ORIGINAL ARTICLE

Mupirocin resistance in clinical isolates of methicillin sensitive and resistant *Staphylococcus* aureus in a tertiary care centre of North India

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ABSTRACT

Background: *Staphylococcus aureus* continues to be major healthcare problem worldwide as therapeutic options for its management are limited. Decolonisation regimes using mupiroicin are aimed at reducing the burden of infection due to this microorganism. However resistance to mupirocin poses a threat to the current standard eradication protocols.
Aims: To find out the type and extent of mupirocin resistance in clinical isolates of *S. aureus.*
Material and methods: This cross-sectional study was carried out at a tertiary care centre of North India for a period of 6 months. *S. aureus* recovered by standard microbiological procedures form various clinical samples such as blood, urine, pus and other body fluids was subjected to antimicrobial susceptibility testing along with detection of mupirocin resistance using 5 and 200µg discs. Minimum inhibitory concentration (MIC) of mupirocin was determined using E -test strips. Fisher's exact test was done to determine the statistical significance. A *P*-value of <0.05 was considered as statistically significant.
Results: A total of 247 *S. aureus* isolates were recovered of which 81 (32.8%) were resistant to methicillin (MRSA) whereas 166 (67.2%) were sensitive to this antibiotic (MSSA). Low level resistance to mupirocin was seen in 7 (8.6%) MRSA and 3 (1.8%) MSSA isolates. Prior use of this topical antibiotic and previous hospitalisation were found to be the risk factors associated with mupirocin resistance.
Conclusion: Low level mupirocin resistance was seen in *S. aureus* isolates which if left unchecked could in future pave way for high level resistance and subsequent treatment failures.
Key words: *MRSA, Mupirocin, Staphylococcus aureus*
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INTRODUCTION

Methicillin resistant *Staphylococcus aureus* (MRSA) continues to be a major cause of healthcare associated infections worldwide with increased morbidity, mortality and escalating healthcare costs.[1] Colonization with MRSA increases the risk of adverse health outcomes and it is estimated that 10-30% of carriers subsequently develop infection due to this organism.[2] Despite the implementation of evidence based infection control practices, both colonization as well as infection due to MRSA continues to increase.[3] Eradication of MRSA carriage from sites such as anterior nares that harbor these bacteria is an important component of strategies aimed at reducing or preventing

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infections due to MRSA.[4-6]

The topical antibiotic mupirocin (pseudomonic acid A) possesses potent activity against *Staphylococci* and has been used for the treatment of skin as well as postoperative wound infections, and more importantly for the prevention of nasal carriage of MRSA.[7,8] It specifically binds to bacterial isoleucyl-tRNA synthetase (IRS) and inhibits protein synthesis.[9,10] However increased use of this antibiotic in recent years has led to outbreaks of MRSA that are resistant to mupirocin.[11] Persistence of low levels of this antibiotic in the pharynx, after nasal application can induce or select for the emergence of mupirocin-resistant *Staphylococci* in general and MRSA strains in particular.[12]

Resistance to mupirocin occurs due to either a plasmid mediated *mupA* gene that confers high-level resistance or chromosomal point mutations that confer low-level resistance.[13] High level mupirocin resistance is a strong predictor of decolonization failure where as low level resistance is associated with higher rates of recolonization after using mupirocin for the eradication of *S. aureus*.[13] Disc diffusion using 5µg and 200µg discs can differentiate isolates having low or high level mupirocin resistance.[14,15] From a clinical perspective a cursory glance at the susceptibility pattern of *S. aureus* to mupirocin can help the physicians in deciding the most appropriate eradication regimes in patients who are candidates for such an intervention rather than blindly prescribing this antibiotic.

Though mupirocin resistance is often associated with methicillin resistance, the true extent of such an association and its impact on decolonization regimes in our country is not known. Thus, this study was carried out primarily to determine the rates of high-level and low-level mupirocin resistance in *S.aureus* isolates by disc diffusion and MIC methods and secondarily to compare its association with methicillin-resistant isolates.

MATERIAL AND METHODS

Study design: This prospective cross-sectional study was carried out in the Department of Microbiology at a tertiary care hospital in North India over a period of six months from 1st Jan 2018 to 30th June 2018. Samples were obtained from patients attending the OPD or admitted in the hospital.

