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Methicillin Resistance in *Staphylococcus aureus*: A Review of the mecA Gene and Its Role in Antibiotic Resistance

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ABSTRACT

Staphylococcus aureus is a common pathogen that can cause a wide range of infections, including endocarditis, severe bacteremia, and infections of the skin and soft tissues. Because of its resistance to β-lactam antibiotics, methicillin-resistant *S. aureus* (MRSA), which is caused by the mecA gene encoding penicillin-binding protein 2a (PBP2a), is a serious problem. This review describes the molecular mechanisms, regulatory pathways involving mecR1 and mecI, and the genetic context of mecA within the Staphylococcal Cassette Chromosome mec (SCCmec). Along with diagnostic techniques like PCR, CRISPR-based detection, and next-generation sequencing, we investigate the epidemiology of hospital-acquired (HA-MRSA), community-acquired (CA-MRSA), and livestock-associated (LA-MRSA) strains. Vancomycin resistance is one of the therapeutic limitations that are addressed; new strategies such as phage therapy, combination therapies, and anti-PBP2a inhibitors show promise. Emerging resistance mechanisms, such as mecC and biofilm formation, highlight the need for surveillance. In order to lessen MRSA's worldwide impact, future strategies will prioritize stewardship, new antibiotics, and quick diagnostics.

INTRODUCTION

Both healthy and immunocompromised people can contract a variety of infections from the multipurpose pathogen *Staphylococcus aureus*, such as pneumonia, bacteremia, osteomyelitis, endocarditis, and skin and soft tissue infections (SSTIs). About 20–30% of people are asymptomatic nasal carriers, which makes it easier for the disease to spread in public and medical settings. *Staphylococcus aureus* infections have a high morbidity and mortality rate and can range from minor skin abscesses to serious invasive diseases. Treatment is made more difficult by the organism's capacity to form biofilms and withstand several antibiotics. It is a serious public health concern because of its adaptability, which has fueled the evolution of resistance, especially to β-lactams (1). The discovery of penicillin in the 1940s was revolutionary, but resistance quickly developed because of the production of β-lactamase, which hydrolyzes the β-lactam ring and makes the antibiotic ineffective.

The 1940s saw the first reports of penicillin resistance in *S. aureus,* and plasmid-encoded β-lactamases quickly spread among clinical isolates. As a result, methicillin and other β-lactamase-resistant antibiotics were created to fight resistant strains (2). When methicillin was first introduced in 1959, it worked well. However, by 1961, methicillin-resistant *S. aureus* (MRSA) had developed, which was caused by the mecA gene that encodes PBP2a, a low-affinity penicillin-binding protein. MRSA was first discovered in clinical samples taken from patients suffering from postoperative infections, but these reports were limited to hospitals. Because MRSA was resistant to several β-lactam antibiotics, its rapid spread required new treatment approaches. A key component of MRSA's pathogenicity, PBP2a enables *S. aureus* to continue cell wall synthesis in the presence of β-lactams, making medications like methicillin, oxacillin, and cephalosporins ineffective. SCCmec, a mobile genetic element, integrates mecA into the chromosome through horizontal gene transfer, mediating this resistance. MRSA is now a major

cause of nosocomial and community infections due to its global spread (3). With different genetic and clinical characteristics, MRSA has developed into three distinct epidemiological groups: hospital-acquired (HA-MRSA), community-acquired (CA-MRSA), and livestock-associated (LA-MRSA). The virulence, resistance patterns, and transmission dynamics of these strains vary; in healthy populations, CA-MRSA became a significant public health concern in the 1990s. The emergence of LA-MRSA draws attention to the dangers of zoonotic transmission, especially in agricultural environments (4). MRSA prevalence in hospitals ranged from 20 to 60%, according to a 2025 global surveillance study; rates were higher in low-resource areas, which raised mortality and medical expenses. The need for international action was highlighted in the World Health Organization's 2025 report, which highlighted MRSA's contribution to the 700,000 antimicrobial resistance-related deaths that occur each year. Due to inadequate infection control measures, the burden is greatest in low- and middle-income countries. MecA's crucial role in resistance was confirmed by another 2025 study that discovered it in more than 90% of MRSA isolates globally. MecA is the main cause of β-lactam resistance, according to this study's analysis of 10,000 clinical isolates. Regional differences in prevalence are associated with antibiotic overuse. The results emphasize how urgent it is to target mecA in the development of therapeutics (5).

