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Methicillin Resistant *Staphylococcus aureus* (MRSA): A Comprehensive Review of Pathogenesis, Resistance Mechanisms, Clinical Manifestations, and Therapeutic Strategies

Pooja Kumari[1]; Kunwar Aditi[1]; Dr. Ayesha Fatima[2*]

[1]Pharm D Scholar, Department of Pharmacy Practice, RBVRR Women's College of Pharmacy, Osmania University, Barkatpura, Hyderabad, Telangana, India.
[2]Assistant Professor, Department of Pharmacy Practice, RBVRR Women's College of Pharmacy, Osmania University, Barkatpura, Hyderabad, Telangana, India.

Corresponding Author: Dr. Ayesha Fatima[2*]

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Abstract: Methicillin resistant *Staphylococcus aureus* (MRSA) is a non motile bacterium that frequently colonizes the nose and skin without causing disease. When it enters the body through breaches like cuts or invasive procedures, it can disseminate, causing a wide range of infections, from skin and soft tissue infections (painful nodules, abscesses) to life threatening conditions like pneumonia and endocarditis. Both healthcare associated (HA-MRSA) and community associated (CA-MRSA) strains contribute significantly to a rising global disease burden. Diagnosis of MRSA is achieved through culture and sensitivity testing, Gram staining, quantitative PCR, and antibiotic susceptibility assays. The organism employs multiple resistance mechanisms, including biofilm formation, efflux pumps, and modification of antibiotic targets, a challenge increasingly evident during recent global health crises. The clinical presentation is often characterized by painful erythematous nodules and purulent lesions, frequently accompanied by fever. Severe cases can rapidly progress to necrotizing soft tissue disease. Standard first line therapy relies on agents like vancomycin and daptomycin, with alternatives including linezolid and ceftaroline. However, resistance and drug toxicity complicate management. To combat these issues, novel therapeutic strategies are being developed, including newer antibiotics (e.g., tigecycline, tedizolid), optimized delivery systems (e.g., inhalable vancomycin nanoparticles), and bacteriophage therapy. Core prevention measures meticulous hand hygiene, environmental cleaning, and targeted decolonization remain essential to limit transmission. The increasing prevalence and expanding resistance mechanisms of MRSA underscore the critical need for continued research and robust infection control in the 21st century.

Keywords: *MRSA, Antimicrobial Resistance (AMR), Biofilm Formation, Tigecycline, Bacteriophage Therapy, Vancomycin, Antimicrobial Resistance, AMR, Efflux Pumps, Cephalosporins.*

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I. INTRODUCTION

MRSA is a strain of Staphylococcus aureus that is resistant to methicillin and other related beta lactam antibiotics. It typically lives on the skin or in the nasal passages of healthy people and is harmless. Still, it is capable of causing infections such as pneumonia, skin and soft tissue infections, boils, pimples, abscesses, and endocarditis. [1, 2] This dangerous bacterium can cause severe infections in both hospitals and communities and has emerged as one of the leading causes of illness and death among people globally compared to other infections. [3, 4] It has spread globally, resembling a pandemic pattern. Treating MRSA remains difficult, as the bacteria rapidly adapt to antibiotics and produce protective biofilms that shield them from treatment. Bacteria that have evolved biofilms are more difficult to eliminate than the target free floating (planktonic) bacteria. Planktonic forms develop one thousand times less resistance when compared to bacteria that have developed biofilm. While research on biofilm - breaking compounds, called anti

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biofilm compounds, is still evolving, cationic small molecules have recently been developed that have the ability to disrupt both already evolved biofilm bacteria and also stop their development in multiple pathogens. [4, 5, 6, 7]

The World Health Organisation (WHO) classifies it as a high priority pathogen due to its resistance to multiple antibiotics. These biofilms limit antibiotic entry through mucopolysaccharide layers, shelter inactive, drug resistant cells, and promote gene transfer that spreads resistance[8]. The overuse and misuse of antibiotics are factors in the development of bacterial resistance. The COVID - 19 pandemic has accelerated the rise of antimicrobial resistance (AMR). According to a Lancet study, drug - resistant bacterial infections resulted in approximately 1.27 million deaths globally in 2019. If current trends continue, AMR could claim up to 10 million lives each year by 2050 more than cancer and inflict a devastating economic toll, with an estimated global loss of around $120 trillion due to reduced productivity and deaths in both humans and livestock. [9]

Staphylococcus aureus can cause a wide range of infections, and antibiotics are the main line of defence. These drugs combat bacteria by disrupting essential cellular processes, including cell wall synthesis, protein production, DNA replication, chromosomal mutations, developing new genes, and altering gene expression. Bacteria become resistant to antibiotics in several ways: by changing the drug's target, breaking down the antibiotic with special enzymes, pumping the drug out of their cells, or blocking it from getting in at all. The failure of therapies has increased medication costs. These antibiotics target specific cellular mechanisms that include the synthesis of DNA, the synthesis of the cell wall, transcription, and translation [10, 11]. In contrast, a particular strain is susceptible to some drugs, and one additional challenge in therapy is the emergence of intermediately resistant strains, such as Vancomycin Intermediate Staphylococcus aureus (VISA), which require longer therapy durations compared to completely resistant cases and can lead to serious infections. [1, 10,12] . Reports of reduced glycopeptide sensitivity compromise the activity of vancomycin and teicoplanin. Researchers have developed many new antibiotic therapies to treat infections caused by MRSA[12, 13].Current treatment options for MRSA include linezolid, vancomycin, telavancin, and beta - lactam antibiotics such as cephalosporins [2,3]. Ceftaroline is as effective as first - line agents in treating CAP, and among test subjects, ceftaroline fosamil showed a 91.6% success rate[14, 15]. Vancomycin and daptomycin are first - line monotherapies; however, reduced sensitivity and resistance often lead to treatment failure. Combination therapy of vancomycin and daptomycin with other susceptible antimicrobials, especially β lactam antibiotics like ceftaroline fosamil, may enhance efficacy against MRSA through the seesaw effect, reduce treatment failure, and lower mortality. [10, 16, 17]. It shows the need for the development of new therapies for the future. A few drugs, such as new generation tetracyclines, Tedizolid, Delafloxacin, daptomycin, oxazolidinones, and combination drugs with vancomycin, anti virulence agents, and bacteriophage therapy, are under study for their use against MRSA. [3, 10, 18]. Laurocapram is an excipient used as a transdermal enhancer, which has improved the efficacy of cephalosporin antibiotics against MRSA. Overuse or non adherence to prescribed antibiotics has led to resistance to many antibiotics, like methicillin and vancomycin (fully or partially). It has made it difficult to treat the infection.

