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Review

Perspectives in Prevention of Biofilm for Medical Applications

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Abstract: The opportunity of decreasing the development of biofilm on the implant surface is one of the biggest research problems. It is connected with the existing prevention of microorganism hyperplasia. The application of numerous modifications is concerned with surface treatments leading to minimizing bacterial colonization. In the case of non-use antibacterial therapy, this leads to tissue infection. It can lead to a decreased opportunity to fight infection using antibiotherapy. One way is to decrease the increasing biofilm application which requires a method of modification. These techniques ensure properties like homogeneity or repeatability. The structure and chemical composition are changed with methods like CVD (Chemical Vapor Deposition), PVD (Physical Vapor Deposition), sol–gel, or ALD (Atomic Layer Deposition). Antibacterial properties of metals are connected with their impact on proteins and the nuclear proliferation of fibroblasts, causing improvement in biocompatibility and also growth corrosion resistance, and the decline of biofilm adhesion. The prevention of biofilm with medicines and antibiotics is a crowded-out treatment. Traditional methods of preventing biofilm are based on compounds that kill or inhibit the growth of the microbes but at the same time lead to frequent development of resistance to antibiotics. This review summarizes the current knowledge of reducing and preventing the creation of biofilm.

Keywords: biomaterials; surface modification; antibacterial layer

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1. Introduction

Nowadays, there are a lot of classifications of antibacterial coating technologies. This method can be achieved in different ways. We have not found the best and universal way to prevent the development of bacterial biofilm on the patient and implant. Finding a perfect coating technology can be classified into three groups. The first one is passive surface finishing modification (PMS), which is focused on preventing and reducing bacterial adhesion without releasing germicide to the surrounding tissues. Active surface finishing/modification (ASM) is the next way of creating ideal coatings. This kind of layer includes pharmacologically active agents, germicide, metal ions, and different organic or inorganic ingredients. Last but not least is peri-operative antibacterial local carriers or coatings (LCC). The strategy allows for using concentrations of biodegradable or not-biodegradable antibacterial carriers or coatings [1].

2. Issues of Bacterial Biofilm

Biofilms are sedentary populations of one or many species of microorganisms that are attached to biotic or abiotic solid surfaces or are formed at the boundary phase [2]. Cells in biofilms are surrounded by extracellular polymeric substances, mainly composed from polysaccharides, but also from proteins and nucleic acids, called matrix or biofilm matrix [3]. A biofilm comprises a concentration of microorganisms like bacteria or mushrooms. When this occurs, the spontaneous reaction of joining creates something like a

protective matrix. This formation attaches to the biological membrane of a living or dead surface and it can contain several to a dozen species. The microorganisms are attached in a dense and slimy barrier. This substance is composed of sugars and proteins. Biofilm is a separation of bacteria from external factors. It allows for survival despite antibiotics or organism defense mechanisms. The creation of biofilm can often lead to disturbing wound healing, inflammatory diseases, periodontal disease, cystic fibrosis, chronic acne, osteoarthritis, and orosteomyelitis. The healed complications can reoccur and create a chronic condition [4,5]. Bacteria that have increased biofilm creation are protected from the effect of antibacterial medicines and mechanisms of the immune system [6]. It is connected with decreasing the microorganisms' increase rate. The bacteria features like antibiotic resistance have caused lower medicine insertions to the cell interior. In this way, using antibiotic therapy does not always bring therapeutic results observed in the fight against non-forming biofilm microorganisms [7].

About 60–70% of microorganisms attached to the implant surface have a connection with current nosocomial infections [8]. At the same time, most of the infections are connected with creating biofilm on the biomaterial surface. The most popular bacterial strains are *Staphylococcus epidermidis*, *Streptococcus viridans*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*. *S. aureus* and *S. epidermidis* are caused mostly by creating layers on heart implants. This kind of bacteria is responsible for about 40–50% of infections in the cardiovascular system and 50–70% of infections on catheters. The bacterial strains of *E. faecalis* spread during the central line or intubation. Infections connected with creating biofilm deal with 80% of all chronic responses of organisms during hospitalization. The process of creating biofilm is connected with the colonization of microorganisms close to the implant. One of the main reasons is infections of the operation area during the application of surgical meshes during hernia surgery. On the surface of the implant, it comes to attach bacteria during translocation from the large intestine. This process is connected to the moment when the patient has microorganisms in the blood. In this way, it contaminates the implant during operation. It makes the integration between the implant and surrounding tissues impossible [4].

The bacterial strains attached to the biomaterial's surface have created a coating that prevents the operation of the immune system or antibiotics [9]. In this way, it deepens the infection or recurrence inflammation of the peri-implant pocket. The examination of biological membrane expansion on the implant surface is conducted by a scanning electron microscope in a concentration of microorganisms. A biofilm is a structure that is hard to detect, especially in the first phases of growing. It does not allow the removal of bacteria before the process of gene expression. This one is extremely dangerous for patients [10].

3. Methods of Prevent Creating of Biofilm Based on Different Authors

There are basically two main methods of preventing the creation of bacterial biofilm-like using antibiotics therapy, silver particles, and methods of surface modification.

