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Prevalence and Susceptibility Pattern of Methicillin-Resistant *Staphylococcus aureus* (MRSA) in Rural Kerala: A Tertiary Care Hospital Study

T.P. Rajesh*, S. Vani, K.A. Faisal and T.S. Shailaja

Faculty at P K Das Institute of Medical Sciences, Vaniyamkulam, Palakkad, Kerala, India

**Corresponding author*

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A B S T R A C T

Infections with *Staphylococcus aureus* continue to be a major problem in the world. Prompt diagnosis is essential to avert the further complications of this infection particularly Methicillin-resistant *Staphylococcus aureus* (MRSA) when compared to Methicillin-sensitive Staphylococcus aureus (MSSA). This retrospective study was done from January 2016 to June 2018 in a tertiary care hospital to know the prevalence of MRSA infections in both the inpatients as well as out patients. Of the 403 total isolates of *S. aureus* the overall prevalence of MRSA in our study was 42.9%, majority of them were accounted by skin and soft tissue infections (SSTI) followed by urinary tract infections, blood stream infections and respiratory infections. The study showed an increased prevalence of MRSA among the inpatients when compared to the outpatients. A single intervention will unlikely to have a significant impact on attenuating MRSA infection rates. Multifactorial bundled approach is the need of the hour in containing the MRSA infections along with robust antimicrobial stewardship and prompt infection control measures and judicious use of the drugs of choice for MRSA infection which have to be preserved for the future use.

Introduction

Hospital-associated infections and community-acquired infections caused by *Staphylococcus aureus* continue to be a dangerous threat for the outcome of the patient. Methicillin resistant was reported to *S. aureus* soon after its introduction in October 1960 (Jevons, 1961). Between regions and between hospitals in the same region the prevalence of MRSA varies (Gadepalli *et al.*, 2009) and it is endemic worldwide in hospitals (Goetghebeur *et al.*, 2006). One of the leading causes of healthcare associated infection is MRSA (Dantes *et al.*, 2011; Kaye *et al.*, 2009). MRSA has been estimated to cause over 80,000 "invasive" infections and over 11,000 deaths in the United States according to Centers for Disease Control and Prevention (CDC) in 2011 (Dantes *et al.*, 2011). The health care cost attributable to MRSA infection is enormous. In order to prevent the enormous economic burden and health care cost to the

individuals with MRSA infection each and every hospital should have the prevalence rates for MRSA infections. This study was carried out to know the prevalence rates of MRSA infections in a tertiary care hospital which will help in taking the appropriate measures in controlling and spreading of MRSA infections in the hospital and will act as a baseline data in deciding the appropriateness of the control measures taken.

Materials and Methods

Patients and hospital setting

This study was done at a tertiary referral hospital with 750 beds. In this retrospective study, all the susceptibility data for *S. aureus* from January 2016 to June 2018 were analyzed. The study population was involved outpatient or inpatient (including Intensive Care Unit) patients.

Sample collection and laboratory analysis

Using standard precautions different samples from the various departments of the hospital were collected and transported to the microbiology laboratory for the isolation and susceptibility testing. The antibiotic susceptibility testing was performed by the Kirby Bauer's' disc diffusion technique, using Clinical and Laboratory Standards Institute (CLSI) recommendations. Cefoxitin (30 µg) was used for methicillin resistance.

The other antibiotics tested included penicillin (10 units), gentamicin (10 µg), co-trimoxazole (1.25/23.75 µg), ciprofloxacin (5 µg), erythromycin (15 µg), clindamycin (2 µg), vancomycin (30 µg) and linezolid (30 µg). Discs from Hi-media were used by the laboratory. Inoculum was prepared by making a direct saline suspension of isolated colonies selected from an 18- to 24-h blood agar plate. Turbidity of the suspension was adjusted to achieve a turbidity equivalent to a 0.5 McFarland standard and five discs were applied on a 100mm Mueller Hinton agar plate as per CLSI guidelines. *S. aureus* ATCC 25923 was used as the quality control strain for disc diffusion.

Variables measured

The following information age, gender, specimen, source of referral (Outpatient, inpatient, IUC), along with the antibiotic susceptibility data for *S. aureus* was collected in a structured excel sheet.

