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Original Article

mupA Mediating Mupirocin Resistance among Clinical Isolates of Staphylococci

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ABSTRACT

Introduction: Mupirocin is used to decolonize methicillin resistant Staphylococcus aureus (MRSA). It acts by inhibiting protein synthesis. Resistance to mupirocin is mediated by the mupA gene. MRSA have a highpropensity of acquiring resistance to mupirocin. Coagulase negative Staphylococci (CONS) are thought to be reservoirs for several resistance genes including mupA. Hence, this study was undertaken the mechanism of mupirocin resistance among clinical isolates of Staphylococci.

Materials and Methods: A total of 336 clinical isolates of Staphylococci were included in this study. Methicillin was detected by phenotypic and genotypic methods. Low and High mupirocin resistance was detected using 5µg and 200µg disc. Presence of mupA was detected by polymerase chain reaction (PCR).

Results: Among the 336 Staphylococci of the current study, 133 were Staphylococcus aureus and 203 were CONS. A total of 85 isolates which included 29 low level and 56 high level mupirocin resistant isolates. Only 53 isolates harbored the mupA gene.

Conclusion: Mupirocin resistance in Staphylococcus aureus and CONS, should be monitored vigilantly. Prudent use of mupirocin and strengthening execution of infection control measures should be mandated to curtail the spread of resistance.

Key Words: *Staphylococcus aureus, CONS, MRSA, MRCONS, mupirocin resistance, mupA*

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INTRODUCTION

Methicillin-resistant Staphylococcus aureus (MRSA) is one of the most common pathogens that causes nosocomial and community related infections. The anterior nares are the primary reservoir for MRSA. Colonizing strains act as endogenous reservoirs for prominent clinical illnesses or disseminate to other individuals, infecting them [1]. It acts by inhibiting protein synthesis by binding to the bacterial isoleucyl t-RNA synthetase enzyme that is encoded by the *ileS* gene [2]. Mupirocin is principally used to decolonize patients and health care workers from MRSA. Given this selective use, MRSA has a higher frequency of mupirocin resistance than methicillin sensitive *Staphylococcus aureus* (MSSA). There are two types of mupirocin resistance levels: low level mupirocin resistance (MupL) and high-level mupirocin resistance (MupH). Point mutations in the native isoleucyl tRNA synthetase (IRS) gene (*ileS*) cause low level mupirocin resistance. High level resistance is caused by *mupA* (ileS2), a plasmid mediated gene that produces a second modified IRS with lower affinity for mupirocin. Recently, a novel *mupB* gene mediating high level mupirocin resistance has been reported. A higher frequency of MupH may potentially be attributable to selective reports from hospital MRSA outbreaks. There is diminutive research in the general prevalence of mupirocin resistance among coagulase negative *Staphylococci*. The mechanism of mupirocin resistance in *Staphylococcus* species has not been studied extensively in Indian isolates [3]. Hence, this study was undertaken to understand the mechanism of mupirocin among the clinical isolates of Staphylococci in a tertiary care centre.

MATERIALS AND METHODS

Bacterial isolates

The study was conducted in a 1600 bed university teaching hospital in South India from 2019 to 2021. A total of 336 clinically significant, consecutive, non-repetitive *Staphylococci* isolated from patients hospitalized for >48 hours were included in the study. Repetitive isolates from the same patients and isolates from out-patients were excluded from the study. Clinical history of the all the study patients was collected from the medical records department retrospectively. The study protocol was approved by Institutional Ethics Committee (REF: IEC-NI/19/FEB/68/12).

The source of the isolates was exudates (n=200), blood (n=113), urine (n=20) and respiratory specimens (n=3). The significance of the study isolates was ascertained by correlating with Gram stain, significant growth in cultures and the patient clinical history. The isolates were identified up to species level by standard biochemical tests and automated systems: VITEK2 GP-card (bio Merieux, Marcy l'Etoile, France) and MALDI-TOF MS (bio Merieux, Marcy l'Etoile, France).

Phenotypic methods

Antimicrobial susceptibility testing

Susceptibility various classes of antimicrobial agents done by Kirby Bauer disc diffusion method using CLSI 2019 [CLSI-M100-S29] guidelines [4]. The antibiotics tested: ampicillin (10µg), cefuroxime (30µg), erythromycin (30µg), clindamycin (2µg), amikacin (30µg), ciprofloxacin (5µg), linezolid (30µg) and teicoplanin (30µg). Methicillin resistance was detected using cefoxitin (30µg) and oxacillin (1µg) disc. Low level and high-level mupirocin resistance were detected using mupirocin disc with concentration of 5µg and 200µg respectively (Himedia Laboratories, India)

Genotypic methods

DNA template preparation:

DNA was extracted from the study isolates by boiling method [5]. A single colony was inoculated from nutrient agar plate was mixed into 1.5ml of sterile water. This was centrifuged at 12,000 rpm for 10 minutes. Further they were lysed by heating at 100ºC for 10 minutes and centrifuged for one minute. The supernatant was used as template for amplification reactions.

