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REVIEW
ОБЗОР

Bacteriophages: an alternative to antibiotics in the era of antimicrobial resistance

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Abstract. *Relevance.* Antibiotic resistance is one of the most urgent global health challenges, caused by the widespread and often inappropriate use of antibiotics and by evolutionarily entrenched bacterial adaptation mechanisms. By 2050, antimicrobial resistance is projected to cause up to 10 million deaths annually, underscoring the urgent need for novel therapeutic strategies. In this context, bacteriophages — viruses that specifically infect bacteria — emerge as a promising alternative to antibiotics. This review analyzes the primary mechanisms by which bacteria develop resistance, including β-lactamase–mediated drug inactivation, efflux pump activity, target modification, and horizontal gene transfer, as well as the clinical significance of the ESKAPE pathogen group. We discuss phage classification into lytic and lysogenic types, their morphological characteristics, and life cycles. Special attention is given to modern methods of phage delivery (oral, topical, parenteral, and inhalational) and to phage–host immune interactions, including antibody production and immunomodulatory effects on macrophages, neutrophils, and lymphocytes. A dedicated section addresses the clinical applications of phage therapy in surgery and chronic wound management. We summarize outcomes from cardiothoracic, abdominal, and orthopedic surgical settings, combined phage–antibiotic regimens, and the implementation of vacuum-assisted wound therapy with phage instillation, all of which demonstrate accelerated healing, reduced microbial burden, and fewer postoperative complications. *Conclusion.* Phage therapy offers several advantages — high specificity, efficacy against multidrug-resistant strains, compatibility with antibiotics, and minimal side effects. On the other hand, its broad clinical implementation requires addressing challenges such as standardizing phage preparation manufacturing, establishing centralized phage banks, developing algorithms for strain selection in personalized therapy, and addressing regulatory barriers. Further randomized clinical trials and the creation of an appropriate legal and regulatory framework are essential for the full utilization of phages as an effective tool in the fight against antibiotic resistance.

Keywords: antimicrobial resistance, bacteriophages, alternative to antibiotics, chronic wound treatment, surgery, purulent surgery, phage therapy, multidrug-resistant infections

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Introduction

Antibiotic resistance has become one of the main threats to modern medicine, calling into question the effectiveness of traditional methods for treating bacterial infections. The constant increase in the number of antibiotic-resistant strains of bacteria is forcing the search for alternative approaches to therapy. One of the research areas in this direction is the study of bacteriophages — viruses that selectively infect bacteria without harming the human body. The use of bacteriophages in medicine, known as phage therapy, was successful in the last century, but interest in it temporarily waned with the advent of antibiotics. Today, in the context of the growing crisis of antibiotic resistance, phage therapy is being revisited as a potential solution.

Antibiotic resistance

Antibiotic resistance is a complex biological phenomenon that reflects the ability of bacteria to adapt to the effects of antibiotics through evolutionarily established mechanisms and genetic variability [1]. This phenomenon is seen not only as a result of modern human activities, including the irrational use of antibiotics, but also as a natural adaptation of bacteria that formed long before humans existed. After the introduction of new antibiotics, the emergence of resistant strains of bacteria that were previously sensitive to these drugs is inevitable. The variety of resistance mechanisms contributes to the development of resistant phenotypes in bacterial pathogens, rendering the treatment of human infections caused by them extremely difficult [2, 3].

Antibiotics are the primary means for preventing and treating bacterial infections. However, their widespread and often irrational use contributes to the development of antibiotic resistance — the ability of bacteria to adapt and resist the action of antimicrobial drugs. This complicates the treatment of infections, increases their spread, and raises the level of morbidity and mortality [4].

Between 2000 and 2018, global consumption of antibacterial drugs increased by 46% [5]. This increase is particularly noticeable in low- and middle-income countries, where access to antibiotics is growing [6]. According to experts, by 2050, antimicrobial resistance could cause up to 10 million deaths worldwide each year [7].

Antibiotic resistance is one of the leading global health challenges. It threatens the effectiveness of treatment for diseases such as pneumonia, tuberculosis, sepsis, and gonorrhea. The World Health Organization warns that new resistance mechanisms are spreading rapidly, reducing the clinical value of antibiotics [8].

Without the implementation of comprehensive measures to control and prevent resistance, there is a real risk of entering a post-antibiotic era, when even routine infections and minor injuries could become fatal.

Strategies to combat antibiotic resistance include surveillance, reducing the use of antibiotics in livestock, improving access to quality medicines, and developing new therapeutic alternatives such as nanoparticles and bacteriophages [5, 9].

Mechanisms of antibiotic resistance development

Bacteria are constantly competing for resources, which leads to the evolution of chemicals that can inhibit or eliminate other microorganisms [10].

Bacteria develop resistance mechanisms very quickly due to selective pressure. Defensive mechanisms against antibacterial drugs include the following [10–12]:

1. Destruction or modification of antibiotics. Certain bacteria produce enzymes that can eliminate or modify antibiotics, rendering them inactive against microorganisms, such as several classes of beta-lactamases and the like.
2. Efflux pumps. Bacteria can use special proteins to pump antibiotics out of their cells, reducing their concentration to an ineffective level.
3. Alteration of cell wall permeability. Bacteria can change the permeability of their cell walls to prevent antibiotics from entering the cell.
4. Antibiotic target modification. Bacteria can alter the structure of the molecules to which antibiotics bind, rendering the antibiotics ineffective.
5. Metabolic changes or auxotrophy. Bacteria can modify their metabolic pathways to reduce the effectiveness of antibiotics.
6. Target protection proteins. Bacteria can synthesize proteins that protect the targets of antibiotics.
7. Cell morphology changes. Bacteria can change their cell shape to reduce the impact of antibiotics.
8. Cooperative resistance in a colony. Bacteria can interact within a colony to enhance overall resistance to antibiotics.
9. Horizontal gene transfer. This mechanism enables bacteria to acquire new genetic material from external sources, facilitating the exchange of a diverse array of genes that encode traits advantageous for adaptation to their local environment [13, 14]. This is achieved through conjugation, transduction, and natural transformation, which allows resistance genes to spread rapidly among different species of bacteria [15].

