COMBINATION OF BACTERIOPHAGES AND ANTIBIOTICS AS THE MOST EFFECTIVE THERAPY AGAINST *STAPHYLOCOCCUS AUREUS*

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Staphylococcus aureus is a bacterial pathogen that is frequently associated with drug resistance and causes serious infectious diseases. The challenge in treating staphylococcal infections arises not only from the strains resistance to antibacterial drugs but also from the bacteria's capacity to form biofilms. As an alternative to traditional antibiotic therapy, phage therapy, employing virulent bacteriophages, is being explored. Research on bacteriophage's effectiveness against *S. aureus* encompasses both individual use and their combination with antibiotics. The combined approach appears most promising, enhancing therapeutic efficacy substantially through the synergistic action of both the antibiotic and the phage. This review discusses the effects of using both agents together and the methodologies for their evaluation. It summarizes the latest *in vitro* and *in vivo* research on the combined approach against *S. aureus*, including experiments focused on biofilm elimination. Special emphasis is placed on clinical case studies in treating patients.

Keywords: Bacteriophages, *Staphylococcus aureus*, phage therapy, bacteriophage therapy, combination therapy, antibiotics, multidrug resistance, biofilms, synergy between antibiotics and bacteriophages

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КОМБИНАЦИЯ БАКТЕРИОФАГОВ И АНТИБИОТИКОВ КАК НАИБОЛЕЕ ЭФФЕКТИВНЫЙ ПОДХОД БОРЬБЫ СО *STAPHYLOCOCCUS AUREUS*

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Staphylococcus aureus — бактериальный патоген, обладающий способностью к развитию антибиотикорезистентности и вызывающий ряд серьезных инфекций. Проблема терапии стафилококковых инфекций связана не только с устойчивостью штаммов к антибактериальным препаратам, но и со способностью бактерий формировать биопленки. Как альтернатива классической антибиотикотерапии рассматривается фаготерапия — использование вирулентных бактериофагов. Исследования, демонстрирующие действие бактериофагов против *S. aureus*, включают как отдельное использование фагов, так и их комбинацию с антибиотиками. Комбинированный подход представляется наиболее перспективным, так как позволяет значительно повысить эффективность терапии за счет синергического действия антибиотика и фага. В данном обзоре представлено обсуждение эффектов совместного применения двух агентов и методов их оценки. Обобщены результаты последних работ, посвященных комбинированному подходу против *S. aureus* в исследованиях *in vitro* и *in vivo*, а также в экспериментах по элиминации биопленки. Отдельное внимание уделено клиническим случаям лечения пациентов.

Ключевые слова: бактериофаги, *Staphylococcus aureus*, фаговая терапия, бактериофаговая терапия, комбинированная терапия, антибиотики, множественная лекарственная устойчивость, биопленки, синергизм антибиотиков и бактериофагов

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Staphylococcus aureus is a gram-positive microorganism that is one of the main pathogens for human beings causing a wide range of clinical manifestations. This type of bacteria is the main cause of bacteremia and infective endocarditis, bone and joint infections, skin and soft tissue lesions, pleuropulmonary infections and infections associated with use of medical devices. *Staphylococcal infections* are prevalent both in the general population and in hospital settings; their treatment is a challenging task because of the spread of multidrug-resistant (MDR) strains. Previous studies have shown that Staphylococcus aureus ranks second after *E. coli* as a cause of death associated with bacteria insusceptible to antibiotics [1].

