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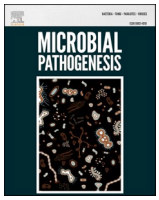

Phage therapy: A targeted approach to overcoming antibiotic resistance

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ABSTRACT

The rise of antibiotic-resistant bacterial infections has become a significant global health threat, necessitating the need for alternative therapeutic strategies. The use of bacteriophages—viruses that particularly infect and lyse bacteria—in phage therapy has resurfaced as a potentially effective substitute for conventional antibiotics. This narrative review aims to explore the mechanisms, applications, challenges, and prospects of phage therapy in combating antibiotic-resistant infections. A thorough analysis of the literature was carried out by exploring online databases, such as Google Scholar, PubMed, Scopus, and Web of Science. The search focused on peer-reviewed articles, clinical trials, and authoritative reports published in the last 10 years. The review synthesized findings from studies on phage mechanisms, therapeutic applications, regulatory challenges, and advances in phage engineering. Phage therapy demonstrates several advantages over antibiotics, including high specificity for target bacteria, the ability to penetrate biofilms, and a lower propensity for resistance development. However, significant challenges remain, such as regulatory and production hurdles, the potential for phage resistance, and interactions with the host immune system. Advances in genetic engineering have enhanced the therapeutic potential of phages, and personalized phage therapy is emerging as a viable approach for tailored treatments. Phage therapy holds significant promise as an alternative to antibiotics, particularly in the fight against antibiotic-resistant bacteria. While challenges persist, ongoing research, technological advancements, and collaborative efforts are crucial for integrating phage therapy into mainstream clinical practice, potentially revolutionizing the treatment of bacterial infections and addressing the global antibiotic resistance crisis.

1. Introduction

Antibiotics have revolutionized medical practice since their discovery in the early 20th century, transforming once-fatal bacterial infections into diseases that can be managed or even cured. Alexander Fleming's 1928 discovery of penicillin was a turning point in medical history since it sparked the creation of a wide range of antibiotics that have saved countless lives [1]. However, the extensive success of antibiotics has resulted in their excessive use and misuse [2]. Frequently, antibiotics are inappropriately prescribed for viral infections, where they are ineffective or used excessively in agriculture and animal husbandry to promote growth and prevent disease in livestock [3]. This rampant misuse has created an environment conducive to the evolution of antibiotic-resistant bacteria, which presents a major threat to global health.

Antibiotic resistance arises when bacteria evolve mechanisms that allow them to withstand the effects of antibiotics, which would typically kill them or prevent their growth. This resistance can develop through several mechanisms, including genetic mutations or the acquisition of resistance genes from other bacteria through horizontal gene transfer [4,5]. As these resistant bacteria spread, they render conventional treatments ineffective, resulting in prolonged illnesses, elevated healthcare

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costs, and an increased risk of mortality [6,7]. The World Health Organization (WHO) has recognized the severity of this issue, declaring antibiotic resistance as one of the top ten global public health threats [8]. The rise of multidrug-resistant (MDR) and extensively drug-resistant (XDR) bacteria has brought the world to a critical juncture where some infections are becoming increasingly difficult, if not impossible, to treat with current antibiotics [9–11]. The necessity of alternative treatments that can effectively tackle bacterial infections without making the issue of resistance worse has been sparked by this predicament [12].

Among the most promising alternatives to traditional antibiotics is phage therapy, a treatment approach that predates antibiotics but has gained renewed interest considering the current resistance crisis. Bacteriophages, or phages, are viruses that exclusively target and infect bacteria. These microscopic entities were first discovered independently by Frederick Twort in 1915 and Félix d'Hérelle in 1917 [3]. In contrast to broad-spectrum antibiotics, which can impact a wide variety of bacterial species, phages are highly specific, typically targeting only a single species or even a specific strain of bacteria. This specificity stems from the phage's ability to recognize and bind to specific receptors located on the surface of bacterial cells, initiating a process that leads to the bacterium's destruction [13].

Phage therapy entails the deliberate the application of phages to fight bacterial infections. The treatment approach is simple: once a phage attaches to its bacterial target, it inserts its genetic material into the bacterium, hijacking the bacterial machinery to produce new phage particles. This process, called the lytic cycle, ends with the lysis or rupture of the bacterial cell, releasing new phages capable of infecting additional bacteria. The ability of phages to self-amplify at the infection site presents a notable benefit, potentially diminishing the need for repeated doses [14]. The specificity of phages presents both strengths and challenges in their therapeutic application [15]. On one hand, phages can precisely target pathogenic bacteria, sparing beneficial bacteria and reducing the disruption to the host's microbiota. However, this specificity necessitates a thorough understanding of the bacterial pathogen in order to choose the correct phage, making treatment more complex compared to the broad-spectrum effectiveness of conventional antibiotics [2]. Despite these hurdles, the prospects of phage therapy to address antibiotic-resistant infections represents a promising and innovative avenue in the fight against bacterial diseases.

As conventional antibiotics become increasingly ineffective, phage therapy presents a novel and promising approach to addressing this challenge by leveraging the natural bactericidal properties of bacteriophages. This review seeks to offer an in-depth analysis of the present status of phage therapy, highlighting its potential advantages over traditional antibiotics, particularly in treating multidrug-resistant infections. The novelty of this review lies in its in-depth analysis of the latest research, clinical trials, and technological advancements in phage therapy, offering insights into how this century-old treatment could be integrated into modern medical practice. The objective is to critically assess the feasibility of phage therapy as a mainstream alternative to antibiotics, identify the key challenges that must be overcome, and outline future directions for research and clinical application, ultimately contributing to the broader discourse on innovative solutions to combat bacterial infections.

2. Method

This narrative review was conducted to synthesize existing literature on the use of phage therapy as an alternative to antibiotics, particularly in the context of combating antibiotic-resistant bacterial infections. The review process involved a comprehensive search and analysis of relevant academic articles, clinical studies, and reviews published in peer-reviewed journals, as well as authoritative reports from global health organizations such as the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC). The literature search was conducted using electronic databases including PubMed, Scopus, Web of Science, and Google Scholar. Keywords used in the search included "phage therapy," "bacteriophages," "antibiotic resistance," "multi-drug resistant bacteria," "clinical trials," and "alternative therapies." The search focused on publications from the past 10 years to ensure that the review incorporated the most recent and relevant research, though seminal works and key historical studies were also considered to provide context.

Selection criteria for the articles included in the review were based on their relevance to the topic, the robustness of the study design, and the quality of the evidence presented. Studies that addressed the mechanisms of phage action, clinical applications, challenges, and advancements in phage therapy were prioritized. Articles that provided insights into the regulatory and ethical considerations surrounding phage therapy were also included to offer a comprehensive overview of the field. The gathered literature was systematically reviewed and categorized into key thematic areas, such as the history and background of phage therapy, mechanisms of action, therapeutic applications, challenges, and future directions. Data and findings from the selected studies were critically analyzed to identify trends, gaps in knowledge, and areas for further research.

