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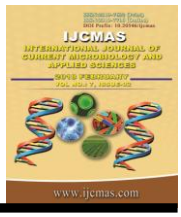

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Mupirocin Resistance in *Staphylococcus aureus* isolated from the Anterior Nares of Health Care Workers, in a Tertiary Care Hospital

Ragini Ananth Kashid[1*] and Kausalya Raghuraman[2]

[1]Department of Microbiology, BGS Global Institute of Medical Sciences, No.67, BGS Health and Education City, Uttarahalli Main Road, Kengeri Bangalore – 560060, India
[2]Department of Microbiology, Raja Rajeswari Medical College and Hospital, Kambipura, Mysore Road, Bangalore-560074, India

**Corresponding author*

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A B S T R A C T

Nasal carriage of *methicillin resistant Staphylococcus aureus* (MRSA) is a key factor in the epidemiology and causation of infection. Health care workers, who are nasal carriers of MRSA, act as reservoirs of infection. This is an important risk factor in the development of nosocomial infections. Mupirocin is used to decolonise MRSA carriers. But with the widespread use of mupirocin, resistance to mupirocin has set in. This poses a challenge to the use of mupirocin against MRSA. This study was carried out to know the occurrence of high and low level mupirocin resistance in *Staphylococcus aureus. Staphylococcus aureus* isolated from the anterior nares of health care workers (HCWs) were identified using standard protocol. Methicillin resistance was identified using cefoxitin disc (30µg). High level and low level mupirocin resistance was identified using 5µg and 200µg mupirocin discs. The tests were done by Kirby Bauer disc diffusion method as per CLSI guidelines. SPSS Version 20 software was used to give percentage analysis of the data. Chi-square test was used for statistical analysis (p value <= 0.05 is taken as statistically significant). Of the 300 nasal swabs taken from HCWs, 28 *Staphylococcus aureus* were isolated, of which 24 isolates were MSSA and 4 isolates were MRSA. One MSSA (1/24, 4.1%) isolate showed high level mupirocin resistance. Only 1 MRSA isolate (1/4, 25%) had high level resistance to mupirocin. No low level resistance to mupirocin was detected in the MSSA and MRSA isolates. Presence of mupirocin resistance in *Staphylococcus aureus* isolates is a cause of grave concern. The hospital infection control activities and surveillance have to be stepped up, to identify and control mupirocin resistance.

Introduction

Staphylococcus aureus is a well-known nosocomial pathogen with high mortality and morbidity. It increases the treatment cost and prolongs the hospital stay of the patient. Nasal carriage of Staphylococcus among health care workers is one of the means of transmission of this deadly organism. Colonized individuals (patient or health care worker) serve as a potential reservoir of infection, even if they are asymptomatic (Agarwal *et al.*, 2015). Mupirocin is used for the decolonization of *Staphylococcus* from anterior nares of health

care workers (Kaur, 2014). Mupirocin (Pseudomonic acid A) is produced by *Pseudomonas fluorescence*. It is used for the treatment of skin and soft tissue infection caused by *Staphylococcus* spp. and Streptococcus spp. It is also used to decolonise nasal carriage of methicillin resistant *Staphylococcus aureus* (MRSA). Mupirocin, an analogue of isoleucine, acts by inhibiting protein synthesis, as it competitively binds to isoleucine t- RNA synthetase (IRS) (Sanju *et al.,* 2015; Wattal, 2014).

United Kingdom was the first country to introduce mupirocin in 1985 (Sanju *et al.,* 2015). Within a short span of 2 years, the emergence of drug resistance was reported (Wattal, 2014). The widespread use of mupirocin as a topical decolonizing agent for MRSA in health care facilities has led to emergence of mupirocin resistance (Kaur, 2014). Resistance to mupirocin can be high level resistance and low level resistance, based on the zone diameter or minimum inhibitory concentration (MIC). Mupirocin sensitive isolates have a zone diameter ≥ 14mm for both 5µg and 200 µg discs or have a MIC ≤4µg/ml. Low level mupirocin resistant (MuL) isolates show a zone diameter < 14 mm in the 5µg disc, but more than or equal to 14mm in the 200µg disc or have a MIC of 8-256µg/ml. High level mupirocin resistant (MuH) isolates that show zone diameter < 14 mm in both the 5µg disc and 200µg disc or have a MIC ≥ 512 µg/ml (Kaur, 2014, Sanju *et al.,* 2015, Wattal, 2014). High level mupirocin resistance is by *mup* A gene, which is plasmid mediated and codes for a novel IRS. Low level mupirocin resistance is associated with a chromosomal point mutation associated with a change in the native IRS. Novel gene, *mup* B has been identified, also being responsible for high level resistance (Wattal, 2014)

The plasmid which harbours the *Mup* A gene is known to carry resistance to other antibiotics like macrolide, gentamicin, tetracycline and trimethoprim, thus increasing the drug resistance (Wattal, 2014). Detection of low level mupirocin resistance is important as nasal isolates can still be controlled with mupirocin therapy as the ointment has a higher mupirocin concentration (20,000 µg/ml) (Oliveria *et al.,* 2007).

