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Methicillin-resistant *Staphylococcus aureus* and intensive care unit

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Abstract

The intensive care units (ICUs) are a vital component of the healthcare system, focusing on the management of patients with acute, life-threatening diseases, they also highlight the serious hazards of healthcare-associated infections (HAIs) in ICUs, which can result in increased morbidity, mortality, and healthcare costs, device-associated infections, such as central line-associated bloodstream infections, catheter-associated urinary tract infections, and ventilator-associated pneumonia, are especially common in intensive care units, the pathogenic role of *Staphylococcus aureus*, a leading cause of HAIs in ICUs, because of its capacity to grow in a variety of host conditions, this Gram-positive bacterium can cause a wide range of illnesses, including bloodstream, skin, and respiratory infections.

Additionally, *S. aureus*, a common bacteria in ICU settings, has virulence, antibiotic resistance, and persistence due to its accessory genetic elements and *SCCmec* elements, these elements, including the mecA gene and the spa gene, confer antibiotic resistance and promote the acquisition of new virulence traits, the mecA gene encodes an alternate penicillin-binding protein with reduced affinity for beta-lactam antibiotics, while the spa gene encodes protein A that binds to the Fc region of immunoglobulins, facilitating invasive infections.

Keywords: Staphylococcal protein A; Staphylococcal cassette chromosome mec; Accessory gene regulator

1. Introduction

The methicillin-resistant *Staphylococcus aureus* (MRSA), is a significant risk to ICU patients due to its resistance to many antibiotics, the prevalence of MRSA in ICUs varies but is reported to be between 8.7% and 34.2%. Risk factors include prolonged stay, age over 65, underlying medical conditions, previous antibiotic use, skin/soft tissue infections, and invasive devices, the common sources of MRSA transmission include environmental contamination and healthcare worker contamination (1)(2).

MRSA infections can lead to complications like skin/soft tissue infections, pneumonia, sepsis, bacteremia, endocarditis, and surgical site infections, the mecA gene and toxins contribute to its pathogenicity, while biofilms help maintain its persistence. Preventing MRSA in ICUs involves contact precautions, hand hygiene, environmental cleaning, patient monitoring, and education on infection control practices. Understanding MRSA risk factors, transmission, prevalence, and preventive strategies can help reduce mortality and morbidity in critically ill ICU patients (3).

The genotyping of MRSA is the identification of specific genetic characteristics of MRSA isolates, providing advantages such as epidemiological tracking, infection control measures, antibiotic resistance monitoring, strain identification and characterization, and research and surveillance, also it helps trace the spread of MRSA strains within healthcare facilities, communities, and regions, guiding interventions and preventing further spread, and helps predict the effectiveness of antibiotics against specific strains, aiding in the selection of appropriate treatment and managing

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antimicrobial resistance risks (4). To understand the patterns of prevalence and review knowledge on prevention measure of MRSA in the ICU setting

2. Intensive care unit (ICU)

The intensive care unit, also known as the critical care unit, focuses on managing patients with acute, life-threatening organ dysfunction; various technologies are utilized to support failing organ systems like the kidneys, heart, and lungs; the main goal of intensive care unit is to prevent further physiological deterioration, the underlying condition is simultaneously treated and resolved(5). The specialty excels in treating conditions such as sepsis and acute respiratory distress syndrome by focusing on understanding the underlying mechanisms and supporting organ dysfunction rather than directly managing the diseases causing the acute illness, it is important to acknowledge the substantial differences between countries in their capacity to care for the most critically ill patients within the healthcare system when defining an intensive care unit (ICU); this involves identifying the essential components of intensive care and categorizing them to evaluate ICUs based on the level of care they can provide, which is determined relative to the specific healthcare system in which they operate(6).

Intensive care units are a branch of medicine that treats patients who are extremely sick, in danger of developing life-threatening illnesses, or who are recovering from such disorders; it involves administering resuscitation, intrusive monitoring methods, life support, and end-of-life care if a patient's medical needs beyond the capabilities of a standard hospital ward, the critical care unit admits patients with conditions like unstable blood pressure, severe infections, and complications after a heart attack, or abnormal heart rhythms that need blood pressure support (6). Patients requiring mechanical ventilation or assistance with breathing due to respiratory problems add to the demands on the ICU, furthermore, advanced treatment is needed for the complex complications arising from multiple organ failure, often referred to as multiple organ dysfunction syndrome, intensive care units are designed in two main configurations: closed and open, in a closed critical care unit, the intensivist is the primary physician responsible for the care of all patients, even if they have separate primary care physicians who may not be intensivists; national differences exist in the management of critical care patients; in the US, open units are the most common, although large academic centers sometimes have closed units, there are also hybrid units that include features of both closed and open units (7).

