

INCIDENCE OF INDUCIBLE CLINDAMYCIN RESISTANCE IN CLINICAL ISOLATES OF STAPHYLOCOCCUS AUREUS ISOLATES FROM TERTIARY CARE HOSPITAL; EXPERIENCE IN KOSHI AREA (NORTHERN BIHAR), INDIA

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ABSTRACT

BACKGROUND

Staphylococcus aureus is one of the most common pyogenic bacteriae infecting man, causing both hospital and community acquired infections. Staphylococcus aureus can produce a wide variety of diseases, from relatively benign skin infections. The Clinical and Laboratory Standards Institute (CLSI) recommends D-test, which is a phenotypic screening method for inducible clindamycin resistance. Therefore, all erythromycin resistant *S. aureus* should be tested for inducible clindamycin resistance to prevent clindamycin treatment failures and to report prevalence of resistant phenotypes which varies widely.

MATERIALS AND METHODS

This cross-sectional study was conducted for a period of one year from January 2016 to January 2017. We analysed 110 non-duplicate consecutive isolates of *S. aureus* isolated from various clinical specimens like pus, wound swab, aspirates, blood, and sterile fluids. A total of 110 *S. aureus* isolates derived from wound infection were evaluated for antimicrobial susceptibility testing by Kirby Bauer disk diffusion method. Methicillin resistance was detected using cefoxitin (30 µg) disk and inducible clindamycin resistance was determined in all erythromycin resistant isolates by using D-zone test.

RESULTS

Out of 110 *S. aureus* isolates of the MRSA 38 (34.6%) were derived from respectively pus samples 16 (41.53%), the *S. aureus* isolates derived from wound samples were MRSA 7 (18.03%), the *S. aureus* isolates derived from blood samples were MRSA 9 (22.40%), the *S. aureus* isolates derived from miscellaneous samples were MRSA 5 (13.66%) and the *S. aureus* isolates derived from urine samples were MRSA 1 (3.75%). A total of 26 *S. aureus* isolates showed inducible clindamycin resistance by giving a positive D-zone test, hence, its prevalence was found to be 21.10% (23/110), with percentage distribution of cMLSB phenotype and MS phenotypes in all *S. aureus* isolates as 19.6% and 24.4% respectively. The antimicrobial susceptibility test result of all the 24 *S. aureus* isolates with iMLSB phenotype revealed that they were 100% sensitive to vancomycin and linezolid, with moderate sensitivity (71.14%) to gentamicin, cefuroxime and least sensitivity to (23.81%) doxycycline, (20.95%) ciprofloxacin.

CONCLUSION

Due to high prevalence of erythromycin resistance amongst *S. aureus* isolates, we suggest that D-zone test should be routinely done in all laboratories for appropriate prescription of clindamycin and thereby preventing emergence of inducible resistant strains and treatment failure.

KEYWORDS

Staphylococcus aureus, Inducible Clindamycin Resistance, Wound Infection.

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BACKGROUND

Staphylococcus aureus is one among the most common pyogenic bacteriae infecting man, causing both hospital and community acquired infections.¹ Staphylococcus aureus can produce a wide variety of diseases, from relatively benign skin infections such as folliculitis and furunculosis to deep-seated and life-threatening conditions, including cellulitis, deep abscesses, osteomyelitis, pneumonia, sepsis, and endocarditis.² The increasing prevalence of resistance to most antimicrobial agents in staphylococci signifies the need for new effective agents to treat staphylococcal infections.

Macrolides, lincosamides and type B streptogramin (MLS_B) are structurally unrelated but act through common mechanism of inhibition of protein synthesis, and are widely used to treat such infections.³ Clindamycin (a lincosamide) in particular, is an attractive alternative for clinicians as it is available for parenteral and oral use, distributes well in tissues, and is bacteriostatic against *S. aureus*.⁴ Staphylococcal strains resistant to MLS_B antibiotics have increased in number following the widespread use of these antibiotics for treating serious staphylococcal infections.^{5,6}

The MLS_B resistant phenotype in *S. aureus* can be either constitutive MLS_B (cMLS_B) or inducible MLS_B (iMLS_B). Staphylococci that express ribosomal methylases (erm) genes may exhibit in vitro resistance to erythromycin, clindamycin, and other drugs of MLS_B group. This resistance is referred to as the cMLS_B phenotype. However, in some Staphylococci, those express erm genes require an inducing agent to synthesize methylase for clindamycin resistance. This type of is referred to as iMLS_B phenotype. These organisms are resistant to erythromycin and falsely susceptible to clindamycin in vitro.⁷ This type of inducible clindamycin resistance cannot be detected by standard Kirby-Bauer disk diffusion method, broth micro dilution testing, automated susceptibility testing devices, or Epsilon meter test.⁸ Thus, falsely susceptible clindamycin will lose its effectiveness in vivo and thereby increase the chance of therapeutic failures.⁹

