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MRSA Trends: A 2 Year Retrospective Observational Study at a Tertiary Care Hospital in Gurugram

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Introduction

Staphylococcus aureus, is an opportunistic human pathogen commonly found in nose, throat, intestine, vagina and skin of human body[1].It is one of the most virulent species producing infections ranging from localized pyogenic infections to life-threatening systemic infections in man[2]. Furthermore, it has an incredible ability to adapt fast to various antibiotic therapies.

Antimicrobial resistance (AMR) is a serious threat to the hospital industry of which Methicillin resistance in Staphylococcus aureus is a rising global concern. Methicillin resistant Staphylococcus aureus (MRSA) has been enlisted as the 'High' priority pathogen by World Health Organization (WHO)[3]. MRSA isolate is resistant to all currently available beta-lactam antibiotics, namely penicillins, cephalosporins and carbapenems with the exception of ceftaroline. The global prevalence of MRSA is difficult to determine, whereas national surveillance data and publications from all WHO regions reported a prevalence ranging from 0% to 100%. African Region (0%–100%), Region of America (21%–90%), Eastern Mediterranean region (10%–53%), European region (0.3%–55%), South-east Asia region (10%–26%), Western Pacific region (4%–70%)[4,5,6] . One report from Nepal showed the prevalence ranging between 13% and 74% in different parts of the world [7]. MRSA is a common emerging pathogen in India, with an overall prevalence rate ranging from 26% to 59% in intensive care units (ICUs)[8,9] . A systematic review and a meta-analysis reported a 37% overall prevalence of MRSA (2015 to 2019) in India[10]. According to a recent Indian Council of Medical Research–Antimicrobial Resistance Surveillance Network (ICMR–AMRSN) report, the total MRSA prevalence in India escalated from 32.9% in 2017 to 38.6% in 2018, with North India reporting the highest MRSA prevalence of 52.8%, followed by West India (48.1%)[11].