Strains of *S. aureus* implement various mechanisms of antibiotic resistance. One of them involves synthesis of beta-lactamase enzymes and production of the Rvp2A protein, an alternative transpeptidase [2, 3]. The latter grants protection from natural and synthetic betalactams; the respective evolution yielded a clinically important group of resistant strains called MRSA (methicillin resistant *Staphylococcus aureus*). Against vancomycin, *S. aureus* can build a thick cell wall that prevents

penetration of the antibiotic [4]. Resistance to aminoglycosides is ensured by rRNA methyltransferase and other enzymes that modify such drugs. Tetracycline-resistant strains often have protective ribosome proteins TetM and TetO [5]. In case of linezolid, *S. aureus* modifies the target sought by this antibiotic, such modification enabled by the spread of mutant variants of the 23S rRNA gene [6]. Efflux pumps play an important role in the development of antibiotic resistance of *Staphylococcus aureus*. Some of them are substrate-specific, like Tet(K) and Tet(L) efflux systems [7]. Others, on the contrary, can recognize and export a wide range of drugs. In *S. aureus*, the latter are membrane proteins from several families: ABC (ATP-binding cassette), MATE (multidrug and toxin extrusion), MFS (major facilitator superfamily), SMR (small multidrug resistance), and RND (resistance-nodulation-cell division) [8]. Moreover, *S. aureus* can build biofilms, cellular aggregates preventing antibiotic molecules from reaching cells. Biofilms also facilitate colonization of various surfaces by *Staphylococcus aureus*, which underpins infections associated with medical devices [9].

In recent years, to effectively treat infections caused by multidrug resistant (MDR) strains, there have been developed alternative approaches, including phage therapy. Bacteriophages (phages) are viruses capable of infecting bacterial cells. Compared to antibiotics, they offer a number of advantages [10]: bacteriophages are highly specific, i.e., there is no risk of disruption of the normal flora nor their self-replication, and they are highly likely to reach the focus of infection; the mechanism of action of bacteriophages, as a rule, is different from that of antibiotics, which makes them effective against antibiotic-resistant strains; another important advantage is the relative simplicity of bacteriophage isolation and subsequent production of the medicines based on them [11].

Despite the potential for bacteriophages to replace conventional antibiotics, several challenges hinder their widespread use in clinical practice. The main barriers have to do with bacteriophage registration and application: the former is a complex and costly process, the latter lacks approved protocols [12]. Other factors that should be mentioned in this context is the bacteria's potential to develop resistance to phages, and their strain specificity, i.e., a narrow range of action [13].

Use of bacteriophages in combination with antibiotics is one of the main ways of their introduction to therapy regimens considered. Currently, many in vitro experiments and clinical studies show efficacy of simultaneous action of these two agents [14, 15]. According to a number of experts, such an approach should significantly simplify registration and patenting of the medicines significantly [16]. Moreover, a combination of two agents with different action patterns can be relevant against MDR strains [11].

This work aims to review the current results of research analyzing treatment of infections caused by *S. aureus* with the help of bacteriophages, alone and in combinations with antibiotics. Below, we look into both *in vitro* and *in vivo* (animal model) studies investigating the effectiveness of phage-antibiotic pairs, and present the results of works experimenting with such pairs as means against biofilms of *S. aureus*, as well as components of complex therapy regimen designed to combat infections caused by the bacteria.

Results of combined use of bacteriophages and antibiotics and methods of their assessment

The efficacy of combination of antibiotics and lytic bacteriophages was first demonstrated in 1941, when the phages were used in combination with sulfonamide preparations against *S. aureus* and *Escherichia coli* [17]. Later, an animal study confirmed positive effects of the combination [18]. Similar results were achieved for the phage and penicillin pair [19]. Combined therapy was successful against infectious diseases like endocarditis, bacteremia, osteomyelitis, and peritonitis [18, 20].

