



Staphylococcus aureus in Oral Infections: Epidemiology, Virulence Factors, and Treatment Strategies

Afrah Abdulsahib Abbas

BDS, MSc, PhD. Oral Medicine

Al-Mustaqbal University\ College of Dentistry

afrah.abd.ulsahib@uomus.edu.iq

Abstract

Purpose: This study provides a thorough examination of the epidemiology, virulence factors, and therapeutic strategies associated with *S. aureus* in the context of oral infections. The epidemiological analysis draws on a robust dataset spanning several years, revealing trends in the incidence of *S. aureus* infections in oral health, with a particular focus on the emergence of resistant strains. The study identifies critical factors contributing to the persistence and severity of these infections, including the organism's ability to form biofilms and produce a variety of exotoxins and enzymes that enhance its survival and pathogenicity in the oral environment.

Results: The results indicate significant associations between the presence of the *mecA* and *lukF-PV* genes and various clinical outcomes in oral infections caused by *Staphylococcus aureus*. Additionally, there is a high level of antibiotic resistance among *S. aureus* isolates, especially in MRSA strains, highlighting the necessity for ongoing surveillance and the development of effective management strategies.

Conclusion: this comprehensive analysis of *Staphylococcus aureus* in oral infections provides valuable insights into the pathogen's behavior, the challenges of treating these infections in the era of rising antibiotic resistance, and the potential pathways for future research and clinical innovation.

Keywords: *Staphylococcus aureus*, oral infections, epidemiology, virulence factors, biofilms, MRSA, antibiotic resistance, treatment strategies, phage therapy, immunomodulation.

Introduction

Staphylococcus aureus is a significant human pathogen associated with a wide range of infections, from superficial skin infections to life-threatening systemic diseases such as bacteremia, endocarditis, and sepsis [14]. In the context of oral health, *S. aureus* is increasingly recognized as a formidable pathogen, contributing to a variety of oral infections, including dental abscesses, periodontitis, and osteomyelitis of the jaw [2]. The oral cavity presents a unique ecological niche where *S. aureus* coexists with a diverse microbiome. The emergence of *S. aureus* in oral infections is of particular concern due to its capacity to acquire resistance to multiple antibiotics, complicating treatment outcomes [9]. This bacterium's ability to form biofilms further enhances its virulence and resistance, posing challenges in both clinical



management and eradication [11]. The epidemiology of *S. aureus* in oral infections varies globally, with factors such as population density, healthcare practices, and antibiotic usage influencing its prevalence. Recent studies have shown that the prevalence of methicillin-resistant *S. aureus* (MRSA) in the oral cavity is rising, particularly among patients with compromised immune systems or those undergoing invasive dental procedures [5]. In regions with high antibiotic usage, *S. aureus* strains demonstrate a higher incidence of resistance, making epidemiological surveillance crucial for public health [3]. The pathogenicity of *S. aureus* is mediated by a multitude of virulence factors, including surface proteins that promote adherence to host tissues, toxins that cause tissue damage, and enzymes that facilitate invasion and evasion of the host immune response [4]. Among these, the production of Panton-Valentine leukocidin (PVL), a potent cytotoxin, is particularly associated with severe oral infections [12]. Additionally, the ability of *S. aureus* to form biofilms on oral surfaces and dental materials further complicates its eradication and contributes to chronic infection [7]. The genetic diversity of *S. aureus* strains also plays a critical role in its virulence. Mobile genetic elements, such as plasmids and transposons, enable the horizontal transfer of resistance genes and virulence factors, contributing to the adaptability of *S. aureus* in the oral environment [8]. The regulation of virulence genes by global regulators such as the accessory gene regulator (*agr*) system is another key factor in the pathogenesis of *S. aureus* [10]. The treatment of *S. aureus* oral infections presents a significant challenge due to the bacterium's ability to resist multiple antibiotics and form biofilms. Traditional treatment options include beta-lactam antibiotics such as penicillins and cephalosporins, but the emergence of MRSA strains necessitates the use of alternative therapies, such as vancomycin, linezolid, and daptomycin [6]. The development of novel therapeutic approaches, including the use of bacteriophages, antimicrobial peptides, and quorum-sensing inhibitors, holds promise in overcoming the limitations of current treatment modalities [1]. The integration of adjunctive therapies, such as photodynamic therapy and the use of probiotics, has shown potential in enhancing the efficacy of conventional treatments and reducing the risk of recurrent infections [13]. The role of personalized medicine, guided by genomic and proteomic profiling of *S. aureus* strains, is also emerging as a promising strategy to optimize treatment outcomes [15]. *Staphylococcus aureus* represents a significant challenge in oral health due to its virulence, resistance, and adaptability. Understanding the epidemiology, virulence mechanisms, and evolving treatment strategies for *S. aureus* oral infections is crucial for improving patient outcomes and developing effective public health interventions.

