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Beyond Antibiotics: Phage-Based Approaches for Controlling Biofilm-Associated *Pseudomonas aeruginosa* Infections: A Review

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Abstract

Pseudomonas aeruginosa is a pathogen that causes chronic and difficult-to-treat infections, especially in patients with cystic fibrosis, burn wounds, and immunocompromised patients. Its extraordinary ability to establish biofilms and develop multidrug resistance has significantly affected the effectiveness of traditional antibiotic therapy, and the treatment of bacteriophage infections has once again become a subject of scientific concern. This present review provides a general overview of bacteriophage therapy for P. aeruginosa, focusing on the underlying microbiological processes, strategies of biofilm therapy, and progress in clinical translation. Important aspects of phage–host interactions, including adsorption, intracellular replication and bacterial lysis, and factors that determine therapeutic efficacy, such as phage resistance and immune modulation are discussed. The role of phages in destabilizing biofilms of P. aeruginosa by degrading extracellular polymeric substances through enzymatic activity, disrupting quorum sensing, and having synergistic effects with antibiotics and other antimicrobial agents is particularly emphasized. In addition, this review summarized the existing preclinical and clinical information regarding the safety and therapeutic potential of phage therapy in respiratory, wound, and device-associated infections. Issues relating to regulatory guidelines, phage preparations and dosing standardization, and delivery route enhancement are also considered. This review integrates mechanistic knowledge with a translational perspective and introduces bacteriophage therapy as a promising and biologically plausible adjunct or alternative to antibiotics in the management of recalcitrant P. aeruginosa infections and the need to develop well-designed clinical trials to determine the role of phage therapy in routine clinical practice.

Keywords: Pseudomonas aeruginosa, Bacteriophage therapy, Biofilm associated infections, Antimicrobial resistance, Phage–antibiotic synergy.

Introduction

Pseudomonas aeruginosa is a ubiquitous Gram-negative opportunistic pathogen and the most frequent cause of healthcare-associated infections, particularly in patients with cystic fibrosis, burn wounds, and immunodeficiency. It causes a wide spectrum of acute and chronic infections, including pneumonia, wound infections,

urinary tract infections, and medical device-related infections (1, 2). The clinical treatment of *P. aeruginosa* infections is becoming more difficult because of its inherent resistance to a variety of antibiotic classes and its ability to develop additional resistance mechanisms through mutation and horizontal gene transfer (3). One characteristic of the pathogenicity of *P. aeruginosa* is its ability to develop organized biofilms on both biotic and abiotic surfaces. Cells in biofilms have a highly resistant response to antimicrobial agents and immune clearance by the host, contributing to chronic and recurrent infections. Traditional antibiotic therapies often fail to eliminate these biofilms, leading to longer periods of antibiotic therapy, ultimately increasing morbidity and mortality. Therefore, alternative treatment measures capable of overcoming antimicrobial and biofilm-mediated resistance are urgently needed (4,5).Viruses that only infect bacterial cells, bacteriophages, have re-emerged as potential biological agents for controlling multidrug-resistant pathogenic bacteria. They are highly specific, self-amplifying, and can lyse target bacteria, unlike traditional antimicrobial agents (6). Recent molecular biology and genomic research has rejuvenated phage studies, enabling the selection, engineering, and formulation of phages with enhanced antibacterial and antibiofilm activities. Interestingly, bacteriophages and phage-derived enzymes can infiltrate and disrupt Pseudomonas aeruginosa biofilms by breaking down extracellular polymeric substances and disrupting quorum-sensing networks (7, 8). Although there are encouraging preclinical results and an increase in the number of compassionate use and early clinical trial cases, numerous scientific, regulatory, and practical challenges face the clinical translation of phage therapy. These include phage resistance, host immune response, phage preparation standardization, and strong regulatory frameworks (9). This review summarizes the existing knowledge on bacteriophage therapy of *P. aeruginosa* in terms of the microbiological basis of the therapy, antibiofilm approaches, recent advances toward clinical practice, and outlines the key limitations and future research directions necessary to incorporate phage-based interventions into contemporary antimicrobial therapy.

