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Research Article

MUPIROCIN RESISTANCE IN *STAPHYLOCOCCUS AUREUS* IN A TERTIARY CARE HOSPITAL OF SOUTH INDIA – A PROSPECTIVE STUDY

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ABSTRACT

Objective: Mupirocin is a topical antibiotic used for the treatment of skin and soft tissue infections caused by *Staphylococcus aureus* and for the nasal decolonization of methicillin-resistant *S. aureus* (MRSA). The increasing reports of resistance to mupirocin are a matter of concern. We undertook this study to detect and differentiate the mupirocin resistance pattern and to analyze the susceptibility pattern among *S. aureus* isolates of our hospital.

Methods: This is a prospective laboratory-based study conducted during the period May–September 2014. Clinical samples that grew *S. aureus* during the study period were tested for mupirocin resistance using the 5 µg and 200 µg discs. Minimum inhibitory concentration (MIC) detection of resistant strains was performed using the E-test.

Results: Mupirocin resistance was seen in 4.81% of our *S. aureus* isolates; all of which exhibited high-level resistance with MIC ≥1024 µg/ml.

Conclusions: The resistance is bound to rise with the increased usage of mupirocin; regular testing will help in tackling this upcoming problem and in preserving this important antibiotic against MRSA.

Keywords: *Staphylococcus aureus*, Mupirocin, High- and low-level resistance.

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INTRODUCTION

Staphylococcus aureus is a common cause of skin and soft tissue infections worldwide. A significant number of these infections are caused by methicillin-resistant *S. aureus* (MRSA). Carriage of MRSA in nose, axilla, and perineum is an important risk factor for its acquisition. Vancomycin or linezolid is used for the treatment of MRSA whereas mupirocin is an effective topical antibiotic for its elimination in carriers [1,2].

Mupirocin (pseudomonic acid A) is derived from *Pseudomonas fluorescens.* It is in use clinically since 1985. It specifically binds to bacterial isoleucyl tRNA synthetase (IRS) and inhibits protein synthesis. It is used for the treatment of skin and soft tissue infections caused by *S. aureus*. In addition, it is also in use as a nasal ointment for the elimination of MRSA colonization in healthcare workers and adult patients for the control of outbreaks [3].

The first report of mupirocin resistance came 2 years after its introduction [4]. Nasal application of mupirocin at clinically effective concentrations may result in the presence of low levels of the antibiotic in the pharynx, which could lead to resistant strains [5].

Mupirocin-resistant strains are grouped into two distinct categories: Those with low-level resistance showing minimum inhibitory concentrations (MICs) of 8–256 µg/ml and strains with high-level resistance having MIC ≥512 µg/ml. Susceptible strains are those with MIC ≤4 µg/ml. Low-level resistance is due to the mutational change in the chromosomally encoded *ileS-2* (*mupA*) gene [6]. This has been shown to develop in *S. aureus* isolates exposed *in vitro* to progressively higher concentrations of mupirocin [7]. The genetic basis for high-level resistance is the acquisition of a plasmid containing the *mupA* gene encoding an additional IRS enzyme [8]. It is also attributed to another gene *mupB* [9].

Resistance to mupirocin can be routinely detected in the laboratory by disc diffusion using 5 µg and 200 µg discs. The mere detection of resistance does not provide the complete picture; it is also necessary to determine the level of resistance. The concomitant use of the two discs can differentiate between low-level and high-level resistance. Isolates with a zone diameter of ≥14 mm for both 5 µg and 200 µg discs are considered to be susceptible for mupirocin. Isolates with zone diameter of <14 mm in the 5 µg disc but ≥ 14 mm in the 200 µg disc are taken as low level resistant strains. All isolates with zone diameters <14 mm for both 5 µg and 200 µg are considered to be high-level resistant strains [10]. In addition, E-test can be used to know the MIC of mupirocin. High-level resistance is associated with therapeutic failure, whereas low-level resistance can be overcome by recommending a higher than usual dosage [11].

Studies conducted in different parts of the world show varied rates of resistance: Turkey (45%), Trinidad and Tobago (26.1%), USA (13.2%), Spain (11.3%), China (6.6%), and Korea (5%) [12-17]. The resistance seems to be on the rise in the Indian scenario as well. Hence, we undertook this study to look into the prevalence of mupirocin resistance among the *S. aureus* isolates of our hospital, to determine the extent of resistance and to analyze the antibiotic susceptibility pattern of *S. aureus*.

