Original Article

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Detection and Distribution of Low Level and High Level Mupirocin Resistance among Clinical Methicillin Resistant *Staphylococcus aureus* Isolates

Microbiology Section

P GANESH PERUMAL[1], SUBISHA KANNAN[2], B APPALARAJU[3]

ABSTRACT

Introduction: Prolonged and improper use of antibiotics increases the resistance among pathogens and leads to life-threatening implications and increases mortality. The incidence of mupirocin resistance in Methicillin Resistant *Staphylococcus aureus* (MRSA) clinical isolates were reportedly increasing.

Aim: To determine the rate of high level and low level mupirocin resistance in clinical MRSA isolates in a tertiary care hospital.

Materials and Methods: A cross-sectional study was carried out for a period of three months from December 2019 to February 2020 in Department of Microbiology, PSG Institute of Medical Sciences and Research (PSG IMSR), Coimbatore, Tamil Nadu, India. A total of 100 non duplicate *Staphylococcus aureus* isolates from different specimens were subjected to mupirocin susceptibility by Kirby-Bauer disc diffusion method as per Clinical and Laboratory Standards Institute (CLSI) 2019 standards. The low (MuL) and high (MuH) level mupirocin resistance were detected by using 5 and 200 µg mupirocin discs (Himedia) respectively. The isolate exhibiting diameter of ≥14 mm indicates its susceptibility. The isolate exhibiting diameter ≤13 mm for both 5 and 200 µg indicates MuL and MuH strains respectively. Pearson's Chi-square test was calculated and p-value of <0.05 was considered as statistically significant.

Results: Total 51% *Staphylococcus aureus* isolates were found to be MRSA. In present study, 6 out of 51 (11.8%) MRSA isolates were found to exhibit MuL and 5 out of 51 (9.8%) MRSA isolates were found to be having MuH. Low level and high level mupirocin resistance were not observed in Methicillin Sensitive *Staphylococcus aureus* (MSSA).

Conclusion: The incidence of MuH and MuL resistance among MRSA were found to be 9.8% and 11.8%, respectively. Screening for mupirocin resistant MRSA to be carried out periodically and stringent infection control practices to be in place to prevent further spread of mupirocin resistant MRSA.

Keywords: Clinical isolates, Inducible clindamycin resistance, Mupirocin resistant *Staphylococcus aureus*

INTRODUCTION

Staphylococcus aureus is one of the most commonly reported nosocomial pathogen known to cause wide range of infections mainly from skin and soft tissue infections to bloodstream infections [1]. MRSA was considered as a potential pathogen in both community and hospital acquired infections associated with increasing morbidity and mortality among the hospitalised patients [2]. Being a normal flora, *S. aureus* colonise in nasal area and skin has been indiscriminately exposed to various antibiotics, thus acting as a potential risk for the acquisition of MRSA [3]. Removal of *Staphylococcus aureus* from the carriage sites reduces the spread of MRSA and it serves as a perfect modality for treating superficial infections [4].

As MRSA isolates were resistant to most of the antibiotics, Pseudomonic acid A derived from *Pseudomonas fluorescens* commonly known as mupirocin was used for treating topical infections. Mupirocin acts as a protein synthesis inhibitor by binding to isoleucyl-tRNA synthetase of bacteria [5]. Irrational use of mupirocin leads to alteration of isoleucyl-tRNA synthetase gene mutation resulting in development of resistance towards mupirocin [5]. The level of resistance can be two types, low level (MuL) and high level (MuH). The concomitant use of mupirocin with the varying concentration of 5 µg and 200 µg helps in differentiating MuL and MuH strains, and for disk diffusion zone diameter of ≥14 mm with a 5 µg and 200 µg disc was considered as susceptible while zones of ≤13 mm as resistant [6]. The strain with low level resistance (MuL) exhibit the MICs between 8-256 µg/mL whereas, high level resistance (MuH) with MICs ≥512 µg/mL [6]. Mupirocin use has been linked to the formation of resistance due to increased selective pressure and cross-transmission. Mupirocin therapy for wounds and pressure sores available for over the counter use is strongly linked to resistance [4].

