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Original Article

Mupirocin Resistance of *Staphylococcus aureus* in Clinical Isolates of National Hospital and in the Nasal Carriage of Healthy Undergraduates in Colombo, Sri Lanka

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Abstract

Introduction and Objectives : Mupirocin resistance in *Staphylococcus aureus* is increasingly reported in many parts of the world. This study was conducted with the objective of describing high-level and low-level mupirocin resistance of *S. aureus* in clinical isolates and nasal carriage.

Materials and Methods : A descriptive study was conducted including 45 nasal isolates of *S. aureus* collected from healthy university students in Colombo and 249 clinical isolates of *S. aureus* from the patient specimens in National Hospital of Sri Lanka. All of the confirmed *S. aureus* strains were tested for methicillin resistance using cefoxitin disc (30µg). *S. aureus* isolates were considered methicillin-resistant if the diameter of zone of inhibition was 21 mm or less (CLSI, 2017). The *S. aureus* isolates were then tested for mupirocin resistance. Disk diffusion method was utilized with 5µg and 200µg mupirocin discs to determine low-level and high-level resistances respectively. The criterion employed for interpretation of mupirocin resistance was a combination of the widely accepted criterion described by Finlay, Miller, and Poupard (1997) for low-level mupirocin resistance and CLSI (2017) criterion for high-level mupirocin resistance. If both inhibition zone diameters for 5µg disk and 200µg were ≥14mm, the isolate was considered mupirocin sensitive. If 5µg disc displays <14mm and 200 µg disk displayed ≥14mm inhibition zone diameter, the isolate was considered to be mupirocin low level resistant. If there is no inhibition zone in 200µg disk, the isolate was considered as mupirocin high level resistant.

Results : From the 45 nasal carriage isolates, 33 (73%) were Methicillin sensitive *Staphylococcus aureus* (MSSA) and 12 (27%) were Methicillin Resistant *Staphylococcus aureus* (MRSA). Among the clinical isolates, majority (n=158, 63%) were MRSA while only 91 (37%) MSSA. An overall mupirocin resistance rate of 4.4% among *S. aureus* was observed. Low-level mupirocin resistance was observed in 3.7% *Staphylococcus aureus* isolates and high-level mupirocin resistance was observed in 0.7% isolates. Mupirocin low-level and high-level resistance in MRSA isolates were 5.3% and 0.6% respectively. MSSA isolates demonstrated 1.6% (n=2) and 0.8% (n=1) mupirocin low-level and high-level resistances respectively. None of the nasal isolates were resistant to mupirocin while 6% (n=15) mupirocin low-level resistance and 0.8% (n=2) mupirocin high-level resistance was observed in clinical isolates.

Conclusion : This initial survey of mupirocin resistance among *S. aureus* in a country with fairly high usage of mupirocin emphasizes that although the overall mupirocin resistance is relatively low in this population, regular surveillance of mupirocin resistance remains a necessity.

Keywords: Mupirocin, *Staphylococcus aureus*, Nasal carriage, MRSA

Introduction

Staphylococcus aureus is a common pathogen, which also acts as a commensal (Tong et al., 2015). It is one of the most frequently isolated bacteria in the hospital and community setting (Joshi et al., 2013; Stryjewski & Corey, 2014). Within the hospitals and health care institutions, *S. aureus* strains are transmitted from patient to patient principally through hand carriage by health care personnel and by means of fomites. It is responsible for the majority of post-operative surgical wound infections (Guyot & Layer, 2006; Shukla et al., 2009). The spectrum of disease continues to change with the emergence of antimicrobial resistance. In the past two decades, there were clear shifts in the epidemiology of *S. aureus* infections: first, a growing variety of health care associated infections, and second, an epidemic of community-associated skin and soft tissue infections. According to ongoing studies, clinical infections with *S. aureus* will be a common and serious infection in the modern world (Tong et al., 2015).

Nosocomial Methicillin-resistant *Staphylococcus aureus* (MRSA) outbreaks have been a major issue for hospital infection control during the past decade (Fanoy et al., 2009; Harris et al., 2013). Nasal carriage of MRSA by patients as well as health care workers is the primary cause behind this situation (George et al., 2016; Kakhandki & Peerapur, 2012).