The role of intensive care units (ICUs) in patient care is well-established and crucial, but there are costs associated with them and an increase in morbidity and death for patients who receive treatment there; nevertheless, ICUs are critical for managing and treating some of the most complicated and severe illnesses that may impact the human body, although intensive care units (ICUs) are well-established as an integral part of patient care, infections acquired in these facilities significantly elevate healthcare expenses and expose patients to heightened risks of severe consequences or mortality(8). Around 20-25% of all nosocomial infections occur in patients in the Critical Care Unit (ICU) of the hospital, with the risk of such diseases in the ICU being 5-10 times greater than in other sections due to the presence of comorbidities, patient course, mechanical ventilation, use of antibiotics, tracheotomy, frequent contact of medical personnel with patients, invasive procedures, and more frequent utilization of enteral or parenteral nutrition (9).

Hospital-associated infections (HAIs) refer to diseases that are either absent or do not undergo incubation in hospital settings; these infections might jeopardize the safety of patients in healthcare facilities, leading to higher expenses, morbidity, and death; medical-related infections can arise from several sources, such as patient-specific illnesses, healthcare system problems, surgical procedures, invasive equipment, antibiotics, and other drugs, ICU patients in industrialized countries are at a higher risk of healthcare-associated infections (HAIs), HAIs were reported in 5–10% of ICU admissions, but in developing countries, the rate was about 50% higher; the World Health Organization estimates that HAIs account for 7–12% of the global burden of illness (10). Patients in the ICU frequently undergo invasive procedures and the insertion of life-saving devices such as intravascular and urinary catheters, as well as endotracheal intubation for mechanical ventilation; failure to administer proper medical care can result in device-associated healthcare-associated infections (DA-HAIs) (11).

Device-associated infections (DAIs) affect approximately 24.3-27.6% of patients in the intensive care unit (ICU), with most cases occurring at this level; studies show that DAIs related to central line-associated bloodstream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), and ventilator-associated pneumonia (VAP) are frequently seen in ICUs(12). Using a surveillance system, healthcare professionals can identify health issues and prioritize control measures that ensure patient well-being. Continuous monitoring of HAI in Western countries has lowered infection rates compared to other regions, as demonstrated by studies; one of the major concerns is drug-resistant pathogens, which are more difficult to detect, cause morbidity and mortality, and are resistant to standard laboratory tests (13).

Often taking longer to see these pathogens before appropriate antimicrobial therapy can be used, there are multiple risk factors; various internal and external variables contribute to developing nosocomial infections in the ICU; lowering these risk factors can lead to decreased infection rates (14). The ICU's infection control depends on several factors, including the number of patients, whether it is a single or multiple-patient room, the room's size, and architecture, using appropriate heating, cooling, humidity, and air-conditioning systems in hospitals is essential for managing infection. In some cases, like the ICU, these systems are more crucial than others, such as ambulances or night ambulances. (15), nosocomial infections can be caused by several species, such as bacteria, parasites, viruses, and fungi; illnesses can be transmitted through interaction with patients, healthcare personnel, infected items, visitors, or various environmental elements originating from exogenous or endogenous origins (16).

3. *Staphylococcus aureus*

Staphylococcus aureus is a Gram-positive bacterium that produces coagulase and can form clusters resembling grapes; it is normally present in the human body without causing harm; S. aureus can lead to various infections due to its ability to thrive in different hosts and environments; this bacterium is a major pathogen in humans and is a common cause of infections acquired in hospitals and communities (17). *Staphylococcus aureus*, a bacterial pathogen, is a notorious and widespread bacterial strain in an intensive care unit (ICU) that causes an incredulous number of superficial skin infections and potentially hundreds of thousands to even more severe invasive infections worldwide each year; it is a primary comorbidity responsible for causing pneumonia, respiratory tract infections, surgical site, prosthetic joint, and cardiovascular infections, as well as nosocomial bacteremia (18).