3.1. Antibiotics Therapy and Silver Modification

Silver nanoparticles (AgNPs) are one of the most famous antibacterial agents and demonstrate their properties even against multidrug-resistant bacteria and probably provide development of future technology surfaces [11]. Prophylaxis of surgical site infections and the application of antibiotic therapy is one of the ways to prevent the formation of biofilm. According to the authors of [12], the preparation of the patient in case of elective surgery should begin on an outpatient basis and minimize the patient's stay in the hospital ward. Certainly, the shortened length of stay in the hospital will reduce the risk of bacterial colonization. According to the information contained in the document's sources [13,14], most surgical procedures performed in hospitals do not require the application of perioperative antibiotic prophylaxis (OPA). However, each hospital is required to familiarize themselves with the principles of OPA adapted to the given procedures. For most treatments that require the use of OPA, the drugs of choice are first-generation cephalosporins

(cefazolin) or second-generation (cefuroxime, possibly cefamandol). In the case of some surgical procedures, the use of metronidazole is also recommended. Other drugs can practically be used in OPA only if *S. aureus* is detected, or if they are methicillin-resistant or allergic to antibiotics β-lactam (immediate-type hypersensitivity reaction), in some urological procedures, and in ophthalmology. The dosage and duration of intraoperative drugs administration depend on the given antibiotic and the patient's age and weight.

The aim of the short communication of Wan et al. [15] was to determine the influence of silver and copper ion implantation on antibacterial performance and wear and corrosion resistance of the three materials. In connection with silver ions, antibacterial properties were applied on the surface of 317L steel, pure titanium, and TiAl7Nb. The specimens were mechanically polished with Al_2O_3 sandpaper and next ultrasonically washed with acetone and ethanol. In this way, the achieved plates were prepared for ion implantation. Next was the ion implantation machine with an ion source. All samples were sterilized by an autoclave at 121 °C for 20 min. The specimens with the bacterial solution were covered with an aseptic polyethylene film and incubated at 37 °C for 24 h. The bacterial solution was collected and inoculated onto a standard agar culture medium. The corrosion resistance in Hank's solution was examined by the electrochemical method. After the process of ion implantation of copper and silver, there was an increase in antibacterial activity for all materials. Silver and copper ion implantation does not significantly affect the corrosion resistance of all metals, despite the ion dose's level. The experiments have shown that silver and copper implantation into all metals improves their antibacterial activity and wear resistance.

The publication "Influence of Cu and Nb additives on specific surface properties and biological activity of transparent TiO_2 thin-film coatings" [16] was concerned with a comparison of the surface properties and biological activity of TiO_2 and TiO_2 with Cu and Nb additives. According to Ranell et al. [16], for bactericidal activity, titanium dioxide coating hydrophobization of their surfaces significantly hinders the growth of microorganisms. One of the ways that allow you to increase photocatalytic activity is to get a list of hydrophobic results advertising the nanocrystalline structure [17]. In view of the antibacterial properties of Cu, it was chosen as an addition. The thin films were created by high-energy magnetron sputtering of metallic Ti-Nb-Cu target in the oxygen atmosphere. Films that were deposited on glass substrates were investigated by transmission method and with the aid of a transparent optical profiler. Furthermore, wettability measurements and antibacterial tests with *Pseudomonas aeruginosa* were conducted. The measurement procedure was preparation liquid suspension with bacteria in which the prepared samples were then immersed and incubated for 24 h. At that time, charged samples of the slurry were poured onto the agar medium, and bacteria were grown therefrom (Figure 1). The number of bred microorganisms was thus marked with an optical microscope. To sum up, the results of microbiological treatments showed TiO_2:(Nb, Cu)'s very good antibacterial properties. It is related to the release of copper ions from the surface of the layer to the environment, which was a solution with bacteria. The second thin film of TiO_2 did not have these properties.

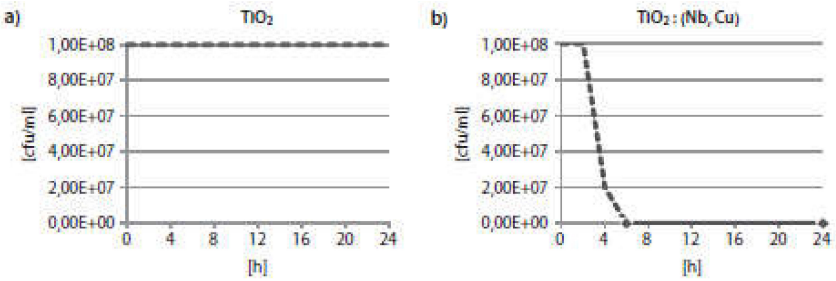


Figure 1. Biological activity over time of TiO_2 and TiO_2:(Nb, Cu) thin films in contact with *Pseudomonas aeruginosa*. Reproduced with permission from Wojcieszak, D.; Domaradzki, J.; Mazur, M., Polim. Med. 2013. [14].

The research of El Habnouni et al. [18] was concerned with finding a method for the antibacterial surface modification of polylactide. This examination is the combination of modification of poly(ε-caprolactone) (PCL) with a mild and versatile chemical modification for PLA. The next step is to produce clickable PLA surfaces bearing propargyl groups. In this way, researchers have described the production of antibacterial PLA surfaces functionalized with various quaternized poly(2-(dimethylamino)ethyl methacrylate) (QPDMAEMA). Plates were prepared in accordance with previously used methods and immersed in a stirred solution 50 °C in an argon inert atmosphere for 30 min. Next, propargyl bromide was added at 30 °C. The mixture was stirred for 1 h at 30 °C and then raised to room temperature. The PLA plate was quenched and washed with water, diethyl ether, and methanol. Residual solvents were removed under vacuum [19]. After processes of synthesis of well-defined quaternized and clickable PDMAEMA (a-N3-QPDMAEMA) they performed immobilization of α-N3-QPDMAEMA on PLA surfaces α-azido QPDMAEMA. In order to characterize polymers and surfaces, ATR-FTIR spectroscopy, SEC, XPS, and ATM studies were conducted. The next step was to observe bacterial the strain's activity and formation. The plates were placed in contact with bacterial cultures for 1 h before being incubated for 24 h. In the results, they observed that the modified PLA plates not only decreased the number of adherent bacteria but also killed the few adherent ones on the surface like C7 QPDMAEMAs (8C7) (Figure 2).