However, the emergence of mupirocin resistance following increased use has not been consistently reported; the degree of mupirocin resistance in our area needs to be monitored for effective antibiotic recommendation; and a comprehensive understanding of all these factors underlying the dynamics of mupirocin resistance in hospitals needs to be researched extensively. Thus present study, aims to determine the rate of resistance towards commonly used antibiotics, mupirocin resistance among MRSA/ MSSA and also in determining the inducible resistance towards clindamycin.

MATERIALS AND METHODS

This cross-sectional study was conducted for the period of three months from December 2019 to February 2020 in PSG Institute of Medical Sciences and Research (PSG IMSR), Coimbatore, Tamil Nadu, India. The study was approved by the Institutional Ethical Committee (IEC) (Ref No: PSG/IHEC/2020/Appr/Exp/035) and informed consent was taken prior to the study.

Inclusion criteria: Various samples like pus, blood, wound swab, urine and sputum were processed for the isolation of *S. aureus* isolates. All staphylococcal isolates obtained during the study period were included in the study.

Exclusion criteria: All other isolates containing other than *Staphylococcus aureus* were excluded.

Sample Procedure

The samples were initially subjected to microscopic observation and cultured onto blood agar and Mac Conkey agar. A total of 100 non duplicate *Staphylococcal aureus* isolates were identified by appropriate biochemical reactions (Catalase test, slide and tube coagulase test and mannitol fermentation test) and were selected for the further study.

Antibiogram of isolates: Antibiogram of all the isolates were studied as per CLSI 2019 guidelines [7] using Kirby-Bauer's disk diffusion method. Test isolates were originally inoculated onto peptone water and the inoculum turbidity was adjusted to 0.5 McFarland standard after incubation. The susceptibility testing was done using amoxy-clavulanic acid (30 µg), cloxacillin, clindamycin (2 µg), co-trimoxazole (1.25 µg/23.75 µg), cephalothin (30 µg), cefazolin (5 µg), doxycycline (30 µg), erythromycin (15 µg), gentamicin (10 µg), linezolid (30 µg), penicillin (10 units), rifampicin (5 µg), vancomycin (30 µg) discs onto Mueller-Hinton agar (MHA) plate. Cefoxitin (30 µg) disc is the surrogate marker for the detection of MRSA. Zone diameter ≤21 mm was recorded to be MRSA and zone diameter ≥22 mm was recorded to be MSSA. Cefoxitin disc (30 µg) was used to assess the sensitivity of cloxacillin as recommended by CLSI guidelines [7]. The zone diameters were read by using both reflected and transmitted light after overnight incubation. *S. aureus* American Type Culture Collection (ATCC) 25923 has been used as control.

The 'D' test was performed for determining the inducible clindamycin resistance among the test isolates. Erythromycin (a macrolide) and clindamycin (a lincosamide) represent two distinct classes of antimicrobial agents that acts by inhibiting protein synthesis. In staphylococci, resistance to both of these antimicrobial agents can occur through methylation of their ribosomal target site. Isolates with inducible resistance are resistant to erythromycin but appear susceptible to clindamycin in routine in-vitro testing [8]. Clinical failures of clindamycin therapy for the treatment of MRSA infections have been documented for strains that were clindamycin sensitive but erythromycin resistant. The failures were due to inducible resistance to clindamycin. It can be detected by using erythromycin disc placed at the distance of 15 mm from clindamycin disc on the MHA plate. The flattening 'D' zone around clindamycin between two antibiotics after incubation indicates the inducible clindamycin resistance [8].

Detection of mupirocin resistance: The low (MuL) and high (MuH) level mupirocin resistance were detected by disc diffusion method (Himedia, Mumbai, India) using 5 and 200 µg mupirocin discs respectively. The isolate exhibiting diameter of ≥14 mm indicates its susceptibility. The isolate exhibiting diameter ≤13 mm for both 5 and 200 µg indicates MuL and MuH strains, respectively [6].