The double disk approximation test (D-test) that involves the placement of an erythromycin disk in proximity to the disk containing clindamycin. As the erythromycin diffuses through the agar, the resistance to the clindamycin is induced, resulting in a flattening or blunting of the clindamycin zone of inhibition adjacent to the erythromycin disk, giving a "S0" shape to the zone. The Clinical and Laboratory Standards Institute (CLSI) recommends D-test, which is a phenotypic screening method for inducible clindamycin resistance.¹⁰ Therefore, all erythromycin resistant *S. aureus* should be tested for inducible clindamycin resistance to prevent clindamycin treatment failures and to report prevalence resistant phenotypes which varies widely. The present study will be aimed to determine the constitutive and inducible clindamycin resistance in *S. aureus* isolated from various clinical specimens at a tertiary care hospital in Saharsa, India.

MATERIALS AND METHODS

This cross-sectional study was conducted for a period of one year from February 2016 to February 2017. We analysed 110 non-duplicate consecutive isolates of *S. aureus* isolated from various clinical specimens like pus, wound swab, aspirates, blood, and sterile fluids. Age and sex of the patients were recorded. This study was approved by the Research and Ethical committees of our institute and informed consent was obtained from each patient.

Clinical Samples and Bacterial Isolates

During of one-year period 110 clinical isolates of *S. aureus* were collected from Department of Microbiology, Lord Buddha Koshi Medical College and Hospital, Saharsa, Bihar and Associated Hospital. The bacteria which were consecutively isolated from patients in various wards and different specimens such as: catheter, blood, wound, discharge, abscess, burn, and so on, were transported to Microbiology Department Lord Buddha Koshi Medical College and Hospital, Saharsa, Bihar and Associated Hospital were confirmed by standard microbiology tests including: Gram staining, catalase, slide and tube coagulase, mannitol fermentation and production of DNase enzyme.¹¹

Antibiotic Susceptibility Test

Antibiotic susceptibility testing was performed on Mueller-Hinton agar (HiMedia Laboratories, Mumbai, India) by Kirby Bauer disk diffusion method as per CLSI guidelines using antibiotic disks (HiMedia Laboratories, Mumbai, India) such as penicillin (10 units), gentamicin (10 µg), tetracycline (30 µg), linezolid (30 µg), trimethoprim-sulfamethoxazole (1.25/23.75 µg), cefoxitin (30 µg), erythromycin (15 µg), clindamycin (2 µg) and ciprofloxacin (5 µg). *Staphylococcus aureus* ATCC 25923 was used as standard quality control strain.¹²

Methicillin Resistance Test

Methicillin resistance amongst *S. aureus* was determined using cefoxitin (30 µg) disk on Mueller Hinton agar as per CLSI guidelines, and results were read after 18 hours of incubation at 35°C. The *S. aureus* isolates which showed zone size ≥ 22 mm were considered methicillin sensitive (MSSA) and those with zone size ≤ 21 mm were considered as methicillin-resistant *S. aureus* (MRSA). (16) Susceptibility of MRSA strains to vancomycin was tested by agar dilution method as per CLSI guidelines by inoculating 0.5 McFarland bacterial suspensions on Mueller-Hinton agar (MHA) plates by using sterile swabs. The plates were analysed after 24 hours of incubation at 35°C. Minimal inhibitory concentration (MIC) of vancomycin of ≤2 µg/mL for *S. aureus* was considered as susceptible to vancomycin.¹³

D-Zone Test (Disk Approximation Test)

The isolates which were resistant to erythromycin were further tested by D-zone test which was performed as per CLSI guidelines by inoculating 0.5 McFarland bacterial suspensions on the Mueller-Hinton agar plates with the help of sterile swabs and placing the erythromycin (E- 15 µg) and clindamycin (CD- 2 µg) disks side by side with edge to edge distance of 15 mm. Plates were analysed after 18 hours of incubation at 35°C.¹²

Phenotypic Inducible Resistance to Clindamycin by D-Test

Isolates were plated on a Muller Hinton agar plate at a McFarland concentration of 0.5 to eventually cover the agar surface. Clindamycin and Erythromycin disks, containing 2 µg and 15 µg each respectively were placed in the center of

the plate separated by a distance of 15 cm between the edges. Plates were incubated at 37° C for 24 hr. Inducible resistance to Clindamycin was defined as blunting of the clear circular area of no growth around the Clindamycin disk on the side adjacent to the Erythromycin disk and was designated D - test positive. Absence of a blunted zone of inhibition was designated D - test negative.

