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High prevalence of mupirocin resistance in methicillin resistant staphylococci and its clinical significance

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Abstract

Background: With the increasing pressure to prevent MRSA infections, it is possible that there will be increased use of Mupirocin for nasal decolonization of MRSA. Mupirocin is bacteriostatic at low concentration near the MIC for staphylococcus aureus but it is bactericidal at concentrations achieved by topical administration (20,000ug/ml) with the 2% formulation. Earlier reported High level Mupirocin resistance strain is associated with decolonization failure. The present study was carried out to determine the rates of high level and low level Mupirocin resistance (MuH and MuL) in methicillin resistant Staphylococcus aureus and methicillin resistant coagulase negative staphylococci.

Materials and methods: A prospective study was carried out on 104 non-duplicate Staphylococcal isolates from various clinical specimens were tested for Mupirocin resistance using 5µg and 200µg discs. Detection of Mupirocin resistance was done by the disk diffusion method using 5 µg and 200 µg Mupirocin disks to determine low- and high-level resistance, respectively.

Results: Mupirocin resistance was 7.8%, and 4.6% in MRSA and 40% and 20% in MR-CONS for 5 µg and 200 µg disc respectively.

Conclusion: Institutions that are considering the implementation of widespread Mupirocin use should consider these resistance issues and develop strategies to monitor the impact of Mupirocin use. Perioperative prophylaxis with nasal mupirocin therapy (PPNMT) can reduce the incidence of MRSA SSIs after orthopaedic surgery, probably by reducing nasal MRSA carriage in the endemic setting, without selecting for mupirocin resistance.

Keywords: MRSA, MR-CONS, Mupirocin, high level resistance (MuH), low level resistance (MuL), D test

Introduction

Mupirocin is a topical antibiotic used for decolonization of Methicillin susceptible Staphylococcus aureus and Methicillin resistant Staphylococcus aureus both in patients and in health care personnel and for the treatment of skin and soft tissue infections caused by Staphylococcus aureus and Streptococcal species [1]. Mupirocin is bacteriostatic at low concentration near the MIC for staphylococcus aureus but it is bactericidal at concentrations achieved by topical administration (20,000ug/ml) with the 2% formulation [1, 2]. Mupirocin resistant strains was first reported was in 1987 after the introduction of Mupirocin into clinical practice in 1985. The risk of emergence of the resistance appears to be greater among MRSA and MR-CONS than MSSA and is often associated with the widespread use of Mupirocin. Prior Mupirocin use is strongly correlated with Mupirocin resistance [3].

Resistance is classified into two categories: low level resistance, with MICs ranging from 8 to 256 µg/ml, and high level resistance, with MICs >512 µg/ml. Low level mupirocin resistance is due to point mutations in the isoleucyl-tRNA synthetase gene(iles) and is associated with higher rates of recolonization after efforts to eradicate S.aureus carriage [4]. High level resistance is conferred by the plasmid borne gene mupA with no affinity for Mupirocin. High level Mupirocin resistance strain is associated with decolonization failure. Mupirocin resistance may also aid in the spread of multidrug resistance through coselection with other resistance genes [4]. Studies have reported high rates of Clindamycin resistance in Mupirocin resistance strains and other non beta lactam antibiotics [1].

Mupirocin susceptibility is often not tested as part of routine clinical care. Though High level Mupirocin resistance has been reported to be relatively rare, studies have reported prevalence ranging from 2% to 15% [2]. Detection and differentiation of both low level and high level resistance has important clinical implications. The presence of high level mupirocin resistance (MuH) excludes its clinical use; whereas low level mupirocin resistance (MuL) can be overcome by higher dosage than usual. Therefore, it is essential for clinical laboratories not only to discriminate between susceptible and resistant strains but also to determine the levels of resistance [5, 9].

This study was carried out to determine the rates of high and low level Mupirocin resistance among clinical isolates of MRSA, and MR-CONS and to find out the prevalence of inducible Clindamycin resistance in Mupirocin resistant MRSA.