Previously, hospital acquired pneumonia was predominant, but community acquired pneumonia has become more common nowadays.[2]. Morbidity and mortality have increased in both hospital acquired MRSA and community acquired MRSA. [19] . To enhance the treatment of MRSA pneumonia and target the lungs more directly, researchers developed a new route of administering vancomycin as an inhalable dry powder, which is attached to a magnetic nanoparticle core with lactose coating. This formulation is produced using a mini spray drying technique, allowing for effective treatment of MRSA pneumonia. [20]. The mecA gene, which makes MRSA resistant to beta lactam antibiotics, and reduces the effectiveness of daptomycin by lowering toxin levels, which helps the bacteria weaken the drug. [21]

Researchers have found that the substances released by fat derived stem cells can kill harmful bacteria, which is a new and natural way to fight antibiotic resistant infections. [22]. The incidence of superinfected dermatoses in patients with existing skin conditions has increased, making them more susceptible to infections such as S. aureus. Given the rise in MRSA infections, prioritizing treatment strategies is essential for optimizing clinical outcomes.[23]

A recent study found that the natural compound Kuraridin (which is a flavonoid commonly found in the Sophora flavescens plant) can reduce MRSA's ability to attach to cells, enter skin cells, invade skin cells, and form protective biofilms even at very low and safe doses. In tests using a *Caenorhabditis elegans* infection model, Kuraridin offered protection against MRSA without causing harm. These results suggest that Kuraridin could be a promising new way to fight MRSA by weakening the bacteria, rather than relying only on traditional antibiotics. [24]

Recent studies suggest that Myrtenol, a natural compound, shows promise in fighting drug - resistant MRSA infections. It not only slows MRSA growth but also reduces its ability to form protective biofilms, and also enhances the effectiveness of antibiotics by weakening MRSA's defences, suggesting it could be a useful natural treatment or given along with antibiotics. [25]

Dalbavancin, oritavancin, ceftobiprole, and ceftaroline fosamil are newly introduced drugs; therefore, therapeutic drug monitoring (TDM) becomes important. TDM helps doctors administer the correct dosage and avoid harmful side effects. But using TDM can be a little challenging as it needs special methods and trained people to do it properly. [15]. A few more new treatment options include combination therapy, phage therapy, monoclonal antibodies, and silver based nanoparticles. These nanoparticles show strong antibacterial effects against S. aureus by damaging cell membranes,

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generating reactive oxygen species (ROS), and disrupting vital cell functions. [26]

S. aureus also worsens a few conditions, such as Chronic obstructive pulmonary disease (COPD) so there must be a special drug that can eradicate the worsening of COPD due to S. aureus. Once such an agent is doxifluridine which enhances the efficacy of antibiotics and effectively inhibits the growth of S. aureus. [33]. There are a few studies conducted on AD-MSCs (Adipose derived mesenchymal stem cells), or simply, they are fat tissue derived stem cells, which can differentiate into various types of tissues, have shown marked results in combating antimicrobial resistance. [22]

➢ *Microbiological Aspects and Identification [27,28,29]*

Staphylococci are species of the Micrococcaceae family and are distinguished by their unique staining characteristics and shape. The genus Staphylococcus is significant in clinical microbiology because it contains more than 30 species that are known to cause illness in people. These organisms may be distinguished from other cocci and are easier to identify in lab settings because they appear as Gram - positive cocci grouped in clusters that resemble grapes when stained with Gram stain.

Typically, Staphylococcus species have a diameter of one micrometre and are not able to move because they lack flagella. They can flourish in a variety of settings since they grow well in both aerobic and facultatively anaerobic environments. It is noteworthy that Staphylococcus aureus is extremely tenacious, able to endure heat, dryness, and other adverse circumstances, allowing it to live for long periods of time on both human skin and inanimate surfaces.

➢ *Identification Features for S. aureus [27,28,29]*

Table 1 Identification Features of S. aureus

S. No	Identification Feature	Characteristics
1	Coagulase Production	Produces coagulase enzyme; differentiates S. aureus from other bacteria, especially catalase negative ones.
2	Protein A	Surface protein A present; important for identification.
3	DNase Production	Produces DNase enzyme, which breaks down DNA.
4	Sugar Fermentation	Ferments mannitol, glucose, sucrose, maltose, and lactose; mannitol fermentation is specific to S. aureus.
5	Latex Agglutination Test	Detects Protein A and clumping factor to differentiate S. aureus from other species.
6	Blood Agar Characteristics	Forms golden yellow β - hemolytic colonies; other species show small white non - hemolytic colonies.
7	Other Biochemical Tests	Urease positive, methyl red positive, indole negative, reduces nitrates to nitrites, and hydrolyzes gelatin.

II. EPIDEMIOLOGY

According to the World Health Organization (WHO), antibiotic resistance ranks amongst the greatest public health challenges faced in the 21st century. If nothing changes, by 2050, antimicrobial resistance could kill around 300 million people. This shows the importance of the urgent need for global action. The decline in antibiotics for treating these multi - resistant infections has left healthcare systems dangerously exposed. [1, 10]

Approximately 2 billion people globally are carriers of some form of Staphylococcus aureus, and among them, 53 million (2.7 %) people are thought to carry MRSA. It is identified as one of the six leading pathogens causing mortality as of 2019, with around 1,00,000 deaths reported due to MRSA. [1]

III. PATHOGENESIS

The pathogenesis of *Staphylococcus aureus* is a sophisticated process that transforms a common commensal bacterium into a formidable pathogen. This journey begins when the bacteria breach the host's primary physical barriers, typically entering through wounds, surgical incisions, or minor skin abrasions. Once inside, *S. aureus* initiates colonization and adhesion, anchoring itself to various host tissues using specialized surface proteins. While it frequently resides on the skin and nasal passages, its ability to adhere to the endocardium of the heart, bone matrix, and soft tissues allows it to establish deep seated infections.

To survive the host's immediate immune response, *S. aureus* employs several highly evolved evasion strategies. One paradoxical mechanism involves SigB - deficiency. While the SigB regulatory protein typically helps the bacteria manage environmental stress, recent studies suggest that a deficiency in this protein can actually enhance virulence and promote extracellular survival, despite making the bacteria more sensitive to certain host defenses. Furthermore, the bacteria utilize Protein EsxB to facilitate internalization into epithelial cells, such as HaCaT cells, effectively hiding from the circulatory immune system. The bacteria also manipulate host signalling through the increased expression of CD55. By forcing the host cell to overexpress this decay accelerating factor, *S. aureus* essentially "camouflages" the infected cell, signalling the complement system to stand down. However, the host body fights back by increasing the expression of UL16 binding proteins, which act as a distress signal to alert the immune system to the infected cell's presence.

As the infection progresses, *S. aureus* releases a potent arsenal of virulence factors, most notably alpha toxins and Panton Valentine leucocidin (PVL). These endotoxins are

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designed to punch holes in host cell membranes and destroy white blood cells, leading to extensive tissue necrosis. The ultimate consequences of this bacterial invasion are diverse and severe; depending on the site of colonization, the infection can manifest as localized skin and soft tissue infections, or escalate into life threatening conditions such as pneumonia, endocarditis (heart valve infection), osteomyelitis (bone infection), and systemic sepsis [30].

