# Antimicrobial coatings as a promising prevention strategy of implants infections triggered by *Staphylococcus aureus*

## Powłoki antybakteryjne jako obiecująca strategia profilaktyczna zakażeń implantów o etiologii *Staphylococcus aureus*

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**Summary**

Technological progress in the development of various types of implants is one of the greatest achievements of contemporary surgery. Such devices can replace or restore the function of damaged tissues, significantly improving people's quality of life and its longevity. Unfortunately, infections are the main reason for removing implants from patients who usually then need expensive and challenging treatment. *Staphylococcus aureus* is the most frequent pathogen detected in such complications. Therefore, prevention methods become more attractive. Antimicrobial coatings are the most important techniques to prevent implant infections. They give the biomaterials from which medical devices are obtained antiadhesive and antibacterial properties. In this paper, we review promising methods of creating such coatings. The majority of concepts are about covering implants with germicidal substances like antibiotics or silver nanoparticles. Interestingly, even changes in the surface topography may be necessary to prevent *Staphylococcus aureus* adhesion effectively.

**Keywords:** *Staphylococcus aureus, antimicrobial coatings, infections prevention*

**Streszczenie**

Postęp technologiczny w tworzeniu różnego typu implantów jest jednym z największych osiągnięć współczesnej chirurgii. Takie urządzenia mogą zastąpić lub przywrócić funkcję uszkodzonych tkanek, co znacząco poprawia jakość i długość życia pacjentów. Niestety infekcje są głównym powodem usuwania implantów. Pacjenci wymagają też zazwyczaj trudnego i kosztownego leczenia. Gronkowiec złocisty jest najczęściej wykrywanym patogenem w tego typu powikłaniach. Powoduje to, że metody profilaktyczne zyskują na atrakcyjności. Najważniejszymi technikami umożliwiającymi zapobieganie infekcjom implantów są pokrycia przeciwdrobnoustrojowe. Dzięki nim biomateriały, z których otrzymywane są urządzenia medyczne mogą uzyskać właściwości antyadhezyjne i bakteriobójcze. W niniejszej pracy dokonujemy przeglądu obiecujących metod tworzenia takich pokryć. Większość koncepcji dotyczy pokrywania implantów substancjami bakteriobójczymi, takimi jak antybiotyki czy nanocząsteczki srebra. Co ciekawe, nawet zmiany w topografii powierzchni mogą być konieczne, aby skutecznie zapobiec adhezji gronkowca złocistego.

**Słowa kluczowe:** *Gronkowiec złocisty, powłoki antybakteryjne, profilaktyka zakażeń*

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## Prevention strategies of implant infections triggered by *Staphylococcus aureus*

**ECM** – extracellular matrix
**EDTA** – ethylenediaminetetraacetic acid
**MIC** – minimal inhibitory concentration
**MLSB** – resistance to macrolide, lincosamide, streptogramin B
**MRSA** – methicillin-resistant *Staphylococcus aureus*
**VISA** – vancomycin-intermediate *Staphylococcus aureus*
**VRSA** - vancomycin-resistant *Staphylococcus aureus*

## 1. Introduction

*Staphylococcus aureus* (*S.aureus*) is a well-known Gram-positive, aerobic, non-motile bacterium classified into phylum Firmicutes, class Bacilli. It can be a human commensal. The carriage status of *S. aureus* ranks from 20 to 25% of the healthy adult population [1]. The main niches of its occurrence include anterior nares, pharynx, perineum, and temporary skin. However, a rich arsenal of virulence factors that *S. aureus* posseses is commonly involved in the skin and soft tissue diseases. Life-threatening bloodstream infections are also no exception [1-3].

