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# Staphylococcus Aureus Toxins and its Pathogenesis: A Review

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**Abstract**

*Staphylococcus aureus* is a grave community-acquired and nosocomial pathogen related to elevated levels of morbidity and mortality and produces a high number of toxins and other virulence agents. So, our review focuses on how *S. aureus* begins, colonizes, and causes the infection and upon the main determinants involved. This bacterium toxins included different types like (Alpha, Beta, Gamma, and Delta) Hemolysins, Leukotoxins, Staphylococcal Enterotoxins (SEs), Exfoliate Toxins (ETs) , Toxic-Shock Syndrome Toxin (TSST) and Toxin-antitoxin (TA) systems.. Studying the determinants of staphylococcal virulence and determining its structure, function, and epidemiology will facilitate the development of strategies to eliminate its resistance to antibiotics, especially in the absence of an anti- *S. aureus* vaccine.

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## 1. Introduction

*Staphylococcus aureus* is an infectious agent for human and is considered a common reason of morbidity and mortality worldwide. It can excite a set of infectious diseases, like soft tissue and skin infections, bacteremia, osteomyelitis, endocarditis, and lethal pneumonia [1], as shown in Figure (1). Furthermore, the antibiotic sensitivity of this bacterium is divided into Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Methicillin-Sensitive *Staphylococcus aureus* (MSSA) [2]. Recently, the gradual increment evolution of bacterial resistance as a consequence to the abuse of drugs for the infection of MRSA reaching throughout the world, and the clinical anti-infectious treatment for MRSA has been extra complicated, and no effective vaccine is obtainable [3,4]. Therefore, this review focus on definition various toxins of *S. aureus* as the most important virulence factors to determine their types , morphology in culture , epidemiology and its pathogenesis to assess the risk of these causative agents that facilitate the discovery of strategies to inhibit bacteria in terms of developing antibiotic production and preparing vaccines.

## 2. Epidemiology

*Staphylococcus aureus* is a widely circulated and pathogenic commensal bacteria; around 60 % of men are colonized with it intermittently. Therefore, there is a comparatively high probability of infection [6]. In fact, *S. aureus* is among bacterial infections in the United States and other industrial republics ; for instance , it was the most recuperate from inpatients among three hundred clinical microbiology laboratories in the USA in the period 1998 – 2005. Later, *S. aureus* was classified at the second rank after *Escherichia coli* among other pathogenic bacteria that recovered from bacteremia in Europe.