Definitions

According to CLSI guidelines 2016 (Clinical and Laboratory Standards Institute, 2016)

MSSA– zone diameter ≥ 22 using cefoxitin (30µg) disc, Kirby Bauer's' disc diffusion technique

MRSA– zone diameter ≤ 21 using cefoxitin (30µg) disc, Kirby Bauer's' disc diffusion technique

Statistical analysis

SPSS version 16.0 for Windows (SPSS, Inc., Chicago, IL) was used for all data analysis.

Continuous variables are expressed as means and range. Simple proportions were calculated to estimate the hospital-based prevalence of MRSA and MSSA.

Qualitative data

For assessing difference between proportions, Pearson's chi-square test was used as a test of significance. When expected value in a cell was less than 5 in a 2x2 table, Fisher's exact test was used as a test of significance. When expected value in a cell was less than 5 in

other tables, likelihood ratio test was used a test of significance. P values less than 0.05 were considered statistically significant.

Results and Discussion

Of the 403 total isolates of *S. aureus* detected from January 2016 to June 2018, 125 (31%) were detected in 2016, 205 (50.9%) were detected in 2017 and rest 73 (18.1%) in 2018. The majority of the isolates were obtained from males 241 (58.9%) rest were from female patients. Mean age of the patient was 47 years. The sample was collected from 1-day old baby to 89-year-old adult patient. Thus, specimen was collected from wide age range of the patient. Majority of patients were referred from General Surgery department, followed by General Medicine, Orthopedics, Pediatrics, Urology, rest all other department had referred less than 5% of patients (Figure 1).

The prevalence of MRSA was 43.2%, 43.9% and 39.7%, for year 2016, 2017 and 2018 respectively (Table 2). The overall period prevalence was 42.9%. The prevalence of MRSA was high in inpatients compared to the outpatients for all the specimens (Table 3). All patients from different intensive care units and operation theater were considered as in patient for analysis purpose.

Antibiotic susceptibility testing data for azithromycin (15µg), amikacin (30µg), ciprofloxacin (5µg), clindamycin(2µg), co-trimoxazole (23.75/1.25 µg), erythromycin (15µg), gentamycin (10µg), levofloxacin (5µg), linezolid (30µg), norfloxacin (10µg), nitrofurantoin (300 µg), ofloxacin (5µg), penicillin (10 units), tetracycline (30µg), tigecycline (15µg), teicoplanin (30µg) and vancomycin (30µg) were compiled. There was no resistance documented against tigecyclin, teicoplanin, vancomycin and linezolid. Resistance to antibiotics amongst the MRSA isolates was more than that in methicillin sensitive *S. aureus* (MSSA) (P<0.05) (Table 4).

Table.1 Source of patients and type of specimen used for isolating *S. aureus*

Source	No. of *S. aureus* isolates	Percent
In Patient (IP)	276	68.5
Out Patient (OP)	108	26.8
Medical Intensive Care Unit (MICU)	7	1.7
Surgical Intensive Care Unit (SICU)	5	1.2
Neonatal Intensive Care Unit (NICU)	4	1
Operation Theatre (OT)	2	0.5
Pediatric Intensive Care Unit (PICU)	1	0.2
Total	403	100
Type of the Specimen	**No. of Specimen**	**Percent**
Pus	306	75.9
Urine	52	12.9
Blood	26	6.5
Sputum	19	4.7
Total	403	100

Table.2 Year wise prevalence of MRSA

Year	MRSA	MSSA	Total
2016	54 (43.2)	71 (56.8)	125
2017	90 (43.9)	115 (56.1)	205
2018	29 (39.7)	44 (60.3)	73
Total	173 (42.9)	230 (57.1)	403

Table.3 Prevalence of MRSA in different specimen

		MRSA	MSSA	
Specimen		**n (%)**	**n (%)**	**Total**
Pus	IP	87 (40.5)	128 (59.5)	215
	OP	33 (36.3)	58 (63.7)	91
Urine	IP	28 (73.7)	10 (26.3)	38
	OP	7 (50.0)	7 (50.0)	14
Sputum	IP	7 (41.2)	10 (58.8)	17
	OP	0 (0.0)	2 (100)	2
Blood	IP	11 (44.0)	14 (56.0)	25
	OP	0 (0.0)	1 (100.0)	1
	Total	**173 (42.9)**	**230 (57.1)**	**403**