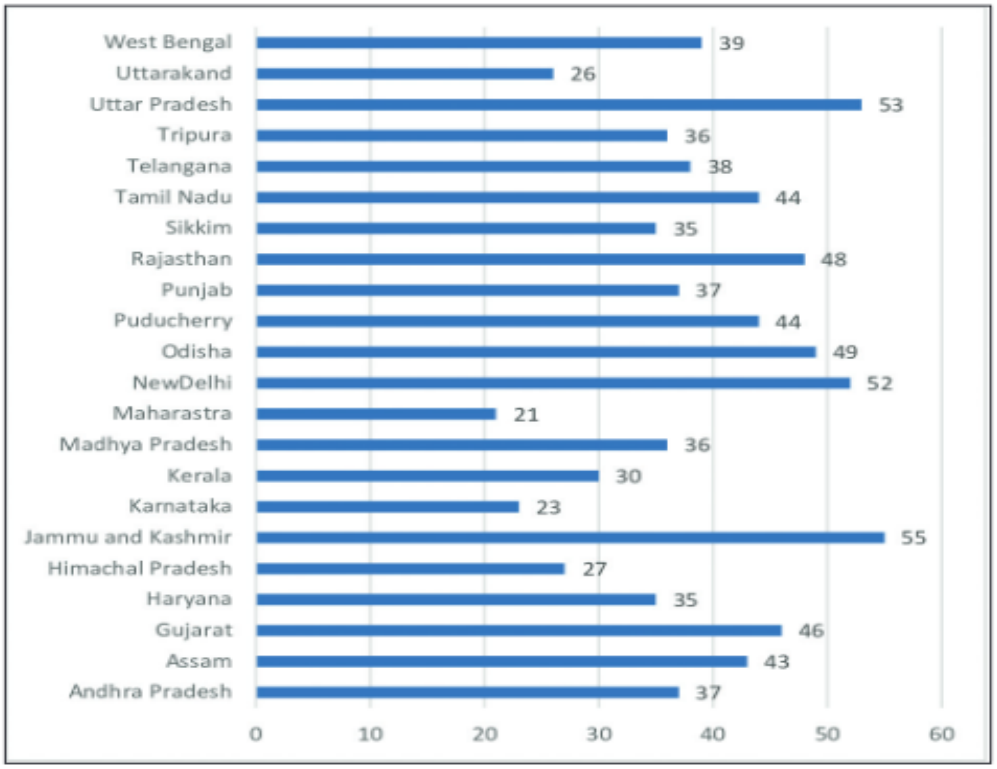


Figure 1. Prevalence of *MRSA* (%) from different states of India between 2015 and 2020.

Methicillin resistance in *Staphylococcus aureus* is mediated by a chromosomally coded gene called mecA gene, which alters penicillin binding protein (PBP) present on S.aureus cell membrance to PBP-2a. This type of resistance is transferred between *S. aureus* organisms by bacteriophages. This is one of the only medically relevant examples of chromosome-mediated drug resistance by phage transduction[12].

Based on the antibiotic susceptibilities, Methicillin resistance in *S. aureus* is defined as an oxacillin minimum inhibitory concentration (MIC) of greater than or equal to 4 micrograms/mL. MRSA is considered a life-threatening nosocomial pathogen as it is associated with worse clinical outcomes and increased complications[13] than patients with methicillin-sensitive strains (MSSA), leading to a higher mortality rate[14]. The factors that are responsible for its pathogenecity include production of enterotoxin, exfoliative toxin and toxic syndrome toxin by the variant.

MRSA infections can be further divided into hospital-associated (HA-MRSA) infections and community-associated (CA-MRSA) infections. They differ not only in respect to their clinical features and molecular biology but also in their antibiotic susceptibility and treatment. *S.aureus* is the most common cause of surgical site wound infections and a leading cause of primary bacteremia, however an increase in skin and soft tissue infections, respiratory tract infections and infective endocarditis (among IV drug abusers) has been observed in the community settings[2].

The commonly associated risk factors for MRSA infection are prolonged hospitalization, intensive care admission, recent hospitalization, recent antibiotic use, MRSA colonization, invasive procedures, HIV infection, admission to nursing homes, open wounds, hemodialysis, and discharge with long-term central venous access or long-term indwelling urinary catheter. It can thrive for months thereby transmitted

from surfaces long after it was initially deposited. A higher incidence of MRSA infection is also seen among healthcare workers dealing with patients infected with this organism, who act as reservoirs for MRSA spread in the community. Extremities of age is indirectly linked to MRSA acquisition due to associated comorbidities.

The drug resistance of MRSA still continues to evolve. Historically, this infection was confined to the healthcare settings, then the community-acquired MRSA emerged and the current status is the boundary between hospital- onset and community-acquired MRSA infections has become blurred[15]. There are several reports focusing on MRSA in both hospital and community settings from different parts of India, however limited studies from Gurugram. Hence, the study was conducted to estimate the percentage of MRSA strains in hospital and community settings, its prevalence and antibiotic susceptibility pattern in the region.