IV. BACTERIAL RESISTANCE MECHANISMS TO ANTIBIOTICS

➢ *Cellular Resistance Mechanisms*

Bacteria employ four primary strategies at the cellular level to neutralize or bypass the effects of antibiotics:

- Efflux Pump Mechanisms: *S. aureus* utilizes specialized membrane proteins known as efflux pumps to actively transport toxic substances, including antibiotics, out of the cell before they can reach their target site [11]. This reduces the intracellular concentration of the drug, leading to Antimicrobial Resistance (AMR). These pumps are categorized into five major families: Major Facilitator Superfamily (MFS), Small Multidrug Resistance family (SMR), Resistance Nodulation Cell Division family (RND), ATP - Binding Cassette (ABC) transporters and Multidrug And Toxic compound Extrusion family (MATE) [11].

- Enzyme - Mediated Resistance: One of the most potent defenses is the production of enzymes that chemically dismantle or modify antibiotics. Through processes like acetylation, phosphorylation, and adenylation, the bacteria change the chemical structure of the drug so it can no longer bind to its target [11]. A prime example is β Lactamase mediated resistance, where the bacteria produce enzymes that hydrolyze the structure of penicillin's, cephalosporins, and carbapenems, rendering them completely inactive [11].

- Reduced Membrane Permeability: For an antibiotic to be effective, it must pass through the bacterial cell envelope. While this is a significant challenge in Gram negative bacteria due to their extra outer membrane, *S. aureus* can also limit drug entry by altering porin channels [11]. By changing the structure or selectivity of these channels, the bacteria effectively "lock the door," preventing the drug from reaching the cytoplasm [11].

- Target Site Protection and Modification: Bacteria can survive by ensuring the drug has nothing to "grab" onto:

✓ Protection: Some bacteria produce "shielding" proteins that block the drug's access to the target site. This is commonly seen with tetracyclines (via Tet proteins), fluoroquinolones (via Qnr proteins), and fusidic acid (via FusB/C) [11].
✓ Modification: Alternatively, the bacteria may genetically alter the structure of the target site itself. If the shape of the target changes, the antibiotic loses its affinity and can no longer interfere with vital bacterial processes [11].

Table 2 Cellular Resistance Mechanism

Types of resistance	Mechanisms for resistance
Efflux mechanisms	Antibiotics are effluxed out of the cell via efflux pumps.
Enzyme - mediated antibiotic resistance	Bacteria develop a few enzymes that modify the chemical nature of the drug and reduce the ability of antibiotics to bind to their target site.
Reduced membrane permeability	They reduce the permeability of antibiotics into the cell by altering the cell membrane.
Protection of target site	Bacteria protect their drug - binding site such that antibiotics cannot bind to their target sites.
Target site modification	The bacteria change the structure of drug - binding sites.

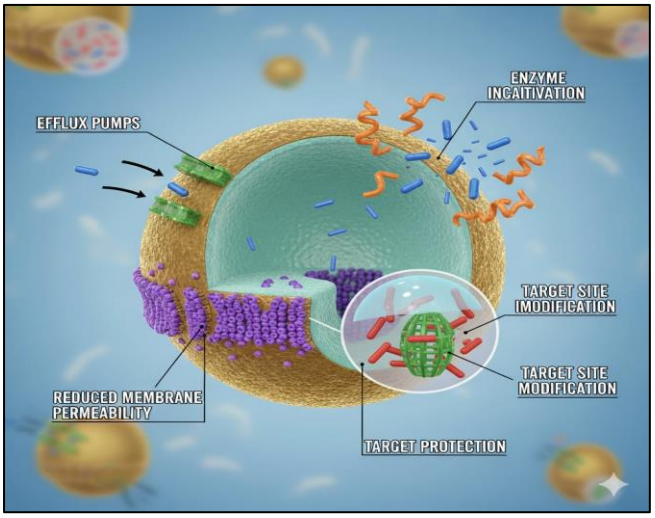

Fig 1 Types of Resistance Mechanism in MRSA

➢ *Biofilm Formation: The Shield of MRSA:*

The formation of biofilms is perhaps the most significant factor in the spread of Methicillin - resistant *S. aureus* (MRSA) and its resistance to treatment [8]. A biofilm is a complex colony of bacteria encased in a self secreted extracellular polymeric substance (EPS). Biofilms are implicated in up to 80% of human infections, particularly those involving medical implants such as catheters, heart valves, and joint prostheses [38]. They are also major drivers of chronic conditions like endocarditis and osteomyelitis [38].

- *Mechanisms of Biofilm Resistance:*

Biofilms provide resistance through several layers of defense:

✓ Physical Barrier: The mucopolysaccharide layer restricts the penetration of antibiotics into the colony [8].

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- ✓ Metabolic Inactivity: Cells in the deeper layers of the biofilm are metabolically inactive (persister cells), making them intrinsically resistant to drugs that target active growth processes [8].
- ✓ Genetic Exchange: The high density of cells in the matrix facilitates horizontal genetic transfer, allowing resistance genes to spread rapidly among the population [8].

- *The Process of Biofilm Development:*

Biofilm development is a multi - step process involving:

- ✓ Adhesion: Bacteria attach to surfaces (biotic or abiotic) using Microbial Surface Components Recognizing Adhesive Matrix Molecules (MSCRAMMs) [7]. Key proteins include ClfA and ClfB (which bind fibrinogen), Bbp (bone sialo binding), and Cna (collagen binding) [7]. Additionally, alpha enolase facilitates binding by coating plasminogen [7].
- ✓ Maturation: After initial attachment, the colony grows and matures by secreting the EPS matrix [7].
- ✓ Dispersal: Finally, bacteria detach from the biofilm to colonize new sites within the host.