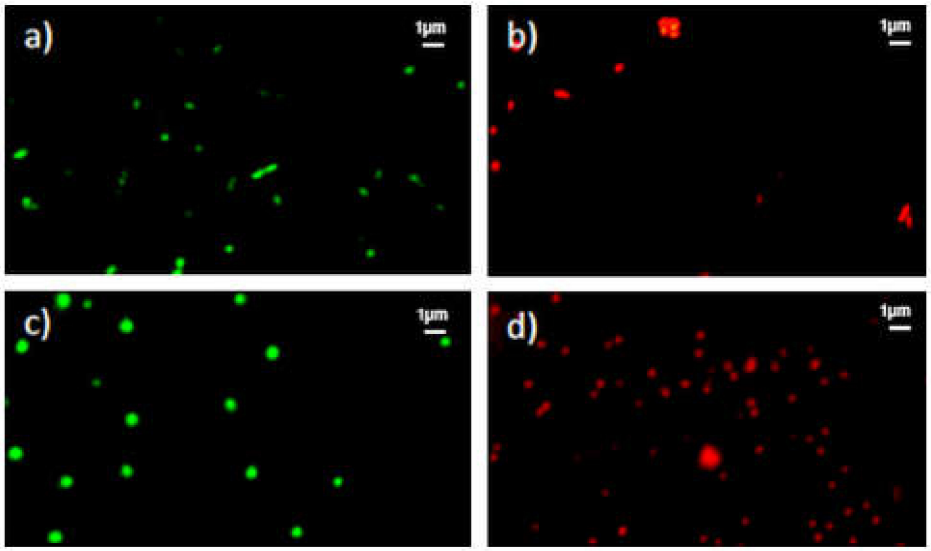


Figure 2. Live/dead assay. (**a**) *E. coli* control plate, (**b**) *E. coli* 8C7 modified plate, (**c**) *S. epidermidis* control plate, and (**d**) *S. epidermidis* 8C7 modified plate; Reproduced with permission from El Habnouni, S.; Lavigne, J.P.; Darcos, V.; Porsio, B.; Garric, X.; Coudane, J.; Nottelet, B., Acta Biomater. 2013 [15].

To sum up, the modified surfaces decreased the adhesion of Gram-negative and Gram-positive bacteria. Biofilm formation was markedly reduced, with 60% fewer bacteria after the application of QPDMAEMA. Antibacterial PLA surfaces were found to be cytocompatible which is promising for the implantation of biodegradable biomaterials in the future. The antibacterial properties of silver and its compounds have been known for a long time. Already in the 19th century, silver salt and its colloids were commonly used in the treatment and prevention of infections caused by companion microorganisms, burns, or chronic wounds, but also in the case of sepsis [20]. Microscopic observations showed that nanoparticles attacking the shields change cell morphology. After the cell is coated, bacteria cause depressions on its surface and modify the potential electrostatic shields [21]. The increasing bacterial resistance to available antibiotics forces them to deal with creating a new opportunity to decrease biofilm creation. New methods of replacing typical antibiotics include metals nanoparticles [22]. Silver nanoparticles have bactericidal properties. Furthermore, they can be used to provide medicines like antibiotics to the

place of bacterial infection. In this way, they create an opportunity for dose decreasing and frequency of dosing. It allows medicine accumulation in the main infection place until reaching the cells' interior [3]. Silver nanoparticles have an effective bactericidal activity against bacteria and viruses, they are used in combating microbe therapies. Innovative application of silver nanoparticles not only reduces hospital infections but also improves the quality of life and well-being of patients that result from the reduction percentage of postoperative infections [22].

The research of Ziąbka et al. [23] was concerned with the biological and morphological assessment of poly(lactide-co-glycolide)/silver nanoparticle (nAg) composites prepared by the slip-casting method. The mechanism responsible for the bactericidal activity of nAg has not been fully explained yet. Probably it is connected with the absorption of free silver ions and then with the interruption of ATP and DNA replication or direct cell membrane damage. The materials were subjected to the examination of antibacterial activity against Gram-positive Staphylococcus aureus and Gram-negative *Escherichia coli* strains. SEM and EDS assessments were conducted. Furthermore, angle measurement, roughness, and the surface character of the investigated materials were determined. To sum up, the test of antibacterial activity proved that nanosilver-modified composites have bactericidal activity against the tested bacteria strains. The more modified phases there were and the lower the degree of composite homogenization and contact angle, the greater the increase of roughness. In this way, composites showed a higher degree of wettability. The antibacterial efficacy of the tested materials depends on the number of modifier phases of the silver nanoparticles (nAg). Biomaterials impregnated with silver have a wide range of applications in medicine, because of their antibacterial properties, it is also an indication for their use in vascular surgery [24,25]. Recently there are attempts to use silver salts impregnated polyester prostheses in type I vascular reconstruction with bovine collagen [26]. Silver acetate inhibits bacterial colonization of the vascular prosthesis and neighboring tissues in the postoperative period. In vivo and in vitro animal studies have shown antibacterial activity the effectiveness of the prosthesis impregnated with silver salt and the lack of local and systemic toxicity with its use [26–28]. In these tests, the presence of silver salts was found in vascular prosthesis (25%) 20 days after its implantation [27,28]. However, there is no extensive clinical research on the use of a silver salt impregnated prosthesis in infections of vascular prostheses [26–28]. In recent years, attempts have been made to use vascular prostheses impregnated with silver in the treatment of infections of vascular prostheses. The author of the [26] began on the use of a silver acetate impregnated prosthesis. However, nonclinical studies involving more patients with massive vascular prosthetic infections treated with their replacement with dacron prostheses impregnated with silver salts [29]. The clinical trials conducted so far concern few patients in several centers, who qualified for implantation of a prosthesis impregnated with silver salts [26]. Evaluation of the results also included patients with limited infection of the vascular prosthesis and mycotic aneurysm. According to some authors, the effect of silver salt in dentures is debatable, both those impregnated with silver and soaked with antibiotics [30]. There are positive results of in vitro studies on the effectiveness of this material, but they are not always confirmed in experimental studies. Based on experimental studies [30], it is believed that dentures impregnated with silver salts do not have or have negligible antibacterial effects. In experimental studies, antibacterial resistance develops faster and easier against antibiotics than antiseptics like silver salts.

