Section: Microbiology

Original Research Article

COMPARISON OF ANTIBIOTIC SUSCEPTIBILITY PATTERN AND BIOFILM FORMING ABILITY OF METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS ISOLATED FROM ANTERIOR NARES OF OUTPATIENTS & ADMITTED PATIENTS OF A TEACHING HOSPITAL IN THE HILLS OF KUMAON

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Received *: 09/05/2025*
Received in revised form *: 03/07/2025*
Accepted *: 20/07/2025*

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DOI: 10.70034/ijmedph.2025.3.477

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (3); 2597-2602

ABSTRACT

Background: Aim: Methicillin-resistant *Staphylococcus aureus* (MRSA) is a significant human pathogen associated with both hospital-acquired and community-acquired infections. Biofilm formation is an important virulence factor that contributes to its pathogenicity. This study aimed to evaluate the biofilm-forming capacity of MRSA clinical isolates from a tertiary care hospital.

Materials and Methods: A total of 454 *S. aureus* isolates were obtained from various clinical specimens collected at Soban Singh Jeena Government Institute of Medical Sciences and Research, located in the Kumaon region of Uttarakhand. The study population was equally divided into inpatient (IPD, n = 227) and outpatient (OPD, n = 227) groups. Nasal swabs were collected and cultured for *S. aureus* detection. Antibiotic susceptibility testing (AST) was performed using the disc diffusion method. Biofilm-forming ability was assessed using the crystal violet microtiter plate assay.

Results: Among IPD samples, *S. aureus* was isolated in 67 cases (29.5%) and MRSA in 22 cases (9.7%). In the OPD group, *S. aureus* was found in 33 cases (14.5%) and MRSA in 12 cases (5.3%), indicating a higher MRSA prevalence in hospitalized patients. Most isolates were resistant to cefixime and penicillin. A sex-wise comparison revealed a higher MRSA prevalence in male patients. Biofilm formation was observed in 91.7% of MRSA isolates from OPD and 63.6% from IPD.

Conclusion: The study highlights a significant presence of community-acquired *S. aureus* within hospital settings. The high prevalence of biofilm formation and antibiotic resistance in MRSA underscores the urgent need for enhanced surveillance and infection control measures, particularly in high-risk patient groups.

Keywords: Surveillance; nasal carriage; Biofilm; MRSA

INTRODUCTION

Staphylococcus aureus is a Gram-positive bacterium recognized for its ability to cause a wide range of human infections, from superficial skin lesions to severe, life-threatening systemic illnesses. The pathogen's virulence is largely attributed to its production of diverse extracellular enzymes and surface-associated factors that facilitate immune evasion, tissue invasion, and persistence.[1] Over the years, the emergence of antibiotic-resistant S. aureus strains has posed a significant challenge, particularly within healthcare environments. The evolution of methicillin-resistant Staphylococcus aureus (MRSA)

has escalated this concern due to the presence of altered penicillin-binding proteins (PBPs), which significantly reduce the efficacy of β-lactam antibiotics and several other antimicrobial agents.[2] Consequently, MRSA infections are often difficult to treat and require alternative therapeutic strategies. It is known that MRSA is endemic in India with variation in the antimicrobial susceptibility patterns based on geographical region.[3] As per systemic review and meta-analysis done on prevalence of Methicillin-resistant S. aureus (MRSA) in India, overall prevalence of MRSA was reported as 37%. Zone-wise pooled prevalence of MRSA was found as 41%, 43%, 33%, 34%, 36%, and 40% respectively for north, east, west, south, central and north-east zones.[4]

Furthermore, the irrational use of conventionally available antibiotics and ability of forming biofilms has increased antibiotic resistance among S. aureus and MRSA isolates often show multi-drug resistance (MDR), resistance to β-lactam antibiotics and tetracyclines, macrolide, chloramphenicol, and Fuoroquinolones commonly used in the treatment and management of S. aureus infection.[5] Biofilms are intricate microbial communities embedded within a self-produced extracellular polymeric substance (EPS) matrix. These structures adhere to both living and non-living surfaces, promoting bacterial colonization while offering increased resistance to antimicrobial agents and immune defences. Biofilm formation relies on the synthesis of polysaccharide intercellular adhesin (PIA), a β-1,6-linked N-acetylglucosamine. This polymer is synthesized as a gene product of the icaADBC operon.[6,7] Understanding the relationship between biofilm formation and methicillin resistance in S. aureus is of paramount importance in clinical settings. It has been suggested that biofilm formation may enhance the development and spread of antibiotic resistance as the densely packed biofilm matrix allows for the exchange of genetic material between bacterial cells, facilitating the transfer of genes encoding antimicrobial resistance.[8] Aminoglycosides, erythromycin, and fluoroquinolones are the most commonly prescribed antibiotics for MRSA treatment. Vancomycin remains the most frequently used antibiotic in the therapy of MRSA.[9]

