

BACTERIOPHAGES: COMPLEMENTARY THERAPY IN ANTIMICROBIAL RESISTANT BACTERIAL STRAINS

Abstract

Bacteriophages, or phages, constitute a class of viruses that selectively infect and replicate within bacterial hosts. Although phage therapy has been employed for nearly a century, the global surge in antibiotic-resistant bacterial strains has revitalized interest in phages as a plausible alternative or adjunctive therapeutic strategy. Traditional phage therapy involves utilizing naturally occurring phages to target and eliminate bacteria at the infection site. Distinguishing themselves from conventional antibacterial agents, phages execute parasitic and enzymatic bactericidal activities, rendering them effective against a broad spectrum of multidrug-resistant bacteria. Recent biotechnological progress has introduced innovative approaches, encompassing bio-engineered phages, phage cocktails, and purified phage lytic proteins, thus expanding the arsenal of phage-based therapeutics. The integration of phage therapy, either as an alternative to antibiotics or in synergy with antibiotic regimens, holds promise for mitigating the escalating challenge of infectious diseases amid the prevailing antibiotic crisis. However, a comprehensive understanding of phage biology is imperative, along with the imperative for rigorous clinical trials to assess phage efficacy across various pathogens, infections, and diseases.

Keywords: Bacteriophages, Antimicrobial Resistant Bacterial Strains

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I. INTRODUCTION

Phages, considered one of the most abundant and widespread biological entities on Earth, were independently discovered in the early 20th century by Frederick Twort and Félix d'Hérelle. Phage therapy, among a spectrum of alternatives to antibiotic treatment, has demonstrated effectiveness in addressing various bacterial infections in both human and animal populations. This arises from the rapid proliferation of multidrug-resistant bacteria globally, coupled with a decline in the development and production of novel antibacterial agents. While the application of phage therapy dates back a century, there remains a notable paucity of randomized clinical trials that align with contemporary standards, which could definitively establish the efficacy of utilizing bacterial viruses to combat bacterial infections. The challenges posed by numerous life-threatening bacterial infections have prompted a reevaluation of bacteriophages by the scientific community. Numerous investigations exploring the use of phages *in vitro*, in experimental animal models, and in human subjects have been conducted in both the United States and Europe (Principi et al., 2019).

Phages typically adhere to specific receptors located on the surface of bacterial cells. They proceed to inject their genetic material into the host cell, after which two scenarios unfold: in the case of temperate phages, this material is integrated into the bacterial genome, allowing for replication alongside the bacterial genetic material and subsequent transmission to daughter cells. Conversely, lytic phages take control of the bacterial replication machinery, orchestrating the production of the succeeding generation of phage progeny. The mature phage particles are ultimately released through the lysis of bacterial cells. Among the most prevalent lytic phages linked to human pathogens and the gut microbiota, the orders Caudovirales stand out. Commonly referred to as "tailed phages," they carry double-stranded DNA genomes. Additionally, the Microviridae group, characterized by tailless, single-stranded DNA viruses, also plays a significant role (Lin et al., 2017). Traditional phage therapy hinges on the utilization of strictly lytic phages, which possess the inherent capacity to decisively exterminate their bacterial hosts.

Bacteria have the capability to establish biofilms, wherein bacterial cells are shielded and possess tolerance against antibiotics, antiseptics, antimicrobials, and host immune responses. Biofilms, comprised of common opportunistic and nosocomial drug-resistant pathogens, have been identified on medical devices such as catheters and prosthetics, leading to numerous complications and secondary bacterial infections. Within the spectrum of investigational approaches, the utilization of bacteriophages stands out as a promising strategy to infiltrate biofilms, potentially subjecting bacteria to unfavorable growth conditions (Singh et al., 2022). The landscape is witnessing an increasing number of clinical trials aimed at assessing the safety and effectiveness of phage therapy in human subjects. As empirical evidence accumulates, regulatory bodies are concurrently working towards establishing guidelines for the clinical application of phages as a therapeutic avenue.