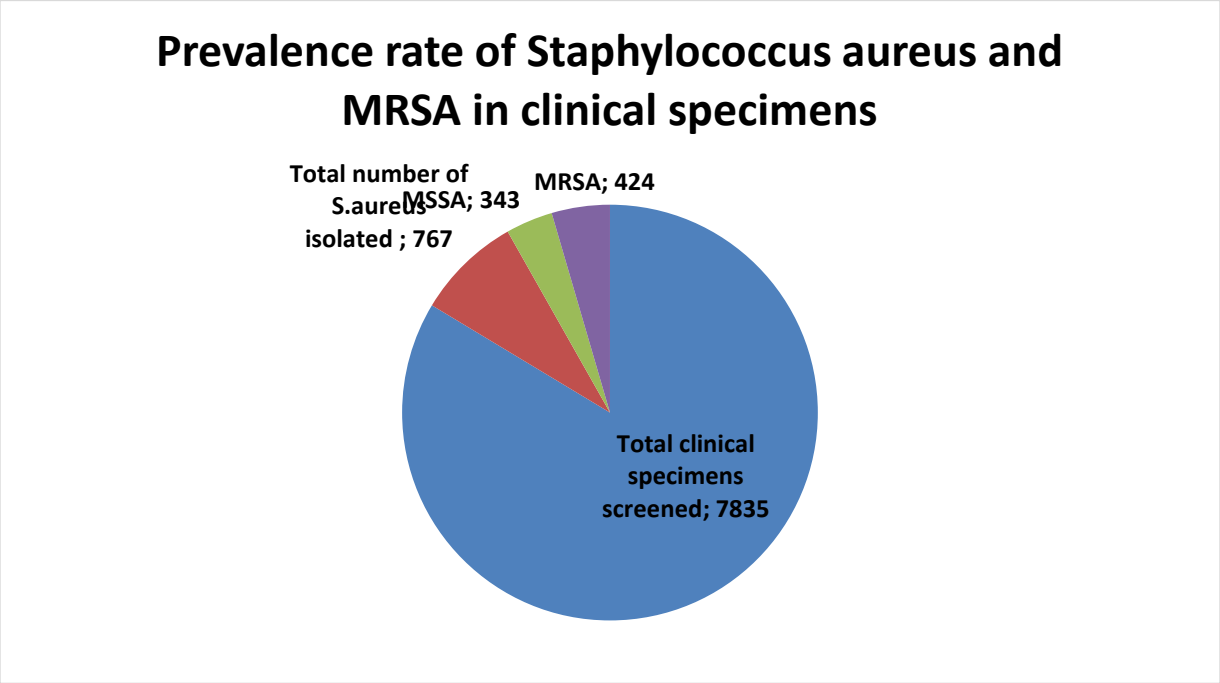
MATERIAL AND METHODS

This is a 2-year retrospective observational analysis of the specimens received for aerobic culture and sensitivity from July 2022 to June 2024 at a tertiary care hospital in Gurugram, India. The samples were processed using standard microbiological techniques. All the samples were plated on 5% sheep blood agar, Mac Conkey's agar. Chocolate agar was used for respiratory samples and body fluids like cerebrospinal fluid (CSF). Sterile body fluids and tissue were also inoculated in automated blood culture bottle for enrichment. After doing gram staining and rapid tests like catalase and coagulase, identification and sensitivity were done using Vitek2 (BioMérieux, France). The antibiotic susceptibility results were reported as per the Clinical and Laboratory Standards Institute (CLSI) guidelines[16]. All pathogens were reported with clinical correlation. The commensals were reported only when they were grown in another specimen collected at a different time or from a different site.

RESULTS

In this present study, the prevalence and antibiotic susceptibility pattern of various MRSA strains isolated from clinical specimens, namely urine, pus, sputum, ET secretion, BAL fluid, pleural fluid, blood, tissue and swabs from vaginal, nasal, throat, ear and eye were analyzed. The total number of 7835 clinical specimens were subjected for *S.aureus* screening. Out of which 767 (9.7%) were *S.aureus.* (Fig2)

Fig 2



S.aureus was majorly isolated from skin and soft tissue infections (35.7%) followed by lower respiratory tract infections (31.1%) and blood stream infections (6.2%) . The percentage isolation of *S.aureus* from urine and other fluids was <1%. Table 1 represents the percentage distribution of *S.aureus* and MRSA isolated from various clinical specimens. Out of 767 identified *S.aureus*, 343 (44.75) isolates were MSSA and the major bulk were 424 (55.2%) MRSA strains. The *S.aureus* isolate obtained from OPD,IPD and ICU's were 395 (51.4%), 235 (30.6%) and 137 (19%) respectively. The percentage of MRSA isolates from OPD was 52.3% followed by 30.8% in ICU and 17.4% in IPD healthcare settings as per Fig3.

