Review
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Efficiency of using antibacterial coatings on titanium implants in the treatment of gunshot fractures

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Abstract

Introduction High risk of infectious complications in gunshot wounds remains a pressing issue in military medicine. Analysis of the structure of sanitary losses shows that limb injuries account for 55 % to 81.4 %, with about 35 % of them accompanied by bone fractures. Performing operations for the final stabilization of these fractures under the conditions of primary microbial contamination is associated with a high risk of infectious complications. However, the use of antibacterial coatings on internal implants significantly reduces the risk of such complications.

The **purpose** of the work, based on the analysis of Russian and foreign literary sources, is to determine the effectiveness of using antibacterial coatings on titanium implants for gunshot fractures.

Materials and methods The search for scientific publications was carried out in the search engines eLibrary, PubMed and Connected Papers using the keywords: antibacterial coatings, gunshot fractures, implant-associated infection, internal osteosynthesis, infectious complications, antibacterial coating, gunshot fractures, infectious complications, peri-implant infection. The sources were selected based on the hypothesis of the possibility of using antibacterial coatings in clinical practice. The search depth was from 2009 to 2025.

Results and discussion The existing systems for delivering antibacterial drugs to the surgical intervention area demonstrate high clinical efficacy in the prevention of peri-implant infection. To date, the most studied agents for creating coatings are metal ions, polymers, as well as composites containing antibacterial / antiseptic drugs. The most effective are multifunctional and intelligent coatings that have a combined effect on microbial biofilms due to their pronounced anti-adhesive and biocidal properties. There is a shortage of research on the use of multifunctional coatings in traumatological and orthopedic practice. There are no publications in the world literature devoted to the use of antibacterial coatings in the treatment of gunshot fractures and their consequences.

Conclusion The use of polymer and multifunctional antibacterial coatings, hydrogels, as well as oxides of silver, iodine and zinc demonstrate high efficiency in the prevention of infectious complications after internal osteosynthesis, and, in our opinion, can be considered for use in clinical practice in the treatment of gunshot fractures of limb bones.

Keywords: antibacterial coating, internal osteosynthesis, gunshot fractures, infectious complications, peri-implant infection

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INTRODUCTION

To date, two most significant problems can be identified in the treatment of combat surgical pathology that have not lost their relevance over a long period of time: the combination of gunshot wounds with extensive tissue defects and a high rate of infectious and inflammatory complications caused by multiresistant microflora [1, 2]. The development of infectious complications related to bone fractures caused by firearms and ammunition is primarily associated with the severity of the resulting tissue damage, primary microbial contamination of the wound canal, as well as the development of secondary necrobiotic changes in the tissues surrounding the wound canal caused by the damaging effect of firearms.

Wounds caused by firearms and explosives have a number of characteristic features that have a direct impact on the rate of complications and treatment tactics. Among them are a complex configuration of the wound canal, uneven extent of dead and necrotic tissue around the wound canal, primary microbial contamination, and frequent combination of these wounds with bone fractures and injuries to the vascular-nerve structures [3]. The peculiarities of wound ballistics under the influence of wounding projectiles lead to extensive complex (soft tissue and bone) defects, which, according to their pathomorphological properties, are characterized by significant damage to the bone marrow cavity and their own nutrient arteries, thereby causing hypoxia of the surrounding tissues that slows down the reparative processes and is often the trigger for the development of gunshot osteomyelitis [4]. Thus, the analysis of the treatment outcomes of 148 wounded with gunshot fractures of the limb bones conducted by Khominets et al. revealed the development of infectious complications among patients in the main and control groups in 5.8 % and 9.7 %, respectively [5]. Lee et al. established the development of infectious and inflammatory complications after osteosynthesis in 14 % of cases in a multicenter retrospective study analyzing complications of gunshot fractures of the tibia [6].

Additional complications in the treatment of gunshot fractures are caused by the presence of microflora in the wound canal that is diverse in composition and resistant to antibiotics. It largely determines the ineffectiveness of classical treatment methods [7].

Based on the above, final reconstructive and restorative operations (osteosynthesis, joint arthroplasty, etc.) in gunshot fractures are possible only with stabilization of the patient's general condition and compliance with strict recommendations for switching to internal fixation [8]. However, even if these requirements are met, there remains a high risk of infectious complications during osteosynthesis.

In this regard, the development and optimization of existing systems for the delivery of antibacterial, antiseptic and reparative agents to damaged tissues for the prevention and treatment of infectious and inflammatory complications is one of the promising advanced technologies in the provision of comprehensive specialized medical care to patients with gunshot wounds accompanied by skeletal bone fractures [9, 10].

The **purpose** of the work, based on the analysis of Russian and foreign literary sources, is to deter mine the effectiveness of using antibacterial coatings on titanium implants for gunshot fractures.

MATERIALS AND METHODS

The search for Russian-language sources was conducted on the eLibrary platform (electronic library) using the following keywords and phrases in Russian and English: antibacterial coatings, gunshot fractures, implant-associated infection, internal osteosynthesis, infectious complications. The search depth was from 2009 to 2025 inclusive. The search for foreign sources was carried out in the PubMed search system, as well as using the ConnectedPapers analytical tool based on artificial intelligence using the Seminal works functions to display a list of key thematic works and Derivative works functions

to display new, relevant works, systematic reviews and meta-analyses that are in the area of interest of the authors. The search on the ConnectedPapers resource started with the article: Akshaya S, Rowlo PK, Dukle A, Nathanael AJ. Antibacterial coatings for titanium implants: recent trends and future perspectives. *Antibiotics (Basel)*. 2022;11(12):1719. doi: 10.3390/antibiotics11121719.

