

Conventional Treatment of Burn Wound Infections Versus Phage Therapy

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ABSTRACT

Wound infections are the primary cause of sepsis in burn wound patients and increase burn-related morbidity and mortality. Gram-negative and Gram-positive bacteria induce infections in burn wounds. Conventional antimicrobial therapy is recognized as the most successful therapeutic intervention to combat infections of burn wounds. Unfortunately, antimicrobial resistance could be catastrophic and lead to treatment failure. Burn wound infections need topical treatment. Phages as an alternative for antibiotics can be used as a monotherapy for infections with antibiotic-resistant pathogens or can be applied in combination with antibiotic therapy. Phages are species-specific bacterial natural viruses. Worldwide, many phage-producing companies are emerging. However, not many countries implement phage therapy in their patient management.

Clinical trials are needed to convince the health care system in those countries that do not have confidence in phage therapy in infectious diseases. This study reviewed several aspects of phage therapy in burn wound patients.

Keywords: Burn wounds, Conventional antimicrobial treatment, Infections, Phage therapy

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1 Introduction

Burn and Antimicrobial Resistant Pathogens

Patients with serious thermal injuries need immediate intensive care to stabilize the patient and decrease mortality and morbidity (1).

Burn injuries are still one of the main causes of death in the US. About 486,000 burn injuries are annually admitted to the emergency department (2). More than 60% of the US acute cases of hospitalization are related to burn injuries and were admitted to 128 burn centers (2, 3).

The immune response of burn injuries is instant, fulminant, and severe. Immunosuppression may help

patients to survive (4). Extensive and deep thermal injuries reduce both the cellular as well as the humoral immune defense systems. After the thermal injury, reduction in lymphocyte proliferation and consequently mixed lymphocyte response are triggered by the release of prostaglandins, kinins, superoxides, leukotrienes, and anaphylatoxins. The formation of membrane attack complexes (MAC), decrease in immunoglobulin levels, and activation of complement lead to cytolysis (5).

Immediate antibiotic treatment of a burn wound infection is highly relevant. It will improve wound healing, limit the formation of scarring, and prevent

bacteremia, sepsis, or multiple-organ dysfunction syndrome (1). The main cause of death (28%) in burn patients is sepsis. Additional to antibiotic therapy, topical burn wound medication (see Table 1) reduces the risk of burn wound sepsis (6).

Bacteria is the major cause of burn ulcers. These microbes may form biofilms in burn wounds within 48-

72 hours after injury [1]. These organisms are commensal skin flora, the intestinal or the respiratory tract flora of the patient. These organisms can also originate from contact with contaminated environments or (hands of) co-workers (7). The most common pathogens are listed in Table 2.

Table 1. Commonly used antimicrobial agents

Agent Class	Description	Application	Ref
Topical antibiotics			
Mafenide acetate	Sulfamylon acetate cream is a broad-spectrum antibiotic that affects Gram-negative bacteria, especially <i>Pseudomonas aeruginosa</i> , but little activity against aerobic Gram-positive bacteria	Clinical 2nd/3rd-degree burns	
Bacitracin	This is a good alternative for silver sulfadiazine in burn patients with allergies to sulfa	Clinical 2nd/3rd-degree burns	
Mupirocin	An inhibitor of Gram-positive skin flora such as <i>Staphylococcus aureus</i> and coagulase-negative staphylococci	Clinical 2nd/3rd-degree burns	
Neosporin	An ointment containing bacitracin, neomycin, and polymyxin B	Clinical 2nd/3rd-degree burns	
Nitrofurazone	Nitrofurazone is a disinfectant against both gram-negative and gram-positive bacteria	Clinical 2nd/3rd-degree burns	
TOPICAL SILVER PREPARATIONS			
Silver nitrate	Silver nitrate is usually given topically by gauzes in patients with severe burns. Some references show that nitrate is toxic to tissues and wounds	Clinical 2 nd /3 rd -degree burns	(8-21)
Silver sulfadiazine (SSD)	SSD is a gold standard in burn treatment	Clinical 2nd/3rd-degree burns	
Cerium nitrate-SSD	Burnt skin makes a lipid-protein complex that suppresses the immune system. Cerium nitrate denatures this lipid complex protein, thus preventing suppression of the immune system	Clinical 2nd/3rd-degree burns	
Sustained silver Releasing systems	Silver Nitrate, SSD, and Cerium Nitrate-SSD are silver products in solutions, salts, or compounds used for gauze spraying. Silver-based dressings are newer products that are used alone	Clinical 2nd/3rd-degree burns	
Silver-impregnated biological material	Silver incorporated into the amniotic membrane is more effective than the amniotic membrane alone	Clinical 2nd/3rd-degree burns	
IODINE PREPARATIONS			
Povidone-Iodine	The povidone-iodine solution is active against a wide spectrum of bacteria, fungi, protozoa, and viruses	Clinical 2nd/3rd-degree burns	