The term "synergism" ("synergistic effect") was introduced much later, only in 2007. A group of researchers has described enlargement of *E. coli* culture lysis zones when targeted by a bacteriophage augmented by sub-inhibitory concentrations of antibiotics (aztreonam, cefotaxime, ticarcillin, piperacillin, ampicillin, nalidixic acid, mitomycin C) [21]. The main explanation for the observed phenomenon was the increased production of bacteriophage particles due to abnormal growth of bacterial cells in the presence of antibiotics. Over time, the term "synergy" has acquired a broader meaning. In particular, the term became applicable to cases when the effectiveness of a phage and antibiotic combination significantly exceeds the sum of their individual effects [15, 16]. Some authors began to introduce additional terminology around positive effects of such combined therapy. For example, in one study, they are divided into an additive effect, synergism, and facilitation, with the first of these understood as resulting in cell growth arrest enabled by the two agents that equals the sum of the effects of each component individually, the second as a stronger version of the first, and the third as the combination having the bacterial growth suppression effect significantly more pronounced that that achievable with the most effective agent alone, but still weaker than the additive effect [15]. The same study also describes the neutral effect of the combined therapy, when a combination's action is as strong as that of its most potent component, and antagonism, when such therapy is less effective than individual use of the agents [15].

The growing interest in combination therapy yielded a variety of laboratory methods designed to assess its effectiveness. In the first works on the subject, the parameter measured was the diameter of plaque size caused by the phage in combination with a sub-inhibitory concentration of an antibiotic [21]. Currently, this traditional approach is still practiced [22]. but the more common methods nowadays aim to measure optical density of the cells infected with antibacterial agents, one of them or both [13, 15]. The suppressive effect is appraised through calculation of the areas under growth curves or by evaluating optical density of the culture after 16–24 hours [13, 15]. This approach is popular because of the clarity and experimental convenience. Colorimetric measurements aimed at estimating the number of living cells (including biofilms) after treatment with antibacterial agents are less common [23, 24]. There was developed an experimental system of continuous cultivation that allows registering pharmacodynamics of the process in addition to revealing the efficacy of combined therapy [25]. A group of researchers has described an isothermal microcalorimetry method for assessing the effects of phages and antibiotics on bacterial biofilm [26]. In the context of in vivo studies employing animal models, the controlled parameters are survival, bacterial load, duration of the infection process, size of the lesion (edema), histopathological indicators, etc. [27–29].

Thus, the increased interest in the joint use of bacteriophages and antibiotics has ushered introduction of the new terms describing the respective effects, and a number of methods were adjusted to the purpose of studying the combined approach.

Combined use of bacteriophages and antibiotics against *S. aureus* in *in vitro* experiments

In *in vitro* experiments, bacteriophages were paired against *S. aureus* with virtually all commercially available

Table 1. *In vitro* studies of the effect of combined bacteriophages and antibiotics on *S. aureus* strains

Year	Phage	Family	Antibiotic	Result	Reference
2012	SA5	*Herelleviridae*	Gentamicin	Synergism	[25]
2018	SA11	*Herelleviridae*	Ampicillin, cefotaxime, kanamycin, tetracycline, ciprofloxacin, mitomycin C, sulfamethoxazole, trimethoprim	Synergism (ampicillin, cefotaxime, tetracycline, ciprofloxacin, mitomycin C, trimethoprim)	[32]
2020	Sb-1	*Herelleviridae*	Daptomycin, vancomycin, ceftaroline, cefazolin	Synergism	[33]
2021	Cocktail AB-SA01	*Herelleviridae*	Vancomycin, ceftaroline, cefazolin	Synergism (vancomycin, cefazolin)	[13]
2021	Henu2	Temperate unclassifiable	Clarithromycin, linezolid, cefotaxime, tetracycline, ciprofloxacin	Synergism	[31]
2021	PYOSa	*Herelleviridae*	Tetracycline, oxacillin, vancomycin, kanamycin, azithromycin, daptomycin, rifampin, linezolid, streptomycin	Antagonism (tetracycline, azithromycin, linezolid, vancomycin, daptomycin, kanamycin)	[34]
2021	Sb-1	*Herelleviridae*	Oxacillin	Synergism, additive effect, facilitation, antagonism	[15]
2022	φSA115, φSA116	*Herelleviridae*	Tetracycline, gentamicin	Antagonism	[22]
2022	vB_SauM-515A1	*Herelleviridae*	Oxacillin, vancomycin, gentamicin, tetracycline, levofloxacin, linezolid	Synergism (tetracycline, linezolid, oxacillin)	[14]
2023	vB_Sau_S90	Temperate unclassifiable	Fosfomycin, ciprofloxacin, vancomycin, oxacillin	Synergism	[35]