MRSA colonization, especially in the anterior nares, plays a pivotal role in both community and hospital-associated infections. Nasal carriers may act as reservoirs, contributing to the transmission of MRSA within healthcare facilities and the general population.[10,11] The colonization dynamics and resistance profiles may differ between admitted patients who are often exposed to prolonged antibiotic use and invasive procedures and outpatients, who may carry community-acquired strains with distinct characteristics.[12]

Despite the clinical importance, limited data are available on the antibiotic resistance and biofilm-forming potential of MRSA strains colonizing the anterior nares in hospital settings, particularly in geographically unique regions like the Kumaon hills. This study aims to compare the antibiotic susceptibility profiles and biofilm-forming capabilities of MRSA isolates obtained from the anterior nares of outpatients and admitted patients at a teaching hospital in the Kumaon region. Understanding these characteristics will provide insights into colonization patterns, inform infection control strategies, and guide targeted therapeutic interventions to mitigate the burden of MRSA-associated infections.

MATERIALS AND METHODS

Study Design and Sample Collection

This cross-sectional observational study was conducted in Soban Singh Jeena Government Institute of Medical Sciences and Research, Almora located in the hills of Kumaon region of Uttarakhand. Nasal swab samples were collected from both inpatients and outpatients in hospital over a defined study period. All individuals included in the study gave informed consent. Samples were collected aseptically from the anterior nostrils using sterile cotton swabs and transported to the microbiology laboratory for further analysis.

Laboratory Processing and Identification

Nasal swabs were inoculated onto mannitol salt agar (MSA) and 5% sheep blood agar plates. The plates were incubated aerobically at 37°C for 24 h. Colonies displaying typical morphology of *S. aureus* on MSA were further processed for identification. Initial identification was done using Gram staining and standard biochemical tests including catalase test, slide and tube coagulase test, DNase test and phosphatase test. Only isolates confirmed as *S. aureus* were included in further analysis.

Antimicrobial susceptibility testing (AST)

Antibiotic susceptibility testing was performed using the Kirby-Bauer disk diffusion method (13) following Clinical and Laboratory Standards Institute (CLSI) guidelines. A bacterial suspension of each isolate was prepared and adjusted to the 0.5 McFarland turbidity standard. The standardized inoculum was then spread evenly on Mueller-Hinton agar (MHA) plates, and antibiotic-impregnated disks (HiMedia, Mumbai, India) were placed on the agar surface. The antibiotics tested included penicillin, cefoxitin cefazolin, clindamycin, erythromycin, linezolid, cotrimoxazole, gentamicin, and ciprofloxacin. Methicillin resistance was examined using cefoxitin, which served as a surrogate marker. Isolates showing a zone of inhibition of ≤21 mm were considered methicillin-resistant and further confirmed using the PBP2a latex agglutination test, which detects penicillin-binding protein 2a (PBP2a) encoded by the mecA gene. After incubation at 37°C for 18–24 hours, the diameter of the zones of inhibition around each disc was measured in millimetres. Results were interpreted according to the CLSI breakpoints.

Biofilm Formation Assay

Biofilm formation was assessed using the Crystal Violet Assay, following a modified protocol based on Stepnovich et al. (14). The bacterial isolates were initially grown on Tryptic Soy Agar (TSA) plates for 24 hours. Subsequently, 3–4 well-isolated colonies were transferred to test tubes containing 10 mL of Tryptic Soy Broth (TSB) supplemented with 1% glucose. The cultures were incubated overnight at 37°C and adjusted to a turbidity equivalent to 0.5 McFarland standard.

For the assay, 100 µL of the adjusted bacterial suspension from each strain was inoculated in triplicate into wells of a sterile 96-well polystyrene microtiter plate and incubated at 37°C for 24 hours. After incubation, the wells were gently aspirated and washed four times with 200 µL of phosphate-buffered saline (PBS; pH 7.2) to remove non-adherent cells. The remaining adherent biofilm was fixed with 2% sodium acetate, followed by staining with 0.1% crystal violet solution. The plate was incubated at room temperature for 5 minutes, after which excess stain was removed and the wells were rinsed twice with deionized water. After drying, 95% ethanol was added to each well to make the bound dye soluble.