Agent Class	Description	Application	Ref
Cadexomer iodine	Cadexomer iodine is an antimicrobial product. There are some reports that show cadexomer iodine has effectiveness against <i>S. aureus</i> and MRSA	Clinical chronic wounds	
PHOTODYNAMIC THERAPY	Light with the wavelength excites the PS (photosensitizer) to its exciting uniqueness, which can pass through the system into the exciting triple mode for a long time. In the presence of oxygen, the triple state of PS produces energy into the molecular oxygen of the ground state (a triplet), which produces reactive oxygen species (ROS) and can kill microbial cells		
CHITOSAN PREPARATIONS	Chitosan has antimicrobial effects due to destruction of the outer membrane and permeabilization of the plasma membrane	Clinical 2nd-degree burns	
ANTIMICROBIAL PEPTIDES	Antimicrobial peptides are depicted to kill gram-positive bacteria and gram-negative (especially strains that are resistant to routine antibiotics), <i>Mycobacteria</i> (including <i>Mycobacterium tuberculosis</i>). The antimicrobial peptides also have the ability to improve immunity (22)		

Table 2. Pathogens responsible for burn infections and their occurrence in drug resistance

Group	Species	Drug Resistance
Gram-positive bacteria	<i>S. aureus</i>	
	Methicillin-resistant <i>S. aureus</i>	By definition
	Coagulase-negative staphylococci	MRSE (methicillin-resistant <i>Staphylococcus epidermidis</i>) increasing
	<i>Enterococcus sp.</i>	
	Vancomycin-resistant enterococci	by definition
Gram-negative bacteria	<i>P. aeruginosa</i>	High innate resistance
	<i>Escherichia coli</i>	ESBL(extended spectrum beta-lactamases) increasing
	<i>Klebsiella pneumoniae</i>	ESBL increasing
	<i>Serratia marcescens</i>	increasing
	<i>Enterobacter sp.</i>	ESBL increasing
	<i>Proteus sp.</i>	ESBL increasing
	<i>Acinetobacter sp.</i>	High innate resistance
	<i>Bacteroides sp.</i>	uncommon

Unfortunately, antimicrobial resistance (AMR) is emerging worldwide. We will end in the so-called post-antibiotic era without any urgent precaution measurements. In the European Union and the United States, antibiotic resistance causes 25,000 and 23,000

deaths, respectively, per year (23, 24). For patients infected with methicillin-resistant *S. aureus* (MRSA), the mortality rate is 64% (25). Most serious Gram-negative infections (*Klebsiella pneumoniae*, *P. aeruginosa*, and *Acinetobacter spp.*) are healthcare-associated

ted and are becoming resistant (ESBL) to all conventional antimicrobial agents available (26, 27).

Overuse and misuse, wrong prescription, extensive veterinary and agricultural use, lack of rapid laboratory tests, poor hygiene, sanitation practices, poor infection control measurements in healthcare, lack of new antibiotics are the reasons for the worldwide emergence of antibiotic resistance (24, 28).

Main Body

Treatment of Burn Wound Infections

Treatment of infections in burnt patients is an emergency, as delay in treatment may significantly increase mortality. Different conventional treatment schedules are used to reduce and control burn wound infections (Table 1). As antibiotic resistance increases, conducting research on and applying probable alternatives such as phage therapy can be relevant.

Phage therapy

For the antibiotic era, time is running out. Colistin-resistant bacteria, the only sensitive antimicrobial agent, have been isolated. Bacteria have evolved to build up resistance to new antibiotics within a few months to a year. For the pharmaceutical industry, it takes billions of dollars and approximately ten years or even more to develop and approve a new antimicrobial agent (29). Alternative therapeutical methods are strongly required to combat bacterial infections. Bacteriophage therapy may have potential characteristics to be such an alternative therapeutic strategy.