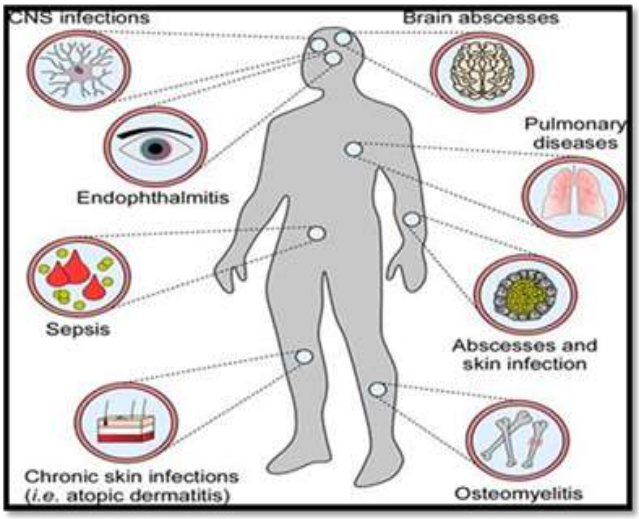


**Figure 1:** The diseases associated with *S. aureus* in humans.[5]

The spread of *S. aureus* bacteremia were amplified from 2002 to 2008 [7,8]. In Iraq some studies reached to diagnosis 54 MRSA isolates from 150 by *mecA* gene using molecular technique from atopic dermatitis from Baghdad city , The other clinical isolates appeared to be related to other species of staphylococci or identified as another genera of pathogenic bacteria and fungi. ,which was highly productive for a group of virulence[9]. In addition to the diagnosis of methicillin-resistant *S. aureus* in approximately fifty percent of a total of 109 swabs for hospitals and community in Dohuk Governorate, Iraq (2019), only four isolates were diagnosed as MSSA, in addition to carrying the PVL toxin gene [10]. In another study of Iraqi and Syrian refugees in Kurdistan (2020), the prevalence rates of infection with MRSA were investigated based on the genotype that was determined using PCR technique and investigate sensitivity to antibiotics and detection group of virulence factors include *pvl*, *arcA*, *tst*, *lukE/lukD, hla, hlb, eta, etb* and *agr*, and infection rates among Iraqis were higher than among Syrian refugees[11].

In another study , the prevalence of MRSA from nasal carriage collected from healthcare workers is totally resistant to Pencillin G with hundred percent and highly resistant to Cefoxitin as alternative to Methicillin were 94.3% ,While Vancomycin intermediate *S. aureus* VISA was higher than Vancomycin resistant *S. aureus* VRSA. [12] .Recently, MRSA has been considered a chronic disease in health care centers in all industrial cities, though novel data reference a reduction in a wide number of invasive MRSA infections in United States care centers. In 1990, Community-associated MRSA (CA-MRSA) appeared as a main issue in considerable countries worldwide [13]. The yearly rates of bacteremia by *S. aureus* in the USA ranged from (38.2 -45.7) per 100,000 persons. In other European countries, it is approximately 10 to 30 people per 100,000 people, and the rates have increased for patients with hemodialysis [14]. The prevalence of VRSA recurrence showed two percentage before 2006, five percentage between 2006-2014, and seven percentage between 2015-2020. In comparison, it presents a 3.5-fold rise from 2006 to 2020. The spread of VRSA was 5, 1, 4, 3, and 16%, respectively, in Asia, Europe, America, South America, and Africa, as shown in Figure (2). [15] Regarding a distribution of MRSA in cystic Fibrosis patients whom aged between two to eighteen years, females were the largest group . MRSA frequency was 77.8% in various countries of Middle East from 1999 to 2020. The highest resistance in *S. aureus* strains was reported to Penicillin G and Ciprofloxacin[16].

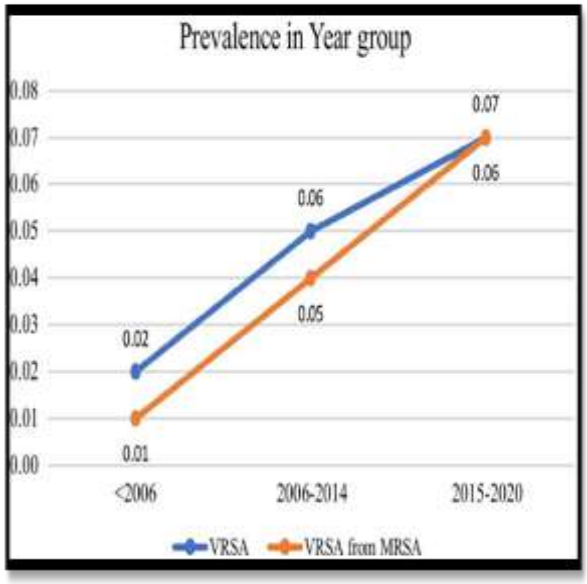


**Figure 2:** The frequency of Vancomycin-Resistant and Methicillin-Resistant of *S. aureus* [17]

### 3. Pathogenicity

The progression of *S. aureus* infections consists of five phases [18]: (1) Colonization, (2) Local infection, (3) Systemic spread( sepsis, (4) Dissemination of infection, (5) Toxinosis. These bacteria circulate in the blood systemically to reach all organs; various infections may occur, including osteomyelitis, endocarditis, and septic arthritis. Also, this bacterium causes some infections outwardly of blood stream as a result of the cytotoxins that are produced and cause serious syndromes, including scalded skin syndrome and toxic shock syndrome [19]. *S. aureus* colonizes the mucous membranes such as the respiratory tract, wounds, burns, digestive tract, and the vagina, but it was found that the nose is one of the most colonized sites, especially the anterior nares of it [20]. Its transmission is higher among family members and health workers as a nosocomial infection [21]. Studies have shown that infection with staph bacteria stimulates the adaptive immune response at a low level, and subsequent infections are mild, and this is linked to the production of maintenance antibodies against some virulence factors, including toxins like Staphylococcus toxic shock syndrome [22].