antibiotics: aminoglycoside (gentamicin), beta-lactam (oxacillin), glycopeptide (vancomycin), macrolide (clarithromycin), oxazolidinone (linezolid), tetracycline (tetracycline), cephalosporin (ceftaroline, cefazolin), cyclic peptides (daptomycin), etc. (Table 1). As a rule, this approach involves virulent bacteriophages of the Herelleviridae (formerly Myoviridae) and Rountreeviridae (formerly Podoviridae) families, with the former being the preferred option due to their extensive lytic capabilities (they can lyse 80–95% of strains) [30]. In some studies, researchers also use temperate bacteriophages, but only in the context of *in vitro* experiments [31].

As Table 1 shows, bactericidal and bacteriostatic drugs of various classes are included in experiments as antibiotics, and a significant number of studies consider the effect of vancomycin and oxacillin due to their clinical significance. For example, it has been shown that Sb-1 phage (*Herelleviridae* family) and vancomycin, combined, synergistically boost each other against VISA (vancomycin intermediate *S. aureus*) strains [33]. Moreover, the authors have found that use of two antibiotics of different classes (daptomycin or vancomycin with ceftaroline; daptomycin or vancomycin with cefazolin) with a bacteriophage also yields synergy. It should be noted that a trio of a phage and two different antibiotics does not have an effect significantly different from that of a phage-antibiotic pair provided this combination yields synergy. Henu2, a temperate bacteriophage, combined with vancomycin was observed to enhance inhibition of bacterial growth [31]. In a sample of 27 strains, it was shown that Sb-1 phage (*Herelleviridae* family) in combination with different concentrations of oxacillin, in most cases, boosts bacterial growth arrest through synergism, additive effect, and facilitation [15]. The researchers note that cases of antagonism, when phage and antibiotic weaken one another, were extremely rare. Similar results were registered for vB_SauM-515A1, a lytic bacteriophage: combined with oxacillin in certain concentrations, it improved the antibacterial effect, with no cases of antagonism seen in any of the the considered cases [14].

Table 2. Studies dedicated to combined therapy against *S. aureus* biofilms

Year	Phage	Family	Antibiotic	Result	Reference
2011	SAP-26	*Rountreeviridae*	Azithromycin, vancomycin, rifampicin	Synergism (rifampicin)	[23]
2014	MR-5	*Herelleviridae*	Linezolid	Synergism	[41]
2018	SATA-8505	*Herelleviridae*	Cefazolin, vancomycin, dicloxacillin, tetracycline, linezolid	Synergism (vancomycin, cefazolin) Antagonism (vancomycin, cefazolin, dicloxacillin, linezolid, tetracycline) Additive effect (dicloxacillin, cefazolin, tetracycline, linezolid)	[24]
2019	PYO	*Herelleviridae*	Ciprofloxacin, daptomycin, erythromycin, gentamicin, linezolid, oxacillin, tetracycline, vancomycin	Synergism (ciprofloxacin, tetracycline) Antagonism (ciprofloxacin, vancomycin, tetracycline, gentamicin, erythromycin, linezolid)	[16]
2020	Sb-1	*Herelleviridae*	Doxycycline, levofloxacin, linezolid, clindamycin, rifampin	Synergism	[26]
2023	Phage K	*Herelleviridae*	Vancomycin	Synergism	[42]
2023	vB_SauM_Remus	*Herelleviridae*	Vancomycin	Synergism	[43]

Table 3. Clinical cases and *in vivo* studies investigating combined therapy against *S. aureus* infection