3. Mechanisms of phage action

Bacteriophages, or phages, represent a highly specialized form of viral life that specifically targets bacteria. Their mechanism of action is unique and differs significantly from that of traditional antibiotics [16]. While antibiotics often exert a broad-spectrum effect, indiscriminately killing or inhibiting a wide range of bacteria, phages operate with precision, attacking only their designated bacterial hosts as highlighted in Table 1. This specificity, combined with their ability to evolve alongside bacterial populations, positions phages as a powerful tool in the fight against antibiotic-resistant infections [17]. Fig. 1 illustrates an overview of the phage therapy application process in mainstream medical practice. Understanding the mechanisms of phage action is critical to appreciating their therapeutic potential and the challenges that must be addressed to integrate phage therapy into mainstream medical practice.

3.1. Phage life cycles

One of the most fundamental aspects of phage action is their life cycle, of which there are two main types: the lytic and the lysogenic cycles respectively [17]. The lytic cycle is particularly relevant for therapeutic applications because it involves the direct destruction of bacterial cells. In this cycle, a phage uses its tail fibers to attach to the surface of a susceptible bacterium, which recognizes specific receptors on the bacterial cell wall. The phage inserts its genetic material into the host cell after attaching, effectively hijacking the bacterial cellular machinery. The phage's DNA then directs the bacterium to produce viral components—such as proteins and nucleic acids—required to assemble new phage particles. As the phage replicates within the bacterium, the bacterial cell becomes filled with newly formed phages. After the bacterial cell is eventually forced to rupture due to the buildup of phage particles, fresh phages are released into the surrounding environment. These phages can then infect adjacent bacteria, perpetuating the cycle of infection and destruction [10,35,52]. The bactericidal nature of the lytic cycle underpins the therapeutic potential of phages, making them an effective weapon against bacterial infections—especially antibiotic-resistant ones. (See Fig. 2).

In contrast, the lysogenic cycle, although not typically utilized in phage therapy, offers a different perspective on phage-bacterial interactions. The genetic material of the phage merges with the bacterial genome during the lysogenic cycle and remains dormant, replicating alongside the bacterial DNA during cell division (See Fig. 2). This state can persist until specific triggers, such as environmental stress, induce the phage to enter the lytic cycle. While the lysogenic cycle does not

Table 1
Comparison of phage therapy and antibiotics.

Aspect	Phage Therapy	Antibiotics
Mechanism of Action	Phages are viruses that specifically infect and lyse bacterial cells by injecting their DNA, hijacking the bacterial machinery to replicate, and ultimately causing cell lysis [18].	Antibiotics function by disrupting bacterial processes such as cell wall synthesis, protein synthesis, DNA replication, or metabolic pathways, depending on the specific class of the antibiotic [19–21].
Specificity	Highly specific; phages target only specific bacterial strains or species, depending on their receptor-binding proteins. This reduces collateral damage to beneficial microbiota [22].	Varies by antibiotic; broad-spectrum antibiotics affect a wide range of bacterial species, including non-pathogenic ones, while narrow-spectrum antibiotics are more selective [23].
Resistance Development	Lower likelihood; phages co-evolve with bacteria, potentially reducing the chances of long-term resistance. However, bacteria can develop resistance through receptor mutations or CRISPR-Cas systems [24–27].	High likelihood; that bacteria can develop resistance through mutations, efflux pumps, biofilm formation, or acquiring resistance genes, leading to multidrug-resistant (MDR) strains [2].
Impact on Microbiota	Minimal impact; due to their specificity, phages generally do not affect non-target bacteria, preserving the host's normal microbiota and reducing the risk of dysbiosis [28].	Broad-spectrum antibiotics have the potential to disturb the balance of the host's microbiota, leading to dysbiosis and potential secondary infections like *Clostridium difficile* [29].
Self-Amplification	Yes; phages replicate at the site of infection, potentially increasing their concentration where they are most needed and reducing the frequency of administration [30,31].	No; antibiotics do not replicate and require repeated dosing to maintain therapeutic levels in the body.
Biofilm Penetration	Effective; phages can breakthrough and disturb biofilms, which are organised bacterial colonies that are often resistant to antibiotics [32–35].	Often ineffective; many antibiotics struggle to penetrate biofilms, making these bacterial communities particularly difficult to treat [36].
Immune Response	Phages can be recognized and neutralized by the host immune system, potentially limiting their efficacy, especially after repeated administrations. Strategies like encapsulation are being explored to mitigate this [37–39].	Generally stable; antibiotics are chemical agents that are less likely to be neutralized by the immune system, though resistance development remains a concern [40].
Regulatory Approval	Complex; each phage or phage cocktail must be approved for specific bacterial strains, requiring detailed characterization and validation, which complicates the approval process [41,42].	Standardized; antibiotics typically undergo a more streamlined approval process, especially broad-spectrum agents, though approval is still rigorous to ensure safety and efficacy [43].
Production and Quality Control	Challenging; large-scale production of phages requires stringent quality control to ensure purity, stability, and consistent efficacy, with challenges in standardizing phage cocktails [44,45].	Well-established; antibiotic production is standardized with well-developed protocols for ensuring purity, stability, and consistency across batches [46].
Dosing and Administration	Dosing can be complex due to phage replication dynamics; often administered topically, orally, or intravenously, depending on the infection type and location [47,48].	Typically straightforward; dosing is usually standardized and can be administered orally, intravenously, or intramuscularly, depending on the infection and antibiotic used [49].
Cost and Accessibility	Currently higher due to production challenges and the need for personalized treatments; accessibility is limited outside research settings, though this may improve with technological advancements [50].	Generally lower and more accessible due to mass production, established supply chains, and the availability of generic formulations [51].

result in immediate bacterial destruction, it represents a form of coexistence between the phage and the bacterium. This cycle may aid in the horizontal transmission of genes that confer resistance to antibiotics, among bacterial populations, a phenomenon that complicates the landscape of bacterial resistance [30,35,53,54]. However, it is the lytic cycle that holds the most promise for therapeutic applications due to its ability to rapidly reduce bacterial populations through cell lysis.

The phage binds to the bacterial cell during the lytic cycle, injecting its DNA, which then circularises. To create new phage DNA and proteins and assemble them into new virions, the phage DNA hijacks the machinery of the host cell. As a result, additional phage particles are released, and cells lyse. During the lysogenic cycle, the phage DNA combines with the bacterial chromosome to form a prophage. During regular cell division, the prophage and the bacterial DNA are reproduced. The prophage may occasionally be removed from the bacterial chromosome and re-enter the lytic cycle. The major steps in both cycles are depicted in the diagram, along with the variations in phage behaviour and the bacterial host's outcome.