Decolonization of nares of patients and healthcare workers has become a necessity in hospital environment, especially in operating theaters to improve the patient outcomes (Kakhandki & Peerapur, 2012). Mupirocin can be effectively utilized to decolonize anterior nares and to treat skin infections caused by *S. aureus* and MRSA (Wertheim et al., 2005; Mody et al., 2003).

Mupirocin (Pseudomonic acid A) is structurally analogous to isoleucine, which allows it to competitively bind to isoleucyl-tRNA synthatase and inhibit protein synthesis leading to a bacteriostatic or bactericidal effect (Hughes & Mellows, 1978). Mupirocin resistance plays a vital role in successful *S. aureus* or MRSA eradication. Additionally, it is vital in the management of patients prior to surgical procedures to reduce post-operative MRSA infection, and the presence of mupirocin resistance significantly reduces the effectiveness of MRSA eradication regime.

Two levels of mupirocin resistance phenotypes called low level (MuL) and high level (MuH) mupirocin resistance are defined for *Staphylococci* (Poovelikunnel, Gethin, & Humphreys, 2015). Presence of high-level mupirocin resistance renders mupirocin ineffective against MRSA decolonization or treatment. Low-level mupirocin resistance indicates previous exposure to mupirocin with probable incomplete decolonization or persistent carriage of MRSA (Poovelikunnel, Gethin, & Humphreys, 2015). Thus, it is crucial to detect and differentiate between MuH and MuL in the clinical laboratory setting.

There is a paucity of scientific studies conducted regarding the rate of mupirocin resistance in Sri Lanka. Lack of available knowledge regarding the mupirocin resistance may lead to uncontrolled use of the drug, which will eventually render it almost completely ineffective against MRSA. Therefore, the present study is undertaken to determine mupirocin resistance of *Staphylococcus aureus* in clinical isolates and nasal carriage.

Methodology

A descriptive study was conducted including 45 *Staphylococcus aureus* nasal carriage isolates kept stored from a previously conducted study at the University of Sri Jayewardenepura and 249 clinical isolates of *Staphylococcus aureus* collected from the National Hospital of Sri Lanka from 15/03/2019 to 15/05/2019 using convenience-sampling method. Ethical approval was obtained from the ethics review committee of KIU (KIU/ERC/18/30). Both nasal and clinical

isolates were inoculated to blood agar and incubated aerobically for 24 hours at 35±2°C. Identification of *S. aureus* was done by standard biochemical identification techniques (Collee et al., 1996). All of the confirmed *S. aureus* strains were tested for methicillin resistance using cefoxitin disc (30µg). *S. aureus* isolates were considered methicillin-resistant if the diameter of the zone of inhibition was 21 mm or less (CLSI, 2017). The *S. aureus* isolates were then tested for mupirocin resistance. Disk diffusion method was employed with 5µg and 200µg mupirocin discs to determine low-level and high-level resistances respectively. Mupirocin resistance level was determined using the criteria given in Table 1. This criterion was chosen since it is a combination of the widely accepted criterion described by Finlay, Miller, and Poupard (1997) for low-level mupirocin resistance and CLSI (2017) criterion for high-level mupirocin resistance. Descriptive statistics, chi square test and Fisher's exact test were utilized for data analysis and SPSS version 23 was employed as the statistical analysis tool.

Table 1: Interpretative criteria for disk diameters

Inhibition zone diameter		Interpretive criteria
5 µg disc	200 µg disc	
≥14mm	≥14mm	Mupirocin susceptible
<14mm	≥14mm	Low-level mupirocin resistance
Not relevant	No Inhibition zone	High-level mupirocin resistance

Results

Among the 45 nasal carriage isolates, 33 (73%) were Methicillin sensitive *S. aureus* (MSSA) and 12 (27%) were MRSA. In contrast, among the clinical isolates, majority 158 (63%) were MRSA as shown in Table 2.

According to the results obtained, there is a statistically significant difference between methicillin resistance among the clinical isolates and the nasal carriage isolates ($p<0.001$).

Table 2: Methicillin resistance among the *Staphylococcus aureus* isolates.

		Methicillin resistance		Total
		Sensitive	Resistant	
Sample Type	Nasal Carriage	33 (73%)	12 (27%)	45
	Clinical Isolate	91 (37%)	158 (63%)	249
Total		124	170	294

The level of mupirocin resistance is shown in Figure 1 and it indicates that, both low level and high-level resistance could be observed among less than 5% of the samples.

