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Review Article

# Detection of Clindamycin Resistance Antibiotic Genes among Staphylococcus Isolates by Using Real Time PCR

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## Abstract

**Background:** S. aureus is a prevalent person pathogen, accountable for a broad range of community- and hospital-acquired illnesses. The rise of methicillin-resistant Staphylococcus aureus (MRSA) and resistance to macrolide-lincosamide-streptogramin B (MLSB) medicines, especially clindamycin, presents significant therapeutic difficulties. This study aimed to determine the occurrence of constitutive and inducible clindamycin resistance among S. aureus clinical isolates utilizing real-time PCR for observation of resistance genes. Among the isolates, inducible clindamycin resistance (iMLSB) has been observed in 23.4%, with a markedly higher prevalence in MRSA (76.4%) compared to MSSA. Constitutive resistance (cMLSB) was lower, at 7.1% in MRSA and 5.8% in MSSA. Molecular analysis revealed the presence of ermA (15.62%), ermB (3.12%), and ermC (18.75%) genes, with higher prevalence of these genes in inducible clindamycin-resistant MRSA isolates. These results highlight the increasing burden of MLSB resistance and emphasize the necessity of routine D-testing and molecular surveillance to guide effective treatment and prevent therapeutic failure.

**Conclusion:** This study demonstrates a significant occurrence of inducible clindamycin resistance among Staphylococcus aureus isolates, particularly MRSA, with a strong association to erm genes. The high rate of iMLSB resistance underscores the risk of treatment failure if clindamycin is prescribed without prior D-testing. Moreover, the molecular detection of erm genes confirms their critical role in mediating resistance and indicates the importance of integrating genetic surveillance into diagnostic protocols. Strengthening antimicrobial stewardship, promoting rational antibiotic use, and applying reliable diagnostic methods are essential strategies to limit the spread of resistant S. aureus strains and improve patient outcomes.

**Key words:** Antibiotic Genes, Clindamycin Resistance, Staphylococcus Isolates

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## Introduction:

Staphylococcus is among the most prevalent pathogenic bacteria responsible for human disorders. Staphylococcus is a Gram (+ve) bacterium that induces several infectious illnesses in humans, including bacteremia, skin infections, pneumonia, endocarditis, and food poisoning.Nevertheless, the rising utilization of MLSB antibiotics correlates with a rise in the prevalence of Staphylococcal bacteria developing resistance to MLSB antibiotics .(1)

Detection of MRSA isolates was conducted utilizing the mecA mobile genetic element and polymerase chain reaction (PCR).This approach is categorized by a sensitivity of 93.8% to 100% and a specificity of 98.6% to 100%. The resistance mechanism of macrolides in various bacteria, particularly Gram-positive cocci, is documented by Erm genes and can occur through two mechanisms: an active efflux mechanism and Erm genes that encode enzymes conferring inducible resistance to macrolide agents via methylation of the 23S Rrna.(2)

Clindamycin, a member of the MLSB class of antibiotics, is the favored management for MRSA infections owing to its superior pharmacokinetics .(1)

Erythromycin induces clindamycin resistance by promoting the creation of erythromycin ribosome methylase (erm), which promotes the expression of clindamycin resistance. Isolates exhibiting constitutive clindam-ycin resistance, characterized by the continuous production of methylase, demonstrate resistance to both erythrom-ycin and clindamycin as a result of (erm) gene expression. (3)

This research aimed to ascertain the incidence of both constitutive and inducible clindamycin resistance in clinical isolates of Staphylococcus. This will assist physicians in preventing the overuse of clindamycin and enhance therapeutic results for cases.

