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# The Role of Staphylococcus Aureus in Chronic Infections: Mechanisms and Treatment Strategies

**Bahaa Sufyan Hamid Abdul Aziz, Sura Numan Sarhan hamed, Omar Talal Arabi Abdullah, Sabrin Hameed Saleh Alwan, Murad Mudher Madab**
Samarra University College of Applied Sciences Pathological Analysis Department

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**Annotation:** Due to increasing antibiotic resistance, huge efforts are being put into the understanding and biotechnological design of extremely specific, novel antimycotics and their application to staphylococcal infections in various body compartments. In chronic infections, antibiotics are often ineffective. In joints, the bacteria induce synovitis and produce toxins that cause joint destruction. For osteomyelitis, standard treatment involves extensive surgery and prolonged use of antibiotics. Non-specific immune stimuli might activate the immune system to better outnumber the bacterial load. Cyclodextrins can eliminate more fast-growing, small colony variants of bacteria that reside in the osteoblasts and that might be prone to give a recurrent infection. It shows how specialized therapies are relevant, but also insists on a better understanding of the niches that shelter the bacteria and on effective ways to eliminate the organism and lead to a complete cure.

## 1. Introduction

Staphylococcus aureus is an important pathogen that can cause a broad spectrum of diseases, from minor skin infections and food poisoning to wound infections and abscesses, as well as life-threatening conditions like pneumonia, meningitis, endocarditis, and sepsis. The ambition of this review is to highlight S. aureus mechanisms involved in persistent and chronic infections and approaches for such treatments in a patient-adapted manner. Host immune responses and inappropriate antimicrobial treatments with antibiotics contribute to the transition of acute infections to chronic and persistent infections, which require long-term antibiotic therapy. These treatments contribute to the selection of resistant strains, as well as long-term colonization, which is another important niche for the evolution to the chronic and persistent states. These are potential stakeholders in the transition.

It is crucial to understand the disease for the development of new drugs, vaccines, and strategies for effective therapy, which requires increased knowledge about S. aureus's function in different invasion niches and how responses modulate infection outcomes. The increasing incidence of S. aureus antibiotic resistance, combined with the lack of new antibiotics entering the pipeline, poses a substantial challenge to the medical community in the ability to treat infections. S. aureus is prevalent in concentrated oral tenacity at asymptomatic colonization centers on the anterior nares, skin, pharynx, intestine, and skin wounds. [1][2]

## 2. Staphylococcus aureus: Characteristics and Pathogenicity

The bacterium Staphylococcus aureus is a common commensal of the human body, colonizing the skin and mucosal membranes. It is a versatile pathogen that can cause an increasing number of different infections, from superficial wound infections to more serious diseases like osteomyelitis, endocarditis, and sepsis. The capacity of S. aureus to persist for long periods in the host makes it a good example of a microorganism responsible for chronic infections. This chronicity also allows S. aureus to infect deep tissues and form biofilms on medical devices or damaged tissues, thereby avoiding the action of antibiotics and the immune response. In this chapter, we aim to review major mechanisms carried out by S. aureus that allow it to persist in the host and the characteristics of chronic S. aureus infections, and describe host responses to these infections. We will also discuss the current lines of research and management efforts aimed at controlling this major pathogen. Staphylococcus aureus is a versatile pathogen that is responsible for infections affecting an increasing number of different niches in the host, from superficial to life-threatening invasive infections. The chronicity of S. aureus infections and its ability to survive the hostile conditions found in nature, including high salinity, as well as extremes of acidity and alkalinity, have made it a fast-adapting pathogen and a good example of a microorganism responsible for chronic infections. S. aureus, mostly in its methicillin-resistant strains, is a worldwide emerging concern because antibiotic therapeutic options are limited. Moreover, S. aureus has developed the capacity to form biofilms that remain sessile and are not affected by the host defenses or therapeutic concentrations of antibiotics. [3][4]

### 2.1. Microbiological Features

S. aureus is a Gram-positive bacterium that can be found as a secondary commensal, colonizing nasal passages, throat, groin area, or anal region of infected people or in off-mucosal sites of colonization. It can exert a vast range of infections that cover different systems of the human body. It can produce different virulence factors that allow it to cause chronic bone and joint infections, endocarditis, osteomyelitis, and implant/device-related infections. Most importantly, the chronic location of this bacterium inside a host is the nasopharyngeal cavity, throat, tonsils, and colon, which are sites highly exposed to the external environment, thus being an important source of dissemination. It is estimated that the nasal niche is the site where 25% of people can be colonized for long periods of their lives, being recognized that its presence can mean a hospital-related pathogen in up to 82.4% of patients.