STATISTICAL ANALYSIS

MSSA, MRSA, mupirocin susceptible, and resistant isolate proportions were estimated and the pattern of susceptibility to regularly used antibiotics, were tabulated using frequency tables. Pearson's Chi-square test was calculated, and p-value of <0.05 was considered statistically significant. Statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS) version 21.0 Chicago, USA.

RESULTS

Among various samples processed during the study period, only 100 isolates were identified as *S. aureus*. Based on the cefoxitin susceptibility, the isolates were categorised as MRSA (51%) and MSSA (49%). In determining the sample wise distribution, the majority of MRSA were isolated from blood 22 (43.1%) followed by wound swab 20 (39.2%) whereas, majority of MSSA were isolated from wound swab 30 (61.2%) followed by pus 11 (22.4%) [Table/Fig-1].

The incidence of inducible resistance towards clindamycin was screened by 'D test' method. Among the MRSA (51) isolates,

Sample	MRSA, n (%)	MSSA, n (%)
Blood	22 (43.1)	4 (8.2)
Wound swab	20 (39.2)	30 (61.2)
Pus	6 (11.8)	11 (22.4)
Sputum	3 (5.9)	1 (2.1)
Urine	0	3 (6.1)
Total	51 (100)	49 (100)

[Table/Fig-1]: Distribution of MRSA and MSSA isolates in different clinical samples.

18 (35.3%) isolates were found to exhibit the inducible clindamycin resistance. Among MSSA (49) isolates, 5 (10.2%) isolates were found to show inducible clindamycin resistance. The incidence of inducible clindamycin resistance was found to be higher in MRSA isolates [Table/Fig-2].

Isolates	Number	Inducible clindamycin resistance (%)
MRSA	51	18 (35.3%)
MSSA	49	5 (10.2%)

[Table/Fig-2]: Distribution of Inducible clindamycin resistance in MRSA and MSSA isolates.

All staphylococcal isolates were screened for mupirocin sensitivity. About 6 (11.8%) MRSA isolates exhibited low level resistance to mupirocin, whereas 5 (9.8%) isolates were found to be high level mupirocin resistance [Table/Fig-3]. All MSSA isolates obtained in the study were found to be susceptible for mupirocin.

	Mupirocin sensitive	Mupirocin resistant	MuL (%)	MuH (%)
MRSA	45 (88.2%)	6 (11.8%)	6 (11.8%)	5 (9.8%)
MSSA	49 (100%)	0	0	0

[Table/Fig-3]: Comparison of mupirocin resistance with MRSA and MSSA isolates.

Majority of MRSA isolates from blood samples were found to be mupirocin resistant. Among these, around 4 (18.2%) isolates were found to be low level mupirocin resistant and 3 (13.6%) isolates were found to be high level mupirocin resistant. In pus samples, none of them were found to show low level and high level mupirocin resistant [Table/Fig-4].

Sample	MRSA, n (%)	Low level Mupirocin resistant, n (%)	High level Mupirocin resistant, n (%)
Blood	22 (43.1)	4 (18.2)	3 (13.6)
Wound swab	20 (39.2)	1 (5)	1 (5)
Sputum	3 (5.9)	1 (33.3)	1 (33.3)
Pus	6 (11.8)	0	0
Total	51 (100)	6 (11.8)	5 (9.8)

[Table/Fig-4]: Distribution of low level and high level mupirocin resistance in MRSA isolates.

All the staphylococcal isolates were tested with antibiotics, all the MRSA isolates were found to be sensitive to linezolid (100%) and vancomycin (100%). All MRSA isolates were found to be resistant to penicillin (100%), cloxacillin (100%), cefazolin (100%), cephalothin (100%) and amoxy-clavulanic acid (100%). Co-resistance was found in erythromycin (76.4%), doxycycline (68.6%) and rifampicin (58.8%). Co-trimoxazole and gentamicin were less resistant.