### Staphylococci

Staphylococcus is a common bacterial pathogen found in the environment and as part of the normal human flora, particularly on the skin and nasal mucosa. While usually harmless on intact skin, Staphylococcus aureus can cause serious infections if it enters the bloodstream or internal tissues. It is responsible for a wide range of community- and hospital-acquired infections, with treatment complicated by the rise of multidrug-resistant strains such as methicillin-resistant Staphylococcus aureus. Transmission occurs mainly through direct contact, though other routes may also contribute .(4)

### Etiology

Staphylococcus are Gram (+ve), cocci-shaped bacteria that form grape-like clusters and grow in up to 10% salt, with S. aureus producing golden colonies; they are facultative, growing aerobically or anaerobically between 18 and 40°C. Identification relies on biochemical tests, including catalase positivity, novobiocin sensitivity (to distinguish from S. saprophyticus), coagulase positivity (for S. aureus), and mannitol fermentation positivity (to distinguish from S. epidermidis). Methicillin-resistant strains (MRSA) carry the mec gene within the SCCmec region, encoding penicillin-binding protein 2a (PBP-2a), which has low affinity for beta-lactams, allowing continued cell wall synthesis despite antibiotic exposure. Consequently, MRSA is resistant to nafcillin, oxacillin, methicillin, and cephalosporins .(5)

### Epidemiology

Staphylococcus aureus, involving MRSA, colonizes the mucous membranes and skin, with people serving as the main reservoir. Around 50% of adults are colonized, and 15% persistently carry *S. aureus* in the anterior nares. Higher colonization rates (up to 80%) occur among healthcare workers, IV drug users, diabetics, hospitalized individuals, and immunocompromised individuals. Transmission is mainly through direct contact or fomites .(6)

### Features of S. aureus

Belonging to class Bacilli and family Micrococcaceae, S. aureus can be differentiated from other staphylococci by its golden colonies and positive outcomes for coagulase, deoxyribonuclease, and sugar fermentation tests .(7)

### Cell Wall

The cell wall consists of ~50% peptidoglycan made of NAM and NAG linked via β-1,4 bonds, cross-linked by pentaglycine bridges. Ribitol teichoic acids and lipoteichoic acids are key components, with peptidoglycan also showing endotoxin-like

activity that triggers cytokine release, platelet aggregation, complement activation, and macrophage stimulation. [8]

**Capsules**

Most staphylococcal species produce microcapsules, with 11 serotypes identified. Types 5 and 8 are mainly responsible for human infection, with type 5 frequently isolated from methicillin-resistant Staphylococcus aureus strains. [9]

**Surface Proteins**

S. aureus expresses 24 cell wall–anchored (CWA) proteins, more than other staphylococci. Their expression depends on growth conditions, often induced in iron-deficient environments. CWA proteins are grouped into MSCRAMMs, the G5–E repeat family, 3-helical bundle proteins, and NEAT motif proteins, with MSCRAMMs playing a central role in host adhesion .[10]

**Genetic Materials**

The genome consists of a circular chromosome (~2800 base pairs), transposons, plasmids, and prophages. Resistance genes are located on both chromosomal and extrachromosomal elements, enabling horizontal gene transfer with other Gram-positive species .[11]

**Toxins**

S. aureus produces diverse toxins: cytotoxins (e.g., α-toxin) that form pores and cause inflammation, superantigens that bind MHC-II and induce cytokine release, and enterotoxins/exfoliative toxins that cause toxic shock syndrome, food poisoning, and skin damage. [11]

**Enzymes and Other Components**

Enzymes such as hyaluronidase, lipase, and protease degrade host tissues and aid spread. β-lactamase confers penicillin resistance, while coagulase promotes fibrin clotting, enhancing virulence. [12]

**Pathogenesis of S. aureus**

S. aureus expresses virulence factors enabling survival and severe infections. [13]

**Colonization**

It colonizes skin and mucosa (nasal chamber, axillae, vagina, throat, groin, and GI tract). About 20% are persistent nasal carriers and 30% transiently colonized. Adhesion occurs via MSCRAMMs and other components, while host defenses (IgA, lysozyme, lactoferrin, and antimicrobial peptides) counter colonization. Higher colonization occurs in diabetics, HIV patients, and children. [14]