The development of chronic S. aureus infections requires the production of specific virulence factors like bacterial surface receptors with different affinities for host structures, the activation of tissue hydrolyzing enzymes, as well as the utilization of surface proteins capable of inducing internalization, while they often express resistance to opsonization and intracellular killing. Engaging eukaryotic cell surfaces, the MSCRAMMs are a class of pathogenicity factors with the ability to efficiently mediate the accumulation of S. aureus onto different sites. They greatly contribute to promoting the capacity of this linear cellular pathogen to attach to and invade non-professional phagocytic host cells, safeguarding them from host defense systems and consequently from immune response approaches. Certain strains of S. aureus produce a series of strongly regulated toxins that play a central role in pathogenicity, with the enterotoxin opioid peptide-like superantigen being discovered in the majority of cases. This interferes with cellular immune responses by influencing both the recruitment and amplification of the immune response within the host, while also harming the function of cells responsible for hosting immunity and consequently affecting the maintenance of immune liminality. With the potential to pose a permanent threat, this might help to explain S. aureus's ability to act as a chronic colonizer of the host during the year and throughout life. [5][6]

### 2.2. Virulence Factors

In an evolutionary perspective, successful human pathogens are highly adapted to their host. S. aureus produces a considerable number of different enzymes, exo- and cell wall-bound proteins, and toxins, all of which contribute to virulence. The number of different virulence and fitness factors of S. aureus ranges from 10 self-targeting genes to the global virulence regulator Agr. In addition, small hydrophobic peptides, the phenol-soluble modulin peptides, also contribute to virulence. Interestingly, these peptides are part of a new, essential, and conserved quorum sensing system which has been found in all Staphylococcaceae species that were tested, whereas the classical AIP-based Agr system is not. Overall, among the established virulence factors, mechanisms can be elicited with human cellular systems in vitro. Known antimicrobial resistance mechanisms include biofilm, small colony variants, and the metabolic diversity of formate using prototrophic strains. However, these traits will not be part of our discussions here.

Since this review is about the role of S. aureus during the adaptation to the chronic state of infection, we will only partially discuss factors that enable S. aureus to withstand nutrient limitation and immunity challenges, such as catalase, the staphyloxanthin and carotenoid pigments, SodA, the hydrogen peroxidase detoxifying enzymes and alkyl hydroperoxide reductase, S. aureus thioredoxin, and the non-ribosomally derived siderophore Staphyloferrin B, as these virulence factors are of particularly high relevance for S. aureus T3SS, one of the best-studied toxin-exporting transporters in S. aureus, and the environmental function of certain endolysins in cell separation phenomena. Of these cell cycle relevant proteins, cell wall hydrolases, also called endolysins, are involved in cell cycle related functions such as peptidoglycan splitting and cleavage of teichoic acids. [7][8]

## 3. Chronic Infections: Overview

The world’s population is rapidly aging, and many individual conditions become chronic. Chronic infections can have an extreme negative impact on individual health, both regarding the quality and expectancy of life. By definition, chronic infections are persistent and long-lasting infections caused by microorganisms capable of overcoming the host defense barriers. Some of the most common bacteria leading to chronic infections include Staphylococcus aureus, Pseudomonas aeruginosa, and Mycobacterium tuberculosis, whereas common fungi often include Candida spp. Chronic infections can be divided according to the host impairment or a specific pathogen. Aging and chronic diseases are not only risk factors, but they may also lead to a persistent infection that is very difficult or sometimes even impossible to treat. As antibacterial resistance becomes more intense, especially in intensive care units, therapy costs increase.

Some educated guesses may predict the upcoming challenges with children endangering from

common tonsillectomy operations. Based on these facts, chronic infections should be seen as one of the highest importance. They can further penetrate the venous system and switch to hematogenous spreading, localized mostly in the heart, liver, and brain. The action of sepsins caused by the proteolytic activity of the bacterium may produce hepatomegaly, splenomegaly, and local thrombosis in affected organs. In the last case, sepsis may be accompanied by possible organ dysfunction with fever and extensive hypotension that may also affect the outcome, even with appropriate antibiotic treatment. [9][10]