Table1:

Percentage distribution of MSSA and MRSA in various clinical specimens

Clinical Specimen	**S.aureus (Total- 767)**	**MSSA (343)**	**MRSA (424)**
Pus	468	194	274(35.7%)
Sputum	36	18	18(2.3%)
ET secretion	6	3	3(0.4%)
BAL fluid	45	31	14(31.1%)
Vaginal swab	3	1	2(0.2%)
Nasal swab	3	2	1(0.1%)
Throat swab	2	1	1(0.1%)
Ear swab	5	2	3(0.4%)
Urine	8	6	2(0.2%)
Blood	83	35	48 (6.2%)

Fig 3

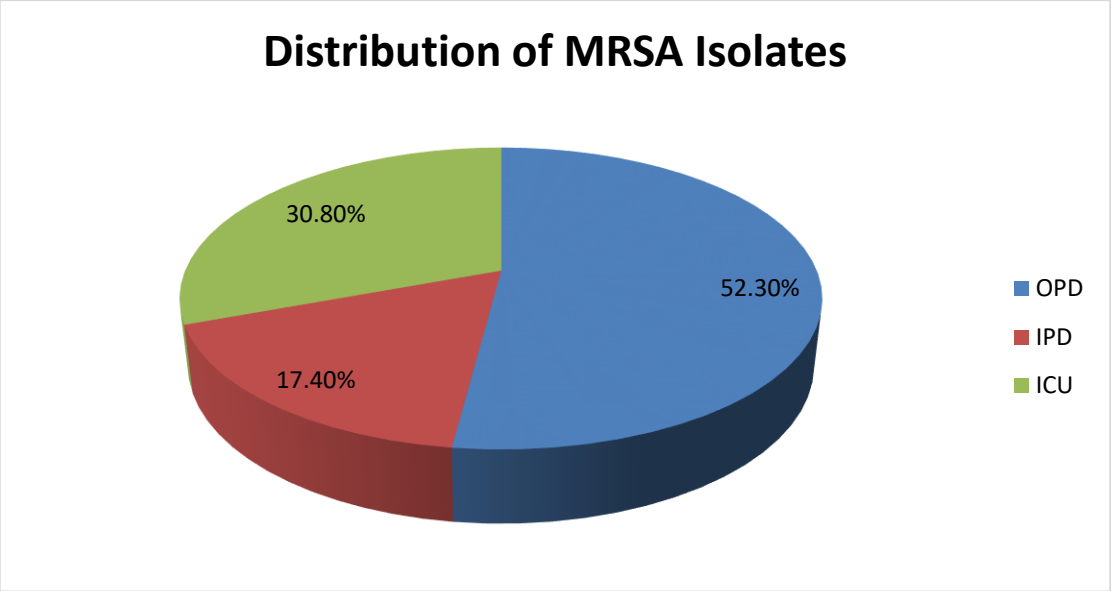
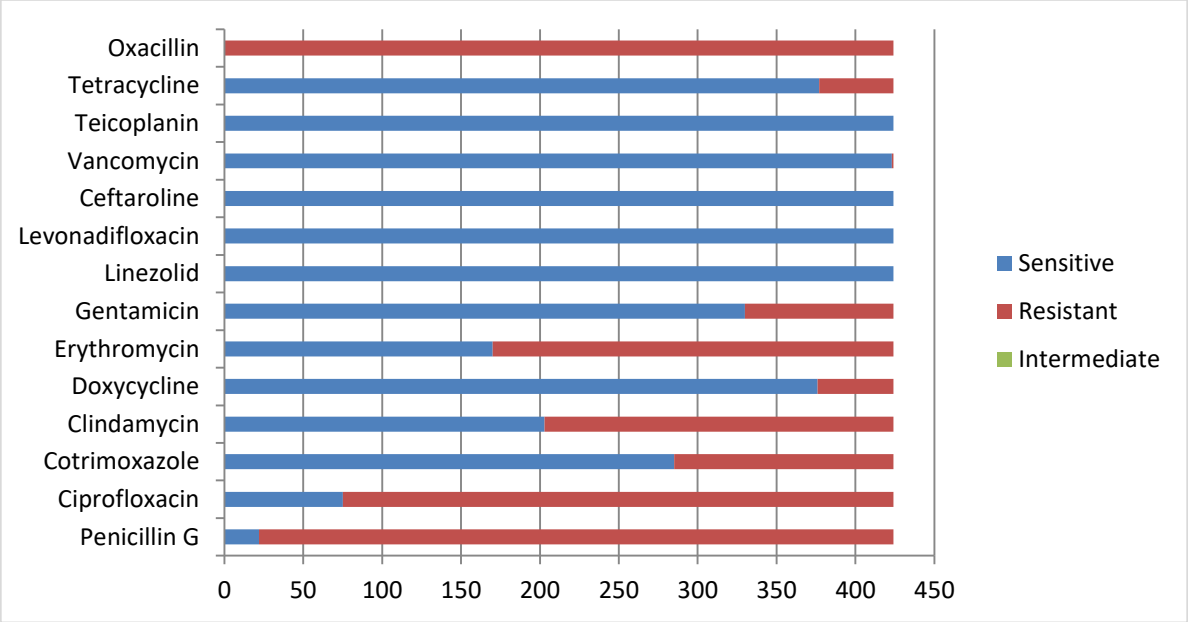