3.2. Specificity and selectivity

A critical feature of phages is their specificity and selectivity for their bacterial hosts [52,55]. Unlike antibiotics, which often affect a broad spectrum of bacteria, including beneficial commensal species [56], Phages have high specificity, typically just affecting one species of bacteria, or perhaps only one specific strain [30,57]. The phage's capacity to identify and attach to particular receptors on the bacterial cell surface determines this specificity. For instance, a phage that infects *Escherichia coli* may not affect other bacterial species, such as *Staphylococcus aureus* [35]. This targeted action is advantageous in therapeutic contexts because it minimizes collateral damage to the host's normal microbiota, preserving the beneficial bacteria that play crucial roles in human health, such as those in the gut microbiome. However, this specificity also poses a challenge: accurate identification of the bacterial pathogen is necessary for the successful application of phage therapy. and the corresponding phage. This necessitates sophisticated diagnostic tools and a well-characterized library of phages, which can complicate treatment compared to the use of broad-spectrum antibiotics [58,59].

3.3. Advantages over antibiotics

In the age of increasing antibiotic resistance, phage therapy presents a viable substitute due to its several noteworthy benefits over conventional antibiotics. The ability of phages to precisely eliminate harmful bacteria while protecting healthy microbiota is one of their most prominent advantages. This is particularly important in environments such as the human gut, where the preservation of beneficial bacteria is crucial for maintaining health and preventing secondary infections [17]. Another advantage is the self-amplifying nature of phages at the site of infection. As phages replicate within bacterial cells, they increase in number, potentially reducing the need for repeated dosing [30,31,60].

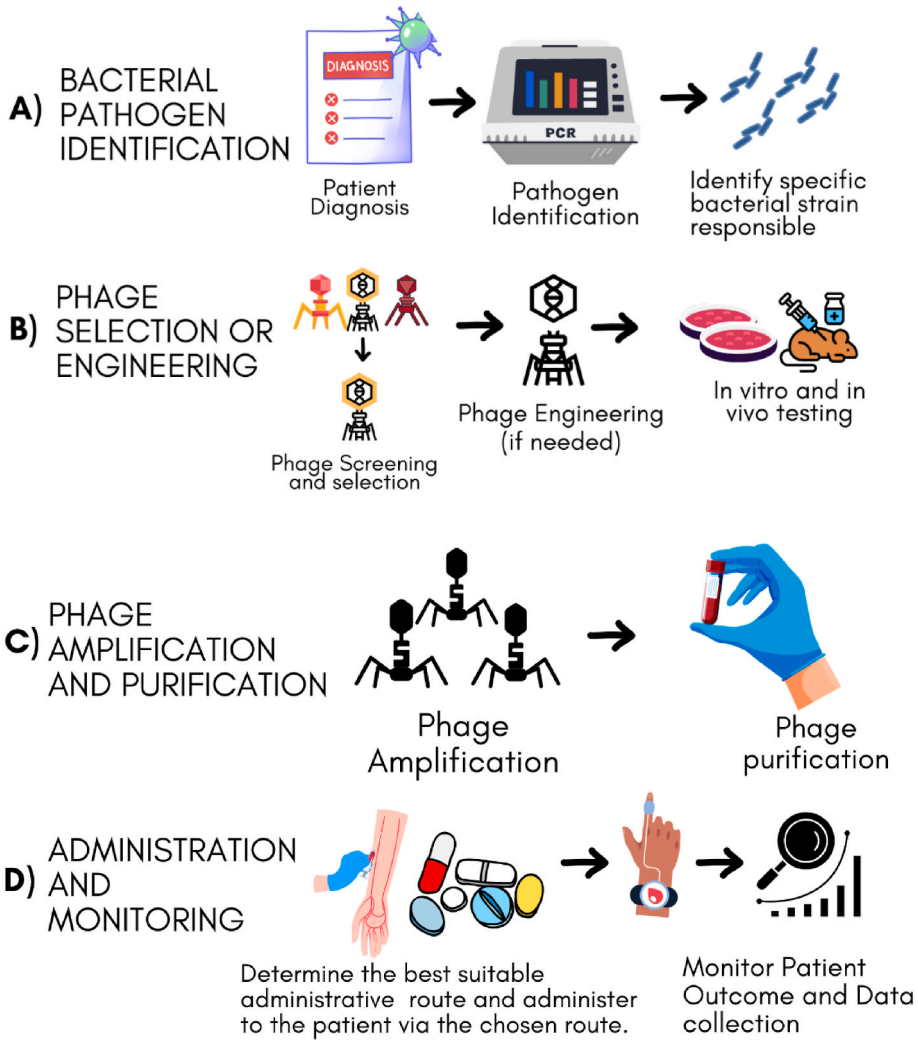

Fig. 1. Overview of the phage therapy application process in mainstream medical practice A) **Bacterial Pathogen Identification**, where patient diagnosis is followed by the identification of the pathogen through techniques like PCR to determine the specific bacterial strain responsible for the infection. B) **Phage Selection or Engineering**, which includes screening phages to find those effective against the pathogen and, if necessary, engineering them for enhanced effectiveness, followed by in vitro and in vivo testing to ensure safety and efficacy. C) **Phage Preparation**, where effective phages are amplified and purified to produce high-quality preparations for therapeutic use. D). **Administration and Monitoring**, where the best route for phage administration is selected, the phages are administered to the patient, and the patient is monitored to evaluate the therapy's effectiveness and collect data for potential adjustments.

This characteristic could improve treatment efficacy and reduce the burden on patients, particularly in situations of severe or chronic infections.

Additionally, phages have the special ability to enter and disrupt bacterial biofilms, the structured groups of bacteria enclosed in a protective extracellular matrix [61,62]. Biofilms are notoriously resistant to antibiotics due to the physical barrier they create and the presence of dormant bacterial cells that are less susceptible to antibiotic action [63]. Phages, however, can infiltrate biofilms and lyse bacteria from within, offering a powerful tool to combat biofilm-associated infections, which are common in chronic wounds, medical implants, and respiratory infections in people with cystic fibrosis [64–69]. Moreover, the evolutionary link that exists between bacteria and phages adds another layer of advantage [70]. Phages can evolve in response to bacterial defense mechanisms, potentially reducing the likelihood of long-term resistance development. This dynamic interaction contrasts with the static nature of antibiotics, where once resistance develops, it tends to persist and spread. Phage flexibility to co-evolve with their bacterial hosts offers a promising solution to one of the most important problems in modern medicine: the relentless rise of antibiotic resistance.

