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ORIGINAL ARTICLE

Role of Biofilm Forming Staphylococcus Aureus in Urinary Tract Infection

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ABSTRACT

Background: Urinary tract infections (UTIs) are a widespread and recurring health issue that is increasingly becoming a public health concern worldwide. Each year, approximately 150 million people experience UTIs, with over half of the population reporting having had at least one UTI in their lifetime, making it one of the most prevalent bacterial infections globally. One of the main bacterial problems facing public health today is Staphylococcus Aureus (S. Aureus), which is most common in those suffering from urinary tract infections. While S. aureus has been linked to 0.5–6% of urinary tract infections, untreated S. Aureus infections can result in serious, perhaps fatal conditions. The aim of this review is to examine how biofilm-forming S. aureus contributes to the pathogenesis of UTIs and its role in antibiotic resistance and recurrent infections. The review focuses on the mechanisms by which S. aureus biofilms exacerbate the persistence and severity of UTIs, especially in the context of multi-drug resistant strains, highlighting the challenges in treating catheter-associated urinary tract infections (CAUTI) and chronic bacterial prostatitis. **Conclusions:** In fact, because of its multi-drug resistant (MDR) forms, S. aureus has grown to be a global health concern. A significant contributing factor to recurrent urinary tract infections with increased resistance to antibiotics is the biofilm of S. Aureus.

Keywords: Biofilm; Staphylococcus Aureus; Urinary Tract Infection.

INTRODUCTION

The name staphylococcus comes from the Greek noun "Staphylé," which means a cluster of grapes. The suffix "coccus," which means grain or berry, is added later. The genus Staphylococcus contains gram-positive cocci (0.5-1.5 µm) that are facultative anaerobes, non-sporing, and non-motile. Moreover, Staphylococcus can be grouped singly, in pairs, tetrads, short chains, or in an irregular way"grape-like" clusters. The majority of species are catalase positive and grow at 18–40°C. Most of the time, they are encapsulated [1,2].

S. Aureus is commonly responsible for human disease and is an asymptomatic colonizer.

Most healthy people have S. aureus as typical human flora on their skin and in the nasal area. However, if it enters the bloodstream or tissues, it can cause a number of potentially fatal diseases [3].

Because of its extreme adaptability, S. Aureus can produce a variety of clinical symptoms with varying degrees of severity. It is the most common cause of septicemia, septic arthritis, pneumonia, endovascular infections, osteomyelitis, foreign-body-associated illness, and skin and soft tissue infections [4]. All ages are susceptible to S. aureus infections, although young children, the elderly, and the immune-compromised are more vulnerable [5].

The incidence of S. aureus infection in low-income countries is highest in neonates and infants up to one year of age, with fatality rates of up to 50%. This is in contrast to high-income countries where the disease appears to worsen with age or is most common at the extremes of the age spectrum. Unfortunately, there aren't many epidemiological studies conducted in low- and middle-income nations, and it's likely that these countries under report S. aureus-associated diseases in general, especially when it comes to the elderly [6]. Both in the community and in hospital settings, S. aureus infections are frequent and often serve as the major pathogens in hospital-acquired illnesses. Regretfully, there is an uprising prevalence of multi-drug resistant bacteria, such as methicillin-resistant Staphylococcus Aureus (MRSA) [7].

The aim of this review article is to examine how biofilm-forming S. Aureus contributes to the pathogenesis of UTIs and its role in antibiotic resistance and recurrent infections. The review focuses on the mechanisms by which S. Aureus biofilms exacerbate the persistence and severity of UTIs, especially in the context of multi-drug resistant strains, highlighting the challenges in treating CAUTI and chronic bacterial prostatitis. [8].

Virulence factors

Many different kinds of poisons, enzymes, and extracellular proteins are created by S. aureus **(Fig. 1)** [9]**.**

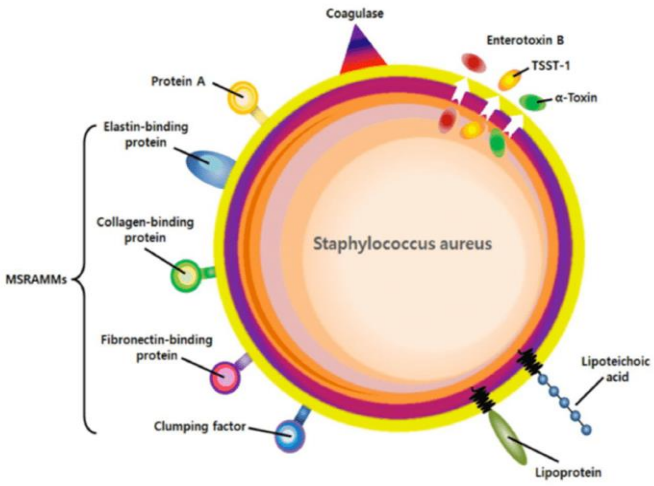

Figure 1: Virulence factors of S. aureus [9].