The ESKAPE pathogen group and their characteristics

The ESKAPE group is a collection of six nosocomial pathogens known for their ability to “evade” the effects of antimicrobial drugs. These pathogens include *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae*, *Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter spp* [12]. They have natural resistance to a number of antibiotics due to various resistance mechanisms, including the exchange of plasmid-encoded resistance genes through horizontal gene transfer, which leads to an increase in the level of antimicrobial resistance in these microorganisms [16].

1. *Enterococcus spp*. These are gram-positive cocci, facultative anaerobes, and gastrointestinal commensals that can survive in various conditions [17]. They can cause infectious diseases in humans,

particularly in patients with weakened immune systems. More than 50 species of this microorganism have been described, yet enterococcal infections are most often caused by two species: *E. faecalis* and *E. faecium*. *E. faecalis* is the most pathogenic species, although *E. faecium* is more resistant to various antimicrobial drugs [18].

2. *Staphylococcus aureus*. These are gram-positive cocci that can cause a wide range of diseases in humans, as well as various infectious complications, particularly in surgery. They are facultative anaerobes and are catalase- and coagulase-positive cocci [19]. This microorganism poses a significant threat due to its ability to quickly adapt and develop resistance to antibiotics. Staphylococcus aureus can cause systemic and deep infections (endocarditis, osteomyelitis, pneumonia), hospital-acquired infections (surgical wound infections, catheter-associated infections), skin and soft tissue infections (boils, abscesses, cellulitis, phlegmon), and others.

The literature describes three antibiotic-resistant forms of *S. aureus*: methicillin-resistant Staphylococcus aureus (MRSA), which is resistant to methicillin and other beta-lactam antibiotics [20]; vancomycin-intermediate Staphylococcus aureus (VISA); and vancomycin-resistant *Staphylococcus aureus* (VRSA). The latter two forms are resistant to vancomycin, one of the last effective antibiotics against *S. aureus* [21].

3. *Klebsiella pneumoniae*. This is a gram-negative bacterium of the Enterobacteriaceae family. This microorganism is opportunistic — it lives in the intestines of humans and animals and under certain conditions can cause serious infections. *K. pneumoniae* is one of the leading etiological agents of nosocomial pneumonia, especially among immunocompromised patients. It also causes infections of the urinary tract, including cystitis and pyelonephritis. *K. pneumoniae* is involved in the pathogenesis of intra-abdominal inflammatory processes, such as peritonitis and abdominal abscesses, especially after surgery or traumatic injuries. Additionally, it can cause postoperative wound infections [22,23]. Numerous strains of K. pneumoniae exhibit high resistance to antibacterial drugs, including beta-lactam antibiotics (penicillins, cephalosporins) and carbapenems. Certain strains of *K. pneumoniae* produce enzymes called carbapenemases, which can inactivate carbapenems — the last line of antibiotics effective against a number of multidrug-resistant microorganisms [24]. Strains demonstrating carbapenem resistance are classified as CRKP (carbapenem-resistant *Klebsiella pneumoniae*) [25].

4. *Acinetobacter baumannii*. This is an aerobic gram-negative bacterium, which is a common causative agent of nosocomial infections [26]. *A. baumannii* contributes to infectious complications such as pneumonia (especially in patients on mechanical ventilation), urinary tract infections (common in patients with catheters or other medical devices), wound infections (often occur in patients with open wounds), as well as sepsis and bacteraemia. There are mechanisms of resistance, including the production of β-lactamases, efflux, and modification of the antibiotic target [27,28].

5. *Pseudomonas aeruginosa*. This is a gram-negative opportunistic pathogen that is widespread in the environment and frequently found in hospitals. It exhibits natural resistance to a number of antibiotics and can cause serious infections, especially in patients with weakened immune systems [29, 30]. The pathologies associated with this microorganism include pneumonia (especially common among patients on mechanical ventilation and can be associated with the development of lung abscesses), urinary tract infections, and skin and soft tissue infections. The mechanisms of resistance in P. aeruginosa are related to the production of β-lactamases, efflux, and mutation of antibiotic targets [31].

6. *Enterobacter spp*. This is a genus of gram-negative bacteria of the Enterobacteriaceae family. The most common pathogens are Enterobacter cloacae and Enterobacter aerogenes [32]. They form part of the commensal intestinal microbiota in both humans and animals, but can also cause a number of serious infectious diseases, including urinary tract infections; pneumonia (especially in patients on mechanical ventilation); bacteremia and sepsis; intra-abdominal infections (peritonitis and abdominal abscesses can occur due to the spread of infection from the gastrointestinal tract). They employ the following resistance mechanisms: production of extended-spectrum beta-lactamases (ESBL); certain strains of

Enterobacter spp. produce enzymes that eliminate carbapenems; presence of mechanisms for developing antibiotic resistance through efflux pumps; mutation of antibiotic targets [33].

Pathogens from the ESKAPE group pose a serious threat to public health due to their ability to adapt to existing antibiotics and quickly develop resistance to new drugs. Therefore, addressing these pathogens necessitates the development of new treatment strategies, including combination therapy, new classes of antibiotics, and improved methods of infection prevention.

In response to the widespread threat of antibiotic resistance, the World Health Organization has developed a Global Action Plan aimed at minimizing the impact of antibiotic resistance on the health of humans and animals. The "One Health" concept unites the efforts of various international organizations, such as the Food and Agriculture Organization of the United Nations and the World Organization for Animal Health, to provide an integrated approach to ensure a coordinated response to this threat, considering the integrated nature of human, animal, and environmental health [34, 35]. At the national level, a number of countries, including Japan, Tanzania, and China, have developed their own action plans to combat antibiotic resistance, aimed at monitoring and reducing the spread of antibiotic resistance. An important element in the fight against antibiotic resistance is raising public awareness about the causes and consequences of this threat, which helps to form the right attitude towards the use of antibiotics [7].

In the face of the growing global threat of antibiotic resistance, there is an increasing need to develop new effective methods for treating bacterial infections that are resistant to antibiotics. In this context, experts are increasingly viewing bacteriophage therapy as a promising alternative. Although interest in using bacteriophages to treat infectious diseases was rekindled in recent years, current research has confirmed their significant therapeutic potential. Whether used alone or in combination with antibiotics, bacteriophages remain a promising replacement for traditional antibacterial agents [2, 36, 37].

Tables 1 and 2 present the most critical dangerous antibiotic-resistant pathogens according to the World Health Organization (WHO). This challenge requires the development of alternative treatment methods, which is stimulating renewed interest in the use of bacteriophages in medical practice [38].