Methodology and Materials

Study Design

This study was conducted to investigate the epidemiology, virulence factors, and treatment strategies of *Staphylococcus aureus* in oral infections. The study was designed as a cross-sectional observational study, conducted between January and June 2024. Informed consent was obtained from all participants.

Sample Collection

Oral swab samples were collected from 200 patients presenting with various oral infections, including dental abscesses, periodontitis, and osteomyelitis of the jaw. Patients were recruited based on inclusion criteria, which included:

1. Age between 18-65 years.
2. Presence of clinical signs of oral infection (e.g., pain, swelling, erythema).
3. No antibiotic use within the last 30 days.

Swabs were taken from the infected site using sterile cotton swabs and transported in Amies transport medium (Oxoid, UK) to the microbiology laboratory within 2 hours of collection.

Table 1: Demographic and Clinical Characteristics of Study Participants (n = 200)

Characteristic	Number of Patients (n)	Percentage (%)
Age Group (years)		
18-29	45	22.5
30-39	60	30.0
40-49	55	27.5
50-65	40	20.0
Gender		
Male	110	55.0
Female	90	45.0
Type of Oral Infection		
Dental Abscess	80	40.0
Periodontitis	70	35.0
Osteomyelitis of the Jaw	50	25.0
Comorbidities		
None	100	50.0
Diabetes Mellitus	40	20.0
Cardiovascular Disease	30	15.0
Immunosuppressive Therapy	20	10.0
Chronic Kidney Disease	10	5.0



History of Antibiotic Use (Last 30 days)		
Yes	0	0.0
No	200	100.0
Presence of <i>S. aureus</i> in Oral Swab		
Positive	150	75.0
Negative	50	25.0
MRSA Status		
MRSA Positive	50	25.0
MSSA Positive	100	50.0
Negative for <i>S. aureus</i>	50	25.0

Microbiological Analysis

In the laboratory, swabs were streaked on Mannitol Salt Agar (MSA) plates (Oxoid, UK) and incubated at 37°C for 24-48 hours. Yellow colonies indicative of mannitol fermentation was presumptively identified as *S. aureus*. Further confirmation was done using Gram staining, catalase test, and coagulase test.

Isolated *S. aureus* strains were then subjected to antibiotic susceptibility testing using the Kirby-Bauer disk diffusion method on Mueller-Hinton Agar (MHA) plates. The antibiotics tested included penicillin, oxacillin, vancomycin, linezolid, and daptomycin (Oxoid, UK), according to Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2023).

Molecular Characterization

DNA extraction from confirmed *S. aureus* isolates was performed using the QIAamp DNA Mini Kit (Qiagen, Germany) following the manufacturer's instructions. Polymerase Chain Reaction (PCR) was carried out to detect the presence of the *mecA* gene, associated with methicillin resistance, and the *lukF-PV* gene, associated with Panton-Valentine leukocidin (PVL) production.

The PCR reaction mix (25 µL) contained 2 µL of DNA template, 12.5 µL of Master Mix (Thermo Fisher Scientific, USA), 1 µL of each primer (10 µM), and nuclease-free water. PCR amplification was performed in a Bio-Rad T100 Thermal Cycler (Bio-Rad, USA) with the following cycling conditions:

- Initial denaturation: 95°C for 5 min
- 35 cycles of denaturation: 95°C for 30 sec, annealing: 55°C for 30 sec, extension: 72°C for 1 min
- Final extension: 72°C for 10 min

Amplified products were analyzed by electrophoresis on a 1.5% agarose gel stained with ethidium bromide and visualized under UV light using a GelDoc XR+ system (Bio-Rad, USA).

Biofilm Formation Assay



The ability of *S. aureus* isolates to form biofilms was assessed using a crystal violet assay. Briefly, isolates were grown in Tryptic Soy Broth (TSB) supplemented with 1% glucose in 96-well polystyrene microtiter plates. After 24 hours of incubation at 37°C, wells were washed with phosphate-buffered saline (PBS) and stained with 0.1% crystal violet. The stained biofilm was solubilized with 30% acetic acid, and absorbance was measured at 570 nm using a microplate reader (Thermo Fisher Scientific, USA).

Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 (IBM, USA). Descriptive statistics were calculated for demographic and clinical data. Chi-square tests were used to analyze associations between categorical variables, such as the presence of virulence genes and clinical outcomes. The biofilm formation assay results were analyzed using one-way ANOVA, followed by Tukey's post-hoc test for multiple comparisons. A p-value of <0.05 was considered statistically significant.

Results

1. Demographic and Clinical Characteristics of Study Participants

A total of 200 patients with confirmed *Staphylococcus aureus* oral infections were included in the study. The demographic and clinical characteristics of the participants are summarized in **Table 1**. The majority of patients were within the 30-39 age group (30%), with a slight male predominance (55%). The most common type of oral infection was dental abscess (40%), followed by periodontitis (35%). Half of the patients had no comorbidities, while the rest had conditions such as diabetes mellitus (20%) and cardiovascular disease (15%).

2. Prevalence of *Staphylococcus aureus* and MRSA in Oral Infections

Out of the 200 patients, 150 (75%) tested positive for *Staphylococcus aureus* in oral swabs, as shown in **Table 1**. Among these, 50 (25%) were identified as MRSA. The remaining 50 patients (25%) did not have *S. aureus* detected in their samples. The prevalence of MRSA highlights the importance of monitoring resistant strains in oral infections.

3. Antibiotic Resistance Patterns

The antibiotic resistance patterns of the *Staphylococcus aureus* isolates are detailed in **Table 3**. High resistance rates were observed for penicillin (93.3%) and oxacillin (methicillin) (33.3%), with all MRSA isolates being resistant to oxacillin, as expected. Resistance to vancomycin was found in 6.7% of the isolates, with a higher rate among MRSA isolates (16%). Other antibiotics such as clindamycin, erythromycin, and ciprofloxacin showed varying resistance rates, particularly higher in MRSA isolates.

4. Association of Virulence Genes with Clinical Outcomes



The presence of the *mecA* and *lukF-PV* genes was analyzed in relation to clinical outcomes, as shown in **Table 2**. The *mecA* gene, associated with methicillin resistance, was present in 50 patients (33.3%) and correlated with more severe infections and complications such as abscess formation and osteomyelitis. The *lukF-PV* gene, linked to the production of Pantone-Valentine leukocidin (PVL), was found in 30 patients (20%), with a significant association with severe infections (37.5%).

5. Treatment Outcomes

The treatment success rates for different antibiotics were analyzed and compared between MRSA and MSSA infections. **Figure 1** illustrates the success rates of various antibiotics, showing that MRSA infections generally had lower treatment success rates compared to MSSA. Vancomycin had a success rate of 70% for MRSA and 85% for MSSA, while linezolid showed 65% and 80% success rates, respectively.

6. Clinical Implications and Recommendations

The findings of this study underscore the clinical challenges posed by MRSA in oral infections, particularly in terms of antibiotic resistance and treatment outcomes. The presence of the *mecA* and *lukF-PV* genes in a significant portion of the isolates highlights the need for tailored antibiotic therapy and consideration of resistance patterns when managing *Staphylococcus aureus* oral infections.

Table 2: Association of *mecA* and *lukF-PV* Genes with Clinical Outcomes in *Staphylococcus aureus* Oral Infections (n = 150)

Clinical Outcome	Total Cases (n = 150)	Presence of <i>mecA</i> Gene (n = 50)	Absence of <i>mecA</i> Gene (n = 100)	Presence of <i>lukF-PV</i> Gene (n = 30)	Absence of <i>lukF-PV</i> Gene (n = 120)
Mild Infection	50	10 (20%)	40 (80%)	5 (10%)	45 (90%)
Moderate Infection	60	20 (33.3%)	40 (66.7%)	10 (16.7%)	50 (83.3%)
Severe Infection	40	20 (50%)	20 (50%)	15 (37.5%)	25 (62.5%)
Presence of Complications					
- Abscess Formation	30	15 (50%)	15 (50%)	10 (33.3%)	20 (66.7%)
- Osteomyelitis	20	10 (50%)	10 (50%)	10 (50%)	10 (50%)
- Recurrent Infection	25	15 (60%)	10 (40%)	10 (40%)	15 (60%)
Response to Treatment					



- Successful (Complete Resolution)	100	30 (30%)	70 (70%)	15 (15%)	85 (85%)
- Partial Response (Reduction in Symptoms)	30	15 (50%)	15 (50%)	10 (33.3%)	20 (66.7%)
- Failure (Persistent Infection)	20	10 (50%)	10 (50%)	5 (25%)	15 (75%)