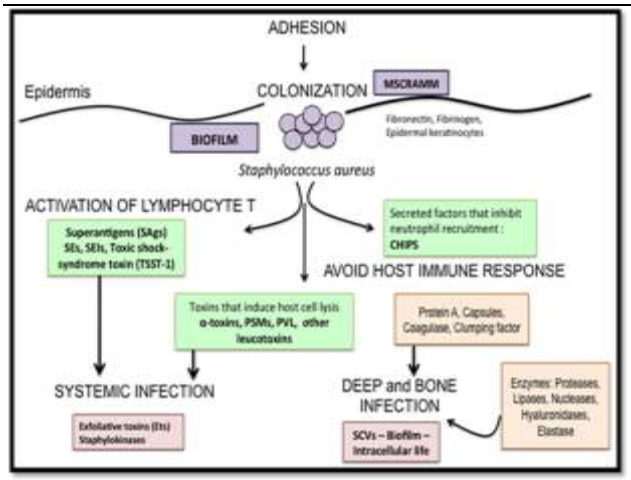


**Figure 3:** Contagion progression of *Staphylococcus aureus* [22].

## 4. Virulence factors

Mobile genetic elements (MGEs), such as prophages or plasmids, carry numerous virulence genes that may transferred among strains via horizontal gene transfer (HGT) , that may pass through conjugation, phage transduction, or it was also found recently via uptaking of "naked" DNA directly by genetic transformation [23]. A combination of virulence factors produced by *S. aureus* bacteria, like immune-invasive factors (capsule and protein A), toxins (enterotoxins and leukocidins), and enzymes can stimulate soft tissue infestation; neuraminidase, protease, staphylokinase, coagulase, and hyaluronidase which represent the reason of varied sort infections for humans and animal that enables it to bind to the target cell, destroy the body's immunity, and invade tissues, which leads to blood sepsis and triggers toxin syndromes. [24,25]. The other type of virulence factor is pathogenicity islands (SaPIs), which are accessory genes ranging between 14-17 kilobases. SaPIs mostly consist of two super antigen genes, like toxic shock syndrome toxin (TSST) and enterotoxin type C, correlated with food poisoning [26]. The key determinants of MRSA genetic divergence are the genomic islands and gene nurseries. There are three groups of genomic islands that have been recorded: *vSA*α, *vSA*β, and *vSA*γ, all of them are flanking with transposase genes. The genomic islands display an essential inter-strain assortment; however, they have a tendency to be very steady once gained via (HGT) [27]. Insertion sequences (IS) and transposons (Tn) , and chromosome cassettes (segments of DNA) are another type of (MGEs) transmissible elements, which is transmission of genetic information from parent to progeny cell [28]. Restriction-modification system and CRISPR "clustered regularly interspaced short palindromic repeats" are developed to keep bacterial strains against strange DNA to limit the prolific genetic exchange [29]. The Genomic level research of MRSA MGEs is a revealer complication of MRSA progression, where the spread, acquisition, and waste of the specific MGEs differ over time, likely affected via selective pressures stabled counter to fitness cost [30].