Fig 4: Drug Susceptibility pattern of Methicillin-Resistant S.aureus isolated from various clinical specimens



An antibiotic susceptibility pattern for ciprofloxacin, erythromycin, clindamycin, tetracycline, doxycycline, gentamicin, linezolid, vancomycin, teicoplanin, benzylpenicillin and trimethoprim (TMX)/sulfamethoxazole (SMZ) were determined for MRSA isolates. The newer antibiotics namely Ceftaroline and Levonadifloxacin susceptibility pattern was also assessed.

Fig 4 shows the total susceptibility pattern of MRSA isolates against various tested antimicrobials. The S.aureus isolates showed lower susceptibility towards Benzylpenicillin (5%), Ciprofloxacin (17.6%), Erythromycin (40%), Clindamycin (47.8%), Cotrimoxazole (67.2%), Gentamicin (77.8%), Doxycycline (88.6%) and tetracycline (88.9%). All the S.aureus isolates were found to be highly sensitive towards

linezolid, levonadifloxacin, ceftaroline and teicoplanin (100%). Only single VRSA strain was isolated during the study period.

Highly effective drugs in case of MRSA in skin and soft tissue infections were found to be linezolid, vancomycin ,teicoplanin along with the newer drugs levonadifloxacin and ceftaroline. Lesser drug susceptibility was reported for penicillin and fluroquinolones. Similar observance was noted for blood stream infections. Almost all classes of drugs were found to be susceptible in respiratory tract infections.