Although the utilization of bacteriophages shows potential, it has yet to achieve widespread adoption. Further research is imperative to ascertain its efficacy and safety profile. The potential non-direct toxic effects of phages on humans and animals remain a topic of uncertainty. Phage therapy remains an evolving field, exhibiting substantial promise while grappling with challenges, including the emergence of phage resistance and the necessity for a tailored treatment approach. Notwithstanding these challenges, advancements

in biotechnology play a pivotal role in the exploration, development, and integration of phage therapy to combat antibiotic-resistant bacteria.

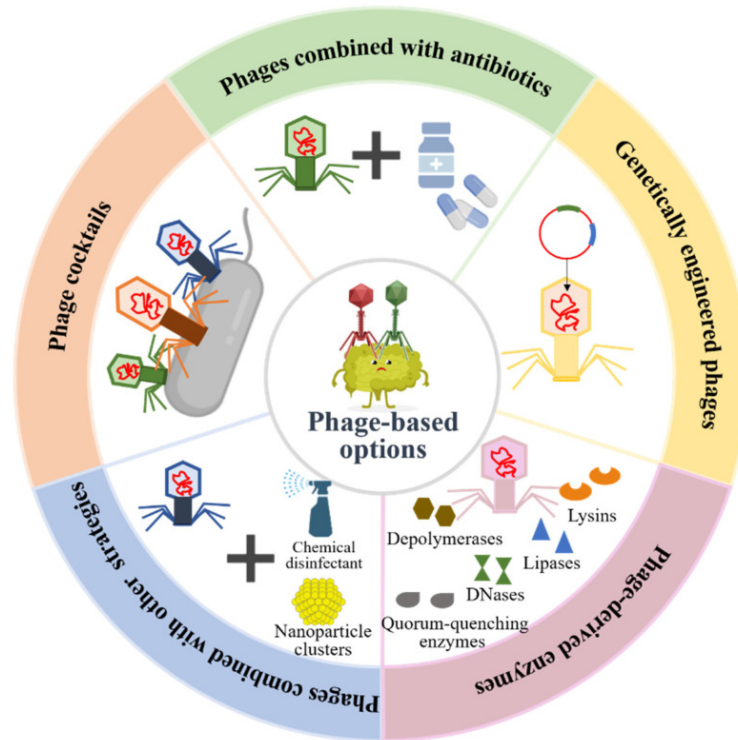
Hence, this chapter delves into the multifaceted ways in which bacteriophages are being investigated to combat antimicrobial resistance. It offers a comprehensive assessment of the advantages and limitations inherent to the application of bacteriophages as complementary therapeutic agents.

II. APPLICATIONS OF BACTERIOPHAGES

Bacteriophages are undergoing active exploration as promising tools in the battle against antimicrobial resistance. Their distinctive ability to selectively target and infect bacteria is the driving force behind their diverse applications:

- 1. Phage Therapy for Specific Antibiotic-Resistant Bacteria:** Phage therapy entails using specific bacteriophages to combat bacterial infections. These phages are either chosen or engineered to eliminate particular bacteria, including antibiotic-resistant strains. This precision allows for targeted treatment, sidestepping the disruption of beneficial microbiota—common with broad-spectrum antibiotics. Administration can be topical, oral, or systemic, contingent on the infection site. Promising results have emerged from phage therapy, particularly in localized infections. Innovations like CRISPR/Cas gene editing have opened novel avenues for phage therapy. Bioengineered phages, for instance, can deliver CRISPR/Cas systems to disrupt antibiotic resistance genes and obliterate antibiotic resistance plasmids, enabling programmed lytic phages to exclusively target antibiotic-resistant bacteria while sparing antibiotic-sensitive counterparts.
- 2. Phage Cocktails:** To counter the limitation of phage therapy, which primarily targets and lyses specific bacterial strains, researchers employ phage cocktails – blends of multiple phages designed to attack various strains or species of bacteria. This strategy augments the prospects of effectively treating infections originating from intricate bacterial populations, including those harboring antimicrobial-resistant strains. Phage cocktails amplify the range and effectiveness of phage therapy, enabling the targeting of a broader spectrum of strains while diminishing the likelihood of bacterial resistance to phages. Phage cocktails can encompass individual phages that, collectively, impact diverse bacterial species. By targeting multiple species, these cocktails can be empirically employed to treat general disease conditions. For instance, Pyophage-type cocktails can be directed at multiple bacterial genera, such as Enterococcus, Escherichia, Proteus, Pseudomonas, Staphylococcus, and Streptococcus, known to cause skin or soft-tissue infections (Abedon et al., 2021).