Table 1

List of priorities for the development of new antibiotics according to the World Health Organization [39]

Priority	Types of pathogens	Resistance to antimicrobials
Critical	Acinetobacter baumannii	Carbapenem-resistant
	Pseudomonas aeruginosa	Carbapenem-resistant
	Enterobacteriaceae* (*Enterobacteria include: *Klebsiella pneumonia, Escherichia coli, Enterobacter spp., Serratia spp., Proteus spp.* и *Providencia spp., Morganella spp.*)	Carbapenem-resistant, third-generation cephalosporin-resistant
High	*Enterococcus faecium*	Vancomycin-resistant
	Staphylococcus aureus	Methicillin-resistant, vancomycin-intermediate and vancomycin-resistant
	Helicobacter pylori	Clarithromycin-resistant
	Campylobacter	Fluoroquinolone-resistant
	Salmonella spp.	Fluoroquinolone-resistant
	Neisseria gonorrhoeae	Third-generation cephalosporin-resistant, fluoroquinolone-resistant
Medium	*Streptococcus pneumoniae*	Penicillin-resistant
	Haemophilus influenzae	Ampicillin-resistant
	Shigella spp.	Fluoroquinolone-resistant

Table 2

Comparative overview of bacterial pathogen priority tiers, 2017 versus 2024. According to Sati H. et al., 2025 [40]

Priority tier	2017	2024
Critical	*Acinetobacter baumannii*, carbapenem-resistant; *Pseudomonas aeruginosa*, carbapenem-resistant; *Enterobacteriaceae*, carbapenem-resistant, third-generation cephalosporin-resistant	*A.baumannii*, carbapenem-resistant; *Enterobacterales*, third-generation cephalosporin-resistant; *Enterobacterales*, carbapenem-resistant; *Mycobacterium tuberculosis*, rifampicin-resistant
High	*Enterococcus faecium*, vancomycin-resistant; *Staphylococcus aureus*, meticillin-resistant, vancomycin intermediate and-resistant; *Helicobacter pylori*, clarithromycin-resistant; *Campylobacter spp*, fluoroquinolone-resistant; *salmonellae*, fluoroquinolone-resistant; *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant	*Salmonella enterica* serotype Typhi, fluoroquinolone-resistant; *Shigella spp*, fluoroquinolone-resistant; *E. faecium*, vancomycin-resistant; *P. aeruginosa*, carbapenem-resistant; non-typhoidal *Salmonella*, fluoroquinolone-resistant; *N. gonorrhoeae*, third-generation cephalosporin-resistant, fluoroquinolone-resistant; *S. aureus*, meticillin-resistant
Medium	*streptococcus pneumoniae*, penicillin non-susceptible; *Haemophilus influenzae*, ampicillin-resistant; *Shigella spp*, fluoroquinolone-resistant	*Group A streptococci*, macrolide-resistant; *S. pneumoniae*, macrolide-resistant; *H. influenzae*, ampicillin-resistant; *group B streptococci*, penicillin-resistant

Bacteriophages

On September 10, 1917, F. J. d'Herelle published a brief note in the journal "Comptes rendus de l'Académie des sciences", describing a new type of microbe, which he characterized as an "obligate intracellular parasite" of bacteria [41]. This discovery became a turning point in d'Herelle's career, earning him international recognition, honorary academic degrees, a Nobel Prize nomination, and a long-lasting yet controversial scientific reputation. D'Herelle's work, published in 1917, includes the first clear and experimentally grounded description of a bacteriophage. Although in 1915 F.W. Twort provided observations of phenomena that he called "glassy transformation" and "transmissible lysis", he did not offer an explanation for the viral nature, intracellular parasitism, or the ability of the infectious agent to reproduce serially [42]. On September 15, 1917, Dr. Emile Roux presented d'Herelle's note to the Academy of Sciences, introducing the medical community to an invisible microbial antagonist of the dysentery bacillus; this antagonist was named a bacteriophage [43, 44].

In the USSR, as well as in the rest of the world, research was conducted on the use of bacteriophages in the treatment of infectious diseases and the search for other effective means to solve this problem. For instance, prior to the advent of antibiotics, Z.V. Ermolyeva was investigating bacteriophages and lysozyme, which is mentioned in an article by Yu.V. Belchich (a review of the monograph by A.V. Gorshenin "History of scientific activities by the Soviet microbiologist Z.V. Ermolyeva on the study and use of antibacterial agents in the 1930s"). The article describes the significance of Ermolyeva's contribution to science, namely the creation of a new direction in medical bacterial biochemistry, the development of antibacterial drugs based on lysozyme and bacteriophages, active training of personnel in the field of microbiology, and the fight against infectious diseases [45]. This significantly increased the effectiveness of medical practice and improved the health of the USSR population, and her work received international recognition.

In the modern medical community, a significant number of specialists remain skeptical about the potential of phage therapy for treating severe bacterial infections. The first successful attempts to use virulent bacteriophages to treat several infectious diseases in the first quarter of the 20th century did not receive further active development, as antibiotics appeared on the historical scene and demonstrated high effectiveness in combating bacterial infections [46].

Phages are small viral particles that are sensitive to certain strains of bacteria and can specifically infect bacteria, effectively eliminating the bacterial cells [47]. Currently, phage therapy is experiencing a resurgence of interest as an alternative to antibiotics in the fight against resistant bacterial infections [48–50].

The interest in phage therapy is driven by a number of primary factors. Firstly, the increasing number of antibiotic-resistant bacteria poses a serious health threat, necessitating development of alternative treatment methods. Phage therapy, due to the high specificity of bacteriophages, can effectively combat bacterial infections while minimizing the impact on beneficial microbial flora and reducing the risk of side effects.

Scientific and technological advances, such as progress in molecular biology and biotechnological production, allow for a deeper understanding of the mechanisms of interaction between bacteriophages and bacteria, and the development of more effective therapeutic strategies. Additionally, phage therapy is being explored as a potential strategy to address multidrug-resistant infections and can be combined with antibiotics to enhance the therapeutic effect. These factors, along with economic and social aspects, stimulate interest in phage therapy from both the scientific community and potential funders. Structural model of bacteriophage is presented on Figure 1.