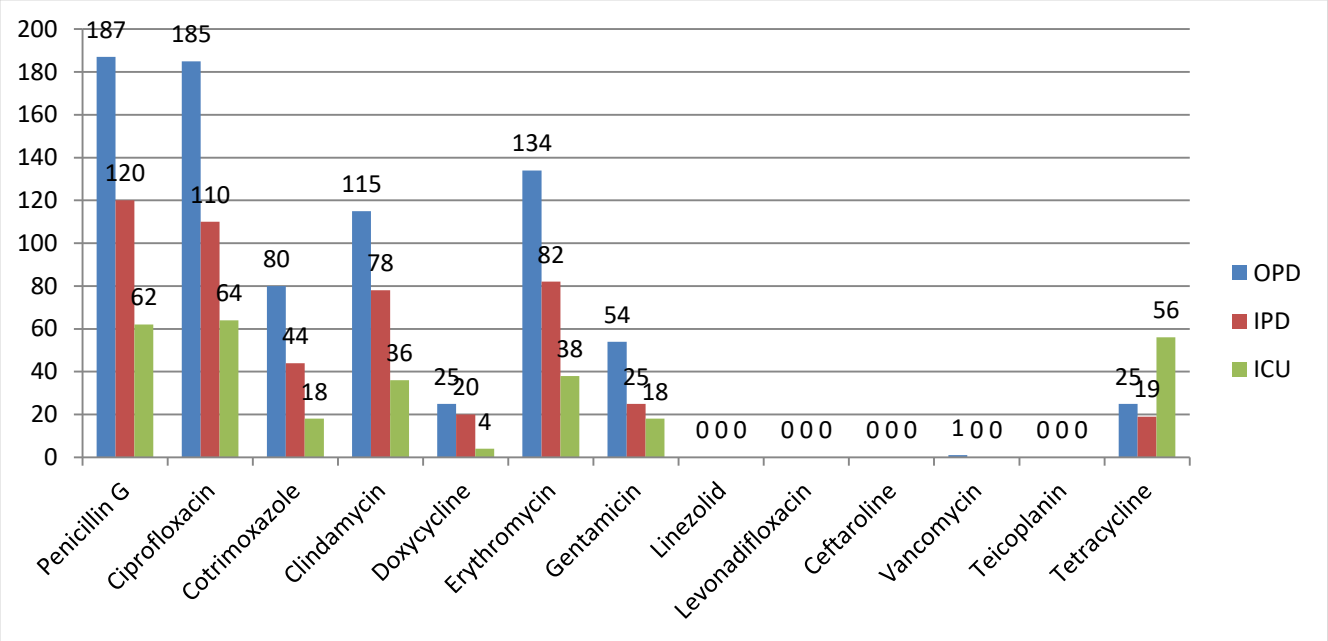
Table 2: MRSA antibiotic resistance pattern in clinical specimens

Clinical sample	Penicillin G (%)	Ciprofloxacin (%)	Cotrimox (%)	Clinda (%)	Doxy (%)	Erythro (%)	Genta (%)	Linezolid (%)	Levonadi (%)	Ceftaroline (%)	Vanco (%)	Teico (%)	Tetra (%)
Pus	59.4	52.8	20.7	33.7	6.6	39.3	13.4	0	0	0	0	0	6.3
Sputum	4	3.7	1.1	2.1	0	1.9	1.6	0	0	0	0	0	0
ET secretion	0	0	0	0	0	0	0	0	0	0	0	0	0
BAL fluid	3	2.5	0	1.8	0	2.1	0	0	0	0	0	0	0
Vaginal swab	0	0	0	0	0	0	0	0	0	0	0	0	0
Nasal swab	1	0	0	0	0	0	0	0	0	0	0	0	0
Throat swab	0	0	0	0	0	0	0	0	0	0	0	0	0
Ear swab	1	0	0	0	0	0	0	0	0	0	0	0	0
Urine	0	0	0	0	0	0	0	0	0	0	0	0	0
Blood	11	6.6	4.9	4.7	1	5.8	2.8	0	0	0	0	0	0

The prevalence of MRSA in hospital ICU settings showed better efficacy to linezolid, vancomycin, teicoplanin, levonadifloxacin and ceftaroline (100%) compared to fluoroquinolones, macrolides and tetracycline as shown in fig 5. Better susceptibility was observed with Doxycycline (94.4%) ,

Gentamicin (74.7%) and Cotrimoxazole (74.7%). However, not much difference was observed in the drug susceptibility pattern in IPD and OPD settings.

Fig 5: Location wise MRSA antibiotic resistance pattern in healthcare setting



DISCUSSION

Among the Gram positive pathogens, *S.aureus* especially MRSA has become a notorious nosocomial pathogen causing skin and soft tissue infection in community and invasive infections in hospital settings[17]. The growing concern over rising multi-drug resistant strains has led to increased usage of reserve drugs. MRSA poses a considerable public health threat, especially in highly populated Indian settings with high volumes of international travel. Various studies have been conducted worldwide to raise this grave concern.