➢ *Possible Health Effects: [31, 32]*

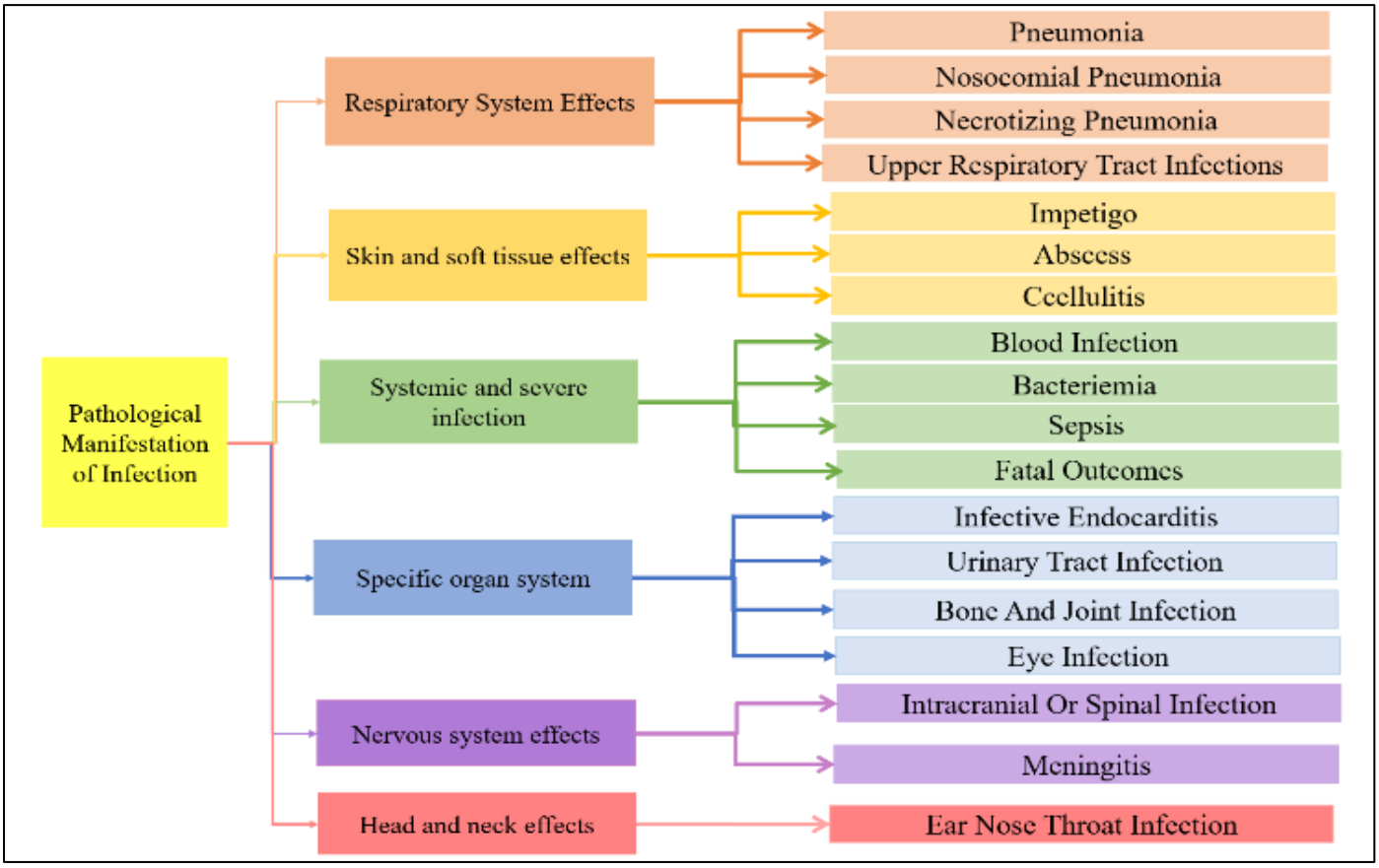

Fig 2 Pathological Manifestation of MRSA Infection

V. CLINICAL MANIFESTION OF MRSA INFECTION

The clinical presentation of MRSA, is highly variable and primarily dictated by the anatomical site of infection. Pathogenesis typically initiates via a breach in the dermal barrier such as a laceration, abrasion, or surgical wound which serves as a portal of entry for the pathogen.

➢ *Primary Cutaneous Presentation:*

Initial MRSA pyoderma often manifests as localized inflammation characterized by erythema, edema, and significant tenderness. Key clinical features of these skin and soft tissue infections (SSTIs) include: Lesions often present as indurated, painful nodules or erythematous patches. Accumulation of purulent material (pus) or serous fluid is common, frequently progressing to a furuncle (boil) or abscess. Affected areas typically exhibit localized hyperthermia (warmth to the touch). Mild infections may be accompanied by a low grade fever and general malaise.

Due to their rapid onset and inflammatory appearance, these lesions are frequently misdiagnosed by patients as arachnid bites. Without prompt clinical intervention, these localized infections can escalate rapidly.

➢ *Secondary and Systemic Symptomatology:*

Beyond localized abscesses, MRSA can present with a constellation of secondary symptoms. These may include pruritus (itching), burning sensations, and the formation of fluid filled bullae that may eventually develop a honey coloured crust. As the infection progresses or disseminates,

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patients may experience systemic toxicity characterized by: Rigors (chills) and high - grade fever**,** Gastrointestinal distress (nausea)**,** Neurological symptoms (dizziness and syncope), Marked asthenia (weakness) and skin dimpling (peau d'orange).

➢ *Severe and Life - Threatening Complications:*

In the most aggressive manifestations, such as necrotizing soft tissue infections (NSTIs), the clinical trajectory becomes life threatening. These cases necessitate immediate surgical and pharmacological intervention.[35]

Table 3 Sign and Symptoms of MRSA Infection

Signs	Symptoms
Dermal Signss	Rapidly spreading erythema, crepitus (crackling sensation under the skin), blackened necrotic tissue (eschar), and foul smelling gray discharge (dishwater pus).
Sensory Signs	Extreme pain (often out of proportion to physical findings) followed by localized anesthesia (numbness) due to nerve destruction.
Systemic Signs	Tachycardia, hypotension, and septic shock.

VI. DIAGNOSIS

The identification of Staphylococcus aureus and the subsequent detection of methicillin resistance require a multi step laboratory approach, ranging from traditional biochemical assays to advanced molecular diagnostics.

- Specimen Collection and Initial Identification: The diagnostic process begins with the collection of clinical isolates from the suspected site of infection. Validated specimens include purulent discharge, wound swabs, whole blood, urine, respiratory secretions (sputum), and anterior nares swabs for colonization screening [1, 27].
- Gram Stain Kinetics: Microscopic examination typically reveals Gram - positive cocci arranged in characteristic grape like clusters [27].
- Catalase Testing: This biochemical assay differentiates *Staphylococcaceae* from *Streptococcaceae*. The presence of the catalase enzyme in *S. aureus* facilitates the rapid catalytic decomposition of hydrogen peroxide into water and oxygen, evidenced by immediate effervescence ($2H_2O_2 \rightarrow 2H_2O + O_2$) [27, 29].
- Coagulation Assay: *S. aureus* is distinguished by the production of the coagulase enzyme, which converts soluble fibrinogen into insoluble fibrin, resulting in visible clot formation in rabbit plasma [28].
- Identification of Methicillin Resistance (MRSA): Once *S. aureus* is confirmed, determining the resistance profile is critical for therapeutic stewardship.

✓ Latex Agglutination for PBP2a: This rapid diagnostic test detects the presence of Penicillin - Binding Protein 2a (PBP2a). This protein, encoded by the *mecA* gene, has a low affinity for beta lactam antibiotics, serving as the primary mediator of resistance against oxacillin and other penicillin's [1, 27, 28].

✓ Quantitative PCR (qPCR): For accelerated clinical decision making, real time PCR is employed to detect specific genetic markers, such as the *mecA* or *mecC* genes, allowing for the rapid identification of MRSA strains directly from clinical samples [1].

- Antimicrobial Susceptibility Testing (AST): Final therapeutic protocols are guided by standardized antibiotic sensitivity testing. This ensures the efficacy of the chosen pharmacological intervention and monitors the emergence of multidrug resistant (MDR) patterns within the isolates [27, 28].

