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Abstract: Methicillin-resistant *Staphylococcus aureus* is one of the most well-known pathogens today. Despite recent declines in its prevalence in some areas, MRSA remains a significant clinical concern with a high rate of morbidity and death. As a result of antibiotic use in the clinic, methicillin-resistant *S. aureus* has arisen (MRSA). Throughout the last few decades, new MRSA clones have been discovered. Unlike traditional MRSA, which is only seen in hospitals, the new clones can spread throughout the community and infect people with no known risk factors. This pattern will continue to emerge as the MRSA reservoir in companion and food animals increases. The aim of this review was to conduct a literature evaluation of basic and clinical MRSA research, with an emphasis on epidemiology, evolution, and *S. aureus* virulence factors. The study goes on to explain how molecular techniques have been used to classify methicillin resistance determinants as well as their evolutionary history.

Key: Methicillin resistant, *Staphylococcus aureus*, Infection, epidemiology, History, evolution

INTRODUCTION

Staphylococcus aureus is a coagulase-positive, Gram-positive Coccus that forms clusters resembling grapes. *S. aureus* is a commensal that is often present asymptotically on parts of human body such as skin, skin glands, and mucous membranes, including noses and guts of healthy individuals (Sahreena and Kunyan, 2018).

One of the first pathogens identified was *Staphylococcus aureus*. This is hardly unexpected, given that it was and continues to be one of the most common causes of human infection. It is significant because of its ability to cause a variety of diseases and its ability to adapt to a variety of environmental situations. *S. aureus* is one of the most common causes of hospital and community-acquired infections, which can be fatal. It can cause infections related to medical instrumentation, such as central-line associated bloodstream infection (CLABSI), as well as some deadly deep-seated infections, such as endocarditis and osteomyelitis, in the bloodstream, skin and

soft tissues, and the lower respiratory tracts (Rachel *et al.*, 2016).

Staphylococcus aureus has a diverse set of virulence factors and toxins, making it a common cause of toxin-mediated disorders such as toxic shock syndrome, staphylococcal foodborne infections (SFD), and scalded skin syndrome. *S. aureus* can also respond to challenges posed by the human immune system, virulence factors and toxins (Rachel *et al.*, 2016; Sahreena and Kunyan, 2018).

Clinically, one of the most concerning aspects of *S. aureus* is the high rate of resistance to numerous antibiotic classes, which makes treatment more difficult. Resistance to penicillin developed in *S. aureus* within two years of its introduction (Tong *et al.*, 2015). The first penicillin-resistant strain of *Staphylococcus aureus* was discovered in 1942 (Akanbi *et al.*, 2017). In the late 1950s, the semisynthetic antibiotic methicillin was created, and in 1960, methicillin-resistant *S. aureus* (MRSA) was clinically recognized (Lakhundi and Zhang, 2018).

S. aureus epidemics linked to antibiotic resistance come in waves (Akanbi *et al.*, 2017). Epidemic of penicillin-resistant bacteria following *S. aureus* strains were the so-called "archaic" MRSA strains, which were initially discovered in the United Kingdom. Initially, the outbreak was mostly confined to Europe. However, new lineages began to develop in the 1980s, resulting in a worldwide catastrophe that is still ongoing (Akanbi *et al.*, 2017).

Methicillin-resistant *S. aureus* infections are associated with higher mortality rates than infections caused by methicillin-susceptible *S. aureus* strains. Furthermore, they lead to longer hospital stays and higher health-care costs (Bale *et al.*, 2018). MRSA strains produce an altered penicillin-binding protein (PBP) that has a lower affinity for most semisynthetic penicillins, as mentioned below. *MecA*, an acquired gene, encodes the protein (Bale *et al.*, 2018). This methicillin-resistant genetic component is carried by the staphylococcal cassette chromosome *mec* (SCC*mec*), a mobile genetic element (MGE) (Cuny *et al.*, 2015; Bitrus *et al.*, 2017). As a result, the acquisition and insertion of these mobile genetic elements into the chromosomes of susceptible staphylococci strains is responsible for the formation of methicillin-resistant staphylococci strains. The development of antibiotic resistance has been a problem to the medical community in terms of staphylococcal infection treatment and control. In most cases, MRSA is responsible for 25 to 50 percent of *S. aureus* infections in hospitals. Their high morbidity and mortality, as well as their resistance to all available penicillins and most other β -lactam drugs (except ceftaroline and ceftobiprole), make them a major concern (Rahimi, 2016).