Bacteriophages (phages) were found by Frederick Twort in 1915 and Félix d'Herelle in 1917, eleven years before penicillin (1928) was discovered. The name was formulated from "bacteria" and "phagein" (Greek: to eat or devour). It is estimated that phages in the biosphere are about 10^{31} , showing their extreme abundance [32] (30).

General Characteristics of Bacteriophages

Most phages are classified as *Caudovirales*, which are double-stranded DNA phages with a tail. *Caudovirales* are subdivided into three families; *Siphoviridae*, contain a long flexible tail, *Myoviridae* have a contractile tail, and *Podoviridae* contain a tiny or no tail. Bacteriophages can infect, multiply, and eventually kill bacterial cells, as they are specific for their bacterial host (30). Depending on the life cycle of the phage (lytic or lysogenic), lysis can occur immediately after infection of the bacterial cell (lytic cycle) or after a short delay (lysogenic cycle) (31). Phages are natural but not chemical species-specific. This means that phages specific to bacterial pathogens only kill those bacteria, not the commensal flora. For effective phage therapy, an appropriate and efficient phage will be selected by determining the host range and burst size of phages as two important parameters can be helpful. If they can control or even suppress the bacterial population, phages can surpass antibiotics (32). Table 3 and Figure 1 show the advantages of phages over antibiotics.

Table 3. Advantages of phages over antibiotics

Bacteriophages	Antibiotics
Specific, do not affect the commensal flora (33, 34)	Antibiotics affect both pathogenic and natural microorganisms. This may lead to patient's microbial unbalance, which may cause secondary infections (34) and antibiotic resistance
No descriptions of any serious side effects	Multiple side effects (35)
Phages capable to kill antibiotic-resistant bacteria (36)	Antibiotic-resistance is considerable these days
Phages replicate and are available at the site of infection	They are eliminated from the body and do not necessarily exist at the site of infection
Selection of new phages is a process that takes only several days or weeks	Developing a new antibiotic is a time-consuming process that can take several years
Phages are self-replicative and easy to isolate (35)	Antibiotics are not
Other advantages include auto "dosing". Phages during the process of killing bacteria can increase the number, especially in places where the hosts are placed; the phages themselves help to create a dose of phage (37)	-
Bacteria in biofilms are more resistant to antibiotics compared with planktonic bacteria. However, phages can	-

Bacteriophages	Antibiotics
<p>clear some biofilms because of the ability for active penetration into the biofilm path by slipping a bacterial layer at once or because of the release of biofilm exopolymer-degrading depolymerizes (21)</p> <p>Other advantages of phages are the ability to replicate in situ when a sufficient bacterial population exists; they can reduce phage doses needed to achieve efficacy. Low dose phage can also increase the safety of the product because phages only increase in density if they actively kill bacteria (38)</p>	<p>It is sometimes inevitable to use antibiotics in high dose</p>