METHODS

This is a prospective laboratory-based study. Clinical samples received in our laboratory which grew *S. aureus* during the period May–September 2014 were included in the study. The following samples grew *S. aureus*: Pus (70%), ear, nose, and throat swabs (18%), blood (5%), respiratory samples (3%), and other samples such as intravascular catheter tips, urine, and sterile body fluids (4%). Blood culture was done using BacT/Alert 3D (BioMérieux, France). Intravascular catheter tips were processed by Maki's roll culture technique. The other samples were inoculated onto standard media using standard techniques. Following incubation, identification of *S. aureus* was done on the basis of the colony morphology, Gram's stain, catalase test, and the tube coagulase test. Antimicrobial susceptibility testing was performed by Kirby–Bauer disc diffusion method and interpreted as per the Clinical and Laboratory Standards Institute standards [18]. The following

antibiotics were tested: Penicillin (10 units), gentamicin (10 µg), cotrimoxazole (1.25/23.75 µg), ciprofloxacin (5 µg), erythromycin (15 µg), clindamycin (2 µg), linezolid (30 µg), and teicoplanin (30 µg). Detection of methicillin resistance was carried out using cefoxitin (30 µg) discs. D zone test was done do determine inducible resistance to clindamycin. Vancomycin MIC was determined using the E-test. (BioMérieux, France) Mupirocin 5 µg and 200 µg discs were used for the detection of resistance. MIC determination of mupirocin-resistant strains was done using the E-test. Mupirocin sensitive and resistant isolate were included as controls in each batch of strains tested.

RESULTS

We had a total of 187 non-duplicate *S. aureus* isolates during the study period. This comprised 117 methicillin-sensitive *S. aureus* (MSSA) (62.5%) and 70 MRSA (37.4%) strains. Inducible clindamycin resistance was seen in 33 (17.64%) isolates.

Out of the 187, 9 isolates showed mupirocin resistance (4.81%), of which 4 were MRSA (2.13%), and 5 isolates were MSSA (2.67%). All the isolates showed high-level resistance, with MIC ≥1024 µg/ml. 6 of these samples were from pus, 2 were from ear swabs, and one isolate was from a nasal swab.

DISCUSSION

Mupirocin resistance has been reported from many parts of the world with varied frequencies. It is still not a huge problem in the Indian scenario. Oommen *et al.* have reported 2 and 28% incidence of mupirocin resistance in MRSA and methicillin-resistant coagulase-negative *Staphylococci* (MRCoNS), respectively [19]. According to a study by Gadepalli *et al*. high-level and low-level resistance was detected in 10 (5%) and 2 (1%) *S. aureus* strains, respectively [20]. As per Jayakumar *et al*., mupirocin resistance was seen in 3.3% of Staphylococcal isolates [21]. Rajkumari *et al*. did not detect any mupirocin resistance among MRSA isolates [22]. Kaur and Narayan conducted a study on detection of mupirocin resistance in *S. aureus* and CONS from the nasal swabs of 140 healthcare workers. They reported 100% sensitivity to mupirocin among MSSA and methicillin-sensitive coagulase-negative *Staphylococcus* isolates. The rates of resistance from MRSA and MRCoNS were 1.43% and 3.57%, respectively [23]. A study by Chaturvedi *et al*. reported 18.3% mupirocin resistance in MRSA; there were almost an equal number of high- and low-level resistances seen in their study [24].

According to our study, mupirocin resistance was seen in 4.81% of our *S. aureus* isolates, all of which exhibited high-level resistance. The interesting finding of our study is the presence of mupirocin resistance in MSSA almost equal to that in MRSA. According to a study by Kim *et al*. mupirocin resistance was seen in 39 isolates of *S. aureus* (7.8%) which comprised 30 (9.5%) MRSA and 9 (4.9%) MSSA [25]. Another study by McNeil *et al*. reported 14.7% incidence of mupirocin resistance among *S. aureus*. Molecular analysis showed that 15 isolates (11%) carried *mupA*, and the gene was more common in MSSA (21.4%) than MRSA (8.3%; p=0.03) [26]. This is an important finding to note as these MSSA strains which carry the resistance genes can serve as reservoirs. Studies suggest that the *mupA* gene is transferred from other *Staphylococcus* species to MRSA during mupirocin prophylaxis [27]. Thus, increasing prevalence of transferable mupirocin resistance is an important threat to its future use.

CONCLUSION

Mupirocin resistance in *S. aureus* is bound to rise due to its increasing use. Routine hospital screening for MRSA colonization may increase its usage which may further lead to resistance. The only alternative to mupirocin for nasal decolonization is retapamulin, which is under investigation [28]. Oral antibiotics for decolonization are to be considered only in conjunction with topical agents and when all other measures have failed [29]. Therefore, mupirocin is the cornerstone for the decolonization of MRSA, the current picture of its resistance seems to be just the tip of an iceberg; regular testing will help in tackling this upcoming problem and in preserving this important antibiotic against MRSA.

AUTHOR'S CONTRIBUTION

Dr. Malavalli Venkatesh Bhavana has conducted the study and has provided the concepts, design, literature search, intellectual content, performed data analysis, and manuscript preparation. Dr. Sangeeta Joshi has provided the concepts, design, study protocol, data, and intellectual content and has performed the manuscript review. Dr. Ranjeeta Adhikary and Hosdurg Bhaskar Beena have provided the concepts, data, and intellectual content and have performed the manuscript review.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this article.

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