MRSA was formerly only linked to health-care settings, such as hospitals and other medical facilities, as well as the people who worked in them. It has, nevertheless, become a major source of community-acquired diseases and has established reservoirs in both environments. As a result, MRSA isn't

just a nosocomial pathogen any longer. Since they were initially documented in the 1980s, community-acquired MRSA infections have become more common (Harrison *et al.*, 2013; Perrero *et al.*, 2014). The widespread introduction of community-associated MRSA (CA-MRSA) strains, the epidemiology of MRSA may have changed. These strains were formerly linked to skin and soft tissue infections (SSTIs), but they now can because illnesses associated with health care (Harrison *et al.*, 2013; Perrero *et al.*, 2014), CA-MRSA differs from hospital-associated MRSA (HA-MRSA) in that it is resistant to fewer non-lactam antibiotics, has a smaller form of SCC*mec*, and frequently produces the cytotoxin Pantone-Valentine leukocidin (PVL) (Akanbi *et al.*, 2017). CA-MRSA strains have traditionally been restricted to people outside of health-care settings, as previously stated. MRSA's prevalence and epidemiology are always evolving, with new MRSA clones arising in different parts of the world. The following sections discuss the epidemiology and history of MRSA; MRSA resistance mechanism, evolution and virulent factor of *S. aureus*.

Antibiotic Resistance in *S. aureus*

Antibiotic resistance is believed to have emerged in four waves in *Staphylococcus aureus*, the most recent of which was the appearance of community-acquired methicillin-resistant *S. aureus* (Hiramatsu *et al.*, 2014). Antibiotics were not previously used to treat *S. aureus*. *Staphylococcus aureus* resistant strains were uncommon outside of the hospital environment (Hiramatsu *et al.*, 2014).

Following World War II and the widespread use of antibiotics, penicillin-resistant *S. aureus* emerged. Resistance to penicillin is associated with production of penicillinase, a predominantly extracellular enzyme that hydrolyses the β -lactam carrying antibiotics encoded by *blaZ* gene controlled by two adjacent regulatory genes, the anti-repressor *bla RI* and the repressor *bla I* (Bitrus *et al.*, 2018).

Regardless of the environment, the vast majority of *Staphylococcal* isolates now develop penicillinase. The gene for -lactamase, as well as other antimicrobial resistance genes, is located on a large plasmid (genes for gentamycin and erythromycin), and resistance to penicillin is spread primarily through the spread of resistance strains. It started in hospitals and then spread to the general public (Bitrus *et al.*, 2017).

Since the introduction of methicillin in 1959, the prevalence of penicillin-resistant *S. aureus* has decreased (Bitrus *et al.*, 2018). However, methicillin-resistant *S. aureus* was discovered less than a year after its launch (Bitrus *et al.*, 2017; Rasheed and Hussein, 2020). Antibiotic use in animals for therapeutics, food processing, and disease prevention, in addition to human use, has contributed to antibiotic resistance in humans (Ndi and Barton, 2012). Antibiotics delivered in inadequate doses to food-producing animals can cause bacterial resistance in livestock, increasing the risk of resistant bacterial strains crossing species boundaries, particularly in livestock imported from countries where antibiotics are used carelessly (Bitrus *et al.*, 2017; Rasheed and Hussein, 2020).