Methods

This narrative review summarizes the available evidence on the use of bacteriophages as a treatment for Pseudomonas aeruginosa, especially regarding their anti-biofilm effect and clinical use. Studies published from 2015 to 2026 were collected from PubMed, Scopus, Web of Science, and Google Scholar using various combinations of the following keywords: *Pseudomonas aeruginosa*, bacteriophage therapy, biofilm, phage–antibiotic synergy, and multidrug resistance. Articles were selected based on scientific relevance, novelty, and importance to the understanding of phage-based therapy strategies.

Microbiological Characteristics of *Pseudomonas aeruginosa*

P. aeruginosa is an opportunistic pathogen, which has been found to reside in many reservoirs, such as soil and water, and it is one of the most difficult-to-control opportunistic pathogens known to man. The highly variable nature of this organism

and its large gene content provide for both metabolic adaptability and a very strong ability to quickly adjust to its environment, whether in a clinical setting or otherwise. Due to the innate flexibility of this bacterium, it can continue to thrive in hospital environments, where it causes chronic and recurrent infections (10, 11). Virulence factors of *Pseudomonas aeruginosa* contribute to its ability to infect hosts by facilitating adherence to host surfaces, evasion of the immune response, and tissue destruction. Exotoxin A, elastases (LasA and LasB), alkaline protease, phospholipase C, and the Type III Secretion System (T3SS) are some examples of virulence factors produced by *P. aeruginosa* (12). In addition, pigment production such as pyocyanin contributes to increased oxidative stress and altered host cell function leading to greater severity of disease. Ultimately, a variety of mechanisms including virulence factors, *P. aeruginosa* can colonize the host and grow in environments with extreme conditions. The formation of structured biofilms by *P. aeruginosa* on biological and non-biological surfaces is a characteristic property of this bacterial species. Biofilm formation is a very complex process which undergoes multiple phases to grow from primary adherence phase to microcolonies formation, maturation to the final stage of dispersion (14). Biofilm structure is embedded in a polymer matrix that consists primarily of polysaccharide compounds such as alginate, Pel, Psl , protein and extracellular DNA (15). The quorum sensing (QS) systems are majorly responsible for regulating virulence gene expression and biofilm formation in P. aeruginosa. The networks of Las, Rhl, and Pqs coordinate the processes of toxin production and biofilm maturation with those of chemotaxis and flagellar motility at various cell densities. The process of forming a biofilm also provides high levels of antibiotic resistance as well as generates highly drug-resistant subpopulations which can be difficult to kill (16,17). These microbiological features, including high genomic plasticity, complex virulence regulation, and its capacity to form biofilms illustrate that *P. aeruginosa* is an important pathogen. Biofilm formation is a significant factor in the development of effective bacteriophages that can address the survival mechanisms of bacteria associated with their biofilms (18). Table 1 summarizes the major virulence factors and biofilm-associated traits of Pseudomonas aeruginosa.

Table.1: Key virulence factors and biofilm-related traits of *Pseudomonas aeruginosa* (References: 12, 14–17)

Factor	**Function**	**Role in biofilm and infection**
Exotoxin A	Inhibits host protein synthesis	Causes tissue damage and persistent infection
Elastases (LasA/LasB)	Degrade host proteins	Promote invasion and biofilm maturation
Type III secretion system	Injects effector toxins	Enhances virulence and immune evasion
Pyocyanin	Induces oxidative stress	Supports chronic infection
Alginate, Pel, Psl polysaccharides	EPS matrix formation	Structural backbone of biofilm
Quorum sensing systems	Regulates virulence genes	Controls biofilm development
Flagella and pili	Motility and adhesion	Required for surface attachment
Efflux pumps	Antibiotic extrusion	Increase tolerance in biofilm cells

Bacteriophages Targeting *Pseudomonas aeruginosa*

Pseudomonas aeruginosa bacteriophages constitute a diverse and rapidly growing category of viruses with important therapeutic applications. These phages are regularly found in environmental samples, such as sewage, soil, and water bodies, where *P. aeruginosa* is naturally abundant (19). Most *P. aeruginosa* phages are morphologically and genetically related to the Myoviridae, Podoviridae, and Siphoviridae families. Phages used in clinical settings are primarily lytic strains because temperate phages are associated with the risk of horizontal gene transfer and lysogenic conversion (20).