A well-constructed single-species cocktail should, at a minimum, include one phage targeting a specific group of bacterial strains and a second phage focusing on a slightly different group, both associated with the same species. Alternatively, a phage cocktail could intentionally encompass multiple phage types targeting a solitary bacterial strain. This approach finds relevance when a bacterial pathogen is isolated from an individual patient or when targeting a specific pathogenic bacteria strain prevalent within a community (Abedon et al., 2021).



(Liu *et al.*, 2022)

Figure 1: Phage-based therapeutic options

- Biocontrol in Agriculture and Aquaculture:** Bacteriophages are harnessed as effective biocontrol agents in agricultural contexts, aimed at combatting plant pathogens and foodborne pathogens. This strategy, through the targeted elimination of specific bacterial pathogens, holds the potential to curtail the necessity for antibiotics in agriculture, thereby mitigating the emergence and dissemination of antimicrobial resistance. The notable feature of lytic phages, which infect and eliminate target bacterial species, their self-replicating nature, and compatibility with animal and human species, renders them optimal candidates for roles as agents of food biocontrol and bio-preservation (Garvey, 2020).

In the context of livestock, phages can be administered either through animal feed or by applying them to animal bodies before their sacrifice or slaughter. This precautionary measure aims to prevent meat contamination during harvest. Furthermore, in post-harvest scenarios, phages find utility in disinfecting surfaces, employing the action of phage enzymes to potentially function as food preservatives. Phages have also demonstrated successful applications in agriculture, effectively controlling various bacterial and fungal diseases affecting plants and crops. The utilization of phages as biocontrol agents within aquaculture has shown efficacy through direct applications in water, oral administration through food, and even injection. Consequently, the exploration of phages as a preventive strategy to combat bacterial infections in crops and livestock is gaining momentum.

- 4. Phage-Derived Enzymes:** Bacteriophages contribute a valuable resource of lytic enzymes, functionally akin to the antimicrobial eukaryotic enzyme lysozyme. These enzymes serve to degrade bacterial cell walls, facilitating the liberation of phage progeny. Within the majority of phage species, two principal protein classes play pivotal roles in bacterial host lysis. One class involves the transmembrane protein holin, while the other encompasses a peptidoglycan cell wall hydrolase known as endolysin (or lysin) (Lin et al., 2017). In tandem, these two proteins orchestrate the cascade leading to bacterial cell lysis. Notably, phage endolysins, synthesized towards the culmination of the phage infection's lytic cycle, exhibit the capacity to independently induce bacterial cell lysis. In contrast, holins alone lack this capability. As a result of their rapid action, potent properties, and inactivity against eukaryotic cells, endolysins have garnered substantial attention as potential antimicrobial agents. Demonstrating efficacy against a spectrum of bacteria, including antibiotic-resistant strains, they are being explored as viable alternatives to conventional antibiotics.

Innovative strides have led to the development of bioengineered chimeric lysins, capable of rescuing mice afflicted with MRSA bacteremia (Yang et al., 2014). It's important to note that endolysins exhibit diminished efficacy against gram-negative bacteria due to the impermeable lipopolysaccharide outer membrane characteristic of these organisms. Researchers have consequently endeavored to expand lysin activity towards gram-negative pathogens. This pursuit has led to the creation of artificial lysin molecules termed Artilynsins, proficient at breaching the outer membrane barrier (Briers et al., 2014).

- 5. Phage Sensitization or combination therapy:** Phage sensitization, also referred to as phage-assisted antibiotic therapy, presents a compelling approach wherein phages collaborate with antibiotics to sensitize antibiotic-resistant bacteria. This dynamic duo renders previously ineffective drugs potent against resistant strains. The strategy involves the concurrent application of phages and conventional antibiotics or alternative antimicrobial agents, culminating in an augmented bacterial eradication. The underlying mechanism hinges on the notion that phages disrupt bacterial defense mechanisms, rendering them more susceptible to the actions of antibiotics. The synergy resulting from this combination heightens treatment efficacy while concurrently diminishing the likelihood of phage resistance emergence.