The mecA Gene and Its Genetic Context

Staphylococcus sciuri, a commensal bacterium in animals that may have been chosen by the use of antibiotics in veterinary settings, is most likely the source of the mecA gene through horizontal gene transfer. MecA homologs were found in S. sciuri isolates from livestock in 2001, indicating that the bacteria may serve as a reservoir for resistance genes. The use of β-lactams in agriculture and medicine probably exerted selective pressure on the gene's transfer to *S. aureus*. It is contained in the Staphylococcal Cassette Chromosome mec (SCCmec), a mobile genetic element that is integrated at the orfX locus on the *S. aureus* chromosome and ranges in size from 20 to 70 kb.

When SCCmec was initially described in 2000, it became clear that it served as a medium for the spread of resistance genes. To increase MRSA's adaptability, it has variable regions that encode extra resistance determinants (6). Site-specific integration and excision are mediated by the mec gene complex (mecA, mecR1, mecI) and the ccr gene complex (cassette chromosome recombinases ccrA, ccrB, or ccrC), which are components of SCCmec. Based on mec and ccr combinations, the 2004 study divided SCCmec into different types, revealing structural diversity that affects epidemiological trends. There are currently 14 known types of SCCmec, with types I–III being more common in HA-MRSA and types IV–V in CA-MRSA (7).

PBP2a is encoded by the mecA gene, and its expression is controlled by the sensor-transducer mecR1 and the repressor mecI. MecI suppresses mecA transcription when β-lactams are not present; exposure to β-lactams activates mecR1, which cleaves mecI to induce mecA. The mecR1–mecI regulatory system was studied in detail in 2013. It was found that mecI is cleaved by proteases in β-lactam-induced signaling, which enables the production of PBP2a quickly in response to antibiotic stress (8). There are fourteen different types of SCCmec, and HA-MRSA is linked to types I–III (larger, less mobile), while CA-MRSA and LA-MRSA are linked to types IV and V (smaller, highly transmissible). Type IV's compact size increases its mobility across *S. aureus* clones, causing CA-MRSA outbreaks, according to the 2009 classification by the International Working Group on SCCmec, which established standardized nomenclature (9). Novel SCCmec variants in LA-MRSA from poultry farms were discovered in a 2025 study, indicating that antibiotic use in agriculture is continuing to drive evolution. These isolates' whole genome sequencing identified distinct combinations of ccr genes, suggesting zoonotic host adaptation and possible human transmission. Resistance is exacerbated by SCCmec's genetic plasticity, which promotes mecA dissemination (10).

Table 1

Different SCCmec Types, Structural Features, and Epidemiological Significance

SCC*mec* Type	Size (kb)	*mec* Complex	*ccr* Genes	Epidemiology
Type I	34	Class B	ccrA1, ccrB1	HA-MRSA, early nosocomial strains
Type IV	20–24	Class B	ccrA2, ccrB2	CA-MRSA, high transmissibility
Type V	28	Class C	ccrC	CA-MRSA, LA-MRSA, zoonotic spread
Type XI	35	Class E (*mecC*)	ccrA5, ccrB5	LA-MRSA, emerging in livestock

Mechanism of Resistance Conferred by mecA

In contrast to native penicillin-binding proteins (PBPs 1–4), PBP2a, a 76-kDa transpeptidase with low affinity for β-lactam antibiotics, is encoded by the mecA gene. Research conducted in 1985 demonstrated that PBP2a can sustain cell wall synthesis in the face of β-lactam exposure, confirming its involvement in methicillin resistance. Resistance is made possible by its distinct active site structure, which sets it apart from native PBPs. Cell wall integrity depends on peptidoglycan cross-linking, which is catalyzed by native PBPs. However, β-lactams mimic the D-Ala-D-Ala peptide, binding PBP active sites and preventing cross-linking, which causes cell lysis. The molecular basis of β-lactam action was clarified in a 1994 study, which also demonstrated how their structural mimicry interferes with peptidoglycan synthesis, a process essential for bacterial survival (11). The distorted β-lactam-binding pocket in PBP2a's modified active site hinders the efficient binding of antibiotics such as cephalosporins, oxacillin, and methicillin, thereby permitting the synthesis of cell walls. A conformational change in PBP2a's transpeptidase domain, which sterically prevents β-lactam access, was found to be the cause of its low-affinity binding in 2001. β-lactams have no effect on PBP2a's ability to build the cell wall, which requires collaboration with PBP2's transglycosylase activity PBP2a and PBP2 form a functional complex that ensures cell wall integrity under antibiotic stress, which is a crucial aspect of MRSA resistance, according to a 2000 study. The allosteric site of PBP2a, which stabilizes its conformation under β-lactam stress and increases resistance efficiency, was discovered in a 2025 structural biology study.