4. Therapeutic applications of phage therapy

Phage therapy, with its highly targeted action against specific bacterial pathogens, has become apparent as a promising substitute for traditional antibiotic treatments, particularly in the context of the increasing risk that bacteria resistant to antibiotics represent. The ability of phages to selectively infect and lyse bacterial cells offers a potential solution to infections that are no longer responsive to conventional antibiotics. This section explores the various therapeutic applications of phage therapy, ranging from its use in treating antibiotic-resistant infections to its combination with antibiotics and its application in agriculture and veterinary medicine. Some techniques enable precise genetic modifications to increase bacteriophages' potential for therapeutic use in targeting bacterial infections as shown in Fig. 3.

4.1. *Treatment of antibiotic-resistant infections*

One of the most compelling applications of phage therapy is its potential to treat infections caused by multi-drug resistant (MDR) bacteria [71]. As antibiotic resistance continues to rise globally, illnesses brought on by bacteria, like *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and

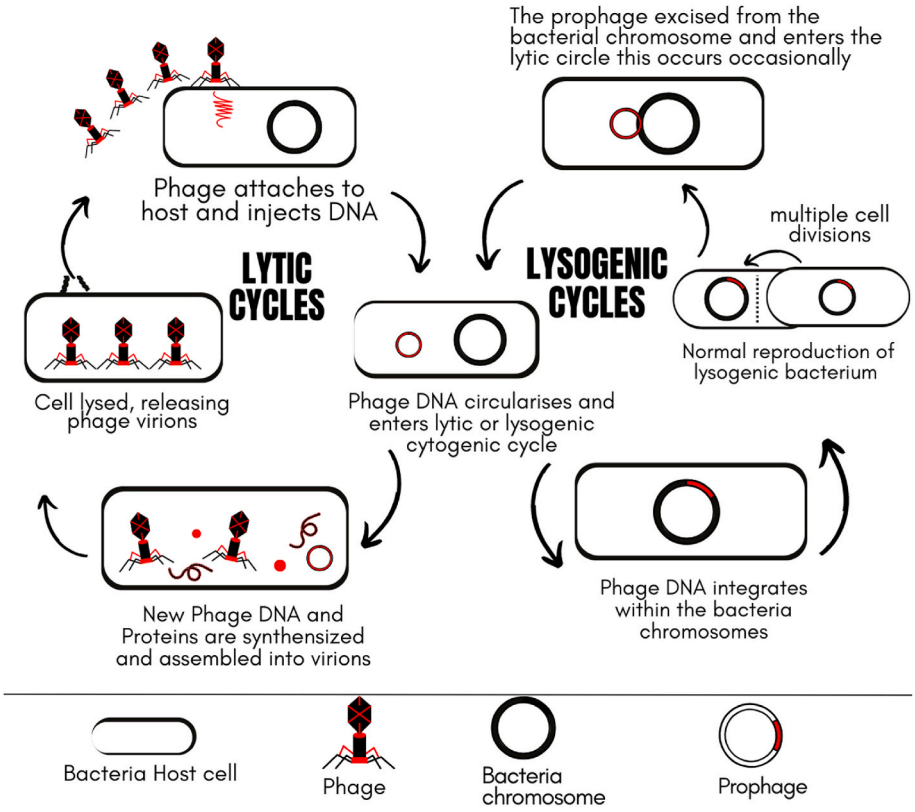

Fig. 2. Mechanism of phage action in the lytic and lysogenic cycles.

Escherichia coli have become increasingly difficult to manage [72,73]. Numerous diseases, including sepsis, respiratory tract infections, urinary tract infections, and infections of the skin and soft tissues, are caused by these bacteria. In numerous clinical cases, phage therapy has demonstrated its efficacy in eradicating infections that were unresponsive to standard antibiotic treatments. For instance, in cases of chronic wound infections where *Staphylococcus aureus* is resistant to methicillin (MRSA), phage treatment has been effectively applied to clear the infection, often after all alternative forms of therapy had been tried and failed [74]. Similarly, phages targeting *Pseudomonas aeruginosa*, a common pathogen in cystic fibrosis patients, have been employed to reduce bacterial load and improve patient outcomes, especially in instances where the bacteria have developed resistance to multiple antibiotic classes [75,76]. The success of these cases underscores how effective phage therapy may be in treating infections that are resistant to antibiotics, offering hope in situations where traditional therapies fail.

4.2. Phage therapy in combination with antibiotics

While phage therapy alone has shown significant promise, combining it with antibiotics can further enhance treatment efficacy, particularly in complex or persistent infections [77]. One of the key obstacles in treating bacterial infections is the presence of biofilms—communities of bacteria that are encased in a defensive extracellular matrix, which increases their resistance to antibiotics. Phages possess a special capacity to infiltrate and disturb these biofilms, which not only aids in reducing the bacterial population but also makes the remaining bacteria more susceptible to antibiotic treatment. This synergistic effect has been demonstrated in several studies where combining antibiotics with phages resulted in more effective clearance of illnesses caused by bacteria compared to either treatment alone [78–81]. For instance, in chronic respiratory infections caused by *Pseudomonas aeruginosa*, a pathogen known for its ability to form robust biofilms, the use of phages in conjunction with antibiotics has led to significant improvements in patient outcomes [82–85]. This combination approach is particularly valuable in treating persistent infections where bacteria have become entrenched in biofilms or when the bacterial load is high, thereby requiring a multi-faceted therapeutic strategy.

Moreover, combination therapy can potentially prevent or delay the development of antibiotic and phage resistance. By simultaneously attacking bacteria through different mechanisms—phages disrupting cell walls and biofilms, and antibiotics targeting bacterial metabolism or protein synthesis—the likelihood of bacteria developing resistance to both agents is reduced [86,87]. This approach not only enhances the immediate efficacy of the treatment but also helps in maintaining the long-term effectiveness of both antibiotics and phages, which is crucial in the ongoing battle against antibiotic resistance.

4.3. Phage therapy in agriculture and veterinary medicine

Beyond its applications in human medicine, phage therapy is also being increasingly explored in agriculture and veterinary medicine as an approach to lessen the reliance on antibiotics in livestock and poultry farming [88]. The widespread use of antibiotics in these industries has contributed to the acceleration of antibiotic resistance, as bacteria in animals can develop resistance that may then be transferred to humans through the food chain. Phage therapy offers a promising alternative for controlling bacterial infections in animals, thereby promoting improved animal health and decreased antibiotic usage [89].