Similar results were presented by Shah Sarita et al. [31], who stated the success of tissue engineering strategies will depend on their ability to adequately address infectious complications. Regeneration and repair of tissue cannot occur in the presence of infection, so an effective method of eradicating and preventing infections must be developed. The most robust strategies will address immediate infection and prevent later failure of the implant due to delayed infection by preventing biofilm formation. One method to achieve this is to develop local delivery vehicles for antibiotics and anti-biofilm agents that pro-

vide controlled sustained release but do not themselves host biofilm formation and can accommodate the emergence of new antibiotics.

In turn, Yufang Bi et al. [11] believed that with the deepening understanding of biofilms, more potential therapeutic strategies will be found for the prevention and control of bacterial biofilms. The integration of advanced biology and nanotechnology is also a new direction for the future development of biofilm-related infection treatment. Future exploration on novel antimicrobial agents, new drug delivery strategies for biofilms, and new biofilm disruption principles altogether may shed some light on this formidable challenge. Nevertheless, biosafety and biocompatibility are also major concerns and considerations when designing new antibiofilm systems for biomedical application. Glass and silver nanoparticles with antibacterial properties have a great potential for biomedical applications in hospitals, e.g., in hematology, oncology, isolation rooms, burns units, sterilization rooms, showers, and bathrooms or as extremely prospective material as display cover glass for wall panels or doors [32].

3.2. Surface Modification

The authors of the publication "Biofilm as the basic mechanism of surgical site infection-prevention methods in local treatment" proposed estimation of the biofilm production ratio among 25 examined strains, a silicon-coated latex catheter was used along with a non-absorbable polyamide surgical thread. The purpose of this publication was an assessment of the impact of octenisept (0.5% saponin working solution, neutralizing agent composed of 3% Tween 80, 3% saponin, 0.1% histidine, 0.1% lecithin) on the survival rate of bacteria which were produced biofilm layers. A set of 25 strains were gathered from wound infections. There were 14 coagulase-negative staphylococci like *S. epidermidis*, *S. haemolyticus*, and *S. warneri*, 5 strains of *Klebsiella pneumoniae*, 3 *E. coli*, and 3 *Pseudomonas aeruginosa*. After the process of the production of biofilm from strains was the assessment of the reduction ratio of TTC to red formazan according to a color scale. In the results, a significant reduction of biofilm in the impact of the octenisept solution was observed.

The results were read as the number of colony-forming units per 1 mL of suspension (CFU/mL). The number of living cells was decreased from 107 CFU/mL and 109 CFU/mL to 102 CFU/mL within one minute from solution application. To sum up, the application of the octenisept solution compiled all requirements and prevented the formation of biofilm and the creation of complications in the operation area [1].

The other report of authors Sowińska et al., "The effect of TiN on formed biofilm cell behavior in vitro" was concerned with the assessment of the biocompatibility of TiN using human fibroblasts in terms of biofilm morphology, cell arrangement, and physiological behavior. The samples of Ti6Al4V were subjected to nitriding treatment under glow discharge conditions at a temperature of 850 °C in an atmosphere of nitrogen and under 4 hPa pressure. Samples were cleaned with ethanol and distilled water and sterilized for one cycle in a plasma-Sterrad 100 apparatus in an atmosphere of H_2O_2 at 54 °C for 1 h. The created layers of TiN + Ti_2N + αTi(N) type had 50 mm thickness of TiN. Microstructures were etched in a solution with the chemical composition 96 cm^3 H_2O + 2 cm^3 HNO_3 + 2 cm^3 HF.

The fibroblasts from human skin were cultured for 48 h on biomaterials samples. In the next step, changes were observed on the biomaterial surface and the process of growing the bacterial biofilm. Investigations by LSC revealed a lower amount of fibronectin on the TiN substrate than on the titanium alloy. After the process of sterilization in plasma, there was a decreased phase of growth of the human fibroblast population. The results of the investigation confirmed the improvement of biocompatibility and the decrease of living cells on the biomaterial's surface. In addition, layers of TiN indicated better osteointegration and integration with human tissues than titanium implants only [33].