Integrating phages alongside antibiotics yields several benefits. It facilitates the achievement of therapeutic goals with reduced antibiotic dosages, thereby potentially minimizing side effects and attenuating the selective pressure fostering antibiotic resistance. This tandem approach engenders a heightened impact on bacteria compared to the individual application of each treatment component.

However, it is imperative to acknowledge that while the concept of combining phages and antibiotics exhibits promise, navigating this terrain involves complexities and challenges. Notable challenges encompass the identification of apt phages capable of effectively infecting targeted bacteria, comprehensive comprehension of potential interactions between phages and antibiotics, and rigorous preclinical and clinical investigations to ascertain safety and efficacy. As researchers delve into the realm of

phage-antibiotic synergy, they must be attuned to these intricate dynamics and undertake comprehensive explorations to unlock the full potential of this approach.

- 6. Biofilm Disruption by Phages:** Antibiotic-resistant bacteria frequently adopt protective biofilm formations, intricate structures that exacerbate the difficulty of treating infections. Phages have emerged as promising agents for tackling biofilm-associated infections, owing to their ability to disrupt and penetrate these resilient structures. Within this context, approximately 160 putative depolymerases in 143 phages have been identified. These enzymes are categorized into two primary classes: hydrolases encompassing sialidase, levosidase, xylosidase, glucanase, rhamnosidase, and peptidase; and lyases including hyaluronidase, alginate lyase, and pectin/pectin lyase (Pires et al., 2016). These depolymerases, primarily present as free enzymes or tail-spike proteins of phages, exhibit the ability to specifically recognize, adhere to, and digest extracellular polymeric substances (EPSs) associated with host bacterial cells. Consequently, biofilm structures are disrupted, enabling the penetration of phages into the deeper layers of the biofilm.

Parallel to phage-derived enzymes, phages exert a substantial reduction in biofilm viability when employed in conjunction with antimicrobial drugs, compared to individual treatment regimens. This combined approach demonstrates either synergy or facilitation, enhancing overall efficacy. Notably, a study investigating the potential synergistic effect of phages and chemical disinfection against the opportunistic pathogen *Pseudomonas aeruginosa* highlights the effectiveness of combining phages with chemical disinfectants like sodium hypochlorite and benzalkonium chloride. This synergistic interaction improves the removal of wet biofilms and bacterial spots from surfaces, simultaneously thwarting the reconstitution of dry biofilms (Stachler et al., 2021).

The potential of phages to disrupt biofilms presents a promising avenue for addressing biofilm-associated infections, with the prospect of significant therapeutic advancements.

- 7. Genetically Engineered Phages:** While natural phage therapy exhibits limitations owing to their restricted host range and specificity, genetic engineering techniques have emerged as a transformative avenue to bolster the therapeutic capabilities of phages. This innovative approach involves modifying phages to amplify their therapeutic attributes. Genetic manipulation aims to enhance various facets, encompassing phage stability, broadening host range, adjusting host specificity, and curbing the likelihood of resistance development. These enhancements ultimately contribute to long-term efficacy in combating bacterial infections.

Researchers are diligently engaged in formulating biocontainment strategies to forestall inadvertent dissemination of genetically engineered phages within the environment or the human body. This precautionary measure augments safety by preventing unintended consequences. Notably, the utilization of CRISPR-Cas systems, renowned gene-editing tools, empowers researchers to meticulously and selectively modify phage genomes. This precision editing enables targeted and specific alterations that optimize the therapeutic potential of the engineered phages.

It is imperative to emphasize that the development and deployment of genetically engineered phages are rigorously governed by stringent regulatory oversight and comprehensive safety assessments. These measures ensure that potential risks are meticulously minimized, underscoring the paramount importance of safety and efficacy in the utilization of genetically engineered phages for therapeutic purposes.

