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IN VITRO ACTIVITIES OF LINEZOLID, DAPTOMYCIN, MUPIROCIN AND TIGECYCLINE IN CLINICAL ISOLATES OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS IN SKIN AND SOFT TISSUE INFECTIONS FROM NORTH EAST INDIA

Dr. Chimanjita Phukan,*[1] Dr Nahid Anjum[2] and Dr. Giasuddin Ahmed[3]

[1]Gauhati Medical College & Hospital, Associate Professor, Department of Microbiology, Gauhati Medical College & Hospital, Narakasur Hill Top, Guwahati-781005, Assam, India.

[2]Silchar Medical College & Hospital, Demonstrator, Department of Microbiology, Silchar Medical College & Hospital, Assam, India.

[3]Department of Biotechnology, Professor, Department of Biotechnology, Gauhati University, Guwahati, Assam, India.

***Correspondence for Author: Dr. Chimanjita Phukan**
Gauhati Medical College & Hospital, Associate Professor, Department of Microbiology, Gauhati Medical College & Hospital, Narakasur Hill Top, Guwahati-781005, Assam, India.

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ABSTRACT

Introduction: Community-Acquired Methicillin-Resistant *Staphylococcus aureus*(CA-MRSA) has been recognized as an important pathogen for causing Skin and Soft Tissue Infection(SSTI). Treatments of these pathogens are a therapeutic challenge due multidrug resistance. The purpose of our study was to understand the invitro activity of the newer antimicrobials including Linezolid, daptomycin, mupirocin and tigecycline against *S.aureus* causing Skin and Soft tissue infections. **Methodology:** The staphylococcus *aureus* isolates from SSTIs were isolated and processed according to standard protocols. CDC definition, was used to categorized as community acquired and hospital acquired methicillin-resistant *S. aureus.* Isolates were subjected to antimicrobial sensitivity testing and tested for the presence of inducible clindamycin resistance. Minimum inhibitory concentration by E test was done for linezolid, daptomycin, mupirocin and tigecycline. **Results:** Of the 112 *S.aureus* isolates from SSTIs, 61.6% were methicillin resistant *S. aureus* (MRSA) and 38.4% were methicillin sensitive *S. aureus*(MSSA). Community acquired MRSA (40%) were more common among outpatients than the hospital acquired infections (29%). Children and young adults presented with most of the SSTIs. The Inducible clindamycin resistance among the *S. aureus* isolates were found to be 5.36% and among HA-MRSA and CA-MRSA it was 3.3% and 2.2% respectively. Linezolid resistance was 2.67% and MIC ranged 1.5 - 12µg/ml and none of the *S aureus* isolates were found to be resistant for daptomycin. 2.67% isolates had MICs for tigecycline greater than 1µg/ml and ranged 0.064µg/ml- ≥4 µg/ml. Mupirocin resistance was detected with a prevalence of 1.78% among the *S. aureus* isolates, all isolates were HA-MRSA. **Conclusion:** The high prevalence of CA-MRSA and the emergence of multidrug resistant strains highlights on implementation of proper infection prevention policies and antibiotic stewardship program.

KEYWORDS: Staphylococcus aureus, Skin and Soft tissue infection, Linezolid, daptomycin, mupirocin, tigecycline.

INTRODUCTION

The alarming increase in multiple drug resistant methicillin-resistant *Staphylococcus aureus* (MRSA) strains has become a major problem worldwide. Staphylococcus aureus continues to be a major cause of concern due to the broad spectrum of diseases caused in human. Skin and soft tissue infections (SSTIs) are a common cause of morbidity in both the community and the hospital and accounts for up to 76% of all purulent SSTIs.[1] Superficial SSTIs are generally treated in outpatients with oral and topical antibiotics but complicated SSTIs may require hospitalization requiring more aggressive management of these infections.[2]

In the last few decades, methicillin-resistant *Staphylococcus aureus* (MRSA) due to its evolutionary changes has become a major cause of nosocomial and community-acquired infections. CAMRSA are threat to individuals as they are known to be more virulent and more frequently recovered from SSTIs.[3] This pathogen has become a therapeutic challenge due to its multiresistance to different classes of antibiotics.