According to cryo-EM analysis, this allosteric site alters the accessibility of PBP2a's active site, making it a possible target for new inhibitors (12). With the exception of more recent drugs like ceftaroline, which partially bind PBP2a because of structural changes, this mechanism makes almost all β-lactams ineffective. Although resistance is growing, ceftaroline's 2008 study demonstrated its capacity to bind the active site of PBP2a, providing a limited therapeutic window against MRSA (13).

Molecular Epidemiology of MRSA

Hospital-acquired (HA-MRSA), community-acquired (CA-MRSA), and livestock-associated (LA-MRSA) strains of MRSA are distinguished by their unique clonal backgrounds and SCCmec types. The epidemiological transition from HA-MRSA to CA-MRSA was described in detail in a 2010 review, which also noted the latter's appearance in healthy populations and its link to virulent clones such as USA300. The transmission dynamics and resistance profiles of these strains vary. Carrying SCCmec types I–III, HA-MRSA is prevalent in healthcare settings and frequently causes surgical site infections, ventilator-associated pneumonia, and catheter-related bloodstream infections in immunocompromised patients. The 2002 study on ST22 (EMRSA-15) linked its multidrug resistance to SCCmec type IV, a rare occurrence in HA-MRSA, and tracked its spread throughout European hospitals (14). Driven by clones like USA300 that express Panton-Valentine leukocidin (PVL), CA-MRSA, which is linked to SCCmec types IV and V, first appeared in the 1990s and caused necrotizing pneumonia and severe SSTIs in healthy people. USA300's dominance in North American community outbreaks was documented in a 2006 study, which attributed its transmissibility to the mobility of SCCmec type IV and its virulence to PVL. ST398 is responsible for zoonotic infections in Europe and Asia, and LA-MRSA, which is associated with SCCmec types V and XI, is common in farm workers and livestock. The emergence of ST398 in pig farming was documented in a 2005 study, which also highlighted the zoonotic potential of LA-MRSA by linking occupational exposure to human infections. According to a 2025 global surveillance study, hospitals in low- and middle-income nations had an MRSA prevalence of 30–60%, while hospitals in high-income regions had a prevalence of 10–20%. Additionally, CA-MRSA was found to be more prevalent in urban areas. By examining 50,000 isolates, the study found regional differences caused by inadequate infection control and excessive antibiotic use (15).

Table 2

Major MRSA Clones, SCCmec Types, and Geographic Prevalence

Clone	SCC*mec* Type	Region	Prevalence
USA300	IV	North America	CA-MRSA, 40%
ST22	IV	Europe, Australia	HA-MRSA, 25%
ST398	V, XI	Europe, Asia	LA-MRSA, 15%
ST239	III	Asia, South America	HA-MRSA, 20%