VII. TREATMENT

For the treatment of MRSA, first - line options include intravenous vancomycin or daptomycin. If the strain is susceptible, oral or intravenous trimethoprim - sulfamethoxazole or clindamycin may be used. Alternative agents consist of ceftaroline, linezolid, or telavancin. For acute bacterial skin and skin structure infections, dalbavancin, oritavancin, and tedizolid are also effective choices. [37]

➢ *Treatment Approaches for Mrsa*

The choice of antimicrobial agents to treat both coagulase positive and coagulase negative staphylococcal infections is usually problematic because of the prevalence of multidrug resistant strains. Staphylococcus is resistant to most of the antibiotics, such as β lactams, aminoglycosides, fluoroquinolones and, (to some extent, resistance to glycopeptides has increased in the last twenty years) and is the most important cause of nosocomial infection worldwide. Although MRSA strains (40–50% of nosocomial isolates in the United States) are resistant to β lactamase resistant penicillins (oxacillin, nafcillin, cloxacillin, dicloxacillin) and to cephalosporins, resistance to β lactamase resistant penicillins in the coagulase - negative staphylococci (CoNS) is even higher (70–80%).[27]

➢ *Vancomycin*

Vancomycin is a complex branched, tricyclic, glycopeptide antibiotic first derived in 1956 from the bacterium Streptococcus orientalis found in soil of Indonesia and India. It is used to treat and prevent various bacterial infections caused by gram -positive bacteria, such as Methicillin Resistant Staphylococcus aureus (MRSA).[39]

- MOA: The mechanism of action of Vancomycin and other glycopeptide antibiotics is binding to the terminal dAladAla moiety of uncross linked Lipid II (undecaprenyl-diphospho-N-acetylmuramoyl-[N-acetylglucosamine]-l-alanyl-γ-d-glutamyl-l-lysyl-d-alanyl-d-alanine), an intermediate in the peptidoglycan layer maturation process. This binding inhibits the activity of penicillin binding proteins (PBPs) to cross link Lipid II into mature peptidoglycan and thus compromises the

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integrity of the cell envelope, resulting in osmotic stress and cell bursting this inhibiting cell wall biosynthesis.[40]

- Toxicity: The Vancomycin has very high systemic toxicity. At elevated concentrations (if serum concentrations exceed 60mg/l), it causes nerve related hearing loss (it may be permanent). The risk of renal damage also increases with elevated concentrations. Other ototoxicity and nephrotoxic drugs like aminoglycosides must be administered with caution. [41]

- Adverse Effects: The adverse effects of vancomycin persist even in the latest highly purified formulations. Most common adverse effects are Red man syndrome, ototoxicity, nephrotoxicity, fever, chills and phlebitis at the site of infusion, hypersensitivity reactions in up to 5% of individuals (this include maculopapular diffuse erythematous skin rashes). Some effects can be minimized by modifying mode of administration and through the use of long infusions (>60 min) Nephrotoxicity is now rare because of availability of highly purified Vancomycin preparations. [42]

Vancomycin can cause two types of hypersensitivity reactions, the red man syndrome and anaphylaxis. Red Man Syndrome (RMS) is an infusion - related hypersensitivity reaction unique to vancomycin. It occurs due to non–IgE - mediated degranulation of mast cells and basophils, leading to the histamine release. Symptoms usually appear within 4–10 minutes of starting or soon after completing the infusion and the symptoms include pruritus, erythematous rash on the face, neck, and upper torso, and sometimes hypotension, angioedema, chest pain, dyspnea, or fever. RMS is dose - and rate - dependent, with younger patients (<40 years) being more susceptible. Slow infusion over ≥60 minutes and antihistamine premedication can help prevent it. Red man syndrome was in the past attributed to impurities found in vancomycin preparations, earning the drug the nickname 'Mississippi mud'. But reports of the syndrome persisted even after improvements in the compound's purity. [43]

- Vancomycin Resistance: The extensive use of antibiotics has inevitably led to the emergence of resistant bacterial strains. Vancomycin is primarily utilized for infections caused by Staphylococcus aureus and other Gram - positive organisms such as streptococci and enterococci, particularly when the resistance to β - lactam antibiotics is present. One of the major challenges in clinical therapy has been the development of methicillin - resistant Staphylococcus aureus (MRSA), which evolved after prolonged exposure to various penicillin derivatives such as Methicillin. Although vancomycin has remained effective against MRSA, the emergence of vancomycin - resistant strains has become a growing concern. Resistance to vancomycin most commonly originates from enterococcal species, known as vancomycin - resistant enterococci (VRE). These organisms possess a van gene cluster that alters the target site of the drug by replacing the terminal D - alanyl - D - alanine in the peptidoglycan precursor with D - alanyl - D - lactate. This structural modification reduces vancomycin's ability to bind to its target, thereby diminishing its inhibitory effect on cell wall synthesis. When this resistance determinant is transferred from enterococci to Staphylococcus aureus, the resulting strain is referred to as vancomycin - resistant Staphylococcus aureus (VRSA). Such infections pose significant therapeutic challenges and often necessitate the use of alternative antimicrobial agents. [44]

➢ *Daptomycin*

Daptomycin is a cyclic lipopeptide antibiotic produced by Streptomyces roseosporus. It exhibits potent activity against a wide range of Gram - positive pathogens, including methicillin - resistant Staphylococcus aureus (MRSA) and vancomycin - resistant enterococci (VRE). It is used in several FDA approved as well as off label clinical conditions. FDA - Approved Indications include Bacteraemia caused by Staphylococcus aureus in adults, including cases associated with right - sided infective endocarditis. Bacteraemia due to S. Aureus in paediatric patients. Off - Label Indications includes Vancomycin - resistant enterococcal (VRE) infections. Osteomyelitis and septic arthritis caused by MRSA. [45]

- MOA: Daptomycin is a cyclic lipopeptide antibiotic which is composed of 13 amino acids and a decanoyl side chain, that contributes to its unique antibacterial activity and novel mechanism of action. It acts by inserting its lipid tail into the bacterial cell membrane, leading to membrane depolarization and potassium ion leakage. This disrupts vital processes such as DNA, RNA, and protein synthesis, ultimately causing cell death. Daptomycin shows rapid bactericidal action against both MRSA and MSSA, achieving over 99.9% kill within an hour, and remains effective even against stationary phase and high - density bacterial populations. [46]

- Adverse Effects: In adult patients treated for Staphylococcus aureus bacteraemia or endocarditis with daptomycin (6 mg/kg), the most commonly reported adverse effects occurring in over 5% of patients include the systemic infections such as sepsis and bacteraemia, along with abdominal or chest discomfort, swelling, throat irritation, itching, and excessive sweating. Other commonly seen adverse effects are difficulty sleeping, elevated creatine phosphokinase (CPK) levels, and increased blood pressure. [47]

- Daptomycin Non-Susceptibility: The term "non-susceptibility" is preferred over "resistance" for daptomycin, according to CLSI (2016) guidelines, S. Aureus isolates with a daptomycin MIC <1 mg/L are considered susceptible, while those with MIC >1 mg/L are regarded as non - susceptible. Although rare, daptomycin non - susceptible strains have been reported in patients treated with daptomycin, other antibiotics, and even in the untreated cases. Proposed mechanisms for reduced susceptibility include increased positive surface charge of the bacterial membrane, altered membrane fluidity due to fatty acid changes, enhanced carotenoid pigment, and the higher teichoic acid synthesis. Genetic studies reveal that multiple mutations affecting cell membrane homeostasis