The investigation "Examination of mechanical, corrosion and antimicrobial of ZrC based coatings" was concerned with the assessment of ZrC layers on medical steel for use in dental implantology. Layers were applied by reactive impulse magnetron sputtering

method on polished samples from 316 L steel in the form of discs. RMS sputtering from the Zr target was led in an Ar + C_2H_2 atmosphere. The layers with different carbon concentrations were created by different partial pressures of a reactive gas in the technological chamber. The examination was carried out on different species of bacteria strains like Streptococcus salivarius, Candida albicans, and Staphylococcus aureus. It was observed that ZrC coatings were characterized by a low colonization potential when the amount of carbon is higher than 49% [34]. In the article "Antibacterial Efficacy of Iron-Oxide Nanoparticles against Biofilms on Different Biomaterial Surfaces" the authors studied the effect of iron-oxide nanoparticles on biofilm formation on different biomaterial surfaces and pluronic coated surfaces. The examination was investigated on biomaterials like PMMA-poly(methyl methacrylate), PS- polystyrene, TCPS- tissue culture polystyrene well plates, and PEO-polyethylene oxide. All samples except hydrophilic PEO coating and TCPS were rinsed thoroughly with ethanol and washed with sterile water before use. Surfaces were made hydrophobic by the application of dimethyldichlorosilane coating. The bacteria were applied on different surfaces at 37 °C for 30 min. Then, iron-oxide nanoparticles were introduced in different concentrations and biofilm was increased for 24 h (Figure 3). In the examination, they used bacteria like *E. coli*, *P. aeruginosa*, and *S. aureus*. Along with the increase in the concentration of iron nanoparticles, the growth of bacteria decreased, regardless of their type. To sum up, a significant reduction in biofilm growth was observed due to the influence of iron-oxide nanoparticles on biofilms formed on polymer brush-coated biomaterial surfaces [35].

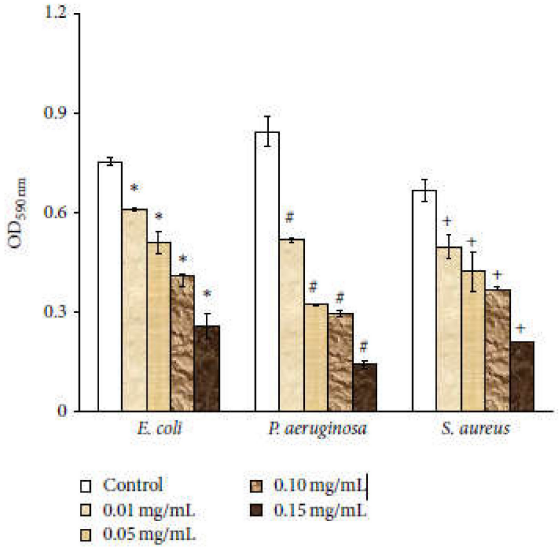


Figure 3. Optical density measurements of 24 h biofilm growth on pluronic coated TCPS surface in the presence of different concentrations (0.01 mg/mL, 0.05 mg/mL, 0.10 mg/mL, and 0.15 mg/mL) of iron-oxide nanoparticles [35]. * is for *E.coli*, # is for *P. aeruginosa*, + is for *S. aureus*.

The examination of "Penetration of a selected antibiotic and antiseptic into a biofilm formed on orthopedic steel implants" was concerned with the impact of octenidine hydrochloride and gentamicin on bacterial survival and reduction of biofilms formed on orthopedic metal implants. The research group studied metal orthopedic and a bone sequester. The presence and intensity of biofilm formation on the medical biomaterials were determined using the method of Richards et al., by the visual evaluation of 2,3,5-triphenyl tetrazolium chloride (TTC) reduction by viable bacteria. The presence and structure of the biofilm on the components of the Ilizarov device, screws, and bone sequester were also studied by electron microscopy using different types of bacterial strains like *S. aureus*, *S. epidermidis*, *E. coli*, and *Enterobacter*. Liquid strains were applied in each well and incubated at 37 °C for 24 h. In the results, most strains that were isolated from orthopedic implants obtained from patients were capable of forming a biofilm following 24 h incuba-

tion and formed moderately or highly developed biofilm structures in either both or one sample. Planktonic culture of bacteria survivability and biofilm development were significantly reduced with the solution of octenidine hydrochloride (Figure 4). The conducted research allows for the conclusion that using octenidine hydrochloride is more effective than gentamicin in the treatment of infections associated with the formation of a biofilm on orthopedic implants [36].

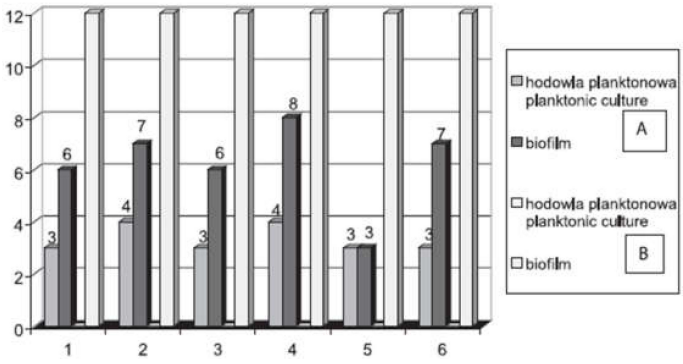


Figure 4. Survival of bacteria in the planktonic culture and the biofilm by antibiotic and antiseptic used (MIC). A—octenidine hydrochloride, B—gentamicin [36].

The publication "Adhesion of staphylococcus epidermidis cells on Ti6Al4V titanium alloy surfaces modified by bioceramic layers" was focused on titanium implant modification's impact on improved biocompatibility and prevention of bacteria adhesion and biofilm formation. The materials were TiN, SiO_2-TiO_2, and Hap (hydroxyapatite) layers on Ti6Al4V titanium alloy, which was manufactured by glow discharge assisted by nitriding in a pure nitrogen atmosphere. The sample was covered by SiO_2-TiO_2 sol–gel layers and the external surface of hydroxyapatite was produced by the electrophoresis method and was deposited and annealed at 750 °C. The chosen strains of S. epidermidis bacteria were examined. Microorganisms were applied on clean plates and were incubated for 72 h at 37 °C. In the next step, the plates were washed 10× with PBS, and the remaining bacterial cells were incubated for 15 min in darkness with 50 µL 0.9% NaCl containing 3 µL/mL fluorescent dye. In this way, they observed bacteria cells in a fluorescence microscope and the process of biofilm formation. To sum up, the investigation of modified titanium alloy samples showed that the presence of a SiO_2-TiO_2 layer on the sample surface caused a decrease in the ratio of S. epidermidis adhesion (Figure 5). The TiN layer as a factor modifying titanium alloy surfaces increases its abrasion resistance but does not prevent bacterial adhesion. However, if one adds a SiO_2-TiO_2 layer on the TiN one it was causes a decrease in bacteria–cell adhesion [37,38].