Inclusion criteria:

— full-text scientific studies that report on the results of the analysis of the efficiency of various antibacterial coatings used in traumatology and orthopaedics, including open and gunshot fractures;

— full-text systematic literature reviews and meta-analyses that depict the topic of antibacterial coatings in surgery published 5 to 10 years ago.

Exclusion criteria: abstracts of scientific conferences, authors' theses of their candidate and doctor-of medical sciences dissertations, and articles that do not fully correspond to inclusion criteria.

Eighty studies were selected for analysis (70 foreign and 15 domestic).

RESULTS

Current state of the problems of implant associated infection

The development of purulent and inflammatory processes in the area of surgical intervention is a serious complication of osteosynthesis. Their treatment is significantly complicated by the presence of a metal implant colonized by microbial biofilms in the inflammation focus. The rate of these complications in the postoperative period after the operation of internal osteosynthesis ranges from 2 to 22.4 % in civil fractures [11]. Implant-associated infection is the most challenging issue in the treatment of gunshot fractures as infectious complications develop more frequently than in open fractures sustained in the peacetime [12].

According to the results of various studies, the rate of periprosthetic infection can grow up to 15 % even in planned surgical interventions of large joint replacement [13]. Traditionally, the prevention and treatment of implant-associated infection implies radical surgical treatment, local and systemic antibiotic therapy, and implantation of cement "spacers" that release antibacterial drug molecules [14]. However, the widespread use of broad-spectrum antibiotics can have pronounced toxic effects on the body and lead to an increase in the number of antibiotic-resistant bacteria, which requires a search for alternative methods of prevention and treatment of peri-implant infection [15].

The presence of orthopaedic implants in the inflammation focus inevitably leads to the adhesion of colony-forming bacteria which form a microbial biofilm on their surface, that is capable of resisting the effects of the body's defense system and antibiotics [16]. A biofilm can be defined as a microbial community of bacteria attached to the substrate and embedded in the matrix that they produced during their life activity [17]. Bacteria in the biofilm state demonstrate increased resistance to antimicrobial agents and lower susceptibility to the effects of the body's immune defense systems [18]. There is information in the international literature that the formation of biofilms on the surface of implants can develop within 12-18 hours after surgery [19]. In this regard, the main goal of treatment for implant-associated infection is precisely the prevention of biofilm formation.

Characteristics of the main agents of implant-associated infection in gunshot injuries

Injuries caused by firearms and explosives are the most complex type of wounds due to massive tissue damage in various locations, exposing sterile areas of the body to contamination by a huge number of bacteria. In combat injuries, the basis for the development of infectious complications is contamination by bacteria from one's own microflora or by those that have entered the wound from

the environment along with exogenous agents (bullets, tissue fragments, dust, dirt, water). Moreover, secondary contamination from nosocomial sources is also possible at the stages of providing medical care [20]. In addition, the species composition of etiologic agents in contaminated gunshot wounds is influenced by the type of wounding projectile, the damaged area of the body, the time interval between the injury and surgical treatment, climatic factors, and the ecological/geographical and sanitary/hygienic conditions of the area.

Among the microbiological agents associated with the formation of microbial biofilm on implants and the subsequent development of implant-associated infection, the most studied are *S. aureus, S. epidermidis, P. aeruginosa*, and also methicillin-resistant *S. aureus* (MRSA) [21].

Kryukov et al. devoted their work to the analysis of antibiotic resistance of the microflora in the wound discharge and compared the results of the study of wound discharge in 2022 and in 2020. They discovered a sharp change in the spectrum of pathogens of wound infection: an increase in the proportion of *Acinetobacter spp., Bacillus spp., Enterococcus spp., P. aeruginosa, Klebsiella pneumoniae*; a decrease in the proportion of a number of gram-negative bacteria, including *Proteus spp*. и *Esherichia coli*; an expressed 5-fold reduction of *Streptococcus spp*. and *S. aureus* [7].

Bacterial adhesion to the surface of a titanium implant is the first stage in the development of implant-associated infection. The most common microbial agents causing the development of this infectious complication are staphylococci *S. aureus* and *S. epidermidis*; they are encountered in 18.4 to 37.4 % of cases [22]. The ability of *S. aureus* to form a 3-D structure that is composed from bacteria and extra-cellular polymers (polysaccharides and/or proteins), called a biofilm, is a central link in the development of infection associated with the presence of implants in the body.

The development of multidrug resistance in microorganisms is one of the most significant problems worldwide and is considered a threat to the national security [23]. Multidrug-resistant strains of *S. aureus* determine the difficulties in preventing and treating infectious complications of bone fractures, which is especially important for providing care in resource-limited settings. In a cohort study, Vijayakumar et al. reported that 75 % of isolates obtained from 100 patients were resistant to gentamicin, 81 % to ciprofloxacin, and 59 % to cefotaxime [24].

Another significant microbial agent that causes the development of infectious complications in the injured is *P. Aeruginosa*, a gram-negative opportunistic pathogen that plays an important role in the development of infectious complications in gunshot fractures due to its ability to reproduce in various environments, form biofilms, and be resistant to antibiotics [25]. Gunshot wounds, especially those sustained outdoors and/or in combat conditions, are often contaminated with soil, water, and other objects that act as reservoirs for *P. aeruginosa* in the environment. In medical facilities *P. aeruginosa* is also able to colonize the body of the injured patients, especially during their prolonged stay in hospital [26].

The above-mentioned bacteria exist on the surface of titanium implants in the form of microbial colonies and are protected by a capsule, which causes the resistance of microorganisms to the action of antibacterial agents. It should be noted that not all cases of microbial contamination of implants during surgical intervention are accompanied by the development of clinically expressed peri-implant infection and frequently develop in the form of microbial carriage, which is confirmed by the data of Knabl et al. [27].