The combination of antibiotic resistance and high virulence makes *S. aureus* a dangerous pathogen. *S. aureus* exchanges antibiotic resistance-coding genetic material and virulence determinants amongst strains and other species such as *S. epidermidis* suggest an emerging hyper virulent, multidrug-resistant superbug (Davies and Davies, 2010).

As a “superbug” *S. aureus* has higher morbidity and mortality due to multiple mutations encoding it with high levels of resistance to different antibiotic classes specifically recommended for their treatment. The *Staphylococcal* genome's complexity and maturity have enabled it to modify and adapt to a variety of situations, including exposure to a new antibiotic, adherence to a clinical device, and transition

from an animal to a human host (Humphreys, 2012).

Staphylococcus aureus is unlikely to show a change in sensitivity to a drug administered for a single short course, unless the mutation rate of resistance to that drug is very high, like in the case of streptomycin (aminoglycoside) and erythromycin (macrolide) (Rahimi, 2016).

Staphylococcus aureus is less sensitive to erythromycin than *Pneumococci* or *haemolytic Streptococci* and rapid development of resistance has been observed, especially of *Staphylococci* in vitro (Rahimi, 2016). It was noticed in vivo that resistance is usually not a serious clinical problem with short course of treatment with erythromycin but resistance is more likely to develop with prolonged use.

Epidemiology and History of MRSA

In 1961, methicillin was introduced as the first semisynthetic penicillinase-resistant penicillin. Following its publication, reports of methicillin-resistant isolates surfaced (Turner *et al.*, 2019). Clinicians have been concerned about Methicillin-resistant strains are becoming more common. *S. aureus* is resistant to the antibiotic methicillin. Methicillin-resistant *S. aureus* (MRSA) infections have a greater clinical outcome than methicillin-sensitive *S. aureus* infections. Infections caused by *Staphylococcus aureus* (MSSA) (Gnanamani *et al.*, 2017). MRSA clones spread quickly across foreign boundaries after being discovered in a British hospital (Oliveira *et al.*, 2018; Bitrus *et al.*, 2018). When these uncommon MRSA clones are discovered in a new setting, they rapidly spread, leading to the formation of resident clones and an increase in the number of nosocomial infections (Plano *et al.*, 2011; Gnanamani *et al.*, 2017).

MRSA isolates, including penicillin-resistant strains, contain antimicrobial resistance genes (Malachowa and DeLeo, 2010). In the same way that penicillin resistance spread in the 1940s, MRSA is spreading now.

In the 1960s, methicillin resistance was first discovered in hospitals and it is becoming more well-known among the general public (Kandala *et al.*, 2017). While many of these diseases occurred in patients who had previously visited a hospital, the number of patients who had never visited a hospital has recently increased (Kandala *et al.*, 2017). Both rural and urban patients have been identified with these community-based infections (Kandala *et al.*, 2017; Tong *et al.*, 2015).

MRSA's evolutionary origins are unknown, and there is no agreement on nomenclature, the number of major MRSA clones, or the relationship between clones identified in different countries (Brurec *et al.*, 2011). Over 3,000 MRSA isolates from various regions of the world were characterized by Oliveira *et al.* (2018), just a few disease clones, namely the Iberia, Brazilian, Hungarian, New York/Japan, and Paediatric clones, have been confirmed worldwide. This suggests that acquisition of the *Staphylococcal* cassette chromosome SCC mec, the mobile genetic elements harboring the *mecA* gene that confer methicillin resistance, has been a rare event (Brurec *et al.*, 2011).

The evolutionary changes of MRSA have resulted in its continuing threat to public health. The rising prevalence of MRSA infections in hospitals has resulted in a rise in the use of vancomycin, the last antibiotic that MRSA strains were reliably susceptible to (Howden *et al.*, 2011; Raymund *et al.*, 2013).

Evolution of MRSA

Our understanding of MRSA evolution has been greatly helped by the development of molecular methods that classify both the methicillin resistance determinants and the strain phylogeny (evolutionary history) (Bitrus *et al.*, 2018).