The present study indicates the prevalence and antibiotic susceptibility pattern of MRSA isolates obtained from various clinical samples namely urine, pus, sputum, ET secretion, BAL fluid, pleural fluid, blood, tissue and swabs from vaginal, nasal, throat, ear and eye were determined. We isolated 767 (9.7%) *S.aureus* strains from a total of 7835 specimens. The proportion of MRSA was found to be 424 (55.2%) however the MSSA was found to be 343 (44.7%). The reported incidence of MRSA infection ranges from 7% to 60% globally[18,19,20]. However, In India, the prevalence of MRSA varies by region. The prevalence of MRSA in India rose from 38% in 2015 to 69% in 2020 .In a recent study by Sharanagounda S.Patil et al, the highest number of MRSA isolates were reported from Jammu and Kashmir (55%) and Maharashtra showed the lowest pooled prevalence of MRSA as 21%. A single article from Sikkim had a prevalence of MRSA as 35%, which is lesser than the prevalence observed in our study. Similar pattern was observed in a study conducted at a rural medical college at Delhi by Lohan K et al where MRSA prevalence rose from 28% in 2017 to 35.1% in 2019. The observed

differences may be due to the time when the studies were conducted , the methods of sampling more importantly catering different population and their antibiotic consumption pattern.

Out of 424 MRSA isolates, the highest number of MRSA isolates (35.7%) were obtained from wound pus samples, 31.1% from sputum and BAL fluid followed by 6.2% from blood. The percentage isolation of *S.aureus* from urine and other fluids was <1%. A similar observation was reported by Sharma S et al, where majority of MRSA isolates were obtained from pus swabs (55%) followed by respiratory samples (17.14%) and catheter tips (12.85%). Less isolation was observed from throat and ear swabs (7.8%) and genital swabs (2.14%).According to ICMR report 2023, 55% MRSA strains were obtained from blood and pus aspirates.

The majority of the isolates were obtained from OPD patients (52.3%) followed by 30.8% from ICU patients. However, only 17.4% isolates were reported from IPD settings. Contrarily, as per ICMR Report 2023, the overall MRSA rates among *S. aureus* isolates were lowest in OPD (40.1%), moderate among ward isolates (47.3%) and highest among isolates obtained from ICU patients (50.1%).The prevalence of MRSA at IPD and ICU settings at our health care settings was much lower when compared to other studies and is considered a benchmark for hospital infection-control practices.

Although MRSA infections were originally acquired only from hospital settings (HA-MRSA), and community acquired (CA-MRSA) were restricted to community settings in healthy, young patients. However, the lines have blurred and now CA-MRSA infections are now being increasingly reported in community and hospital settings as well[21]. A recent Indian study by Thakur A, Ray P et al reported 44% and 24% cases of CA-MRSA having SCCmecIV and SCCmecV genes among 400 cases of MRSA isolated from clinical samples at a tertiary care hospital[22].

Glycopeptides are commonly used to treat MRSA and Vancomycin is considered the drug of choice. A surge in studies reporting vancomycin MIC (creep) and reduced vancomycin susceptibility limits its use as a reserve drug in severe infections. In a recent global study by Keikha M et al, the rate of hVISA was reported as high as 6.1% in Asian countries. Not much difference was observed in its prevalence in European/American (6.8%) nations. In addition, infection with hVISA bacteria was higher in bacteraemic patients than other infections (9.4% vs. 5.5%) which adds to long hospital stays, treatment costs and mortality in these patients[23]. However, in our study, the Staphylococcal species were highly sensitive to vancomycin with only a single isolate reported as VRSA in a span of 2 years.