Other infections, such as furuncles, abscesses, and wound infections, are usually not life-threatening but may involve significant morbidity and pain, particularly in moderately severe skin infections, such as furuncles, abscesses, and wound infections; S. aureus can generate a broad spectrum of virulence factors, including toxins, immune evasion factors, and protein and non-protein factors that help in colonizing the host during infection (19). *Staphylococcus aureus* is a highly adaptive organism that employs various mechanisms of antibiotic resistance, making it extremely challenging to treat; one mechanism is enzymatic inactivation, where beta-lactamase enzymes hydrolyze beta-lactam antibiotics such as penicillin, rendering them ineffective; another mechanism is efflux pumps that actively pump out antibiotics from the bacterial cell, preventing therapeutic concentrations from accumulating (20). Target site alterations are a frequent resistance mechanism in *Staphylococcus aureus*; mutations in genes responsible for the bacterial cell wall or protein synthesis can lead to modifications in antibiotic binding sites, making them ineffective; in certain instances, bacteria can develop new binding sites to avoid the antibiotic's effects (21).

4. The Methicillin-resistant *Staphylococcus aureus* (MRSA)

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a bacteria that is resistant to the antibiotic methicillin; it can cause serious infections that spread in hospitals, healthcare facilities, and the community, MRSA responsible for difficult-to-treat infections in humans and cause over 100,000 deaths worldwide due to antimicrobial resistance in 2019(22). There are two main types of MRSA infections: Healthcare-associated (HA-MRSA): These infections occur in people who have been in healthcare settings, such as nursing homes, dialysis centers, surgeries, intravenous tubing, or artificial joints(23), and 2- Community-associated MRSA infections occur in individuals outside of healthcare facilities, MRSA infections are caused by a strain of staph bacteria called *Staphylococcus aureus* that can reside on the skin, in the nose, armpits, groins, and other body areas; the increase in antibiotic-resistant bacteria like MRSA is attributed to prolonged and unnecessary use of antibiotics over the years, leading to the emergence of drug-resistant strains(24).

Methicillin-resistant MRSA, resistant to multiple antibiotics, presents a major risk to ICU patients due to its resistance to commonly prescribed antibiotics; MRSA is known for its capability to survive and flourish in hospital and healthcare settings; it is a significant factor in healthcare-associated infections, resulting in longer hospital stays, higher morbidity, and death (25). Patients who have recently undergone surgery are at a higher risk of developing MRSA infections while in the ICU, are on prolonged antibiotic treatment, or have weakened immune systems; other risk factors include lengthy hospital stays and close contact with MRSA carriers. MRSA can spread rapidly within the ICU through contact with contaminated surfaces, equipment, or healthcare workers; patients with indwelling catheters, ventilators, or surgical wounds are particularly vulnerable to MRSA infections in the ICU (26). Methicillin-resistant *Staphylococcus aureus* (MRSA) is usually transmitted through direct or indirect contact with infected individuals or contaminated objects; in the ICU, medical equipment and invasive devices can harbor MRSA and serve as sources for spreading the bacteria, MRSA is a serious threat to patients in the intensive care unit (ICU), leading to poor clinical outcomes and impacting infection control practices; the prevalence of MRSA in the ICU varies, with studies reporting rates around 8.7% to 34.2% in different settings(27).

The risk of acquiring MRSA in the ICU is primarily associated with the length of stay. It can be transmitted within the ICU environment, including through patient-healthcare worker interactions and environmental contamination; preventive measures, including comprehensive sampling for MRSA, isolation policies, and additional infection control strategies, are necessary to address the challenges posed by MRSA in the ICU (28). Understanding MRSA's prevalence, risk factors, and transmission dynamics in the ICU is crucial for guiding empirical antibiotic choices, enhancing infection control, and reducing mortality and morbidity; effective control of MRSA infection requires a thorough knowledge and analysis of its risk factors (29). As well as the development of future strategies to combat its spread and impact in the ICU; the search results provide insights into the prevalence, transmission dynamics, and challenges associated with MRSA in the ICU, emphasizing the importance of preventive measures and strategic allocation of healthcare resources to address this issue (30).