All the MSSA isolates were found to have maximum sensitivity to cloxacillin (100%), cefazolin (100%), cephalothin (100%), amoxy-clavulanic acid (100%), linezolid (100%) and vancomycin (100%) followed by doxycycline (89.8%) and erythromycin (89.8%). Rate of resistance for MSSA isolates were found to be higher to penicillin (83.7%), followed by clindamycin (24.5%). The rate of resistance was statistically significant to all tested antibiotics including mupirocin (both MuH and MuL) except gentamicin [Table/Fig-5].

Antibiotics	*Staphylococcus aureus* n=100		p value
	Resistant isolates in MRSA, n (%)	Resistant isolates in MSSA, n (%)	
Penicillin (10 units)	51 (100)	41 (83.7)	0.003
Cloxacillin	51 (100)	0	<0.001
Amoxy-clavulanic acid (30 µg)	51 (100)	0	<0.001
Cephalothin (30 µg)	51 (100)	0	<0.001
Cefazolin (5 µg)	51 (100)	0	<0.001
Erythromycin (15 µg)	39 (76.4)	5 (10.2)	<0.001
Clindamycin (2 µg)	29 (56.8)	12 (24.5)	0.001
Co-trimoxazole (1.25/23.75 µg)	25 (49)	10 (20.4)	0.003
Gentamicin (10 µg)	10 (19.6)	7 (14.2)	0.48
Doxycycline (30 µg)	35 (68.6)	5 (10.2)	<0.001
Rifampicin (5 µg)	30 (58.8)	0	<0.001
Linezolid (30 µg)	0	0	NA
Vancomycin (30 µg)	0	0	NA
Mupirocin (5µg)	6 (11.7)	0	0.01
Mupirocin (200 µg)	5 (9.8)	0	0.02

[Table/Fig-5]: Antimicrobial susceptibility pattern of isolates.
NA: Not applicable; p-value <0.05 considered significant

DISCUSSION

Mupirocin has been widely used for management of colonisation and infection of *S. aureus* in both medical personnel and patients. Soon after two years of mupirocin introduction, first mupirocin resistant *S. aureus* isolate was reported from the UK (1987). Globally mupirocin-resistance was increased in MRSA as irrational, uncontrolled, prolonged and multiple courses of this drug are the main reasons for the development of resistance [9]. This study focuses on determining the low level and high level mupirocin resistance in *Staphylococcus aureus* isolates. In the present study, about 100 non duplicated isolates (*S. aureus*) obtained during the study period were included for the further analysis of which 51 isolates (51%) were MRSA and 49 isolates (49%) were MSSA. The rate of high level and low level mupirocin resistance among MRSA were found to be 9.8% and 11.8% respectively. Similarly, in a study conducted by Dardi CK and Rudresh MS et al., the rate of high level mupirocin-resistant MRSA was 5.99% and 14.7 respectively, and low-level mupirocin resistance was 15.35% and 10.5%, respectively [10,11], which concords with the present study. Whereas Orrett FA and Vasquez JE et al., observed the higher rate of low level and high level mupirocin resistance to the tune of 26% and 44%, 58% and 42% respectively [12,13]. In above studies the rate of resistance varies according to the demographic condition, local antibiotic policy and sample number.

In the present study, the incidence of MRSA were found to be high in blood samples (43.1%) followed by wound swab (39.2%). Nada KK et al, reported lower incidence of *Staphylococcus aureus* from blood (14%) and deep wounds (13.5%) [14]. Clindamycin has emerged as an effective treatment for various *Staphylococcus aureus* infections, particularly skin and soft tissue infections, and as a penicillin substitute in penicillin-allergic patients. Reporting *S. aureus* without checking for inducible resistance may result in treatment failure. In present study, the incidence of inducible resistance were studied against all isolates and the rate were found to be high in MRSA isolates (35.3%) when compared to MSSA isolates (10.2%). Similarly, the incidence of inducible clindamycin resistance were found to be high in MRSA isolates (24.8%) in the study conducted by Majhi S et al., [15]. In present study, MRSA isolates were found to show 76.4% and 56.8% being resistance to erythromycin and clindamycin, respectively. Similar result reported by Adhikari RP et al., in which MRSA isolates showed higher rate of resistance to erythromycin (68.42%) and clindamycin (45.71%) and none of the MRSA isolates were found to be resistant to vancomycin and linezolid [16].