Another alarming issue related to this bacterium is its ability to acquire resistance to the first-line antibiotics – β-lactams. Such methicillin-resistant *S. aureus* (MRSA) strains were firstly observed only in a hospital environment. Over the years, community-associated MRSA occurred. It has been reported that the percentage of MRSA strains in the United States intensive care departments increased from 30-40% in 1997 to 57% in 2002 [4]. It shows the dynamics of the staphylococcal resistance development process. Later on, the widespread use of vancomycin, the first-line treatment in the case of MRSA infections, resulted in the development of isolates with reduced susceptibility or complete resistance to this antibiotic - VISA and VRSA, respectively. It is worth mentioning that there are also reports on *S. aureus* resistance to macrolide, lincosamide, streptogramin B (MLSB), streptogramin A, pleuromutilin, florfenicol, or linezolid [5,6]. Difficulties in treating *S. aureus* infections make prevention strategies very attractive [2].

In the present paper, we show that *S. aureus* is a big challenge for various kinds of surgical treatment. Such phenomenon is mainly caused by the ability of this bacteria to make biofilm by attaching to abiotic surfaces. Almost every implanted device such as catheters, prosthetic joints, or artificial pacemakers are exposed to covering by bacteria and host immune proteins. Such biofilm-related infections or inflammations are severe complications for patients with implanted medical devices. Moreover, their removal from patients' bodies is frequently necessary to treat such infections. Therefore, creating an effective prevention strategy may be a groundbreaking discovery for surgery because it would probably improve the effectiveness of many procedures [1,7].

## 2. Biofilm formation

Biofilm is defined as a tridimensional microbial colony in which cells attach to a surface or other bacteria cells. The process of biofilm formation is presented in Figure 1. It is worth emphasizing that the most critical step in biofilm development is the production of extracellular matrix (ECM) by bacteria. This substance consists of proteins, carbohydrates, extracellular DNA, teichoic acids, thus creating the protective layer [8]. The exact composition of mentioned ECM depends on bacterial strain background, a kind of strain, and environmental conditions. The principal substance responsible for *S. aureus* biofilm integrity is polymeric N-acetylglucosamine. Other factors include surface-associated proteins like protein A, fibrinogen binding protein, biofilm-associated protein, and *S. aureus* surface protein. They allow both adhesion and accumulation of bacteria [1].

As mentioned above, ECM creates a "protective coat" that provides a defense against the host immune system. One of the most important impaired human immunologic mechanisms in such cases is a restriction of macrophages penetration into biofilm structure. It causes that phagocytosis (the innate mechanism of bacteria eradication from the body) is ineffective. Furthermore, the penetration of various substances such as antibiotics is also disrupted [1]. Interestingly, bacteria embedded in the biofilm structure usually exhibit more excellent antibiotic resistance due to the increased frequency of horizontal gene transfer (main mechanism responsible for resistance acquisition). These features determine the difficulties in biofilm eradication and treatment. Therefore, staphylococcal biofilm-induced infections of implants are such an enormous challenge for clinicians. Moreover, the process of secondary colony-forming may lead to life-threatening systemic infections, like sepsis [1,7,8].

## 3. Antimicrobial coatings

The primary prevention strategy of implant-associated infections is related to the development of "antimicrobial coatings". Biomaterials are natural or synthetic materials used in the production of various implants. They must have several features that enable their safe implantation into the patient's body. The fundamentals are cytocompatibility and the ability to preserve the differentiated phenotype of the cells surrounding the implant. However, biomaterials are exposed to various bacteria, especially *S. aureus* attachment. Therefore, it has been suggested that the development of coatings that are safe for patients, while also giving antibacterial and antibiofilm properties to biomaterials, could be an effective prevention strategy. Moreover, it has been observed that appropriate changes in the surface of biomaterial may prevent biofilm development [7,9]. Below we discuss the most important techniques proposed in the available literature.