5. Risk factors for (MRSA) in ICU patients

The length of stay in both the ICU and the hospital are significant risk factor for MRSA infection in ICU patients. The longer a patient remains in the ICU, the greater their risk of acquiring MRSA, patients aged over 65 years are at an increased risk of MRSA colonization or infection (31). Patients with trauma or medical conditions are more likely to develop MRSA infections and urinary catheter use, which higher the risk of MRSA infections (32). Previous antibiotic treatment patients who have received previous antibiotic treatment are more likely to develop MRSA infections (33). Skin-soft tissue or post-surgical superficial skin infections, patients with skin infections are at an increased risk of MRSA colonization or infection, Contact precautions: patients who are colonized with MRSA may transmit the disease to others, making contact precautions essential for reducing transmission (34).

6. The common sources of MRSA in ICU patients

Include persistent environmental contamination (e.g., bed rails, blood pressure cuffs, room phones, bed linen, infusion pump panels, call buttons, vital sign monitor screens, door handles, and portable computers in hospital rooms) and healthcare worker (HCW) contamination (e.g., clothes, stethoscopes, and phones)(35). Additionally, a study highlighted that the risk of acquiring MRSA in the ICU is largely a function of length of stay, and effective control of MRSA infection requires thorough knowledge, analysis of risk factors, and implementation of preventive measures (36). Furthermore, the prevalence of MRSA in the ICU is influenced by the proportion of high-risk patients, and control strategies and genomic analysis have emphasized the role of persistent environmental contamination and healthcare worker contamination in the transmission of MRSA within and between ICUs(37). The presence of invasive devices is a significant risk factor for MRSA acquisition in ICU patients; patients in the ICU often require invasive devices such as tracheostomy or gastroenteric feeding tubes, which can increase the risk of MRSA acquisition; these devices can cause skin breaches, which can lead to infections(38).

7. The complications associated with MRSA infections

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections can lead to various complications, depending on the severity and location of the infection; some of the complications associated with MRSA infections include Skin infections, MRSA infections often start as swollen, red, and painful bumps that may resemble pimples or boils, these infections can progress to cellulitis, furuncles, or abscesses (39). Also, MRSA can cause pneumonia, which is a lung infection that can be severe and life-threatening; symptoms of MRSA pneumonia include severe respiratory symptoms, high fevers, hemoptysis, and hypotension. MRSA pneumonia can also cause lung abscesses, empyema, and pathological features such as pulmonary hemorrhage and microabscess (40).

If left MRSA infections untreated can become severe and cause sepsis, which is the body's extreme response to an infection; sepsis can lead to organ failure, amputations, and even death. (41). MRSA can also infect the blood, leading to bacteremia and endocarditis, which can be associated with increased morbidity and mortality. (42) Soft tissue infections caused by MRSA can spread to the soft tissues, causing diseases such as necrotizing fasciitis and diabetic foot ulcers. (43) Healthcare-associated MRSA (HA-MRSA) infections can lead to more severe complications, such as surgical site infections, catheter-related infections, and pneumonia.

8. The virulence factors of MRSA

The virulence factors of MRSA infections in the ICU can be categorized into several groups, including adhesions, derivative enzymes, and toxins; the adhesions of MRSA strains have been shown to express Clf A and Clf B; these proteins are part of the microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) class of surface proteins that are covalently attached to peptidoglycan. (44). ClfA is responsible for bacterial buildup in the plasma; ClfA also promotes bacterial adherence and penetration of biomaterials coated with plasma proteins and biofilm development, ClfB binds to fibrinogen through the α-chain; in contrast to ClfA, although ClfB enhances attachment to keratinized envelope proteins loricrin and cytokeratin 10 in the nasal epithelial cells, ClfB is significantly more abundant in Agr mutants compared to wild-type cells. (45).

9. The accessory gene regulator (AGR)

The Agr system is a crucial virulence regulator in *Staphylococcus aureus*. It acts as a 'switch' that controls the expression of numerous virulence factors, such as proteins on the bacterial surface, toxins, enzymes, and other molecules that contribute to infection. The Agr system itself is composed of two adjacent transcripts, RNAII and RNAIII, which are controlled by the P2 and P3 promoters, respectively (46). The RNAII transcript contains four genes: agrB, agrD, agrC, and agrA. The agrD gene produces a precursor molecule that becomes an auto-inducing peptide (AIP), the agrB gene encodes an enzyme, an endopeptidase, which is responsible for processing the AIP, the genes agrC and agrA encode proteins that act as a two-component regulatory system, known as AgrC and AgrA, respectively (47), agrC and agrB. Pan agr: a primer that is universally applicable for forward amplification, the reverse primers I, II, III, and IV are used to detect the four forms of agr system in S. aureus. (48). Upon activation of the Agr system, the AIP propertied undergoes processing by AgrB, resulting in the formation of an octapeptide; this octapeptide is then released into the extracellular area; the histidine kinase AgrC, which is attached to the membrane, undergoes autophosphorylation and becomes active, this activation process leads to the addition of a phosphate group to the response regulator AgrA (49).