Surface antigens

• **Capsular polysaccharides:**

Certain S. Aureus strains have capsular polysaccharides surrounding them. The pathophysiology of staphylococcal infection involves these capsular polysaccharides in a significant way. The majority of bacteria express either type 5 (CP5) or type 8 (CP8) of the 11 serotypes of capsular polysaccharides that have been discovered. The capsular polysaccharide has the ability to resist destruction by leukocytes through suppressing opsonization and phagocytosis [10].

Teichoic acids (TAs):

Whereas cell wall TAs (WTAs) are covalently attached to peptidoglycan in the bacterial cell wall, lipo-TAs (LTAs) are anchored in the cytoplasmic membrane. WTAs participate in the production of biofilms and cell division, as well as staphylococcal adhesion and colonization. Their overexpression increases The pathogenicity of S. aureus [11].

Protein A is a key virulence factor that enables S. Aureus to evade innate and adaptive immune responses[12].

Adhesins Surface proteins such as fibronectin, collagen, and others that bind to matrix proteins are involved in the pathophysiology of S. Aureus infections and colonization [13].

Extracellular proteins (membrane-damaging toxins)

S. Aureus generates a number of extracellular proteins that influence the severity of infections in different ways.

Hemolysins[14].

Their capacity to cause hole formation and damage to eukaryotic cellular membranes is crucial for the development and maintenance of opportunistic infections. Among them are α, ß, γ, δ toxins.

α-toxin, the strongest toxin that damages membranes targets erythrocytes and is what causes the visible hemolysis zone that has been seen in vitro [15].

ß-toxin is distinguished by its neutral sphingomyelinase activity, which damages membranes rich in this lipid and causes red blood cells to lyse and immune cells to die. Additionally, β-toxin has a second, less well-studied biofilm ligase function that aids in the production of biofilms [16].

γ-toxin This toxin belongs to the family of bicomponent pore-forming toxins, which means it consists of two separate protein components that work together to form pores in the membranes of target cells [17].

δ-toxin is a well-known peptide that is made by different S. aureus strains and is sometimes referred to as δ-hemolysin and δ-lysin. It is inhibited by phospholipids and has a wide hemolytic range [18].

Exotoxins–superantigens

Staphylococcus aureus Superantigens (SAgs): SAgs are among the most potent T-cell mitogens found. They activate a substantial number of T cells by the cross-linking of their T cell receptor with major histocompatibility complex class II molecules on antigen-presenting cells. This results in T cell proliferation and an enormous release of cytokines [19].

Enterotoxins-superantigens: causative agents of human food poisoning with sudden onset of nausea, vomiting, and diarrhea with incubation period of 1-6 hours [20].

Toxic shock syndrome toxin (TSST-1): the superantigen action of TSST-1 causes hypotension with cardiac and renal failure [21].

Exfoliative toxins (ET): S. Aureus secretes highly selective serine proteases called exfoliative toxins (ETs), also referred to as

epidermolytic toxins [22].

Other exoproteins

Leukocidin: A family of bicomponent pore-forming toxins known as leukocidins are non-hemolytic but highly leukotoxic. They aid in pathogenicity in necrotizing skin infections. Granulocytes and macrophages are killed by it [23].

Coagulase is a significant component of S. aureus's pathogenicity, an enzyme that causes the host's plasma to clot. It results in fibrinogen's conversion to fibrin, and the creation of fibrin may protect Staphylococcus against phagocytosis. Positive for coagulase and negative for coagulase Two groups comprise the species of S. aureus [24].

Staphylokinase (Sak, fibrinolysin): Sak is a plasminogen activator that most strains of S. aureus release. It combines to create complexes with traces of plasmin found in the plasma of the host. After cleaving plasminogen, these complexes produce Strong, all-purpose protease active plasmin targets host proteins, including fibrin clots [25].