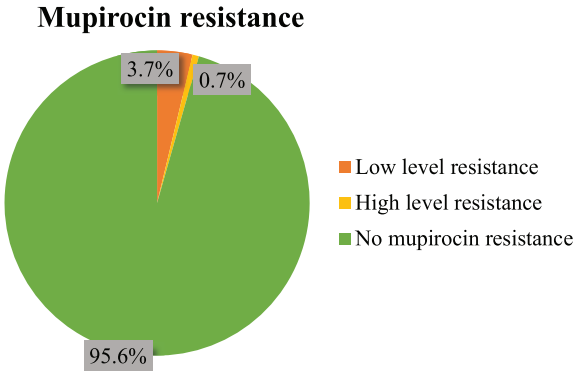

Figure 1: Mupirocin resistance in *Staphylococcus aureus* isolates

Majority (97.6%, n= 121) of MSSA isolates were sensitive to mupirocin while 2.4% (n=3) were resistant. Among the MRSA positive isolates 94.1% (n=160) were sensitive to mupirocin while the rest 5.9% (n=10) were resistant.

Table 3: Mupirocin resistance in MSSA and MRSA

	Methicillin resistant (MRSA) total number	Methicillin sensitive (MSSA) total number
Low-level resistance	9(5.3%)	2(1.6%)
High-level resistance	1(0.6%)	1(0.8%)
No mupirocin resistance	160(94.1%)	121(97.6%)

There was no significant association between methicillin resistance and mupirocin resistance according to Fishers exact test ($P=0.25$). Hundred percent (100%) of nasal isolates were sensitive to mupirocin and 93% (n=232) of clinical isolates were sensitive to mupirocin as described in Table 4. There was no significant difference in mupirocin resistance between clinical isolates and nasal colonizing isolates ($p=0.0849$) according to Fisher's exact test.

Table 4: Mupirocin resistance in nasal carriage isolates *vs* clinical isolates

	Nasal Carriage	Clinical Isolates
Low-level resistance	0(0%)	15(6%)
High-level resistance	0(0%)	2(1%)
No mupirocin resistance	45(100%)	232(93%)

Discussion

Majority (95.58%) of the *S. aureus* isolates in this study were mupirocin sensitive. Among the 4.4% mupirocin resistant isolates, 0.7% demonstrated high-level resistance and 3.7% showed low-level resistance to mupirocin. These results indicate that the overall mupirocin resistance is not very high in the study population, but even this low rate is a cause for concern since the rate can rapidly increase with time.

In similar studies, low-level mupirocin resistance and high-level mupirocin resistance of 17% and 8.2% in India (Rudresh et al., 2015), 2.9% and 11.7% in USA (McNeil et al., 2011), 0% and 2% in Ireland (O'Shea et al., 2009) have been reported. The low-level resistance rate in this study is lower than India but higher than USA and Ireland. High-level resistance in this study is lower than most of the other studies reported previously.

Presence of high-level mupirocin resistance causes decolonization failure. Presence of low-level mupirocin resistance causes temporary suppression of the growth of organisms, however does not eradicate the colonization (Poovelikunnel et al., 2015). Over-the-counter availability of mupirocin, widespread prescription for the general patient population (nasal and skin lesions), and repeated use in peritoneal dialysis (nasal and exit site) are recognized as common reasons behind the emergence of mupirocin resistance. Evidence suggests that the usage in perioperative prophylaxis, limited use to control of outbreaks/recurrent infections, and routine nasal use in hemodialysis patients rarely cause emergence of mupirocin resistance (Fanoy, 2009). In this study, only 27% (12/45) of nasal isolates collected from university students were MRSA while 63% (158/249) of clinical isolates were found to be MRSA. It was observed that 5% were resistant and 94.1% were sensitive for mupirocin among 170 MRSA isolates while 2.4% were resistant and 97.6% were sensitive to mupirocin among 124 MSSA isolates in this study.