Once activated by phosphorylation, AgrA acts as a master switch. It boosts the production of AIP by promoting the creation of its own RNAII transcript. Simultaneously, AgrA activates the P3 promoter, leading to increased production of RNAIII, more AgrA itself, and even more RNAIII. This intricate feedback loop ultimately controls the expression of genes responsible for S. aureus virulence, playing a critical role in its ability to cause infections (50).

AgrA can stimulate the production of PSM peptides, the only toxins directly controlled by this regulatory system, While AgrA primarily influences PSM production, RNAIII plays a broader role in controlling the expression of a variety of crucial virulence factors and other regulatory molecules (51). The Agr system in S. aureus is classified into four categories, namely AgrI, AgrII, AgrIII, and AgrIV, based on the polymorphisms of AgrB, AgrD, and AgrC, every Agr variation generates a distinct auto-inducing Peptide (AIP) that initiates auto-induction, the diverse specializations within *Staphylococcus*, resulting from different forms of adaptation, create unique functional units, these specializations contribute significantly to the evolutionary diversity of this bacterium, ultimately impacting the severity of illnesses in infected hosts (52).

Earlier studies have found associations between specific farming groupings and certain disease predispositions; for instance, most clinical strains of S. aureus belonging to the AgrII group are associated with acute infections, notably, about half of all MRSA isolates found in the bloodstream belong to this AgrII group (53). AgrIII and AgrIV strains of *Staphylococcus aureus* mainly cause toxic shock syndrome.,specifically, AgrIV infections are linked to exfoliative syndromes and bullous impetigo; the AgrII and AgrIV strains demonstrate a greater ability to build biofilms. (54). The presence of specific toxin genes and mobile genetic elements varies among different Agr groups, there is evidence suggesting that the lineage and geographical spread of S. aureus can be linked to specific Agr types, interestingly, dysfunctional Agr systems have been associated with the development of intermediate-level resistance to glycopeptide antibiotics and are frequently found in healthcare-associated and multidrug-resistant isolates (55).

10. Staphylococcal protein A (Spa)

This protein is a key virulence factor in *Staphylococcus aureus* infections. It's a surface-associated protein that binds to the Fc fragment of immunoglobulin from various mammals, potentially playing a crucial role in the development of S. aureus infections, the expression of this protein is controlled by a complex interplay of multiple factors, including Sara (staphylococcal accessory regulator), SarS (originally named SarH1), Rot (repressor of toxins), SarT, and the ArlR-ArlS two-component system (56). Staphylococcus protein A (Spa) is expressed during the bacterium's rapid growth phase (exponential phase) but its production is subsequently reduced, Studies using Spa mutants have demonstrated that this

protein is essential for S. aureus' ability to cause disease in mice, furthermore, the highly variable Xr region within the spa gene is commonly used to classify S. aureus strains, a technique known as spa typing (57). The staphylococcal accessory regulator (SarA) regulates a wide variety of genes; according to gene chip research, SarA inhibits the transcription of some genes (such as spa) while promoting the transcription of others (such as the Agr promoters), both Agr-dependent and Agr-independent processes achieve the regulation exerted by SarA.(58) SarS, previously known as SarH1, belongs to a family of transcriptional regulators called the Sar family, Located just upstream of the spa gene, the SarS determinant acts as a positive regulator, boosting the production of Spa, research has shown that SarS binds directly to DNA, indicating that it likely enhances Spa production by directly interacting with the Spa promoter. (59)