These features of the infectious process in the presence of orthopedic implants in the body necessitate the development of a strategy to prevent colonization on the implant surface, and one of them may be a coating containing antibiotics or intraoperative application of a therapeutic gel to the implant.

Antibacterial coatings of titanium implants

Titanium and its alloys are currently recognized as the "gold standard" due to their resistance to corrosion and good biocompatibility with bone tissue. Over the past fifty years, they have been widely used in traumatology and orthopedics as a material for the manufacture of implants, endoprosthesis components and fixators for osteosynthesis of bone fractures (intramedullary pins, bone plates and screws) [28]. According to Wang et al., titanium or its alloys by themselves are not able to prevent possible implant-associated infection while systemic antibiotic therapy, despite its proven effectiveness, has a number of shortcomings (toxic effects on organs and tissues, difficulty in delivering the drug to the surgical site, development of antibiotic resistance in bacteria) [29]. A promising direction for the prevention of implant-associated infection in the surgical area is coating of titanium implants with antimicrobial agents. To achieve these properties, the surface of the implants is coated with antibacterial substances using various surface modification methods.

The existing coatings against bacterial infections can be divided into two categories: passive (to prevent bacterial attachment) and active (to kill bacteria and inhibit their growth). Passive coatings are designed to prevent infection by resisting pathogen adhesion instead of directly killing them. This strategy is commonly used to modify the surface structure of the implant. Standard materials for passive coatings include polyethylene glycol, hyaluronic acid, and otheers. Active coating uses metal ions, antibiotics, and antimicrobial peptides to functionalize the implant surface and kill bacteria through contact elimination or release of antibacterial agents into the surrounding tissue. In addition, other biomaterials that promote osseointegration, angiogenesis, and immunomodulation can be applied with antibacterial materials [30].

According to Bruellhoff et al., the “ideal” antibacterial coating applied to the surface of implants used in traumatology and orthopedics should be biocompatible and not cause a local irritating effect; it should also exhibit pronounced bactericidal properties in the early postoperative period while maintaining surface bactericidal activity against a wide range of microorganisms throughout the entire period of implantation. Moreover, the coating should prevent bacterial adhesion to the implant surface and suppress the formation of microbial biofilms [31].

Currently, the application of an antibacterial coating mostly creates an additional layer on the surface of the implant without damaging the natural properties of the basic material. This can be done using various methods, such as electrochemical deposition, ionized jet deposition, sol-gel method, microarc oxidation, and others [32, 33]. To prevent infectious complications or formation of biofilms and improve integration into tissues, coatings can contain various antimicrobial agents: antibiotics, inorganic elements, polymers, hybrid organic and organic components, bacterial peptides [34] (Fig. 1).

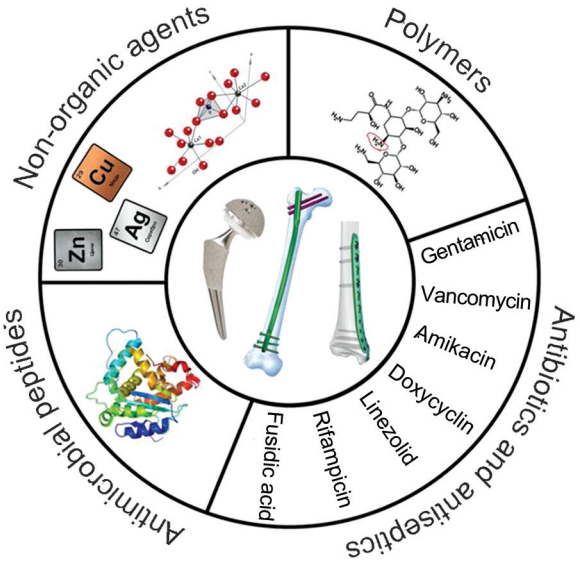

Fig. 1 Types of antibacterial coatings on implants (authors’ diagram)

Coatings containing antibacterial and/or anticeptic preparations

According to the literature, the most commonly used agents for the prevention of infectious complications after internal osteosynthesis surgery are coatings based on antibacterial drugs. For the coating of an implant that releases an antibiotic, the concentration of the drug and the rate of its release are of decisive importance. Clinical trials have proven the effectiveness of coatings

containing antibiotics (gentamicin, vancomycin, amikacin, doxycycline, linezolid, rifampicin and fusidic acid) against a wide range of pathogens of surgical infection [21].

Gentamicin is a popular antibiotic with a broad bactericidal spectrum, low toxicity, and high biocompatibility; it is widely used in clinical practice for many infections. The degree of gentamicin's bactericidal effect depends on the concentration of the drug in the antibacterial coating. According to some reports, gentamicin-based coatings improve osseointegration and prevent the development of osteomyelitis, and are also effective against infections caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*. Numerous studies have been conducted proving the effectiveness of amoxicillin, vancomycin, and tetracycline as implant surface coatings to prevent infection [35].

According to the results of the study by Harris et al., implants having an anti-adhesive coating with the addition of amikacin showed a combined effect on the main pathogens of implant-associated infection and exhibit high biocidal activity *in vitro*, and can be used in the manufacture of coatings for orthopedic implants [36]. However, the use of antibiotics on the surface of the implant raises concerns about antibiotic resistance due to the prevalence of antibiotic-resistant bacterial strains.