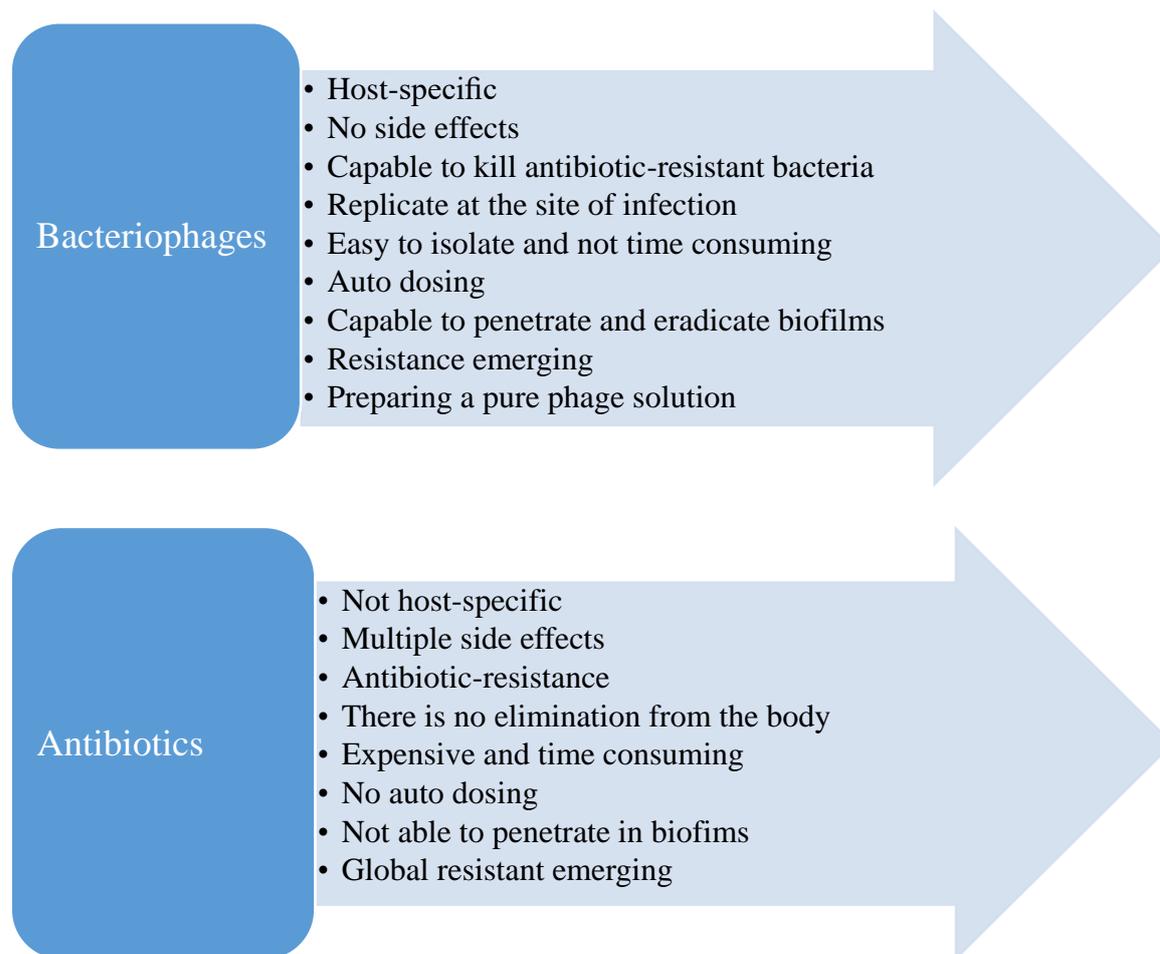


Figure 1. Summary of bacteriophage and antibiotic pros and cons

In many countries, antibiotic therapy is the only option for treating bacterial infections. Unfortunately, phage therapy has been ignored, even as an alternative therapy (31, 39). Challenges in phage therapy are 1. The success of phage therapy is strongly dependent on the safety of phage production GMP (good manufacturing practices) conditions and approval by the authority; 2. Avoid phages encoding for lysogeny, virulence factors, and antibiotic resistance determinants; 3. Purification and stabilization of the phages are key requirements. Furthermore, scientists need to use a high bacterial inoculum, the

natural host of bacteria [(40)]. Bacteria become infected with the phages and reproduce in the bacterial cell, resulting in lysis. Remnants of bacteria in the final solution may develop sepsis. The whole phage treatment seems to cause immune system activation. Using low doses of isolated phages for treatment is a probable way to avoid activation of the immune system. The next challenge is to acquire the optimal concentration of phages. The phage concentration cannot be measured directly. If the concentration is under the optimal dose, phage therapy is ineffective. Monthly enrichment may be

helpful to maintain optimal concentration in some cases (31, 32). The disadvantage of phage therapy is the prolonged time of preparation. Phages are host-specific, so phage preparation is critical to target their unique bacterial host. A mixture of multiple different phages as a cocktail can improve therapeutical results.

Antibiotics are relatively indiscriminate and can be applied for patient treatment before the availability of diagnostic microbiological results (31).

There is evidence that shows the anti-inflammatory and immunomodulatory ability of phages (41).

A great concern of phage therapy is the gap between its safety and effectiveness because there is a lack of knowledge in this field. For example, phages can introduce resistance markers in pathogens or commensals. Of concern, bacteria may develop phage resistance after phage therapy; however, a combination of phage and antibiotic therapy could be an interesting option to tackle the phage resistance issue of bacteria (39, 42).

Abedon *et al.* have listed some key factors that should be considered in phage therapeutical studies, such as the characteristics of phages, target individuals (humans) and bacterial dosing, formulations, and phages efficacy. The specificity of most phages in mono-microbial infectious diseases is very eligible, but not in poly-microbial infections, unless the phage is combined with a suitable antibiotic (40).