### 3.1 Antimicrobials for implant coating

It has been proposed to cover the biomaterial with agents that present antimicrobial or antibiofilm properties. If a thin protective layer on implant surfaces is formed,

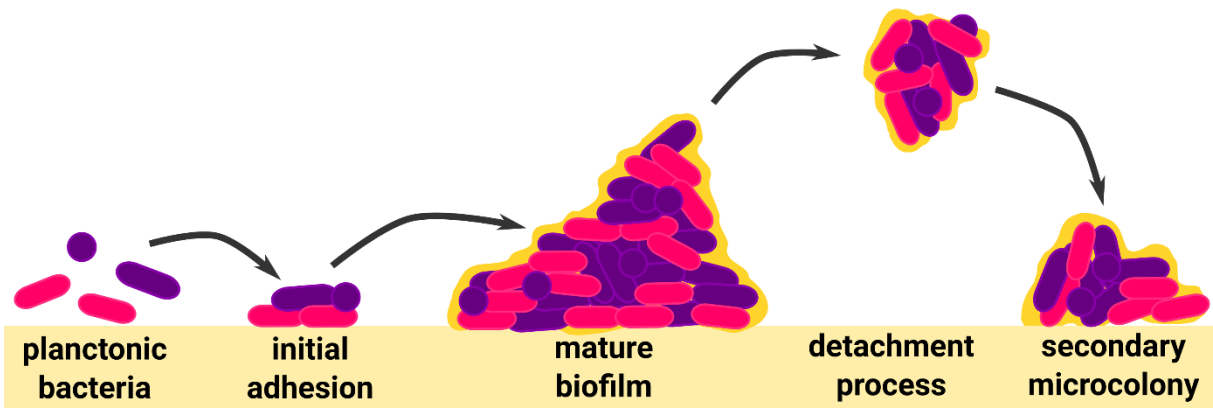


Figure 1. Schematic illustration of biofilm formation.

the whole medical devices should be resistant to bacterial colonization [7,10,11]. Many attempts have been made to investigate the available healing substances for the mentioned purpose. The substances promising effectiveness are presented in Table I. [10,12-16]

Close attention has been given to antibiotics. Sacar et al. [10] studied the prophylactic efficacy of linezolid combined with rifampicin and compared it with teicoplanin. Using rat model, they analyzed the impact of perioperative intraperitoneal prophylaxis with linezolid and teicoplanin alone and combined with rifampicin which covered grafts, against MRSA. Their analysis confirmed the significant advantage of linezolid combined with rifampicin-coated grafts. The difference between linezolid and teicoplanin was not observed. Despite the high effectiveness of rifampicin against biofilm formation, it should not be used alone in prophylaxis because of its toxicity. There is a danger of producing high MIC MRSA strains, either [10,17]. Intraperitoneal daptomycin with rifampicin-soaked vascular grafts also manifested great effectiveness against staphylococcal biofilm development. Moreover, this strategy prevented the uprising of rifampicin resistance [18].

Other observations have indicated that the solution consisting of N-acetylcysteine (an antibiofilm agent), gentamicin, and amphotericin B is promising in preventing colonization of ventricular assist devices. It has been confirmed on an animal model that the mentioned antibiofilm combination decreases the risk of colonization by *S. aureus* [12]. According to Manner et al. [13] work, doxycycline has similar to rifampicin antibiofilm activity. The oxacillin shows reduced activity compared to them [13]. It has also been reported that a solution composed of minocycline and ethylenediaminetetraacetic acid (EDTA – a popular metal chelator with inhibition activity against staphylococci) is significantly more effective than EDTA or heparin in suppressing catheter colonization by various bacteria and fungi [14].

However, there is a significant danger that the worldwide use of antibiotic-coated implants could induce the emergence of resistant *S. aureus* strains [19]. Therefore, there is a growing number of studies on other substances for implant covering. It has been proposed that neuraminidase could be a proper choice. The enzyme regulates the number of sialic acids on the cells. This compound plays a vital role in cell-cell interactions. The conducted experiment has demonstrated that the addition of neuraminidase leads to a significant decrease of *S. aureus* colonization due to the reduced bacterial adherence ability [16].