Samples: Clinical samples such as blood, pus, body fluids and urine submitted to the Microbiology laboratory for culture and sensitivity testing were screened for the growth of *Staphylococci*. Isolates were identified as *S. aureus* by standard microbiological methods.[16] A history of prior mupirocin use in the last one year was recorded for all the patients from whom *S. aureus* was isolated, along with the socio-demographic characteristics like age, gender, residence, any underlying medical condition, intake of antibiotics (particularly beta-lactam group of antibiotics), immunosupression and history of hospitalization (in the last one year).

Antimicrobial susceptibility testing: Susceptibility to various antimicrobials was carried out by disc diffusion method as per the Clinical Laboratory Standards Institute (CLSI) guidelines.[17] Following antibiotic discs were used: penicillin (10 units), ciprofloxacin (5µg), clindamycin (2µg), erythromycin (15µg), cotrimoxazole (1.25/23.75 µg), linezolid (30µg), vancomycin (30µg) and rifampicin (5µg). Methicillin resistance was detected using cefoxitin (30µg) discs. For the detection of mupirocin resistance, mupirocin (5µg and 200µg) discs were used. All the discs were procured from Hi-Media Mumbai. Both methicillin sensitive as well as resistant isolates were included in the study. For mupirocin, a zone diameter of ≥14 mm for both 5 and 200 µg discs was considered to be susceptible. Isolates that showed zone diameters <14 mm with the 5µg disc but ≥14 mm with the 200 µg disc were considered to be MuL strains whereas those with a zone diameter of <14 mm for both 5 and 200 µg discs were considered to be MuH strains.[14]

Minimum inhibitory concentration: MIC for mupirocin was determined by the E-test strips (AB Biodisk, Solna, Sweden). For the E-test, MIC of ≤4 µg/ml was considered as susceptible (Mup^{S}), 8256 µg/ml was taken as low level resistance (Mup^{RL}) and ≥512 µg/ml was taken as high level resistance (Mup^{RH}).[17] S. aureus ATCC 25923 was used as quality control strain.

Statistical methods: Proportions of mupirocin resistant and susceptible Staphylococcal strains were calculated. All clinical variables were tabulated using frequency tables, along with pattern of susceptibility to commonly used antibiotics. Fisher's exact test was done to determine the statistical significance. A P-value of <0.05 was considered as statistically significant.

Ethical clearance: The study was conducted in accordance with the helsinki declaration and was considered in the exempt category by the ethics committee of the institute.

RESULTS

Of the 247 (non-repetitive) *S. aureus* isolates recovered from various clinical specimens, 81 (32.8%) were resistant to methicillin (MRSA) whereas 166 (67.2%) were sensitive to this antibiotic (MSSA). A zone size of <14 mm with the 5µg disc was seen in 7 (8.6%) MRSA isolates whereas 3 (1.8%) MSSA isolates were resistant to mupirocin. A zone size of ≥14 mm was seen for all the *S. aureus* isolates with the 200µg disc. Picture 1 Minimum inhibitory concentration (MIC) of mupirocin using E-test strip was done for all the *S. aureus* isolates. All the 10 mupirocin resistant isolates (7 MRSA and 3 MSSA) exhibited MIC between 8 to 24µg/ml. Picture 2

The socio-demographic parameters of the 247 patients are given in table 1. Most common age group from whom MRSA were recovered was 40 to 59 years (n=32), whereas most common age group from whom MSSA were recovered was 20 to 39 years (n=58). Both MRSA and MSSA were recovered more from male patients (n=48, n=104 respectively). Likewise the isolation of MRSA and MSSA was more from patients residing in urban areas (n=52, n=96). Diabetes mellitus was the most common co-morbid condition seen in patients from whom MRSA (n=31) and MSSA (n=58) were recovered. Folliculitis was seen in 12 patients from whom MRSA was isolated and 27 patients from whom MSSA was recovered. Most of the samples from which MRSA were recovered came from in-patients (n=55), whereas majority of the MSSA were recovered were from out-patients (n=92).