Studies have shown that phages can effectively target and eliminate bacterial pathogens in animals, leading to healthier livestock and safer food products. For instance, phage therapy has been used to control *Salmonella* and *Campylobacter* infections in poultry, *E. coli* infections in cattle, and *Staphylococcus aureus* infections in dairy cows [90–93]. These applications not only improve the health and productivity of livestock but also reduce the risk of transmitting antibiotic-resistant bacteria to humans through meat, dairy, and other animal products. Additionally,

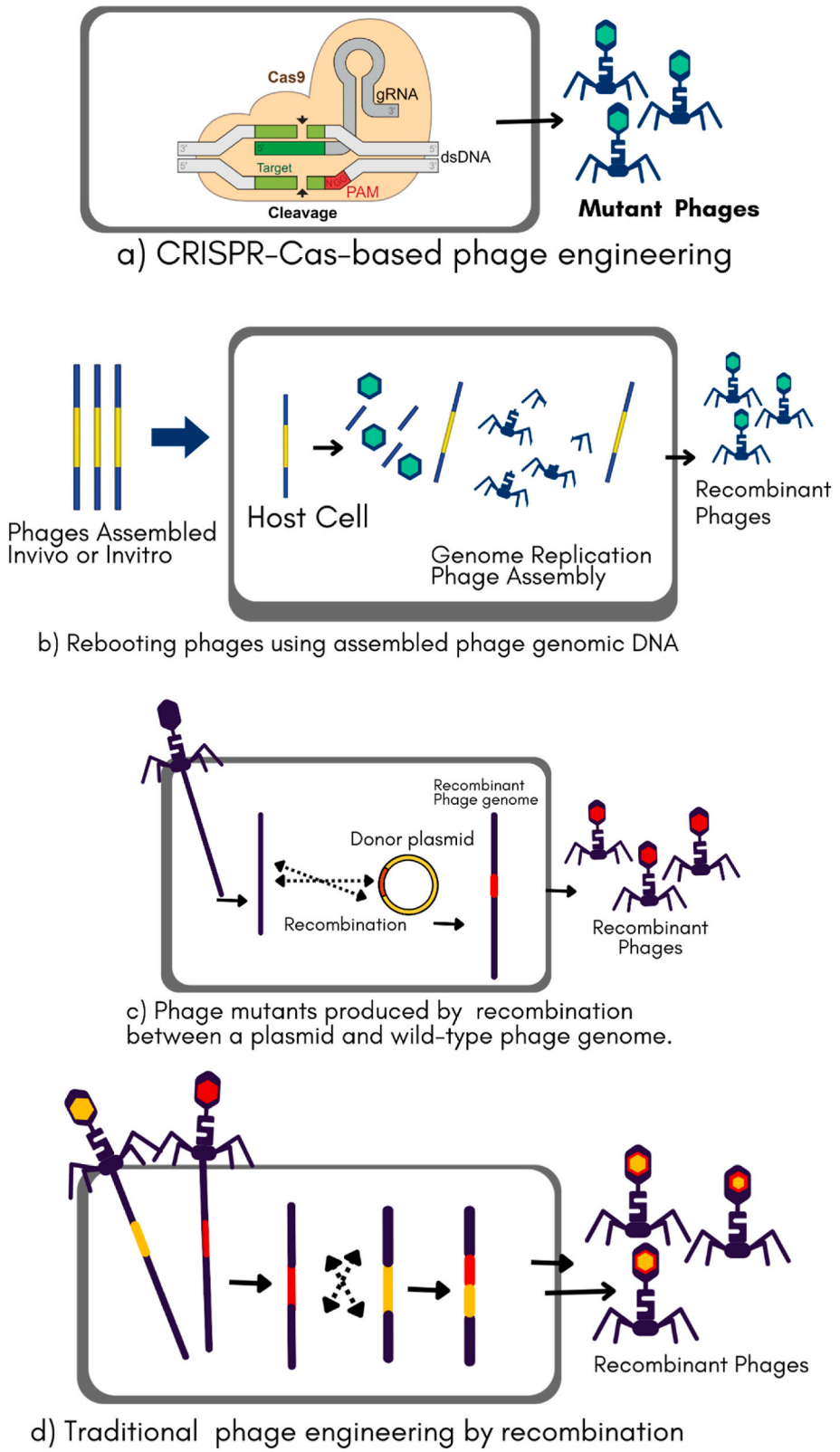

Fig. 3. Key approaches and techniques to modify bacteriophages for enhanced therapeutic potential. *(a)* ***CRISPR-Cas-based phage engineering*** *involves using the CRISPR-Cas9 system to introduce specific mutations into the phage genome, resulting in mutant phages with desired traits. (b)* ***Rebooting phages using assembled phage genomic DNA*** *involves synthesizing phage genomes* in vitro *or* in vivo*, which are then introduced into host cells to generate recombinant phages through genome replication and phage assembly. (c)* ***Phage mutants produced by recombination*** *use a donor plasmid and wild-type phage genome to create recombinant phages with altered genetic material. (d)* ***Traditional phage engineering by recombination*** *involves exchanging genetic material between phage genomes, resulting in recombinant phages with modified characteristics.*

phage therapy in agriculture aligns with the growing demand for antibiotic-free and sustainable farming practices, offering a natural and targeted approach to disease management in animals [94–96]. The use of phage therapy in agriculture and veterinary medicine also has significant implications for food safety and public health. By controlling bacterial infections in livestock without the use of antibiotics, the spread of antibiotic-resistant bacteria can be curtailed, ultimately reducing the burden of antibiotic resistance in human populations.

5. Challenges and limitations of phage therapy

Despite the promising possibility of phage therapy as a substitute or complement to antibiotics, prior to its widespread adoption, a number of obstacles and restrictions need to be resolved. in clinical practice. These challenges range from regulatory and production issues to biological obstacles such as phage resistance and immune system interactions [97–100]. Phages entering the bloodstream can interact extensively with the host immune system, triggering both innate and adaptive responses as shown in Fig. 4. Each of these factors plays a crucial function in establishing the feasibility and efficiency of phage treatment and must be carefully considered to advance this therapeutic approach. Despite its potential, phage therapy faces significant challenges, including regulatory hurdles, production complexities, and phage resistance, as outlined in Table 2. Addressing these issues requires innovative strategies such as phage cocktails, enhanced production methods, and better regulatory frameworks. Overcoming these challenges is crucial for integrating phage therapy into mainstream clinical practice.

5.1. Regulatory and production challenges

One of the most significant challenges facing the widespread implementation of phage therapy is the regulatory framework, particularly in regions like the United States and Europe. Unlike antibiotics, which typically have broad-spectrum activity and can be approved for a wide range of infections, phages are highly specific to particular bacterial strains [42]. This specificity requires that each phage or phage cocktail be individually evaluated and approved for specific bacterial infections, greatly complicating the regulatory approval process. The current regulatory landscape, largely designed with broad-spectrum antibiotics in mind, does not easily accommodate the unique nature of phage therapy, causing delays and barriers in introducing phage-based treatments to market.