Doxycycline is a broad-spectrum antibiotic with documented high bactericidal activity against the main pathogens of implant-associated infection (including MRSA). It is less nephrotoxic and penetrates into body cells more effectively than gentamicin [37]. Linezolid is a synthetic antibiotic with a low potential for the development of intrinsic resistance and no cross-resistance to other systemically administered antibiotics. It has 100 % oral bioavailability, good pharmacokinetics and good penetration into connective tissues. Moxifloxacin used in sol-gel coatings provides anti-infective activity both *in vivo* and *in vitro* in Ti-implants [38]. The use of the antibiotic fosfomycin, according to a study by Gulcu et al., is not effective in killing bacteria and preventing biofilm formation [39]. An important disadvantage of coatings based on antimicrobial drugs is a continuous decrease in the concentration of the antimicrobial drug over time.

In our country, researchers of the Ilizarov National Medical Research Center of Traumatology and Orthopedics discovered in an experimental study that applying a calcium phosphate coating containing antibiotics to the titanium surface can effectively suppress the growth of gram-negative microflora and may be successfully used to prevent the development of implant-associated infection. However, the effectiveness of these coatings directly depends on the antibiotic used and its concentration [40].

Bone cement based on polymethyl methacrylate with the addition of heat-stable antibacterial drugs of local bactericidal action has been actively used in orthopedic clinics for a long time both for the treatment and prevention of peri-implant infection [41]. Moreover, bone cement impregnated with antibiotics has proven its effectiveness in the treatment of open fractures, including gunshot fractures, which has been confirmed by a number of studies [42, 43]. However, the study of long-term results of using this method revealed obvious disadvantages: short-term release of antibacterial drugs, formation of biofilms on the cement coating, unpredictable concentration of the drug in the surrounding tissues, and some others. At the same time, despite all the existing shortcomings, this method remains to this day the “gold standard” for treating patients with bone and joint infection, the effectiveness of which ranges from 60 to 87.5 %, and the rates of infection recurrence range from 6.3 to 40 % [44].

Another popular approach to preventing the development of implant-associated infection is the application of antiseptics to the surface of implants. The use of antiseptics has an immediate effect compared to the delayed effect of antibiotics, since they directly affect the bacterial cell membrane, unlike the inhibition of bacterial DNA-dependent RNA synthesis or inhibition of bacterial RNA polymerase and protein synthesis, which are embedded in the mechanism of action of antibiotics [45].

Antibacterial coatings based on metal and metal oxide nanoparticles

Metal nanoparticles and their oxides are capable of exerting selective bactericidal action on prokaryotic cells by recognizing them through metalloproteins and the metal particle transport system. These nanoparticles are capable of providing long-term antibacterial and bacteriostatic action by generating reactive oxygen species that damage the structure of bacterial cells, disrupting metabolic reactions and inhibiting DNA synthesis, which ultimately causes cell death [46]. Moreover, metal oxides interact with bacterial cells based on the action of electrostatic forces that destroy the bacterial cell wall, enzymes and DNA through the so-called "oxygen explosion". Metal nanoparticles and their oxides usually kill bacterial cells in several ways, including interaction with the lipid bilayer of bacterial cell walls, adhesion to cytosolic proteins of bacterial cells (including DNA and enzymes). Examples of metals used in antibacterial coatings include silver, gold, iron, gallium, zinc oxide, magnesium oxide and titanium oxide, which have effective bactericidal effects against various gram-positive and gram-negative bacteria [47]. However, according to Zhang et al., caution should be taken when using coatings based on metals and their oxides, since high concentrations of metal ions and their oxides can cause local and systemic damaging effects on cells and tissues of the body [48].

Silver

Today, silver is one of the most widely used metals for the production of titanium implant coatings. Silver ions have a broad spectrum of antibacterial activity and have a long-lasting antibacterial effect, which is less dependent on the drug resistance of bacteria and is able to prevent bacterial adhesion to the surface of implants. Moreover, coatings with silver ions are characterized by good biocompatibility, very low geno- and cytotoxicity, and potential for use in various types of biomaterials [49].

Silver nanoparticles also have significant biocidal activity against multidrug-resistant bacteria and fungi and, compared to local and systemic use of antibiotics, are an attractive alternative for reducing the risk of drug resistance in bacteria [50].

An analytical review by Q. Yang and L. Chen showed that the antimicrobial properties of silver-containing coatings directly depend on the amount of released ions [51]. Theoretically, a higher concentration of silver ions in the local depot system leads to a better antimicrobial effect. However, toxic effects increase with increasing concentration of silver ions, and their excess in the human body can cause damage to the liver, kidneys, lungs, heart and intestines. The cytotoxicity of silver ions in various mammalian cells depends on their size, dose and shape, as well as on the duration of interaction with the cells. Silver nanoparticles are capable of not only accumulating in the liver and spleen, but also are able to cross the blood-brain barrier, causing brain damage. *In vitro* cell culture tests have shown that silver nanoparticles are toxic to several human cell lines, including human bronchial epithelial cells, human umbilical vein endothelial cells, red blood cells, human peripheral blood mononuclear cells, human immortal keratinocytes, liver cells, and others. However, a number of studies have shown that low concentrations of silver ions can have an antibacterial effect without serious side effects on the body. On the other hand, silver ions exhibit antibacterial properties only at concentrations above 0.2 %. Slow release of silver ions and their therapeutic concentration are key factors in clinical practice. However, it should be taken into account that too slow release of silver ions from the coating surface is not able to exert the desired antibacterial effect [52].

In a study by Thukkaram et al., titanium substrates, legated with silver nanoparticles obtained by plasma electrolytic oxidation of titanium followed by ion implantation, exerted a pronounced bactericidal effect against methicillin-resistant *Staphylococcus aureus* and antibiotic-resistant *E. coli*. The antibacterial activity of the coating and the release of ions depended on the concentration

of silver ions. The study observed an initial rapid release of silver ions at concentrations suitable for preventing infections after implantation, followed by a slow, sustained release of ions over seven days [53].