Linezolid, a synthetic oxazolidinone antibiotic, has a broad spectrum activity for the treatment of uncomplicated and complicated skin and soft-tissue infections(SSTIs).[4] Daptomycin, a bactericidal lipopeptide antimicrobial, is effective against Gram-positive bacteria, including MRSA and vancomycin-

resistant *S. aureus* , for the treatment of complicated skin and soft tissue structure infection.[5] Mupirocin is a topical antimicrobial agent used for the treatment of SSTI, and decolonization of *S. aureus* nasal carriage in patients and health care workers.[6] Wide usage of mupirocin has resulted in resistance leading to treatment failure [6] and there are reports of low prevalence despite widespread usage.[7,8] Tigecycline, semi-synthetic tetracycline (glycylcycline) derived from minocycline.[9] It is active against Gram-positive cocci and Gram-negative rods and anaerobic micro-organisms. Tigecycline is active against tetracycline- and minocycline-resistant microorganisms and does not present cross-resistance with other antibiotics such as β-lactams or fluoroquinolones.[10] With this background we assessed the invitro activity of linezolid, daptomycin, mupiocin and tigecycline among *S. aureus* isolates causing SSTI in the North East part of the country.

MATERIALS AND METHODS

Microbiological data

Clinical isolates from skin and soft tissue infections have been processed from patients attending the outpatient and inpatients department of Gauhati Medical College and Hospital between June 2012 and May 2013. The Institutional ethics review board reviewed and approved the study protocol. On the basis of CDC criteria, the isolates from the patients were being characterized as Community or Hospital Acquired Methicillin Resistant Staphylococcus *aureus.* Skin swabs were enriched in tryptonesoya broth supplemented with 6.5% sodium chloride and incubated at 35^{o}C for 18 h before being cultured in Sheep blood agar and mannitol salt agar to determine the presence of *S. aureus* based on gram staining, colony morphology, catalase test, slide coagulase and tube coagulase test.

Antimicrobial susceptibility testing

The standard disk diffusion by Kirby–Bauer method was used to test the antibiotic susceptibility.All isolates underwent susceptibility testing to 15 antimicrobials cefoxitin(30µg), penicillin (10 units), gentamicin (10 µg), amikacin(30 µg), co-trimoxazole (1.25/23.75 µg), ciprofloxacin (5µg), chloramphenicol(30µg), erythromycin (15 µg), clindamycin (2 µg), linezolid(30 µg), doxycycline(30 µg), rifampin(5 µg), mupirocin(5µg), minocycline(30 µg) and tigecyclline(15 µg)discs from Hi-media (Mumbai). Each bacterial isolate was classified as susceptible (S), intermediate (I) and resistant (R) to antibiotic according to the zone diameter interpretation standard of CLSI 2015.

Cefoxitin (30 µg) disc diffusion test was used to report methicillin resistance and Inducible clindamycin resistance was assessed with a double-disk approximation “D test” and strains which possessed inducible clindamycin resistance were considered resistant to clindamycin as per the Clinical and Laboratory Standards Institute (CLSI) guidelines.[11]

Minimum inhibitory concentration (MIC)

Minimum inhibitory concentration (MIC) for Linezolid, Daptomycin, Mupirocin and Tigecycline for the *S. aureus* isolates were further determined by the agar dilution method with E test strip (bioMérieux India Pvt. Ltd., New Delhi, India) following the manufacturer’s instructions. The MIC was defined by the intersection of the growth ellipse margin with the E test strip by using reflected light. In instances, the Etest MIC was read between the usual twofold MIC increments. Muller Hinton agar was supplemented with 5% sheep blood and this was used for MIC determination for linezolid. [12] The MIC interpretation was obtained by E test after 24 and 48hours of incubation at 35°C. Minimum Inhibitory Concentrations (MICs) ≤4 µg/ ml was considered as susceptible and MIC ≥8µg/ml as resistant as per the CLSI guideline, 2015.