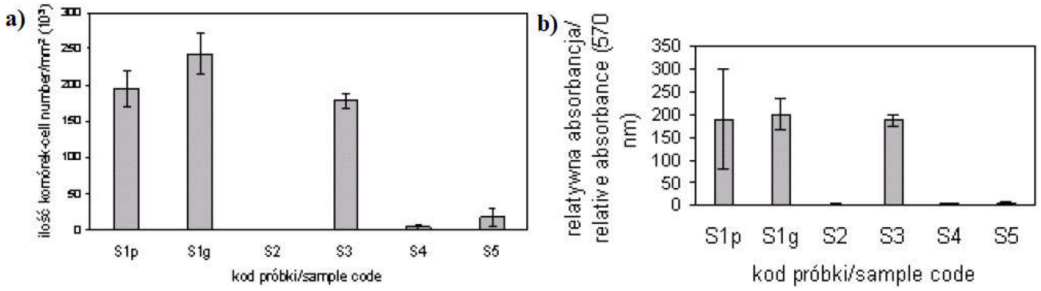


Figure 5. (**a**) Amount of *S. epidermidis* cells on modified titanium alloy surfaces. (**b**) *S. epidermidis* biofilm formation on Ti alloy surfaces. Biofilm formation was presented as a function of extracted crystal violet absorbance (570 nm) per mm^2; value for non-modified titanium alloy S1p was taken as 100%. Reproduced with permission from Belcarz, A.; Bieniaś, J.; Surowska, B.; Ginalska, G., Eng. Biomater. 2009 [11].

The examination of "Evaluation of *Staphylococcus aureus* and *Escherichia coli* biofilm formation on the surface of polypropylene mesh" [39] was concerned with creating biofilm with *Staphylococcus aureus* and *Escherichia coli* on the surface of polypropylene mesh. The examination is connected with the difference between the process of settling on the surface of meshes. The study was carried out by reduction of 2,3,5-triphenyltetrazolium chloride (TTC) and by scanning electron microscopy. The research consisted of 108 strains of bacteria isolated in samples from wound swabs. The research was carried out using the reduction method on colorless 2,3,5-triphenyltetrazolium chloride (TTC) (POCH) to red formazan carried out by metabolically active bacteria [40]. To sum up, in the group of *S. aureus* strains, 88.7% of isolates formed biofilm very strongly, 1.6% strongly, and 9.7% poorly. Among *E. coli* strains, 54.3% of isolates were characterized by very strong biofilm formation, while 45.7% with strong biofilm formation. Strains of *S. aureus* form a biofilm on the surface of monofilament polypropylene mesh more strongly than *E. coli*. One of the factors that has played an important role in the formation of biofilm on the surface of the meshes of hernias includes the structure and hydrophobicity of the implant [41,42].

In a research paper, monofilament mesh made of polypropylene, considered a material, was used as the hydrophobic [43], favoring the adhesion of bacteria with hydrophobic properties [44]. It has been shown that *S. aureus* bacteria are characterized by greater hydrophobicity and stronger adhesion to polypropylene than *E. coli* [43,45]. Perhaps the listed properties are responsible for the stronger biofilm formation by *S. aureus* compared to *E. coli*, as observed by Engelsman et al., and others [39] and in our own research. However, according to Cerca et al. [46], the hydrophobicity of the bacterial cell has little effect on the adhesion, and the initial adhesion does not affect the amount of biofilm formed. They correlate with the above observations the results of the study by Gungor et al. [47] who found no statistically significant difference in adhesion of *S. aureus* and *E. coli* to the surface of the monofilament polypropylene mesh. Different conclusions obtained in the research of the above-mentioned research groups indicate that experience requires follow-up and compilation of the results for a larger and comparable number of strains of *S. aureus* and *E. coli*. In our own research with the use of SEM, it was found that the bacteria colonizing monofilament polypropylene mesh accumulates in the places where the fibers cross. Bellón et al., made similar observations [48]. It is probably caused by the presence of niches between intersecting mesh fibers, constituting favorable conditions for bacterial growth and a large surface area and the resulting increased adhesion bacterial [49].

In the review "Vascular System Infections: Characteristics, Risk Factors, Prevention Methods and Economic Impact" the authors have described problems of modern medicine connected with infections. In the face of increasing bacterial resistance, many are searching for antimicrobials other than antibiotics. As above, the use of biomaterials may be associated with an increased risk of infection. For this reason, it is so important to look for materials and coatings and coatings allowing us to check the microenvironment of the area implantation. For this purpose, the targeted modifications are in biomaterial zones to change their options. Coatings and ion implantation and clusters are used, or gas in the near-surface layer of the material. Metals are used as antibacterial and their oxides, such as copper, silver, gold, platinum, palladium, niobium, silver and zinc oxides, tin dioxide, and titanium [15,50]. Bonding research is underway on biocompatible materials with high activity metals to obtain new products with protective coatings. A thin Ti-Cu layer was developed and tested for the growth of *S. aureus* bacteria and cytotoxicity, using the murine fibroblasts lineage L929. The results confirmed the bactericidal properties of shells, however, testing with fibroblast cell mice, unfortunately, showed its cytotoxic properties caused by migration of copper ions. Research is underway over such a modification of the thin-film coating Ti- Cu to keep its biocidal properties while not being cytotoxic. A different coating of the thin film is made of titanium dioxide doped with Nb and Cu ions, increasing the bactericidal activity of the material [17]. The coating applied in cardiac implants (e.g., in valves heart) is a layer of diamond-like carbon (DLC) that is modified with various elements. Bactericidal properties can be achieved through the addition of silver or copper