SarT, a protein belonging to the Sar family, has been demonstrated to act as a stimulator of SarS; it was shown that SarT has an affinity for the sarS promoter, the expression of sarT leads to the expression of SarS, which in turn leads to the development of Spa, the Rot, another member of the Sar family, was demonstrated to positively regulate the expression of SarS, hence indirectly influencing the expression of Spa. (59)The spa gene codes for protein A, the repeating portion of spa genes, known as region X, is situated at the very end of the gene and can have as man)y as twelve units, each of which can contain twenty-four nucleotides; the number and sequence of repetitions within this 24-nucleotide region exhibit a significant degree of polymorphism, different protein A variants result from diversity in the X region in S. aureus. (60)

The immune suppression on several fronts is driven by SpA IgG-binding capabilities, which are especially significant in pathogenesis and formation of anti-staphylococcal immunity actually, SpA serves as an immunomodulator for B cells when it is secreted in a soluble form. (61) It does this by encouraging the growth of VH3-idiotype cells and controlling the specificity of antibodies that are generated, As a result, SpA limits the bacterium's ability to be opsonized by destroying the traditional pathway of complement deposition and limiting the phagocytosis. (62)

11. The capsular polysaccharide (CP)

This component is essential for both the bacterium's ability to cause disease and its capacity to trigger an immune response. MRSA, a particularly problematic strain, is characterized by two main types of capsular polysaccharides: cap5 (type 5) and cap8 (type 8), the genes responsible for producing these capsular polysaccharides, cap5 and cap8, are present in a vast majority (80-90%) of clinically significant MRSA strains (63). The trisaccharide repeating units of serotypes 5 and 8 consist of N-acetyl mannosaminuronic acid, N-acetyl L-fucosamine, and N-acetyl D-fucosamine; While both cap5 and cap8 are important, they are not identical in their structure or function. while most S. aureus strains fall into type 5 or 8 categories, the remaining 10-20% of clinical strains that don't fit into those groups are classified as antigen 336 (Ag336). (64) The 336 antigens, also known as polysaccharide 336 (PS336), were isolated from a strain deposited in the American Type Culture Collection (ATCC) with the identification number ATCC 55,804. These antigens are used to determine the serotype of S. aureus isolates that don't produce a capsule. (65) Polysaccharides aid the bacterium in avoiding recognition by the immune system of the host; in addition, they can augment the bacterial resistance to non-specific immunological responses, such as complement, the up-regulation of capsular polysaccharides is likely the primary immune evasion technique employed by MRSA, since increased expression confers greater resistance to non-specific immune responses. (66)

Methicillin-resistant *Staphylococcus aureus* (MRSA) strains produce a range of toxins, including alpha, beta, gamma, and delta toxins, which can damage various cellular components of these toxins, alpha toxin is produced by the majority of pathogenic MRSA strains and is considered a major factor in the severity of infection. (67) MRSA strains also have staphylococcal hemolysins; Hla (α-toxin) and Hlb are two types of pore-forming toxins; the majority of S. aureus strains, making up 95% of clinical strains release Hla, a 33-kDa polypeptide, the oligomerization and binding to the host cell membrane's heptameric structure impart toxicity to this toxin. (68)Once Hla attaches to a specific cell, it forms an oligomer with a pre-pore structure, then it propels the β-barrel through the lipid bilayer and attacks the cell membrane, resulting in the formation of a hydrophilic trans-membrane channel, a large variety of human cell types, including epithelial cells, endothelial cells, T cells, monocytes, and macrophages are known to express this pesticide. (69)

Staphylococcal superantigens, such as toxic shock syndrome toxin-1 (TSST-1) and staphylococcal enterotoxins (SEs), are protein toxins that can wreak havoc on the immune system, they bind to MHC class II molecules and specific T-cell receptors (TCRs), causing a massive and uncontrolled release of inflammatory chemicals (cytokines) – a phenomenon known as a "cytokine storm" this cytokine storm can lead to a wide range of symptoms, depending on the amount of toxin and how the body was exposed. (70) These superantigens are powerful toxins capable of causing food poisoning, severe respiratory distress that can be fatal, and toxic shock syndrome, they work by first attaching to MHC class II molecules, which are proteins found on immune cells, next, they bridge these MHC class II molecules to specific T-cell receptors (TCRs) found on T lymphocytes, effectively tricking these immune cells into an uncontrolled activation, This

results in a massive release of inflammatory signals (cytokines), known as a "cytokine storm," which overwhelms the body and leads to the devastating symptoms associated with superantigen poisoning. (71) Staphylococcal enterotoxin B (SEB) and toxic shock syndrome toxin-1 (TSST-1) are two of the most well-known superantigens produced by *Staphylococcus aureus*, SEB is a powerful toxin that can cause severe food poisoning, while TSST-1 is known for its ability to trigger toxic shock syndrome. (72)