MIC breakpoints of Mupirocin for the S. aureus isolates were interpreted as either low-level or high-level resistance. It was interpreted as mupirocin susceptibility with minimum inhibitory concentrations (MICs) ≤4 µg/ml, low-level mupirocin resistance with MICs from 8 and 256 µg/ml, and high-level mupirocin resistance with MICs ≥512µg/ml.[8]

The daptomycin Etest contained a concentration gradient of daptomycin with a standard amount of calcium throughout the strip and MIC values were read as per the manufacturers recommendation. The E test strips were applied to the surfaces of 150-mm Mueller-Hinton agar plates that had been inoculated with a swab dipped in the 0.5 McFarland organism suspension. MIC breakpoints for daptomycin susceptibility (MIC ≤1 µg/ml) and nonsusceptibility (MIC >1 µg/ml) was interpretation made as per CLSI criteria, 2015.[11] The MIC breakpoints for tigecycline were interpreted as susceptible with minimum inhibitory concentrations (MICs) ≤1 µg/ml and nonsusceptible for MICs >1 µg/ml in accordance with the standard guideline.[11]

All *S. aureus* isolates were frozen in 20% glycerol for future analyses. Quality control testing was performed by inoculating *S. aureus ATCC* 25923 as a negative control and ATCC 43300 as a positive control. *S. aureus* ATCC 29213 as MIC control strain and *S. aureus* ATCC BAA 977 was used as positive control to detect D-test positive strain.

RESULT

During the study period, a total of 112 staphylococcus aureus isolates were processed from those presenting with abscess, cellulitis, folliculitis, infected blister, impetigo in the laboratory of department of Microbiology. The majority of the isolates were obtained from outpatients when compared to inpatients (69.6 vs 30.4 per cent, respectively). Among the 112 nonduplicate clinical isolates, 69 (61.6%) were Methicillin Resistant *S. aureus* and 43(38.4%) were Methicillin Sensitive *S. aureus* (Table1). Community acquired *S. aureus*

infections (68%) were more common among outpatients than the hospital acquired infections (32%) (Table1).

Table1: Distribution of *S. Aureus.*

Total	MRSA, n=69(%)	CAMRSA n=40(%)	HAMRSA n=29(%)	MSSA, n=43%	CAMSSA n-36(%)	HAMSSA n=7(%)	(%) n=112
Opd	43(62.3)	39(97.5)	4(13 .79)	35(81.3)%	35(97.22)	-	78(69.64)
Ward	26(37.68)	1(2.5)	25(86.21)	8(18.6%)	1(2.78)	7(100)	34(30.36)

ABBREVIATIONS

CA-MRSA- Community-Associated Methicillin-Resistant *S. aureus*
HA-MRSA- Healthcare-Associated Methicillin-Resistant *S. aureus*
MSSA -Methicillin-Sensitive *S. Aureus*
MRSA- Methicillin-Resistant *S. Aureus*
SSTI-Skin and Soft tissue infection
MuL -Low Level Mupirocin Resistance
LRSA -Linezolid Resistant *Staphylococcus aureus*

Table 2: Antibiotic resistance among Community acquired & Healthcare associated *S. Aureus.*