Phage infection occurs with the help of adsorption to bacterial surface receptors that are specific to lipopolysaccharides, type IV pili, flagella, and outer membrane proteins. This specificity underlies the narrow host range that many phages have; however, it is also an advantage in the selective attack on pathogenic bacteria without killing the normal microbiota (21). After attachment, phages insert their genetic code into the cytoplasm of bacteria, hijack the bacterial replication machinery, and cause the production of viral elements. Later progeny virions are assembled, eventually resulting in the lysis of bacterial cells, mediated by phage-coded holins and endolysins, which release infectious progeny virions (22). Genomic analyses have facilitated the characterization and screening of phages with desirable therapeutic properties, including a broad host range, high burst size, and absence of virulence or antibiotic resistance. In recent years, multi-lytic phage cocktails comprising several lytic phages have been developed to increase the antibacterial spectrum and reduce the likelihood of resistance emergence. Moreover, synthetic biology has enabled the engineering of modified phage genomes to be more stable, efficient in targeting, and active against biofilms (23,24). Notably, the phages that attack *P. aeruginosa* can target bacteria integrated into biofilms, a characteristic not shared by a variety of traditional antimicrobials. Phages carry depolymerases and other enzymes that have the potential to degrade extracellular polymeric substances, increasing their infiltration into biofilm structures. These attributes of *P. aeruginosa* render bacteriophages unique to this bacterial strain especially attractive as an instrument in the fight against chronic and device-associated infections (25). Therefore, the diversity, specificity, and biological plasticity of bacteriophages offer a strong system on which the most specific antimicrobial treatment against *P. aeruginosa* can be developed, and the biological effects and therapeutic applications of bacteriophages can be investigated (26).

Mechanisms of Antibacterial Activity of Phage Therapy

Bacteriophage therapy has a range of complementary mechanisms that result in antibacterial effects, making this approach more specific than traditional antimicrobial agents. The first and direct mechanism is the lytic infection cycle, in which phages attach to bacterial surface receptors, inject their genetic material, and use host cellular machinery to produce progeny virions. This is succeeded by the lysis of bacterial cells, which is caused by holins and endolysins coded by the phages, leading to a rapid decrease in the bacterial population and an increase in the concentration of the therapeutic agent at the site of infection (27). In addition to direct bacterial-killing, enzymes produced by the phage are important in augmenting the antibacterial effects. Endolysins destroy the peptidoglycan layers of the bacterial cell wall, whereas depolymerases destroy

extracellular polymeric substances and capsular polysaccharides that protect bacterial communities. These enzymatic activities not only promote bacterial lysis but also enhance the targeting of biofilms and host immune defense and other antimicrobial agents used in combination with each other (28,29). Bacteriophages infect *Pseudomonas aeruginosa* in several consecutive steps, including adsorption, genome injection, replication, and bacterial lysis (Figure.1).

