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Prevalence of High and Low -level Mupirocin, resistance against MRSA from a tertiary care hospital in eastern UP

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ABSTRACT

Aim: To determine the prevalence of High and Low -level Mupirocin, resistance against MRSA from a tertiary care hospital in eastern UP was the aim of this study**. Methods and Material:** A total of 62 non duplicate previously confirmed MRSA isolates were included in this study. The Susceptibility testing andresult interpretation for determining the high and low level of mupirocin resistance was performed by disk diffusion method using 200 µg and 5 µg disc respectively as per Clinical and Laboratory Standards Institute (CLSI) M100-S25 recommendations. **Results:** A total of 60 isolates (96.8 %) were found sensitive to mupirocin, 2 isolates (3.2 %) had low-level mupirocin resistance whereas none of the isolates was found to have high-level mupirocin resistance. **Conclusion:** The high-level mupirocin-resistant is uncommon in our patient population. The Periodic monitoring is useful for detecting changing trends in mupirocin resistance as a risk of emergence of high level mupirocin resistant strains is there.

Keywords: Mupirocin, MRSA, disk diffusion method.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most common pathogens responsible for hospital-acquired infections [1]. Common risk factor for the development of MRSA strain is indiscriminate use of antibiotics, intravenous drug use, prolonged stay in hospitals, and carriage of MRSA in anterior nares, axilla, and perineum [2]. Vancomycin and linezolid are commonly used drugs for systemic MRSA infection, while Mupirocin is successfully used as topical antibiotics for the treatment of skin infection and decolonization and eradication of MRSA from nasal carriers[3,4].

The antimicrobial Mupirocin is chemically pseudomonic acid A, is derived from *Pseudomonas fluorescens* and is active against most 'Gram-positive' and some 'Gram-negative' bacteria. Mupirocin competitively binds to bacterial isoleucyl-tRNA synthetase, inhibits protein synthesis and ultimately leading to bacterial death[5].

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Mupirocin is mainly bacteriostatic but appears bactericidal at lower pH in many parts of the skin. Increase use of mupirocin leads to outbreaks of resistance against MRSA to this antibiotic, however, the frequency of resistance is still low. Nasal application of mupirocin at clinically effective concentrations may result in the presence of low level of the antibiotic in the pharynx, which could induce the emergence of mupirocin-resistant MRSA [6]. Mupirocin-resistant strains are grouped into two distinct categories: low level (MupRL), with MICs of 8–256 µg/ml, and high level (MupRH), with MICs ≥512 µg/ml [7]. Susceptible strains are defined as those with a MIC ≤4 µg, showing zone diameters of ≥14 mm around 5 µg mupirocin discs [8,9]. Strains presenting diameters ≤14 mm are considered to be mupirocin resistant (either MupRH or MupRL).Clinical laboratories are able to differentiate Mup Susceptible strains using the 5 µg disc, but the resistant strains can only be distinguished empirically, as MupRH isolates show heavy growth around the 5 µg mupirocin disc, whereas MupRL isolates produced hazy zones of inhibition [10]. Low-level resistance is probably due to mutations in a chromosomally encoded IleS, is stable and non-transferable. Recent work has shown that the

substitution of a single amino acid in the synthetase of *Escherichia coli* significantly altered its mupirocin susceptibility [11,12].High-level resistance has been shown to be due in vivo to the acquisition of an additional novel IleS and also believed to be the result of a mutated gene on a plasmid [12,13]. However, others have postulated that there may be other mechanisms for resistance, e.g. an altered tRNA synthetase protein complex that might reduce the ability of mupirocin to gain access to IleS, enzymatic destruction has yet to be described [14]Mupirocin resistance is of significant concern for infection prevention and control personnel who are engaged in MRSA control efforts. Moreover, the presence of MRSA infection with mupirocin resistance significantly reduces the likelihood of MRSA eradication. Thus this study was planned to determine the prevalence of High and Low -level Mupirocin, resistance against MRSA from a tertiary care hospital in eastern UP.

Material and methods

The study was carried out in the Department of Microbiology, Institute of Medical Science Banaras Hindu University, Varanasi, U.P., India. The total duration of study is one year; period extends from July 2015 to June 2016. A total of 62 non-duplicate MRSA isolates from various clinical specimens like pus, blood, urine, tracheal aspirates, sputum, central venous catheters tips, CSF and other sterile body fluids were randomly selected. MRSA isolates were identified by standard microbiological techniques. Methicillin resistance was screened by using cefoxitin disc (30 µg Himedia). After isolation and identification, the MRSA strains were kept at -200C in peptone/glycerol (30% w/v), and before Mupirocin susceptibility testing, the strains were purified twice on blood agar plates.