MRSA strain identification based on sequences of seven housekeeping genes (Brurec *et al.*, 2011) and whole genome typing techniques, such as amplified fragment length polymorphism (AFLP), which records nucleotide sequence variation,

insertions, and deletions across the genome (Taylor *et al.*, 2020) have provided convincing molecular epidemiological evidence that MRSA and *S. aureus* as a species developed predominantly through clonal transmission (Wolk *et al.*, 2009; Taylor *et al.*, 2020).

Horizontal migration of DNA from other strains or organisms, on the other hand, has been reported and it's thought to play a role in the growth of *S. aureus* resistance (Brurec *et al.*, 2011). This horizontal transfer is brought about mainly by events (Brurec *et al.*, 2011). It is believed that, MRSA strains have emerged as a result of the introduction of the wide mobile genetic factor SCC mec (*Staphylococcal* Cassette Chromosome methicillin-resistant *S. aureus*) into a methicillin-resistant *S. aureus* strain (Bitrus *et al.*, 2018; Taylor *et al.*, 2020).

Methicillin Resistance Mechanism

The *mecA* gene, which is found on the chromosome, is required for methicillin resistance (Oliveira *et al.*, 2018). Penicillin binding protein 2a is a protein that binds to penicillin (PBP2a, also known as PBP21) is a 78-kilodalton protein that is synthesized by *mecA*. PBPs are membrane-bound enzymes that catalyze the transpeptidation reaction required for peptidoglycan chain crosslinking (Li *et al.*, 2011; Oliveira *et al.*, 2018). They have behavior that is close to that of serine proteases, from which they seem to have descended. It has a poor affinity for β -lactam antibiotics because of this; PBP2a serves as a stand-in for the other PBPs, allowing *Staphylococci* to tolerate large concentrations of them. A soluble PBP2a derivative's crystal structure has been established in some experiments, implying that methicillin resistance confers resistance to all β -lactam antibiotics. PBP2a's active site is distinct from that of other PBPs in that it prevents all β -lactams from binding allowing the transpeptidation reaction to proceed (Cheung *et al.*, 2021). Methicillin resistance is phenotypic, this means that each MRSA strain has a different proportion of bacteria that grow at various methicillin concentrations (Cheung *et al.*, 2021).

In certain MRSA strains, homologues of the *bla_Z* regulatory genes control resistance expression in the same way that the genes *bla_{R1}* do. The *mecA* response to β -lactam antibiotics is regulated by these genes, *mecI* and *mecRI*, while *blaI* control the *bla_Z* response to penicillin. *blaI* regulate the *bla_Z* response to penicillin, the *mecA* response to β -lactam antibiotics is regulated by these genes, *mecI* and *mecRI*. MRSA strains, either *mecI* or *blaI* must be involved, implying that this is a defense mechanism to avoid toxin protein overproduction (Cheung *et al.*, 2021). The *fem* genes are another group of genes involved in crosslinking peptidoglycan strands and leading to methicillin resistance heterogeneity (factor important for methicillin resistance) (Cheung *et al.*, 2021).

Most clinical isolates display under routine culture conditions, there is a heterogeneous pattern of resistance. Under certain culture conditions, such as incubation at 300°C or growth in hypertonic culture medium supplemented with NaCl or sucrose, heterogeneous strains may appear homogeneous (i.e., at 50mg of methicillin per ml, 1% or more of the cell develops) (Brown *et al.*, 2012). Incubation at 37°C to 43°C or the addition of EDTA (PH 5.2) favors a heterogeneous pattern and has the potential to completely eliminate resistance. Methicillin resistance expression variations with various culture conditions are considered to be intermittent and phenotypic. Methicillin resistance express is seen in the borderline (or low level) methicillin-resistant strains of *S. aureus*. Methicillin MICs equal to or just above the susceptibility break point (e.g. Oxacillin MICs of 4.8 mg/ml) define such borderline methicillin resistance (BORSA) strains (Cheung *et al.*, 2021). BORSA strains containing *mecA* develop PBP2a and are highly heterogeneous methicillin resistant strains. These strains have a small

number of cells that are resistant to the drug and can spread at high concentrations (Cheung *et al.*, 2021).