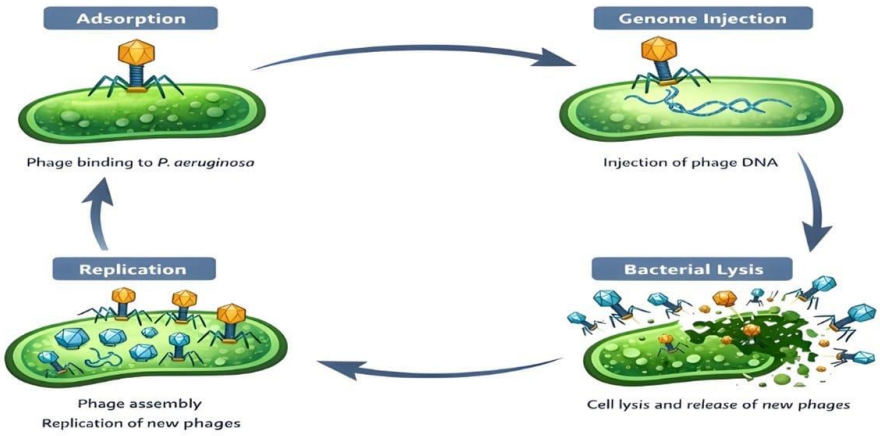

Figure.1. Mechanism of phage action against *Pseudomonas aeruginosa.*

Phage therapy also affects the dynamics of bacterial resistance. Although bacteria may acquire resistance to phages by altering the receptors, restriction-modification systems, or CRISPR-Cas immunity, these adaptations are associated with a fitness cost. Most phage-resistant strains are less virulent or more sensitive to antibiotics, thus regaining the effectiveness of conventional treatment. This evolutionary trade-off highlights the exceptional advantage of phage therapy in redifining bacterial populations in less-pathogenic phenotypes (30). Furthermore, bacteriophages can control immune responses in hosts by lowering the inflammatory burden of bacteria and indirectly by promoting immune clearance. Other studies have suggested that phages can also respond with innate immune components, which could result in localised regulation of the immune reaction without undue systemic reactions. This synergistic effect of bacterial lysis, enzyme disruption of biofilm, and evolutionary pressure of resistance mechanisms leads to a compound antibacterial strategy (31, 32). These mechanisms support the idea that phage therapy has biological grounds as a particular and multifaceted system of antimicrobial therapy. Phage replication dynamics, bacterial defense systems, and host immunity are significant to comprehending the therapeutic efficacy and integrating phage-based therapies into prevailing clinical practice in treating *Pseudomonas aeruginosa* refractory infections (33).

Anti-biofilm Strategies of Phage Therapy

A biofilm infection with *Pseudomonas aeruginosa* poses a unique clinical challenge in terms of drug efficacy because bacteria contained in the biofilm are resistant to both antibiotics and the host's immune response. Bacteriophage therapy can directly disrupt

the architectural integrity and regulatory systems involved in bacterial biofilm development. Unlike traditional antimicrobial drugs, bacteriophages can multiply within the bacterial population and travel deeper into the structure of biofilms, thus providing localized increased antibiotic activity (34). A key anti-biofilm process involves the hydrolysis/degradation of a matrix composed of extracellular polymers (EPS). Depolymerase enzymes produced by phages that infect *P. aeruginosa* can degrade several large polysaccharides, including alginate, Pel, and Psl. The physical disruption of the biofilm matrix by phage action limits diffusional transport, and the enhanced diffusivity of the phage increases the exposure of individual bacterial cells to immune-mediated killing and additional antimicrobial therapies (35). Phages effectively destroy the protective matrix, transforming sessile biofilm populations into more vulnerable planktonic cells. In addition to structural disruption, phage therapy can disrupt the QS systems involved in biofilm maturation and virulence expression. Phages and phage proteins have been shown to silence QS-regulated genes, resulting in the inhibition of toxin synthesis and destabilization of the biofilm structure (36). This is another mechanism by which phages undermine the virulence of *P. aeruginosa* in host tissues. As shown in Figure 2, treatment with bacteriophages leads to the degradation of EPS matrix, destabilization of the biofilm structure, and increased susceptibility of *Pseudomonas aeruginosa* cells to antibacterial agents.

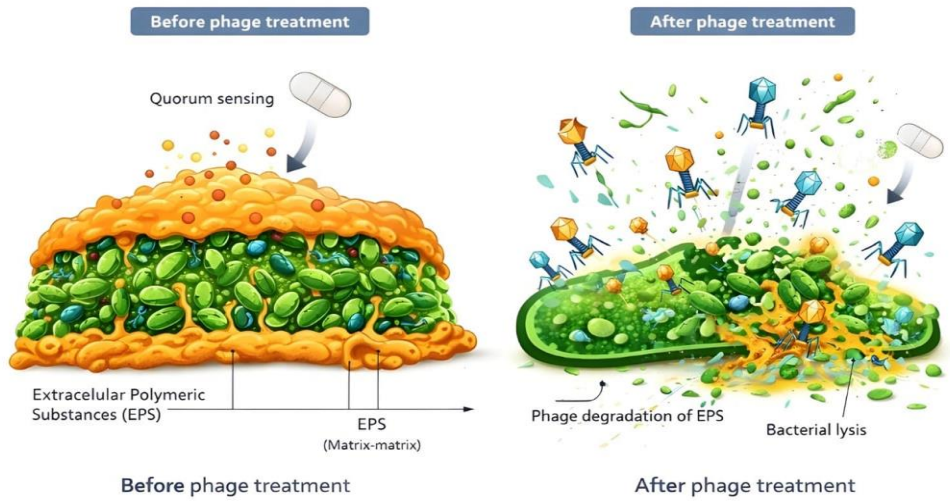

Figure. 2. Phage-mediated disruption of *Pseudomonas aeruginosa* biofilm structure