Thus, silver ions included in antibacterial coatings have a pronounced antibacterial effect against gram-positive and gram-negative bacteria, affecting them by various mechanisms. In addition, various forms of silver can be used as an antibacterial substance in orthopedic implants, gels, ointments and surgical instruments, providing its wide use in medical practice.

Copper, zinc and selenium

In addition to silver, other metals with pronounced antibacterial activity include copper, zinc, and selenium. These alloying metals are in demand due to their antibacterial nature, low cost, and ability to stimulate osteogenesis. The mentioned metals are microelements necessary for the body to ensure the normal functioning of systems and organs, so their use in antibacterial coatings helps to increase the biocompatibility of surgical implants introduced into tissues. Moreover, according to Zhu et al., zinc-containing coatings promote osteoblast differentiation and improve the corrosion resistance of titanium implants [54].

A study by Wang et al. showed that titanium substrates containing polylactic acid-based coatings with different concentrations of copper chloride ($CuCl_2$) effectively inhibited the growth of *Staphylococcus aureus* and exerted an osteogenic effect *in vitro* and *in vivo*. *In vitro* studies demonstrated a dose-dependent burst release of Cu^{2+} ion and its antibacterial effect against *Staphylococcus aureus* [55].

Selenium nanoparticles are a beneficial platform for the development of the next generation of antimicrobial coatings, as they have the ability to kill microbes through multiple mechanisms, are stable *in vitro* and *in vivo*, and can be easily immobilized on various surfaces. Moreover, selenium deposited on microporous titanium dioxide coatings with calcium and phosphorus on titanium substrates can improve the antibacterial, anti-oncogenic, and osteogenic properties of the implant [56].

Zhou et al. found that a coating containing 8 wt. % selenium is optimal and provides 97 % eradication of *E. coli* and *S. aureus*, maximum osteogenic activity, and exhibits anti-oncogenic properties. Higher doses of selenium inhibit cell proliferation, while low doses do not have a significant antibacterial effect [57].

Similarly, zinc in the form of zinc complexes and zinc oxide nanoparticles exerts its antibacterial activity. Zinc complexes exhibit antifungal activity, while zinc oxides exhibit their antimicrobial activity through two different mechanisms, namely the release of reactive oxygen species (photocatalytic process) or zinc oxide nanoparticles, which lead to the formation of intracellular oxygen radicals, causing cell damage [58].

Iodine

Iodine-containing antibacterial coatings and antiseptics have a broad spectrum of bactericidal action, and also exhibit high biocidal activity against various viruses and fungi. Therefore, it makes them a very effective means for preventing the development of postoperative complications [59]. In addition, being a microelement necessary for the synthesis of thyroid hormones, iodine practically does not cause allergic reactions.

Inoue et al. established experimentally that an iodine coating applied to the surface of titanium implants exhibits an active biocidal effect against MRSA, *P. aeruginosa*, methicillin-resistant *S. epidermidis* and *C. albicans*. Moreover, the antibacterial efficiency of the titanium surface coated with iodine was higher than that of titanium implants with an oxide film applied by anodization [60].

Yamaguchi et al. developed a new solution and method for thermal treatment of the implant surface by ion-exchange reaction using a layered calcium titanate structure, in which a large amount of positively charged iodine ions are introduced into the titanium implant and onto its surface. The thus formed iodine-containing calcium titanate slowly releases 5.6×10–6 iodine ions over 90 days [61].

The results of the mentioned studies indicate that titanium implants with iodine coating may have great potential in the development of innovative antibacterial implants that may prevent the early onset of peri-implant infection, including during osteosynthesis of gunshot fractures.

Other metals

Coatings containing calcium, strontium, gallium, and bismuth can also be used to enhance the biologically active properties of titanium implants. Katunar et al. reported that strontium-containing ceramics enhance bactericidal action and promote bone tissue growth and regeneration [62]. In addition, Zhao et al. found that a microporous coating of titanium dioxide legated with zinc or strontium promotes osteoblast adhesion and inhibits the growth of *Staphylococcus aureus* [63].

Thus, one of the most important limitations of all metals used as antibacterial coatings is the lack of available *in vivo* data with long-term results generalizing the use of these implants in clinical practice.

The presented results of the *in vitro* and *in vivo* studies included in this review strongly suggest that trauma- and orthopaedic surgeons use traditional and new antimicrobial implant surface modifications in the treatment of patients with peri-implant infection. The lack of experience with their use in clinical settings raises concerns regarding the long-term results of these implants and the growth of multidrug-resistant microorganisms as a result of their clinical use.

Antibacterial inorganic coatings with osteointegrative properties

Antibacterial coatings that have the property of increasing implant osseointegration include coatings based on hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$), magnesium, and others. Hydroxyapatite, being a natural inorganic component of bone tissue, has proven itself in clinical practice due to its high biocompatibility and bactericidal activity. The crystalline structure of hydroxyapatite allows for the small-scale replacement of Ca^{2+} with various foreign ions, promoting osteoblast adhesion and expanding the possibilities of modifying the surface of implants to increase bactericidal activity and osteoconductive properties [64].

Batebi et al. developed the structure of antibacterial hydroxyapatite by replacing various Ca^{2+} in it with Ag^{+}, Cu^{2+} and Zn^{2+} ions. Among these ions, silver nanoparticles were most effective in disrupting the integrity of the bacterial cell by binding to proteins and enzymes inside the bacteria. This seriously damaged the cell and disrupted its basic functions (regulation of enzymatic signaling activity, permeability, cellular oxidation, respiratory processes), which ultimately led to the death of the bacteria [65]. Turkoz et al. synthesized a hydroxyapatite composite with the addition of silver and fluorine ions by precipitation and found that the presence of fluorine in the composite not only improved the antibacterial effect of hydroxyapatite against *E. coli*, but also increased its density and osteointegrative properties. The authors showed that the resulting compound had good antibacterial activity against *E. coli* and *S. aureus* cells and improved the osteointegrative properties of implants [66].