III. MAJOR ADVANTAGES OF PHAGE THERAPY

Phage therapy's advantageous attributes arise from its specificity, adaptability, and potential for precision treatment. While these merits offer promising solutions for combating antimicrobial resistance, the ongoing research and development of phage-based therapies remain crucial to realizing their full potential in modern medicine.

- 1. Bactericidal Action of Lytic Phages:** Lytic phages, functioning as bactericidal agents, target and eliminate bacterial infections directly. Their ability to lyse bacterial cells contributes to the swift eradication of pathogens.
- 2. Self-Amplification of Phage Dose:** A distinctive characteristic of phage therapy lies in the self-amplification of phage doses. During the bacterial-killing process, phages multiply specifically in locations where their host bacteria are prevalent. This inherent property can enhance treatment efficacy (Abedon and Thomas-Abedon, 2010).
- 3. Low Inherent Toxicity:** Phages consist solely of proteins and nucleic acids, imparting them with low intrinsic toxicity. This natural composition minimizes the risk of harmful side effects.
- 4. Preservation of Normal Flora:** The specificity of phages towards their bacterial hosts translates to minimal disruption of the body's normal microbial flora. This specificity limits collateral damage to beneficial bacteria.
- 5. Narrow Potential for Resistance:** Most phages exhibit a narrow host range, mitigating the potential for inducing widespread phage resistance. This contrasts with antibiotics, where resistance can emerge more readily.
- 6. Versatile Formulation and Application:** Phages offer remarkable formulation and application versatility. They can be administered as phage cocktails, combined with certain antibiotics, and can assume various forms such as liquids, creams, or impregnated solids. This flexibility extends to diverse routes of administration (Loc-Carrillo and Abedon, 2011).
- 7. Efficiency in Achieving Efficacy:** Phages exhibit the ability to proliferate in situ, particularly when bacterial densities are high. This potential holds promise in potentially reducing treatment costs by necessitating lower phage doses to achieve therapeutic effects (Abedon and Thomas-Abedon, 2010). Single-dose treatments can harness this property for optimal efficacy.
- 8. Environmental Friendliness:** As natural entities, phages have a minimal impact on the environment. Their biodegradable nature aligns with eco-friendly therapeutic approaches.

IV. POTENTIAL DISADVANTAGES OF PHAGE THERAPY

The potential disadvantages of phage therapy underline the need for extensive research, rigorous safety assessments, and regulatory frameworks. While these challenges exist, ongoing scientific advancements hold the promise of addressing these concerns and realizing the full potential of phage-based treatments.

- 1. Challenges in Preparation and Standardization:** The preparation and standardization of phages for therapeutic use in humans and animals pose current challenges. Ensuring consistent quality, purity, and safety of phage preparations is a complex endeavor.
- 2. Dose Determination Uncertainty:** The optimal dosage or quantity of phages required for effective therapy remains uncertain. Finding the right balance between achieving therapeutic outcomes and avoiding potential adverse effects is a crucial consideration.
- 3. Uncertain Treatment Duration:** The timeframe within which phage therapy may demonstrate tangible results varies and is not well-established. Predicting the duration of treatment poses uncertainty for both patients and healthcare providers.
- 4. Need for Specific Phages:** The identification and isolation of the precise phage necessary to combat a particular infection can be challenging. Not all infections have readily available phage counterparts.
- 5. Immunological Concerns:** Phages might provoke an immune response, potentially leading to overreaction or immunological imbalances. This immune response's implications and potential long-term effects warrant investigation.
- 6. Single-Bacterium Focus:** While phages are adept at managing infections caused by a single bacterium, clinical cases often involve infections stemming from diverse pathogenic bacteria. Addressing these polymicrobial infections poses challenges.
- 7. Limitation in Phage Diversity:** The existing array of phages may not encompass enough diversity to effectively treat all bacterial infections. The availability of suitable phages for different pathogens may be limited.
- 8. Risk of Phage Resistance:** Similar to antibiotic resistance, the repetitive use of a single phage over extended periods could potentially lead to the development of phage-resistant bacterial strains.
- 9. Lack of Comprehensive Policies:** The clinical application of phages lacks well-defined and comprehensive policies and regulations. A regulatory framework is essential to ensure safe and effective phage therapy.
- 10. Complex Administration:** Unlike antibiotics, administering phages is more intricate. Healthcare professionals require specialized training to accurately prescribe and implement phage therapy, adding complexity to treatment processes.

