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Review Article

Virulence Factors and Genes Diagnosis Treatment and Antibiotic Resistance of Staphylococcus Aureus in Ocular Infections

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Abstract: *Staphylococcus aureus* is a major opportunistic pathogen implicated in various ocular infections. Its pathogenicity is largely due to a wide arsenal of virulence factors and antibiotic resistance genes. This study discusses the surface proteins, toxins, enzymes, adhesins, and biofilm formation contributing to its virulence. The paper also explores diagnostic approaches, current treatment options including antibiotic eye drops, and the global challenge of antimicrobial resistance. Special focus is placed on key resistance genes such as *ermA*, *ermB*, *icaA*, *LukS*, and *mecA*. Awareness and control of antibiotic misuse are crucial in mitigating resistance trends.

Keywords: *Staphylococcus Aureus*, Virulence Factors, Ocular Infection, Antibiotic Resistance, Biofilm, *Meca*, *Erm*, Diagnosis, Treatment.

Virulence Factors

The clinical significance of *Staphylococcus aureus* bacteria lies in the fact that it possesses many virulence factors that give it the ability to grow, multiply and invade host tissues, and thus it contributes significantly to its pathogenesis (Cheung *et al.*, 2021).

The pathogenicity associated with *S. aureus* can be attributed to numerous virulence factors, including capsule, enterotoxins, cytolytic toxins, and cellular components such as protein A. Several cytolytic toxins and exfoliative toxins have been identified. Despite these virulence factors, innate resistance to *S. aureus* is fairly high, and the organism is regarded as an opportunistic pathogen (Jenul and Horswill, 2019).

The following are the most important of these factors.

2.2. 1. Surface Proteins

Protein A: Binds to the Fc portion of antibodies, interfering with antibody-mediated phagocytosis and complement activation (Cruz *et al.*, 2021).

Coagulase:

Converts fibrinogen to fibrin, forming a protective barrier around the bacteria, shielding them from immune cells (Guggenberger *et al.*, 2012).

Fibronectin-Binding Proteins:

Promote bacterial adhesion to host cells and extracellular matrix components, facilitating colonization and invasion (Vaca *et al.*, 2020).

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Clumping Factors: Promote bacterial aggregation, enhancing biofilm formation and resistance to antimicrobial agents (Crosby *et al.*, 2016).

2.2.2. Toxins

Alpha-Toxin: A pore-forming toxin that disrupts cellular membranes, causing cell death (Brito *et al.*, 2019).

Beta-Toxin: A sphingomyelinase that damages host cell membranes and induces inflammation (Herrera *et al.*, 2017).

Gamma-Toxin:

A leukocidin that targets neutrophils, impairing their function and contributing to tissue destruction (Spaan *et al.*, 2017).Toxic shock syndrome toxin (TSST-1): A superantigen that activates a large number of T cells, leading to a systemic inflammatory response and potentially fatal toxic shock syndrome (Sharma *et al.*, 2019).

2.2. 3. Enzymes

Hyaluronidase: Breaks down hyaluronic acid, a component of the extracellular matrix, aiding in tissue invasion and dissemination (Jung, 2020).

Staphylokinase:

Converts plasminogen to plasmin, enhancing the bacterium's ability to dissolve fibrin clots and facilitate tissue invasion (McAdow *et al.*, 2012).

Lipase: Breaks down lipids, contributing to tissue damage and inflammation (Pirahanchi and Sharma, 2023).

2.2.4. Adhesins

Surface proteins: Bind to specific receptors on host cells, allowing the bacteria to adhere and establish colonization.

Polysaccharide intercellular adhesin (PIA): A biofilm-associated adhesin that mediates bacterial aggregation and promotes colonization on medical devices and implants (Paharik and Horswill, 2016).

2.2.5. Biofilm Formation

Biofilm formation is a critical virulence factor that allows *S. aureus* to survive in harsh environments, evade antimicrobial agents, and persist in chronic infections. Biofilm communities exhibit increased resistance to host immune responses and antimicrobial therapies, making them difficult to eradicate (Peng *et al.*, 2022).

2.3. Virulence Genes

Staphylococci possess many virulence genes such as *ermA, ermB, LcaA, Luks and MecA* (Yang *et al.*, 2023; Abdulmanea *et al.*, 2023; Zare *et al.*, 2023). While some *staphylococcal* species are harmless, others can cause a wide range of infections, including skin and soft tissue infections, pneumonia, bloodstream infections, and toxic shock syndrome. *Staphylococci* possess numerous virulence genes, which are genes that encode factors that contribute to the ability of the bacteria to cause disease (Ahmad-Mansour *et al.*, 2021).