Figure 1: Departmentwise referral of Specimen for *S. aureus* isolates

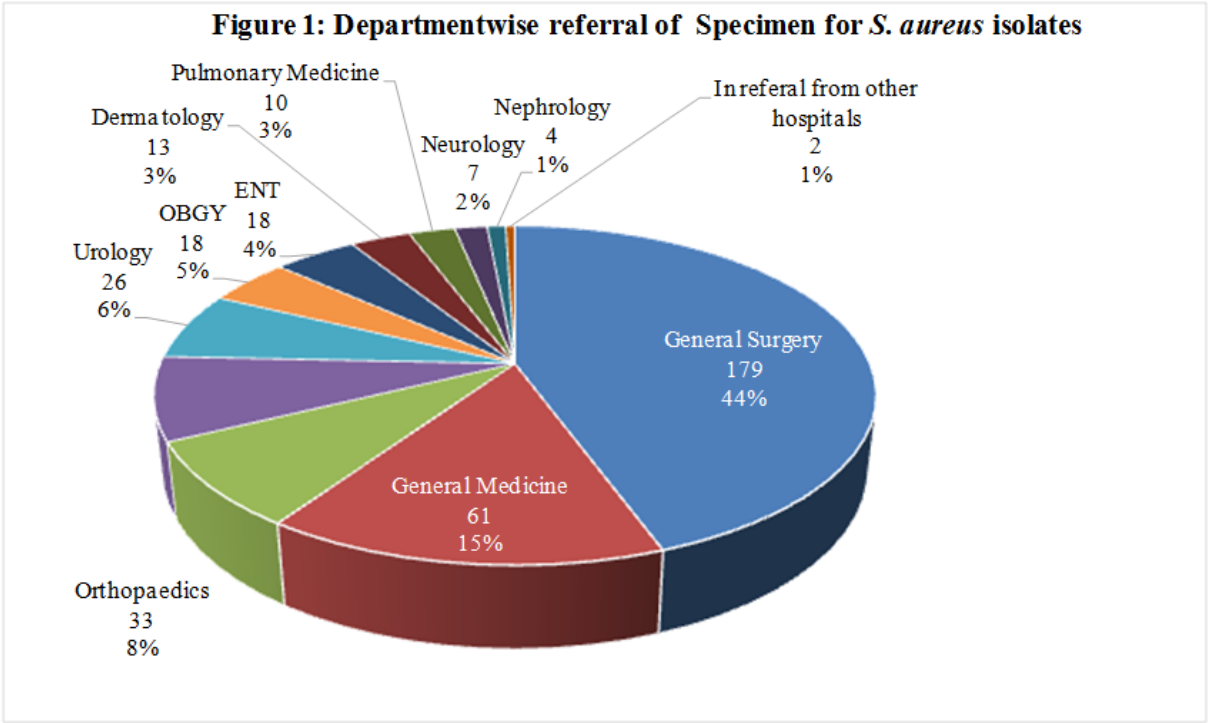

Table.4 Antibiotic susceptibility results of *Staphylococcus aureus* 2016- 2018

Antibiotics	Strain	Total Strain type (n)	Sensitive n (%)	Resistant n (%)	Intermediate n (%)	P value
Amikacin	MRSA	173	151 (87.3)	21 (13.9)	1 (0.57)	0.006
	MSSA	230	218 (94.7)	9 (4.1)	3 (1.3)	
Azithromycin	MRSA	6	1 (16.6)	5 (83.3)		0.013
	MSSA	12	10 (83.3)	2 (20)		
Ciprofloxacin	MRSA	171	41 (23.9)	128 (74.8)	2 (1.1)	0
	MSSA	226	100 (44.2)	124 (54.8)	2 (0.8)	
Clindamycin	MRSA	123	79 (64.2)	44 (35.7)		
	MSSA	186	146 (78.4)	40 (21.5)		
Co-trimoxazole	MRSA	161	108(67.0)	52 (32.2)	1 (0.6)	0
	MSSA	211	181 (85.7)	30 (14.2)		
Erythromycin	MRSA	115	40 (34.7)	75(65.2)		
	MSSA	183	112 (61.2)	71 (38.7)		
Gentamycin	MRSA	170	107 (62.9)	63 (37.0)		0
	MSSA	225	199 (88.4)	26 (11.5)		
Levofloxacin	MRSA	172	47 (27.3)	125 (72.60		
	MSSA	224	117 (52.3)	107 (47.7)		
Linezolid	MRSA	172	172 (100)	0		
	MSSA	227	227 (100)	0		
Nitrofurantoin	MRSA	35	33 (94.2)	2 (5.7)		0.203
	MSSA	17	17 (100)	0		
Norfloxacin	MRSA	35	2 (5.70	33 (94.2)		0.002
	MSSA	17	7 (41.7)	10 (58.8)		
Ofloxacin	MRSA	81	29 (35.8)	52 (64.1)		0.021
	MSSA	102	54 (52.9)	48 (47.0)		
Penicillin	MRSA	173	0	173 (100)		0
	MSSA	229	102 (44.5)	127 (55.4)		
Tetracycline	MRSA	124	58 (46.7)	66 (53.2)		0.581
	MSSA	178	89 (50)	89 (50)		
Tigecycline	MRSA	127	127 (100)			
	MSSA	198	198 (100)			
Teicoplanin	MRSA	138	138 (100)			
	MSSA	213	213 (100)			
Vancomycin	MRSA	173	173 (100)			
	MSSA	230	230 (100)			