**Pathogenesis**

Infection usually follows wound exposure. Virulence genes are upregulated upon host contact, triggering inflammation and immune cell recruitment. MSCRAMMs enable adhesion to host compo-nents (fibrinogen, collagen, and fibronectin), which is critical in device-related, bone, and vascular infections. S. aureus forms biofilms and small-colony variants (SCVs) that evade immunity and antibiotics, contributing to persistent infections. It evades host defenses by inhibiting neutrophil chemotaxis, secreting leukocyte toxins, resisting opsonization, and modifying NAM–NAG bonds to resist lysozyme cleavage. [15]

**Pathogenesis of HA-MRSA**

Resistance in *S. aureus* arises from the *mecA* gene, which encodes PBP2A with low affinity for beta-lactams. HA-MRSA strains carry SCCmec elements encoding multiple resistance genes. These strains may cause asymptomatic colonization and thrive in antibiotic-rich environments. Compared with MSSA, HA-MRSA shows longer generation times, increased susceptibility to neutrophils, and lower pathogenicity in mice .[16]

**Pathogenesis of CA-MRSA**

Initially noted in immunocompromised patients in the late 1990s, CA-MRSA appeared as a distinct strain causing severe infections, including fatal pediatric pneumonia in 1997. Unlike HA-MRSA, CA-MRSA carries SCCmec type IV encoding Panton–Valentine leukocidin (PVL), which enhances virulence. [16]

**Clinical Manifestations**

*S. aureus* bacteremia (SAB), whether MSSA or MRSA, commonly arises from vascular catheter infections, pleuropulmonary infections, SSTIs, osteoarticular infections, and infective endocarditis (IE), though ~25% of patients lack a clear focus. Trends shift with infection control, as reductions in catheter-related cases contrast with increases in

SSTI-associated SAB, particularly with USA300 CA-MRSA and in indigenous populations. SAB is categorized as "complicated" or "uncomplicated," influencing diagnosis, treatment duration, and prognosis. Predictors of complicated SAB include community acquisition, persistent fever at seventy-two hours, positive monitoring cultures at forty-eight to ninety-six hours, and systemic skin findings. Mortality varies by infection source: highest in bacteremia without focus (twenty-two to forty-eight percent), IE (twenty-five to sixty percent), and pulmonary infections (thirty-nine to sixty-seven percent), and lower in catheter-related bacteremia (seven to twenty-one percent), SSTIs (fifteen to seventeen percent), and UTIs (ten percent) .[17]

### Antibiotic-Resistant Staphylococcus aureus

### Mechanisms of antibiotic-resistant MRSA

The introduction of penicillin by Alexander Fleming in the 1940s effectively controlled S. aureus infections, but widespread use led to resistance in the 1950s through penicillinase production, which hydrolyzes the β-lactam ring .[7] To overcome this, methicillin, a semi-synthetic penicillin resistant to β-lactamase, was developed in 1959, though it has been later replaced by more stable derivatives such as flucloxacillin, oxacillin, and dicloxacillin. Despite these advances, MRSA has been 1st stated in 1961 by Jevons, and the term "MRSA" continues to be used. β-lactam antibiotics normally target penicillin-binding protein a (PBPa), a bi-functional transglycosylase-transpeptidase that facilitates peptidoglycan synthesis and cross-linking. In MRSA, structural modifications in PBP2a prevent β-lactam binding, leading instead to the formation of a penicilloyl-O-serine intermediate that confers resistance. [11]

The resistance mechanism is mediated via the mecA gene, which encodes PBP2a. Integrated into the chromosomal SCCmec element of methicillin-sensitive S. aureus, mecA spreads through horizontal gene transfer and confers broad resistance to most β-lactam antibiotics, except ceftobiprole and ceftaroline. SCCmec contains 2 major components: the mec gene complex (including mecA and associated regulators) and the ccr gene complex encoding recombinases (ccrA, ccrB, ccrC) that mediate integration and excision of SCCmec into the chromosome. Based on gene composition and recombinase allotypes, SCCmec has been categorized into eight types and various subtypes by the International Working Group on the Staphylococcal Cassette Chromosome elements. [7]