Another concept is based on the knowledge that one of *S. aureus* actions in the human organism is coagulation. This microbe can bind and activate human pro-thrombin, leading to clot development. This mechanism is also essential for staphylococcal biofilm formation. Therefore, it has been suggested that direct thrombin inhibitors may be components of antibiofilm coatings. Hogan et al. investigated the effectiveness of oral anticoagulants, such as argatroban, hirudin, and dabigatran. The results of the study showed that all of them could reduce the number of cells forming the biofilm. However, the hirudin coating was the most promising solution [15].

## 3.2 Metal nanoparticles in implants

The results of many studies indicate that a good solution may be to cover the biomaterial with a metal having antibacterial properties. The use of silver has been proposed because its germicidal activity is well-known. This metal has a long history in human healthcare and it has been used since antiquity. Silver is an electron-positive element. Its cation presents the ability to bind proteins and anions [20]. Silver used to be administered in various forms, such as silver nitrate or phosphate. The introduction of metal nanoparticles is an achievement in therapeutic and prevention strategies [21]. Silver nanoparticles release silver ions and this form of administration allows for a higher concentration of intracellular silver ions. It increases the effectiveness of silver germicidal activity (see Figure 2). Although, the mechanism of silver action has not been fully elucidated [22,23].

There are many concerns about the dangerous health effects of silver. However, previous studies have not confirmed them. The most important clinical syndromes triggered by prolonged exposure to silver are argyria and argyrosis. Both are not life-threatening. It is also possible that patients may develop an allergic reaction after silver administration [24]. Interestingly, the study performed by De Simone et al. suggests that even low concentrations of silver manifest antimicrobial activity [25].

The properties of other metals have also been investigated. It seems that cooper could be a promising alternative for silver in implant surface modifications. This metal is characterized by high cytocompatibility and low eukaryotic cell toxicity. The effectiveness of inter-metals Ti-Cu film was also investigated. Available literature suggests that this method may be successfully introduced to patients. [26] However, more studies have to confirm this hypothesis.

Nanostructured selenium may also be a good solution for implanted devices. It has been reported that selenium nanoparticles show a high ability to prevent *S. aureus* colonization. Interestingly, the nanoparticle size plays an essential role in the effectiveness of the inhibition process. Probably, smaller particles of various metals are preferable [27,28].

## 3.3 "Race for the surface"

Several scientists point out that biofilm formation on implant surfaces also depends on the natural competition between host and bacterial cells. This concept is called "race for the surface." If human fibroblasts win such competition, a cellular layer covers the implant surface. It means that bacteria are usually unable to colonize such biomaterial. However, if bacterial cells attach to the implant first, the biofilm development and severe infection occur. The idea arose to support host fibroblasts in this fight. For this purpose, fibronectin-functionalized hydroxyapatite coatings enriched additionally with silver were investigated. Both hydroxyapatite and fibronectin increase fibroblast adhesion. Silver is used to slow down bacterial cells attachment due to its antimicrobial properties. The results of the mentioned investigation are hopeful. Namely, it has been confirmed in *in vitro* model that the above described surface allows fibroblasts to colonize it faster than *S. aureus* cells, which is favorable [29].

## 3.4 "Nano-pillar surface"

The above described techniques are based on the biochemical interactions of bacterial cells with antibiotics, chemotherapeutics, or metals. However, it has been re-

Table I. Substances tested as implant coating agents with promising antimicrobial effectiveness.