A previous study conducted in Sri Lanka reported a MRSA rate of 15.4% in nasal carriage of the patients before admission (Thevanesam et al., 2013). India has reported 28% of MRSA rate in outpatients (Joshi et al., 2013) and a 9.2% MRSA percentage was reported from a study in Nashville (Creech, Kernodle, Alsentzer, Wilson, & Edwards, 2005). A study from Spain reported a MRSA rate of 3.1% (Chaves, García-Martínez, de Miguel, & Otero, 2004). When comparing with the previous studies, MRSA rate in nasal carriage is relatively high in the current study.

In this study, 63% of clinical isolates were detected to be MRSA. Similar studies have disclosed MRSA rates of 22.4% in India (Rudresh et al., 2015) and 43.8% in the children from china (Tan, Wan, Wang, Zhou, & Shu, 2019). Further 42% and 43% MRSA rates were reported from inpatients and ICU patients in India (India, Indian Network for Surveillance of Antimicrobial Resistance (INSAR) group - Joshi et al., 2013). MRSA rate observed in the clinical isolates of this study stands out to be higher than all the rates disclosed from previous studies. High MRSA rates in both clinical and nasal isolates showcase an increasing trend over time in Sri Lanka leading to an issue that needs to be addressed immediately.

Current study revealed 5.3% of low level and 0.6% high level mupirocin resistance in MRSA isolates. In a study conducted in Belgium 2.1% and 3.1% resistance rates were observed (Nagant et al., 2016), while a study from USA outlined 2.7% and 10.1% rates (McNeil et al., 2011) respectively for low level and high level mupirocin resistance. Yet another study from Ireland reported 0% and 3% rates (O'Shea et al., 2009), and an Indian study revealed 0.71% and 0.71% (Kaur & Narayan, 2014) rates for

mupirocin low-level and high-level resistances. Therefore, this study brings out higher percentage of mupirocin low-level resistance than Belgium, USA, and India. However, high-level mupirocin resistance is lower than Belgium, USA and India.

In the current study, 1.6% and 0.8% mupirocin low-level and high-level resistances were significant from MSSA isolates. In similar studies conducted in Belgium a rate of 0.1% and 0.6% (Nagant et al., 2016), in USA a rate of 3.5% and 17.8% (McNeil et al., 2011) were disclosed while 0% and 1% were reported in Ireland (O'Shea et al., 2009) for low-level and high level mupirocin resistances respectively. This study delineates a lower rate of mupirocin low-level resistance than USA. However, the rate is higher when compared to Belgium and Ireland. The high-level resistance rate is lower than USA and Ireland, but it is higher than Belgium in the current report.

It was observed that the mupirocin resistance rate identified in this study is higher in MRSA isolates than MSSA isolates. This needs to be taken into consideration, since mupirocin has a significant role as a topical agent in eradication of MRSA.

None of the nasal isolates was resistant to mupirocin but 7% of clinical isolates were resistant to mupirocin in this study. In a similar study conducted in Lebanon, 0% resistance was highlighted for mupirocin in nasal colonizers (Halablab, Hijazi, Fawazi, & Araj, 2010). A study conducted in Spain reported 14.8% of MRSA and 0.6% of MSSA from nasal samples resistant to mupirocin (Chaves et al., 2004). This study revealed that, mupirocin resistance is not yet detectable in the community. However, it sends out an alert since the MRSA rate in the community studied, was relatively high.

Further, it was apparent that, there were 6% and 0.8% mupirocin low-level and high-level resistance in clinical isolates respectively. An Indian study revealed 1% and 5% low-level and high-level mupirocin resistances respectively (Gadepalli et al., 2007) while an USA study reported 14.3% low-level and 85.7% high-level mupirocin resistance out of the 31.3% of mupirocin resistant isolates (Antonov et al., 2015). In addition, an Ireland study has reported 0% low level and 2% high level resistances to mupirocin in clinical isolates (O'Shea et al., 2009). These results indicate that the low-level mupirocin resistance rates identified in the current study are higher than other countries and the high-level mupirocin resistance rate is lower than that of other reported countries' rates.

Conclusion

This is an initial survey of mupirocin resistance among *S. aureus* in a country with a fairly high usage of mupirocin. Mupirocin resistance is higher in MRSA than in MSSA and in clinical isolates than in nasal isolates. Even though the overall mupirocin resistance is relatively low in this population, regular surveillance of mupirocin resistance remains a necessity.

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