC 25923 according to standard disc diffusion QC procedure (Pal *et al.*, 2010, Lyallsingh *et al.*, 2013, Deotalev *et al.*, 2010, CLSI M2-A7 2005).

Results and Discussion

A total of 4513 samples including 1860 blood samples, 294 pus samples 1530 urine samples, 598 sputum samples, 54 throat swabs &177 body fluid samples were processed for the study. 500 Staphylococcal strains were Isolated from total 4513 Samples. Out of 500 Staphylococcus isolates, 214 (42.8%) were *Staphlococcus aureus* and 286 (57.2%) were coagulase negative Staphylococci.75 (15%) MRSA, 139 (27.8%) MSSA, 153 (30.6%) MRCONS & 133 (26.6%) MSCONS were isolated. Majority of the Staphylococcal isolates were MRCONS 153 (30.6%) & the least were MRSA 75 (15%) (Table 1). In our study, out of 500 total Staphylococcal isolates, 253 (50.6%) isolates were found to be resistant to erythromycin.

In present study a total of 93(18.66%) isolates tested were found to be positive for inducible macrolide-linocosamides-streptogramin ($iMLS_B$) resistance by D test, 60 (12%) were shown to have constitutive macrolide-linocosamides-streptogramin ($cMLS_B$) and 100 (20%) were macrolide-streptogramin (MS) phenotype (Table 2). In our study 23(30.66%) MRSA &22 (15.82%) MSSA showed $iMLS_B$ phenotype. In our study 13 (17.33%) of MRSA & 7(5.03%) of MSSA were reported as $cMLS_B$ phenotype. Our study shows the prevalence of MS phenotype in MRSA & MSSA 15 (20%) and 20 (15.32%) respectively (Table 3). In our study prevalence of $iMLS_B$ phenotype in MRCONS & MSCONS is 32 (21.56%) & 15 (11.21%) respectively while $cMLS_B$ phenotype in MRCONS & MSCONS is 20 (13.07%) & 20 (15.03%) respectively. The prevalence of MS phenotype in MRCONS &MSCONS is 30 (19.60%) & 35 (26.31%) respectively (Table 4). All Staphylococcal strain [500(100%)] isolated in our study were found to be sensitive to vancomycin followed by tetracycline 451 (90.2%) and least 242 (48.4%) were sensitive to cotrimaxazole (Table 5).

Good oral absorption makes this drug an important option in outpatient therapy or as a follow up after intravenous therapy (ND Gade *et al.,* 2012). In infections due to MRSA, clindamycin is less costly than some of newer agents that might be considered for these infection (Shantala *et al.,* 2011)

One of the major concerns with regard to the therapeutic use of clindamycin in Staphylococcal infection is the possible presence of inducible resistance to clindamycin, and subsequent clinical failure of therapy (Aleksandra *et al.,* 2014). In our study, out of 500 total Staphylococcal isolates, 253 (50.6%) isolates were found to be resistant to erythromycin. Lyall *et al.* (2013) reported 51%, Pal *et al.* (2009) reported 50.2% and Simitkumar *et al.* (2011) reported 56.9% Staphylococci showing resistance to erythromycin.

In present study a total of 93(18.66%) isolates tested were found to be positive for inducible macrolide-linocosamides-streptogramin ($iMLS_B$) resistance by D test, 60 (12%) were shown to have constitutive macrolide-linocosamides-streptogramin ($cMLS_B$) and 100 (20%) were macrolide-streptogramin (MS) phenotype.

Both Manjunath *et al.* (2009) and V Gupta *et al.* (2008) reported $iMLS_B$ phenotype 18% which is comparable with our study while Delialiogu N *et al.* (2004) and N Selfi *et al.* (2010) reported lower prevalence of $iMLS_B$ phenotype 11.70% and 10.52% respectively. Alexandra *et al.* (2013) and Lyall *et al.* (2013) reported higher prevalence of $iMLS_B$ phenotype 39% and 33.3% respectively.

Gade *et al.* (2011) and Ciraj *et al.* (2009) reported $cMLS_B$ phenotype 12.4% and 10.25% respectively which are comparable with our study while Velvizhi *et al.* (2005), Pal *et al.* (2009) and Delialiogu *et al.* (2004) reported higher prevalence of $cMLS_B$ phenotype 32%, 46.97% &33.20% respectively. Deotale *et al.* (2008) and Mittal *et al.* (2009) reported lower prevalence of $cMLS_B$ phenotype 3.6% &6.15% respectively.