In present study, all the isolates (100) were found to be sensitive towards linezolid and vancomycin. All MRSA isolates were found to be resistant to penicillin, cefazolin, cefalothin, cloxacillin, and amoxy-clavulanic acid as expected. This report was concords with the study conducted by Ghosh S and Banerjee M, where all isolates sensitive to vancomycin (100%) and linezolid (100%) [17].

MRSA isolates were found to show higher rate of resistance to all beta-lactam antibiotics (100%) followed by erythromycin (76.4%) and doxycycline (68.6%). The rate of resistance coincides with the study conducted by Madhumati B et al., where all isolates were resistant to beta-lactam antibiotics followed by erythromycin (86%) and tetracycline (60%) [4].

Similarly, in screening of inducible clindamycin resistance, it was found to be higher in MRSA as compared to MSSA. In present study, MRSA isolates showed higher rate of resistance than MSSA isolates to erythromycin (76.4% vs 10.2%) and clindamycin (56.8% vs 24.5%). Thus present study correlates with the study conducted by Adhikari RP et al., in which MRSA isolates showed higher rate of resistance than MSSA isolates to erythromycin (88.2% vs 39.1%) and clindamycin (71.4% vs 41.9%) [16]. Similar to present study, none of the MRSA isolates were found to be resistant to vancomycin and linezolid, as reported by Adhikari RP et al., [16].

Vancomycin or linezolid are two medicines routinely used to treat MRSA infections. Mupirocin is a topical antibiotic that is efficient in eradicating MRSA in carriers [3]. It is approved for the treatment of superficial skin and soft tissue infections, and some evidence suggests that widespread use in the community for this purpose can lead to an increase in resistance [5]. Nasal application of mupirocin in MRSA carriers may result in the presence of low levels of the antibiotic in the pharynx, which could induces the emergence of mupirocin resistant MRSA. Detecting and distinguishing between the two types (MuL and MuH) has significant therapeutic implications. High-level mupirocin resistance (MuH) precludes its usage in therapeutic settings; however, low-level mupirocin resistance (MuL) can be overcome by prescribing a higher-than-usual dose [5]. The risk of emergence of resistance appears to be greater among MRSA, and is often associated with widespread use of mupirocin [16]. As a result, clinical laboratories must be able to distinguish between susceptible and resistant strains as well as determine the level of resistance (MuL and MuH) [17].

In sample wise distribution, the MRSA isolates from blood samples predominantly revealed mupirocin resistance. About 4 (18.2%) isolates were found to be low level mupirocin resistant and 3 (13.6%) isolates were found to be high level mupirocin resistant. Among wound swab (20 isolates), 1 (5%) isolate exhibited low and 1 (5%) isolate exhibited high level mupirocin resistance. Among sputum (3 isolates) samples, 1 (33.3%) isolate exhibited low level and 1 (33.3%) isolate exhibited high level mupirocin resistance in present study. In urine samples, none of them were found to show mupirocin resistance. Similarly in sample wise distribution, higher rate of mupirocin resistance (MuL and MuH) were from pus (26.92% and 10.25%), followed by blood (17.14% and 5.71%), sputum (15.38% and 6.15%), and the lowest was in urine (1.42% and 0%) respectively, as reported by various studies [Table/Fig-6] [9-11,18-20].