Magnesium and its compounds are biodegradable materials used in traumatology and orthopedics, have high mechanical strength and rigidity, along with other biodegradable materials, which allows them to firmly hold bone fragments when used as a material for the manufacture of orthopedic implants. Moreover, being a macroelement that is required for normal vital activity, magnesium passes from implant coatings into the surrounding bone tissue, accelerating reparative bone

regeneration and osteointegrative properties of implants. Besides, magnesium actively prevents colonization of *S. aureus* on the surface of implants which allows it to be used as a material for the manufacture of antibacterial coatings. At the same time, magnesium also exhibits pronounced antifungal properties [67]. According to the review by Pogorielov et al., the inclusion of magnesium in surgical implants accelerates the formation of hard bone callus due to osteoblast adhesion and bone remodeling [68].

Coatings based on antimicrobial peptides

Coatings based on antimicrobial peptides (AMPs) are currently widely used as an alternative to conventional methods of treating the surface of titanium implants, since they have a broad spectrum of action and require low concentrations for an effective antimicrobial effect. They are also able to reduce the growth of antibiotic-resistant bacterial strains. The amino acids that make up these peptides can be cationic or amphipathic, interacting with the plasma membrane of bacteria, leading to their death [69]. Currently, there are many studies devoted to studying the effectiveness of using AMPs. Caselli et al. claim that AMPs on the surface of implants enhance the antimicrobial effects of photocatalytic titanium oxide nanoparticles without having a toxic effect on the body [70]. Keikhosravani et al. demonstrate the successful use of CATH–2 AMP in the development of titanium implant coatings, which suggests promising results in the development of antibacterial coatings for the prevention of biofilm formation and the treatment of peri-implant infection [71].

Coatings based on polymers

Both natural and synthetic polymers are used to create antibacterial coatings for the surface of titanium implants, as they can be easily modified with bioactive components. Polymers based on chitosan, nitrogen-containing polyethyleneamines and quaternary ammonium compounds have their own biocidal properties, while other polymers are included in antibiotics to obtain antibacterial activity. Although the application of antibiotics to polymers does provide the desired antibacterial effect, it does not provide long-term release of the drug. Compared to synthetic polymers, most natural polymers lack mechanical strength and rapid degradation, which can lead to uneven release of drug particles from the implant. Therefore, these polymers are often included in inorganic systems such as metal oxides, hydroxyapatite, etc., to enhance the antibacterial effect. Therefore, to provide biocidal action, it is possible to modify the polymer chain by adding a quaternary amine unit, which will give the polymer bactericidal properties, instead of converting the polymer into a carrier of antibiotics [72].

There are many examples of using such modifications of polymer coatings. Kaleli-Can et al. found that titanium implants coated with diethyl phosphite, applied by plasma polymerization, demonstrate excellent cytocompatibility and suppress biofilm formation. *In vitro* studies have shown the antibacterial activity of this coating against *S. aureus* and *C. albicans* cells, which proves the promising potential of their use in the treatment of patients with peri-implant infection [73]. The antibacterial coating based on polyhexamethylene biguanide developed by Peng et al. allowed for almost 100 % suppression of *S. aureus* and *E. coli* growth on the implant surface. *In vivo* studies on the infected rat model also confirmed the bactericidal nature of the developed coating [74].

One of the promising polymers with antibacterial properties which are currently actively used for the development of implant coatings is chitosan. It is a natural cationic polysaccharide with good biocompatibility and lack of cytotoxicity. Its positively charged amino groups can generate electrostatic interactions with negatively charged membranes of bacterial cells, thereby changing the permeability of cell membranes and causing lysis and death of bacteria. Therefore, chitosan is expected to become an effective means for preventing biofilm formation on the surface of orthopedic implants. Peng et al. evaluated the effect of hydroxypropyltrimethylammonium chloride chitosan

at three different component concentrations (6 %, 18 % and 44 %) on preventing biofilm formation on the surface of titanium implants using *in vitro* tests and found that three types of the developed compound, especially the last two, could significantly inhibit biofilm formation on the surface of implants and also exert an effective therapeutic effect on previously formed mature biofilms [75].

Multifunctional and intelligent coatings

Along with imparting bactericidal properties to the implant surface, the strategy of developing antibacterial coatings can be implemented by increasing the biocompatibility of implants, enhancing their osteogenic effects, and providing them with immunomodulatory and antitumor properties. Coatings with such additional functions can directly stimulate reparative bone regeneration. At the same time, stimulation of osteogenesis and osseointegration can also reduce bacterial adhesion and proliferation. However, bone regeneration is suppressed under the conditions of bacterial infection, presence of bone sequesters and vascularization deficiency what will lead to infection persistence. In this regard, future research in this area should determine how to effectively restrain infection and enhance the bone regeneration process using multifunctional coatings [76].

To date, there are many works in the world literature devoted to the study of smart coatings. Zhang et al. developed a peptide sequence sensitive to *S. aureus* using vancomycin and a peptide conjugate, and then conjugated an antibiotic with this specially created peptide. The conjugate was then bound to the surface of a titanium implant, where the peptide can be recognized and cleaved by an enzyme secreted by *S. aureus*, which allows the release of the antibiotic only in the presence of *S. aureus*, thereby achieving delivery of the antibacterial agent precisely when the infectious process occurs [77].