Material and methods

A prospective study was carried out in the Department of Microbiology, and Orthopaedic, IRT Perundurai Medical College from July 2016 to December 2017 after ethical committee permission was obtained. A total of 104 Non Consecutive Staphylococcal species from various clinical specimens like pus, blood, urine, central venous catheter tips, tracheal aspirates and sputum from patients admitted to the orthopaedics department were included in this study. MRSA isolates were identified by standard Microbiological techniques. MRSA isolates were tested for antimicrobial susceptibility testing by Kirby-Bauer's disk diffusion method on Mueller Hinton agar as per CLSI guidelines [6]. Discs were procured from Hi-Media Laboratories –Mumbai. Detection of Mupirocin resistance was done by the disk diffusion method using 5 µg and 200 µg Mupirocin disks to determine low- and high-level resistance, respectively. Criteria of zone diameter breakpoints for susceptible and resistant isolates were set at >14 and <13 mm, respectively [4, 5].

Three different phenotypes are:

- A zone diameter of greater than or equal to 14 mm for both 5 and 200 µg disks was considered to be susceptible for mupirocin.
- Isolates that showed zone diameters less than 14 mm in the 5 µg disk but more than or equal to 14 mm in the 200 µg disk were considered to be MuL strains.
- All isolates with zone diameters less than 14 mm for both 5 µg and 200 µg were considered to be MuH strains.

Erythromycin-resistant isolates of MRSA were further studied for inducible Clindamycin resistance by "D test" as per Clinical and Laboratory Standards Institute (CLSI) guidelines [6].

Statistical analysis

We organized the data in three different ways for statistical analysis. First, the "per-isolate" analysis included all 104, unique isolates. In this analysis, all patient may have been represented more than once due to inclusion of isolates from more than one visit. Second, the "initial-isolate" analysis included a single isolate from the first culture date collected from each patient during the study time period. Third, the "ever-resistant" analysis included a single isolate for each patient on the visit when mupirocin resistance was first, if ever, recorded or from the initial culture date if mupirocin resistance was never recorded. Unpaired *t* test results P value and statistical significance: The two-tailed P value equals

0.0251 By conventional criteria, this difference is considered to be statistically significant.

Results

Among the 104 staphylococcal isolates 64 were MRSA and 10 were MR-CONS. One isolate of MRSA showed resistant to Linezolid. 82% isolates of MRSA were resistant to Ciprofloxacin. 7.8% MRSA showed low level Mupirocin resistance whereas high level Mupirocin resistance was seen in only 4.6% of the isolates. Higher prevalence of Mupirocin resistance MuL and MuH 40% and 20% resistance were observed in MR-CONS. 6.25% of the Mupirocin resistant isolates were from Pus samples.

Mupirocin resistance for high level mupirocin by disk diffusion were confirmed by MIC -E Strip. No MRSA and MR-CONS were found to be Vancomycin resistant and none of the isolates showed inducible Clindamycin resistance by D test.

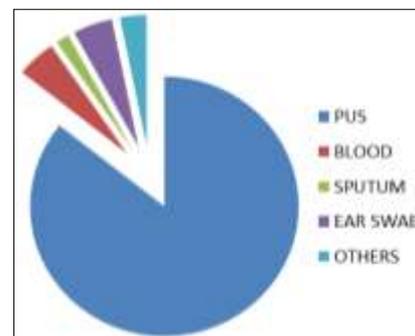


Fig 1: Specimen wise distribution of S. Aureus

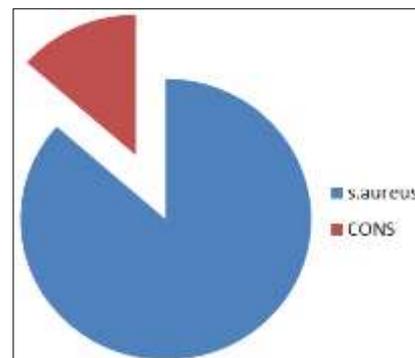
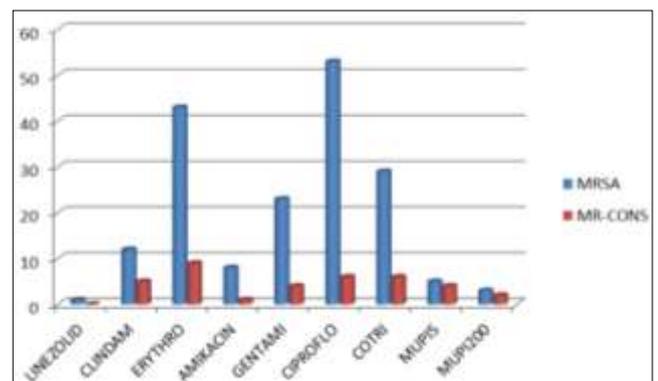