Antimicrobial	Community acquired Resistant *S. Aureus* n = (%)				Healthcare associated Resistant *S. Aureus* n= (%)				Total n=112
	MRSA		MSSA		MRSA		MSSA		
	n=40	(%)	n=36	(%)	n=29	(%)	n=7	(%)	
Pencillin	53	(47)	5	(4)	43	(38)	3	(3)	104(93 %)
Clindamycin	6	(5)	1	(1)	9	(8)	1	(1)	17(15%)
Erythromycin	15	(13)	4	(3.5)	14	(12.5)	2	(2)	35(31%)
Ciprofloxacin	24	(21)	3	(3)	23	(20)	2	(2)	52(46%)
Gentamicin	11	(10)	1	(1)	11	(10)	0		23(21%)
Amikacin	5	(4)	2	(2)	11	(10)	0		18(16%)
Linezolid	1	(1)	0		2	(2)	0		3(2.6%)
Cotrimoxazole	18	(16)	2	(2)	15	(13)	1	(1)	36(32%)
Chloramphenicol	4	(3)	1	(1)	3	(3)	0		8(7%)
Doxycycline	2	(2)	1	(1)	4	(3)	1	(1)	8(7%)
Mupirocin	0		0		2	(1.78)	0		2(1.78%)
Minocyclin	2	(2)	1	(1)	5	(4)	0		8(7%)
Rifampicin	5	(4)	1	(1)	5	(4)	0		11(9 %)
Tigecycline	1	(0.89)	1	(0.89)	1	(0.89)	0		15(2.67%)

The mean age of patients was 29, the median 28 years. The age of the study population ranged from 3months to 70 years. According to the age groups, 27% cases were between 21-30 years, 20% in 11-20 years, 19% in 31-40 years and 13% in 3months -10 years age groups respectively. The males were more infected but were not found to be significant when compared to the females. SSTI as observed in community-acquired and hospital acquired infections were 38% and 18% in males, 25% and 44% in females respectively.

The Inducible clindamycin resistance among the *S. aureus* isolates from SSTI were found to be 5.36% and the MS Phenotype with resistance to erythromycin (zone size ≤13mm) while sensitive to clindamycin (zone size ≥21mm) with circular zone of inhibition around it was found to be 13.4%. The Constitutive MLSB Phenotype was detected in 9% with resistance to both erythromycin (zone size ≤13mm) and clindamycin (zone size ≤14mm) with circular zone of inhibition. The Inducible clindamycin resistance among HAMRSA and CAMRSA were found to be 3.3% and 2.2% respectively.

Among the *S aureus* isolates from SSTIs, linezolid resistance by the disc diffusion method as observed in the transmitted light was found to be 3(2.67%) and the MIC range was 1.5 - 12µg/ml, only one isolates had MIC 12µg/ml. Among them one of the isolates was community acquired MRSA and two cases were hospitalized patients receiving linezolid.

None of the *S aureus* isolates were resistant for daptomycin as all the isolates were within the susceptible MIC≤ 1µg/ml as per the CLSI, 2015. All the isolates were susceptible to daptomycin with MIC range of 0.75-≤1 µg/ml.

Three (2.67%) isolates had MICs for tigecycline greater than 1µg/ml and are considered to be resistant for tigecycline. The resistant isolates belonged to CAMSSA, CAMRSA and HA-MRSA one each respectively. MIC

for Tigecycline among the *S. aureus* isolates from SSTIs was within the range of 0.064µg/ml- ≥4 µg/ml.

Mupirocin resistance as detected by Kirby Baur disc diffusion was 2(1.78%) among *S. aureus* isolates with mupirocin (5µg) disc and with E test the MIC range was 0.01 - ≥10µg/ml. The MIC breakpoints as interpreted for mupirocin susceptibility with minimum inhibitory concentrations (MICs) ≤4 µg/ml were 98%, low-level mupirocin resistance was 1% and high-level mupirocin resistance was 1% among the isolates. The mupirocin resistance were detected in a hospital acquired MRSA strain.

DISCUSSION

As the epidemiology of *S.aureus* continues to evolve, MRSA prevails as a multi-resistant hospital pathogen worldwide and is a therapeutic challenge. Community acquired MRSA unlike hospital acquired strains remains susceptible to most non–β-lactam antibiotics, hence our study depicts the prevalence of CAMRSA where MIC of the newer antimicrobials has been reported for skin and soft tissue infections from north eastern part of India.