### 3.1. Definition and Types

Staphylococcus aureus, similar to many other bacterial species, is capable of life either free-living or settled in biofilm communities. It also exhibits different patterns of life during different stages of chronic infections. To establish infection, S. aureus must penetrate the host barriers and can lead to systemic manifestations. The biofilm pattern of an established chronic infection can evolve from different phenotypes and has two typical forms of display. Colonization of hosts is also based on phenotypically distinct S. aureus cells. Finally, during episodes of bloodstream invasion, so-called scattered phenotypes are acquired. This spectrum of phenotypic manifestations of S. aureus ensures success both as a commensal colonizer and as a pathogen of humans. Understanding each of these transitions is crucial for the development of strategies to control the different human-associated S. aureus lifestyles. The spectrum of conditions caused by Staphylococcus aureus is wide and consists of both localized and systemic diseases. Infection kinetics and specific patterns of life of staphylococcal cells depend on the stage of the infectious process. Moreover, the life of staphylococcal cells in chronic infections is different from that in classical infections. However, all those different forms typically start with colonization of the host, exhibiting very distinct colonization behavior. While researchers have overwhelmingly addressed understanding established infections, just a few studies have studied the colonization phase prior to infectious disease. For that reason, in the present paper, patterns of S. aureus life and the mechanisms of their establishment at the distinct stages of the infectious process, first and foremost, of chronic infections, are neglected. The aim was to merge accumulated data to clarify the distinct patterns of life established by S. aureus and to give a snapshot of what is currently known about the distinct lifestyle stages of the bacterium occurring during the establishment of chronic infections. [11][12]

### 3.2. Impact on Public Health

This bacterium is present on human skin and in mucous membranes, such as in the nose. When alterations occur in the host, such as diseases, inflammatory processes, and the use of drugs like immunosuppressive agents or glucocorticoids, this bacterium increases its virulence, causing different diseases. Antimicrobial resistance represents one of the main threats, and there has been an increase in the prevalence of MRSA as a cause of chronic infections. This bacterium contributes not only to the mortality it causes but also to the days spent in the hospital, the appearance of other secondary diseases, and an indirect cost to society in general of about $12 million for bacteremia and $1.4 billion for surgical site infections.

Unfortunately, antimicrobials such as vancomycin and teicoplanin are the current treatments for chronic infections, and this is one of the main problems because this bacterium generates resistance to these antibiotics. The development of other therapeutic strategies is necessary due to the increase of resistant strains of this bacterium. Some studies are beginning to demonstrate in vitro and in vivo the potential of some natural compounds by acting against different mechanisms and/or virulence, and not by killing the bacteria, which would not favor resistance as quickly. The objective of this review is to discuss the most innovative alternative strategies currently being used and evaluated against chronic infections caused by this bacterium. [13][14]

## 4. Mechanisms of Staphylococcus aureus Persistence

Staphylococcus aureus is reported to display a range of mechanisms underlying staphylococcal chronic persistence. These mechanisms include biofilm formation by which it is protected and deep-

seated persistence, immune mimicry employed by different S. aureus regulatory systems, and quorum sensing suppressing chronic staphylococcal persistence. In this review, we summarize reports dedicated to S. aureus persistence during chronic infections with a focus on S. aureus in cutaneous tissues and osteomyelitis. Chronic infections occur due to staphylococcal persistence and are often treatment-refractory. Staphylococcal persistence is associated with complex and costly treatment. S. aureus is reported to display a range of mechanisms underlying staphylococcal chronic persistence. These mechanisms include biofilm formation by which it is protected and deep-seated persistence, immune mimicry employed by different S. aureus regulatory systems, quorum sensing suppressing chronic staphylococcal persistence, the upsurge of toxin and TSST-1 production in a subpopulation or cell reprogramming associated with community or phage-induced S. aureus reprogramming, the emergence and persistence of phenotypic resistance, S. aureus pathogenicity islands, the occurrence of a subset of coagulase-negative staphylococci, modification in S. aureus virulence factors and antibiotic resistance, the resistance of S. aureus against host innate immunity and antibiotics, and immune evasion strategies that allow intracellular survival, as well as different phenotypic resistant S. aureus subpopulations and recurrent S. aureus in mouse models. [15][16]

### 4.1. Biofilm Formation

Over the past few decades, it has become increasingly apparent that rather than living in the planktonic state, where the majority of antimicrobial agents are effective, bacteria are more commonly found living in densely packed aggregates known as biofilms. It is thought that over 80% of chronic infections involve biofilm formation on host tissue or an indwelling medical device. In light of this, antimicrobial agents have to be at least 100 times more potent to be effective against biofilm-associated bacteria. The biofilm represents a protective lifestyle where bacteria live in a lipid membrane matrix, consisting of bacterial cells, proteins, exopolysaccharides, blood cells, and platelets, at a ratio unique to each type of biofilm. The biofilm cells are thought to become unique using quorum sensing, in which they sense each other, leading to the upregulation of specific proteins and the downregulation of planktonic factors, ultimately resulting in enhanced intrinsic tolerance to antimicrobials.