Antibiotic intake, previous hospitalisation and prior mupirocin use for the 247 patients is shown in table 2. Quinolones followed by beta-lactams/cephalosporins were the commonest antibiotic classes taken by the patients during the last one year. A significantly higher number of patients from whom MRSA was isolated gave a history of prior hospitalization during the preceding one year (58.0%) as compared to those from whom MSSA was recovered (24.7%). Majority of the patients from whom MRSA and MSSA were recovered did not have a history of mupirocin use in the last one year. Antibiogram of the MRSA and the MSSA isolates is shown in table 3. Generally MRSA isolates were more resistant to the antibiotics tested as compared to the MSSA. In the MRSA isolates higher resistance was seen for penicillin (100%), followed by ciprofloxacin (81.5%), erythromycin (76.5%) co-

Table 1: Socio-demographic profile of patients from whom MRSA and MSSA isolates were recovered

	Methicillin resistant N (%)	Methicillin sensitive N (%)	*P*-value
Age			
0-19	2 (2.5)	11 (6.6)	
20-39	21 (25.9)	58 (34.9)	
40-59	32 (39.5)	54 (32.5)	>0.05 (NS)
≥60	26 (32.1)	43 (25.9)	
Gender			
Male	48 (59.3)	104 (62.7)	
Female	33 (40.7)	62 (37.3)	>0.05 (NS)
Residence			
Urban	52 (64.2)	96 (57.8)	
Rural	29 (35.8)	70 (42.2)	>0.05 (NS)
Associated medical condition			
Diabetes	31 (38.3)	58 (34.9)	
HTN	26 (32.1)	42 (25.3)	
CKD	10 (12.3)	18 (10.8)	
CAD	6 (7.4)	14 (8.4)	
Malignancy	2 (2.5)	9 (5.4)	
COPD	16 (19.8)	32 (19.3)	
Skin lesions	12 (14.8)	27 (16.3)	>0.05 (NS)
OPD	26 (32.1)	92 (55.4)	
IPD	55 (67.9)	74 (44.6)	

Table 2: Risk factors in patients from whom MSSA and MRSA isolates were recovered

	Methicillin resistant N (%)	Methicillin sensitive N (%)	*P*-value
Prior antibiotic intake			
Beta lactams	48 (59.3)	56 (33.7)	>0.05 (NS)
Cephalosporins	41 (50.6)	77 (46.4)	
Quinolones	52 (64.2)	92 (55.4)	
Tetracyclines	6 (7.4)	14 (8.4)	
Macrolides	11 (13.6)	21 (12.7)	
Vancomycin	12 (14.8)	28 (16.9)	
Linezolid	10 (12.3)	19 (11.4)	
Prior hospitalization (last one year)			
Yes	47 (58.0)	41 (24.7)	<0.05 (S)
No	34 (41.9)	125 (75.3)	
Prior mupirocin use (last one year)			
Yes	16 (19.8)	21 (12.7)	>0.05 (NS)
No	65 (80.2)	145 (87.3)	

Table 3: Table showing antimicrobial susceptibility pattern of MRSA and MSSA isolates

Antibiotics	Methicillin resistant (n=81)		Methicillin sensitive (n=166)		*P*-value
	Sensitive N (%)	Resistant N (%)	Sensitive N (%)	Resistant N (%)	
Penicillin	0	81 (100)	4 (2.4)	162 (97.6)	<0.05 (S)
Cefoxitin	0	81 (100)	166 (100)	0	-
Clindamycin	32 (39.5)	49 (60.5)	102 (61.4)	64 (38.6)	>0.05 (NS)
Erythromycin	19 (23.5)	62 (76.5)	57 (34.3)	109 (65.7)	<0.05 (S)
Co-trimoxazole	31 (38.3)	50 (61.7)	74 (44.6)	92 (55.4)	>0.05 (NS)
Ciprofloxacin	15 (18.5)	66 (81.5)	68 (41)	98 (59)	<0.05 (S)
Vancomyicn	81 (100)	0	166 (100)	0	-
Linezolid	81 (100)	0	166 (100)	0	-
Rifampicin	80 (98.8)	1 (1.2)	166 (100)	0	-
Mupirocin	74 (91.4)	7 (8.6)	163 (98.2)	3 (1.8)	<0.05 (S)

Note: *P*-value of <0.05 is considered significant, >0.05 is not significant

Table 4: General characteristics of patients from whom mupirocin resistant *S. aureus* were recovered

	Methicillin resistant Mupirocin resistant (n=7)	Methicillin sensitiveMupirocin resistant(n=3)	*P*-value
Prior hospitalization	4 (57.1)	0	<0.05 (S)
Prior mupirocin use	6 (85.7)	1 (33.3)	
Diabetes	3 (42.9)	0	
Skin lesions	3 (42.9)	0	
OPD	5 (71.2)	3 (100)	
IPD	2 (28.6)	0	