BORSA that lack the *mecA* gene fall into the second group. This can be distinguished from extremely heterogeneous *mecA*-positive BORSA strains phenotypically by the absence of highly resistant clones in the population of cells (Brown *et al.*, 2012). The hypothesis is that BORSA in *mecA* negative strains is either as a result of modification of normal PBP genes or overproduction of *staphylococcal* β -lactamase (Brown *et al.*, 2012).

Staphylococcus aureus is resistant to the antibiotic methicillin. *S. aureus* is resistant to the antibiotic methicillin. The penicillin binding protein of *S. aureus* is special (PBP2a). *S. aureus* chromosome contains the *mecA* gene. PBP2a is coded by *S. aureus*. a 76-kDa penicillin binding protein. The *mec* factor (40-60kb) isolates aureus (also referred to as PBP21). *S. aureus* has been proposed as the origin of the *mecA* gene (Chakraborty *et al.*, 2011). Although the mechanism by which this species acquires genes is unclear, two genes on the *mec* portion of one isolate, *ccrA* and *ccrB*, have been discovered to make recombinase proteins that can remove and replace the *mec* element on the chromosome (Chakraborty *et al.*, 2011; Magiorakos *et al.*, 2012). PBP2a shares the common structure motifs associated with penicillin binding with other PBPs, however, it has a lower tolerance for β -lactam antibiotics. As a result, PBP2a remains active, maintaining peptidoglycan glycan crosslinking, even at therapeutic methicillin levels, Other PBPs' transpeptidational activities would be inhibited. Crosslinking is significantly reduced in cells grown in the presence of methicillin. PBP2a cannot fully compensate for the other PBPs. The cell's survival is, however, ensured by the minimal degree of crosslinking.

Altered penicillin Binding Protein (PBP2a)

MRSA vary generally from methicillin-sensitive *S. aureus* isolates by the existence of the *mecA* gene, which encodes the 76 kDa penicillin binding protein, PBP2a can be located on the *mec* element's chromosome, which is a 40-60kb foreign DNA stretch (also referred to as PBP21). The *mecA* gene is believed to originate in *S. aureus* (Bitrus *et al.*, 2018), *ccrA* and *ccrB*, two genes located on the *mec* element of one isolate, code for recombinase proteins that can remove and integrate the *mec* portion into the chromosome (Chakraborty *et al.*, 2011). PBP2a, like other PBPs, has penicillin-binding motifs in its structure, on the other hand, has a low affinity for β -lactam antibiotics. PBP2a is active at therapeutic methicillin concentrations, which would otherwise inhibit other PBPs' transpeptidational activities, preventing peptidoglycan crosslinking. Crosslinking is significantly reduced in cells grown in the presence of methicillin, PBP2a is unable to fully compensate for the other PBPs. On the other hand, a low level of crosslinking is adequate to ensure cell survival (Chakraborty *et al.*, 2011).

Expression of PBP2a Regulation

Two genes, *mecR1* and *mecI*, are found on the *Staphylococcal* chromosome are located next to *mecA* and are co-transcribed in a different way than *mecA*. *MecR1* (membrane bound signal transduction protein) is produced by the *mecR1* gene, while *mecI* (transcriptional regulator) is produced by the *mecI* gene (*MecI*). The promoters of these genes, as well as an operator region containing the -10 sequence of *mecR1*, are located between *mecA* and *mecR1* (Bitrus *et al.*, 2017). *MecR1* and *MecI* have protein sequences that are very similar to *BlaR1* and *BlaI*, which are involved in the plasmid-mediated *Staphylococcal* β -lactamase gene, *blaZ*, inducible expression. The *BlaR1* and *BlaI* genes are arranged similarly to those of the *mecA* system, implying that *mecA* may have

inherited the *blaZ* system's regulatory genes at some stage (Sowash *et al.*, 2014). *BlaI* will regulate PBP2a expression because the operator regions are close enough (Shibabaw *et al.*, 2013).

