**ABSTRACT**

*Staphylococcus aureus* is gram-positive cocci, which is consistently one of the four causes of hospital infections. *S. aureus* is a member of the normal nasal and intestinal flora in 30-50% of the population. But this organism is carried in almost 90% of the clinical staff of hospitals. *S. aureus* is an important cause of a wide variety of infectious diseases in humans. This bacterium often causes infections such as endocarditis, bacteremia, and pneumonia. *S. aureus* species are typically resistant to a large number of drugs. These bacteria are able to sustain and grow properly in the hospital environment and are easily transmitted to people who have weak immune systems. So far, methicillin-resistant *S. aureus* (MRSA) has been limited to hospitals, but with the increase in skin and soft tissue infections and necrotizing pneumonia in younger patients, methicillin-resistant staphylococci in the community (CA-MRSA) has spread throughout the world.

**Keywords:**

Gram-Positive Bacterium, MRSA, CA-MRSA, Antibiotic Resistance, Toxin

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**1. Introduction**

*S. aureus* is a gram-positive bacterium that can infect host tissues and cause severe complications and lead to death. Among drug-resistant pathogens, *S. aureus* clinical isolates have become a leading cause of hospital infections, with the emergence of antimicrobial resistance [1]. In cases of bacteremia, *S. aureus* bacteria circulate in the blood and have the potential to seed vital organs, leading to disseminated infections such as osteomyelitis, endocarditis, and urinary tract infections [2]. Surgeon Alexander Ogston discovered *S. aureus* in 1880 while studying patients with ulcerative lesions. *S. aureus*, a member of the Firmicutes genus in the Staphylococcus family, exhibits gram-positive staining. It thrives at 37°C and pH 7.4, displaying beta hemolysis and positive reactions for catalase, coagulase, and mannitol fermentation [3].

The purpose of this study is to investigate *S. aureus* and the risk of infection with this bacterium in medical centers. PubMed.gov and Google Scholar were searched for published articles on *S. aureus* bacteriology, toxins, antibiotic resistance, healthcare infections, and infection control.

**2. Bacteriology**

*S. aureus* is catalase-positive and spherical cocci and looks like a grape cluster in the smear. *S. aureus* is the only species that produces coagulase [4-6]. Staphylococci have different surface antigens and some species of staphylococci have a weak antiphagocytic capsule. This capsule is destroyed during cultivation and is not known to be pathogenic [7]. Protein a form *S. aureus*, abbreviated as (SpA). It is a 40 KD protein that binds to the Fc-region (Figure 1). *S. aureus* can be part of the natural flora of the skin, eyes, gastrointestinal tract, and upper respiratory
tract. But it appears as a human-invasive pathogen that is able to persist and spread in vivo [8].

Fig. 1. Protein a binds to peptidoglycan in S. aureus and immunoglobulin (IgG 1, IgG 2, IgG 4) are connected to the FC region.

Biofilm production by bacteria is a very important factor that leads to treatment failure. One of the most important factors of S. aureus is the ability to form biofilm. S. aureus forms a complex structure of extracellular polymeric biofilm that provides a completely safe environment for the formation of microcolonies and their maintenance. The S. aureus biofilm protects cells from temperature changes, nutrient deprivation, and dehydration, and protects cells from antibacterial drugs. And the drugs are partially or completely inactivated against S. aureus, because they are either less permeable or completely impermeable due to the presence of biofilms that surround the bacterial cells. In S. aureus, polysaccharide intercellular adhesion (PIA) is coded by icaA and icaD genes. PIA production is responsible for staphylococcal biofilm growth [9-12].

2.1. S. aureus toxins

Many pathogens of S. aureus are toxins. Toxins are molecules secreted by the host organism that directly affect the host. The main toxins of S. aureus are divided into three main groups: exfoliating toxins (ETs) and superantigens (SAgs), pore-forming toxins (PFTs), pore-forming toxins including hemolysin-α, hemolysin-β, phenol-soluble modulins (PSMs) are leukotoxins [13]. S. aureus produces three types of exotoxins: staphylococcal enterotoxin, exfoliative toxin and toxic shock syndrome toxin-1 (TSST-1) [14].