The ability to form a biofilm depends on the staphylococcal genetic background, such as collagen adherence or fibronectin-binding protein gene expressions. Biofilm formation is associated with the production of an adhesin, or a group of adhesins, enabling adherence not only to the host but also to other bacteria, proteins, and foreign materials. The biofilm formation of most S. aureus strains in vitro is intercellular adhesin gene-dependent, and further studies have led to the understanding of accumulation-associated protein and biofilm-associated protein as effector molecules, resulting in some strains in elaborated, thick biofilm structures, also referred to as hyperbiofilms. However, the understanding of the genetics of S. aureus biofilm production is incomplete, suggesting that we may be underestimating the complexity and mechanisms of staphylococcal biofilms. Multiple reports have documented phenotypes associated with unique biofilm formation in an S. aureus strain background. While novel therapeutic options, including anticoagulants and vaccines, are of interest to treat staphylococcal biofilm formation, it has also been proposed to use enhanced biofilm formation to control closely related alpha-toxin-producing bacterial pathogens, to prevent alpha-toxin-mediated tissue destruction, shock, and hemorrhage, and to stimulate an immune response to remove the circulating pathogen. [17][18]

### 4.2. Immune Evasion Strategies

The development of chronic infections often involves evasion of the host immune system. Immunoevasive properties of S. aureus are represented at any hierarchy level of the immune response: from the first association with host cells in the process of bacterial invasion to a general description in case of systemic parasitism in blood and internal organs. S. aureus successfully escapes from the host immune response by producing a multitude of escape factors that are able to interfere with both the innate and adaptive immune systems of the host. The first and foremost prerequisite for S. aureus to cause chronic infections in humans is the production of numerous

virulence factors that allow the bacterium to adhere to and invade through the host epithelium, resist innate immune mechanisms, as well as evade host adaptive immune responses. All of these S. aureus immune subversion strategies have at least partially contributed to genotypic shifts and an increase in the chronic outcome of S. aureus infections.

The study of cellular immune evasion mechanisms is important for comprehending the role of phagocytes in host defense and disease by staphylococcal determined strategies, which allow the bacteria to persist inside phagocytic cells. S. aureus evolved multiple extracellular and intracellular immune evasion strategies to escape destruction from professional phagocytes. Upon neutrophil activation, S. aureus co-opts and converts prostaglandins to potent immunosuppressive mediators. Neutrophil lifespan is prolonged and bacterial elimination is dulled, helping neutrophils survive longer while S. aureus spreads infections, evading detection for longer periods. Only after being engulfed, S. aureus uses an arsenal of strategies such as modulation of the bacterial capsule, modulation of surface proteins, modulation of phagosome-lysosome fusion, and modulation of cytolysins to interfere with the destruction of the S. aureus-containing phagocytes. [19][20]

## 5. Treatment Strategies for Staphylococcus aureus Chronic Infections

Staphylococcus aureus is a versatile and dangerous pathogen that can be associated with a vast array of infections. In addition to this versatility, S. aureus possesses distinctively unique virulence factors, including a remarkable ability to evade the human immune response, which strongly contributes to resistance to therapy. Research on therapies to combat S. aureus infections has been intense since the first humans succumbed to infections. Several antimicrobials have been shown to be active against S. aureus, but within a few months, resistance against each new drug has been discovered. This situation led to a worldwide spread of these strains and the evolution in rapid genetic transfer to other susceptible bacteria. New therapeutic approaches and new multi-target drugs are essential to provide effective multidrug chemotherapy and to mitigate the problem of S. aureus suppression in chronic infections. The overall aim of this review is to discuss treatment strategies, the action mode of existing antibacterial compounds, proposed new antimicrobial strategies, including targeting S. aureus virulence factors, as well as exploring the potential of resistance modifying adjuvants in order to improve the activity of existing antimicrobials, increasing their effectiveness and reducing the risk of evolution of resistant strains. At present, as in the past, S. aureus infections necessitate the application of prolonged and multidrug chemotherapy, with all its associated toxicities and expenses, and still have a tendency to relapse, very often leading to difficulties in management, disability, and sometimes lethal outcomes. Nowadays, conferring immunity against this pathogen, able to protect against the development of any of its infections, is a real biosafety challenge, which could provide a significant improvement in the standard of life. The future development of drugs capable of potentiating the human macrophages and stimulation of both the human innate and acquired immune system could represent an alternative approach to prevent and treat chronic staphylococcal infections. However, to reach these ambitious goals, a hundred years after the original hypothesis, we need to develop newly tailored drugs that recognize these highly conserved pathogen structures. These drugs should contribute to enhancing nitric oxide production, to balance the runaway inflammatory response developed in the chronic course of the infections and to reinforce the immune system. [21][22]