Nuclease (deoxyribonuclease): A structural component of the biofilm matrix nuclease Nuc1 enzyme, which inhibits the production of biofilms. The generation of eDNA may also be influenced by solid surface hydrophobicity. There are two distinct forms of micrococcal nucleases are expressed by S. aureus: the membrane-bound Nuc2 and the expelled Nuc1. Nevertheless, Nuc2 expression regulation has not yet been found. According to descriptions, Nuc1 is the main enzyme in charge of S. aureus nuclease activity in vitro [26].

Lipase and esterase: By degrading structural elements such as phosphatidylinositol and hydrolyzing complex lipids, these processes release free fatty acids or other small compounds that modify the host's response to bacterial invasion [27].

Hyaluronidase: Bacterial hyaluronidases are known to contribute to infection by breaking hyaluronic acid, an essential extracellular matrix component [28].

Protease:S. aureus has ten primary secreted proteases that are necessary for survival during interactions of the innate immune system significant throughout systemic community-acquired MRSA (CA-MRSA) infections, and contribute to resistance to antimicrobial peptides [29].

Biofilm Forming Staphylococcus aureus in Urinary Tract Infection

Biofilm-forming bacteria are thought to be responsible for up to 65% of infections and 80% of chronic illnesses, according to the NIH [30]. Urology is one of the key specialties where biofilm formation might pose a significant threat. Recurrent infection: called a "relapse" when it results from the same strain of bacteria that initially caused the infection, or a "reinfection" when it involves a different strain, can result from an acute urinary tract infection (UTI) caused by bacteria. Relapses are classified as more complex UTIs, necessitating lengthier antibiotic regimens. About 25% of women who experience an episode of acute cystitis also have recurring UTIs, which place a considerable financial burden on the healthcare system. Women's relapses have been linked to the bacteria' ability to build biofilms [31].

Furthermore, the development of biofilms by strains responsible for acute prostatitis enhances their capacity to endure inside the prostatic secretory system, resulting in the recurring urinary tract infections that are typical of chronic bacterial prostatitis. These infections are exceedingly challenging to treat

with traditional therapy [32].

Biofilms and Antimicrobial Resistance

The greater resistance shown by bacterial cells in biofilm, which can be greater than those of their planktonic counterparts by up to 1000 times, has been explained by a number of different mechanisms. Nonetheless, the biofilm stage determines the resistance level. Since During the reversible attachment process, drugs may be helpful since the bacteria are still sensitive to the host immune system and antibiotics because they have not yet joined to the matrix. Biofilm resists host immune responses better and antibiotics after the attachment is permanent [33].

One explanation that has been proposed is the need for longer times for antibiotics, including aminoglycosides, to penetrate biofilm due to impaired diffusion across the matrix. It has also been noted that the high cellular density and close proximity of bacterial cells in biofilms facilitate the spread of resistance indicators through the transmission of resistance genes on various mobile genetic components. It has been demonstrated that S. Aureus's capacity to spread the biofilm development mode increases plasmid-borne antibiotic resistance determinants by conjugating and mobilizing these mobile genetic components. The biofilm matrix's ability to stabilize the intimate cell-to-cell contact may make this event more likely [34].

It has also been proposed that the antibiotic can be rendered inactive by altering the pH or metal ion concentrations inside the biofilm, or by the efflux pumps' expression. Furthermore, the presence of metabolically inactive persister cells—which are dormant, but not mutant, variations of normal cells—can greatly reduce the efficiency of antibiotics. Because of their lowered metabolic rates and capacity to block antibiotic targets like DNA replication and protein synthesis, these cells have a high tolerance to antibiotics. This allows them to develop a supply of live cells that the biofilm population can repopulate [35].

Biofilms can form on devices like urinary catheters and cause CAUTI, one of the most common conditions linked to healthcare diseases globally, in addition to adhering to uroepithelium, renal, and prostatic tissues [36].

Bacterial colonization of an indwelling urinary catheter's surfaces occurs after it has been inserted, mostly due to contamination that occurred while the catheter was set. Colonization occurs in 3-5 days for patients with open drainage systems and in 1 month for those with closed drainage systems [37].

Since S. Aureus is typically linked to antibiotic-resistant strains, which raise the chance of experiencing severe consequences, it has become a common cause of CAUTI. This has been demonstrated by the fact that MRSA infections often develop into more dangerous invasive infections [38].