While excellent susceptibility was noted with Teicoplanin (100%), Linezolid (100%), Ceftaroline (100%) and Levonadifloxacin (100%) in all Staphylococcal MRSA isolates from soft tissue infection. These results were in line with previous studies. Some studies have reported resistance to linezolid and also some outbreaks of linezolid-resistant S. aureus in intensive care units[24].The efficasy of ceftaroline was comparative to vancomycin plus aztreonam according to a clinical trial and the results demonstrated that ceftaroline was noninferior to vancomycin plus aztreonam, with a clinical response of 91.6%[24].

Levonadifloxacin is an oral FDA approved formulation for MDR gram-positives, including MRSA, VISA, and VRSA. In a recent study by Balinga S et al, all 424 S.aureus and other Gram-positive isolates were found to be susceptible to levonadifloxacin as per the prespecified interpretive criteria identified based on population pharmacokinetic model and Monte Carlo simulation enabled probability of

pharmacodynamic target attainment analysis[25]. Similar findings were observed with a study by Bakthavatchalam Y D et al, Levonadifloxacin showed MIC50 and MIC90 values of 0.25 and 0.5 mg/L, respectively, for all S. aureus, which included hVISA and Bengal Bay clone MRSA. The potency of levonadifloxacin was found to be 16 times superior compared with levofloxacin[26].
Oral agents with MRSA activity that are recommended by IDSA guidelines include sulfamethoxazole/trimethoprim(SMX/TMP), clindamycin, linezolid, and oral tetracyclines (ie,doxycycline and minocycline)[27].

The assessment of the antimicrobial susceptibility profile of the MRSA in our study showed excellent susceptibility to tetracycline, doxycycline (89%), Cotrimoxazole (67.2%) and clindamycin (47.8%). However, as expected a higher percentage of MRSA strains were resistant to oxacillin (100%), penicillin G (95%), Ciprofloxacin (82.4%) and Erythromycin (60%). A study by Kaur D C et al, reported 100% resistance to fluoroquinolones, aminoglycosides, macrolides, and lincosamides showed 97.22% resistance[28].

As per our study, the most effective oral drug in skin and soft tissue infection is tetracycline, linezolid, clindamycin and doxycycline. As per Annual Report 2023, the most effective formulations for abscess were linezolid, clindamycin, doxycycline, teicoplanin, cotrimoxazole and gentamicin, however macrolides were the lease effective. Similar susceptibility pattern was observed in MRSA isolates reported from blood stream infections. Annual Report 2023 reported similar findings in IPD and OPD patients. However, Clindamycin resistance and teicoplanin resistance were greater in OPD than IPD patients. Controversially, tetracycline in ICU settings reported higher resistance than IPD/OPD settings[29]. In this study, OPD resistance rate was much higher than IPD/ICU settings. Majority isolates in OPD were resistant to Penicillin G, Ciprofloxacin, Erythromycin, Cotrimoxazole and Clindamycin.

Due to resource constraints, the differentiation and sequencing for different CA-MRSA and HA-MRSA could not be performed.

CONCLUSION

The overall prevalence of MRSA during the study period was 55.2%. Maximum isolation of MRSA was obtained from pus aspirates. Prevalence of MRSA was found to be more among outpatient (52.3%) than patients admitted in hospitals (17.4%) or requiring ICU level care (30.8%).

The colonization of MRSA on skin and in nose may enter a break in the skin causing localized to severe infections including skin wound infection to septicemia. Also, people harbouring MRSA may not have signs of infection, but they can spread the bacteria to others[30].

In general, person colonized by MRSA need not be treated. Transmission to others can be prevented by practicing hand hygiene and environmental cleaning and disinfection.Routine surveillance cultures should be a part of the infection control policy. Continuous monitoring of antibiotic resistance profile of local strain is one of the most effective intervention to prevent MRSA infection. The antibiotic stewardship should be diligently followed. A local antibiogram availability with the clinicians should be

frequently revised and checked to start the therapeutic drug. Lately, there has been studies on MRSA dynamic circulation between community and the hospital settings[31].

In a country like India, where rampant usage of antibiotic is usual, regular surveillance is the only last hope.

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