### 5.1. Antibiotic Therapy

The standard treatment approach for chronic S. aureus infections is based on the use of antibiotics. Several drug classes are available that have been seen as effective treatments for these infections, for example, beta-lactam antibiotics, fluoroquinolones, lincosamides, glycopeptides, and oxazolidinones. Unfortunately, an increasing number of S. aureus isolates are observed to be resistant to multiple antibiotics, which results in chronic, difficult-to-treat infections that impose high quality of life and cost burdens on patients. Furthermore, non-antibiotic treatments could restrict the emergence of drug resistance and diminish antibiotic side effects. Recent studies have suggested that non-antibiotic therapy might be more promising to resolve chronic S. aureus

infections rather than standard antibiotic therapy.

It is accepted that enhancing the in vivo effectiveness of currently available therapeutic agents is necessary to address the treatment difficulties of chronic S. aureus infections. The first step toward developing new treatments is to assess the therapeutic agents that are available. Clinical studies have shown that, in patients with chronic S. aureus infections, antibiotics are the most common treatment. However, successful antibiotic therapy for these infections remains a challenge. This review also described several cases of antibiotic therapy failure against chronic S. aureus infections primarily due to drug resistance. In general, the evolution of drug resistance affects the clinical effectiveness of antibiotic therapy for chronic S. aureus infections, and these impacts should not be neglected. What follows is a brief summary of each drug class and the key resistance mechanisms to these classes of drugs that are associated with chronic S. aureus infections. Finally, we describe currently available non-antibiotic therapies targeting chronic S. aureus infections, as well as their shortcomings. [11][23]

### 5.2. Alternative Approaches

The increasing resistance of Staphylococcus aureus to antibiotics has led to the development of alternative therapeutic applications. Instead of killing the bacteria, these aim to control the virulence of the bacterium, thus attenuating the bacteria or changing its behavior, hopefully leading to the stimulation of the host's immune system to clear the bacteria or prevent the development of antimicrobial resistance. One approach is based on the interaction between the host and S. aureus, interfering with this interaction by adding compounds that stimulate either the host's innate immune system or by targeting the bacterial signaling system that regulates the expression of toxins and immune modulators in S. aureus.

To stimulate the innate immune system of the host, whole S. aureus cells are used. These are killed; for instance, by filtration, and hereby cell wall components, like peptidoglycan, wall teichoic acids, N-acetyl glucosamine, and lipoteichoic acids are released. In addition, toxin-derived components present in dead whole-cell preparations, like alpha-toxin or Panton-Valentin leukocidin, can stimulate the host's immune system and are suggested to be used in the preparation of vaccines against S. aureus. As dead staphylococcal cells are required for the preparation of these stimulants, the use of methicillin-resistant S. aureus in the stimulation of the host's immune system is not a concern. [24][25]

## 6- Conclusion

Chronic infections are associated with the production of immunosuppressive molecules by pathogens. S. aureus is a pathogen that produces many immunosuppressive molecules that interfere with the host immune response. In chronic infections, S. aureus interferes with the healing process of the skin by regulating wound closure and also triggers the chronic inflammation necessary for its survival. In this review, we summarized all the molecular mechanisms used by S. aureus to establish chronic infections and pointed out potential therapeutic targets to intervene in the immune evasion and the progression of the inflammation that will lead to a wound that is no longer capable of healing. The current scenario of antibacterial resistance requires new strategies that intervene at multiple levels. The possibility of disrupting these virulence factors is a promising option and is addressed in the second part of the review, pointing out several potential strategies for treating chronically infected patients. The combination of both in-depth knowledge of these mechanisms and new treatment strategies will succeed in controlling chronic infections. In conclusion, this review focuses on the different evasion, persistence, immune modulation, and signaling factors used by S. aureus for enabling chronic infections and suggests potential treatment strategies for these factors. Host-directed therapy offers potential advantages over conventional antimicrobial therapy because interfering with these molecules would minimize selective pressure on antibiotic susceptibility patterns. Given the ever-worsening threat of antibiotic resistance and the gravity of chronic infections, these findings and their putative importance could yield exciting opportunities for therapeutic manipulation and long-term control. The combination of these strategies will succeed

in generating alternative treatment strategies for chronic infection control.

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