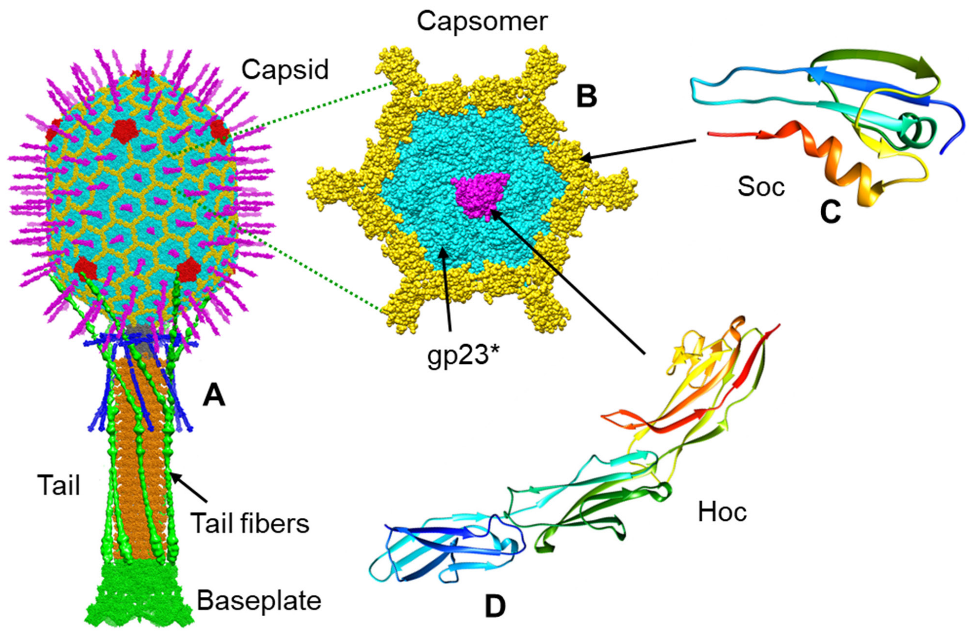

Fig. 1. Structural model of bacteriophage T4 virion. According to Rao V.B. et al., 2023 [51]

Advantages and disadvantages of using phage therapy

The use of bacteriophages (phages) to treat infections, including chronic wounds, demonstrates several advantages that render them a promising alternative or addition to traditional antibiotic therapy [52]. The main advantages of using bacteriophages include:

1. High specificity: bacteriophages selectively target specific strains of bacteria without disrupting the beneficial microbiota of the host. This reduces the risk of dysbiosis and other side effects associated with the elimination of beneficial bacteria. Bacteriophages are highly specific viruses that can effectively target pathogenic bacteria and eliminate them, rendering them a promising alternative to antibiotics in the treatment of infections [50]. In N.S. Kuptsov's study, it is shown that commercial bacteriophage preparations effectively eliminate strains of Staphylococcus aureus, Klebsiella pneumoniae, and Pseudomonas aeruginosa, but their effectiveness remains low against Enterococcus faecium [53]. Although certain monoisolates of bacteriophages also showed activity against these pathogens, commercial preparations have shown enhanced effectiveness.

2. Effectiveness against multidrug-resistant bacteria: phage therapy can be effective even against antibiotic-resistant bacteria. This is of great importance given the growing challenge of antibiotic resistance. Bacteriophages are highly specific viruses that can effectively target and eliminate pathogenic bacteria, rendering them a promising alternative to antibiotics in the treatment of infections [50]. Phage therapy has demonstrated its effectiveness in combating outbreaks of healthcare-associated infections caused by antibiotic-resistant bacteria such as *S. aureus* and *K. pneumoniae* [54].

3. Compatibility with other treatment methods: bacteriophages can be used in combination with antibiotics and other standard treatment methods, enhancing the overall effectiveness of therapy [55].

4. Minimal side effects: since bacteriophages are natural components of the ecosystem, they demonstrate a favorable safety profile in clinical use and exhibit a low level of toxicity [56, 57].

5. The ability to adapt: due to their nature, bacteriophages can quickly adapt to changing conditions and bacterial mutations, remaining effective despite resistant bacterial mutants [58, 59].

6. Convenience of use: modern research allows for development of convenient forms of bacteriophage-based preparations, such as ointments, creams, and gels, which are easy to use in clinical practice.

However, there are also disadvantages to using phage therapy [60]:

1. Specificity to bacteria. Phages have high specificity for certain strains of bacteria, which requires identifying and selecting the appropriate phage for each specific case of infection. This can complicate the treatment process, as different patients may require different phage preparations.

2. Development of bacterial resistance. Bacteria can develop resistance to phages, analogous to their development of antibiotic resistance. Although it happens less frequently than the development of resistance to antibiotics, this challenge still requires attention.

3. Immune response. The use of phages can stimulate the human immune system to produce neutralizing antibodies, which may reduce the effectiveness of therapy. It is especially critical when therapy extends over a prolonged period.

4. The need for extensive libraries of diverse bacteriophages. Successful phage therapy requires well-characterized libraries of phages ready for use. Developing and maintaining such libraries requires significant resources and effort.

5. Regulatory restrictions. In numerous countries, there are strict regulatory barriers to the approval of phage therapy, which slows down its implementation in medical practice.

Separately, the debatable issue of the possibility of the participation of bacteriophages in the transfer of antibiotic resistance genes should be noted. Modern research shows that phages can have various effects on bacteria, contributing to both the development of sensitivity and the formation of antibiotic resistance. One of the possible mechanisms is the horizontal transfer of genetic material containing antibiotic resistance genes (ARGs) by transduction [61]. The use of cocktails containing lytic phages, their clinical efficacy, confirmed by cytomorphological analysis, the administration of bacteriophage drugs after receiving phagogram results, and the certification of phages with their sequencing, make it possible to minimize the possibility of this phenomenon. At the same time, the availability of data in the literature indicating the potential role of phages in the spread of antibiotic resistance requires further research.

Despite these promising results and advantages, as well as the disadvantages of using bacteriophages (the need for refrigerated storage, frequent dosing), additional randomized clinical trials are needed to fully establish the effectiveness and safety of phage therapy [56].

Classification and morphology of bacteriophages

Based on their life cycle bacteriophages can be classified as either lytic or lysogenic. Lytic (virulent) phages: after infecting a bacterium, these phages multiply rapidly and eliminate (lyse) the host cell, releasing new phage particles [60]. This process is called the lytic cycle.