12. Resistance to antibiotics

The *Staphylococcus aureus* bacteria are inherently weak to almost all antibiotics; while chromosomal mutation and antibiotic selection play significant roles, horizontal gene transfer is a common way for bacteria to develop resistance, thanks to this remarkable sensitivity of S. aureus, a genuinely miraculous medication. (73) However, penicillin enabled the eradication of invariably lethal illnesses; penicillin resistance was already a problem in hospitals by the mid-1940s, just a few years after it was first used in clinical practice; within a decade, it had spread across the community; it is pretty astounding how S. aureus may develop resistance to any medication. (74) Worldwide, the prevalence of infections caused by *Staphylococcus aureus* strains that are resistant to antibiotics has reached epidemic proportions; community and healthcare-associated staphylococcal infections, especially those caused by methicillin-resistant *Staphylococcus aureus* (MRSA), are on the rise in many nations. (75)The causes of healthcare-associated infections (HAIs) might be either internal or external infectious pathogens. Local microbial flora is commonly found in the nose, skin, mouth, gastrointestinal tracts, and other patient-specific regions, making them endogenous sources. (76)

These bacteria may invade and cause sickness under the right conditions; these germs can come from sources outside the patient, such as other people, equipment, or even the surrounding environment; antimicrobial resistance (AMR) poses a significant health hazard, leading to over 700,000 deaths annually, and is projected to cause up to 10 million deaths globally by 2050. (78) Prolonged antibiotic medication can cause bacteria that are initially susceptible to develop resistance; as the microorganism adapts and gains resistance, the drugs lose their effectiveness; when an antibiotic attacks bacterial cells, the sensitive ones will die off while the relatively resistant ones will survive. (79).

Resistance genes carried by plasmids can quickly infect all members of a bacterial species and even other bacterial taxa; bacteria that have resistance genes in their DNA will multiply at a slower pace, when *Staphylococcus aureus* carries antibiotic resistance genes, it complicates, understanding the prevalence and mechanisms of antibiotic resistance in *Staphylococcus aureus* is crucial for developing effective treatments and preventing the emergence of resistant infections. By delving into the molecular mechanisms of drug resistance in S. aureus, we can gain insights that will inform the development of new therapies and strategies to combat these challenging infections. (79)

Staphylococcus aureus, particularly methicillin-resistant S. aureus (MRSA), has developed various mechanisms of resistance to antibiotics; the primary reason behind MRSA's resistance to beta-lactam antibiotics is the presence of the mecA gene, this gene produces a protein called PBP2a, which is a transpeptidase. PBP2a has a much lower affinity for beta-lactam antibiotics compared to the normal transpeptidases found in non-resistant strains, making MRSA resistant to the effects of these drugs. (80)

This resistance is usually conferred by the acquisition of a nonnative gene encoding a penicillin-binding protein with a significantly lower affinity for β-lactams, additionally, MRSA strains have evolved resistance mechanisms to almost all antimicrobial drugs used in the treatment of Gram-positive bacteria, including beta-lactams, glycopeptides, and oxazolidinones. (81) These mechanisms include target modification, enzymatic drug inactivation, and decreased antibiotic uptake or efflux; understanding these resistance mechanisms is crucial for developing new anti-infective drugs and mitigating the evolution of MRSA.(82)The mecA gene is at the heart of methicillin-resistant *Staphylococcus aureus* (MRSA) it produces an alternative penicillin-binding protein, PBP2a, which has a much weaker attraction to beta-lactam antibiotics like methicillin, this weakened binding makes these antibiotics less effective against MRSA. (83)The presence of the mecA gene is a crucial mechanism of resistance to β-lactam antibiotics in MRSA; additionally, the mecA gene is widely disseminated in the *Staphylococcus aureus* population and is associated with multi-resistance to non-β-lactam antibiotics, the development of a modified penicillin-binding protein (PBP), known as PBP 2a or PBP 2′, has a reduced binding affinity for β-lactams, leading to resistance to almost all β-lactam medications that are now available. (84)The mecA gene is spread through the staphylococcal chromosome cassette (SCCmec) genetic element and can undergo horizontal gene transfer, allowing it to be disseminated widely in *Staphylococcus aureus* populations. (85) The regulation of mecA involves various regulatory elements and proteins, such as MecI and MecR1, which are involved in the transcriptional regulation of mecA; the detection of the mecA gene is essential for identifying antibiotic-resistant strains of *Staphylococcus aureus*. (86)