When *BlaR1* and *BlaI* are present, as they often are in clinical MRSA isolates, PBP2a expression is typically induced by a plasmid containing the *blaZ* regulatory genes (Shibabaw *et al.*, 2013).

The inducible β -lactamase speech signaling mechanism has been deciphered (Shibabaw *et al.*, 2013). *BlaI* is a DNA-binding protein that forms a homodimer with the operator region and prevents *blaZ* and *BlaR1*-*blaI* from transcribing RNA. In the absence of a β -lactamase antibiotic, β -lactamase is expressed at low levels. Using a penicillin-binding extracellular domain, *BlaI* recognizes the β -lactam and transmits the signal to the cytoplasmic membrane through a second intercellular zinc metalloprotease signaling domain. As the intracellular zinc metalloprotease domain of *BlaR1* binds to β -lactam, it converts from an inactive proenzyme to an active protease (Bitrus *et al.*, 2017). *BlaI* is thought to be cleaved by the active form of *BlaR1* either resulting in fragments that are unable to form dimers or bind DNA, either directly or indirectly (Bitrus *et al.*, 2018). Transcription of both *blaZ* and *blaI*-*blaI* can begin without *BlaI* bound to the operator site, and β -lactamase synthesis can confer β -lactam resistance. Another gene product, *BlaR2*, regulates β -lactamase synthesis as well, though its function is unknown. It's still unclear whether or not other proteins are involved in the signaling mechanism. In isolates carrying the normal regulatory genes (*mecA* and *mecR1*-*mecI*), PBP2a expression is not strongly inducible, and induction is much slower (15 minutes for β -lactamase expression vs. up to 48 hours for PBP2a synthesis), unlike β -lactamase synthesis. This is because *MecI* controls *mecA* transcription very tightly (Shibabaw *et al.*, 2013), and most pre-MRSA isolates, while carrying the *mecA* gene, are methicillin-resistant.

Methicillin-resistant *S. aureus* has emerged as a result of antibiotic use. selective strain on *aureus* mutated strains of *S. aureus* or deletions in the promoter operator regions of the *mecI* or *mecA* genes, resulting in an inactive repressor and constitutive PBP2a expression (Shibabaw *et al.*, 2013; Bitrus *et al.*, 2018).

Virulence Factors of *S. aureus*

Toxin production or direct invasion and degradation of tissue are two ways that *S. aureus* causes disease. *Staphylococcus aureus* causes some diseases include impetigo, *staphylococcal* scalded skin syndrome (SSSS), *Staphylococcal food poisoning*, and *Toxic Shock Syndrome (TSS)*. Other diseases are caused by the species spreading, resulting in abscesses and tissue destruction (Bitrus *et al.*, 2017).

Beta toxin

The majority of *S. aureus* strains β toxin, also known as Sphingomyelinase C is a heat-labile 35 KDa enzyme found in *S. aureus*. This enzyme is toxic to erythrocytes, leukocytes, macrophages, and fibroblasts, among other cells, and has sphingomyelin and lysophosphatidylcholine specificity. In susceptible cells, it catalyzes membrane phospholipid hydrolysis, with the amount of sphingomyelin exposed on the cell surface determining the degree of lysis. The differences in toxin sensitivity between organisms are thought to be the result of this. The development of beta-toxin is influenced by the species. The erythrocytes of sheep, cows, and goats are most vulnerable. Human erythrocytes are the most responsive, Murine and canine erythrocytes were next, followed by human erythrocytes. The amount of sphingomyelin in the membrane affects the erythrocytes' sensitivity. The function of β toxin in human disease is unknown, when paired with a toxin; it is thought to be linked to tissue deterioration and abscess formation in *staphylococcal* diseases (Cheung *et al.*, 2021).