Three different phenotypes of erythromycin resistant isolates were interpreted as follows-

- 1. The constitutive MLSB phenotype (cMLSB):** The *S. aureus* isolates resistant to both E (zone size ≤ 13 mm) and CD (zone size ≤ 14 mm), with circular shape of zone of inhibition if any around clindamycin. This suggests selection of *erm* gene mutants.
- 2. The MS phenotype:** The *S. aureus* isolates which showed resistance to E (zone size ≤ 13 mm) and a complete circular zone of inhibition around CD (zone size ≥ 21 mm), indicated negative D zone test. This suggests resistance due to the *msrA*-coded active efflux pump mechanism.
- 3. The inducible MLSB phenotype (iMLSB):** The *S. aureus* isolates which showed resistance to E (zone size ≤ 13 mm) and susceptibility to CD (zone size ≥ 21 mm) with flattening of zone of inhibition around clindamycin in the area adjacent to the erythromycin (D shaped zone), indicated positive D-zone test. This suggests a resistance phenotype due to expression of *arm*-gene coded methylases.

Statistical Analysis

The collected data was statistically analysed using SPSS Data Editor Software, Chicago, version 20. The statistical association between inducible clindamycin resistance phenotype and methicillin resistant *S. aureus* isolates were evaluated using Chi-square test and $p < 0.05$ was considered as statistically significant.

RESULTS

- Among 110 *S. aureus* isolates included in our study, 59 (54%) were isolated from pus samples, 31 (27.8%) were isolated from blood, 7 (6.2%) were isolated from Urine, 5 (4.8%) were isolated from sputum, and 8 (7.2%) were isolated from miscellaneous samples as shown in (Table 1).
- Out of 110 *S. aureus* isolates, 38 (34.6%) were methicillin resistant (MRSA) and 72 (65.4%) were methicillin-sensitive *S. aureus* (MSSA). (Table 2)
- Out of 110 *S. aureus* isolates of the MRSA 46 (36.6%) were derived from respectively Pus samples 16 (41.53%), the *S. aureus* isolates derived from Wound Samples were MRSA 7 (18.03%), the *S. aureus* isolates derived from Blood Samples were MRSA 9 (22.40%),

the *S. aureus* isolates derived from Miscellaneous Samples were MRSA 5 (13.88%) and the *S. aureus* isolates derived from Urine Samples were MRSA 1 (3.55%). This finding was found to be statistically significant ($p=0.003474$). (Table 2)

- A high percentage of erythromycin resistant *S. aureus* isolates (70%, 77/110) was detected of which 86.89% (33/38) were MRSA and 60.25% (43/72) were MSSA. All the erythromycin resistant isolates were subjected to D-zone test and the resulting distribution of *S. aureus* isolates was shown in (Table 3).
- A total of 26 *S. aureus* isolates showed inducible clindamycin resistance by giving a positive D-zone test, hence, its prevalence was found to be 21.10% (23/110), with percentage distribution of cMLSB phenotype and MS phenotypes in all *S. aureus* isolates as 19.6% and 24.4% respectively. (Table 2) (Figure 1, 2).
- The susceptible phenotype (E-S and CD-S) predominated in MSSA (39.75%) as compared to MRSA (13.11%). Whereas, the constitutive resistant (cMLSB) predominated in MRSA (50.27%) as compared to MSSA (15.46%), Both the MS phenotype and the inducible resistant (iMLSB) phenotypes predominated in MSSA (19.87 and 24.92% respectively) as compared to MRSA (22.40% and 14.20% respectively). This finding was found to be highly significant ($p < 0.00001$). (Table 3)
- The antimicrobial susceptibility test result of all the 24 *S. aureus* isolates with iMLSB phenotype revealed that they were 100% sensitive to vancomycin and linezolid, with moderate sensitivity (71.14%) to gentamicin, cefuroxime and least sensitivity to (23.81%) doxycycline, (20.95%) ciprofloxacin as shown in (Table 4).