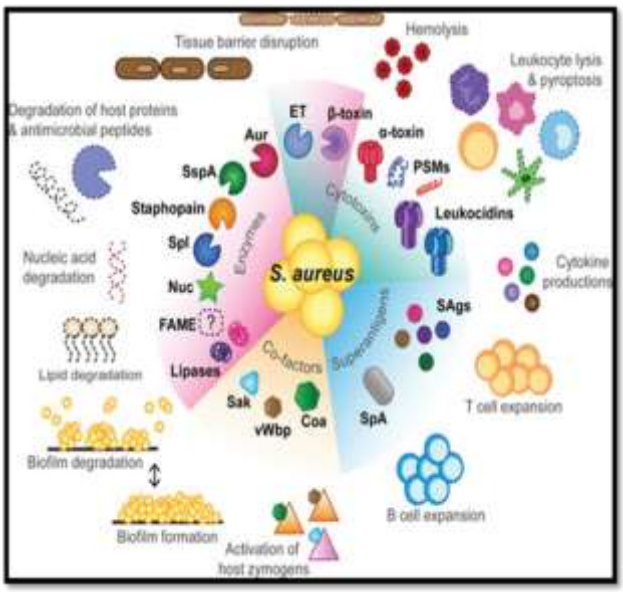


**Figure 4:** *Staphylococcus aureus* secretes many different toxins and enzymes. [31]

## 5. Staphylococcal Toxins:

A. Hemolysins (Alpha, Beta, Gamma, and Delta) - lyse red blood cells. Hemolysin outputs at least four hemolytic actions, α, β, δ, and γ. This virulence agent can deteriorate the host's cell membrane called MRSA toxins, which is characterized as a phenol-soluble modulin (PSM) that doesn't need receptors for its hemolysis action [32].

i. **α-hemolysin** (Hla) is caused a damage of the RBCs of blood not lysis ; the blood agar is transpicuous with a greenish color all over the colonies and is the most important cytotoxic agent that was the first recognized type of the pore-forming beta-barrel toxin family. In most, this toxin is composed of alpha-helices and beta-sheets. This toxin produced by *S. aureus* and caused hemolysis and tissue damage. This toxin structure permits the conduct of its major

function, pores development in the cellular membrane, and lastly, causing cell death, which leads to lyse erythrocytes and leukocytes, except neutrophils, by linking to its ADAM10 protein receptor, a metalloproteinase and disintegrin [32].

ii. **ß-Hemolysin** is one of the remarkable toxins of *S. aureus* that produces the ideal ß-hemolytic phenotype that is known as complete hemolytic phenotype and produces a wildish zone of complete hemolysis with unclear edges on sheep blood agar . It is a form of sphingomyelinase. This enzyme is poisonous to various cells; leukocytes, erythrocytes, macrophages, and fibroblasts. This toxin most possibly undermined the plasma membrane and led to regularity in plasma membrane liquidity [33,34].

iii. **δ-Hemolysin** is a low-molecular-weight exotoxin (amphipathic peptide), produced by almost isolates of *S. aureus*. Delta toxin is only hemolysin that cause the degranulation of mast cell and is related to dermatitis and chronic inflammatory skin disease [35]. It is a narrow region of incomplete hemolysis accompanied unclear edges. δ-Hemolysis is potentially synergistic with ß-hemolysis, making a puddle zone that is greater than that made through δ-hemolysis. These exotoxins represent pore-forming toxins that may lead to injury to the host plasma membrane. [36]

iv. **γ-hemolysin** are water-soluble monomers that represent dicomponent ß- barrel pore formation toxins of S. aureus. AB and CB are efficient toxins may be formed via fusion the class-F component HlgB with one of the class-S components, HlgA or HlgC, which gather into oligomeric pores on the lipid bilayer surface. Its membrane-destructive efficacy is obvious in leukocytes (macrophages, neutrophils, granulocytes, and monocytes). [37]

B. Leukotoxins- lyse neutrophils and macrophages. Leukotoxins are called Anton-Valentine leukocidin (PVL) is a *S. aureus* exotoxin, which kills human granulocytes and monocytes *In vitro*. These toxins are di-component pore-forming *(Luk)* family, which are significant virulence agents. Thus, receptors were fixed for all of the di-component leukocidins: in addition to CCR5, *Luk*ED targets CXC chemokine receptor (CXCR1) and (CXCR2), PVL recorded a relationship with community-acquired (CA)-MRSA infections, that is still argumentative.[38]