One of the most promising approaches is the use of phages in combination with antibiotics, known as phage–antibiotic synergy (PAS). Based on complementary mechanisms of action, phage-mediated biofilm disruption exacerbates penetration by antibiotics, and antibiotics can augment the susceptibility of bacteria to phage infection by stress response or changing surface receptors. Experimental models have demonstrated that PAS can considerably decrease bacterial load compared to monotherapy and restrain the development of resistant subpopulations (37, 38). All these approaches highlight the ability of phage therapy to engage both mechanical and molecular factors that define biofilm durability. Bacteriophages can be considered a biologically rational and innovative strategy because they combine enzymatic

degradation, regulatory interference, and synergistic combination therapy to overcome the limitations of conventional antimicrobial treatment in chronic *P. aeruginosa* infections (Table 2) (39).

Table. 2. Antibiofilm mechanisms of phage therapy (References: 28,35–39)

Mechanism	Description	Effect on biofilm
Direct bacterial lysis	Phages lyse bacterial cells	Reduces bacterial biomass
EPS degradation	Breakdown of biofilm matrix	Enhances penetration
Quorum sensing interference	Disrupts signaling pathways	Impairs biofilm maturation
Phage–antibiotic synergy	Combined therapy with antibiotics	Increases efficacy
Fitness trade-offs	Selection of less virulent mutants	Limits resistance

Engineered and Synthetic Phages

Recent innovations in synthetic biotechnology and molecular biology have enabled the creation of engineered and synthetic bacteriophages with enhanced therapeutic efficacy against *Pseudomonas aeruginosa.* In contrast to phages found in nature, engineered phages can be genetically modified to enhance their host range, stability, and antibiofilm traits, and to reduce undesirable traits, such as lysogeny or horizontal gene transfer. These advances represent a major milestone in precision antimicrobial therapy (40). Genetic engineering of phage genomes is one of the strategies that can be used to broaden receptor recognition and allow the infection of a broad spectrum of clinical isolates of *P. aeruginosa.* Genetic alterations may also be made to improve phage lytic efficiency or improve persistence in the areas of infection. Importantly, engineered phages are engineered to produce enzymes, such as depolymerases, endolysins, in higher amounts, which amplify the capacity to degrade biofilm matrices, destabilize well-established bacterial communities (41,42). The other potential concept is the use of CRISPR-Cas systems with phage platforms. Phages with CRISPR can target and cut antibiotic resistance genes or virulence genes of bacteria in a targeted way, resulting in either highly specific bacterial kill or pathogenic effects silencing. This approach can eliminate resistant subpopulations sequentially and reduce the targeting of commensal microbiota. These tools have been suggested as next-generation antimicrobials that can transform, rather than destroy, bacterial populations (43). The development of phage-derived delivery systems using synthetic biology has enabled the use of phages as delivery vehicles for AMPs or regulatory RNAs that disrupt quorum sensing and biofilm formation. These multifunctional constructs have a dual mechanism of action, combining direct lytic activity with molecular interference in bacterial signalling pathways (44). Engineered and synthetic phages are a major safety and regulatory concern, despite their potential. Genetic modifications should be carefully considered to avoid unwanted environmental effects or gene flow. Notably, mass manufacturing and standardization of engineered phages have not yet been technically achieved. Nevertheless, these novel platforms have embraced unprecedented customization of phage-based therapeutics in the treatment of multidrug-resistant and biofilm-associated infections of *P. aeruginosa*, and could possess tremendous potential in the future to expand their therapeutic use in clinical practice (45, 46).

Preclinical Evidence (In Vitro and Animal Models)