Phage Therapy Revitalization

A 2014 report predicted that by 2050, approximately 10 million people would die each year from antibiotic-resistant infections, approximately 4.73 million in Asia and 4.15 million in Africa, compared to 0.39 million in Europe and 0.32 million in the United States (23, 43). This report shows the importance of the introduction of a suitable alternative therapy to combat antibiotic-resistant bacterial infections.

Human phage therapy has been used in the early years to treat conditions such as typhoid fever, surgical wound infections, dysentery, peritonitis,

septicemia, external otitis media, and urinary tract infections (44). There is a lot of criticism on these studies, and it was aimed at the lack of good methodological design, standards, controls, characterization of phage preparation, and contradictory results.

Worldwide, some clinical trials have confirmed the importance of phage application in defeating bacteria, for instance: 1. Topical administration (45), Wright *et al.* tested the effect of a phage cocktail in the treatment of chronic otitis media due to an antibiotic-resistant *P. aeruginosa* in a double-blind placebo-controlled study. The phage cocktail improved all outcomes compared to the placebo; 2. FagoBurn, a European clinical trial (2015-2017) describing the prophylactic application of phages to prevent skin infections in burn patients, is highly interesting. Full-scale clinical trials for phage therapy are still rare, but a few case studies are published mentioning the phage therapy application (46-48).

Clinical trials were conducted to apply phage therapy to treat or prevent bacterial infections, tuberculosis, and MRSA infections included. Phage therapy has not been approved by the FDA. However, phages have already been applied in experimental therapies in phage therapy centers. The Hirsfeld Institute (Poland) provides phage therapy for various pathogenic genera such as the *Enterobacteriaceae* family, *Acinetobacter*, *Pseudomonas*, *Staphylococcus*, and *Stenotrophomonas*. The therapeutic results were positive in 50% of the cases (38, 40). The Eliava Phage Therapy Center (Georgia) provides phages for treating *Enterococcus faecalis*, various genera of *Enterobacteriaceae*, *P. aeruginosa*, *Salmonella*, *S. aureus*, and various genera of the *Streptococcaceae* family. Some reports described the recovery of severe comatose patients after phage therapy (38).

A mixture of multiple phages (phage cocktail) containing several bacteriophage strains may be useful to increase the antimicrobial activity and may reduce the risk of phage resistance, which is inevitable. A variety of phage companies that offer phage-based products commercially are listed in Table 4.

Table 4. Phage Companies

Company	Use of Phages
Center for Innovative Phage Applications and Therapeutics (US)	
Eliava Phage Therapy Center (GE)	
Phage Therapy Center (GE)	They facilitate patient phage therapy treatment
Phage Therapy Unit (PL)	

Company	Use of Phages
Ecolyse (US) Fixed Phage (UK) InnoPhage (PT) ACDPharma (NO)	They provide Phage-mediated biocontrol
Biochimpharm (GE) Imbio (RU) Microgen (RU)	They are involved primarily in phage product distribution
Adaptive Phage Therapeutics (US) AmpliPhi Biosciences (US) Evolution Biotechnologies (UK) InnoPhage (PT) iNtODEWorld (KR) Phagelux (CN) Phagomed (AT) Pherecydes Pharma (FR)	They are currently in pre-clinical phage therapy research and development (R&D) step
GangaGen (US/IN) Lysando GmbH (DE) Microcos Food Safety (NL) New Horizons Diagnostics? (US)	Development of enzybiotics
GeneWeave (US) Micromensio (CA) Sample6 (US)	Phage-based bacterial detection technologies
JAFRAL (SI) Clean Cells (FR) Paragon Bioservices (US)	Phage manufacturing/production for others (49)]

Phage Therapy of Burn Wound Infections and Biofilm

The high mortality rate in burn wound infections may move scientists towards phage studies with the high potential to save patients suffering from burn wound infections. A clinical trial report of a phage cocktail specific to *P. aeruginosa* and *S. aureus* on burn wounds showed satisfying results without any adverse effects or any other abnormalities in burnt patients (50). Another report mentioned before as a randomized phase 1/2 trial indicated that the phage was effective but less than the normal therapy (sulfadiazine silver emulsion cream). The authors made some comments: 1. The recruitment period was halved, leading to a small patient sample size; 2. The titer of the phage cocktail was significantly decreased after manufacturing, leading to a lower dose than was originally intended; 3. The pathogens were resistant to

low doses of phages—a warranty for future studies (51).