2.3. 1. Erythromycin (*ermA* and *ermB*) Genes

The *ermA* and *ermB* genes are responsible for conferring resistance to macrolide antibiotics, such as erythromycin and clindamycin. These antibiotics work by binding to the 50S subunit of the bacterial ribosome and inhibiting protein synthesis (Miklasińska-Majdanik, 2021). However, the *ermA and ermB* genes encode enzymes that modify the 23S rRNA of the 50S subunit, which prevents the macrolide antibiotics from binding and thus renders the bacteria resistant to these antibiotics (Lade *et al.*, 2022).

The presence of *ermA and ermB* can make it difficult to treat infections caused by staphylococcal bacteria (Mlynarczyk-Bonikowska *et al.*, 2022). *Staphylococci* are a type of Gram-positive bacteria that are commonly found on the skin and mucous membranes of humans. They can cause a variety of infections, including skin and soft tissue infections and bloodstream infections (Linz *et al.*, 2023). Macrolides are commonly used to treat staphylococcal infections, so the presence of *ermA and ermB* can make it necessary to use alternative antibiotics or combination therapy (Pardo *et al.*, 2020).

The *ermA* and *ermB* genes are located on plasmids, which are small, circular pieces of DNA that can be transferred between bacteria. This means that *ermA and ermB* can spread rapidly among staphylococcal bacteria, making it more difficult to treat infections caused by these bacteria (Malachowa and DeLeo, 2010).

2.3. 2. Intercellular adhesion (*icaA*) Gene

Cell aggregation and biofilm accumulation are mediated by the products of a gene locus composing of the genes *icaADB* and C, which encode the essential proteins for the production of polysaccharide intercellular adhesion (PIA) and capsular polysaccharide/adhesion (PS/A) in *Staphylococcus spp* (Namvar *et al.*, 2013).

The *icaA* plays primary roles in exopolysaccharide synthesis the *icaA* gene encodes N-acetylglucosaminyl-transferase (Abdel-Shafi *et al.*, 2022). The *icaA* gene in *S. aureus*, which is involved in synthesis of poly N-acetylglucosamine for intercellular adhesion, may play a role in biofilm formation (Lee *et al*., 2018).

2.3. 3. Leukocidin (*LukS*) Gene

LukS, also known as Panton-Valentine Leukocidin S component, is a crucial gene involved in the production of a potent toxin in *Staphylococcus aureus*. This toxin, termed leukocidin, possesses a unique ability to target and destroy white blood cells, particularly neutrophils and monocytes. The presence of *LukS*, along with its partner gene *LukF*, leads to the formation of a two-component leukocidin complex. The *LukS* component forms pores in the target cell membrane, allowing the *LukF* component to enter the cell and cause extensive damage (Haapasalo *et al.*, 2018).

The leukocidin produced by the *LukS-LukF* complex contributes significantly to the pathogenicity of *S. aureus* by employing a dual mechanism of action:

1. Tissue Destruction: Leukocidin directly damages host tissues by disrupting the integrity of cell membranes, leading to tissue necrosis and abscess formation. This destructive effect is particularly evident in skin and soft tissue infections caused by *S. aureus* (Masters *et al.*, 2022).
2. Immune Evasion and Spread of Infection: Leukocidin targets and kills white blood cells, which are essential components of the host's immune defense system. By eliminating these immune cells, leukocidin impairs the host's ability to effectively combat the infection. This immune suppression facilitates the survival and spread of *S. aureus* within the host, contributing to the development of more severe and invasive infections (Tam *et al.*, 2020).

2.3. 4. Methicillin (*MecA*) Gene

MecA is a crucial gene that plays a pivotal role in the development of methicillin resistance in *Staphylococcus aureus* (*S. aureus*). It encodes a protein known as penicillin-binding protein 2a (PBP2a), which has a high affinity for beta-lactam antibiotics like penicillin and methicillin. Unlike other PBPs, *MecA* has a modified active site that exhibits reduced affinity for beta-lactams, thereby conferring resistance to these antibiotics (Fergestad *et al.*, 2020).

The expression of *MecA* is regulated by various factors, including the *mecA* promoter and the two-component signal transduction system GraRS. When exposed to beta-lactam antibiotics, the GraRS system activates the transcription of *mecA*, leading to increased production of PBP2a and subsequent antibiotic resistance (Cai *et al.*, 2021).

The prevalence of MRSA has prompted extensive research efforts aimed at developing alternative treatment strategies to combat methicillin resistance. One approach involves designing antibiotics that can effectively target PBP2a and overcome the resistance conferred by *MecA*. Researchers are also exploring the potential of using inhibitors of the *mecA* promoter or the GraRS system to prevent or reduce *mecA* expression (Nandhini *et al.*, 2022).