The optical density (OD) of each well was then measured at 595 nm using a microplate reader. The biofilm-forming ability of each isolate was interpreted based on the OD values. The cut-off OD was defined as the mean OD of the negative control plus three times its standard deviation (ODc = mean OD of negative control + 3 × SD). An OD value ≥3.0 was used as the upper threshold for strong biofilm production. *S. aureus* ATCC 35556 served as the positive control, while sterile TSB was used as the negative control. All media, reagents, and antibiotic discs were obtained from HiMedia Laboratories Pvt. Ltd., Mumbai, India.

Statistical analysis

All collected data were initially entered into Microsoft Excel and subsequently analyzed using SPSS software (version 21). The Chi-square test was applied for comparison of categorical variables, while the Student's *t*-test (two-tailed) was used for continuous variables. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Demographics of the patients and S. aureus isolates

A total of 454 clinical samples were collected during the study period, of which 227 samples were taken from inpatients (IPD) and 227 from outpatients (OPD). In the OPD, 121 patients (53.3%) were male and 106 (46.7%) were female. In the IPD, 127 patients (55.9%) were male and 100 (44.1%) were female. The mean age of OPD patients was 46.5 ± 16.8 years (range 12–98 years), while the mean age of IPD patients was 43.5 ± 14.1 years (range 17–87 years). In the IPD group, 127 (55.9%) were males and 100 (44.1%) were females. In IPD samples, S. aureus was found in 67 cases (29.5%), Methicillin-resistant S. aureus (MRSA) in 22 cases (9.7%), and coagulase-negative staphylococci (CONS) in 14 cases (6.2%). Additionally, 19 isolates (8.4%) were identified as Escherichia coli, 83 (36.6%) as gram-positive bacilli (GPB), and 23 (10.1%) as Klebsiella species. In the OPD group, the most frequently isolated organisms were GPB in 107 cases (47.1%) and CONS in 45 cases (19.8%). Other isolates included S. aureus in 33 cases (14.5%), MRSA in 12 cases (5.3%), E. coli in 15 cases (6.6%), and Klebsiella spp. in 15 cases (6.6%). Data showed the prevalence of MRSA and S. aureus in hospitalized patients, whereas CONS and GPB were more frequently isolated from outpatients.

Antibiotic Susceptibility

Methicillin-resistant S. aureus (MRSA) was isolated from 12 of the 227 OPD patients and 22 of the 227 IPD patients.

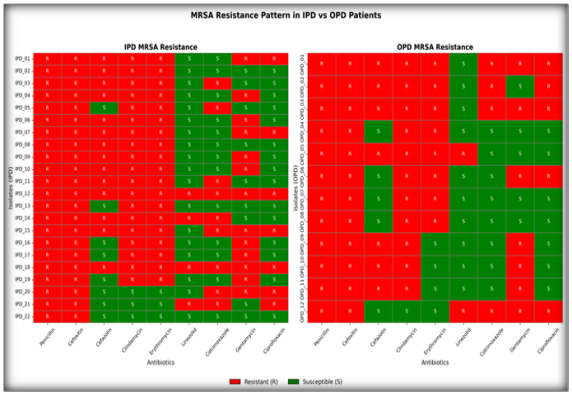

Figure 1: Heatmap representation of antibiotic susceptibility profiles of Staphylococcus aureus MRSA isolates from inpatients (IPD) and outpatients (OPD). Each row represents an isolate and each column represents an antibiotic tested

All 12 OPD isolates and all 22 IPD isolates were resistant to penicillin and cefoxitin. High susceptibility to linezolid was observed in both groups (83.3% of OPD isolates vs. 81.8% of IPD isolates). Susceptibility to ciprofloxacin and cotrimoxazole was moderate in both groups (58.3% vs. 68.2% for ciprofloxacin; 66.7% vs. 59.1% for cotrimoxazole, OPD vs. IPD).

In contrast, only 8.3% of OPD isolates and 13.6% of IPD isolates were susceptible to clindamycin, and only 33.3% of OPD isolates versus 13.6% of IPD isolates were susceptible to erythromycin (Figure 1). These findings indicate very high resistance to penicillin, cefoxitin, clindamycin, and erythromycin in MRSA from both groups (Figure 2). In each case, no statistically significant differences in susceptibility were observed between OPD and IPD isolates. These findings indicate broadly similar resistance patterns in nasal MRSA from outpatients and inpatients.