In addition to regulatory hurdles, the production of phages at a large scale presents several challenges [107,108]. Phage therapy requires the production of phages that are pure, stable, and consistent across batches, which is more complex than the production of traditional antibiotics. The quality control measures necessary to ensure that phages do not contain contaminating bacteria or other pathogens and that they maintain their infectivity and stability over time are rigorous and costly. Furthermore, phages must be produced in sufficient quantities to meet therapeutic needs, which can be challenging given the need for customization based on the specific bacterial strain being targeted. These production challenges add to the cost and complexity of developing phage therapies, potentially limiting their availability and accessibility.

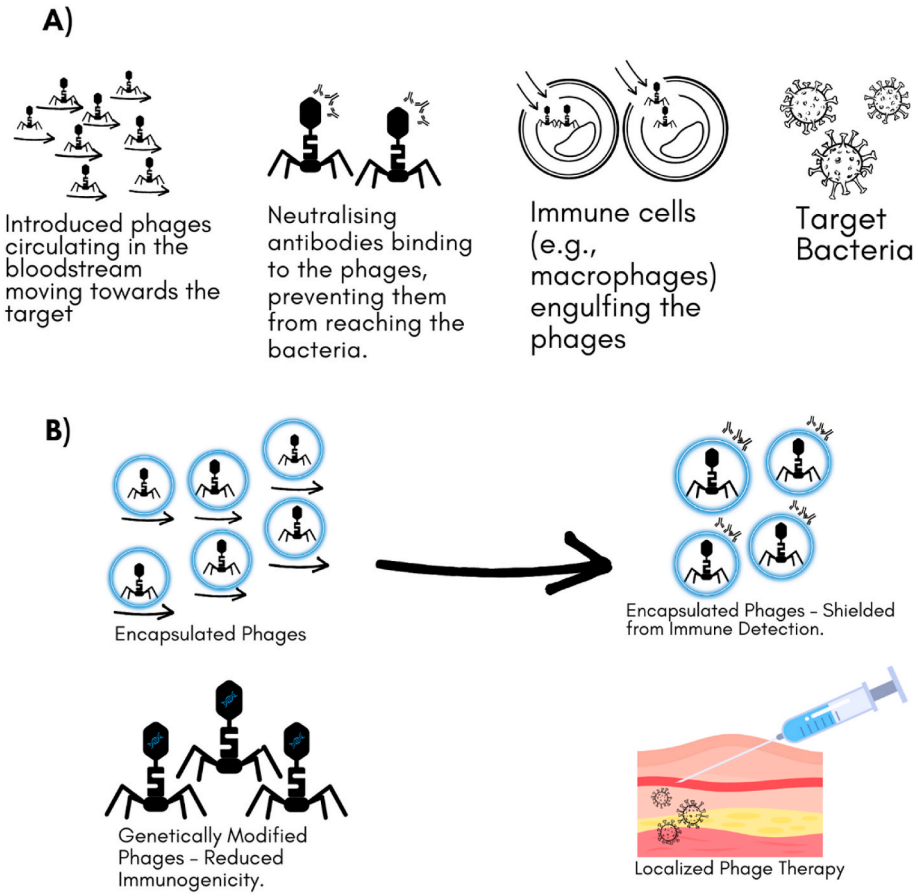

Fig. 4. Phage immune detection in the bloodstream and approaches for overcoming it. A) The immune system recognizes phages when they are injected into the bloodstream. As a result, immune cells such macrophages engulf the phages and neutralizing antibodies attach to them, blocking the phages from reaching their bacterial targets. B) Using genetically modified phages to lessen their immunogenicity, encapsulating phages to prevent immune recognition, and localised phage therapy to reduce systemic exposure.

Table 2
Challenges in phage therapy implementation.

Challenge	Description	Potential Solutions
Regulatory Approval	Phages require individualized approval for each bacterial strain; regulatory frameworks are not yet standardized for phage therapy [97].	Develop flexible, adaptive regulatory frameworks; create guidelines specific to phage therapy.
Production and Quality Control	Ensuring purity, stability, and consistency in large-scale phage production is complex and costly [101].	Invest in advanced biomanufacturing technologies [102]; establish standardized production protocols.
Phage Resistance	Bacteria may get resistant to phages via receptor mutations or defense mechanisms [27,103].	Use phage cocktails; engineer phages to target multiple bacterial receptors [58,104].
Immune System Neutralization	The immune system of the host may identify and neutralize phages, reducing their efficacy [99].	Develop encapsulated or genetically modified phages to evade immune detection.
Phage-Bacteria Matching	Effective treatment requires precise matching of phages to bacterial strains, complicating treatment [42].	Expand phage libraries; improve diagnostic tools for rapid bacterial identification [105].
Public and Clinical Awareness	Limited awareness among clinicians and patients about phage therapy and its benefits [101].	Conduct educational campaigns; publish successful case studies and clinical trial outcomes.
Clinical Guidelines	Lack of standardized protocols for phage therapy use in clinical settings [106].	Develop and disseminate clinical guidelines based on emerging research and trial data.
Cost and Accessibility	High costs associated with personalized phage therapy and limited availability [50].	Scale-up production; research cost-effective manufacturing processes; establish funding mechanisms.

5.2. Phage resistance

Although phage therapy presents a novel method for fighting bacterial infections, it is still susceptible to the issue of resistance. Just as bacteria can develop resistance to antibiotics, they can also evolve mechanisms to resist phage infection. Phage resistance can develop through various pathways, including mutations in the bacterial receptors that phages rely on for attachment and penetrate the cell, or through the acquisition of defense mechanisms against phages, like CRISPR-Cas, which allows bacteria to "remember" and target phage DNA [103,109]. Phage resistance can develop through various pathways, including mutations in the bacterial receptors that phages rely on for attachment. However, unlike antibiotic resistance, which tends to be permanent and transmissible, phage resistance can sometimes be mitigated or reversed. One strategy to overcome phage resistance is the use of phage cocktails, which are mixtures of different phages that target the same bacterial species but use different receptors or mechanisms of action [110]. By attacking the bacteria from multiple angles, phage cocktails reduce the likelihood that bacteria will simultaneously develop resistance to all the phages in the mixture. Another strategy is the genetic engineering of phages to alter their binding sites or to bypass bacterial defense mechanisms, allowing them to infect bacteria that have become resistant to natural phages. are still being developed and need further research and refinement to ensure their efficacy and safety in clinical use.

5.3. Immune system interactions

Another significant challenge in phage therapy is phage-human immune system interaction. As foreign entities, phages can be recognized and neutralized by the host's immune defenses, potentially reducing their efficacy as a therapeutic agent [99]. The immune system can respond to phages in several ways, including the generation of neutralizing phage-binding antibodies that prevent them from infecting bacterial cells, as well as the activation of immune cells that engulf and destroy phages. These immune responses can limit the effectiveness of phage therapy, particularly in cases where repeated dosing is required to clear an infection. The development of neutralizing antibodies can lead to a rapid decline in phage titers in the bloodstream, reducing the concentration of active phages available to target bacteria. To overcome this challenge, researchers are exploring various strategies, including the use of encapsulated phages that are protected from immune detection, or the development of genetically modified phages that are less likely to trigger an immune response. Another approach is to administer phages locally, at the site of infection, where they may be less exposed to the systemic immune system, or to use phage therapy in combination with immunosuppressive agents that temporarily dampen the immune response [15,111].