| Substance group | Substance name | Important remarks | Ref. |
|---|---|---|---|
| Antimicrobial | Rifampicin | • Recommended to be used in combination with another antibiotic due to tendency used alone to yield high MIC strains, especially against MRSA.<br>• Showed synergistic efficacy *in vivo* with linezolid or teicoplanin in the prevention of vascular graft infection due methycylin-resistant staphylococci. | [10, 11, 13] |
| | Doxycycline | • Showed *in vitro* efficacy in staphylococci biofilm reduction. | [13] |
| | Oxacyllin | • Showed *in vitro* efficacy in staphylococci biofilm reduction. | [13] |
| Antimicrobial/ anticoagulant | Minocycline/ EDTA | • Showed very effective *in vitro* efficacy in staphylococci biofilm reduction. | [14] |
| Antimicrobial/ mucolytic | N-acetylcysteine/ gentamicin/ amphotericin B | • Reduced the risk of colonization *in vivo* by SA.<br>• The prophylactic effect persisted only for up to 1 week. | [12] |
| Anticoagulant | Argatroban | • Efficiently reduced staphylococci biofilm formation *in vitro*.<br>• Lack information about stability and activity duration of this prophylactic effect. | [15] |
| | Dabigatran | • Efficiently reduced staphylococci biofilm formation *in vitro*.<br>• Lack information about stability and activity duration of this prophylactic effect. | [15] |
| | Hirudin | • Efficiently reduced staphylococci biofilm formation *in vitro*.<br>• Lack information about stability and activity duration of this prophylactic effect. | [15] |
| Viral enzyme | Neuraminidase | • Reduced *in vitro* the adherence of slime-forming *S. aureus* and subsequently reduced biofilm formation.<br>• Did not show the effect in non-slime-forming *S. aureus.* | [16] |

**Legend**: Ref. – references, MIC – minimal inhibitory concentration, MRSA – methycilin resistant Staphylococcus aureus, EDTA – ethylenediaminetetraacetic acid

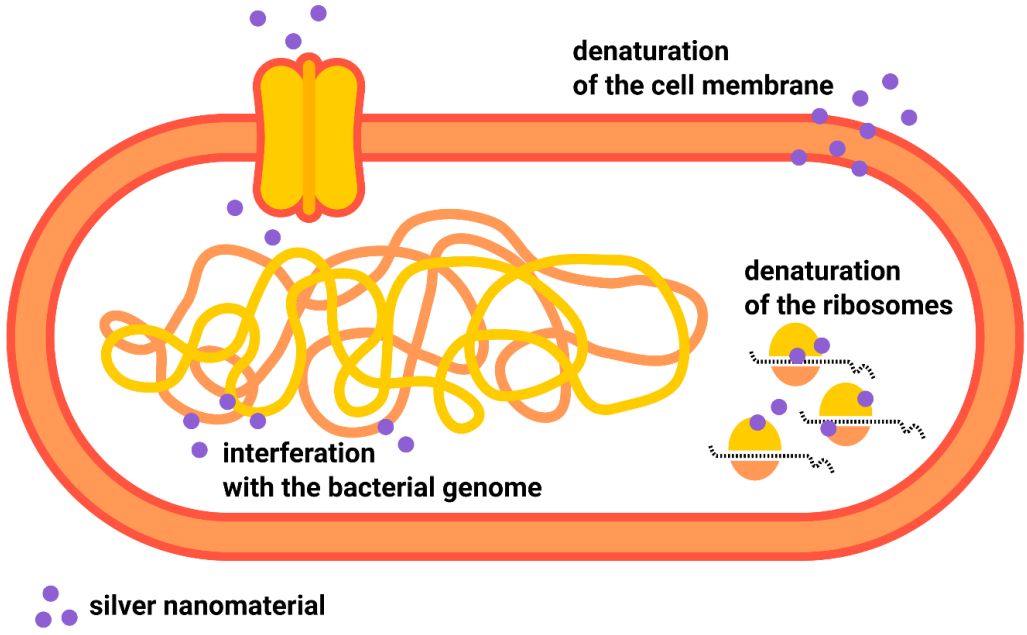


Figure 2. Schematic illustration of silver nanoparticles action in bacterial cell.
Silver nanoparticles release silver ions that adhere to the cell wall due to binding thiol, sulfhydryl, imidazole, amino, carbonyl, and phosphate groups. This mechanism results in the disruption of the bacterial envelope. The essential intracellular mechanism of action includes the denaturation of bacterial ribosomes. It leads to the cessation of protein synthesis and cell death. Moreover, deactivation of respiratory enzymes and unfavorable modifications of deoxyribonucleic acid is also feasible cell-killing pathways.