Lysogenic (temperate) phages — these phage particles integrate their genetic material into the genome of the host bacterium and remain there in a latent state until conditions become favorable for transitioning to the lytic cycle [62]. Unlike lytic phages, lysogenic phages integrate their nucleic acid into the genome of the bacterial host. The phage genome can consist of DNA (double-stranded or single-stranded) or RNA (also double-stranded or single-stranded) [63].

In the review article by Liang Huang and Ye Xiang bacteriophages that infect gram-positive bacteria exhibit various morphological characteristics depending on their tail appendages type: podoviruses have short non-contractile tails, siphoviruses have long non-contractile tails, and myoviruses have long contractile tails [64]. These differences in morphology are associated with adaptation to specific conditions for infecting and penetrating host cells. The main structural components of bacteriophages include the capsid, which protects the genetic material, and the tail apparatus, which plays a primary role in the infection process by allowing the virus to attach to the cell wall and membrane of the host and deliver its genetic material into the cell. An important element is also the connector, which joins the head of the capsid to the tail and performs several functions, including initiating capsid assembly, holding the packaged genome, and mediating tail assembly. The process of infecting a cell with a bacteriophage occurs with the virus recognizing and attaching to the surface of the host cell via special receptors. The virus then injects its genetic material into the cytoplasm of the cell, leaving the empty capsid outside. Inside the cell, the viral genetic material is used to synthesize viral proteins and replicate the viral genome. The assembled viral components merge to form new viral particles. In the final stage, the progeny virions exit by lysing the cell or by budding from its membrane, preserving cell viability and perpetuating infection

Phage delivery methods

There are several main methods for delivering bacteriophages [65]:

1. *Oral administration*

Oral administration is one of the most common methods for delivering bacteriophages. This method is used to treat gastrointestinal infections and various systemic diseases. A major challenge is that the acidity of the stomach can eliminate the phages, therefore it is necessary to develop special protective coatings or capsules to increase their stability [66].

2. *Topical administration*

Topical use of bacteriophages includes the application of ointments, creams, gels, or sprays to treat skin infections, wounds, ulcers, and other superficial lesions [67]. This method allows phages to be delivered directly to the site of infection, bypassing the gastrointestinal tract.

3. *Parenteral administration*

Systemic delivery involves intravenous, intramuscular, or subcutaneous administration of bacteriophages [52]. This method is used to treat more severe infections, when rapid distribution of phages throughout the body is required. However, it necessitates a high degree of purification of the preparations and consideration of possible immune reactions of the organism.

4. *Inhalation*

Inhalation is used to deliver phages to the respiratory tract, especially in the treatment of respiratory infections [68]. This method allows for quick delivery of phages to the site of infection, but it requires special equipment and preparation of the phage solution.

Immune response to phage therapy

When a foreign agent (antigen) enters the body, the immune system of humans and animals initiates the process of synthesizing specific protective proteins — antibodies (immunoglobulins). This adaptive response plays a primary role in protecting the body from pathogenic microorganisms and toxic substances. However, the high variability of potential threats determines the ability of the immune system to respond not only to pathogens, but also to other agents, including non-pathogenic microorganisms such as bacteriophages [69].

In the book section “Phage as a Modulator of Immune Responses: Practical Implications for Phage Therapy”, Andrzej Górski describes fundamental research on the interaction between bacteriophages and immune system cells and their potential applications, particularly in the field of phage therapy [70]. Two main aspects of these interactions are considered:

1. The immunogenicity of bacteriophages. The ability of bacteriophages to elicit specific immune responses, including the production of antibodies against viral antigens. The mechanisms of this process and its potential consequences for the effectiveness of phage therapy are being investigated;

2. The immunomodulatory activity of bacteriophages. The indirect effects of bacteriophages on the functions of immune system cells, such as phagocytosis, cytokine production, and the proliferation of T and B cells. These studies provide a valuable insight on how bacteriophages can influence the course of infections and the effectiveness of treatment.

The leading aspects of immunogenicity include antibody production and cellular immune response. Regarding the former, bacteriophages can stimulate the body to produce antibodies that specifically recognize and neutralize phage particles. This can significantly limit the effectiveness of phage therapy, as antibodies can bind to phages and interfere with their interaction with bacteria. As for the cellular immune response, there is less data on the cellular response to bacteriophages, but there is evidence that phages can trigger cellular reactions similar to those observed during viral infections. For instance, they can stimulate the proliferation of T lymphocytes and other immune system cells. Bacteriophages can also affect immune system cells by altering their functions. Phages can influence the ability of macrophages and neutrophils to ingest and eliminate pathogens. Various studies show that phages can either enhance or suppress phagocytosis depending on the experimental conditions. Bacteriophages can affect the synthesis of various cytokines, such as interferons and interleukins, which can influence the overall course of infection and inflammation.

There is evidence that phages can modulate the proliferation and function of lymphocytes, which can have both positive and negative effects on the immune response. Thus, bacteriophages assume dual immunomodulatory functions in interactions with the mammalian immune system. On the one hand, they elicit specific immune responses, including the production of antibodies and cellular reactions, which can limit their therapeutic effectiveness. On the other hand, bacteriophages can modulate the functions of immune cells, such as macrophages and lymphocytes, influencing phagocytosis, cytokine production, and cell proliferation, which exhibits the potential to create new therapeutic strategies. However, when using phages therapeutically in patients, the expected formation of antibodies was not always observed, or proved to not enhance the effectiveness of the phages in combating bacterial infection [71–73].

Bacteriophages, as viruses that infect bacteria, can be used for creating vaccines and therapy due to their ability to interact with the immune system [74]. Phage-based vaccines use phage display technology, which allows antigens to be attached to phage capsids, stimulating an immune response. Additionally, bacteriophages can serve as carriers of epitopes, which are small antigen fragments recognized by the immune system. In a therapeutic context, bacteriophages are used to eliminate pathogenic bacteria in phage therapy, particularly effective against antibiotic-resistant infections. Moreover, bacteriophages can enhance the immune response by stimulating phagocytosis and the activation of T lymphocytes. Despite the advantages of high specificity and low toxicity, there are risks associated with possible allergic reactions and the development of resistance in bacteria. This requires further research and optimization for safe and effective use.

