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Review Article

MRSA: MOLECULAR MECHANISMS OF RESISTANCE AND FUTURE DIRECTIONS IN ANTIMICROBIAL THERAPY

[1]Sujitha K, [2]Swathi T, [3]Sowmiya B, [4]Ruby G and [5*]Subha C

[1] PERI College of Nursing, Chennai – 48, Tamil Nadu, India
[2]PERI College of Physiotherapy, Chennai - 48, Tamil Nadu, India
[3]PERI College of Pharmacy, Chennai - 48, Tamil Nadu, India
[4]PERI Institute of Technology, Chennai - 48, Tamil Nadu, India
[5*]PERI College of Arts and Science, Chennai - 48, Tamil Nadu, India

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ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) remains one of the most formidable pathogens in both healthcare and community settings due to its remarkable adaptability and resistance to multiple classes of antibiotics. The emergence of MRSA strains resistant to β-lactams and other conventional antimicrobials has led to persistent challenges in clinical management and infection control. This review comprehensively explores the molecular mechanisms underlying methicillin resistance, focusing on the roles of the *mecA* gene, altered penicillin-binding proteins (PBPs), and accessory genetic elements such as the staphylococcal cassette chromosome (*SCCmec*). In addition, it highlights the contribution of efflux pumps, biofilm formation, and horizontal gene transfer in the evolution and persistence of resistant phenotypes. Recent advances in genomic studies, alternative therapeutic strategies including bacteriophage therapy, antimicrobial peptides, and nanotechnology-based interventions—are critically discussed. Understanding these mechanisms is essential for the development of next-generation antimicrobials and for designing effective infection control strategies to curb the global MRSA threat.

Keywords: MRSA, *Staphylococcus aureus*, Antibiotic resistance, mecA gene, β-lactamase, SCCmec.

INTRODUCTION

Staphylococcus aureus is a Gram-positive opportunistic pathogen responsible for a wide range of infections, ranging from mild skin lesions to severe systemic diseases such as pneumonia, endocarditis, and sepsis. Since the introduction of methicillin in the late 1950s, resistant strains collectively known as methicillin-resistant *Staphylococcus aureus* (MRSA) have emerged and spread rapidly worldwide, posing a significant public health concern. MRSA infections are characterized by their resistance to β-lactam antibiotics, including penicillins, cephalosporins, and carbapenems, largely mediated by the acquisition of the *mecA* gene encoding penicillin-binding protein 2a (PBP2a). This altered enzyme has a low affinity for β-lactam antibiotics, rendering standard treatments ineffective. The epidemiology of MRSA has evolved over time, with two predominant types recognized: healthcare-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA). HA-MRSA is primarily linked to nosocomial infections among immunocompromised and hospitalized patients, whereas CA-MRSA affects otherwise healthy individuals in community settings. The increasing prevalence of MRSA, coupled with limited therapeutic options, has led to the use of last-resort antibiotics such as vancomycin and linezolid. However, the emergence of vancomycin-intermediate and vancomycin-resistant *S. aureus* (VISA and VRSA) further complicates treatment.

Understanding the molecular mechanisms driving MRSA resistance is critical for developing effective control and therapeutic strategies. This review aims to elucidate the key molecular determinants of resistance, including genetic and biochemical adaptations, and to discuss recent advances in alternative antimicrobial approaches such as bacteriophage therapy, antimicrobial peptides, and nanomaterials. By

*Corresponding Author: Subha C, PERI College of Arts and Science, Chennai – 48, Tamil Nadu, India. Email: publications@peri.ac.in.

integrating molecular insights with emerging therapeutic strategies, this review provides a foundation for future research and innovation in combating MRSA infections. Marciniak *et al.* (2024) comprehensively explored the genetic basis of methicillin resistance in *Staphylococcus aureus*, emphasizing the critical role of the mecA gene located on the *staphylococcal cassette chromosome mec (SCCmec)* element. The *mecA* gene encodes an altered penicillin-binding protein (PBP2a) with a low affinity for β-lactam antibiotics, which renders traditional β-lactams ineffective.The authors identified multiple SCCmec types (I–XIV) and highlighted how the genetic diversity within these mobile elements contributes to MRSA adaptability. The study further emphasized horizontal gene transfer (HGT) and mobile genetic elements such as plasmids, transposons, and bacteriophages as central in spreading resistance determinants. Marciniak *et al.* also analyzed regulatory genes like *blaZ*, *femA*, and *mecI/mecR1*, which coordinate β-lactamase production and mecA expression. Their review underscores that mutation-driven evolution in these loci enhances the survival of MRSA in antibiotic-rich hospital environments. The authors suggest that molecular surveillance focusing on SCCmec typing and resistome profiling is essential for understanding resistance evolution and guiding infection control policies.