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contribute to this phenomenon. These mutations can differ between in vitro and clinical isolates. Non-susceptible strains often display more fluid membranes, elevated lysyl - phosphatidylglycerol content, and higher transmembrane potential compared to the susceptible ones.[48]

➢ *Clindamycin*

Clindamycin is a semi synthetic antibiotic belonging to the class lincosamide, it is developed from the parent compound lincomycin, its name derived from Lincoln, Nebraska, where it was first discovered from Streptomyces lincolnensis found in the soil .it has narrow spectrum of activity and is effective against gram positive cocci and bacilli and gram - negative bacilli. And also effective against protozoans, so it has been also used in treatment of toxoplasmosis, malaria and babesiosis. Clindamycin is also used topically for acne vulgaris. [49]

- MOA: Clindamycin inhibits bacterial protein synthesis by binding reversibly to the 50S subunit of the ribosome, thereby blocking the transpeptidation step and preventing peptide bond formation. This interference stops the elongation of the polypeptide chain, suppressing the bacterial growth. Depending on the drug concentration, infection site, and susceptibility of the organism, clindamycin may act as either bacteriostatic or as bactericidal. [50]

- Resistance: Resistance to macrolides, lincosamides, and streptogramin antibiotics can occur through several Mechanisms. These mechanisms include mutations at the drug target site, chemical modification of the binding site by specific enzymes, enzymatic inactivation of the drug itself, and active efflux of the antibiotic out of the bacterial cell. [51] Resistance to clindamycin commonly occurs from the point mutations in the 23S rRNA component of the 50S subunit, which reduce the antibiotic's binding affinity. Because the macrolides, lincosamides, and streptogramin B contain overlapping ribosomal binding sites, cross-resistance can occur among these drug classes. [50]

➢ *Linezolid*

Linezolid belongs to the class oxazolidinones it is indicated in the treatment of nosocomial and community acquired pneumonia, complicated and uncomplicated skin and skin structure infections and vancomycin resistant Enterococcus infections. The drug is also indicated for use in complicated skin infections and nosocomial pneumonia caused by methicillin resistant Staphylococcus aureus, concurrent bacteraemia associated with vancomycin resistant Enterococcus faecium and concurrent bacteraemia associated with community acquired pneumonia caused by penicillin susceptible Streptococcus pneumoniae.

Linezolid is administered at the same dose either intravenous (IV) or oral with the 100% bioavailability after oral administration. [52]

- MOA: Linezolid, the first oxazolidinone antibiotic. It works by blocking bacterial protein synthesis (i.e.) It binds to the 23S rRNA of the 50S ribosomal subunit, preventing the formation of the 70S initiation complex needed for the translation. As a result, bacterial protein production is stopped, stopping their growth. Linezolid acts as a bactericide against the streptococci and as a bacteriostatic against staphylococci and enterococci. [53]

- Resistance: In MRSA, the resistance to linezolid usually occurs due to a mutation in the 23S rRNA, which causes reduce in the drug's ability to bind to the ribosome. Another mechanism involves a methyltransferase enzyme produced by the CFR (chloramphenicol–florfenicol resistance) gene. This gene, located on a plasmid, and it can be transferred between staphylococcal strains, causing the resistance to spread easily. [53]

➢ *Trimethoprin-Sulfamethoxazole*

Methicillin resistant Staphylococcus aureus (MRSA) is a major pathogen responsible for numerous skin and soft tissue infections (SSTIs), for Management of these infections' oral antibiotic such as trimethoprim–sulfamethoxazole (TMP-SMX) is used. [54] Sulfamethoxazole and trimethoprim, commonly known together as co-trimoxazole. It is widely used to treat a variety of bacterial and parasitic infections such as Urinary tract infections (UTIs), Acute otitis media (middle ear infections), Acute exacerbations of chronic bronchitis, Shigellosis, (a bacterial infection affecting the intestines), Pneumocystis jirovecii pneumonia (PJP)(, particularly in immunocompromised individuals), Traveler's diarrhea, Toxoplasmosis. Hence, co-trimoxazole remains a valuable antimicrobial agent due to its broad spectrum of activity and effectiveness in both common and opportunistic infections. [55] The optimal synergistic effect of trimethoprim and sulfamethoxazole occurs at a ratio of 1:20. To maintain this balance, formulations are produced in a fixed 1:5 ratio of trimethoprim to sulfamethoxazole, ensuring both drugs reach ideal serum levels for maximum therapeutic effectiveness. [56]

- MOA : Sulfamethoxazole, a sulphonamide antibiotic, it inhibits bacterial folate synthesis by competing with the para aminobenzoic acid (PABA) and blocking the enzyme dihydropteroate synthase. Trimethoprim, on the other hand, inhibits the dihydrofolate reductase thus preventing the conversion of dihydrofolate to tetrahydrofolate, an essential cofactor for DNA and protein synthesis. When this combination is used together, trimethoprim and sulfamethoxazole produce a synergistic effect by blocking two consecutive steps in the folate pathway, making the combination bactericidal rather than only bacteriostatic. [57]

- Resistance: Trimethoprim (TMP) inhibits bacterial folic acid synthesis by blocking dihydrofolate reductase (DHFR). Resistance mainly occurs through the acquisition of alternative DHFR enzymes encoded by dfr genes, which make TMP ineffective. These genes are often found within integrins and are linked to ISCR1 elements thus promoting their spread. Combined with Sul

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genes, they contribute to trimethoprim sulfamethoxazole (TMP-SMX) resistance in various bacteria. [58]

➢ *Rifampin*

Rifampin belongs to the rifamycin class of antibiotics that is a semisynthetic antibiotic derived from Amycolatopsis rifamycinica. [74]Commonly used along with the other drugs to treat tuberculosis and also other antibacterial infections. It is available under brand names like Rifadin and Rimactane, and is classified as an antitubercular agent. [59, 60]

- MOA: Rifampin acts as a bactericidal antibiotic by targeting the DNA dependent RNA polymerase (RNAP) enzyme in the bacteria. It binds to RNAP and blocks the initial stages of RNA synthesis thereby preventing bacterial cells from producing essential proteins. Because rifampin specifically acts on bacterial RNAP and not the human enzyme, it causes minimal harm to human cells.[61]

- Resistance: Rifampicin resistance in MRSA usually occurs due to mutations in the rpoB gene, which encodes the β subunit of RNA polymerase that is the target site of rifampicin. These mutations can alter the rifampicin binding region (known as the rifampicin resistance determining region, RRDR) and prevent the drug from attaching effectively. Specific substitutions such as H481N, I527M, and occasionally K579R were identified in the resistant MRSA strains (especially the ST612 MRSA IV). These genetic changes reduce the antibiotic's binding affinity that leads to the high level resistance while allowing the bacteria to continue normal RNA synthesis. [62]