The clinical relevance of detecting mupirocin resistance is that in high level mupirocin resistance, patients on mupirocin therapy are unable to clear the organism (Oliveria *et al.,* 2007; Malaviolle *et al.,* 2008; Simor *et al.,* 2007). Few studies have suggested that low level mupirocin resistance has been detected, can predict treatment failure (Malaviolle *et al.,* 2008; Simor *et al.,* 2007). Resistance to mupirocin ranges from 8.3-10% (Krishnan *et al.,* 2002).

It has been observed that the prevalence of colonization by MRSA in HCWs varies with different locations and with the institution (Kaur, 2014). Therefore, there is a need to detect both high level and low level mupirocin resistance among health care workers and to treat them with other alternate decolonizing agent. Hence, the present study was undertaken to know the occurrence of mupirocin resistance in those health care workers, whose anterior nares were colonized with *Staphylococcus aureus*. This data will help our hospital infection control team to devise more effective strategies to control MRSA and to keep alternate therapeutic options ready, to keep mupirocin resistance in check.

Materials and Methods

A prospective study was conducted for duration of 6 months among health care workers, in a tertiary care hospital, south India. All the health care workers who had given an informed written consent were

enrolled in the study. Health care workers with recent history of nasal surgery, fever, upper respiratory tract infection and on any topical medication were excluded from the study. The study was cleared by the institutional ethical committee.

Using a prepositioned swab, samples were collected from the anterior nares of the health care workers. The samples were inoculated on MacConkey agar, blood agar and mannitol salt agar. *Staphylococcus aureus* was identified using the standard microbiological technique.

Methicillin resistance was detected as per CLSI guidelines using cefoxitin disc diffusion method. A 0.5 McFarland standard suspension of the isolate was prepared. A lawn culture on Mueller Hinton agar was prepared with the standard inoculum, and a cefoxitin disc (30µg, Himedia, Mumbai, India) was placed. After overnight incubation, a zone diameter of <=21mm was considered resistant and an inhibition zone =>22mm was considered as methicillin sensitive.

Resistance to mupirocin was tested using two different strengths of mupirocin disc: mupirocin 5µg (Himedia, Mumbai, India) and mupirocin 200 µg (Oxoid, Basingstroke, UK). A 0.5 McFarland standard suspension of the isolate was prepared, was lawn cultured on Mueller Hinton agar. The mupirocin 5 µg and mupirocin 200 µg discs were placed on the plate. After overnight incubation the zone of inhibition was measured. An inhibition zone of <=13mm is considered as mupirocin resistance and an inhibition zone of =>14mm is considered as sensitive (Oliveria *et al.,* 2007).

Statistical analysis

The results were recorded and analysed statistically using Microsoft excel sheet 2009. Percentage description of data was given using SPSS Version 20 software. Chi-square test was used for statistical analysis. A p value <= 0.05 is taken as statistically significant.

Results and Discussion

A total of 300 nasal swabs were collected from health care workers and were processed as per standard microbiological procedures. Of the 300 nasal swabs taken, we isolated 28 *Staphylococcus aureus* (9.33%). Among the 28 *Staphylococcus aureus* isolates, only 4 strains were found to be Methicillin resistant *Staphylococcus aureus* (MRSA) and the remaining 24 strains was Methicillin sensitive *Staphylococcus aureus* (MSSA). The overall positivity of MRSA was 1.33% (4/300) and the positivity of MSSA was 8% (24/300) (Table 1).

Among the 24 strains of MSSA, high level mupirocin resistance was found in one isolate. The overall positivity of mupirocin resistance in MSSA was 4.1%. Out of the 4 MRSA isolated only 1 isolate had high level resistance to mupirocin. The overall positivity to mupirocin resistance among MRSA was 25 % (Table 2). No low level resistance was detected in the MSSA and MRSA isolates (Table 3).

Nasal carriers of *Staphylococcus aureus* are three times more prone to infection than non-carriers. It is observed that almost 30% of the world population is persistently or occasionally colonized with *Staphylococcus aureus* strains in the anterior nares (Trouillet – Assant *et al.,* 2015). Various decolonizing agents used against *Staphylococcus aureus* include chlorhexidine, mupirocin, rifampin, povidone iodine and doxycycline (Vedavati *et al.,* 2014). Although some have been used for nasal carriage, they show good response only for a short period of time and recolonization is seen again (Schmitz *et al.,* 1998). Ability to eliminate 97% *Staphylococcus aureus* in the

anterior nares in health care workers, within 24 hours, makes mupirocin the best drug for decolonization (Vedavati *et al.,* 2014). Mupirocin can be used for decolonization of both MSSA and MRSA isolates (Hetem, 2013). Lately it has been used for pre - surgical decolonization and there is a 58% reduction in the rate of post - surgical infection. It is also being used in dialysis patients (haemodialysis and peritoneal dialysis), to prevent infections in these patients (Hetem, 2013, Wattal, 2014).