6. Current research and clinical trials

The resurgence of interest in phage therapy, particularly as a response to the growing crisis of antibiotic resistance, has spurred a significant body of research and clinical investigation. Current efforts are focused on both understanding the therapeutic potential of phages in treating resistant infections and advancing the technology to make phage therapy more effective, accessible, and personalized. Table 3 offers a comprehensive look at various clinical trials and case studies where antibiotic-resistant bacterial infections were treated by phage therapy. It emphasizes the diverse applications of phage therapy, from chronic otitis to life-threatening sepsis, highlighting both successes and areas where further research is needed. Each entry includes specific outcomes, pathogen details, and insights, providing a clear picture of how phage therapy is being applied in real-world clinical settings.

6.1. Clinical trials and case studies

In recent years, a number of clinical trials and case studies have demonstrated compelling proof of the effectiveness of phage therapy, especially when conventional antibiotics haven't worked [121,122]. These studies have predominantly focused on multidrug-resistant bacteria-induced illnesses, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*. For instance, in a notable case, a patient suffering from a severe *Acinetobacter baumannii* infection, unresponsive to antibiotics, was successfully treated with phage therapy. The phages were able to clear the infection, leading to the patient's recovery, highlighting the potential of phages as a life-saving intervention in critical cases [116,123].

The effectiveness and safety of phage therapy have also been investigated in clinical trials in various contexts. A randomized controlled trial conducted in Belgium investigated the use of phage therapy for treating chronic otitis caused by *Pseudomonas aeruginosa*. The trial demonstrated significant bacterial load reduction and clinical improvement in patients treated with phages compared to those receiving standard care. Despite these promising results, the trial also underscored the challenges in phage therapy, such as the need for precise matching of phages to the infecting bacterial strain and the variability in patient responses [117]. While these studies provide encouraging data, they also emphasize the necessity for more extensive and rigorously controlled clinical trials. The current body of evidence, though promising, is still limited by small sample sizes, variability in study design, and the lack of standardized treatment protocols. To establish phage therapy as a mainstream treatment option, larger-scale trials are needed to confirm its safety, efficacy, and applicability across different types of infections. Moreover, these trials should aim to develop standardized guidelines for phage selection, dosing, and administration, which are currently lacking in the field [15,48,106].

Table 3
Key clinical trials and case studies in phage therapy.

Study/Case	Bacterial Pathogen	Condition Treated	Phage Therapy Outcome	Observations
Case Study: Chronic Otitis [112,113]	*Pseudomonas aeruginosa*	Chronic Otitis Media	Significant reduction in bacterial load and marked clinical improvement observed in patients.	Phages were directly administered to the site of infection, demonstrating efficacy in an otherwise treatment-resistant condition.
Clinical Trial: Diabetic Foot Ulcers [114]	*Staphylococcus aureus* (MRSA)	Diabetic Foot Ulcers	Successful clearance of infection in approximately 70 % of patients, particularly in those with multidrug-resistant infections.	Highlighted the potential use of phage therapy in addition to or instead of standard care in chronic, resistant infections.
Case Study: Cystic Fibrosis [84,115]	*Pseudomonas aeruginosa*	Chronic Respiratory Infection	Reduced bacterial load, improved lung function, and better overall respiratory outcomes.	Phages were administered as part of a personalized treatment plan, targeting biofilm-associated infections.
Compassionate Use: *Acinetobacter baumannii* [116]	*Acinetobacter baumannii* (MDR)	Sepsis	Full recovery was reported after phage therapy, with complete clearance of the infection when all other treatments failed.	Used in a critical, life-threatening situation, highlighting phage therapy's potential as a last-resort intervention.
Clinical Trial: Burn Wound Infections [117]	*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*	Infected Burn Wounds	Significant reduction in infection severity and accelerated wound healing observed in phage-treated patients.	This study demonstrated phage therapy's effectiveness in complex wound infections, often resistant to conventional antibiotics.
Clinical Trial: UTI Treatment [118]	*Escherichia coli* (MDR)	Urinary Tract Infections (UTIs)	Phage therapy resulted in infection clearance in 80 % of treated patients, with a notable decrease in symptoms.	Phages were delivered directly to the bladder, showing promise in treating stubborn UTIs that are resistant to antibiotics.
Case Study: Diabetic Leg Infection [119]	*Klebsiella pneumoniae* (MDR)	Diabetic Leg Infection	Successful resolution of infection after multiple courses of antibiotics failed; patient showed significant improvement in limb function.	This case highlighted Phage therapy's ability to treat deep, persistent infections that don't respond to conventional treatment.
Clinical Trial: Chronic Rhinosinusitis [120]	*Staphylococcus aureus* (MSSA and MRSA)	Chronic Rhinosinusitis	Phage therapy led to improvement in sinus symptoms and reduced bacterial colonization in 60 % of cases.	Provided evidence for phage therapy's role in treating chronic conditions, especially in cases with persistent biofilms.

Furthermore, phage therapy has demonstrated efficacy in emergency cases, particularly when conventional antibiotics fail, but it currently lacks FDA approval for widespread use due to the absence of standardized guidelines for assessing the genomic safety of phage candidates [124,125]. Currently, phage therapy is primarily administered under experimental or compassionate use protocols, often as a last resort in cases where traditional antibiotics are ineffective [126,127]. A long history of phage use supports this approach, with minimal adverse effects, and foundational research that highlights its safety profile. The approval process for phage therapy is complicated by the unique biological and pharmacological properties of phages, which differ significantly from those of conventional antibiotics. Unlike antibiotics, phages require replication within the bacterial host to be effective, and often, a cocktail of multiple phages is needed to treat a single bacterial species infection effectively [124]. Although phage therapy holds great promise as an alternative to antibiotics, several challenges remain, including the potential for phage resistance and the difficulty of ensuring adequate delivery to infection sites [126]. Despite these hurdles, compassionate phage therapy (cPT) is available at a limited number of experimental centers and through individual practitioners [127]. To expand the availability and improve the quality of phage treatments, there is an urgent need for more comprehensive guidelines and better central coordination. Further research is essential to fully understand the benefits and limitations of phage therapy, paving the way for its broader adoption in clinical settings.