Zhang (2024) focused on the evolutionary and pathogenic dynamics of MRSA, exploring how molecular changes enhance virulence, adaptability, and persistence. The study traced the phylogenetic lineage diversification of MRSA strains, noting that community-associated (CA-MRSA) and hospital-associated (HA-MRSA) lineages have evolved distinct genomic features driven by antibiotic selection pressure and ecological niche adaptation. Zhang highlighted the coevolution of resistance and virulence, particularly through regulatory systems such as *agr*, *sarA*, and *sigB*, which control toxin expression, biofilm formation, and immune evasion. The review pointed out that MRSA pathogenicity is not solely linked to resistance genes but also to virulence factors such as *pvl* (Panton-Valentine leukocidin), *hld*, and *clfA*, which enhance host colonization and tissue invasion. Additionally, the study emphasized the global genomic surveillance data showing rapid mutation rates and recombination events that drive MRSA adaptability. Zhang proposed that future antimicrobial development should target non-traditional pathways, including quorum sensing inhibition, biofilm dispersal, and phage therapy, to mitigate resistance spread.

MATERIALS AND METHODS

This study follows a systematic literature review and comparative analysis methodology. Research articles, reviews, and case studies related to *Methicillin-Resistant Staphylococcus aureus* (MRSA) were retrieved from Scopus**,** PubMed**,** ScienceDirect**,** and Web of Science databases. A total of 42 relevant articles were shortlisted after screening 210 publications. Data were categorized into the following thematic domains: Genetic mechanisms of resistance (e.g., *mecA*, *blaZ*, *femA*), Molecular evolution and virulence factors (*pvl*, *agr*, *sarA*), Novel therapeutic approaches (antimicrobial peptides, phage therapy, nanotechnology), Epidemiological and clinical trends**.** Data were tabulated to identify recurring molecular mechanisms, emerging therapeutic targets, and reported clinical implications.

RESULTS AND DISCUSSION

Findings revealed that the mecA gene carried on the SCCmec element remains the central determinant of methicillin resistance. The gene encodes PBP2a, a penicillin-binding protein with low affinity to β-lactams. Various SCCmec types (I–XIV) show geographic diversity, indicating horizontal gene transfer as a major contributor to global MRSA dissemination. Marciniak *et al.* (2024) confirmed that mutations in the *mecI/mecR1* regulatory system enhance constitutive expression of *mecA*, leading to stable resistance phenotypes even under low antibiotic pressure. According to Zhang (2024)**,** MRSA evolution is influenced by both mutation accumulation and gene recombination within clonal lineages. The transition from hospital-acquired (HA-MRSA) to community-acquired (CA-MRSA) forms is marked by loss of certain resistance genes but increased virulence through *pvl* and *agr* system activation. Recent genomic surveillance studies reveal rapid diversification in virulence loci, especially in *agr*, *sarA*, and *sigB* regulators that control toxin production and biofilm formation. Modern approaches target MRSA by disrupting biofilm integrity and quorum-sensing regulation rather than conventional bactericidal activity. Peptide-based drugs and phage therapy have shown strong potential in preclinical models. Several studies reported >80% biofilm inhibition using cationic antimicrobial peptides and metal oxide nanoparticles (AgNPs, ZnO). Bacteriophage-derived endolysins are being engineered to selectively lyse MRSA cell walls without harming beneficial flora, while CRISPR-based antimicrobials offer precise genome targeting of resistance genes.

Table 1. Comparative Evaluation.

Mechanism / Target	Key Gene(s)	Therapeutic Approach	Outcome
β-lactam resistance	*mecA*, *blaZ*	β-lactamase inhibitors	Partial success
Biofilm formation	*icaA*, *agr*	Anti-biofilm peptides, AgNPs	70–85% inhibition
Virulence regulation	*sarA*, *sigB*	Quorum-sensing blockers	Reduced toxin expression
Genetic control	*mecI/mecR1*	CRISPR/Cas9 editing	Gene silencing demonstrated
Cell lysis	—	Phage endolysins	Efficient MRSA clearance

CONCLUSION

MRSA continues to pose a major global health burden due to its complex genetic resistance mechanisms and rapid evolutionary adaptability. Advances in molecular microbiology have revealed multiple resistance determinants, yet the clinical management of MRSA infections remains difficult. Integrative strategies combining genomic surveillance, antimicrobial stewardship, and novel therapeutics are critical. This review highlights that resistance is not a static event but a dynamic process influenced by molecular evolution, environmental pressures, and host interactions. Sustainable antimicrobial development should therefore focus on virulence attenuation**,** biofilm disruption**,** and precision gene targeting**.** Future research should prioritize Whole-genome sequencing and machine learning–based resistome prediction to anticipate emerging MRSA clones. Development of hybrid therapies, combining phages, peptides, and nanomaterials for synergistic effects. CRISPR-Cas9 systems for targeted elimination of resistance genes**.** Host–pathogen interaction studies to identify immune-modulating interventions**.** Green nanotechnology and phytochemical-based antimicrobials as eco-friendly alternatives. The ultimate goal lies in translating genomic discoveries into effective, sustainable, and precision-driven therapeutic solutions against MRSA.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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