Shantla *et al.* (2010) and Kumar Simit *et al.* (2011) reported 15.65%&16.9%MS phenotype respectively in their studies which are comparable with our study while Lyall *et al.* (2013) and Yilmaz *et al.* (2007) reported higher prevalence of MS phenotype 44.8% and 49.8% respectively. On the other hand Delialiogu *et al.* (2004) and Selfi *et al.* (2010) reported lower prevalence MS phenotype 10.17% and 8.42% respectively.

Table.1 Distribution of Staphylococcal isolates to their methicillin susceptibility pattern

	MRSA (%)	MSSA (%)	MRCONS (%)	MSCONS (%)	Total (%)
Number of Isolates	75 (15%)	139 (27.8%)	153 (30.6%)	133 (26.6%)	500 (100%)

Table.2 Prevalence of different MLS_B phenotype

S.No.	Phenotype	Number	Percentage (%)
1	$iMLS_B$	93	18.66
2	$cMLS_B$	60	12
3	MS phenotype	100	20

Table.3 Comparison of MLS_B phenotype between MRSA and MSSA

MLS_B types	MRSA(n = 75)	MSSA(n = 139)
$iMLS_B$	23 (30.66%)	22 (15.82%)
$cMLS_B$	13 (17.33%)	7 (5.03%)
MS phenotype	15 (20%)	20 (15.32%)

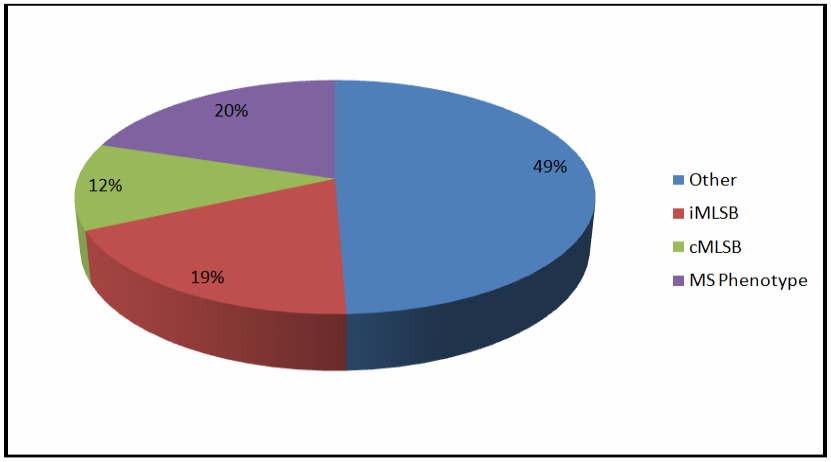
Table.4 Comparison of MLS_B phenotype between MSCONS and MRCONS

MLS_B Types	MSCONS(n =133)	MRCONS(n = 153)
$iMLS_B$	15 (11.21%)	33 (21.56%)
$cMLS_B$	20 (15.03%)	20 (13.07%)
MS phenotype	35 (26.31%)	30 (19.60%)

Table.5 Antibiotic sensitivity pattern of *Staphylococcus* isolates from different clinical samples

Antibiotics	Antibiotics Sensitivity		Total
	Sensitive	Resistant	
Vancomycin (30µg)	500 (100%)	0 (0%)	500 (100%)
Teracyclin (5 µg)	451(90.2%)	49 (9.8%)	500 (100%)
Ofloxacin (10 µg)	372 (74.5%)	128 (25.5%)	500 (100%)
Gentamycin (10 µg)	394 (78.9%)	106 (21.1%)	500 (100%)
Amoxyclav (20/10 µg)	339 (67.8%)	161 (32.2%)	500 (100%)
Erythromycin (15 µg)	247 (49.4%)	253 (50.6%)	500 (100%)
Clindamycin (2 µg)	347 (69.4%)	153 (30.6%)	500 (100%)
Co-trimaxazole (1.25/23.75 µg)	242 (48.4%)	258 (51.6%)	500 (100%)
Oxacillin (1 µg)	282 (56.4%)	218 (43.6%)	500 (100%)
Cefoxitin (30 µg)	272 (54.4%)	228 (45.6%)	500 (100%)

Graph.1 Percentage (%) of different phenotypes



The different patterns of resistance observed in various studies are because $iMLS_B$ resistance varies by geographical region, age group, methicillin susceptibility and even from hospital to hospital (Pal *et al.,* 2010).