V. FUTURE DIRECTIONS AND PROSPECTS OF BACTERIOPHAGE RESEARCH AND THERAPY

As the realm of bacteriophage research and therapy continues to evolve, several future directions and prospects hold immense promise in advancing this innovative field:

- 1. Phage Cocktails Advancement:** Further exploration and refinement of phage cocktails, consisting of diverse phages targeting different bacterial strains, could enhance their efficacy against complex infections. Research into optimal combinations and ratios of phages within cocktails may lead to improved therapeutic outcomes.
- 2. Phage Engineering Breakthroughs:** Genetic engineering techniques offer the potential to engineer phages with enhanced properties, such as broader host ranges, increased stability, and optimized therapeutic potential. Continual advances in phage engineering could revolutionize precision targeting and treatment outcomes.
- 3. Synergy with Other Therapeutic Modalities:** Integrating phage therapy with other therapeutic approaches, including antibiotics, immune modulators, and probiotics, holds potential for synergistic effects and improved treatment outcomes. Research into optimal combinations and timing of interventions could lead to more comprehensive treatment strategies.
- 4. Overcoming Bacterial Resistance:** Strategies to counteract bacterial resistance to phages, such as the development of phage cocktails and bioengineered phages, offer avenues to mitigate the emergence of resistance. Continued research into mechanisms of resistance and effective countermeasures is critical.
- 5. Regulatory Framework Enhancement:** The establishment of robust and standardized regulatory frameworks for phage therapy is essential to ensure its safe and effective clinical application. Collaborative efforts between researchers, clinicians, and regulatory authorities will be pivotal in this regard.
- 6. Clinical Trial Expansion:** Conducting well-designed and rigorously controlled clinical trials across various infections and patient populations will provide valuable insights into phage therapy's efficacy, safety, and potential long-term effects. This expansion of clinical evidence is crucial for widespread adoption.
- 7. Personalized Treatment Approaches:** Developing personalized phage therapy approaches, guided by genomic and microbial analysis, could optimize treatment outcomes by tailoring interventions to individual patients' unique microbial profiles.
- 8. Environmental Impact Assessment:** As phage therapy gains traction, assessing its ecological impact on microbial communities in the environment and human microbiomes becomes important. Investigating potential unintended consequences will be crucial for responsible implementation.

9. Educational Initiatives: Initiatives to educate healthcare professionals, researchers, and the public about phage therapy's principles, benefits, and limitations can facilitate its acceptance and responsible use.

10. Global AMR Mitigation: Bacteriophages' potential role in addressing the global antimicrobial resistance (AMR) crisis cannot be understated. Continued research, collaboration, and strategic implementation can contribute significantly to combatting AMR.

VI. CONCLUSION

In the backdrop of an escalating global concern over antibiotic-resistant bacterial infections, the potential of phages as alternative therapeutic agents stands out prominently. The advantages they offer, coupled with their relatively limited drawbacks, present a promising avenue in the battle against antimicrobial resistance.

However, it is imperative to recognize that while phages hold immense potential, their integration into mainstream medical practice comes with its share of challenges. Paramount among these challenges is the imperative for standardization, ensuring the safety of phage therapies, refining the selection and delivery mechanisms of phages, achieving large-scale production capacities, and cultivating a deeper comprehension of the intricate dynamics between phages and bacteria. A looming concern involves the possible emergence of phage resistance, necessitating comprehensive investigations into strategies to counter this potential development.

Yet, the landscape is marked by hope and progress. Unwavering research endeavors and the continued march of technological innovations propel the trajectory of phage-based treatments forward. As the scientific community delves deeper into the nuances of phage therapy, the potential to forge effective interventions against the scourge of antibiotic-resistant bacteria becomes increasingly tangible. With each breakthrough and insight, we edge closer to unlocking the full potential of phages, ushering in an era where precision antimicrobial therapies revolutionize the battle against infectious diseases.

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