ions [15]. In the case of artificial vascular prostheses, increasing immunity from the infection is achieved through the use of polytetrafluoroethylene (PTFE), soaking with antibiotics (e.g., rifampicin, mupirocin, or triclosan), coating in silver (in the form of salt ions and nanoparticles), and collagen sealing [51,52]. Nanoparticle silver is used in creating material composites. For example, a composite of polylactide-co-glycolide with silver ions showed biocidal activity against strains of Gram-positive bacteria *S. aureus* and Gram-negative *Escherichia coli*. They also found the effectiveness of the antibacterial action depends on the amount of silver particles [23].

The examination "The possibilities of using nanotechnology in dentistry" [53] was concerned with the opportunity of preventing biofilm with nanotechnology. Nanoparticles have become the future of dentistry. These particles can be used in new methods and may reach unavailable structures. Dental prevention is closely linked with using nanotechnology in tooth decay or periodontal disease. Nanoparticles like zinc oxide [54], silver, or polyethyleneimine have been added to composite material to stop increasing of bacteria by blocking the bacterial cell wall function, inhibiting active transport and metabolism of sugars, production of reactive oxygen species, displacement of magnesium ions necessary for the enzyme bacterial biofilm activity, disturbances in the transport of electrons through the bacterial wall, and preventing DNA replication. It was used and was effective in reducing biofilm in in vitro models [55,56]. Covering the surface of the teeth with antibacterial nano-coating was found to be effective in inhibiting the adhesion and elimination of bacteria. It was introduced into dental prophylaxis recently a cream-like preparation containing casein which provides bioactive calcium and phosphates. Nanomaterials compared to conventional materials show promising results in controlling oral cavity biofilm, facilitating the elimination of bacterial plaque, and replenishment of the nanoscale glaze. That is why nanoparticles have an increasingly important role in cancer diagnostics of the oral cavity, diagnostics of periodontal diseases, glaze remineralization, and implant–bone connections. Nanoparticles have also strengthened composite materials, giving them a longer lifetime, and have also taken part in the fight against hypersensitivity dentin. The application of nanotechnology in dentistry has opened up new opportunities for research development, hoping to solve many dental problems [53]. Prosthetic hip joint infection is one of the most serious complications of hip arthroplasty, which is associated with bacterial biofilm growing on the implant's surface. Despite many significant advantages, arthroplasty procedures carry a high risk of complications. Recently, as the main cause of the instability of the prosthesis, an aseptic base consisting of exfoliation was considered using particles of materials from which prosthesis the is made, which leads to osteolysis within the implant. Sonication is in a water bath is used on the denture's parts removed during the revision procedure, which are then placed in sterile containers. The process is enriched with multiple vortexing steps increasing the amount of strengthening air bubbles the phenomenon of cavitation which allows for the detachment of biofilm fragments from the surface. Sonication fluid can be used to set up bacterial and molecular analyses [57–61]. A certain limitation is the sensitivity of some living bacteria to ultrasound. This is due to the stress to which others are subjected in vivo during the removal and transport of the prosthesis to the laboratory, compared to typical laboratory strains without ultrasound sensitivity. Perhaps it is also due to the strong adaptation of "biofilm" bacteria to the conditions in this specific "ecosystem", so the use of nutrient substrates and diagnostic procedures aimed at their isolation may not provide sufficient conditions for growth in vitro [6].

The aim of "Recent trends in surface modification of the titanium biomaterials used for endoosseus dental implants" was to characterize the modern ways of modifying surfaces used in dental implants. They mention various methods of surface modification like micro- or nanostructure modification or modifying chemical properties. The problem of creating bacterial biofilm is a key issue in the case of dental implants. Patients who have been diagnosed with infection are treated with general antibiotic therapy. The application of antibiotics can eliminate depressing acute symptoms of inflammation but it will not be effective in eliminating the reason for biofilm infection. It is connected with the complex

structure of plankton bacteria. The widespread and often unjustified use of antibiotics favors the formation of an increasing number of resistant strains. Moreover, it may cause side effects such as nausea, gastrointestinal discomfort, or allergic reactions [62]. Puckett and others [63] attached different bacteria to nanostructural surfaces. The results show that all titanium plates with nanostructure roughness were colonized to a much lesser extent than plates with machined surfaces. They found that by applying an appropriate surface modification, a titanium surface with inhibitory properties towards the adhesion of bacterial cells can be obtained.