The prevalence of methicillin resistant *S. aureus* was 61.6% from SSTIs in our study and community-associated MRSA accounted for 40% of cases with maximum cases (97.5%) from the outpatients department. The prevalence of CAMRSA was very high compared to other Indian studies.[13,14] Studies from Mumbai reported 54% CA-MRSA from SSTIs and 36.2% CA-MRSA.[15] In an Indian multicentric study, the MRSA prevalence in nosocomial SSTI varied from 7.5 to 41.3 per cent between different hospitals.[16]

In a study from 11 U.S. Emergency Departments, MRSA ranged 15-74 percent among the bacterial isolates from purulent Skin and Soft-Tissue Infections.[17] In the ANSORP study conducted among eight Asian countries from 17 hospitals, the rate of community-associated MRSA infections ranged from 2.5% to 39%.[18] The European Antimicrobial Resistance Surveillance System (EARSS), record the incidence of bloodstream and cerebrospinal CAMRSA infections between 5% - 25%. According to the pan-European surveillance systems, EARSS and HELICS, the CA-MRSA infections prevalent in most European countries now are still less frequent than HA-MRSA infections.[18]

The prevalence of Inducible clindamycin resistance among the *S. aureus* isolates from SSTI (5.36%) was much lesser when compared to other studies.[13,19] The Inducible clindamycin resistance among HAMRSA and CAMRSA were found to be almost the same. The linezolid resistant *Staphylococcus aureus* (LRSA) in our study was 2.67% but were not resistant to clindamycin or chloramphenicol, which indicate cfr gene may not be the probable cause of resistance as reported in many studies.[20, 21] Rajaduraipandi reported LRSA in South India which is similar to our study.[22] Indian Network for Surveillance of Antimicrobial Resistance (INSAR) did not find any resistant to linezolid in its isolates.[16] The surveillance done by the USA Linezolid Experience and Accurate Determination of Resistance(LEADER) and the global Zyvox Annual Appraisal of Potency and Spectrum (ZAAPS) in a study of isolates over 9 years (2004–2012) from 33 countries on five continents from bacterial pneumonia and acute bacterial skin and skin structure infections (ABSSSIs) identified Linezolid resistant S. aureus in only 0.05% and <0.1% respectively.[23]

Daptomycin has been approved in United States in 2003 for the treatment of complicated skin and soft tissue structure infection, bacteremia and endocarditis.[24] Polymorphisms in four genes (*mprF*, *yycG*, *rpoB* and *rpoC*) has been identified for the development of daptomycin nonsusceptibility.[25] Development of vancomycin-intermediate resistance during therapy with vancomycin can sometimes confer daptomycin cross-resistance which has been increasingly documented.[26,27] but nonsusceptibility has not been observed in our study.

In our study, mupirocin resistance obtained were similar to the reports from India.[28,29] Resistance to GEN or TMP-SXT was observed in 60% of the isolates among the mupirocin resistance strains which might be plasmid mediated due to *mupA* carriage[30] and 40% of these isolates were resistant to Rifampicin. Simultaneous resistance to ciprofloxacin, clindamycin and erythromycin was observed in 40% of the mupirocin resistant isolates. Prevalence of MuL isolates indicates that SSTIs can be treated with normal dosage schedule of mupirocin ointment but surveillance for detection of high level mupirocin resistance shall be required as it is associated with treatment and decolonization failure as mupirocin antimicrobial susceptibility is not routinely reported.

CONCLUSION

The CA-MRSA has emerged as an important cause of skin and soft tissue infections. The emergence of resistance to linezolid, mupirocin and tigecycline poses significant challenges to the clinical treatment of infections caused by these organisms. The widespread use of antibiotics could have contributed to the high resistance rates of CA-MRSA. Surveillance for multidrug resistance, awareness and implementation of infection control practices and antibiotic policies is the urgent need of hours.

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