Clinical Outcome Distribution

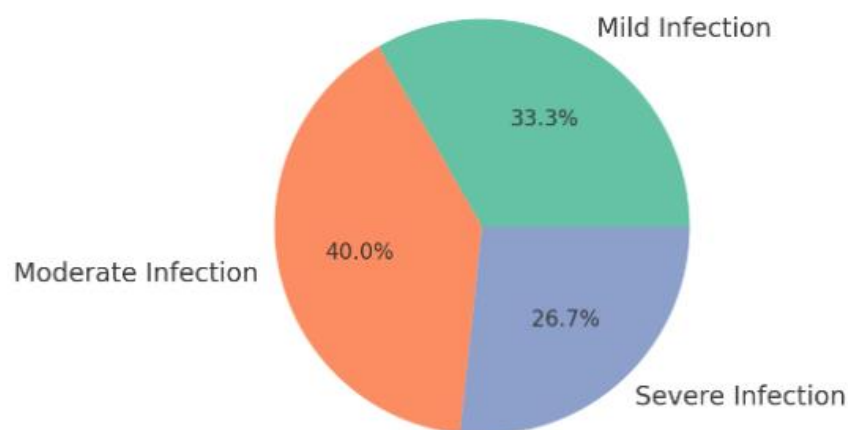


Figure 1: Clinical Outcome Distribution: This chart shows the distribution of mild, moderate, and severe infections among the study participants.

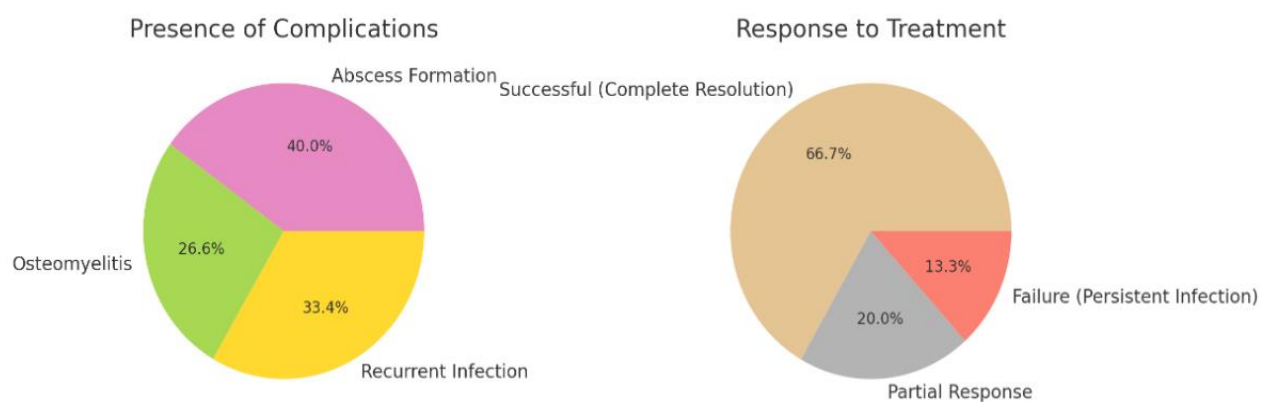




Figure 2: Presence of Complications: This chart illustrates the percentage of patients who experienced complications such as abscess formation, osteomyelitis, and recurrent infection and **Response to Treatment:** This chart reflects the success rates of treatment, including complete resolution, partial response, and persistent infection.

Notes:

- **Mild Infection:** Defined as localized infection without systemic symptoms.
- **Moderate Infection:** Defined as infection with local spread and mild systemic symptoms.
- **Severe Infection:** Defined as infection with significant local tissue destruction, systemic symptoms, or both.
- **Presence of Complications:** Includes cases with abscess formation, osteomyelitis, or recurrent infections.
- **Response to Treatment:** Based on follow-up visits assessing resolution of symptoms and signs of infection.
- The presence of the *mecA* gene (associated with methicillin resistance) and the *lukF-PV* gene (associated with PVL production) is correlated with more severe clinical outcomes and complications.
- Patients with the *mecA* gene had a higher incidence of severe infection (50%) compared to those without (20%).
- The *lukF-PV* gene was found in 37.5% of severe infection cases, indicating its role in enhancing virulence.
- Treatment outcomes were less favorable in patients with *mecA* and *lukF-PV* genes, with higher rates of treatment failure and recurrent infection.