Chronic wounds

Chronic wounds are tissue injuries in which the healing process is disrupted, and they do not achieve complete anatomical and functional integrity [52]. Such wounds are often associated with vascular, endocrine disorders, or prolonged mechanical pressure. The challenge related to chronic wounds is relevant for global healthcare, as it affects significant segments of the population. According to various estimates, 1 to 2% of the population in developed countries experience chronic wounds at certain point in their lives [75]. The incidence of chronic wounds is increasing, which is due to the ageing population, the rise in obesity and the associated risk of developing diabetes mellitus. Chronic wounds negatively affect the quality of life of the patient and their environment, leading to pain, reduced functional activity, psychoemotional disorders such as stress, anxiety and depression, as well as social isolation.

Wound healing

Wound healing is a complex and carefully regulated process that plays a leading role in maintaining the barrier function of the skin and its other functions. This process can be influenced by various factors, both modifiable and non-modifiable, and includes several phases, each with its own characteristics and potential complications. The skin is the largest organ in the human body; it acts as a waterproof mechanical barrier between the organism and the environment, thereby preventing the loss of various biological components of the organism and providing protection against external aggressive factors [76]. The skin is often subjected to various injuries of chemical, physical, or mechanical origin. After any such impact, the wound healing process occurs immediately, consisting of four consecutive phases and lasting a certain amount of time.

The wound healing process includes the following phases: hemostasis, inflammation, proliferation, and remodeling. These phases can overlap and occur simultaneously, requiring a comprehensive approach to treatment to ensure that the healing process is not interrupted and proceeds without complications [77–79].

1. Hemostasis. During hemostasis, vasoconstriction occurs, platelets aggregate, and a thrombus (fibrin clot) is formed, which restores the protective properties of the skin and maintains its structural integrity. Fibrin also promotes cell migration to the site of injury and stimulates the proliferative activity of fibroblasts [80, 81].

2. Inflammation. The inflammation phase occurs immediately after the skin is injured, initiating healing processes. The inflammation phase lasts approximately 4–6 days, during which neutrophils, monocytes, and lymphocytes migrate to the damaged area. Monocytes differentiate into macrophages, which engage in phagocytosis and secrete reactive oxygen species, cytokines, and a spectrum of mediators that drive angiogenesis, inflammation, and fibrosis [52, 81–83].

3. Proliferation. During the proliferation phase, primary processes such as angiogenesis, synthesis of connective tissue (fibroplasia), and re-epithelialization occur [52, 77, 84, 85]. During this stage, granulation tissue forms, filling the wound cavity. Fibroblasts are activated and acquire the ability to contract, thereby promoting the approximation of the wound edges. Simultaneously, migration and proliferation of keratinocytes surrounding the wound edges occur, leading to the closure of the affected area.

4. Tissue remodeling. This is the final stage of the healing process, which occurs several weeks after the injury and can last up to one year [86]. During this period, the newly formed tissue undergoes restructuring and strengthening, which ultimately leads to the formation of a scar. Scar tissue generally exhibits greater thickness and lower elasticity compared to the original skin [76].

Impaired wound healing

Wound healing disorders are a complex issue associated with numerous factors, both local and systemic. The main factors affecting wound healing include: infectious agents, occurrence of biofilms in the wound, systemic diseases, and the impact of medications.

- Infections: bacterial agents, especially bacteria of the genera *Proteus* and *Pseudomonas*, significantly slows down the wound healing process [87].
- Hypoxia and inflammation: chronic wounds are characterized by persistent inflammation and, as a rule, bacterial biofilms, which complicate healing and prolong the transition to the proliferation phase of the wound process [88];

- Wound size: greater depth, complex topography, and larger wound dimensions correlate with an increase in the duration of the healing process [87];
- Type I and II diabetes mellitus: impaired wound healing in patients with diabetes mellitus is a significant clinical complication associated with complex pathophysiological mechanisms. Hyperglycemia, characterized by elevated plasma glucose levels, promotes the formation of bacterial biofilms and impedes the effectiveness of treatment measures. Chronic inflammation and polymicrobial infections also significantly impede normal tissue regeneration. Additionally, reduced angiogenesis activity, expressed as decreased formation of new blood vessels, impairs the recovery processes. Dysfunction of fibroblasts, which play a primary role in healing, exacerbates these impairments. The combination of these factors leads to significant difficulties in wound healing in diabetic patients [89–92].
- Clinically significant atherosclerosis is a major systemic factor affecting wound healing [87]. Atherosclerotic changes in blood vessels impede the wound healing process due to impaired vascular function and a chronic inflammatory response. These factors contribute to reduced angiogenesis and cell proliferation, which impairs the regeneration processes [93–95];
- Medications: numerous drugs, such as chemotherapy agents and immunosuppressants, non-steroidal anti-inflammatory drugs, as well as certain antibacterial drugs, can have a negative impact on wound healing [96].

Other factors contributing to impaired wound healing include age, poor nutrition, chronic diseases, immune dysregulation, and genetic aberrations [88,97–99].

Microorganisms in wounds

Microorganisms present in chronic wounds significantly impact the delay in the healing process. The spread of bacterial infection in a wound can impede the immune response. Evidence of bacteria in a wound goes through various stages, from initial contamination to colonization by microorganisms. With prolonged presence of bacterial agents, bacterial biofilms form, leading to critical colonization. This stage is often accompanied by an unpleasant odor. Surrounding tissues may also become infected, leading to deep or systemic infections [86].

Exposed subcutaneous fat, necrotic tissue within wounds of diverse etiology, and a weakened immune system of the patient provide optimal conditions for the colonization and growth of microorganisms in the wound [100]. Contamination by bacterial agents occurs through endogenous pathways and directly from the surrounding skin [101].

The most common bacteria found in chronic wounds are *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, and Klebsiella pneumoniae*. These microorganisms can cause both mono-infections and polymicrobial infections, which complicates treatment [102–104].