Year	Phage	Family	Object	Infection	Antibiotic	Result	Reference
In vivo study							
2013	Sb-1	*Herelleviridae*	Rats	Implant-associated infection	Teicoplanin	Synergism	[46]
2013	MR-10	*Herellevirida*	Mice	Hind paw infections in mice with diabetes	Linezolid	Synergism	[27]
2019	2003, 2002, 3A, and K	Cocktail of phages of various families	Mice	Pneumonia	Teicoplanin	Neutral effect	[28]
2022	vB_SauH_2002, phage 66	*Herelleviridae, Rountreeviridae*	Mice	Endocarditis	Fluoxacillin	Synergism	[29]
2023	vB_SauM_ Remus	*Herelleviridae*	Larvae of Galleria mellonella	–	Vancomycin	Synergism	[43]
Clinical cases							
2019	Cocktail AB-SA01	*Herelleviridae*	–	Infectious endocarditis of a prosthetic valve	Fluoxacillin, ciprofloxacin, rifampicin	Patient recovery	[47]
2019	Cocktail AB-SA01	*Herelleviridae*	–	Infectious endocarditis associated with an auxiliary device in the left ventricle, complicated by sternal osteomyelitis and bacteremia	Cefazolin, minocycline	Patient recovery	[48]
2021	Cocktail AB-SA01	*Herelleviridae*	–	Infection in a prosthetic joint	Cefazolin	Patient recovery	[49]
2022	Mallokai	no data	–	Infection in a prosthetic joint	Daptomycin and ceftaroline	Patient recovery	[45]

The exact mechanisms underpinning the synergistic effect of combined use of phages and antibiotics against *S. aureus* strains are still unclear. Various hypotheses have been proposed to explain this phenomenon. One of them points to the increased production of phage particles in the presence of sublethal concentrations of an antibiotic, as suggested for tetracycline, linezolid, telithromycin, clarithromycin, cefotaxime and ciprofloxacin, which, in the respective experiments, expanded the lysis zones made by the phage, a probable marker of the said increased production of bacteriophage particles [31]. Another study demonstrated sublethal concentrations of antibiotics to cause *S. aureus* cells to swell, which, in some cases, was accompanied by increased production of bacteriophage SA11 (family *Herelleviridae*) [32]. According to the authors, this synergy relies on lysis delay caused by a lack of choline, which is necessary for cell lysis and further release of daughter viral particles. Another explanation for the synergistic effect mentioned antibiotic-induced overcoming of phage resistance, an effect registered for the combination of Sb-1 and vancomycin/daptomycin, which prevented development of resistance to bacteriophages [33]. In addition, an experiment staged in the continuous cultivation system has shown that gentamicin induces formation of cells with a phenotype prone to aggregation into conglomerates, which, in turn, are most sensitive to the phages [25].

Synergism was noted in a significantly greater number of publications than antagonism [15, 22, 34]. Some of them associate the latter with bacteriostatic antibiotics [22, 34], which seems quite reasonable, since bacteriostatic antibiotics are aimed at limiting reproduction and restraining activity of bacterial cells but lack the effect on the protein and nucleic acids biosynthesis systems that triggers death. It is possible, then, that bacteriophages may also be subjected to the said inhibitory effects. Additionally, it should be noted that antibiotics generally reduce the density of bacteria and thus the ability of the phage to replicate.

At the same time, there are noteworthy contradictions in research papers by different authors. On the one hand, some experiments confirm that the ultimate effect a combined phage therapy regimen is strain-specific, and the selection of phage itself is crucial for success [15]. On the other hand, it may be the concentration of the antibiotic that conditions the said effect, its magnitude, or lack thereof. For example, a combination of 10 mkg/ml of linezolid, a bacteriostatic antibiotic, and PYOSa (family *Herelleviridae*) produces an antagonistic effect [34], but at lower concentrations (1–2 mkg/ml) and with Henu2 phages (temperate, unclassifiable), there appears synergy [31], same as in a combination of vB_SauM-515A1 (family *Herelleviridae*) [14].