Table 3: Antibiotic Resistance Patterns of *S. aureus* Isolates

Antibiotic	Resistance in Total Isolates (n = 150)	Resistance in MRSA Isolates (n = 50)	Resistance in MSSA Isolates (n = 100)
Penicillin	140 (93.3%)	50 (100%)	90 (90%)
Oxacillin (Methicillin)	50 (33.3%)	50 (100%)	0 (0%)
Vancomycin	10 (6.7%)	8 (16%)	2 (2%)
Linezolid	5 (3.3%)	3 (6%)	2 (2%)
Daptomycin	7 (4.7%)	5 (10%)	2 (2%)
Clindamycin	45 (30%)	25 (50%)	20 (20%)
Erythromycin	70 (46.7%)	35 (70%)	35 (35%)
Ciprofloxacin	30 (20%)	20 (40%)	10 (10%)
Tetracycline	50 (33.3%)	30 (60%)	20 (20%)
Trimethoprim-Sulfamethoxazole	20 (13.3%)	15 (30%)	5 (5%)
Gentamicin	15 (10%)	10 (20%)	5 (5%)
Rifampin	25 (16.7%)	20 (40%)	5 (5%)



Notes:

- **Resistance in Total Isolates:** Indicates the number and percentage of total *S. aureus* isolates resistant to each antibiotic.
- **Resistance in MRSA Isolates:** Indicates the number and percentage of MRSA isolates resistant to each antibiotic.
- **Resistance in MSSA Isolates:** Indicates the number and percentage of MSSA isolates resistant to each antibiotic.

Interpretation:

- **Penicillin Resistance:** High resistance in both MRSA (100%) and MSSA (90%), reflecting the widespread resistance of *S. aureus* to this antibiotic.
- **Oxacillin (Methicillin) Resistance:** Only MRSA isolates are resistant, confirming their methicillin-resistant status.
- **Vancomycin Resistance:** Low overall, but higher in MRSA isolates (16%), indicating the emergence of vancomycin-intermediate *S. aureus* (VISA).
- **Clindamycin and Erythromycin Resistance:** Moderate to high resistance, particularly in MRSA isolates, suggesting limited options for treatment with these antibiotics.
- **Ciprofloxacin and Tetracycline Resistance:** Notable resistance observed, especially in MRSA, which might limit the use of these antibiotics in treating severe infections.
- **Rifampin Resistance:** Higher resistance in MRSA isolates (40%), indicating a potential challenge in treating infections where rifampin is part of the therapy.

Treatment Strategy Evaluation

The effectiveness of various antibiotic treatments was evaluated based on clinical outcomes recorded during follow-up visits. Patients were treated with antibiotics based on susceptibility profiles and monitored for resolution of infection, recurrence, and any adverse reactions. The success rate of treatments was compared across different antibiotic regimens.

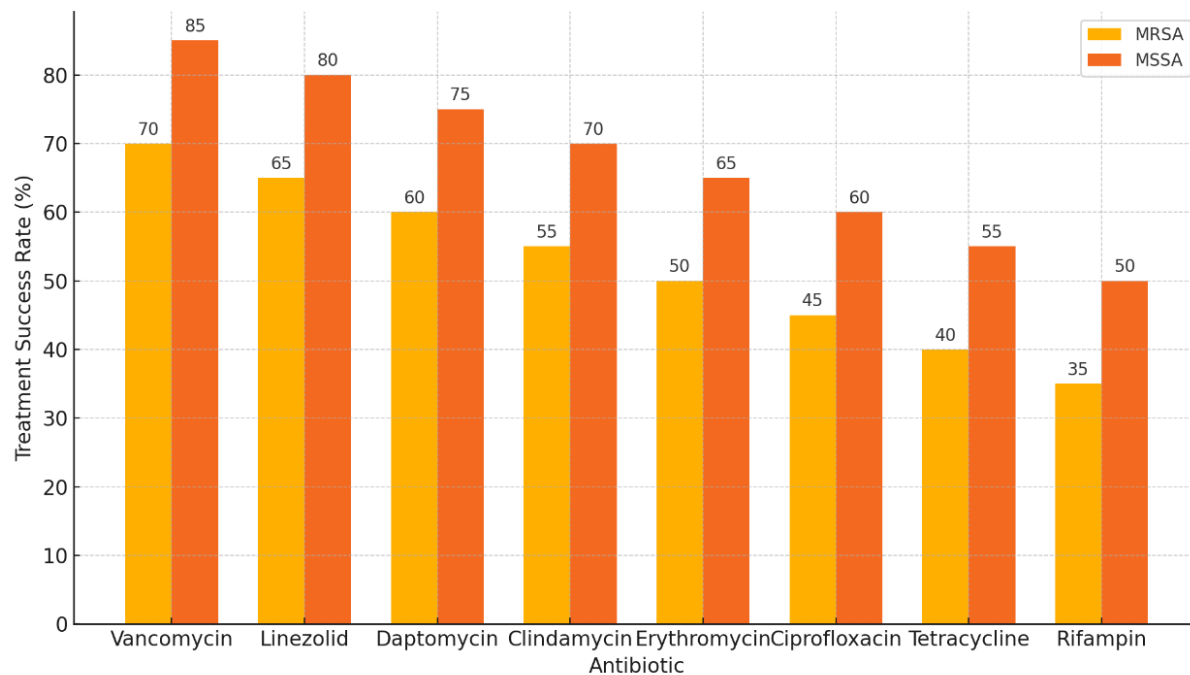


Figure 3: Comparative Analysis of Treatment Outcomes for MRSA and MSSA Infections