Zhang et al. described a pH-sensitive self-adapting coating with antibacterial, anti-inflammatory, and osseointegration properties. This smart coating consisted of an antibacterial copolymer containing quaternary ammonium salts deposited on a titanium surface by self-assembly of layers. The change in surface charge of the coatings was confirmed by measuring the zeta potential, the coatings demonstrated a negative charge in a neutral environment and a positive charge in an acidic environment. An acidic environment triggers the antibacterial effect of the positive control. This effect is reversed when the pH is high, creating a self-adapting coating. *In vitro* tests showed that this coating was highly effective against *E. coli* and *S. aureus* [78].

Polymeric gels

In recent years, the use of so-called polymer gels as local depot systems for the prevention of postoperative infectious complications has attracted increasing attention from researchers. A clinical review by Pressato et al. showed that modification of the surface of titanium implants and delivery of antimicrobial substances using local depot systems, in addition to systemic antibiotic therapy, are promising and highly effective in reducing the risk of peri-implant infection. However, this area requires further study, since there is no literature data on the long-term effectiveness and safety of this technique [79].

A clinical study of polymer hydrogels based on unsaturated derivatives of polyvinyl alcohol, conducted in 2023 at the Priorov National Medical Research Center of Traumatology and Orthopedics, demonstrated the release of more than 70 % of the antibacterial drug loaded into the gel from the matrix composition versus 10 % from polymethyl methacrylate over the entire study period (28 days). Moreover, the maximum release of the drug (up to 90 %) was observed during the first week [80].

Thus, polymer hydrogels containing antibacterial drugs have a wider range of potential clinical applications compared to bone cement due to their bioresorbable nature and controlled release of the antimicrobial agent, providing a ten- to hundred-fold increase in local drug concentrations

around the implant. In addition, hydrogel resorption eliminates the risk of developing antibiotic resistance in bacteria, which is typical for polymethyl methacrylate.

Application of additive technologies in the production of antibacterial coatings

In recent years, additive (3D) technologies have come to the forefront in the production of medical devices. The main advantage of 3D printing is the ability to manufacture customized implants with complex geometric shapes for specific patients, as well as parts with high fatigue strength and corrosion resistance. In traumatology and orthopedics, additive technologies have been successfully used for a long time in joint replacement and other reconstructive surgeries. However, due to the relative novelty of 3D printing technology, there is a lack of basic scientific knowledge about this process (phase formation, new alloying elements, etc.) in the production of titanium medical implants along with the difficulties in carrying out post-processing procedures (sterilization, polishing, filling the mesh structures in implants) [81].

Golovko et al. analyzed the effectiveness of the antibacterial coating they produced based on chitosan and polyvinylpyrrolidone. They showed that the antibacterial coating developed using 3D printing had high biocompatibility, atraumatic properties, elasticity, and adhesion to the wound surface. In addition, the team of the authors found that the use of additive technologies for the production of a bioengineered structure ensures the maintenance of aseptic conditions, the necessary humidity, pH, and temperature in creating implants [82].

Inzana et al. studied the effectiveness of additive manufacturing in the treatment of implant-associated infection and demonstrated that local delivery of rifampicin and vancomycin to the surgical site from a 3D-printed calcium phosphate scaffold is more effective than antibacterial spacers made of polymethyl methacrylate, which is not capable of transporting rifampicin. However, this method does not lead to the eradication of microbial biofilm, which creates the need to modify the surface of these implants in order to impart bactericidal properties to them [83].

DISCUSSION

Based on the analysis of current literature, it can be concluded that the diversity of existing coatings with antibacterial properties indicates that the search for an “ideal” method for preventing peri-implant infection is still incomplete. The development of these technologies remains a relevant topic for scientific research.

Local depot systems for the delivery of antibacterial and antiseptic drugs to the surgical intervention area used in clinical practice prevent the development of implant-associated infection with varying degrees of effectiveness (Table 1). However, there is still no consensus on the properties that an “ideal” antibacterial coating should have. Most researchers are inclined to believe that the combination of highly effective bactericidal action and resistance to bacterial attachment, good biocompatibility, stimulation of osseointegration and osteogenesis is a promising direction for the development of new antibacterial implant coatings [10, 30, 31, 84].

Based on the analysis, we concluded that the main requirements for antibacterial coatings are:

1) biological compatibility of coatings and the absence of local irritating effects on tissues;
2) high biocidal activity, maintained over a long period of time and under conditions of fluctuating thermochemical parameters of the internal environment of the body;
3) effective biocidal action against a wide range of microorganisms (bacteria, viruses, fungi);
4) combination of anti-adhesive and biocidal properties in coatings, which have a complex effect on pathogens of implant-associated infection;
5) prevention of the development of bacterial resistance to antibiotics by using coatings.