Types of Sample	Samples Number	Samples Percentage
Pus	59	54.00%
Blood	31	27.8%
SNCU	11	09.20%
Urine	7	06.20%
Sputum	5	04.8%
Miscellaneous*	8	07.20%
Total	110	100

Table 1. Sample-Wise Distribution of *S. Aureus* Isolates (n=110)

- (Note*: - Miscellaneous samples include ear discharge, abdominal drain fluid, throat swab, conjunctival swab and wound discharges etc.)

Sample	Staphylococcus Aureus			Chi-Square (χ2) & *p-Value
	Resistant to Cefoxitin (MRSA) N = 38 (34.6%)	Susceptible to Cefoxitin (MSSA) N = 72 (65.4%)	Total Isolates N = 110 (100%)	
Pus Due to Any Other Cause, N (%)	16 (41.53%)	33 (45.83%)	49 (44.4%)	Chi²=9.6416 DF=4; P=0.046162
Post-Operative Wound Infection, N (%)	7 (18.03%)	7 (09.73%)	14 (12.6%)	
Blood Samples; N (%)	9 (22.40%)	19 (26.38%)	28 (25.8%)	
Miscellaneous* Sample, N (%)	5 (13.66%)	8 (11.11%)	13 (12%)	Statistically Significant
Urine Due to Any Other Cause, N (%)	1 (4.38%)	5 (06.94%)	6 (5.25%)	
N = Number of Isolates. MRSA = Methicillin Resistant Staphylococcus aureus; MSSA = Methicillin Sensitive Staphylococcus aureus. *p value < 0.05 was considered as statistically significant.				
Table 2. Distribution of Staphylococcus aureus Isolates on the Basis of Sample and Susceptibility to Cefoxitin (30 µg) Disk				

Antibiotic Susceptibility Pattern	Staphylococcus aureus			Chi-Square (χ2) & *p-Value
	MRSA N = 38 (34.6%)	MSSA N = 72 (64.4%)	Total Isolates N = 110 (100%)	
E-S, CD-S (Susceptible Phenotype)	5 (13.11%)	29 (39.76%)	33 (30.00%)	χ2 = 84.001; df = 3 p = 0.00021 Statistically Significant
E-R, CD-R (c MLSB Phenotype) D-zone test= (-)	19 (50.27%)	11 (15.46%)	31 (28.20%)	
E-R, CD-S (MS Phenotype)	9 (22.40%)	14(19.87%)	22(20.08%)	
E-R, CD-S (i MLSB Phenotype) D-Zone Test= (+)	5(14.20%)	18(24.96%)	24 (21.82%)	
N = Number of isolates. MRSA = Methicillin resistant Staphylococcus aureus; MSSA = Methicillin sensitive Staphylococcus aureus; E = Erythromycin (15 µg) disk; CD = Clindamycin (2 µg) disk; S = Sensitive; R = Resistant; cMLSB phenotype = isolates with constitutive resistance to clindamycin; MS phenotype = isolates with susceptibility to clindamycin (circular zone of inhibition) and negative D-zone test; iMLSB phenotype = isolates with inducible resistance to clindamycin and positive D zone test. *p value < 0.05 was considered as statistically significant.				
Table 3. Distribution of Staphylococcus aureus Isolates on The Basis of Their Susceptibility to Erythromycin and Clindamycin Disks Placed Adjacent to Each Other				

Antibiotic Tested	iMLSB Phenotypes N = 24 (100%)	
	Resistant N (%)	Sensitive N (%)
Vancomycin	0(00.00%)	24(100%)
Linezolid	0(00.00%)	24(100%)
Ciprofloxacin	19(79.05%)	5(20.95%)
Cefoxitin	6(24.76%)	18(75.24%)
Gentamicin	6(22.86%)	18 (71.14%)
Cefuroxime	6(22.86%)	18(71.14%)
Amoxiclav	9(36.19%)	15(63.81%)
Amoxicillin	1(33.33%)	2(67.77%)
Doxycycline	18(76.19%)	6(23.81%)
Levofloxacin	10(40%)	14(60%)
N = Number of isolates		
Table 4. Antibiotic Susceptibility Pattern of Inducible Clindamycin Resistant Staphylococcus aureus Isolates (iMLSB Phenotypes) Derived from Infection		



Figure 1. Inducible Clindamycin Resistance *Staphylococcus aureus*

Inducible Clindamycin Resistant *S.aureus* isolates[n=110]