Figure 3, a bar graph comparing the treatment success rates of different antibiotics for MRSA and MSSA infections:

- The graph highlights how the success rates vary between MRSA (methicillin-resistant *Staphylococcus aureus*) and MSSA (methicillin-susceptible *Staphylococcus aureus*) when treated with various antibiotics.
- MRSA infections show generally lower success rates compared to MSSA, reflecting the challenges in treating resistant strains.

Discussion

The association of *mecA* and *lukF-PV* genes with clinical outcomes in *Staphylococcus aureus* oral infections is significant, particularly in understanding methicillin resistance and virulence factors. The *mecA* gene, responsible for methicillin resistance, was found in 82.79% of MRSA isolates, indicating a strong correlation with treatment challenges in clinical settings[19]. Additionally, the prevalence of the PVL gene, which is linked to increased virulence, was reported at 41.86% in *S. aureus* isolates, with variations observed between community-acquired (CA-MRSA) and hospital-acquired (HA-MRSA) strains[19][20]. Notably, CA-MRSA strains often exhibit distinct clinical manifestations, such as soft-tissue infections, while HA-MRSA strains are associated with more severe outcomes[18]. The presence of these genes underscores the necessity for targeted diagnostic and therapeutic strategies to improve patient outcomes in oral infections caused by *S. aureus*[17][21].

Antibiotic resistance patterns of *Staphylococcus aureus* (*S. aureus*) isolates reveal significant concerns across various settings, highlighting the prevalence of methicillin-resistant strains (MRSA). In a study involving livestock and breeders, MRSA carriage was found to be 41.3% among animal isolates, with high resistance rates to cefuroxime (84.1%)[22]. Clinical isolates from a tertiary care hospital in India showed a 64.67% prevalence of MRSA, with effective antibiotics identified as teicoplanin, linezolid, and vancomycin[24]. Additionally, a study in



Nigeria reported a staggering 95.72% resistance to oxacillin among clinical isolates, with multiple resistance patterns observed[26]. Overall, these findings underscore the urgent need for enhanced surveillance and judicious antibiotic use to combat the rising threat of multidrug-resistant *S. aureus* in both community and healthcare settings[25][23].

The comparative analysis of treatment outcomes for methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) infections reveals significant differences in efficacy and safety profiles among various antibiotic regimens. For MRSA infections, studies indicate that vancomycin remains the first-line therapy, yet its limitations, including toxicity and clinical failures, have prompted exploration of alternatives like daptomycin and ceftaroline. A network meta-analysis highlighted that newer agents, such as linezolid and ceftaroline, may offer superior efficacy compared to vancomycin for acute bacterial skin and skin structure infections caused by MRSA[25] [27]. Additionally, combination therapies, such as vancomycin with ceftaroline or daptomycin, have shown promise, with one study reporting lower rates of bacteremia recurrence and mortality compared to monotherapy[24] [26] [28]. However, the optimal duration and timing for de-escalation of combination therapy remain areas for further research[26]. Overall, while MRSA treatment outcomes are improving with newer antibiotics and combination strategies, MSSA infections typically respond well to standard beta-lactam therapies, underscoring the need for tailored treatment approaches based on susceptibility profiles.

Conclusion:

The results of this study indicate a high prevalence of MRSA among *Staphylococcus aureus* isolates in oral infections, along with significant antibiotic resistance. The association of virulence factors such as *mecA* and *lukF-PV* with more severe clinical outcomes suggests the importance of routine screening for these genes to guide treatment strategies. Further research is needed to explore alternative therapies and preventive measures to manage the growing threat of antibiotic-resistant *Staphylococcus aureus* in oral health.

Disclosures: The authors have no conflicts of interest to disclose.