Whitehead [64] et al., Campoccia et al. [65], and Diaz et al. [66] reached similar conclusions in their studies. Harris et al. [67] and Maddikeri et al. [68] showed that titanium surfaces underwent biofunctionalization using RGD peptide sequences in combination with a resorbable polymer promoted faster adhesion of osteoblasts while inhibiting the attachment of bacterial strains from the species *S. aureus*, *S. epidermidis*, *P. aeruginosa*, and *S. mutans*. The suitability was assessed in other studies combining resorbable polymers with various antibiotics in the modification of titanium plates for stable osteosynthesis platelet function (SOP) [69,70]. To avoid this situation, the concentration of a given antibiotic should be higher than the minimum inhibitory concentration while the implant is in the body. Relationships like these are widely used in dentistry, and there is an attempt to use their bactericidal properties to inhibit the development of bacterial biofilm in implantology. Harris et al., showed that polymer coating-containing CHX or QAC have bactericidal properties against Gram-positive and Gram-negative bacteria. Instead, they observed a cytotoxic-9 effect in relation to fibroblasts. Another problem in the use of polymers is if there is sufficient production of a strong connection between the titanium implant and the polymer coating [71]. Another method to modify surface from bacteria is the use of silver and its derivatives, which has been carefully researched. Silver is known for its own bactericidal properties. Unfortunately, classic forms of silver compounds such as silver nitrate or silver salts sulfadiazine show several side effects. The new way of using silver as nanotechnology allows the production of metal particles with a size of on the order of a few to 100 nm. A lot of studies have shown that silver nanoparticles in low concentrations show stronger bactericidal activity than the classic forms of silver. The high reactivity of nanoparticles is due to the small size and a large surface area of interaction with the bacterial cell. In addition, it is believed that bacteria are unable to develop drug resistance against metal nanoparticles like this is the case with antibiotics [62,72,73].

In "Adhesion of *Escherichia coli* rods to urological catheters" [74] the authors examined the adhesion of rods to urological catheters made of different synthetic materials. In the study of catheters, urinary tubes made of various synthetic materials were used: latex, siliconized latex, and polyvinyl chloride (PVC). The adhesion of *E. coli* rods to urological catheters was performed as described by Richards et al. [40] in their own modification. In results among the 74 tested strains, 4 strains were characterized by strong adhesion to all of the types used to test urological catheters. In [75], the authors made an attempt to evaluate the adhesion of *E. coli* rods made from silicone, modified polyurethane, and a material protected by a patent, consisting of polyethylene and polypropylene with an outer heparinized layer. The authors showed different adhesion abilities of *E. coli*, depending on the type of biomaterial used. The lowest susceptibility to adhesion of *E. coli* strains were catheters made of modified polyurethane. The same authors, based on their own results and reports by other authors, stated that the above catheters should be used when the lowest risk of infection complications is intended to be achieved. A different research study was led by Wolska et al. [76]. They assessed the ability of adhesion and creating biofilm strains on a catheter made from polyurethane and PCV, using the methods of Richards [40] and modification created by Różalska [77]. The highest percentage of strongly adhering strains was found in the group of strains showing adhesion to PCV catheters. Similar observations were made in this study. To sum up, there was a relationship between the frequency and intensity of *E. coli* adhesion and a type of polymer. In clinical practice, the use of siliconized latex catheters should be considered to limit the colonization of

biomaterials by *E. coli* and prevent infections with their participation. A relationship was found regarding the differences in the adhesion of bacteria to different types of polymers.

Another research study presented by Hossein Yazdani Ahmadabadi et al. [78] indicated that the use of metallic nanoparticles with strong antibacterial activity (such as silver and copper) can overcome the microbial resistance due to their very low MIC value, multiple modes of bacterial killing action, and rapid diffusion of ions released from nanoparticles through the cell wall. However, the main issue accompanied by such composite coatings is their toxicity due to the uncontrolled release of metal ions, which can result in toxicity. Another approach from the same authors is the use of antimicrobial peptides. Coatings containing antimicrobial peptides have shown promising antibacterial activity along with good biocompatibility. However, the activity of chemically bound antimicrobial peptides was found to be less than that of the physically incorporated ones.

4. Conclusions

It has been reported that the so-called infections associated with the presence of biofilm develop efficiently in humans' working immune systems, and are not always eliminated. Antibiotic therapy does not destroy the entire structure of the film, only the bacteria are killed that are developing outside this structure. It does not cause the complete eradication of microorganisms. So there is no de facto possibility of inhibiting the infection. In connection with the above, alternative elimination methods are sought for such infections. The main goal is the inhibition of subsequent stages of biofilm synthesis. Researchers push out treatment with medicines and antibiotics. Traditional methods of preventing biofilm are based on compounds that kill or inhibit the growth of the microbes. One of the major problems is the frequent development of resistance to antibiotics [79]. The mechanism of killing or terminating the target bacteria is a process that is connected with the development of resistance in bacteria. In this way, it led to the expression of a series of bacterial virulence factors and created the development of resistant strains [80]. Due to these unique properties of the strains, it is extremely difficult to find a single antimicrobial substance that is able to overcome bacterial resistance strategies [81]. It is strongly connected with the phenotypic resistance of bacteria [82]. The development of different compounds due to the risk of the development of bacterial resistance is promising, leading, for example, to QSI (quorum sensing inhibitors) [83]. These compounds have synergized with the weak effects of antibiotics and PMNs on biofilm growing bacteria in vitro and in vivo in animal experiments on terminating biofilm [84,85]. The following methods are distinguished, surface modification or using antibiotics and silver nanoparticles. Frequent failures in the treatment of human and animal infections with antibiotics give little reason for optimism as to the perspectives of this kind of therapy. To sum up, clinical practice has shown that systemic antibiotics are unable to provide effective treatment for these infections. These positively charged metallic ions attach to the negatively charged bacterial cell wall and cause cell lysis and death [86]. According to the shown studies, there is still ongoing research to find out the best method of modification. In this way, we show experiments connected to the optimal surface, temperature, and cycles. The relatively slow development of new antibiotics offers the need for a new approach and development in anti-infection therapy and alternatives to the therapy with known antibiotics. On the other hand, the problem of biofilm is still unsolved and it is still growing.

Further research is needed to develop novel approaches that can be easily applied to different implants and devices and can be easily manufactured for faster clinical translation. Another issue is the need of generating coatings with long-term activity that work against multiple bacterial strains and drug-resistant strains.

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