P. aeruginosa has therapeutic potential as a bacteriophage against bacteria in both in vitro and animal models. In vitro analysis has revealed that lytic phages can significantly reduce the planktonic bacteria population and destabilize formed biofilms. Both models of biofilms, such as the static and flow cell models, have shown phages invading biofilm matrices and significantly eliminating bacterial biomass when phages were applied as phage cocktails or in combination with antibiotics. These studies have also focused on the capacity of phages to overcome physical and physiological barriers that limit the function of conventional antimicrobial agents (47, 48). The in vivo effectiveness and safety of phage therapy have been investigated using animal models. Pulmonary, skin, and burn-induced sepsis models in mice have demonstrated that phage administration can decrease the bacterial burden, improve the probability of survival, and decrease inflammation (49). Inhalation and intranasal phages prevented the colonization of *P. aeruginosa* and destruction of lung architecture in respiratory infection models, demonstrating their potential for treating cystic fibrosis and ventilator-associated pneumonia. Wound and burn models have shown that topical phage treatment improves the rapid removal of bacteria and wound healing with no signs of toxicity (50). Nonetheless, there has also been preclinical research on the pharmacokinetic and immunological effects of phage therapy. The results indicate that phages can remain long enough at the site of infection to exert antibacterial effects, and they are subsequently removed by the host immune system. Regular injections are also well tolerated, and adverse effects have been minimal in most studies conducted to date. In addition, phage cocktails have been shown to decrease the development of phage-resistant bacterial strains and extend therapeutic efficacy during long-term treatment (51). Together, this preclinical evidence provides a good proof-of-concept for phage-based interventions against *P. aeruginosa.* They have a biological and experimental foundation for clinical translation and subsequent controlled human studies. Nonetheless, the differences between animal models and human infections suggest that preclinical results should be interpreted with caution and that common protocols should be developed to better represent clinical outcomes (52).

Clinical Translation and Human Studies

The clinical translation of bacteriophage therapy against *Pseudomonas aeruginosa* has received greater attention in the past 10 years because of the urgency to find alternative therapies to address multidrug-resistant and biofilm-related infections. Primarily used as compassionate-use cases as well as in small-scale clinical trials, its first clinical application was primarily in chronic respiratory infections, non-healing wounds, and device-associated infections that are resistant to conventional antibiotic therapy (53). Successful experiences have been reported in case reports and observational studies after the administration of phages for cystic fibrosis, chronic otitis, osteomyelitis, and burn wound infection caused by *P. aeruginosa*. Phage therapy has resulted in a significant reduction in bacterial population, clinical improvement, and eradication of infection in many reported cases. The flexibility of phages as therapeutic agents has been

demonstrated in several ways, such as topical, inhalation, and intravenous injection. Notably, such treatments have been well tolerated, with few side effects reported (54). There are limited controlled clinical trials assessing phage therapy, although their number is slowly increasing. The clinical trials that are available have been safe and have demonstrated initial signs of efficacy, particularly when used as adjuncts to antibiotic therapy. Nevertheless, due to the heterogeneity of study design, phage preparations, administration plans, and outcome measures, it is challenging to directly compare the trials. Additionally, concerns about regulation and the absence of standard manufacturing guidelines have impeded the adoption of phage-based interventions (55, 56). These challenges notwithstanding, stringent and reproducible clinical uses are becoming possible using phage characterization, genomic screening, and formulation technologies. A promising approach to increase treatment success is personalized phage therapy, in which phages are selected according to the susceptibility profile of the infecting bacterium in the patient. With the development of regulatory frameworks and the use of larger randomized controlled trials, phage therapy can become an integral part of clinical practice rather than an experimental application in the treatment of recalcitrant *P. aeruginosa* infections (Table. 3) (46,57).

Table. 3: Summary of key preclinical and clinical studies (References: 47–57).

Study type	Model / Infection	Phage approach	Main outcome
In vitro biofilm models	Biofilm cultures	Single phage / cocktails	Reduced biofilm biomass
Animal models	Lung, wound, burn infections	Lytic phages	Decreased bacterial load
Combination studies	In vitro and in vivo	Phage–antibiotic synergy	Enhanced efficacy
Compassionate use	Chronic infections	Personalized phage therapy	Clinical improvement
Clinical trials	MDR infections	Standardized phages	Safety and preliminary efficacy

Challenges and Limitations

Despite bacteriophage therapy has great potential against *Pseudomonas aeruginosa*, there are still a number of scientific, clinical, and regulatory issues that hinder its application. The development of phage-resistant bacterial variants is a major challenge. Bacteria can circumvent the effects of phage by modifying their receptors, restriction-modification, or CRISPR-Cas immunity systems. Although phage resistance may be reduced by a combination of phage cocktails or sequential administration of phage, its occurrence is also a significant factor in therapeutic design (58). There is also a challenge related to immunological responses. Phages introduced into the human body can be neutralized by antibodies or cleared by the reticuloendothelial system, which minimizes their bioavailability and the efficacy of therapy. Although phage therapy has been reported to have a favorable safety profile, there is a need for systematic evaluation of long-term immunogenicity and likely inflammatory outcomes, particularly in cases with repetitive dosing schedules (44). Another major constraint is associated with regulatory and production systems. Compared to traditional antibiotics, bacteriophages are not easily