## Vancomycin-resistant S. aureus

### Vancomycin Resistance Development

Vancomycin, a glycopeptide antibiotic presented in 1958, became the first-line treatment for MRSA infections. Resistance was first seen in Enterococci in the 1980s, followed by reduced susceptibility in S. aureus to teicoplanin in Europe. The first VRSA was reported in 2002 in Michigan, USA, with 52 isolates carrying van genes detected globally the same year .[18] According to CLSI, S. aureus is classified as VSSA (MIC below or equal to two micrograms/milliliter), VISA (MIC four to eight micrograms/milliliter), and VRSA (MIC above or equal to sixteen micrograms/milliliter).

### VISA

VISA has been 1st stated in Japan in 1997 with an MIC of 8 μg/ml. It usually develops from heterogeneous VISA (hVISA), which appear vancomycin-susceptible but harbor resistant subpopulations. VISA phenotypes are categorized by increased cell wall thickness, diminished peptidoglycan cross-linking, altered surface proteins, decreased autolysis, and dysfunction of the agr system. Genes such as WalKR, GraSR, and VraSR are implicated, with GraRS mutations affecting capsule biosynthesis, teichoic acid modification, and global regulators like rot and agr. [18]

### VRSA

VRSA resistance is mediated by van gene clusters, first identified in bacteria like Enterococcus, Clostridium difficile, Actinomycetes, and gut flora species. Eleven van clusters have been described: vanA, vanF, vanB, vanD, vanI, vanM (high-level resistance, MIC above 256 micrograms/milliliter), and vanC, vanE, vanL, vanG, and vanN (low-level resistance, MIC 6–8 micrograms/milliliter). The vanA operon, carried on transposon Tn1546, encodes proteins VanS/VanR (two-component regulation) and VanH/VanA/VanX, which alter cell wall precursors from D-Ala-D-Ala to D-Ala-D-Lac, preventing vancomycin binding. Enterococci are the

main reservoir, transferring resistance via conjugative plasmids (Inc18) to S. aureus .[19]

**Clindamycin**

Clindamycin is FDA-approved for the treatment of septicemia, bone, intra-abdominal, gynecological, joint, respiratory, and skin infections, as well as for streptococcal pharyngitis, bacterial vaginosis, acne vulgaris, and severe pelvic inflammatory disease. The IDSA supports intravenous clindamycin for inpatient management of community-acquired and aspiration pneumonia; however, it is not a first-line option. It is widely used in prophylaxis: dentists for endocarditis, surgeons and anesthesiologists per ASHP and IDSA guidelines in operating rooms, and gynecologists in combination regimens for endometritis. It also serves as an alternative to metronidazole for Gardnerella vaginosis. Beyond this, clindamycin is effective in babesiosis, malaria, anthrax, and uncomplicated skin and soft tissue infections, particularly against MRSA, making it a cost-effective and accessible outpatient treatment option .[20]

## Mechanism of Action

Clindamycin is able to block protein synthesis by reversibly binding to the 50S ribosomal subunit. This prevents the creation of peptide bonds. Clindamycin can either be bacteriostatic or bactericidal, depending on the organism, the infection site, and the quantity of the medicine. Clindamycin palmitate must undergo hydrolysis in the gastrointestinal tract prior to absorption; it thereafter distributes extensively but exhibits limited penetration of the meninges, rendering it ineffective for central nervous system infections, with the majority remaining protein-bound in circulation. Metabolized mainly in the liver by CYP3A5 and CYP3A4 into N-desmethyl clindamycin and clindamycin sulfoxide, it reaches peak levels within 60 minutes orally and one to three hours intramuscularly, with a half-life of ~3 hours in adults and ~2.5 hours in kids, and is excreted in urine (major) and inactive metabolites and feces (minor) as active. [21]