Toxins that damage the membrane are mediated by the α-toxin receptor. α-toxin is a 34 KD polypeptide secreted by clinical strains of S. aureus (Figure 2) [15]. ADAM10 is a cellular receptor for Hla. And for this reason, it can investigate the effects of the toxin in a specific cell population. This toxin plays a very important role in the pathogenesis of S. aureus [16, 17].

Fig. 2. The effect of α-toxin on susceptible host cells, Functions of the α-toxin complex (red), ADAM10 complex (blue). The binding of α-toxin to the ADAM10 receptor causes focal destruction of the membrane, Cell Lysis (dependent on toxin concentration) and increased ADAM10 metalloprotease activity (indicated by an asterisk).

2.1.1. Hemolysin-β (β-Toxin)

Hemolysin-β was identified by Glenny and Stevens in 1935. β-hemolysin is a hot-cold hemolysin that is produced by 10-20% of S. aureus strains isolated from humans. This toxin causes the lysis of human erythrocytes. This toxin causes lysis of human erythrocytes when incubated at 37% temperature and then transferred to cold temperature. β-hemolysin is considered toxic for different cultures [18, 19]. This poison is highly hemolytic in sheep, but not in rabbits. This poison is also called sphingomyelinase and the reason for that is the difference in sensitivity to red blood cells and due to the different contents of sphingomyelin in these cells (Figure 3) [20]. The mechanism and the role of this toxin in the disease are not yet clearly known. It has been confirmed that β-hemolysin is produced in many animal isolates. This toxin is produced in strains isolated from bovine mastitis and also in chronic human skin infections [21, 22].
Lecotoxins are composed of two different protein components that assemble to form β-barrel pores [23, 24]. Four two-component leukotoxins structurally similar to Hla have been isolated from *S. aureus* strains associated with human infections: Panton-Valentin leukocidin (PVL), gamma (γ)-hemolysin (HlgA, HlgC, HlgB), Leukotoxin ED (LukE, LukD) and Leukotoxin AB/GH (LukAB/LukGH) [25].

Most species of *S. aureus* produce Panton-Valentine Leukocidin. This toxin contains two components, S and F [26]. Penton-Valentin leukocidin (PVL) plays a very important role in the pathogenesis of methicillin-resistant *S. aureus*. Clinical data from past studies show that there is a relationship between PVL and severe cases of Staphylococcus pneumonia. A clear understanding of the mechanism, structure and function of PVL is very important to develop new therapies [24].

Exfoliative toxins (ETs), which are considered epidermolytic toxins, are serine proteases secreted by *S. aureus*. These proteases identify desmosome cadherins in the surface layers of the skin [27]. ETs are exotoxins that are associated with the cutting of keratinocyte junctions in the host's epidermis, which causes exfoliation of the skin and the formation of blisters [28]. The main known ETs are A/B/C/D (ETA, ETB, ETC, ETD) [8].

Superantigens (SAgs) were first known as staphylococcal enterotoxins (SEs) because they had common symptoms of *S. aureus* food poisoning such as diarrhea and vomiting. However, some of the most recently identified toxins belonging to this group do not exhibit these diarrhea and vomiting properties [29].