Bacteriophages in surgery

Bacteriophages have found application in various fields of surgery: cardiothoracic, abdominal, purulent, traumatology, and orthopaedics. Phage therapy has shown its effectiveness in treating infections associated with cardiothoracic surgery, especially in cases where traditional antibiotic therapy is unsuccessful. According to a study by E. Rubalskii et al., eight patients with infections caused by antibiotic-resistant bacteria were successfully treated with phages. It was noted that the target bacteria were eliminated in seven out of eight patients without serious side effects [105]. In cardiosurgical practice, infections of vascular grafts are one of the significant problems due to the difficulties in therapy and the high mortality rate. Bacteriophages can be used both for the prevention and treatment of these infections, and both monotherapy and a combined approach with antibiotics are possible. However, the successful phage therapy implementation requires standardization of methods for delivering bacteriophages to the site of infection, which will allow achieving the necessary local concentration and minimize the systemic spread of phage agents [106]. The use of combined therapy with bacteriophages and antibacterial drugs during surgical treatment of affected tissue areas is also of interest. For instance, in a clinical observation by K. Racenis et al., a positive clinical effect was achieved using a combined therapeutic approach, specifically the use of the synergy between a bacteriophage and an antibiotic along with surgical intervention in a patient with a left ventricular assist device (LVAD) and recurrent infection with multidrug-resistant *P. aeruginosa* [107]. A systematic review demonstrated the safety and effectiveness of phage therapy in treating infectious complications in cardiac surgery. In the analyzed clinical studies involving 40 patients, 70.3% achieved complete resolution of the infectious process, while 10.8% showed significant improvement. Adverse events associated with the use of phages were minimal and had no direct connection with the therapeutic agent itself [108].

Data demonstrate that the use of polyvalent bacteriophages in the treatment of postoperative purulent-inflammatory complications in emergency abdominal surgery can reduce the development of antibiotic-resistant strains and the risk of nosocomial microbial associations, as well as reduce the number of postoperative complications [109]. In his dissertation research, A.N. Morozov's describes that the use of bacteriophages in the perioperative period during laparoscopic appendectomy leads to a significant reduction in the number of postoperative complications and an improvement in the quality of life for patients [110]. Animal experiments and clinical trials have demonstrated that bacteriophages contribute to faster tissue recovery and a reduction in inflammatory processes compared to traditional antibiotic therapy. Additionally, patients treated with bacteriophages exhibited lower levels of leukocytes and C-reactive protein, as well as more stable temperature readings in the surgical area, indicating the benefits of their use in surgical practice.

Bacteriophages are also becoming a promising tool in the treatment of infections in traumatology, especially in cases of antibiotic resistance. A clinical observation by T. Ferry et al. describes a case of successful use of personalized phage therapy in a patient with a recurrent infection of a knee joint prosthesis caused by a multidrug-resistant strain of *P. aeruginosa* is described [111]. In E.A. Fedorov's dissertation research phage therapy is considered a primary element in improving the outcomes of treatment for deep periprosthetic infection [112]. The study showed that phage therapy offers several potential advantages compared to traditional antibiotic treatment methods. Bacteriophages are able to penetrate the exopolysaccharide matrix of biofilms, destroying bacteria within the biofilm, which makes them effective against antibiotic-resistant bacteria. Additionally, bacteriophages can be successfully impregnated into polymethyl methacrylate (bone cement) used in endoprosthetics.

The author concluded that the use of bacteriophages in combination with antibiotics led to a significant improvement in the treatment outcomes for deep periprosthetic infections of staphylococcal etiology. In the group where phage therapy was used, the treatment effectiveness was 95.5%, while in the comparison group it was only 69.0%.

Surgical treatment of purulent wounds. Bacteriophages in the treatment of wounds and wound infections

In the fundamental work Wounds and Wound Infections by M.I. Kuzin and B.M. Kostyuchenok, a method of active surgical treatment of wounds and wound infection is described which remains relevant to this day [113]. The most important method and the gold standard for treating purulent wounds of various etiologies and locations is the surgical treatment of the purulent focus, aimed at removing all necrotic and non-viable tissues and preparing the wound bed for healing. This is confirmed by numerous articles and literature reviews of recent years [114–117].

The goal of surgical treatment of a purulent-necrotic focus is to ensure wide access, its adequate drainage, removal of nonviable tissue that harbors infection, and prevention of its further spread. The main surgical technique is the radical excision of necrotic tissue. Effective surgical management requires halting infection spread along the anatomical planes of subcutaneous tissue, fascial layers, tendon sheaths, and intermuscular compartments. The approach should be anatomical and low-traumatic, providing a good view of the wound and freedom for surgical manipulations [113]. The preferred surgical corridor follows the most direct route to the infection focus. However, in various situations, utilization of a minimally invasive (remote) approach is essential to preserve critical neurovascular bundles, internal organs, joint capsules, and serous membranes.

Surgical intervention should be performed promptly upon confirmed diagnosis. In cases of extensive areas of damage, staged surgical treatments and necrectomy procedures may be required.

Currently, alternative and additional methods of influencing the wound process are being introduced and widely used, such as the use of biological antibacterial drugs (phage therapy), as well as physical methods of treatment, for instance, ultrasonic cavitation, local negative pressure wound therapy (NPWT), plasma flows, ozone therapy, etc [118].

NPWT is used to treat various types of acute and chronic wounds, including ulcers, surgical infections, and complex injuries. It facilitates wound repair via multiple fundamental mechanisms: improving blood circulation by opening the capillary segment of the microcirculatory bed, which subsequently enhances redox processes in the wound [119]. Additionally, it involves macrodeformation of tissues, drainage of extracellular inflammatory fluids, stabilization of the wound environment, and microdeformation of the wound bed [120].

Research on the use of bacteriophages in surgery has been conducted for an extensive period of time, indicating increased effectiveness when applied in surgical practice. In his dissertation, R.N. Islamov concluded that a polyvalent bacteriophage is effective in vitro, suppressing the growth of the most relevant microorganisms causing nosocomial purulent-septic complications [121]. The introduction of bacteriophages into the preoperative prevention regimen for surgical infections contributes to a significant reduction in the number of suppurations of the surgical wound and extrawound complications.

In R.S. Sufiyarov's dissertation, it is primarily noted that complex surgical treatment using enzyme preparations and a polyvalent pyobacteriophage shows better results compared to traditional methods [122]. The use of the proposed methods leads to a reduction in the average length of stay of patients in the hospital and a decrease in the number of postoperative complications.