**Pharmacodynamics**

Clindamycin acts bacteriostatically by inhibiting microbial protein synthesis, but due to its half-life and short Tmax, it requires dosing every 6 hours to maintain effective levels. A major risk is *Clostridium difficile*-associated diarrhea, which can range from mild to fatal and may occur as much as 2 months following therapy, limiting clindamycin use to serious infections when safer alternatives are unsuitable. It is active vs. gram (+ve) aerobes and both gram (+ve) and (-ve) anaerobes, though resistance may develop through 23S rRNA base modification, with complete cross-resistance to lincomycin and possible cross-resistance with macrolides due to overlapping binding sites. Given regional variations in susceptibility, local antibiograms should be consulted before use .[22]

**Absorption**

Clindamycin has nearly complete oral bioavailability (~90%), with a mean Cmax of 2.50 micrograms/milliliter at 0.75 hours and an AUC of ~11 µg•hr/mL after a 300 mg oral dose. Systemic exposure is much lower with vaginal formulations, being 40–50 times lower with suppositories and only 0.1% of parenteral levels with vaginal cream .[23]

**Volume of distribution**

Clindamycin is extensively disseminated throughout the body, involving bone, but doesn't penetrate cerebral fluid.The volume of distribution was estimated to range from forty-three to seventy-four liters. [23]

**Protein binding**

The protein binding of clindamycin is concentration-dependent, varying from sixty percent to ninety-four percent.It is mostly linked to α-1-acid glycoprotein in the serum. .[23]

**Metabolism**

Clindamycin is metabolized in the liver, predominantly by CYP3A4 and, to a lesser degree, by CYP3A5.2 inactive metabolites were identified: a clindamycin sulfoxide oxidative metabolite and an N-desmethylclindamycin N-demethylated metabolite. [23]

**Route of elimination**

Approximately ten percent of clindamycin's bioactivity is eliminated by urine and 3.6% via feces, while the remainder is excreted as inactive metabolites .[22]

**Half-life**

The removal of The half-life of clindamycin is approximately three hours in adults and 2.5 hours in kids.The half-life is extended to around four hours in the elderly.[22]

**Clearance**

The plasma clearance of clindamycin is predicted to be between 12.3 and 17.4 L/h and is diminished in cases with cirrhosis and modified in those with anemia. [24]

**Detection of Clindamycin Resistance Antibiotic Genes among Staphylococcus**

Clindamycin resistance arises through several mechanisms, including target site modification, drug inactivation, and efflux, mediated by both plasmids and chromosomal mutations. Cross-resistance with lincomycin is complete, and erythromycin-resistant bacteria may rapidly acquire clindamycin resistance. Resistance has been reported in S. aureus (including inducible forms during treatment), S. pneumoniae, group A and B Streptococcus, C. diphtheriae, B. fragilis, Peptostreptococcus spp., and Cutibacterium acnes. Plasmid-mediated resistance via ribosomal methylation confers resistance to macrolides, while adenylation by nucleotidyltransferase, though uncommon, reduces clindamycin activity in staphylococci. Gram-negative organisms like Pseudomonas, Enterobacteriaceae, and Acinetobacter are intrinsically resistant due to poor permeability. Resistance rates in B. fragilis have increased in the U.S. from 3% (1987) to 26% (1997–2004), with some centers reporting up to 44%. Because resistance patterns vary geographically, local susceptibility data are essential, and susceptibility testing may be warranted in severe, recurrent, or refractory infections. C. difficile is usually resistant, while C. perfringens remains mostly susceptible. [25]