Gamma-toxin

Gamma-toxin can lyse human, erythrocytes from sheep and human lymphoblastic cells and rabbits were used in the study. Toxins with two components, the Hlg and luk PV loci code for bicomponent toxins such as gamma-toxin, leukocidin, and other bicomponent toxins. In this class of toxins, two proteins function together: one S (LukS-PV, H1gA, or H1gC) and one F (LukS-PV, H1gA, or H1gC) (LukS-PV, H1gA, or H1gC). (H1gA, H1gC, or LukS-PV). (H1gA, H1gC, or LukS-PV) (LukF-PV or HlgB), which are distinguished by their ion-exchange chromatography mobility (slow or fast). The prototype bicomponent toxins are Pantone-Valentine leukocidin (PVL) and gamma-toxin. LukS-PV and LukF-PV are PVL S and PVL F and F elements, respectively. H1gA and H1gB are the S and F components of gamma-toxin, respectively (Cheung *et al.*, 2021). The F and S components must bind in a specific order for synergistic function. On erythrocytes, gamma-toxin causes H1gB (F) to bind first, then HlgA (S), resulting in the formation of a pore (Cheung *et al.*, 2021).

Delta toxin

Almost every strain of *S. aureus*, as well as the majority of other *Staphylococci*, produces 6 toxins a 3 KDa polypeptide. The toxin affects erythrocytes, other eukaryotic cells, Cell membrane structures, organelles, spheroplasts and protoplasts, and certain mammalian cells. The non-specific membrane toxicity of the toxin backs up the hypothesis that it acts like a surfactant, disrupting cellular membranes in a detergent-like manner. When used at high concentrations, in laboratory animals, it has also been stated to be dermonecrotic and lethal. Phospholipids block the function of delta-toxin (Charaborty *et al.*, 2011). The *hlg* gene generates a 26-residue long peptide that peaks at the end of the exponential growth cycle and can be purified in a number of ways (Cheung *et al.*, 2021). Neutrophils, monocytes, lymphocytes, and erythrocytes have various toxin affinities (Charaborty *et al.*, 2011).

By allowing pores in the membrane to form, the toxin causes erythrocytes and other mammalian cells to lyse. Human and canine strains of *S. aureus* express at least two different variants of 6 toxin. *aureus* is the scientific name for the bacteria *S. aureus*. *S. aureus* are just 62% identical immunologically (Cheung *et al.*, 2021).

Leukocidin

S. aureus has the ability to produce a toxin that targets polymorphonuclear leukocytes. Leukocidin can be a virulence factor since phagocytosis is a key defense against *Staphylococcal* infection. The fact that it can destroy leukocytes gives it its name (of which neutrophils are one type). PVL is made up of two proteins: S and F. In that it binds to GM1 gangliosides, the S portion is close to the B element of an A-B toxin. Both, however, have enzymatic activity and are active in the metabolism of phospholipids and phosphatidylinositol. In eukaryotic cells, phosphatidylinositol, an essential signaling molecule, regulates a range of cellular processes. As a consequence, it appears that this two-component toxin disrupts normal cellular functions by changing phospholipid metabolism (Charaborty *et al.*, 2011; Cheung *et al.*, 2021). According to most studies, the S portion binds first and then forms pores, the PVL's two components bind to human neutrophils in a particular order (Cheung *et al.*, 2021).

Exfoliative toxins A and B

Exfoliative toxin A (ETA) and exfoliative toxin B (ETB) are two serologically distinct exfoliative toxins that have been identified (ETB). These toxins cause SSSS, at the desmosomes, skin layers are separated intraepidermal and is most commonly seen in newborns. The illness starts with a generalized erythema near the mouth that quickly spreads across the body. The epidermal layer wrinkles irreversibly when the skin is gently rubbed, resulting in the classic positive Nikolsky symbol. Wide flaccid sterile bullae occur later, leading to the stratum granulosum layer being

separated. It takes 7 to 10 days from the start of the illness to complete recovery. There are no long-term scars on the skin, and the toxins that cause the infection are not toxic to the host (Cheung *et al.*, 2021).