➢ *Quinupristin - Dalfopristin*

Quinupristin - dalfopristin is the first injectable streptogramin antibiotic with 30:70 ratio which is effective against Methicillin Resistant staphylococcus aureus MRSA, vancomycin resistant Enterococcus faecium (VREF), and also other Gram positive bacteria, but not E. Faecalis. It is bactericidal for staphylococci and streptococci and bacteriostatic for E. Faecium. [63] Dose: 7.5 mg/kg IV every 8–12 hours.[63]

Streptogramins are produced by Streptomyces species and they consist of two components that is group A (dalfopristin) and group B (quinupristin). Individually, both are bacteriostatic, but together they act synergistically to become bactericidal against many gram positive bacteria. Dalfopristin (Group A) binds to the 50S ribosomal subunit and blocks substrate binding at the peptidyl transferase center, inhibiting the early phase of protein elongation. Quinupristin (Group B) binds nearby and prevents peptide bond formation, stopping the polypeptide chain from extending and causing premature release of incomplete proteins. The binding of dalfopristin alters the ribosomal structure, enhancing the quinupristin's action, this synergistic interaction results in strong inhibition of the protein synthesis. [64]

- Adverse Effects: Nausea, vomiting, diarrhea, rash, myalgia, arthralgia, venous irritation, mild hyperbilirubinemia. It also inhibits CYP3A4, increasing levels of some drugs. [63]

VIII. APPROVED, NEW AND EMERGING THERAPIES FOR MRSA

➢ *Cephalosporins*

Cephalosporins are the antibiotics belonging to the class Beta lactams that are effective against various gram positive and gram negative bacterial infections. They are available both as oral and parenteral formulations. [65]

➢ *Ceftaroline Fosamil*

Ceftaroline is a fifth generation cephalosporin that is approved by the FDA in 2010 for treating the community acquired pneumonia and acute bacterial skin infections. It is the only cephalosporin effective against multidrug resistant Staphylococcus aureus, such as the MRSA, heteroresistant vancomycin intermediate S aureus (hVISA), and vancomycin resistant S aureus (VRSA). [66] Ceftaroline fosamil (CPT-F) is approved for treating the MRSA related acute bacterial skin and skin structure infections. however, it is not indicated for the bloodstream infections. [66] Ceftaroline and ceftobiprole are considered to be effective as vancomycin or daptomycin for the treatment of MRSA bloodstream infections. [67]

- MOA: the general mechanism of action of Cephalosporins is to inhibit bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs), thus blocking peptidoglycan cross-linking. This weakens the cell wall and then causes bacterial death. [68]

- Resistance: Staphylococcus aureus develops resistance Cephalosporins by producing altered PBPs (PBP2a) through the mecA gene, making β-lactams ineffective. Another mechanism involves β-lactamase enzymes, which breaks the β-lactam ring. Fifth generation ceftaroline can overcome PBP2a mediated resistance and is active against MRSA. [68]

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Table 4 Comparative Analysis of Antibiotics Used in Treatment of MRSA Infection

Antibiotic	Class	Primary Indications	MOA	Adverse Effects & Toxicity	Resistance Mechanism
Vancomycin	Glycopeptide	MRSA, Gram - positive infections	Binds to D-Ala-D-Ala moiety of Lipid II, Inhibits peptidoglycan cross - linking.	Red Man Syndrome, Ototoxicity, Nephrotoxicity, Phlebitis.	Alteration of target site: D-Ala-D-Ala replaced by D-Ala-D- Lactate.
Daptomycin	Cyclic Lipopeptide	MRSA, VRE, S. aureus bacteraemia	Inserts lipid tail into membrane; causes depolarization and K^+ ion leakage.	Elevated CPK levels, Myopathy, Sepsis - like symptoms.	Increased positive surface charge; altered membrane fluidity.
Clindamycin	Lincosamide	Gram - positive cocci, Acne, Protozoans (Malaria)	Binds to 50S ribosomal subunit, blocks transpeptidation protein synthesis.	GI upset, Potential for *C. difficile* (noted in general clinical use).	Point mutations in 23S rRNA, enzymatic modification.
Linezolid	Oxazolidinone	MRSA, VRE, Nosocomial pneumonia	Binds to 23S rRNA (50S subunit), prevents formation of 70S initiation complex.	Myelosuppression (long - term use), Lactic acidosis.	Mutation in 23S rRNA; CFR gene (methyltransferase enzyme).
TMP - SMX	Folate Antagonists	UTIs, MRSA SSTIs, PJP pneumonia	Synergistic: Blocks two steps in folate synthesis (DHPS and DHFR enzymes).	Rash, Hypersensitivity, Photosensitivity.	Acquisition of alternative DHFR enzymes (*dfr* genes).
Rifampin	Rifamycin	Tuberculosis, MRSA (adjunct)	Targets DNA - dependent RNA polymerase, blocks RNA synthesis.	Hepatotoxicity, Orange discoloration of fluids.	Mutations in the rpoB gene (rifampicin resistance - determining region).
Quinupristin / Dalfopristin	Streptogramin (30:70)	MRSA, VRE (*E. faecium* only)	Synergistic: Binds 50S subunit, blocks peptide bond formation and elongation.	Myalgia, Arthralgia, Venous irritation, CYP3A4 inhibition.	Target site modification, enzymatic inactivation.

➢ *Tigecycline*

Tigecycline is the first antibiotic from the glycylcycline class, of Tetracyclines that is derived from minocycline. It was developed to overcome the common tetracycline resistance mechanisms such as shows a broad spectrum of activity against both the gram positive and gram negative bacteria, including resistant strains like methicillin resistant Staphylococcus aureus (MRSA), Staphylococcus epidermidis (MRSE), vancomycin resistant Enterococcus (VRE) species, and penicillin resistant Streptococcus pneumoniae. Structural modifications in tigecycline give it an enhanced potency and reduced risk of resistance compared to the older tetracyclines. Clinically, it is approved for treating complicated skin, soft tissue, and intra - abdominal infections. [69]

- MOA: Just like other tetracyclines the tigecycline acts by binding to the 30S subunit of the bacterial ribosome, blocking the attachment of aminoacyl tRNA to the mRNA ribosome complex. This prevents the incorporation of amino acids into the growing peptide chain thereby inhibiting the protein synthesis. As a result, the bacterial growth is stopped thus making tigecycline a bacteriostatic agent. [70]
- Resistance: Resistance to tetracyclines typically occurs through the two main mechanisms: 1) Efflux pumps, which expel the drug from bacterial cells. 2) By ribosomal protection proteins, which prevent the drug from binding to its target site. [70] A less common mechanism involves enzymatic modification of the antibiotic molecule. The Tigecycline was structurally modified to overcome these resistance mechanisms, retaining strong activity against many tetracycline resistant bacterial strains. [70]