Fig 2: Percentage of MRSA and MR-CONS from clinical specimens

Among the 104 staphylococcal isolates, 64 isolates were methicillin resistant staphylococcus aureus and 10 isolates were methicillin resistant coagulase negative staphylococcus



The two-tailed P value equals 0.0251

Fig 3: Resistance pattern of MRSA and MR-CONS

The figure shows the comparative resistance between methicillin resistance staphylococcus aureus and methicillin resistant coagulase negative staphylococcus.

MRSA Shows high resistance to all the drugs used including mupirocin compared to MR-CONS, we found the data is highly significant.

Discussion

Mupirocin is an important component of antimicrobial therapy that is recommended for treatment of minor skin infections caused by MRSA and decolonisation of patients with recurrent MRSA skin and soft tissue infections [1, 2], Mupirocin is mainly used as a nasal cream as part of the regimen to decolonize patients who have been found to carry methicillin-resistant *Staph. aureus*. It can also be applied to tracheostomy, gastrostomy and other sites that are frequently colonized with MRSA [3, 4] A small study of local therapy to reduce the risk of peritonitis in patients on continuous ambulatory peritoneal dialysis (CAPD) found that mupirocin applied three times weekly to the dialysis catheter exit site resulted in a 92% reduction in the rate of peritonitis [6, 7].

Mupirocin resistance is being reported in many parts of the world viz-Spain 11.3%, USA 13.2%, Trinidad Tobago 26.1%, China 6.6%, India 6%, Turkey 45% and Korea 5% due to its indiscriminate usage [4, 7, 9, 11].

In our study 8(12.5%, n=64) MRSA strains showed mupirocin resistance by MIC out of which 5(7.8%) and 3(4.6%) were MuL and MuH resistance respectively. Among the 10 CoNS 6 (16%) was resistant to Mupirocin by MIC, showing 4(10%) and 2 (4%) MuL and MuH resistance respectively.

When Mupirocin based decolonisation regimens have been used as routine and sustained strategy to control *S. aureus* endemic infection and transmission among general inpatient population the emergence of Mupirocin resistance has been commonly although not universally observed.

In particular, resistance seems to emerge readily in health care facilities with unrestricted policies that allow widespread Mupirocin use for prolonged periods especially when application to decubitus ulcers and other skin lesions is allowed. There are several studies which have linked mupirocin resistance to mupirocin use [4, 8]. In situations where rates of Mupirocin resistance in MRSA are high, it is possible that indiscriminate use could lead to co selection of Methicillin resistant strains [3, 7].

It seems prudent to test for Mupirocin susceptibility in patients with a history of Mupirocin use, culture positive MRSA We observed high Fluoroquinolone resistance in MRSA strains and we did not see any association between Mupirocin resistance and Clindamycin resistance.

It is well proven from our study and other studies that screening of mupirocin resistance by 5 µg cannot differentiate among the MuL and MuH strains and it needs the concomitant use of both the 5 and 200 µg disc [2, 4, 5, 10]. As evident from our study mupirocin resistance is more in CoNS which remains a threat as they play major contributory role especially *Staphylococcus epidermidis* by transferring mupA gene to MRSA while attempting for decolonization with mupirocin. Perioperative prophylaxis with nasal mupirocin therapy PPNMT can reduce the incidence of MRSA SSIs after orthopaedic surgery, probably by reducing nasal MRSA carriage in the endemic setting, without selecting for mupirocin resistance.

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