### 2.2. Antibiotic resistance in *S. aureus*

Infections caused by *S. aureus* can be controlled with antibiotic therapy. Due to excessive antibiotic use, resistant strains of *S. aureus* have developed, including methicillin-resistant *S. aureus* (MRSA). The ribosome, nucleic acids, and cell envelope are the three major targets of antibiotics in staphylococci. Various mechanisms play a role in the emergence of antibiotic resistance in *S. aureus*, including drug efflux, deactivation of antibiotics, reduced permeability and expression, and mutation of target proteins, resulting in the rapid evolution of treatments (Fig.4). A resistance determinant may be acquired through horizontal transfer from mobile genetic elements, namely plasmids, transposons, or the staphylococcal cassette chromosome, or mutations in chromosomal genes. As the clinical world faces an increasing number of drug-resistant strains of *S. aureus*, this issue is of great concern [30, 31].
destroying the antibacterial properties of the drug. This enzyme is encoded by R plasmids. The plasmid gene that carries the enzyme is blaz. As a result, penicillin antibiotics gradually became less effective, resulting in large-scale resistance worldwide [32].

As a result of penicillin’s failure to treat the Staphylococcus infection, methicillin was used. Following the failure of both of these antibiotics, Quinolones were used. By attacking and inhibiting bacterial topoisomerases, quinolones destroy bacteria and also facilitate supercoiling of DNA and DNA strand separation. Unfortunately, S. aureus has developed resistance against quinolones too, which makes the use ofloxifloxacin and gemifloxacin in treating Gram-Positive bacteria worthwhile. Furthermore, this organism can become resistant to quinolones by point mutations as well. Topoisomerase subunits undergo point mutations. For example, a point mutation at Gr1A in the topoisomerase IV subunit and a point mutation at GyrA in the Gyrase subunit. Also by using NorA efflux pumps, S. aureus acquired resistance to fluoroquinolones [32, 33].

After methicillin failed to treat S. aureus infections due to its formation of MRSA strains, vancomycin became the last hope. The synthetic antibacterial drug methicillin is widely used to treat S. aureus. Since methicillin was highly resistant and failed to treat most MRSA infections, Vancomycin became the most important antibiotic for treating the disease. MRSA infection-causing strains do not acquire vanA, but thickened cell walls that are rich in dipeptides cause resistance, which reduces drug availability. Despite the issues, Vancomycin was regarded as one of the most effective drugs against MRSA strains [34].

2.3. S. aureus infections

As a commensal bacterium and a human pathogen, S. aureus possesses both properties. Innumerable S. aureus colonies can be found within the human population. In addition, it can cause bacterial infections like bacteremia and endocarditis, Osteomyelitis as well as skin and soft tissue infections, joint infections, pulmonary infections and infections related to a medical device [35, 36].

3. Bacteremia and endocarditis

Probably the most well-known manifestation of S. aureus infection is bacteremia. The prevalence, prognosis, and outcome of S. aureus bacteremia have been studied in several industrialized regions. It remains unclear how S. aureus bacteremia spreads, especially in nonindustrial regions. Bacteremia caused by S. aureus is also hampered by a lack of evidence-based guidelines. Several complications may occur in the event of an S. aureus bacteremia, such as endocarditis, sepsis, or metastatic foci of infection. S. aureus bacteremia is associated with infective endocarditis in 12 percent of patients. It is superior to transthoracic echocardiography when it comes to diagnosis of perivalvular abscess, valve replacements, and recognizing smaller vegetation. Infective endocarditis can be diagnosed and predicted more accurately with transthoracic echocardiography. According to a cost-effectiveness study, transesophageal echocardiography is a more cost-effective treatment than two to four weeks of empiric antimicrobial therapy for catheter-associated S. aureus bacteremia in clinically uncomplicated cases. However, this is still a controversial topic [36-39].

4. Skin and soft tissue infections

As well as folliculitis, impetigo, furuncles, carbuncles, hidradenitis suppurativa, and cellulitis, S. aureus can cause a broad range of infections in the skin and soft tissues. Management is influenced by the level of involvement. It may be sufficient to simply cleanse the wound and drain it in cases of minor localized lesions. Topical treatment with mupirocin (Bactroban) can be used for localized impetigo. If there are systemic symptoms in addition to cellulitis, systemic antibiotics are prescribed. There should be incision and drainage of larger carbuncles or abscesses. It is becoming increasingly common to encounter community-acquired MRSA, so purulent lesions that require systemic therapy should be cultured in order to perform an antimicrobial susceptibility test, and initial empiric treatment should take into
account the prevalence of community-acquired MRSA locally [40, 41].