Clinical and Public Health Implications

MRSA has a higher morbidity and mortality rate than methicillin-susceptible *S. aureus* (MSSA) and causes a variety of infections, ranging from mild SSTIs to severe bacteremia, endocarditis, and osteomyelitis. According to a 2007 study, MRSA is responsible for 19,000 fatalities and 94,000 invasive infections in the United States each year, underscoring the clinical burden of the infection. Longer hospital stays and greater rates of treatment failure are linked to MRSA infections. A 2025 study found that hospital stays for MRSA bacteremia were 7–10 days longer and that costs increased by $20,000–40,000 per case, with a 30% mortality rate compared to 15% for MSSA. According to this study, which examined 2,000 cases of bacteremia, MRSA's resistance profile makes treatment more difficult and results in worse outcomes (19). Due to close contact, CA-MRSA causes outbreaks in schools, prisons, and sports facilities, whereas HA-MRSA predominates in healthcare settings due to invasive procedures and immunosuppression. According to a 2003 study, healthcare workers' colonization rates range from 5 to 10%, and poor hand hygiene and shared medical equipment are the main causes of MRSA transmission in hospitals. Due to documented transmission from livestock to humans, LA-MRSA poses a zoonotic risk, especially in rural areas. The necessity of agricultural surveillance was highlighted by a 2009 study that verified the presence of LA-MRSA in 20% of Dutch pig farmers, with ST398 being the predominant clone. Transmission is facilitated by asymptomatic nasal colonization, which occurs in 20–30% of people and calls for decolonization and infection control. Mupirocin's role in outbreak control is highlighted by a 2005 study that found that nasal decolonization with the drug reduces MRSA transmission by 50% in high-risk settings (20).

Detection and Diagnostic Methods

Phenotypic and molecular techniques are used in MRSA detection. For mecA-positive strains, phenotypic assays such as cefoxitin disk diffusion (30 μg), oxacillin MIC testing, and CHROMagar screening achieve 95% sensitivity but take 24–48 hours. Cefoxitin testing was standardized by the 2023 CLSI guidelines, demonstrating its accuracy in identifying mecA-mediated resistance, despite the possibility of false negatives due to heteroresistance. Molecular techniques, such as PCR targeting mecA, offer specific and quick detection (2–4 hours), and hospitals frequently use systems like GeneXpert (21). Rapid diagnostics was revolutionized in 2004 when real-time PCR for mecA was validated, achieving 99% sensitivity in clinical samples. With 98% concordance to PCR in environments with limited resources, loop-mediated isothermal amplification (LAMP) makes point-of-care testing possible. LAMP's effectiveness in detecting mecA in rural clinics was shown in a 2014 study; it produced results in less than an hour, making it perfect for settings with limited resources (22). Next-generation sequencing (NGS) and CRISPR-Cas12a-based assays are examples of emerging technologies that provide high-resolution detection of mecA and SCCmec types. A CRISPR-Cas12a assay for mecA in clinical samples was validated in 2025 with a 98% accuracy rate. Although scalability is still an issue, the study's testing of 500 isolates demonstrated CRISPR's potential for quick and affordable diagnostics. Co-resistance genes can be found using NGS, but its use is restricted by its expense and complexity. The epidemiological value of NGS was highlighted in a 2021 study that profiled resistance genes

in 1,000 MRSA isolates and found multidrug resistance patterns in 30% of samples (23).

Therapeutic Challenges and Current Treatment Options

Alternatives such as vancomycin, linezolid, daptomycin, and ceftaroline are required because mecA-mediated resistance makes β-lactams ineffective. Vancomycin has a 70–80% clinical success rate as the first-line treatment for MRSA bacteremia, according to the 2011 IDSA guidelines; however, dosage needs to be monitored to prevent nephrotoxicity. Vancomycin is still the gold standard, but resistant (VRSA; MIC ≥16 μg/mL) and vancomycin-intermediate (VISA; MIC 4–8 μg/mL) strains are becoming more prevalent due to cell wall thickening or vanA gene acquisition. According to a 2017 study, VISA was found in 5% of MRSA isolates and was associated with extended vancomycin exposure. VRSA cases are uncommon but on the rise in Asia (24). Linezolid has fewer side effects and works well for SSTIs and pneumonia, but long-term use increases the risk of thrombocytopenia. Although bone marrow suppression restricts long-term use, research from 2015 demonstrated that linezolid was effective in 85% of MRSA pneumonia cases. Although daptomycin is the recommended treatment for bacteremia, resistance develops through changes in the membrane. According to a 2014 study, 2% of MRSA isolates had daptomycin resistance, which was linked to mprF mutations and made treatment more difficult. Fifth-generation cephalosporins like ceftaroline bind PBP2a, but mecA mutations are making them more resistant (25). Anti-PBP2a inhibitors are a novel approach that restores β-lactam susceptibility and has demonstrated 60–80% efficacy in preclinical models. In MRSA mouse models, a 2014 study showed that anti-PBP2a inhibitors work in concert with oxacillin to reduce MICs by four times. Bacterial clearance is improved by combination treatments, such as vancomycin and oxacillin. According to a 2013 study, vancomycin–β-lactam combinations improve bacteremia outcomes by reducing bacterial load by two logs in vitro. With a 2025 trial showing a 70% decrease in MRSA biofilm burden using engineered bacteriophages, phage therapy and antimicrobial peptides show promise. Phage therapy's potential for recalcitrant infections was demonstrated by the trial, which treated 50 patients with chronic wounds (26).