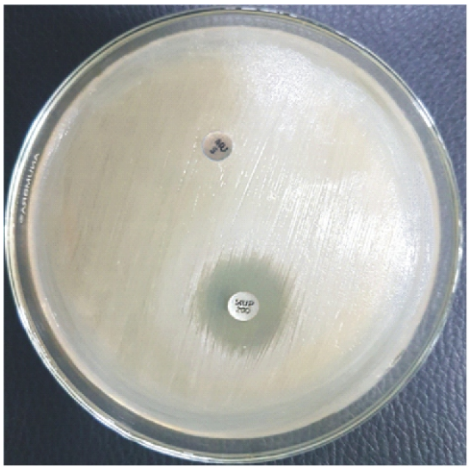


Figure 1: Disc diffusion test using 5 and 200µg of mupirocin with no zone of inhibition around the 5µg disc

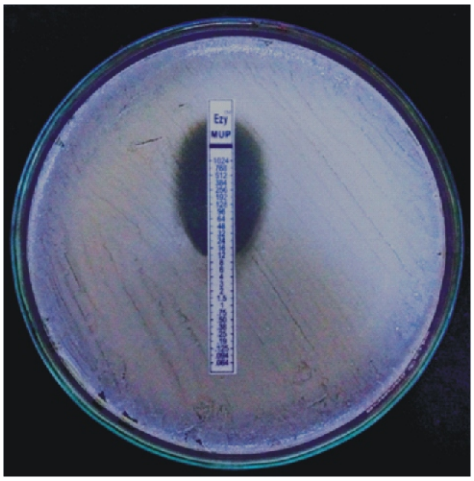


Figure 2: Etest Strip showing MIC of 12 µg/ml for mupirocin in an isolate of *S. aureus*

trimoxazole (61.7%) and clindamycin (60.5%). In addition a single isolate (1.2%) of MRSA was resistant to rifampicin also. For the MSSA isolates, high resistance was noted for penicillin (97.6%), followed by erythromycin (65.7%), ciprofloxacin (59%), co-trimoxazole (55.4%), and clindamycin (38.6%). All the *Staphylococci* were sensitive to vancomycin and linezolid. Resistance to penicillin, clindamycin and erythromycin in MRSA isolates was statistically significant (*P*-value <0.05).

Six (85.7%) of the seven patients from whom mupirocin resistant MRSA isolates were recovered gave a history of mupirocin use in the last one year as compared to those from whom mupirocin resistant MSSA was recovered (n=1, 33.3%). Table 4 A significant history of prior hospital stay was observed in 4 (57.1%) patients from whom mupirocin resistant MRSA isolates were isolated. Three (42.9%) patients whose samples were positive for mupirocin resistant MRSA isolates were suffering from Diabetes mellitus and 3 (42.9%) gave a history of follicutitis and boils in the past for which they had taken treatment in the form of oral medication and topical ointments including intranasal mupirocin. Table 4. Notably majority of the mupirocin resistant samples (71.2% MRSA and 100% MSSA) were recovered from out-patients.

DISCUSSION

This is the first study conducted in this part of the country that highlights the presence of mupirocin resistance in clinical isolates of *S. aureus*. The topical antibiotic mupirocin was introduced into clinical practice in 1985 and in 1987 (within two years) the first report on mupirocin resistance in *Staphylococci* came from United Kingdom.[18] Since then, increasing mupirocin resistance has been reported from various countries, mainly because of its widespread use in the community as well as hospital settings.[19-22]

In the present study low level mupirocin resistance was seen in 8.6% of MRSA (n=7) and 1.8% (n=3) MSSA isolates recovered from various clinical samples whereas none of the isolates harbored high level mupirocin resistance. A higher resistance to mupirocin, 18.3% was detected in MRSA by Chaturvedi *et al*., of which 9.8% and 8.5% isolates had high level and low level resistance respectively.[23] Likewise Murugesan PN *et al*. in their study showed high level mupirocin resistance of 26.5% among MRSA isolates along with chlorhexidine resistance.[24] High□level (MuH) and low□level (MuL) mupirocin resistance was detected in 10 (5%) and 2 (1%) *S. aureus* strains, respectively by Gadepalli *et al*.[25] whereas Oommen *et al*. found that rate of MuH was 2% in MRSA and 28% in methicillin□resistant coagulase□negative *Staphylococci*.[12] Another study from Chennai showed emergence of hospital acquired MRSA with both mupirocin (32%) and inducible clindamycin resistance among MRSA ST239 isolates.[26] Rudresh *et al.* in their study found high level mupirocin resistance in 4.5% MRSA and low level mupirocin resistance in 18.2% MSSA isolates. [27] The prevalence of high level mupirocin resistance was found to be 1.6% in *S. aureus* isolates and 5.6% in CoNS in a study that included

data from 19 European hospitals.[11]