5. Catheter-related infections

*S. aureus* bacteraemia is associated with non-tunneled central venous catheters, according to Infectious Diseases Society of America guidelines. In cases of purulence, erythema, pocket infection, or a complicated deep-seated infection associated with a tunneled device (i.e., Hickman catheter) or implantable device, it should be removed. In cases of catheter-related bloodstream infections, transesophageal echocardiography is recommended. Systemic antimicrobial therapy is recommended if there is no endocarditis, septic phlebitis, or deep-seated infection. In patients with uncomplicated infections, it is advisable to combine antibiotic lock therapy (filling the catheter lumen with high concentrations of antibiotics and leaving them there for several hours or days) with parenteral antibiotic therapy for two weeks to salvage the catheter. Whenever there is a relapse of bacteremia or clinical deterioration after 72 hours of therapy, the catheter should be removed. MSSA catheter-associated infections should be treated with a beta-lactam (e.g., nafcillin) whereas MRSA should be treated with vancomycin [42, 43].

6. Osteomyelitis

More than half of all osteomyelitis isolates are *S. aureus*, and over one-third are MRSA. Symptoms of vertebral osteomyelitis can worsen following the hematogenous spread of *S. aureus*. 4-6 weeks course of antimicrobial therapy should be administered for *S. aureus* osteomyelitis. In patients with vertebral osteomyelitis who have neurologic symptoms, magnetic resonance imaging should be performed in order to evaluate for epidural abscesses. Often, long bone osteomyelitis occurs as a result of hematogenous spread in children. Children who respond promptly to initial antibiotics and have no complications may receive short courses (e.g., two weeks) of intravenous antibiotics followed by oral antibiotics. When osteomyelitis occurs after orthopedic surgery or trauma, in addition to prolonged antimicrobial therapy, surgical treatment is generally necessary. Generally, infected hardware must be removed, and if bone nonunion occurs, antimicrobial therapy may be used to defer this process until it is determined that it is stable [44].

7. Joint infections

Joint infections are often caused by *S. aureus*. The majority of cases are treated with drainage and antibiotics for four weeks. Sometimes, antimicrobials are given orally to patients who do not have bacteraemia within the last two weeks. The presence of foreign materials can make eradicating prosthetic joint infections difficult. Usually, the prosthesis must be removed followed by antibiotic treatment for four to six weeks. In cases of early-onset infection, quinolone plus rifampin (Rifadin) may be used to treat joint prostheses without removal of the prosthesis [36, 45].

8. Pulmonary infections

As a common pathogen in nosocomial pneumonia, *S. aureus* pneumonia can be spread hematogenously or by aspiration. The Panton-Valentine leukocidin has been implicated in community-acquired pneumonia caused by *S. aureus* after influenza infection. Radiology results can vary from localized consolidation to abscesses to multilobe diffuse infiltrates on chest radiographs. Local pneumonia can cause empyema. In addition to chest-tube drainage, thoracoscopic or open drainage may be necessary [36, 46].

9. Central nervous system infections

According to estimates, *S. aureus* causes roughly 2 percent of all cases of meningitis caused by hematogenous sources or postoperative sources. A shunt or epidural catheter was commonly used in patients with postoperative *S. aureus* meningitis. As soon as the infection has cleared, these devices must be removed and replaced. Most brain abscesses and epidural abscesses are caused by *S. aureus*, followed by 60 to 90 percent of septic venous thromboses. Although medical therapy has been successful in treating some small abscesses in patients without neurological deficits, surgical or radiographic drainage is usually necessary [36, 47].
10. Control of \textit{S. aureus} infection in hospitals

In the 1950s and 1960s, penicillin-resistant \textit{S. aureus} infections in hospitals stimulated research into staphylococcal epidemiology. Several hospitals conducted extensive studies to evaluate important issues such as common sources of \textit{S. aureus} infections, routes of transmission, and prevention measures. These studies resulted in the implementation of strict infection control measures, including appropriate isolation facilities and infection prevention measures among hospital staff, which resulted in a decrease in the frequency of \textit{S. aureus} infections over the following several years. Today, methicillin-resistant strains of \textit{S. aureus} have become a major problem in hospitals around the world. In hospitals where MRSA strains are endemic, these strains account for 20-40\% of all \textit{S. aureus} infections \cite{43, 48}.