It was believed that the bladder injury brought on by catheterization would generate an inflammatory reaction that would cause the host protein fibrinogen (Fg) to be released. Given that MRSA is affixed to the urothelium and implanted in patterns that colocalize with deposited Fg, it has been demonstrated that this makes it easier for MRSA to colonize the bladder and the catheter, leading to a persistent infection. Furthermore, this intensifies the inflammatory response of the host, causing more Fg to be released and accumulate in the urinary tract. This promotes MRSA colonization and persistence in spite of the strong immunological response of the host [39].

Diagnosis of Staphylococcus aureus:

Collection of specimens

This is contingent upon the body part impacted. For instance, those with infections of the skin, throat, nose, and wounds should swab for pus and other discharge containing germs. Swabs are sticks with sterile, absorbent cotton tips. Blood samples must be sent by persons who have a widespread blood illness. Blood samples are then put in blood culture bottles after that [40].

Urine culture collection methods include suprapubic aspiration, straight catheter technique, and mid-stream catch. In pediatric patients, diaper collection and sterile bag methods are used. Suprapubic aspiration, which avoids contamination, is the most accurate but is rarely used due to discomfort and invasiveness. The straight catheter technique is a good alternative but is also labor-intensive and carries a risk of introducing bacteria into the bladder. Consequently, the clean-catch midstream technique is the most commonly used method because it is non-invasive, comfortable, and provides reasonably accurate results [41].

Direct smear examination

Wet mount

Wet mount- To determine pyuria a drop of thoroughly mixed urine were put on slide and covered by a cover slip of 18xl8 nun. The number of WBCs / ten average high power field (HPF) were counted.Significant pyuria was inferred by the presence of z l WBCs/HPF [42].

Stained film

The sample is swabbed onto a glass slide in minute amounts. After that, this is examined under a microscope after being stained with Gram stain or dyes like basic fuschin and crystal violet. Gram-positive, blue- or purple-staining S. aureus can take the shape of tiny, spherical cocci, short chains, or clusters that resemble grapes. This test isn't usually confirming because S. aureus can be found on skin and mucous membranes as commensal [43].

Culture of S. Aureus

The patient's sample is cultured using the standard plating technique, blood-containing media is typically utilized regarding S. aureus. Another commonly used selective media that allows S. aureus to grow preferentially is mannitol salt agar, which contains 7–9% or sodium chloride. S. Aureus colonies show macroscopically golden colonies. After that, they are confirmed by staining them with Gram stain and are subjected to particular diagnostic procedures such as the coagulase or catalase tests. Moreover, the standard phenotypic routine test for identifying S. aureus in biological material is the coagulase tube test; however, a number of groups have established the coagulase gene molecular analysis as a precise test [44].

Rapid diagnostic tests

Antigen detection By ELISA

Detection of enetertoxin production by the isolated strains or directly in the sample and detection of TSST-1 in blood [33].

Genotyping

Including real-time PCR [45].

Identification of toxins

This is important for more serious cases such as food poisoning and toxic shock syndrome. The toxins produced by S. aureus, such as enterotoxins A through D and TSST-1, can be identified using latex agglutination tests. The toxins in the samples cause the latex particles to clump, which determines the results of the testing [8].

All ß-lactam antibiotics, such as cephalosporins and carbapenems, are

ineffective against MRSA; however, the most recent Ceftaroline is one of the class of MRSA-active cephalosporins that may work well against them. Healthcare-associated MRSA strains are often resistant to other commonly used antimicrobial agents, such as clindamycin, erythromycin, and fluoro-quinolones, while strains linked to community-associated infections are usually only resistant to ß-lactam antibiotics, erythromycin, and sometimes fluoro-quinolones. Since 1996, there have been reports of MRSA strains with reduced susceptibility to the antibiotic (minimum inhibitory concentration [MIC], 4–8 µg/ml) and bacteria that are completely resistant to vancomycin (MIC > 16 µg/ml). [46].

MRSA diagnosis:

Screening

To test for MRSA, the cefoxitin disk (30 µg) diffusion test, broth microdilution testing, and a plate containing 6 µg/ml of oxacillin in Mueller-Hinton agar supplemented with 4% NaCl are recommended by the Clinical and Laboratory Standards Institute (CLSI) [47].

Another method for identifying MRSA is to use anti-PBP2a monoclonal antibodies, which can be purchased as latex agglutination or immunochromatographic membrane assays. Finally, MRSA can be found using commercially available chromogenic agars [48].