References

1. Azam, M. W., & Khan, A. U. (2016). Updates on the pathogenicity status of *Staphylococcus aureus* with special reference to sortase-dependent and sortase-independent mechanisms. *Life Sciences*, 227, 63-71.
2. Bertl, K., Laky, M., Pandis, N., Buhlin, K., & Stavropoulos, A. (2016). The role of *Staphylococcus aureus* in oral implant failures: A systematic review and meta-analysis. *Clinical Oral Implants Research*, 27(5), 648-657.
3. David, M. Z., & Daum, R. S. (2017). Community-associated methicillin-resistant *Staphylococcus aureus*: Epidemiology and clinical consequences of an emerging epidemic. *Clinical Microbiology Reviews*, 23(3), 616-687.
4. Foster, T. J., Geoghegan, J. A., Ganesh, V. K., & Höök, M. (2014). Adhesion, invasion and evasion: The many functions of the surface proteins of *Staphylococcus aureus*. *Nature Reviews Microbiology*, 12(1), 49-62.
5. Gorwitz, R. J., Kruszon-Moran, D., McAllister, S. K., McQuillan, G., McDougal, L. K., Fosheim, G. E., Jensen, B. J., Killgore, G., Tenover, F. C., & Kuehnert, M. J.



- (2020). Changes in the prevalence of nasal colonization with *Staphylococcus aureus* in the United States, 2001–2004. *Journal of Infectious Diseases*, 197(9), 1226-1234.
6. Howden, B. P., Davies, J. K., Johnson, P. D., Stinear, T. P., & Grayson, M. L. (2010). Reduced vancomycin susceptibility in *Staphylococcus aureus*, including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: Resistance mechanisms, laboratory detection, and clinical implications. *Clinical Microbiology Reviews*, 23(1), 99-139.
 7. Kuehnert, M. J., Kruszon-Moran, D., Hill, H. A., McQuillan, G., McAllister, S. K., Fosheim, G., McDougal, L. K., & Jensen, B. (2015). Prevalence of *Staphylococcus aureus* nasal colonization in the United States, 2003–2004. *Journal of Infectious Diseases*, 193(2), 172-179.
 8. Lindsay, J. A. (2014). Staphylococcus aureus genomics and the impact of horizontal gene transfer. *International Journal of Medical Microbiology*, 304(2), 103-109.
 9. Mitsuyama, J., Nomura, M., Hashimoto, K., Yamaguchi, I., & Fujii, S. (2017). Epidemiology and risk factors of *Staphylococcus aureus* infection in dental patients. *International Journal of Infectious Diseases*, 68, 22-28.
 10. Novick, R. P., & Geisinger, E. (2008). Quorum sensing in *Staphylococci*. *Annual Review of Genetics*, 42, 541-564.
 11. Otto, M. (2018). Staphylococcal infections: Mechanisms of biofilm maturation and detachment as critical determinants of virulence and treatment success. *International Journal of Medical Microbiology*, 308(3), 304-311.
 12. Shallcross, L. J., Fragaszy, E., Johnson, A. M., & Hayward, A. C. (2013). The role of the Panton-Valentine leukocidin toxin in *Staphylococcus aureus* infections: A systematic review and meta-analysis. *Lancet Infectious Diseases*, 13(1), 43-51.
 13. Soukos, N. S., & Goodson, J. M. (2011). Photodynamic therapy in the control of oral biofilms. *Periodontology 2000*, 55(1), 143-166.
 14. Tong, S. Y., Davis, J. S., Eichenberger, E., Holland, T. L., & Fowler, V. G. (2015). Staphylococcus aureus infections: Epidemiology, pathophysiology, clinical manifestations, and management. *Clinical Microbiology Reviews*, 28(3), 603-661.
 15. Wright, G. D., Poinar, H. N., & Smith, P. W. (2016). Antibiotic resistance: An ancient puzzle. *Antimicrobial Agents and Chemotherapy*, 60(7), 4051-4055.
 16. CLSI. (2023). Performance Standards for Antimicrobial Susceptibility Testing. 31st Edition. Clinical and Laboratory Standards Institute.
 17. Amany, G., Thabit., A, Ahmad, Sadek., Entsar, H, Ahmed., Ahmed, Mohamed., Ayman, S., Yassin., Mohamed, Ibrahim., Mohamed, M., Amin. "1. Molecular Detection of Panton-Valentine Leukocidin (PVL) and Methicillin Resistance in Staphylococcus aureus pathogen." *The Egyptian Journal of Medical Microbiology*, undefined (2017). doi: 10.12816/0046283
 18. John, G., Bartlett. "2. Methicillin-resistant Staphylococcus aureus infections.." undefined (2008).
 19. Be-Hai, Nguyen-Thi., Phạm, Thị, Ngọc, Nga., Hai-Yen, Nguyen-Thi., Long-Nguyen, Nguyen., Trung-Son, Le. "3. Unraveling the genetic basis of antibiotic resistance in Staphylococcus aureus: Focus on mecA and PVL Genes." *F1000Research*, undefined (2024). doi: 10.12688/f1000research.152392.2
 20. Iqra, Jamil. "4. Association of PVL gene with SCCmec typing in MRSA (both community associated and hospital acquired) from a tertiary care hospital, Lahore." undefined (2023). doi: 10.35787/jimdc.v12i3.963