Author name [Ref no.]	Place	Year of publication	Rate of MuL (%)	Rate of MuH (%)
Kumar D et al., [9]	Uttar Pradesh	2020	4	9
Dardi CK [10]	Maharashtra	2014	15.35	5.99
Rudresh MS et al., [11]	Karnataka	2015	10.51	14.7
Jayakumar S et al., [18]	Tamil Nadu	2013	0	2.2
Kavitha E and Srikumar R [19]	Pondicherry	2019	15	8
Vijaya S et al., [20]	Karnataka	2018	1	1
Present study	Coimbatore	2022	11.8	9.8

[Table/Fig-6]: Comparison of Mupirocin resistance.

The *mupA* gene is typically found on mobile genetic elements most of time. The "gold standard" method for detection of mupirocin resistance is Minimum Inhibitory Concentrations (MIC) determination by the agar dilution method [21]. In present study, authors used the disc diffusion method for detection of low and high-level mupirocin resistance. Malaviolle X et al., have previously tested sensitivity and specificity of this method. The results of the disc diffusion test were obtained with the concurrent use of 5 µg and 200 µg mupirocin discs. They found that the sensitivity and specificity of 5 µg disc was 100% and 98.1%, respectively, whereas that of 200 µg disc was 100% and 92.3%, respectively, separating MuH in MuL [22]. As a result, the disc diffusion susceptibility test is a less expensive and straight forward option for frequent use.

The presence of mupirocin resistance among MRSA isolates is concerning because mupirocin resistant bacteria have few effective options. Although polysporin triple ointment has been used in the field, no research on its effectiveness has been conducted. When coupled with other antibiotics like vancomycin, fusidic acid has been demonstrated to be successful in the systemic treatment of MRSA, but not when taken alone [23]. As a topical alternative to mupirocin, hydrogen peroxide cream has been suggested [24].

When MRSA is discovered in a healthcare worker, it is routinely treated with 7-day chlorhexidine baths and topical 2% mupirocin ointment, as well as time off or displacement from duty until two negative culture reports are obtained. As a result, all isolates obtained from nasal carriers should be screened with mupirocin (with 5 µg discs and 200 µg discs) before to starting medication, so that MuH strains can be treated with alternate options such as fusidic acid, neomycin, or possibly the newer reptapamulin [23,25].

If various actions are made in the near future, the emergence of mupirocin resistance can be restricted. First of all, more research is needed to determine the efficacy and unintended consequences of using mupirocin as a preventative measure. Then if mupirocin is to be consistently used, a method for monitoring the rate of resistance should be created and executed. The monitoring strategy should not just focus on mupirocin resistance, but also on determining whether mupirocin use could increase the spread of multidrug resistance by linking it to other resistance determinants. Currently, there are no commercially accessible test kits available. Even as testing methods become more widely available, more information is needed to instruct doctors and healthcare facilities on how to appropriately use these tools to guide therapeutic and prophylactic mupirocin use.

Limitation(s)

Mupirocin resistant MRSA isolates can be detected by genotypic methods, such as Polymerase Chain Reaction (PCR) as a final confirmatory test. The lack of confirmatory test is a limitation of present study. Additional studies with larger sample size would be helpful to understand the clinical significance of both high level and low level mupirocin resistance.

CONCLUSION(S)

The rate of high level (9.8%) and low level mupirocin resistance (11.8%) in MRSA is a cause for concern. As a result, even in hospitals where mupirocin is not used, routine testing of MRSA for mupirocin resistance is suggested. This will aid in the early detection of resistance, as well as the control and spread of mupirocin-resistant MRSA in a healthcare settings.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Microbiology, PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India.
2. Student, Department of Microbiology, San International College of Arts and Science, Coimbatore, Tamil Nadu, India.
3. Professor and Head, Department of Microbiology, PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. P Ganesh Perumal,
Assistant Professor, Department of Microbiology, PSG Institute of Medical Sciences and Research, Peelamedu, Coimbatore-641004, Tamil Nadu, India.
E-mail: drganeshp2014@gmail.com

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