Polymerase Chain Reaction (PCR)

All the isolates were subjected to molecular confirmation using the species specific *nuc* gene. *MecA* and *mecC* gene was amplified to detect methicillin resistance [6, 7]. Mupirocin resistance was detected by amplifying the *mupA* [8]. Each reaction contained 10pmol of each primer (Eurofins, India) and 23µl of master mix (Takara, India) and 2µl of template DNA.

The amplicons were separated in a 2% agarose gel containing ethidium bromide (Figure 1). The primers used are described in Table 1. Previously, characterized strains were used as positive controls. Sterile Mili Q water was used as negative controls. The obtained sequences were submitted in the GenBank database under the following accession numbers: OQ572694- *mupA*, ON249039- *mecA*

Table 1: Primer sequences used in the current study

Primersformethicillin resistance		
	GAAATGACTGAACGTCCGATAA	
	ATTCCACATTGTTTCGGTCTAA	
	AAAAAGGCTTAGAACGCCTC	
	GATCTTTTCCGTTTTCAGC	
Primerformupirocinresistance		
	ATTATGCGATGGAAGGTTGG	
	AAAATCAGCTGGAAAGTGTTG	

Statistical analysis

Statistical analysis was done by using SPSS software 16.0 version (IBM Corp., New York, USA). Chi-square test and Fisher's Exact Test The p-value of <0.05 was considered as statistically significant.

RESULTS

Bacterial isolates:

Three hundred and thirty-six clinical isolates of *Staphylococci* were collected from patient specimens, of which 40% (133/336) were *Staphylococcus aureus* and 60% (203/133) were Coagulase negative *Staphylococci*.

Source specimens of the study isolates

Among the Staphylococcus isolates, *Staphylococcus aureus* was isolated from various specimens such as exudate (105) followed by blood (18), urine (7) and respiratory specimens (3).

Among the CONS, majority were isolated from exudates and blood with 95 from each of them. In the present study, 14 different species of CONS were identified, of which the most common were *Staphylococcus haemolyticus* (84), *Staphylococcus hominis* (50) *and Staphylococcus epidermidis* (39) and other species such as *Staphylococcus cohnii*, *Staphylococcus saprophyticus*, *Staphylococcus sciuri*, *Staphylococcus capitis*, *Staphylococcus xylosus*, *Staphylococcus arlattae*, *Staphylococcus hycius*, *Staphylococcus intermedius*, *Staphylococcus pasteurii*, *Staphylococcus simulans* and *Staphylococcus warneri* were isolated less frequently. (Table 2)

Table 2: Distribution of CONS in the clinical specimens

Specimen (203)	Exudates(95)	Blood(95)	Urine(13)
Staphylococcushaemolyticus (84)	38	36	10
Staphylococcushominis(50)	30	20	-
Staphylococcusepidermidis(39)	13	23	3
Staphylococcuscohnii(7)	4	3	-
Staphylococcussaprophyticus (4)	3	1	-
Staphylococcussciuri(4)	1	3	-
Staphylococcuscapitis(4)	-	4	-
Staphylococcusxylosus (3)	2	1	-
Staphylococcusarlattae (3)	1	2	-
Staphylococcushycius (1)	-	1	-
Staphylococcusintermedius (1)	1	-	-
Staphylococcuspasteurii(1)	-	1	-
Staphylococcussimulans(1)	1	-	-
Staphylococcuswarneri(1)	1	-	-

Antimicrobial susceptibility testing

Of the 336 clinical isolates, the resistance exhibited to various classes of antimicrobials is as follows: ampicillin (81.2%), erythromycin (63%), clindamycin (37.5%), ciprofloxacin (56.8%), gentamicin (30.6%), cefoxitin (52.3%), cefuroxime (52.3%), cefotaxime (52.3%) and linezolid (0.89%). All the isolates were susceptible to vancomycin and teicoplanin.

Mupirocin resistance

Of the 336 study isolates, 85 exhibited mupirocin resistance. Of the 85 mupirocin resistant isolates, low level and high-level mupirocin resistance were detected in 29 and 56 isolates respectively.

In this study, among the mupirocin resistant *Staphylococcus aureus*, 12 isolates exhibited low level mupirocin resistance and high-level mupirocin resistance was observed in 4 isolates.

However, among the mupirocin resistant CONS, high level mupirocin resistance was seen in 52 isolates and low-level resistance was exhibited by 17 isolates. Mupirocin resistance was not detected in *Staphylococcus hycius, Staphylococcus pasteurii and Staphylococcus sciuri*. The results of the mupirocin disc diffusion method are depicted in the Table 3. Distribution of mupirocin resistance among the methicillin susceptible and methicillin resistant isolates is given in Table 4.