C. Exfoliative Toxins (ETs)- separate the epidermis from the dermis. Staphylococcal exfoliate toxins (ETs) are protease activity. It is the causal factor of staphylococcal scaled skin syndrome (SSSS), an illness that mainly influences neonates and infants. Infected persons will experience dehydration, secondary infections, the appearance of loss of the superficial layers of the skin and skin ulcers [39]. Desmoglein 1 is the target protein of ETs, which cleaves it and, destroys the desmosomal cell attachments and causes separation of the skin epidermis. Derangement of the epidermis layers further simplifies the contagion progress [40].

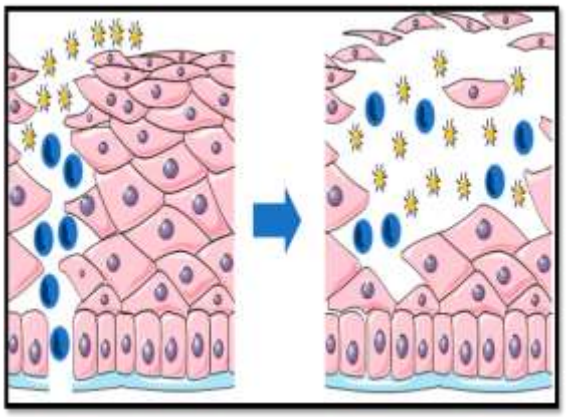

**Figure 5:** ETs invasion and expansion of blistering, *S. aureus* adhere to epidermis then penetrate by neutrophil created intercellular gap. [41]

D. Staphylococcal Enterotoxins (SEs)- induce gastrointestinal distress. Superantigens (SAgs) were known as staphylococcal enterotoxins (SEs) as they cause symptoms of food poisoning by *S. aureus*, like vomiting and diarrhea. [42]. These are secreted via enterotoxigenic food *S. aureus* strains that cause diarrhea and vomiting. These are heat-stable toxins that also resist food operations, excite T-cell stimulation and production, excite the cytokine release and apoptosis, and lethal toxic shock syndrome [43, 44].

E. (TSST)- enhances fever, vomiting, and systemic organ damage. Toxic-Shock Syndrome Toxin (TSST) is a superantigen supposed to be a responsible factor for basically all cases of menstrual-associated toxic shock syndrome. This toxin binds to specific receptors of the host cell and does not depend on the proliferation of T-cells, and it excites the release of some types of chemokines, like TNFα, IL-8, MIP-3α, and IL-2. It stimulates the stimulation of inflammatory cells and disruption of the mucous cell barrier, which increases the interaction and spread of the toxin and leads to toxic shock syndrome. The gene encoding the production of this toxin was observed to be produced by limited isolates, and it is one of the toxins that contribute to morbidity and mortality [45].

F. Toxin-antitoxin (TA) systems. This system consists of toxic proteins that overlap with the most important cellular functions of bacteria. It is an essential motorist for maintenance the virulence of bacteria, their resistance to antibiotics, and their production of biofilms. It was found that the chemical composition of antitoxins is proteins or RNA. TA systems are generally categorized into six different types (I, II and III ) have been recognized in *S. aureus*. (TA) are prevalent regulatory components for bacterial growth , cell survival and stress , it plays a critical action in the defense mechanism of pathogenesis[46].

## 7. Conclusions

This review comes to the conclusion that *S. aureus* toxins are aggressive virulence factors that have an important role in pathogenicity, provide important insights into epidemiology and antibiotic resistance. So, studying their work action is important to determine serious strategies for producing effective bacterial inhibitors and antibiotics. Also, studying bacterial toxins is of interest because of their precise role in inducing diseases, as well as the possibility of determining available strategies for preparing vaccines to prevent the adhesion of *S. aureus* bacteria, as well as to determine their external proteins to control infection .

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