amenable to standardization, quality control, and large-scale production because they are biological products that differ in nature. Some problems that should be strictly controlled to ensure that current pharmaceutical standards are met include phage purity, stability, genomic safety screening, and batch-to-batch consistency. Additionally, regulatory pathways for phage therapy vary greatly across countries, presenting obstacles to standardized clinical practice (6,59). The clinical implications of the practical use of phages include effective dosing, routes of administration, and treatment duration. Clinical decision-making is challenging and prevents reproducibility across studies because there are no standardized methods and guidelines. Furthermore, most phages have a narrow host range; hence, methods to identify bacteria quickly and accurately and their susceptibility to phages must be established and may not be easily accessible in typical clinical laboratories (60). These limitations suggest a necessity to collaborate in an interdisciplinary manner. The collaborations will include professionals from microbiology, clinician, regulatory agencies, and biotechnology. A collaborative approach will assist in overcoming barriers to realizing the therapeutic capabilities of using phages as treatments *for P. aeruginosa* related illnesses by implementing standardization, improved production techniques and structured clinical trials (61).

Future Perspectives and Research Gaps

The future of bacteriophage therapy for treating *Pseudomonas aeruginosa* will need to address the translation of basic science into practice by addressing critical translational research issues. Most notably, these include the need for well-designed and adequately powered clinical studies that can clearly document efficacy and safety in a diverse population. Bacteriophages require "normal" endpoints, standardized clinical trial design, and long-term follow-up to establish the phage therapeutic approach as a viable standard therapeutic modality and not as an experimental therapeutic modality (62). Future research should also focus on optimization of phage formulations and delivery systems. It is possible to enhance stability and bioavailability at the sites of infection using new methods, for example, encapsulation, aerosolized phage preparations against respiratory infections, and biodegradable carriers for localized delivery (63). Concurrently, rationally planned phage cocktails based on genomic and phenotypic screening of clinical isolates would be possible, increasing coverage and reducing the development of resistance. A new direction in personalized phage therapy is the use of technology based on artificial intelligence and machine learning algorithms to predict phage–host compatibility (64).
Another factor is the growth in the use of engineered phages and phage-derived products. CRISPR-Cas-phage (CRISPR-Cas), which can be selectively targeted to resistance or virulence genes, has the potential to disarm pathogens, but not necessarily to destroy them. Similarly, the enzymes produced by the phage, for example, endolysins and depolymerases, can also be exploited as therapeutics, either as monotherapy or in combination with antibiotics, thereby offering alternative measures to eradicate biofilms (65,66). From a regulatory perspective, more explicit international standards and flexible approval guidelines are required to deal with the distinct biological characteristics of phage-based products. Sharing networks between academic laboratories, industry, and clinical centres would facilitate the rapid translation of experimental findings into standardized treatment platforms (67).

Finally, the ecological and evolutionary implications of phage therapy, such as its effects on the human microbiome and possible coevolutionary relationships between phages and bacterial communities over a long period, warrant further investigation. The research gaps will be important in terms of addressing the issue of bacteriophage therapy integration into the contemporary antimicrobial policy and the sustainability of its use in combating the infection of multidrug-resistant *P. aeruginosa* (68, 69).

Conclusion

Bacteriophage therapy is a promising alternative or complementary approach for the treatment of multi-drug-resistant *Pseudomonas aeruginosa* infections that are associated with biofilms. The fact that it can specifically target bacterial cells, disrupt the architecture of biofilms, and amplify the activity of antibiotics against these bacteria suggests its therapeutic potential in cases of difficult-to-treat infections. Although promising preclinical and early clinical results have been reported, there are significant challenges to consider in the field of phage standardization, regulatory approval, production on an industrial scale, and resistance management. The next steps would rely on clinical trials well designed, in the optimization of the systems of delivery of phages, as well as on the harmonization of the regulatory systems, at the international level. As synthetic biology and precision phage engineering continue to evolve, the potential for further advancements in phage-based therapeutics in the practice of modern antimicrobials exists.

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Competing interest’s statement

The authors declare no conflicts of interest.

Author contributions

The author designed the conception of the study, methodology, manuscript writing, coordinated the research activities, and handled the submission and revision process.

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