Table 3: Mupirocindisc diffusiontest

Specimen	Low-levelmupirocin(n=29)	High-levelmupirocin(n=56)
Staphylococcusaureus (133)	12	4
Staphylococcushaemolyticus (84)	3	30
Staphylococcushominis(50)	10	6
Staphylococcusepidermidis(39)	2	8
Staphylococcuscohnii(7)	-	2
Staphylococcussaprophyticus (4)	-	1
Staphylococcuscapitis(4)	1	1
Staphylococcusxylosus (3)	-	1
Staphylococcusarlattae (3)	-	1
Staphylococcusintermedius (1)	1	-
Staphylococcussimulans(1)	-	1
Staphylococcuswarneri(1)	-	1

Table 4: Mupirocinsusceptibilityamongmethicillinresistant *Staphylococci* species

Mupirocin	*Staphylococcusaureus*		CONS		Total
	MSSA	MRSA	MSCONS	MRCONS	
Susceptible	74	43	72	62	251
MupL	5	7	5	12	29
MupH	0	4	4	48	56
Total	79	54	81	122	336

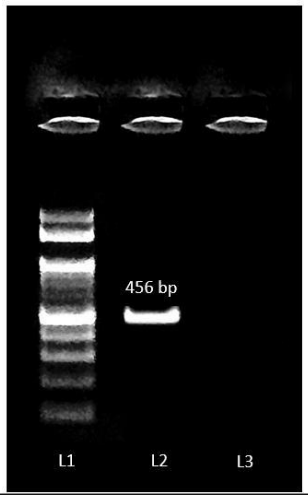
Polymerase Chain Reaction (PCR)

Detection of *mecA*/*mecC* encoding methicillin resistance by PCR

MecA was detected in 52.3% (176/336) isolates which included MRSA 40% (54/133) and MRCONS 60% (122/203). The *mecC* was not detected in any of the isolates.

Detection of *mupA* gene encoding mupirocin resistance by PCR

The *mupA* gene was harbored by 3.7% (5/133) of *Staphylococcusaureus* isolates and among the CoNS, 23.6% (48/203) carried the *mupA* gene. (Figure 1) Table 5 depicts the distribution of the *mupA* gene among the clinical *Staphylococci* isolates.



Lane1–100bpladder
Lane 2 – *mupA* (456 bp) Lane3–negativecontrol

Figure 1: mupAgene

Among the 5 mupirocin resistant *Staphylococcus aureus* that carried the *mupA* gene, 4 were MRSA and 1 was MSSA. The *mupA* gene was harbored by 44 MRCONS and 4 MSCONS.

Table 5: Detection of *mupA*geneencodingmupirocin resistanceby PCR

Species	*mupA*(n=53)	Lowlevel(n=4)	Highlevel(n=49)
Staphylococcusaureus (133)	5	1	4
Staphylococcushaemolyticus (84)	30	1	29
Staphylococcusepidermidis(39)	8	1	7
Staphylococcushominis(50)	6	1	5
Staphylococcuscapitis(4)	1	0	1
Staphylococcussimulans(1)	1	0	1
Staphylococcuswarneri(1)	1	0	1
Staphylococcusxylosus (3)	1	0	1

DISCUSSION

In the current study, majority of the *Staphylococcus aureus* was isolated from exudative specimens followed by blood. *Staphylococcus aureus* is commonly associated with skin and soft tissue infections followed by bloodstream infections [9]. CoNS are becoming significant nosocomial pathogens, with *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* being the most frequently documented species. The growing number of immunocompromised hospitalized patients, combined with the rising use of invasive devices and implants, has resulted in the increasing reputation of these organisms in health care settings. CoNS are difficult to treat due of greater number of isolates displaying methicillin and multidrug resistance. In the current study, the methicillin resistance among the clinical isolates of *Staphylococcus aureus* is 40% (54/133) and 60% (122/203) were methicillin resistant CONS.

In the current study, 25.2% (85/336) of the Staphylococci isolates exhibited resistance to mupirocin. Mupirocin resistance has been reported in many parts of the globe with a range as low as 1.4% to as high as 45% [10]. The clinical characteristics of the study patients, the source of the isolates and the geographic location all affect this rate substantially.