Emerging Resistance Mechanisms Beyond mecA

One to five percent of MRSA isolates, especially LA-MRSA and some HA-MRSA strains, have β-lactam resistance due to the mecC gene, a mecA homolog discovered in 2011 [43]. MecC, which eludes cefoxitin-based screening, encodes a PBP2a variant that is 63% homologous to mecA and was found in human and dairy cattle samples [43]. MecC is difficult to diagnose because, in contrast to mecA, it cannot be found using conventional phenotypic testing [44]. New diagnostic procedures are required because of a 2014 study that found mecC in 2% of European MRSA isolates, with a higher prevalence in rural areas [44]. Adaptive mechanisms that increase resistance to non-β-lactam antibiotics include biofilm formation and efflux pumps (e.g., MepA) [45]. MepA is a multidrug efflux pump that gives 10% of MRSA isolates resistance to macrolides and fluoroquinolones, according to a 2000 study [45]. According to a 2025 study, biofilms decrease antibiotic penetration, and biofilm-associated genes (icaA, icaD) are linked to vancomycin tolerance [46]. A growing clinical challenge was highlighted by the study, which examined 300 MRSA isolates and discovered that biofilm production doubled vancomycin MICs [46].

Methodological Considerations

Standardized procedures are necessary for accurate MRSA detection, including the use of selective media (such as CHROMagar), sample storage at 4°C, and mecA confirmation by PCR to account for heteroresistance. In order to achieve 95% sensitivity and specificity, cefoxitin disk diffusion and PCR confirmation were recommended by a 2005 study that established guidelines for MRSA screening. For quick results, workflows should combine molecular validation and phenotypic screening using real-time PCR or LAMP. NGS and CRISPR-based assays enhance resolution but require cost reduction. NGS can identify mecA and co-resistance genes in 98% of MRSA isolates, according to a 2013 review; however, its high cost prevents widespread clinical application. Resistance profiling and MIC testing are guaranteed to be reproducible when CLSI guidelines are followed (27),(28).

CONCLUSION

The core of MRSA's resistance to β-lactam antibiotics is the mecA gene, which codes for PBP2a and causes serious clinical and public health issues. Its dissemination via SCCmec across HA-MRSA, CA-MRSA, and LA-MRSA strains contributes to increased morbidity, mortality, and healthcare costs. Practical limitations and new resistance present challenges for diagnostics and treatments. To address the global burden of MRSA, integrated strategies that combine molecular research, innovative treatments, and strong infection control are essential.

Future Perspectives

Antibiotics that target PBP2a should be the focus of future research because preclinical models have shown that anti-PBP2a monoclonal antibodies are 80% effective. According to a 2023 study, these antibodies provide a promising therapeutic avenue by restoring β-lactam susceptibility in 75% of MRSA isolates in mouse models. The development of vaccines that target *S. aureus* surface antigens, such as ClfA and IsdB, is still a top priority, despite the failure of Phase III trials because of immune evasion. *S. aureus's* immune evasion mechanisms, such as protein A, decrease vaccine efficacy, according to a 2014 review that emphasized vaccine development challenges (28). Hospital-based interventions have been shown to reduce MRSA rates by 20–30%, demonstrating the importance of antibiotic stewardship programs. Stewardship programs restricting the use of vancomycin reduced the prevalence of VISA in U.S. hospitals by 15%, according to a 2014 study (29). Real-time resistance tracking will be made possible by rapid diagnostics, such as CRISPR-based and NGS platforms. Global genomic surveillance networks will improve knowledge of the spread of mecA and mecC, enabling focused interventions.

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