Susceptibility to Mupirocin was determined by Kirby Bauer disc diffusion method on Muller Hinton Agar as per CLSI 2016. High and low level of mupirocin resistance was determined by using 200 µg and 5 µg HiMEDIA disc respectively. Disc diffusion tests were carried out according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI, 2016). Plates containing Mueller–Hinton agar (HiMEDIA) were swabbed in three directions with 0.5 McFarland inocula and 6 mm discs containing 5 µg and 200 µg mupirocin were applied. The inoculated plates were incubated in ambient air at 37°C for 16 to 18 h. *E. coli* ATCC 25922 was used as control strains and zone of inhibition was interpreted by using CLSI M100-S25(2016) breakpoints.

Result

A total of 62 clinical MRSA isolates were included in this study. Table 1 shows the distribution of MRSA isolates obtained from various clinical samples. The highest number of methicillin-resistant staphylococcal strains were obtained from pus 24 (38.7 %) followed by blood 10 (16.1 %) and sputum 8 (12.9 %).

Table 1: Distribution of MRSA isolates obtained from various clinical samples

S. no	Clinical specimens	Number of isolates (n)	Percentage (%)
1	Pus	24	38.7
2	Blood	10	16.1
3	Sputum	8	12.9
4	Tracheal aspirates	5	8.1
5	Urine	3	4.8
6	Central venous catheters tips	2	3.2
7	CSF	1	1.6
8	Other Sterile body fluids	9	14.5
	Total	62	100

Out of 62 isolates of MRSA tested, 60 isolates (96.8 %) were found sensitive to mupirocin, 2 isolates (3.2 %) had low-level mupirocin resistance whereas none of the isolates had high-level mupirocin resistance Table 2.

Table 2: Interpretative criteria proposed to determine the categories of mupirocin susceptibility by the disc diffusion method and results

Inhibition zone diameter (mm) 5 µg disc	Inhibition zone diameter (mm)200 µg disc	Interpretive criteria	Results n (%)
≥14	≥14	MupS	60 (96.8)
-	≥14	MupRL	02 (3.2)
-	-	MupRH	0

MupS – Mupirocin sensitive; MupRL – Mupirocin low-level resistance; MupRH - Mupirocin high-level resistance

Discussion

The first mupirocin resistant Clinical isolate was reported in 1987, and the resistance rate has been increasing ever since [15]. A Canadian study conducted by Simor et alreported an increase in mupirocin resistance among MRSA over time [16]. Perez- Fontan et al reported the emergence of mupirocin-resistant S. aureus in peritoneal dialysis patients who applied mupirocin for over 10 years [17].

In Korea, topical mupirocin has been used since 1994 to eradicate staphylococcal infections in hospitals and the use of mupirocin has been dramatically increasing. However, there has been little awareness and research about mupirocin resistance. The study conducted in Korea up to 1999 failed to detect mupirocin-resistant strains [18]. Yun et al.first identified high-level resistant isolates in 2003 and the prevalence of mupirocin resistance was 5% [19] .Studies from various centres across the world report difference in the prevalence of mupirocin resistance. While a study from Loyola University Health Systems noted the mupirocin resistance (MR) in 3.4% of MRSA carriers, and high-level MR in 0.62% of carriers, another study from south India found that rate of High-level mupirocin resistance to be 2% in MRSA strains[20,21].

In our study, we looked for high-level and low-level mupirocin resistance among clinical isolates collected from a tertiary hospital in Varanasi, India. In our study we found 2 isolates (3.2%) showing low level mupirocin-resistant. As per Redhead et al., low-level mupirocin-resistant strains are not considered clinically significant, since the concentration of mupirocin in the 2% ointment (20,000µg/ml) exceeds the MICs of low-level mupirocin-resistant strains, so such strains can be treated by topical mupirocin [22]. On the contrary, high-level mupirocin resistance that cannot be treated with mupirocin are more clinically important.None of the isolates in this study were found to be high-level mupirocin resistant.Thus, our study indicates that high-level mupirocin-resistant is uncommon in our patient population. However, there is always a chance of emergence of high level mupirocin resistant strains in our setting where mupirocin is frequently used for the decolonisation of MRSA strains among health care workers.In this scenario periodic monitoring would be useful for detecting changing trends in mupirocin resistance.

The increasing number of reports of high-level mupirocin resistance could mean the potential loss of one of the major treatment methods for controlling MRSA. Therefore, mupirocin treatment should be used cautiously and judiciously

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