2.4. Diagnosis of Ocular Infections

When an eye infection is suspected, the process begins with a clinical examination of the eyes by a specialist ophthalmologist. This examination includes checking for accompanying symptoms such as redness, itching, discharge, eye pressure, and vision (Sharma, 2012). After the clinical examination, some specialized medical tests may be performed to check the type and cause of ocular inflammation, including:

2.4.1. Cultures and Isolation Examination:

A sample of secretions from the eye is collected and cultured in a designated medium to test growth and identify the bacteria causing the infection (Giuliano *et al.*, 2019).

2.4.2. DNA Testing:

If a viral infection such as dilated eye infection is suspected, the sample may be tested to detect viral DNA genome (Russcher *et al.*, 2021).

2.5. Treatments of Ocular infections

2.5.1. Antibacterial Eye Drops:

These drops are used to treat ocular infections caused by bacteria such as *Staphylococcus aureus* and *Escherichia coli*. These drops kill or prevent the growth of bacteria and relieve symptoms (Gill, 2024).

2.5.2. Ciprofloxacin Eye Drops:

These drops are used to treat ocular infections caused by bacteria, including *Staphylococcus aureus*. It helps reduce symptoms such as redness, congestion and discharge (Garhwal *et al.*, 2012).

2.5.3. Tobramycin Eye Drops:

These drops are used to treat bacterial ocular infections that may be caused by *Staphylococcus aureus* and other bacteria. It destroys the bacteria causing the infection and improves the condition (Li *et al.*, 2022).

2.5.4. Gentamicin Eye Drops:

These drops are used to treat a variety of bacterial ocular infections, including those caused by *Staphylococcus aureus* and others. It works to kill bacteria and reduce symptoms (Chaves and Tadi, 2023).

2.5.5. Fluoroquinolone Eye Drops:

This category of drops includes several options, such as ciprofloxacin and levofloxacin, and is used to treat various bacterial ocular infections.(Herbert *et al.*, 2022).

2.6. Antibiotic Resistance

Antibiotics represent crucial medications employed for both the prevention and treatment of bacterial infections. The emergence of antibiotic resistance not only escalates healthcare costs but also prolongs hospitalizations and elevates mortality risks. Immediate reform in the prescription and utilization of antibiotics is imperative. Despite advancements in novel treatments and medications, antibiotic resistance remains a persistent challenge. Multidrug resistance (MDR), characterized by bacterial resistance to at least one antimicrobial medication from three or more antimicrobial groups, exacerbates the complexity of treatment strategies (Dadgostar, 2019)

2.6.1. Main Causes of Antibiotic Resistance

2.6.1.1. Over-prescription of Antibiotics

Appropriate use of antibiotics and injections has contributed to the control of infectious diseases and the reduction of mortality. However, there are serious problems concerning the inadequate use of antibiotics and the overuse of injections in ambulatory practice. Overuse of antibiotics, particularly broad-spectrum antibiotics, in primary care is a major contributing factor to reduced drug efficacy, increased prevalence of resistant pathogens in the community, and the appearance of new co-infections (Buchy *et al.*, 2020).

2.6.1.2. Patients not finishing the Entire Antibiotic Course

Resolving the threat to human and animal health presented by antimicrobial resistance remains a challenge for health care systems across the world. Although an intrinsic characteristic of microorganisms, the prevalence of clinically relevant antimicrobial resistance (AMR) has been accelerated by the inappropriate use of antimicrobial agents, in turn driven by several factors. Some of those key determinants include suboptimal prescribing and inadequate public adherence to recommended behaviors such as completion of prescribed antibiotic courses. Public behaviors around antimicrobials are shaped by multiple and interlinked factors, including structural components such as access to adequate medical services and medications, narratives about the power of antibiotics and social mechanisms (Samreen *et al.*, 2021).

2.6.1.3. Overuse of Antibiotics

Antibiotic misuse, sometimes called antibiotic abuse or antibiotic overuse, refers to the misuse or overuse of antibiotics, with potentially serious effects on health .Among them the most important is antibiotic resistance, including the creation of multidrug-resistant bacteria, informally called "superbugs": relatively harmless bacteria can develop resistance to multiple antibiotics and cause life-threatening infections. There are a number of reasons that doctors (and patients) should think twice before rushing to use antibiotics (Mashura. M, 2016)

3. CONCLUSION

S. aureus is a formidable pathogen in ocular infections due to its numerous virulence factors and increasing antibiotic resistance. Timely diagnosis, appropriate treatment, and antimicrobial stewardship are essential in controlling its impact. Understanding genetic mechanisms such as *mecA*, *icaA*, and *erm* genes is crucial for guiding clinical decisions and developing targeted therapies.

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