We have presented our experience with treating wounds using negative pressure therapy with instillation of a polyvalent bacteriophage after radical surgical treatment of the purulent focus. The advantages of vacuum therapy have been described above. Recent studies demonstrate that instillation-enhanced NPWT achieves superior healing outcomes compared with standard NPWT. In an observational study, H. Duan et al. describe that a vacuum system with instillation effectively removes remnants of necrotic tissue, promotes wound healing, and controls infection in patients with necrotizing soft tissue infection [123]. In a clinical observation, J. Kilo et al. describe a patient with a severe purulent complication after implantation of a left ventricular assist device (LVAD) is described [124]. For local wound treatment, the local negative pressure therapy with instillation method was successfully applied, showing durable therapeutic success. In a large clinical study, V.A. Potapov describes a method for using a combined vacuum-assisted dressing with oral administration and local irrigation with bacteriophage solutions in patients with deep sternal infection [125]. The authors of the article obtained better results compared to traditional methods, especially in the presence of multidrug-resistant microorganisms.

The first publication documenting successful use of negative pressure therapy with bacteriophage instillation was a clinical observation by V.A. Mitish et al [126]. The article presents a clinical observation of complex surgical treatment of a patient with rheumatoid arthritis and a long-term non-healing wound in the right gluteal region, which formed after surgical treatment of a post-injection abscess. The successful use of a domestic negative pressure device with the ability to instill is noted, indicating sustained clinical benefits. In this clinical observation, all the advantages of using vacuum wound therapy were demonstrated, confirmed by cytological and microbiological examinations at all stages of treatment.

Conclusion

Antibiotic resistance represents one of the most urgent threats to public health, requiring an immediate search for alternative treatments for bacterial infections. Bacteriophages represent a promising alternative to antibiotics due to their unique properties.

Bacteriophages exhibit high specificity, allowing them to effectively eliminate pathogenic bacteria while minimizing the impact on beneficial microbial flora. Their ability to adapt to changes in bacterial structure and resistance to antibiotics offers broad opportunities for combating multidrug-resistant infections. Modern advances in molecular biology and biotechnology significantly improve the understanding of the mechanisms of interaction between bacteriophages and bacteria, paving the way for next-generation therapeutic strategies.

However, despite significant advantages, the use of bacteriophages faces certain challenges, including the requirement for personalized phage selection on a per-patient basis for each patient, the possible development of resistance in bacteria, and regulatory barriers. To integrate phage therapy into routine clinical care, further research is required to confirm the safety and effectiveness of this method, as well as to streamline regulatory pathways for its authorization.

In conclusion, bacteriophages represent an important tool in the fight against antibiotic resistance, and their potential deserves close attention from the scientific and medical communities.

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Бактериофаги: альтернатива антибиотикам в эпоху антибиотикорезистентности

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Аннотация. Антибиотикорезистентность представляет собой одну из наиболее острых глобальных проблем здравоохранения, обусловленную широким и часто нерациональным применением антибиотиков, а также эволюционно закрепленными механизмами адаптации бактерий. По оценкам, к 2050 г. ежегодно из-за устойчивости к противомикробным препаратам будет умирать до 10 млн человек, что требует срочного поиска новых терапевтических стратегий. В этом контексте бактериофаги — вирусы, специфически инфицирующие бактерии — выступают многообещающей альтернативой антибиотикам. В обзоре анализируются ключевые механизмы развития антибиотикорезистентности, включая инактивацию препаратов β-лактамазами, работу эффлюксных насосов, модификацию мишеней и горизонтальный перенос генов, а также особое значение группы ESKAPE патогенов в клинической практике. Рассмотрены классификация фагов на литические и лизогенные, их морфологические особенности и жизненные циклы. Особое внимание уделено современным методам доставки фагов (перорально, местно, парентерально, ингаляционно) и взаимодействию фаговой терапии с иммунной системой хозяина, включая продуцирование антител и иммуномодулирующие эффекты на макрофаги, нейтрофилы и лимфоциты. Отдельный раздел посвящен практическому применению фаготерапии в хирургии и лечении хронических ран: описаны результаты клинических наблюдений в кардиоторакальной, абдоминальной и ортопедической хирургии, применения фагов в сочетании с антибиотиками, а также внедрение вакуум-ассистированной терапии с инстилляцией бактериофагов, что демонстрирует ускорение заживления, снижение микробной обсемененности и количества послеоперационных осложнений. *Выводы.* Таким образом, терапия бактриофагами обладает рядом преимуществ — высокой специфичностью, эффективностью против мультирезистентных штаммов, возможностью сочетания с антибиотиками и минимальным уровнем побочных эффектов. Вместе с тем ее широкое клиническое внедрение требует решения задач по стандартизации производства фаговых препаратов, созданию централизованных фагобанков, отработке алгоритмов подбора штаммов для персонализированной терапии и преодолению регуляторных барьеров. Дальнейшие рандомизированные клинические исследования и разработка нормативно-правовой базы необходимы для полноценного использования фагов как эффективного инструмента в борьбе с антибиотикорезистентностью.

Ключевые слова: Антибиотикорезистентность, бактериофаги, альтернатива антибиотикам, лечение хронических ран, хирургия, гнойная хирургия, фаготерапия, мультирезистентные инфекции

Информация о финансировании. Авторы заявляют об отсутствии финансовой поддержки и спонсорской помощи при проведении данного исследования.

Вклад авторов. Г.В. Хамидулин — формулировка целей, разработка исследования, обзор литературы, критический анализ научных источников, написание, редактирование и утверждение окончательной версии рукописи. Ю.С. Пасхалова — сбор и систематизация научных данных, анализ современных подходов к использованию бактериофагов, подготовка разделов по классификации фагов и механизмам действия; критическая доработка рукописи. В.А. Митиш — анализ современных методов диагностики и лечения хронических ран, оценка эффективности фаготерапии при гнойных ранах, обзор клинических исследований по применению бактериофагов. А.А. Ушаков — поиск литературы, отбор соответствующих научных публикаций, подготовка раздела о механизмах развития антибиотикорезистентности и их клинических последствиях. С.А. Оруджева — анализ микробиологических данных, систематизация информации о классификации и морфологии бактериофагов. С.Д. Магомедова — оценка научной достоверности представленных данных и проверка соответствия стандартам научной публикации. В.К. Бораненков — редактирование рукописи. Все авторы внесли значительный вклад в подготовку рукописи, прочитали и утвердили окончательную версию перед публикацией.

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