Resistance to mupirocin is reported to be 5% in Korea, 6% in India, 6.6% in China, 11.3% in Spain, 13.2% in United States of America, 26.1% in Trinidad Tobago and 45% in Turkey (Rajkumari *et al.,* 2014). Although the wide spread use of mupirocin has led to resistance, the other causes of mupirocin resistance are: concentration of the drug in deeper layers of skin is less than in nose, irregular and ineffective application (mupirocin need to be massaged back on the nose for at least 1 min), reinfection due to a different strain with resistance and rarely by aerosol spread especially in dermatology and burns ward (Cookson, 1998). Even when mupirocin is applied in clinically effective concentration in the nose, it will lead to the presence of low level of antibiotic in the pharynx, which could induce or select resistant strains (Oommen *et al.,* 2010). Few others believe that blanket treatment on all health care workers or patients with MRSA carriage has resulted in the resistance (Orett, 2008).

It is well proven that screening with 5µg disc of mupirocin cannot differentiate between MuL and MuH strains. Therefore, we need to use both 5 µg and 200 µg disc for the same (Sanju *et al.,* 2015).

Table.1 Overall sensitivity to methicillin in the isolates of *Staphylococcus aureus*

Organism isolated (n=300)	Methicillin sensitive (%)	Methicillin resistant (%)	Total
Staphylococcus aureus	24(8)	04(1.33)	28

Table.2 Percentage of mupirocin resistance in MRSA versus MSSA with the p value

Mupirocin	MRSA		MSSA		p value
	Number	Percentage (%)	Number	Percentage (%)	
Resistant	1	25	1	4.1	0.1342
Sensitive	3	75	23	95.9	
Total	4	100	24	100	

Table.3 Distribution of MuL and MuH resistant isolates of MSSA and MRSA

Methicillin sensitivity	Mupirocin resistant (%)	Low level mupirocin resistant (MuL)	High level mupirocin resistant (MuH)
MRSA (04)	1(25)	0	1
MSSA (24)	1(4.1)	0	1

Table.4 Distribution of mupirocin resistance (MuL and MuH) in various studies

Studies	MSSA		MRSA	
	Low (MuL)	High (MuH)	Low (MuL)	High (MuH)
Present study	0	1(4.1%)	0	1(25%)
Schmitz FJ *et al.*, (1998)	9(1.8%)	6(1.2%)	7(3.6%)	5(2.6%)
Jayakumar *et al.*,(2013)	1(1.5%)	1(1.5%)	0	1(2.2%)
Kaur DC, (2014)	0	0	1 (1.43%)	1(1.43%)
Sanju AJ *et al.*,(2015)	0	0	4(14.2%)	7(25%)
Oommen SK *et al.*, (2010)	0	0	0	1(2.08%)

In our study MRSA was 1.33% which is similar to the study done by Hetem *et al.*, (2013) who showed 3% resistance rate. High level mupirocin resistance was seen both in MSSA and MRSA in our study. Among MSSA, 4.1% (1/24) of the isolates showed high level resistance. This is comparable with the study done by Schmitz FJ *et al.*, (1998) and Jayakumar *et al.*, (2013).

Among the 4 MRSA isolates in our study, one isolate (1/4, 25%) had produced high level mupirocin resistance. This is comparable with the study conducted by Sanju *et al.*, (2015).Among the 125 MRSA studied by Malaviolle *et al.*, (2008), high level mupirocin resistance was found in 25.6% and low level mupirocin resistance in 31.2%. Agarwal *et al.*, (2015) studied 28 MRSA isolates and found resistance in 4 isolates. Among the 4 isolates, 75% resistance was high level mupirocin resistance (Agarwal *et al.*, 2015) (Table 4). The risk of mupirocin resistance is more with MRSA compared to their counterpart MSSA (Kaur, 2014). Resistance may be transferred between the Staphylococcus species from sensitive to resistant strain. Hence, testing for MSSA becomes important. Conjugative plasmids are known to transmit resistance between *Staphylococcus aureus* and *Coagulase negative Staphylococcus* (Jayakumar *et al.*, 2013). Hence, when mupirocin resistance is encountered, alternative treatment regimen is sought. Alternative treatment includes chlorhexidine, fusidic acid, neomycin cream and reptapumilin (Wattal, 2014; Oommen *et al.*, 2010). These alternative treatments are used when colonization persists even after 2 courses of mupirocin treatment or when the isolate is mupirocin resistant (Kaur, 2014).

Therefore, we conclude that screening for both high and low level mupirocin resistance is warranted and formulation of appropriate decontamination measures, in case of resistance is required. This will help in prevention and containment of these resistant strains in the hospital setup, leading to better infection control measures and better patient outcomes.

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