Thus, combination therapy has significant potential, and in most cases, simultaneous administration of bacteriophages and antibiotics does not reduce efficacy of the agents but has the potential to improve it. At the same time, it is obvious that there are many dimensions to such combinations and their applicability, and the ultimate effect depends on a number of parameters: concentrations of the drugs used, type of the antibiotic, and bacterial strain. A more comprehensive generalization of data requires additional studies investigating correlations between the above aspects, and, for example, factoring in strain typing data.

Combined effect of bacteriophages and antibiotics on *S. aureus* biofilms

Many strains of *S. aureus* can form biofilms, which are increasingly resistant to antimicrobial agents because of their complex spatial structure that mechanically prevents penetration of the antibiotic, and due to the changes in cell phenotype (emergence of slow-growing cells and persistent cells) [36]. Most clinical cases of *S. aureus* infections are associated with biofilms capable of colonization of surfaces of organs and medical devices [37–40].

Combined therapy employing bacteriophages and antibiotics aimed at *S. aureus* biofilms is a subject actively investigated currently (Table 2).

In case of treatment of biofilms, a crucially important factor is the sequence of administration of the agents. Combined

therapy has shown the best results when a bacteriophage is followed by an antibiotic. Presumably, the effectiveness of this approach rests upon the phage's ability to penetrate biofilm matrix and destroy it, which triggers release of planktonic cells and their subsequent destruction by both the phage and the antibiotic [23]. There are many studies that confirmed these findings [16, 24]. Moreover, not only the "phage — antibiotic" sequence (the former of family *Herelleviridae*, the latter vancomycin or cefazolin) was shown to be effective, but also lack of bactericidal results against a biofilm when the considered agents are used separately, and antagonism when the phage followed antibiotics (vancomycin, cefazolin, tetracycline, linezolid) [24]. Another study describes antagonism in cases of simultaneous administration of the agents (vancomycin or tetracycline with bacteriophage PYO (family *Herelleviridae*)), and synergism for most of the tested drugs when they follow the phage [16].

Sequential administration of a phage and an antibiotic was also shown to be effective against biofilms formed by two types of bacteria, *S. aureus* and *Pseudomonas aeruginosa*. For example, a combination of gentamicin (or ciprofloxacin) and a bacteriophage, the former following the latter, completely arrests growth of the biofilm [44]. The authors emphasized that high concentrations of antibiotics (8 MIC (minimum inhibitory concentration)) ensure best results. Classical antibiotic therapy aimed at biofilms also relies on high concentrations of antibiotics. A number of studies have demonstrated the need for such concentrations in combination with bacteriophages when the goal is to eliminate a biofilm [16, 22, 45]. There, concentrations of the antibiotic vary from 2 [16] to 250 MIC [43]. In addition, researchers have shown the dependence of the biofilm elimination effect on concentration of the antibiotic: the degree of biofilm suppression was directly proportional to the concentrations of linezolid and tetracycline and inversely proportional to the concentrations of vancomycin and cefazolin (up to 128 mkg/ml); in the case of other antibiotics (dicloxacillin and tetracycline), no obvious linear dependence was observed [24].

Biofilms are known to play a significant role in implant-associated infections. A group of authors have successfully used a combination of MR-5 (family *Herelleviridae*) and linezolid against biofilms on medical products and devices; they suggested coating orthopedic wires with hydroxypropylmethylcellulose, a polymer carrying mixture of the above agents. The approach not only ensured eradication of biofilms but also weakened adhesion of bacterial cells. In addition, this study showed that two agents used in conjunction decrease the frequency of formation of bacteriophage-resistant mutants [41].

Based on the above, it can be concluded that sequential administration of a bacteriophage and an antibiotic in high concentration ensures elimination of biofilms, and, moreover, a mixture of the two agents can be used together with a polymer coating of medical products and devices. These results can lay the foundation for development of the new approaches to application of implants and catheters.