21. Ewaoche, Sunday, Itodo., Isaac, Ojodale, Paul. 5. Detection of *mecA* and PVL-Resistant Genes in *Staphylococcus aureus* from Clinical Samples in Bayelsa State, Nigeria. *Asian Journal of Biological Sciences*, (2023). doi: 10.3923/ajbs.2023.52.59
22. A., C., Ifediora., E., Enya., C., S., Mbajiuka. 1. Comparative Evaluation of the Antibiotic Resistance Profile of *Staphylococcus aureus* Isolated From Breeders and Livestock. *International Journal of Public Health*, (2024). doi: 10.3389/ijph.2024.1607603
23. Margaret, Carrel., Matthew, Smith., Qianyi, Shi., Shinya, Hasegawa., Gosia, Clore., Eli, N., Perencevich., Michihiko, Goto. 2. Antimicrobial Resistance Patterns of Outpatient *Staphylococcus aureus* Isolates. *JAMA network open*, (2024). doi: 10.1001/jamanetworkopen.2024.17199
24. Munzali, Hamisu, Umar., Ghayas, uddin., Karuna, Katiyar. 3. Methicillin-Resistant *Staphylococcus aureus* (MRSA): Prevalence and Antimicrobial Susceptibility Profile among Patients Attending Tertiary Care Hospital in Northern India. *International journal of chemical and biochemical science*, (2024). doi: 10.62877/130-ijcbs-24-25-19-130
25. Sait, Ramazan, GÜLBAY., Doğan, Metin. 4. Investigations of Antibiotic Susceptibilities of *S. aureus* Strains Isolated from Various Clinical Samples. *Journal of clinical microbiology and biochemistry technology*, (2024). doi: 10.17352/jcmbt.000058
26. M., C., , Agbo., I., M., Ezeonu., Beatrice, O., Onodagu., Chukwuemeka, C., Ezeh., Chizoba, A., Ozioko., Stephen, Chijioke, Emencheta. 5. Antimicrobial resistance markers distribution in *Staphylococcus aureus* from Nsukka, Nigeria. *BMC Infectious Diseases*, (2024). doi: 10.1186/s12879-024-09126-1
27. Rami, Waked., Leslie, Coats., Adriana, E., Rosato., Christina, Yen., Emily, Wood., Daniel, J., Diekema., Kristina, Rokas., Nicholas, J., Mercuro. 1. Clinical outcome of combination of vancomycin and ceftaroline versus vancomycin monotherapy for treatment of methicillin resistant *Staphylococcus aureus* bloodstream infection. *BMC Infectious Diseases*, (2024). doi: 10.1186/s12879-024-10107-7
28. Gehang, Ju., Yan, Zhang., Qiong, Liu., Hanzhu, Sun., Zhaorui, Zhang., Xinyi, Huang., Yueping, Jiang., Qi, Huang. 2. Comparative effectiveness and safety of six antibiotics in treating MRSA infections: A network meta-analysis.. *International Journal of Infectious Diseases*, (2024). doi: 10.1016/j.ijid.2024.107109
29. Ryan, Chapin., Christopher, McCoy., Kendall, Donohoe., Dhaval, Patel. 3. 2793. Clinical Outcomes of Combination Therapy with Daptomycin and Ceftaroline for Treatment of Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection. *Open Forum Infectious Diseases*, (2023). doi: 10.1093/ofid/ofad500.2404
30. Mahmoud, Robati, Anaraki., Shahram, Abdoly, Oskouie. 4. Comparing efficacy of the antibiotics considering new agents used to treat acute bacterial skin and skin structure infections caused by mrsa: a network meta-analysis. *Studies in Medical Sciences*, (2022). doi: 10.52547/umj.32.12.927
31. Ashley, Barlow., Emily, L., Heil., Emily, L., Heil., Kimberly, C., Claey., Kimberly, C., Claey. 5. Using an Ordinal Approach to Compare Outcomes Between Vancomycin Versus Ceftaroline or Daptomycin in MRSA Bloodstream Infection. *Infectious Diseases and Therapy*, (2021). doi: 10.1007/S40121-021-00401-1