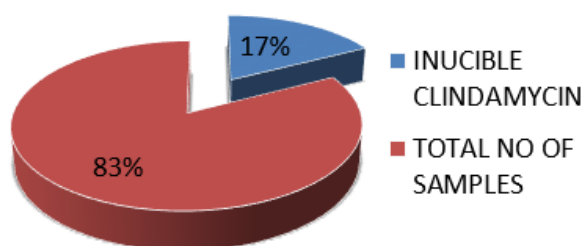


Figure 2. Inducible Clindamycin Resistance *Staphylococcus Aureus*

DISCUSSION

In our study we have included 125 *S. aureus* isolates derived from pus 19 (41.53%), post-operative wound infection 8 (18.03%), blood sample were 10 (22.40%), Miscellaneous Samples were 6 (13.66%) and urine sample 2 (3.75%) from both outpatients and inpatients of orthopaedic department of our institution. The prevalence of methicillin resistance amongst all *S. aureus* isolates was found to be 36.6%. The prevalence of MRSA in other studies was found to vary from 12.9% to 49.8% with the geographical area under study.¹⁴

In the present study, the susceptible phenotypes (susceptible to both erythromycin and clindamycin) were found to predominate in MSSA (39.75%) as compared to MRSA (13.11%). A high percentage of erythromycin resistant *S. aureus* isolates (70%, 88/125) were detected of which 86.89% (40/46) were MRSA and 60.25% (48/79) were MSSA. All these were tested for D-zone test. Amongst them maximum isolates (40.29%, 35/88) were of cMLSB phenotype (D-zone test negative), followed by constitutive and inducible resistance phenotype. This suggests that majority of the erythromycin resistant *S. aureus* isolates can

still be treated successfully with clindamycin. In our study the percentage of inducible clindamycin resistance (iMLSB phenotype, which gave positive D-zone test) amongst erythromycin resistant isolates was 30% (26/88). This is in agreement to studies from Chandigarh and Bangalore which reported inducible resistance to be 26.1% and 22.2% respectively among erythromycin resistant isolates.^{15,16} While in two different studies from Karnataka, the iMLSB phenotype was seen to be quite high in 63% and 55.26% isolates respectively among the erythromycin resistant strains of *S. aureus*.^{17,18}

In our study we also looked forward for treatment options for inducible clindamycin resistant *S. aureus* isolates by detecting their antimicrobial susceptibility to various other antibiotics. It was found that all isolates with iMLSB phenotype were 100% susceptible to linezolid and vancomycin, followed by moderate susceptibility (71, 14%) to gentamicin, cefuroxime and least susceptibility to doxycycline, ciprofloxacin (23.81% and 20.95% respectively). This finding is in concordance to other studies that also found that all the iMLSB isolates were uniformly susceptible to linezolid and vancomycin.^{15,16,19}

CONCLUSION

Clindamycin is an effective oral drug for both methicillin resistant as well as methicillin sensitive *S. aureus*, and is commonly used to treat staphylococcal skin and soft tissue infections. However, it is important for laboratories to be aware of the local prevalence of inducible clindamycin resistant isolates. A therapeutic decision is not possible without the relevant antibiotic susceptibility data. This is where the D zone test becomes significant, as in the absence of D-zone test many erythromycin resistant *S. aureus* isolates would have been misidentified as clindamycin sensitive, but these isolates develop resistance to it during therapy resulting in clinical failure. On the other hand, avoiding clindamycin therapy in every erythromycin resistant *S. aureus* isolate would be inappropriate. Therefore, as recommended by Clinical and Laboratory Standards Institute, D-zone test should be routinely performed in all laboratories thus enabling the laboratory physicians to guide the clinicians regarding judicious use of clindamycin in skin and soft tissue infections; as clindamycin is not a suitable drug for D-zone test positive isolates (iMLSB phenotypes), while it can definitely prove to be a drug of choice in case of D-zone test negative isolates (MS phenotypes).

In our study, we also evaluated treatment options for inducible clindamycin resistant *S. aureus* isolates by detecting their antimicrobial susceptibility to various other antibiotics. It was found that all isolates with iMLSB phenotype were 100% susceptible to linezolid and vancomycin, followed by moderate susceptibility (71, 14%) to gentamicin, cefuroxime and least susceptibility to doxycycline, ciprofloxacin (23.81% and 20.95% respectively). This finding is in concordance to other studies that also found that all the iMLSB isolates were uniformly susceptible to linezolid and vancomycin.

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