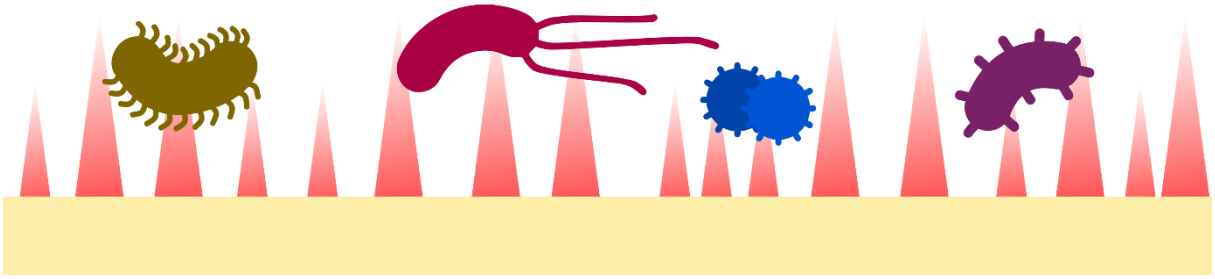

Figure 3. Schematic illustration of nano-pillar surface activity.
The scheme illustrates the nano-pillar surface and its action against a broad spectrum of bacteria species. Each planktonic form of a bacterium tries to adhere to the surface. As mentioned before, it is the first step of biofilm formation (Figure1.). Such a process is easy if the surface of the potential implant is smooth. However, if the surface has changed structure into nano-pillars or something similar, bacteria is due to stretching their cell membranes between the two closest pillars. Then the cell membrane ruptures.

ported that changing the surface structure of the implant to take advantage of biophysical interactions also allows bacterial cells to be killed. It has been suggested that changing the surface structure from smooth to nano-pillar or nano-dagger could be effective in preventing biofilm formation [30,31]. There are several types of interactions between bacterial cells and such changed surfaces. Gravitational force, Van der Walls repulsion force, and hydrophobic interactions belong to the most important. These physical interactions allow not only to reduce the adherence of bacteria to the surface, but also for contact–killing. Interestingly, this microscale topography is based on a natural model, as it resembles the surface of cicada wings whose structure has antimicrobial properties. The crucial role in this concept is the choice of suitable microscale surface morphology [30,31]. It has been demonstrated that pillars, ridges, ripples, and grooves have antibiofilm activity (see Figure 3) [32-36]. Interestingly, a higher degree of effectiveness was achieved when the height of pillars varied. The probable explanation is that bacterial cells interact first with higher columns, making their cell membrane distorted and weaker. Next, bacteria interact with lower pillars. Wu et al. [31] performed an analysis using Scanning Electron Microscopy. They revealed that bacterial cells were ruptured after exposition on the mentioned nano-pillars surface. It confirmed biophysical interactions. Another assay has shown that such cover has no destructive effect on erythrocytes [31].

There are two main advantages of the "nano-pillar surface" concept. First of all, such nano-pillar structures are effective against a broad spectrum of bacteria, not only *S. aureus*. Secondly, this method does not require any chemicals. Therefore, there is no risk of developing bacterial resistance [30,31].

## 4. Conclusions

*S. aureus* is one of the most dangerous bacterial pathogens. This microbe is often implicated in the difficult treatment of implant-associated infections. It leads to increased morbidity in patients, prolonged hospitalization, and enlargements of healthcare costs. Infected implants frequently require surgical removal, which results in long-term treatment failure. Therefore, antimicrobial coatings on implants seem to be a very attractive prevention strategy. In the article, we presented several techniques for obtaining antimicrobial properties of biomaterials. The methods based on surface texture changes seem to be the most promising. Preliminary studies revealed their effectiveness. Importantly, they are not associated with the risk of bacterial resistance development.

## Conflict of interest

The authors declare no conflict of interest.

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