13. Panton-Valentine leukocidin (PVL)

Is a cytotoxin produced by some strains of *Staphylococcus aureus*, including some MRSA strains; PVL, a toxin produced by certain strains of S. aureus, is linked to increased virulence and is more commonly associated with active disease rather than simply colonizing the body, this toxin works by creating holes (pores) in the membranes of infected cells, disrupting their normal function. (87) MRSA strains produce a special set of enzymes called serine proteases, which contribute to their ability to cause disease (virulence and pathogenicity), these proteases are encoded by a single group of genes called the "serine protease-like proteins" (Spls) operon, the bacteria release these Spls, and uniquely, they only target S. aureus, not other bacteria, the production of these Spls is controlled by the Sae regulatory system, a system that also manages the expression of many other virulence factors in S. aureus. (88) The Spls play a crucial role in regulating virulence factors and protein production within S. aureus, they are essential for causing widespread lung damage during pneumonia, while initially thought not to affect staphylococcal proteins, studies using an Spl mutant have revealed changes in the amounts of both secreted and surface proteins, suggesting that Spls might also target human proteins. (89).

MRSA strains have a remarkable ability to form biofilms on both living (biotic) and non-living (abiotic) surfaces, this biofilm formation contributes to their persistence and resistance in healthcare settings, making them a significant challenge for infection control; the biofilm-forming ability of MRSA strains has been associated with various factors, including the presence of specific genes such as icaA, icaD, fnbA, fab, cna, geh, sspA, and sspB, as well as the use of invasive devices and prior antibiotic exposure. (90) MRSA strains are prolific biofilm formers, often exhibiting an increased presence of specific microbial surface components recognizing adhesive matrix molecules (MSCRAMMs), these MSCRAMMs play a crucial role in the ability of S. aureus to stick to surfaces and clump together, forming biofilms (91).

14. The *Staphylococcus aureus* chromosome cassette (SCCmec)

The SCCmec element is a crucial player in the spread of antibiotic resistance, particularly methicillin resistance, among *Staphylococcus aureus* strains, including MRSA, this genetic element carries the mecA gene, which codes for the penicillin-binding protein 2A (PBP2A). PBP2A is responsible for the resistance to methicillin and other beta-lactam antibiotics (92). The *Staphylococcus aureus* chromosome cassette (SCCmec) element can be transferred horizontally between different strains of *Staphylococcus aureus*; the SCCmec element also contains other genes that contribute to the virulence and pathogenicity of *Staphylococcus aureus*, such as the Panton-Valentine leukocidin (PVL) gene, which encodes a toxin that can cause severe infections.(93) *Staphylococcus aureus* chromosome cassette (SCCmec) is composed of two essential gene complexes: the mec-gene complex and the ccr-gene complex; the mec-gene complex encodes methicillin resistance, including the mecA gene and its regulators, mecI and mecR1.(94) The ccr-gene complex encodes the entire SCC element's movement, integration, and precise excision from the chromosome, SCCmec can vary in size and structure, and different SCCmec types have been identified based on the combination of mec and ccr gene complexes. These types, denoted as I, II, III, IV, V, VI, and others, represent different genetic elements responsible for methicillin resistance in *Staphylococcus aureus*. (95) Each type has a distinct genetic organization and is associated with specific *Staphylococcus aureus* lineages and reservoirs; the classification of SCCmec types is essential for understanding the epidemiology and evolution of methicillin-resistant *Staphylococcus aureus* (MRSA) strains, as well as for infection control and surveillance purposes.

15. Conclusion

In intensive care unit (ICU) settings, *Staphylococcus aureus* (MRSA) is a persistent and powerful bacterium that presents considerable difficulty, this bacterium's exceptional genetic adaptability, together with its capacity to quickly acquire and express virulence and antibiotic resistance genes, add to its prominence as a primary source of infections linked to hospital settings.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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