Animal Model Studies

Another study, using a burnt mice infection model, showed that phage Kpn5 was more effective against *K. pneumoniae* B5055 than silver nitrate or gentamicin. Furthermore, a phage cocktail in a burn wound infection caused by *K. pneumoniae* B5055 showed high protection in patients who did not respond to routine antibiotic therapy (52). In contrast, another study described that phages specific to the *Podoviridae* family were ineffective in controlling *P. aeruginosa* in infected burnt mice (53). Soltan Dallal *et al.*'s study in mice suggests that phage SE20 is a promising candidate for controlling salmonellosis caused by *Salmonella* Enteritidis (55).

Sometimes, a phage cocktail has no efficacy to pathogens such as *P. aeruginosa*. When the bacterial load is hardly reduced by the phage cocktail, bacteria seem to adapt themselves in order to defeat stressors (emerging phage resistance). Here are some possible bacterial resistance mechanisms: 1. Prevention of phage adsorption by loss of modification of bacterial receptors and prevention of phage DNA entry; 2. Degradation of phage DNA by restriction-modification and other related systems (BREX (bacteriophage exclusion), DISARM (defense island system associated with restriction-modification), CRISP-Cas (clustered regularly interspaced short palindromic repeats)); 3. Use of abortive infection systems that block phage replication, transcription, or translation; 4. Cyclic oligonucleotide-based antiphage signaling systems [56]. It is of great importance to study the mechanism of phage resistance in bacteria to prevent phage cocktail resistance of the pathogens. Implementation of phages with a broad host range, targeting various distinct bacterial receptors, may reduce the development of phage resistance (54).

Phage-antibiotic synergy has good results because it increases fitness costs. In a study, the authors described that a mixture of a single antibiotic such as an aminoglycoside (gentamicin) or ciprofloxacin combined with two different phages specific to the *Myoviridae* family have high efficacy against *P. aeruginosa* infections and can reduce the bacterial inoculum in approximately 2 logs (42). A study showed no reduction in the *P. aeruginosa* count at culture tube in a combination of phage and antibiotic therapy (55). In developing countries, phage therapy for treating infectious diseases such as cholera can be helpful by designing well-established trials (56).

Biofilm formation is a mechanism produced by bacteria such as *P. aeruginosa* and *S. aureus* to be a winner in a race with unfavorable circumstances. As antibiotics cannot penetrate the biofilm, phages are probable candidates to penetrate biofilms. Reports show that a mixture of phages has a remarkable positive effect on the degradation of *S. aureus* biofilms (57). Phage therapy is also recommended as an effective antimicrobial method to degrade *P. aeruginosa* biofilm (57, 58). Chegini *et al.* demonstrated that a mixture of phages with anti-biofilm compounds, such as nanoparticles or enzymes, was more effective than monotherapy of phages. Phages

can induce penetration of antibiotics in the internal layer of biofilm by making defects in the extracellular matrix; they can also suppress biofilm formation by hurdling the quorum-sensing (59). Another study mentioned the Trojan horse effect of phages by the eradication of biofilms that are established by both *P. aeruginosa* and methicillin-resistant *S. aureus* (60). Phage therapy also effectively prevents *E. faecalis* biofilm formation (36). Another report declared that bacteriophages act as an alternative bacterial biofilm inhibitor (61). These mentioned reports all showed that phage therapy is a new alternative method in combination with antimicrobial treatment, especially in infections caused by biofilm-producing Gram-negative bacteria. More research is needed for the worldwide introduction of phage therapy to combat infectious diseases.

5. Conclusion

Phage therapy can be a suitable alternative to defeating (antibiotic-resistant) pathogens in infectious diseases. Burn wound infections need a topical treatment. Phages can be used as a solution for infections with antimicrobial-resistant pathogenic bacteria as a monotherapy or in combination with antibiotic therapy. Numerous studies have demonstrated the potency of phages for the therapy of infectious diseases. Clinical trials conducted over the last decades confirmed the therapeutic potential of phages, but more data is needed for reliable clinical application. Phage application protocols must move towards a logical operating framework. Ideally, these developments should be classified as standard and universal.

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Conflict of Interest

The authors declared that there is no conflict of interest.

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