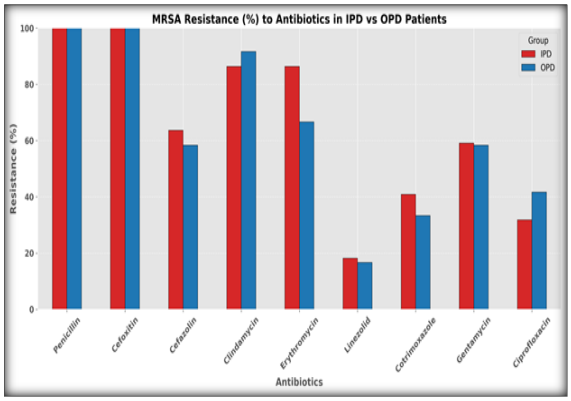

Figure 2: Comparison of antibiotic resistance percentages in methicillin-resistant Staphylococcus aureus (MRSA) isolates from inpatients (IPD) and outpatients (OPD). The bar graph shows the proportion (%) of resistant isolates for each antibiotic tested. Red bars represent IPD isolates, while blue bars represent OPD isolates.

Biofilm Formation

The biofilm-forming ability of MRSA isolates was classified as strong, moderate, weak, or non-forming. Among the 12 OPD MRSA isolates, 25.0% (3 isolates) were strong biofilm producers, 8.3% moderate (1 isolate), 58.3% weak (7 isolate), and 8.3% (1 isolate) showed no biofilm formation. Clinical history analysis revealed that strong biofilm production was observed in cases associated with chest pain, ulcers, and fever, affecting patients working as labourers, teachers, and truck drivers. The only moderate producer was associated with a patient with a history of heart disease. Weak biofilm producers were associated with diverse clinical conditions such as joint pain, urinary tract infection (UTI), body pain, and oesophageal irritation, suggesting that even mild or non-specific complaints may contain virulent strains capable of forming biofilms. Interestingly, patients with diabetes and hypertension were mostly associated with either weak or non-biofilm-forming strains. Of the 22 IPD MRSA isolates, 22.7% (5 isolates) were strong producers, 9.1% moderate (2 isolates), 31.8% weak (7 isolates), and 36.4% (8 isolates) non-producers. When correlated with patient's clinical history, strong biofilm producers were mostly isolated from individuals with diabetes (n=3), while the remaining two were associated with abdominal pain and fever. Moderate biofilm producers were also from individuals with diabetes. Weak biofilm production was detected in isolates from a diverse set of clinical conditions, including fever, renal colic, electric shock, and diabetes. Non-biofilm producers were frequently associated with acute conditions such as fever (n=3) and pancreatitis (n=2), as well as diabetes (n=1). Notably, diabetes appeared to be a common coexisting condition among biofilm-producing isolates, suggesting a possible link between chronic metabolic conditions and enhanced biofilm formation potential in MRSA.

DISCUSSION

S. aureus infections pose a great burden to health, especially in low and middle-income countries. Although S. aureus exists as a normal flora in the human body, it remains a versatile and potent pathogen as it is one of the common causes of nosocomial and community-borne infections. They are significantly associated with various mild to severe life-threatening infections due to their ability to produce biofilms.[6,15] Despite many efforts, the number of antimicrobial resistant organisms is increasing consistently, resulting in frequent nosocomial infections in hospitals, extremely difficult clinical treatment, high mortality rates, and considerable economic losses.[2] In this regard, the screening of virulence characteristics and multi-drug resistance in S. aureus from clinical isolates can be helpful in the prevention and treatment of infections caused by these bacteria. In the present study, S. aureus strains isolated from both outpatient (OPD) and inpatient (IPD) populations were evaluated for methicillin resistance and biofilm-forming capacity. The overall rate of MRSA was higher among inpatients than in outpatients, indicating a higher burden of resistant strains in hospitalized individuals. This finding is consistent with previous reports indicating that hospital-associated MRSA (HA-MRSA) is more prevalent in inpatient settings due to factors such as antibiotic exposure, invasive procedures, and longer hospital stay.[12,16-18]