Toxin-1 in toxic shock syndrome

Fever, hypotension, and rash, as well as desquamation and multiple organ system involvement, are all symptoms of TSS. It is brought about by a toxin. Toxic shock syndrome toxin-1 (TSST-1) is an exotoxin developed by some *S. aureus* strains in a rabbit model; *S. aureus* can mimic many of the clinical symptoms of TSS. It was previously known as enterotoxin F and pyrogenic exotoxin C (there is no rash or desquamation). While not all *Staphylococcal* isolates from TSS patients tested positive for enterotoxin B, the vast majority did. This second toxin's role in TSS is unknown. Coagulase-negative *staphylococci* may also produce TSS (Chakroborty *et al.*, 2011).

Capsule

Staphylococci cultured in vitro seldom have a polysaccharide layer that fits loosely (slime layer), but it is thought to be more normal in vivo. *S. aureus* clinical isolates account for more than 90% of all *S. aureus* isolates. Capsular polysaccharides are generated by *S. aureus*. In *S. aureus*, eleven capsular serotypes have been described. The most common cause of infection is *Staphylococcus aureus*, serotypes 5 and 8 of *Staphylococcus aureus* (Chakroborty *et al.*, 2011; Cheung *et al.*, 2021). The colony morphology can also be used to split these capsules into two classes. On solid medium, serotype 1 and 2 capsules are mucoid, and the strains that make them are heavily encapsulated. Microcapsules, which have a thin capsular layer and grow in non-mucoid colonies on solid medium, make up the rest of the serotype 3 to 11 capsules. Antiphagocytic virulence factors have been discovered, such as mucoid-type capsules that mask C3b accumulated on bacterial cell walls and prevent it from being recognized receptors on phagocytic cells (Chakroborty *et al.*, 2011; Cheung *et al.*, 2021).

The capsule defends the bacteria against polymorphonuclear leukocytes and prevents mononuclear cell proliferation after mitogen exposure. Bacterial adhesion to catheters and other synthetic materials is also made easier. Examples include Grafts, shunts, prosthetic valves, and joints are all examples of grafts. This property is especially essential for coagulase-negative *staphylococci* survival, which are relatively virulent (Chakraborty *et al.*, 2011).

The ability of *S. aureus* Microcapsule-deficient strains to induce experimental infective endocarditis (IE) has been demonstrated. It means that the microcapsule can obscure essential cell wall proteins expressed on the cell surface that are involved in IE pathogenesis (Cheung *et al.*, 2021).

Protein A

Protein A is evenly coated on the surface of most *S. aureus* strains (except those that are coagulase-negative). This protein binds to the peptidoglycan layer covalently and Immunoglobulins (Ig) IgG1, IgG2, and IgG4 bind to the Fc receptor, effectively preventing antibody-mediated immune clearance. Protein A's function in *Staphylococcal* infections isn't entirely clear. Protein A can obstruct opsonized bacteria

phagocytosis by binding IgG to receptors on the host cell. Antibodies can bind to extracellular protein A, forming specific antibodies that are then consumed by the complement system (Chakraborty *et al.*, 2011; Foster, 2016).

Endocarditis, pneumonia, empyema, and osteomyelitis are all examples of skin infections and septic arthritis is only a few of the diseases that can be caused by it, bacterial adherence to von Willebrand factor is mediated by protein A. When a foreign body is present, substantially less staphylococci are required to cause disease, such as a splinter, catheter, shunt, prosthetic valve, or joint (Foster, 2016; Cheung *et al.*, 2021).

Conclusions

Methicillin resistant *S. aureus*, a highly virulent and difficult-to-treat "superbug," can alter its gene content and expression to produce new strains with increased virulence and colonization ability. MRSA is currently regarded an urgent threat to public health because it is an extremely adaptable disease with a shown ability to build resistance.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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