**Detection of Clindamycin Resistance Antibiotic Genes among Staphylococcus**

Staphylococcus is a Gram (+ve) bacterium and one of the most frequent human pathogens, causing infections like bacteremia, endocarditis, skin infections, pneumonia, and food poisoning. The widespread use of MLSB antibiotics has led to a growth in resistant Staphylococcal strains. Detection of MRSA is mainly performed by identifying the mecA gene via polymerase chain reaction (PCR), which demonstrates high sensitivity (93.8–100%) and specificity (98.6–100%). [26]

Resistance to MLSB antibiotics is mediated by various mechanisms. The erm genes encode rRNA methylases that methylate the 23S rRNA of the 50S ribosomal subunit, conferring inducible or constitutive resistance to lincosamides, macrolides, and streptogramin B. Additional resistance mechanisms include active efflux pumps encoded by the msrA gene, leading to the MS phenotype. Inducible MLSB (iMLSB) strains appear clindamycin-susceptible in vitro but may develop resistance through treatment, resulting in management failure. Detection of iMLSB phenotypes requires the "D-test," as standard susceptibility methods fail to identify them. Several risk factors contribute to resistance development, including inappropriate antibiotic use, long hospital stays, chronic illnesses, prior catheterization, and close contact with infected patients .[27]

**Prevalence of Clindamycin Resistance of Staphylococcus aureus**

The overall magnitude of inducible clindamycin resistance among S. aureus isolates in this research was 25.7% (17/66), with a higher frequency in MSSA (26.9%) compared to MRSA (21.4%), aligning with findings from Nepal (21.1%). These rates were higher than those reported in Iran (9.3% and 10.4%), Libya (6.3%), Brazil (10.3%), and India (15.4%). However, clindamycin resistance among MRSA (17.6%) was lower compared with reports from Nepal (27.9%), Tanzania (61%), and India (36%). Factors associated with higher frequencies of inducible resistance included male gender, younger age (11–20), single marital status, larger family size, unemployment, urban residency, and clinical risk factors such as recent illness, surgery, wound infection, hospital admission, and chronic diseases. [28]

**PCR for Detection of Clindamycin Resistance Antibiotic Genes among Staphylococcus**

Correct identification and reporting of S. aureus isolates is essential in clinical practice, particularly to differentiate true clindamycin susceptibility in

erythromycin-resistant isolates utilizing the simple D-test, which prevents inappropriate clindamycin therapy. In this research, the occurrence of iMLSB was 23.4%, consistent with global reports showing variability from 3.3% to 43%. Notably, iMLSB resistance in MRSA was 76.4%, much greater than earlier stated ranges of 12.3–35.9%, reflecting an alarming rise in resistance. Although elevated in MRSA, the prevalence fell within the broader 4–68% range observed in MSSA across other studies .[29] These findings underscore the growing challenge of resistance and the need for routine testing.

Molecular analysis revealed the prevalence of erm genes among inducible clindamycin-resistant isolates: ermA (15.62%), ermB (3.12%), and ermC (18.75%), aligning with previously reported ranges of 11–81.9% for ermA and 0.66–44.44% for ermC across different regions. In inducible clindamycin-resistant methicillin-resistant S. aureus isolates, gene occurrence was higher: ermC (73.38%), ermB (13.33%), and ermA (66.67%) .[30] These results emphasize the genetic diversity contributing to resistance and highlight the importance of molecular surveillance to guide appropriate antibiotic use and mitigate the spread of resistant strains.

## Conclusion

This research demonstrates a significant occurrence of inducible clindamycin resistance among S. aureus isolates, particularly MRSA, with a strong association to erm genes. The high rate of iMLSB resistance underscores the risk of treatment failure if clindamycin is prescribed without prior D-testing. Moreover, the molecular detection of erm genes confirms their critical role in mediating resistance and indicates the importance of integrating genetic surveillance into diagnostic protocols. Strengthening antimicrobial stewardship, promoting rational antibiotic use, and applying reliable diagnostic methods are essential strategies to limit the spread of resistant S. aureus strains and improve patient outcomes.

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