Table 1

Efficiency of antibacterial coatings in clinical practice

Composition	Technique of coating	Antimicrobial efficiency *in vitro/in vivo*	Reference
Coatings that contain antibacterial preparations			
Cis-2-decenoic acid (C2DA) and amikacin	Coating of titanium with phosphatidylcholine and antibiotic additive	Decreased biofilm formation	[36]
Titanium implants coated with a biodegradable polymer-lipid encapsulation matrix with the addition of doxycycline	Polymer-lipid encapsulation	Suppression of MRSA and MSSA growth on implants	[37]
Kirschner wires coated with polylactic acid with added fosfomycin	Chemical precipitation from solution	Addition of fosfomycin to polylactic acid does not have effect on prevention of implant-associated infection	[39]
Antibiotic-impregnated titanium alloy discs with calcium phosphate coating	Micro arc oxidation	High biocidal efficacy against pathogens causing peri-implant infection	[40]
Antibiotic-loaded polymethyl methacrylate mantle on iliac bone graft	Application of the mantle to the surface of the implants	Effective prevention of infection in the treatment of open fractures	[43]
Coatings containing antiseptic preparations			
Titanium discs immersed in solutions of 6 different antiseptics	Immersion of discs in antiseptic solutions	High antibacterial activity against *P. gingivalis* and *S. mutans*	[45]
Coatings based on nanoparticles of metals and their oxides			
Ion legated Ag TiO_2	Plasma electrolytic oxidation	Considerable reduction ($p < 0.05$) in number of *E. coli*, *S. aureus* on implant surface	[53]
Microporous coating of implants with ions of Cu and TiO_2	Micro arc oxidation	Effective inhibition of *Staphylococcus aureus* growth, increased biocompatibility and osteogenic effect *in vitro* and *in vivo*	[55]
Titanium implants coated with TiO_2 and nanoparticles of Se	Surface nucleation	High biocidal activity, antibacterial, anti-oncogenic and osteogenic properties on the surface of the titanium implant	[56]
Se, applied to microporous coatings made of TiO_2 with Ca and P on titanium implants	Micro arc oxidation	97 % eradication of *E. coli* and *S. aureus* in *in vitro* on implants surface, osteogenic and antioncologic properties	[57]
Hydroxyapatite based coating with application of ZnO on implant surface	Chemical precipitation from solution	Sharp reduction in the number of *E. coli* and *S. aureus* after 4 hours of exposition	[58]
Coatings based on nanoparticles of metals and their oxides			
Implants coated with calcium titanate with added iodine	A method of heat treatment of the implant surface that controllably incorporates 0.7 % to 10.5 % iodine into titanium	Antibacterial activity against MRSA, *E. coli* and *S. aureus* 99 %	[61]
Bioactive Si-based coating with Sr-doped bioactive glass particles	Sol-gel	Enhanced antibacterial effect and imparting osteogenic properties to implants	[62]
Coating of implant surface with TiO_2, doped with ions of Zn and Sr	Micro arc oxidation	Reduction in the number of colonies of *S. aureus* on implant surface	[63]
Antibacterial inorganic coatings with osteointegrative properties			
Composite coating containing Ag, F and hydroxyapatite	Sol-gel	Reduction in the number of *E. coli* by 96 % for 6 hours after implantation	[65]
Coating based on hydroxyapatite containing ions of Ag and F	Precipitation method	High antibacterial activity against *E. coli* and *S. aureus* and improved osteointegration properties	[66]

Table 1 (continued)

Efficiency of antibacterial coatings in clinical practice

Composition	Technique of coating	Antimicrobial efficiency *in vitro/in vivo*	Reference
Coatings based on antimicrobial peptides			
Coating of TiO2 with synthesized AMP LL-37	Photocatalytic method	Enhanced antimicrobial effects of TiO_2 without toxic impact on the body	[70]
Titanium implants with applied AMP CATH-2	Polymer layer-by-layer assembly and electrospray method	High antibacterial activity agains *E. coli* and *S. aureus*, biocompatibility with body cells	[71]
Coatings based on polymers			
Titanium coated with plasma-polymerized diethyl phosphite	Plasma polymerization	High biocidal activity *in vitro* against *S. aureus* and *C. albicans*	[73]
Ester block polymers with the addition of diethyl (hydroxymethyl) phosphonate	Reversible addition-fragmentation transfer (RAFT) polymerization	Almostantibacterial activityagainst *S. aureus* and *E. coli*	[74]
Chitosan-based coating with hydroxypropyltrimethylammonium chloride with varying degrees of quaternary ammonium substitution	Polymerization of chitosan and glycidyltrimethylammonium molecules	Significant inhibition of formation and destruction of already formed biofilms	[75]
Multifunctional and smart coatings			
pH-sensitive antibacterial polymer containing cationic quaternary ammonium salts and carboxyl groups	Layer-by-layer self-assembly method	The coating has good antibacterial and anti-inflammatory properties during implantation and shows good osseointegration efficiency	[78]
Polymer gels			
Polymer gel based on hyaluronic acid impregnated with various antibiotics	Polymerization of molecules	Release of more than 70 % of the antibacterial drug impregnated into the gel from the matrix composition versus 10 % from polymethyl methacrylate within 28 days	[80]
Coatings produced using additive technologies			
Coating of 4 % hydrogel of medium molecular weight chitosan with the addition of 1 % povidone-iodine and dermal fibroblasts	Extrusion 3D Bioprinting Method	High biocompatibility, atraumatic nature and adhesion of the coating to the wound surface, effective antibacterial and regenerative effects	[82]
3D Printed Calcium Phosphate Scaffold with Rifampicin and Vancomycin Addition	Extrusion 3D Bioprinting Method	Significant efficacy in preventing implant-associated infection in study *in vivo*	[83]

Our systematic review of the literature allows us to conclude that improving current technologies of antimicrobial coatings for titanium implants should primarily consider the development of polymer coatings, hydrogels, multifunctional intelligent coatings, as well as additive technologies that allow the coating to be applied by 3D printing [10, 30, 31, 84, 85].

As for possible use of the above-mentioned technologies in the treatment of gunshot fractures, we are inclined to believe that even despite the high risks of infectious complications during osteosynthesis of such fractures, their development can be prevented by using polymer, multifunctional coatings, hydrogels, as well as oxides of metals such as silver, iodine and zinc during surgery.

CONCLUSION

To date, there is a wide variety of coatings with antibacterial properties that are successfully used in clinical practice for treatment and prevention of implant-associated infection. However, in the international literature there are still no research works devoted to studying the effectiveness of the above coatings in the treatment of gunshot fractures.

The search for and development of effective methods for the prevention of infectious complications in the treatment of gunshot fractures remains a topical issue for scientific research.

Conflict of interest *Authors declare that they do not have conflicts of interests.*

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