Throughout the world MRSA has become a wide spread pathogen with outbreaks occurring in hospital as well as in community settings (Kil *et al.,* 2008; Boucher *et al.,* 2008; Goetghebeur *et al.,* 2006). A single facility cannot eliminate or control the occurrence of MRSA infection and the prevalence is affected by the measures taken at one facility when compared to the other facility (Lee *et al.,* 2012). Approximately 30 % is the colonization rate of *S. aureus* in the United States (Gorwitz *et al.,* 2008). MRSA colonized patients display a higher risk of developing a MRSA infection (Ramarathnam *et al.,* 2013; Shukla *et al.,* 2009; Gupta *et al.,* 2011; Wenzel *et al.,* 1995; Ziakas *et al.,* 2014). The most frequent pathogen implicated in post-surgical infections was *S.aureus* (Merre *et al.,* 2007) as well as in a survey conducted in Europe (Sader *et al.,* 2010). In this survey MRSA prevalence ranged from 48.4% in Belgium to 0.4% in Sweden (Sader *et al.,* 2010). There was an increase in the overall incidence of community onset MRSA SSTI (skin and soft tissue infections) in a study spanning over 10 years in US (Tracy *et al.,* 2011).

The overall prevalence of MRSA in our study was 42.9%. Different studies from India have reported the prevalence of MRSA ranging from 40 to 50% (Patel *et al.,* 2010; Gopalakrishnan *et al.,* 2010; Wattal *et al.,* 2010; Varghese *et al.,* 2010; Arora *et al.,* 2010; Sangeeta Joshi *et al.,* 2013). In our study we observed a prevalence of MRSA among the inpatients which was 32%.Among the admitted patients the rate of MRSA colonization in patients ranges from 1.3% to 7.6% (Nixon *et al.,* 2006; Chen *et al.,* 2012; Pofahl *et al.,* 2011) and are at an increased risk of acquiring these infections when they undergo a surgical procedure (Dantes *et al.,* 2011).

The prevalence of MRSA among the out-patients was 11% in our study. Other studies from India had a high prevalence of MRSA amongst the out patients which was 54% (D'Souza *et al.,* 2010). Among the *S. aureus* isolated from the SSTI, MRSA accounted for 30% in our study whereas two different study from India have documented 35% and 60% of *S. aureus* isolates respectively from SSTI (Varghese *et al.,* 2010; Sangeeta Joshi *et al.,* 2013). We documented a higher prevalence of resistance to antibiotics in MRSA isolates when compared to MSSA isolates. Significant difference was observed to antibiotics like ciprofloxacin, gentamycin, amikacin, Co-trimoxazole, norfloxacin in our study which correlated with a study from north India.

Antibiotics like glycopeptides, linezolid, should be judiciously used only in MRSA cases. Our study did not document any resistance to these antibiotics. A recent study surveillance of antibiotic resistance in India have also not documented any resistance to glycopeptides and linezolid (Sangeeta Joshi *et al.,* 2013). Our study did not document any resistance to teicoplanin, glycylcylines also which should be preserved for the future use which will be most important in treating the MRSA cases. In all cases of MSSA de-escalation of vancomycin to β-lactams after culture sensitivity report reveals a MSSA isolate which is considered inferior to β-lactams in treating MSSA bacteraemia and endocarditis.

Due to the limited resources the molecular study of the *S. aureus isolates* was not possible. The minimum inhibitory concentration (MIC) testing was also not possible.

To conclude the study highlighted the multidrug resistance of MRSA isolates when compared to MSSA isolates. As the antibiotics used for treating MRSA infections have not shown any resistance, they showed be cautiously and judiciously used which will make a big difference in the future.

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