➢ *Doxifluridine*

Doxifluridine is an antineoplastic agent. It is an oral fluoropyrimidine prodrug of 5-fluorouracil (5-FU) developed to overcome its rapid breakdown by the dihydropyrimidine dehydrogenase enzyme present in the gut. It is converted to active 5-FU by the enzyme pyrimidine nucleoside phosphorylase in tumor tissues. The released 5-FU inhibits DNA synthesis by blocking thymidine formation and disrupts RNA function by competing with the uridine triphosphate, thereby preventing cancer cell growth. [71] Recent studies have shown that doxifluridine possesses strong antibacterial potential against the multidrug resistant Staphylococcus aureus (MDR S. Aureus). It was found to be particularly

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effective against MRSA strains isolated from patients suffering from the chronic obstructive pulmonary disease (COPD). The drug exhibited low MIC (0.5–2 μg/mL) and MBC (1–4 μg/mL) values this indicating that it can inhibit and kill bacteria even at the low concentrations. Thus, doxifluridine has broad activity against resistant bacteria, including MRSA and vancomycin resistant Enterococcus (VRE). [72]

- *Kuraridin*

The natural compound flavonoid Kuraridin is found in Sophora flavescens. It has been shown to possess a broad spectrum of pharmacological properties, such as antitumor, antiviral effects and also anti inflammatory activities. By inhibiting tyrosinase Kuraridin that is derived from the roots of Sophora flavescens, acts as an effective natural agent for skin lightening in hyperpigmentation. It can also reduce inflammation by prohibiting COX and LOX pathways. It was observed in studies that Kuraridin enhances the in vitro antibacterial activity of gentamicin, fusidic acid, and vancomycin against the MRSA infection when combined with epicatechin gallate (ECG). It also exerted anti biofilm activity against MRSA by preventing the biofilm formation thus reducing bacterial adhesion to fibrinogen and host tissues, and inhibiting the SrtA enzyme involved in bacterial attachment. In general, Kuraridin is promising for the development of novel antimicrobial therapies due to its low toxicity. [73]

- *Combination Therapy*

Combination therapy is used in MRSA Because of the bacterial resistance, single antibiotics often don't work well against S. Aureus, such as the MRSA. Combination therapy is used by using two or more drugs together that helps improve effectiveness and lowers the resistance risk. Common pairs include vancomycin or daptomycin with fosfomycin or linezolid. Some non antibiotic compounds like pyridines or icariin also enhance antibiotic action. However, long term or excessive use can cause side effects, higher costs, and more resistance. [34]

- *Phage Therapy*

Phage therapy is a therapy that uses the viruses called bacteriophages to target and kill bacteria like drug resistant Staphylococcus aureus. Unlike antibiotics, phages attack only specific bacteria without harming the normal body flora and can also break down biofilms. Using phage combinations, known as phage cocktails, helps widen their effectiveness. Although, phage therapy faces challenges such as limited host range, lack of standardized methods, and insufficient large scale clinical trials. It also requires personalized design for each infection, and in some cases, results have been inconsistent when used with antibiotics. [34]

- *Antimicrobial Peptides*

Antimicrobial peptides (AMPs) are the natural defence molecules found in almost all the living organisms and are considered as alternatives to antibiotics. They work by damaging bacterial membranes or blocking the protein and nucleic acid synthesis, making them effective even against resistant strains like MRSA and VRSA. Common AMPs in the humans include defensins (HBD1 to HBD4) and cathelicidins (like LL 37), which protect tissues such as the skin, lungs, and nasal passages and help fight the biofilms. Bacterial AMPs, called bacteriocins, like nisin A, also show strong activity against Gram positive bacteria and can enhance antibiotic effects. [9]

- *Vaccine*

Developing a vaccine against the Staphylococcus aureus could reduce infection rates, deaths, and the hospital costs. However, there is no approved vaccine yet. Various targets like surface polysaccharides, iron regulated proteins, and clumping factors have been tested, but results were shown only partially. It is because wide strain diversity and adaptability of S. Aureus. [9]

IX. NATURAL METHODS

Natural alternatives that are being explored to combat the antibiotic resistant infections. Plant extracts, honey, propolis, and essential oils offer promising antimicrobial potential due to the presence of the rich bioactive compounds. Alkaloids like nigritanin from Strychnos nigritana have shown strong anti S. Aureus activity without toxicity. Peptides also display potent effects against MRSA and biofilms. Manuka honey demonstrates safe antibacterial and antibiofilm activity in the clinical use. Essential oils from clove, oregano, thyme, and Schinus areira exhibit strong action against S. Aureus, though challenges like poor solubility and stability remain. [9]

- *Inhalable Vancomycin Loaded Lactose Microparticles for Treatment of MRSA Pneumonia*

Vancomycin (VCM) is the first line treatment for MRSA related pneumonia, but the high intravenous doses can cause kidney toxicity. To reduce side effects, targeted lung delivery systems have been developed. One such method uses nanoparticle based inhalable formulations, where VCM is loaded onto the magnetic iron oxide nanoparticles (MNPs). These can be directed to infection sites using an external magnetic field. To prevent exhalation, MNPs are embedded in microparticles (nano in micro design) made of substances like lactose, which dissolve in the lungs to release the nanoparticles.

Recent studies have developed VCM conjugated MNP microparticles using the spray drying, showing good aerosol performance, safety, and strong antibacterial activity making them a good approach for targeted pulmonary MRSA therapy. [20]

- *Antimicrobial Activity of Adipose - Derived Mesenchymal Stromal Cell Secretome Against Methicillin Resistant Staphylococcus aureus*

The study found that secretions from adipose derived mesenchymal stromal cells (AD MSCs) showed strong antibacterial effects against the Staphylococcus aureus such as the MRSA strains. About 87.5% of MRSA isolates were inhibited, suggesting the secretome could serve as a new approach to fight antibiotic resistant infections. [22]

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X. CONCLUSION

Methicillin resistant *Staphylococcus aureus* (MRSA) represents a critical global health threat as a strain of *Staphylococcus aureus* that has developed resistance to methicillin and other related beta lactam antibiotics. While it often colonizes the skin and nasal passages harmlessly, it can cause severe infections ranging from localized skin abscesses to life threatening conditions such as pneumonia, endocarditis, and systemic sepsis. The pathogen's formidable nature is driven by sophisticated resistance mechanisms, most notably the formation of self secreted biofilms that can make bacteria up to a thousand times more resistant than their free floating counterparts. Cellular defenses like efflux pumps that expel antibiotics, enzymes that dismantle drugs, and the modification of antibiotic target sites such as the *mecA* gene modifying Penicillin Binding Protein 2a further complicate treatment.

Current therapeutic management relies primarily on first line intravenous agents like vancomycin and daptomycin, though rising resistance and significant systemic toxicities, such as nephrotoxicity and ototoxicity, pose major challenges. Alternative treatments include linezolid, ceftaroline, and combination therapies, while emerging strategies explore novel antibiotics, bacteriophage therapy, and natural compounds like Kuraridin and Myrtenol. Given the World Health Organization's classification of MRSA as a high priority pathogen and the projection that antimicrobial resistance could claim 10 million lives annually by 2050, the need for robust infection control, meticulous hygiene, and continued research into innovative treatments is paramount.

➢ *Conflict of Interest*

Authors do not have any conflict of interest with any individual.

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