As a consequence, many MRSA strains are also resistant to other antibiotics, including erythromycin, aminglycosides, tetracyclines, rifampicin, clindamycin, trimethoprim-sulfamethoxazole, and fluoroquinolones. For patients with severe MRSA infections, vancomycin and teicoplanin are often the only antimicrobials available. Practically, septic lesions and transmission sites of patients and staff are the only true sources of \textit{S. aureus} in hospitals. As a result, microorganisms multiply in these areas. From these areas, they are transmitted to other patients and personnel as well as to vehicles for infection, i.e. blankets, clothes, ward dust, etc. Anterior nares are the primary carriers of \textit{S. aureus}. Staphylococci can be found in the anterior nares in some perineal carriers, but not in other persons who carry staphylococci. Throats and axillae are less frequently affected \cite{48-50}.

A significant source of MRSA in hospitals comes from the carriage of patients and hospital personnel. Eliminating this source is vital. The most effective topical agent for the eradication of nasal carriage has been mupirocin. Antiseptics, such as chlorhexidine, hexachlorophane (not marketed in many countries due to toxicity) or povidone-iodine detergents, are the most effective way to reduce \textit{S. aureus} on the skin, especially on hands and the perineum. The amount of \textit{Saureus} on the skin, particularly the hands and perineum, may be most effectively reduced by washing the skin with an antiseptic, e.g. chlorhexidine, hexachlorophane (not marketed in many countries due to toxicity) or povidone-iodine detergents. Antibiotics can greatly reduce \textit{S. aureus} on the skin and prevent it from dispersing into the air when administered intranasally to carriers \cite{51, 52}.

The intranasal treatment also helps reduce wound infections and colonization caused by \textit{S. aureus}. Infection control policies in hospitals must be strictly followed, and programs to educate the hospital staff are essential to controlling \textit{S. aureus}. Medical personnel, including physicians, nurses, technicians, housekeeping, and medical administration, must be educated. An effective infection control system can only be achieved when all staff are motivated to follow the rules established by the infection control committee. A more comprehensive understanding of the best methods for ensuring favorable infection control practices is greatly appreciated. A simple but important step such as handwashing is particularly important in terms of compliance. As in countries with low \textit{S. aureus} rates, such as Denmark and the Netherlands, strict antibiotic prescription policies and effective infection control practices in hospitals have been linked to the control of resistance development. These practices are overseen by doctors and nurses, clinical microbiologists, and infectious disease specialists. Thus, hospitals should have strict antibiotic policies \cite{53-55}.

11. Conclusion

Staphylococci have a highly regulated toxin production system. Which researchers are researching and understanding. However, there is a clear connection between these toxins and some diseases that threaten humans. Toxins are one of the key targets for treatment. The use of neutralizing antibodies and vaccines can be the most promising. Many strains of MRSA are resistant to other antibiotics, which creates a big problem in infection control and treatment. In this study, we examined the bacteriology of \textit{S. aureus} and the toxins they produce, the discussion of
antibiotic resistance and infection control in health centers in order to have a better understanding of infection control and its treatment.

Conflict of Interest
The authors hereby declare that they have no conflict of interest.

Author’s contributions
All authors equally participated in designing experiment analysis and interpretation of data. All authors read and approved the final manuscript.

Ethics approval and consent to participate
No human or animals were used in the present research.

Consent for publications
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Availability of data and material
The authors have embedded all data in the manuscript.

Informed Consent
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