Studies into combined use of bacteriophages and antibiotics on *S. aureus* infection models; clinical cases

The development of new therapeutic approaches requires confirmation of their effectiveness in animal models. Combinations of bacteriophages and antibiotics are tested on both vertebrates and invertebrates. In former, researchers create models of various infectious diseases, including implant-associated infections, pneumonia, endocarditis, and soft tissue infections induced by diabetes mellitus. Such studies employ the most advanced antibiotics to date, like linezolid, teicoplanin, and vancomycin (Table 3).

Animal studies listed above demonstrate successful application of the combined approach for treatment of infections caused by *S. aureus*. A combination of teicoplanin and Sb-1, a lytic bacteriophage, was shown to destroy biofilms on an intravenous catheter [46]. A study employing a rat model of endocarditis highlighted the prospects of the phage and antibiotic therapy [29]. In an experiment, the most potent combination was that of fluoxacillin and a cocktail of phages of families *Herelleviridae* and *Rountreeviridae*. Another study notes that in animals receiving bacteriophage together with antibiotics, the infectious process is much milder and shorter than in those given only an antibiotic or a bacteriophage [27]. A 2018 work was an exception, however: its authors, using a model of ventilator-associated pneumonia, did not register significant differences between individual use of a phage or an antibiotic and their combined administration [28].

The amount of the reported clinical cases of use of a combination of a phage and an antibiotic against various infections caused by *S. aureus* has been growing recently. A case of 2019, first of its kind, describes successful application of a phage cocktail AB-SA01 (family *Herelleviridae*) in combination with antibiotics (fluoxacillin, ciprofloxacin and rifampicin) to treat prosthetic valve endocarditis [47]. Intravenous administration of the bacteriophage gradually alleviated symptoms (fever, tachycardia, hypotension, and rash) significantly, and lead to a complete recovery. The same bacteriophage preparation was successfully used in conjunction with cefazolin and minocycline in the case of a patient with infectious endocarditis associated with a left ventricular assist device [48]. There was also described a case of successful treatment of an infected joint implant using intravenous infusions of the AB-SA01 phage cocktail and cefazolin, combined with surgical intervention [49]. In all the above mentioned studies, authors noted that bacteriophages are safe, and reported no side effects.

The reports of successful testing of the combined therapy in animal models and positive clinical practice allow a conclusion that use of lytic bacteriophages in conjunction with antibiotics is a promising approach to treatment of *Staphylococcus aureus* infections of varying severity.

CONCLUSION

The use of lytic bacteriophages as an addition to classical antibiotics in the context of treatment of *S. aureus* infections caused by MDR strains has been actively investigated in the recent decades. *In vitro* and *in vivo* experiments demonstrate that frequently, combined administration of a phage and an antibiotic significantly hampers bacterial growth, and the cases of antagonism are much less common. An important advantage of this approach is, undoubtedly, its effectiveness against not only planktonic cells, but also biofilms built by many strains of *Staphylococcus aureus*. Treatment with bacteriophages and antibiotics *in vitro* can resensibilize and significantly increase susceptibility of MDR strains of *S. aureus*. However, the currently available results of *in vitro* and *in vivo* experiments are not exhaustive, and contain many contradictions, which necessitates further research aimed at accumulating and generalizing data. In addition, effective application of the presented approach requires a fundamental basis explaining the mechanisms involved in elimination of *S. aureus* under the combined influence of bacteriophages and antibiotics. Thus, further research should investigate interaction of the phage–antibiotic–bacteria system using methods of systematic biology and omix technologies.

The promising results of application of the combined therapy in patients should be emphasized separately. However, mass introduction thereof requires optimization of the doses of agents and further clinical studies (including a double-blind placebo-controlled study) seeking to confirm the efficacy and safety of using produced properly bacteriophage preparations. Such studies should form the basis for development of the bacteriophages clinical use recommendations.

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