Consistent with its well-known adaptability, S. aureus has displayed significant resistance to numerous antibiotics in clinical settings. In our study, most isolates exhibited resistant to cefixime and penicillin. These findings are consistent with other studies from Nepal.[19,20] The well-documented ability of S. aureus in developing resistance to therapeutic agents has been recognized since the emergence of penicillin resistance, particularly in response to selective antibiotic pressure.[21] Another study from similar geographical region to current study was conducted in Garhwal region of Uttarakhand where higher drug resistance was observed in S. aureus isolated from anterior nares of medical students with longer hospital exposure compared to first year medical students who were not posted in hospital.[22]

When comparing MRSA prevalence based on sex, our findings revealed that male patients were more frequently affected (38%) than female patients. This gender-based distribution aligns with previous observations, as several studies have reported higher MRSA prevalence in men, which may be attributed to factors such as greater colonization rates and differences in hygiene practices.[23,24]

The biofilm-forming ability of MRSA isolates was also evaluated, as it plays a key role in immune evasion, bacterial persistence, and treatment failure. A large proportion of MRSA isolates from both OPD and IPD groups displayed biofilm-forming capacity,

although with varying degrees of intensity. Among OPD isolates, 91.7% exhibited biofilm production, with 25% classified as strong producers. In comparison, 63.6% of IPD isolates were biofilm producers, of which 22.7% showed strong biofilm formation. In our study, most strains were weak biofilm producers, while only some isolates were highly virulent and strongly adhered. Our results align with previous studies, which reported the majority of weak biofilm producers in the S. aureus strains.[25,26] These observations support the evidence that biofilm formation is a common and significant virulence trait in MRSA, contributing to chronic and recurrent infections.[27]

To further explore the relationship between host factors and bacterial behavior, we analyzed the resistance and biofilm-forming characteristics of MRSA isolates in relation to patient health status. Interestingly, in the IPD group, two MRSA isolates obtained from diabetic patients exhibited resistance to all tested antibiotics. One of these was a strong biofilm producer, while the other showed no biofilm formation. This dual observation underlines the complex interplay between biofilm formation, antimicrobial resistance and host factors such as diabetes. The strong biofilm-producing, multi-drug-resistant isolate is consistent with previous studies that highlight how biofilms contribute to antibiotic tolerance by impeding drug penetration, facilitating horizontal gene transfer and promoting persistent cell populations.[28,29] However, the presence of a non-biofilm-producing isolate with complete resistance suggests that biofilm-independent mechanisms – such as the acquisition of mobile genetic elements or chromosomal mutations – also play an important role in resistance.[30] The fact that both patients had diabetes supports existing evidence that chronic metabolic conditions may predispose individuals to colonization by highly resistant and potentially persistent MRSA strains.[31] These findings highlight the need for tailored surveillance and treatment strategies, particularly in vulnerable populations with underlying health conditions (28). Diabetes emerged as a frequently associated among patients harboring strong and moderate biofilm-producing MRSA strains, particularly in the IPD group. This observation is consistent with previous studies suggesting that chronic metabolic conditions such as diabetes may impair host immune responses and promote colonization by biofilm-forming pathogens.[32,33] Additionally, several MRSA isolates with strong or moderate biofilm capacity were recovered from patients presenting with relatively non-specific

The study also found that while strong biofilm formation was not limited to any specific occupation or residential status, but it was observed more frequently in those isolated from patients with chronic diseases such as diabetes, hypertension and heart disease. This emphasizes the need for improved screening and infection control strategies, particularly in vulnerable populations with co-morbidities. Overall, these findings reinforce the clinical significance of biofilm formation in MRSA and underscore the continued importance of antimicrobial surveillance in both community and hospital settings. As MRSA strains continue to evolve, understanding their resistance profiles and virulence mechanisms remains critical to improve patient outcomes.

CONCLUSION

The present study highlights the clinical challenge posed by S. aureus, particularly methicillin-resistant strains, in both hospital and community settings. A higher prevalence of MRSA was observed among inpatients, emphasizing the important role of hospitalization, invasive procedures, and antibiotic exposure in the emergence of resistant strains. Antimicrobial resistance, particularly to β-lactam antibiotics such as penicillin and cefixime, was widespread, consistent with global trends. A large proportion of MRSA isolates were found to have the ability to form biofilms, a major virulence factor associated with long-term infection and treatment failure. The association of biofilm production with chronic diseases such as diabetes and hypertension further underscores the frailty of immunocompromised patients.

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