In our study 30.66 % MRSA & 15.82% MSSA showed iMLSB phenotype. These findings correlate with Gadepalli *et al.* (2005) & Chudasamavyoma *et al.* (2013) who reported 30% & 32.53% iMLSB phenotype respectively in MRSA. Yilmaz *et al.* (2007) & Siraz *et al.* (2008) reported 14.8% & 12.9% $iMLS_B$ respectively in MSSA which are comparable with our study. Ajantha *et al.* (2008) reported higher prevalence of $iMLS_B$ in MRSA & MSSA 74% & 45% respectively.

In our study prevalence of $iMLS_B$ phenotype in MRCONS & MSCONS is 21.56% & 11.21% respectively. These findings correlate with Kumar *et al.* (2010) &Yilmaz *et al.* (2007) who reported $iMLS_B$ phenotype in MRCONS 18.8% & 25.7% respectively. Kumar *et al.* (2010) Delialiogu *et al.* (2005) reported $iMLS_B$ phenotype in MSCONS 11.1% & 14.4% respectively.

Due to the emergence of resistance to antimicrobial agents accurate drug susceptibility data of the infecting microbe is an essential factor in making appropriate therapeutic decisions. MLS_B resistance is the most widespread and clinically important mechanism of resistance encountered with Gram-positive organisms due to the production of methylases and efflux proteins. *In vitro* susceptibility testing for clindamycin may indicate false susceptibility by the broth microdilution method and by disk diffusion testing with erythromycin and clindamycin disks in nonadjacent positions. Erythromycin-clindamycin disc approximation test or D-test is a simple, reliable method to detect inducible resistance to clindamycin in erythromycin-resistant isolates of *Staphylococci*. Sensitivity of D-test performed at 15-20 mm disk spacing was 100% when correlated with detection of *erm* and *msr* genes by polymerase chain reaction (PCR).

Clinically, bacterial strains exhibiting $iMLS_B$ have a high rate of spontaneous mutation to constitutive resistance and use of non-inducer antibiotics such as clindamycin can lead to selection of constitutive mutants at frequencies of 10^7 cfu. McGehee and other investigators have confirmed this rapid *in*

vitro conversion of inducible to constitutive MLS $_B$ resistance in *Staphylococci*. There have also been a number of reported clindamycin or lincomycin therapy failures in serious infections due to *Staphylococci* with iMLS $_B$ resistance, indicating that it is not uncommon. Clindamycin has long been an attractive option in the treatment of skin and soft tissue infections (SSTI) and serious infections because of its efficacy against MRSA and MSSA, as well as anaerobes. This has led to questioning the efficacy of clindamycin use against any erythromycin-resistant *Staphylococci* spp. However, if inducible resistance can be reliably detected on a routine basis in clinically significant isolates, clindamycin can be safely and effectively used in patients with true clindamycin-susceptible strains.

In the present study, 100 (20%) of erythromycin-resistant Staphylococcal isolates showed true clindamycin susceptibility (MS phenotype). Patients with infections caused by such isolates can be treated with clindamycin without emergence of resistance during therapy.

The high frequency of methicillin-resistance isolates 56 (60.21%) with *in vitro* inducible clindamycin resistance at our institute raises concern of clindamycin treatment failures with methicillin-resistant infections.

We conclude that it is important for laboratories to be aware of the local prevalence of iMLS $_B$ isolates. On the basis of their data they can choose whether or not to perform the D-test routinely. The D-test is an easy, sensitive, and reliable means for detection of iMLS $_B$ strains in a clinical laboratory setting without specialized testing facilities. This prevalence of iMLS $_B$ may change over time with the emergence of strains with different sensitivity patterns, so periodic surveys should be performed if testing is not routine (Pal *et al.*, 2010).

In conclusion, Clindamycin a lincosamide is one of the most efficient antibiotic in treating staphylococcal skin and soft tissue infections, including osteomyelitis, because of its excellent tissue penetration. It accumulates in abscesses and no dosage adjustment are needed in presence of renal disease. It also directly inhibits the Staphylococcal toxin production and is a useful alternative for patients who are allergic to penicillin.

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