Mupirocin resistance in *Staphylococcus aureus*

In the current study, among the 16 mupirocin resistant *Staphylococcus aureus*, 12 isolates exhibited low level

mupirocin resistance (MupL) and 4 isolates were high level mupirocin resistant (MupH). All the 4 MupH isolates were isolated from exudative specimens, this is consistent with other reports of high-level mupirocin resistant *Staphylococcus aureus* causing skin and soft tissue infections. In the current study, mupirocin resistance was detected in 20.3% (11/54) MRSA and 6.3% (5/79) MSSA respectively. Among the 11 MRSA, four isolates exhibited high level mupirocin resistance while seven isolates were low level mupirocin resistant. All the five MSSA exhibited low level mupirocin resistance only. A recent study from India also reported that none of the MSSA exhibited high level mupirocin resistance [10]. In contrast, a study from China, reported high level resistance among MSSA [11]. The present study, found a higher resistance to mupirocin when compared to a study from China, the frequencies of mupirocin resistance was 2.31% (13/563) and 1.69% (13/770) and postulated that dissemination of MRSA could be the cause of spread of mupirocin resistance. This emphasizes the significance of strategies to stop the spread of hospital clones [11].

Mupirocin resistance in CoNS

In the present investigation, among the 203 CoNS, 69 isolates exhibited mupirocin resistance among which, 17 exhibited low level resistance to mupirocin and 52 high level mupirocin resistance. The resistance to mupirocin was higher in CoNS than in *Staphylococcus aureus*, which is a cause for concern. This finding is comparable to a study from South India [10]. In this study, of the 52 (MupH) isolates, 24 were from exudative specimens followed by blood (20) and urine (6). In this study, high level mupirocin was observed in higher rates among *Staphylococcus haemolyticus*, *Staphylococcus epidermidis* and *Staphylococcus hominis*. This was in alignment to previously reported observations [5].

Molecular detection of mupirocin resistance

In the present study, (49/56) MupH isolates harbored the *mupA* gene, that included 4 MupH *Staphylococcus aureus* and 45 MupH CONS. This finding is consistent to previous studies [12, 13 & 14]. where in the high-level mupirocin resistance is predominantly due to the presence of the *mupA* gene. The current study revealed a 92.4% sensitivity and 97.5% specificity for the phenotypic detection test for mupH and the presence of the *mupA* gene. According to a study from Egypt, the *mupA* gene found in 75% (6/8) of the high-level mupirocin resistant isolates and in none of the low level mupirocin resistant strains carried this gene [15]. In another study, only 9 of the 11 isolates with high level mupirocin resistance carried *mupA* gene. [15] Unlike these discrepant findings, a study from China reported all of the mupH isolates harbored the *mupA* gene [16].

In the current investigation, 4 isolates that include *Staphylococcus aureus* (n=1), *Staphylococcus haemolyticus* (n=1), *Staphylococcus hominis* (n=1) and *Staphylococcus epidermidis* (n=1) harbored the *mupA* gene exhibited low level resistance to mupirocin phenotypically. The mechanism of resistance among these isolates in the current study, could be due to chromosomally encoded *mupA* gene. This mechanism has also been described in a previous investigation [14]. In another study from USA, an isolate was reported with a low level mupirocin resistant phenotype that carried the *mupA* gene. On subjecting to sequencing, it had revealed a single nucleotide deletion that resulted in a frameshift and a nonfunctional peptide resulting in mupirocin resistance [15]. Such sequencing analysis were not performed in the current study.

Methicillin resistance versus mupirocin resistance

In the present study, *mupA* gene was detected in 3.7% (5/133) *Staphylococcus aureus* isolates which included (4/5) MRSA and (1/5) MSSA. Similarly, among the CONS, the *mupA* gene was harbored by 48 isolates which included, 44 MRCONS and 4 MSCONS**.** According to other investigations, during administration of mupirocin prophylaxis, the *mupA* gene may be transferred to MRSA due to selection pressure. Mupirocin resistance therefore poses a significant risk to its future usage [17]. Studies from Greece and Athens detected *mupA* gene mediating high mupirocin resistance among MSSA [18]. which emphasizes that isolates that are methicillin susceptible isolates may be potential reservoirs of *mupA*. Hence, both MSSA and MRSA should be routinely tested for mupirocin resistance.

In the current study, 7 isolates exhibited high level mupirocin resistance but did not carry the *mupA* gene. The possible mechanism of mupirocin resistance in these isolates could be due to the presence of *mupB* gene that was not included in the study protocol. This finding is comparable to other studies from India [2, 19].

In the present study, 25 isolates displayed low level resistance. The detection of the point mutations in the *ileS* gene were not included in the study protocol and is thus the limitation of this study. In addition, an increase in mupirocin use has been linked to a rapid growth in high-level resistance to mupirocin.

CONCLUSION

Mupirocin resistance in *Staphylococcus aureus* and CONS, should be monitored vigilantly, as CONS are reservoir for the *mupA* gene that is transmissible to other Staphylococci. Prudent use of mupirocin and strengthening execution of infection control measures should be mandated to curtail the spread of resistance. Hence, routine screening of resistance should be advised.

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