Diabetes mellitus was the commonest co-morbidity in patients from whom mupirocin resistant MRSA were recovered whereas 3 patients gave history of folliculitis for which they had received treatment including intranasal application of mupirocin. Of note prior mupirocin use and previous hospitalization (within the last one year) were significantly associated with mupirocin resistance among MRSA isolates. Caffrey AR *et al.* [28] identified exposure to mupirocin, *Pseudomonas aeruginosa* infection and cefepime utilization in the year prior to culture as the three significant independent predictors associated with mupirocin resistance in MRSA.

Interestingly 71.2% of mupirocin resistant MRSA and 100% of mupirocin resistant MSSA were recovered from OPD patients. Over the counter availability of mupirocin in community settings and its use for the treatment of general skin infections than for true eradication of MRSA colonization could be one possible reason as to why they were recovered more from the patients attending the OPD. Mono-therapy with mupirocin could be another contributing factor. Rudresh MS *et al.* have reported results similar to ours where the authors found that majority of the mupirocin resistant isolates of *Staphylococci* were recovered from out-patients.[27] Although the number of mupirocin resistant *Staphylococci* (n=10) is low to derive any statistical correlation but majority of the patients from whom this organism was recovered were females (n=4 among MRSA, n=3 among MSSA). The reason for such an association could not be ascertained.

Generally, MRSA isolates were found to be more drug resistant than MSSA isolates in our study. All the MRSA isolates and majority of the MSSA were resistant to penicillin followed by high level resistance to ciprofloxacin and varying resistance to other antimicrobial agents. Similar results have been previously reported by Bashir F *et al*. and Peer M *et al*.[29,30] One isolate of mupirocin resistant MRSA was found to be resistant to rifampicin as well. The isolate belonged to a female patient who gave history for recurrent folliculitis and had received eradication therapy for MRSA in the form of oral amoxicillin + clavulanic acid, rifampicin and intra nasal mupirocin application thrice in the last one year. The patient an urban resident, had used mupirocin very often even when it was not prescribed by a physician. This in effect highlights the injudicious use by patients who want prompt relief in their clinical condition and have easy and unchecked access to over the counter medicines.

Though mupirocin resistance is currently not a major problem in our institution, the use of this antimicrobial agent is likely to increase in individual patients with recurrent skin infections to eradicate MRSA colonization which can select for resistant strains. Another factor that may contribute to increased resistance to mupirocin in times to come is the use of this antibiotic in the preoperative eradication of the *S. aureus* to prevent post-surgical infections. Its use to eradicate *S. aureus* colonization in patients and health care personnel in response to outbreaks of staphylococcal infection can further aggravate the situation.

The less number of mupirocin resistant isolates in this study was a limitation in deducing the exact significance of the variables associated with their isolation. A large multi-centric study needs to be carried out to better understand the dynamics involved in the transmission of mupirocin resistant *S. aureus*, role of various risk factors in its acquisition and disease causing potential of such strains. Nonetheless the factors highlighted in the present study could serve as a guide and incite further research in that direction.

CONCLUSION

Detection of low level mupirocin resistance in the current study may not seem alarming at face value; however it might be a harbinger of much greater resistance in near future. Such a scenario will not only undermine the utility of mupirocin containing eradication regimes for *S. aureus* but will simultaneously pose challenges to finding alternative solutions. Lack of routine testing for mupirocin susceptibility in *S. aureus* is a norm rather than an exception in majority of the health care institutions. Empirical use of mupirocin in the wake of high level resistance in such settings will not only lead to failed eradication regimes but also add to further resistance.

For a patient who desires relief in his clinical condition misuse of antibiotic agents is but natural. In such cases it befalls on the medical community to look for evidence based best treatment options that not only prove beneficial

to the patient but also contribute in preventing the emergence and spread of resistant microorganisms. It is high time continued surveillance for reserved category antimicrobial agents including those that are the last resort in the pipeline is carried out in all medical and research institutions routinely.

DECLARATIONS

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