Genotypic methods

Other techniques to identify oxacillin/ methicillin resistance include nucleic acid amplification assays (PCR), which can be used for the direct detection of mecA, the most common gene mediating oxacillin resistance in staphylococci. However, emerging resistance mechanisms like mecC and uncommon phenotypes like borderline-resistant oxacillin resistance cannot be detected by MecA PCR techniques[48].

Laboratory Methods for Biofilm Detection

Biofilm infections are hard to diagnose because conventional culture methods often fail to adequately detect the biofilm forming bacteria. However, biofilm infection has a number of criteria. These criteria include the presence of a localized infection with aggregated bacteria at the infection site, resistance to antibiotic treatment and ineffective host immune responses [49].

Phenotypic methods

Phenotypic biofilm production in S. aureus was originally studied by using the tube method (TM), Congo red plate assay (CRA), which is highly subjective. As a result, this method has been mostly replaced by the microtiter plate assay (MPA) in which a color-producing chromogen is used and whose color intensity is directly related to the concentration of biofilm [50].

Tube method

It is a qualitative assessment of biofilm formation where the microorganisms are grown in trypticase soy broth with 1% glucose in tubes for 24 h. The tubes are then emptied and washed with phosphate buffer saline (PBS) and stained with crystal violet (0.1%). The tubes are then washed and dried, biofilm formation is considered positive when a visible film lines the wall and the bottom of the tube [51].

Tube adherence method was used to differentiate organisms as biofilm producers and non-biofilm producers, but it was difficult to differentiate between moderate, weak and non-biofilm producers due to lack of a standard to compare the result with it. Therefore, this method was not recommended as a general screening test to identify biofilm producing isolates. However, it has been

shown to be a better method for biofilm detection than CRA method [52].

Congo red agar method (CRA)

A specially prepared agar medium supplemented with brain heart infusion (BHI) broth with 5 % sucrose and Congo red is prepared. Congo red is prepared separately as concentrated aqueous solution and autoclaved at 121°C for 15 min, then it is added when the agar is cooled to 55°C. Plates are inoculated and incubated aerobically for 24 h at 37°C [53].

A five-color reference scale is used to accurately detect all color variations shown by the colonies. Isolates presenting 2 grades of black which may be bright black or opaque black are considered positive for biofilm production whereas red, pink and bordeaux colonies are considered as negative [51].

While biofilm forming bacteria have been evaluated using CRA methods in many previous studies, the mechanism of these methods is still unclear. Currently, CRA method is not considered a precise method for detecting biofilm forming strains [54].

Microtiter plate assay (MPA)

The MPA assay is currently the most commonly used method for detection of biofilm formation. The microorganisms are grown in culture plates for 24 h then after washing, are fixed with sodium acetate (2%) and stained with crystal violet (0.1% w/v). Biofilm formation is assessed by measuring optical density with enzyme linked immunosorbent assay (ELISA) reader [55].

Previous studies have been carried out to compare the mentioned three methods. According to a previous study which was carried out in Surabaya, the MPA method has been shown to be the gold standard to detect the presence of biofilm on medical devices in patients' body [56].

Additionally, the MPA method was shown to be a more quantitative and reliable method for the detection of biofilm forming micro-organisms as compared to TM and CRA methods and was recommended as a general screening method for detection of biofilm producing bacteria in laboratories in another study [57].

Genotypic methods

The molecular detection of biofilm-forming S. aureus is performed by PCR-based amplification of adhesion genes of the icaADBC operon (icaA, icaB, icaC, and icaD) and biofilm-associated proteins (bap gene). PCR is considered simple, fast and reliable [58].

CONCLUSIONS

In a nutshell, biofilm-forming Staphylococcus Aureus plays a crucial role in the persistence and severity of urinary tract infections (UTIs), especially in cases involving multi-drug resistant strains. The ability of S. Aureus to form biofilms significantly enhances its resistance to antibiotics and the host's immune response, leading to recurrent and chronic infections that are challenging to treat. This is particularly problematic in catheter-associated urinary tract infections (CAUTI) and chronic bacterial prostatitis, where biofilm formation on medical devices and tissues exacerbates the difficulty of eradicating the infection. The increasing prevalence of antibiotic-resistant S. Aureus strains, including methicillin-resistant Staphylococcus Aureus (MRSA), underscores the urgent need for new therapeutic strategies and better management practices to combat these persistent infections effectively. As biofilm formation remains a key factor in the pathogenicity of S. Aureus, addressing this issue is critical for reducing the burden of UTIs and improving patient outcomes globally.

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