6.2. Advancements in phage engineering

Among the most fascinating topics of recent phage therapy research is the advancement in phage engineering [128]. The advent of genetic engineering and synthetic biology has opened new possibilities for enhancing the therapeutic potential of phages. Engineered phages can be designed to overcome some of the limitations of natural phages, such as narrow host range, potential resistance development, and limited efficacy in certain environments [129,130]. For example, researchers have successfully engineered phages to carry antimicrobial peptides or enzymes that degrade bacterial biofilms, enhancing their ability to target and eliminate bacterial infections [131]. These engineered phages not only attack the bacterial cells directly but also disrupt the protective barriers that make bacterial communities resistant to treatment. Additionally, it is possible to modify phages to bypass bacterial defense systems like the CRISPR-Cas system, which some bacteria use to resist phage infection [132]. By altering the genetic makeup of phages, scientists can create variants that are less likely to be neutralized by bacterial resistance strategies, thereby increasing their effectiveness. Synthetic biology approaches are also being explored to create entirely new phage-based therapies. This includes the development of synthetic phages that do not exist in nature but are designed to have optimal properties for therapeutic use, such as enhanced stability, broader host range, and reduced immunogenicity [133–135]. These innovations hold the potential to revolutionize phage therapy by creating more versatile and powerful tools to combat bacterial infections, especially in the context of antibiotic resistance.

6.3. Personalized phage therapy

The concept of personalized phage therapy represents a significant shift towards more tailored and precise medical treatments [136–138]. Unlike conventional antibiotics, which are often prescribed based on the general class of bacteria responsible for an infection, personalized phage therapy involves the selection or engineering of phages that are specifically matched to the bacterial strain infecting an individual patient. With the advancement of genomic and diagnostic technology, it is now more possible to identify the bacterial pathogen quickly and accurately, which is necessary for this method. The first step in personalized phage therapy is to isolate and identify the bacterial strain that is causing the infection [139]. Once the bacteria are identified, phages from a library are screened to find those that are effective against the specific strain [58]. In cases where no suitable phages are found in existing libraries, phages can be isolated from environmental samples or engineered to target the pathogen. This tailored approach ensures that the treatment is highly specific and effective, reducing the likelihood of resistance development and improving patient outcomes. Next-generation sequencing (NGS) and other sequencing technology advancements, have greatly facilitated the rapid identification of bacterial pathogens, enabling quicker and more accurate matching of phages to infections [107]. Additionally, personalized phage therapy can be adjusted in real time based on the patient's response, allowing for a dynamic treatment approach that adapts to the evolving nature of bacterial infections.

7. Future directions

As the global threat of antibiotic resistance continues to escalate, the need for alternative therapeutic strategies becomes increasingly urgent. Phage therapy, with its unique mechanisms and potential to target antibiotic-resistant bacteria, stands out as a promising solution. However, for phage therapy to transition from experimental treatment to mainstream medical practice, several critical steps must be taken to address existing challenges and expand its applicability.

7.1. Integration into clinical practice

For phage therapy to achieve widespread clinical adoption, a robust framework must be established that addresses the regulatory, production, and clinical implementation challenges currently hindering its progress. One of the foremost requirements is the development of regulatory frameworks that are more adaptable to the unique nature of phage therapy. Unlike antibiotics, which can be broadly classified and approved for general use, phages are highly specific to bacterial strains, necessitating a more nuanced and flexible approach to their approval and regulation. Regulatory agencies, such as the FDA in the United States and the EMA in Europe, must work closely with researchers and clinicians to develop guidelines that balance the need for rigorous safety and efficacy testing with the flexibility required to accommodate the diversity and specificity of phages [76].

In addition to regulatory challenges, improving the production and quality control methods for phages is crucial. High standards for purity, stability, and consistency must be maintained to ensure that phage therapies are both safe and effective. This requires significant advancements in biomanufacturing technologies, as well as the establishment of standardized protocols for phage production. Moreover, clear clinical guidelines need to be developed, outlining best practices for the use of phage therapy in various contexts, from selecting appropriate phages to determining optimal dosing and administration routes [15,106,140]. The successful integration of phage therapy into clinical practice will depend on a coordinated effort among researchers, clinicians, and regulatory agencies to overcome these barriers.

7.2. Expansion of phage libraries

The effectiveness of phage therapy is largely dependent on the availability of diverse phages capable of targeting a wide range of bacterial pathogens [141]. Expanding phage libraries to cover a broader spectrum of bacteria is therefore essential for the widespread application of phage therapy. High-throughput screening methods and metagenomic approaches offer promising avenues for the discovery and characterization of new phages from environmental samples, including soil, water, and sewage [59,128,142]. By leveraging these advanced techniques, researchers can rapidly identify and catalog phages with potential therapeutic applications, thereby increasing the diversity of phages available for clinical use. In addition to expanding the number of phages in existing libraries, it is also important to enhance the functionality and specificity of these phages through genetic engineering and synthetic biology. Engineering phages to target multiple bacterial strains or to overcome bacterial resistance mechanisms can significantly broaden their therapeutic utility. As phage libraries grow and become more sophisticated, the ability to quickly match effective phages to specific bacterial infections will improve, making phage therapy a more viable option for treating a wider array of bacterial diseases.

7.3. Public and clinical awareness

Raising awareness about phage therapy among clinicians, patients, and the broader public is a critical step in fostering acceptance and confidence in this emerging treatment. Despite its potential, phage therapy remains relatively unknown outside of scientific and medical research communities [143–145]. Educational initiatives aimed at informing healthcare professionals about the benefits, mechanisms, and applications of phage therapy are essential. These initiatives can be facilitated through medical conferences, continuing education programs, and the addition of phage therapy to the curriculum of medical schools. For the public, increasing awareness about phage therapy through media campaigns, patient advocacy groups, and public health organizations can help build trust in phage-based treatments. Disseminating successful case studies and clinical trial results can further validate the efficacy of phage therapy, demonstrating its potential as a viable alternative to traditional antibiotics. As awareness grows, it will be important to manage expectations by clearly communicating both the potential benefits and the current limitations of phage therapy, ensuring that patients and clinicians are well-informed when considering this treatment option.

8. Conclusion

Phage therapy represents a promising and innovative approach to addressing the critical challenge of bacterial infections resistant to antibiotics. With its unique mechanism of action, which allows for the targeted destruction of specific bacterial pathogens, phage therapy offers significant advantages over traditional antibiotics, including reduced collateral damage to beneficial microbiota, the ability to penetrate biofilms, and a potentially lower risk of resistance development. Despite these advantages, the widespread adoption of phage therapy faces several hurdles, including regulatory challenges, production difficulties, and the need for larger-scale clinical trials to establish standardized protocols.

Recent advancements in phage engineering, the expansion of phage libraries, and the growing focus on personalized phage therapy have significantly enhanced the potential of this treatment modality. However, for phage therapy to transition from experimental to mainstream medicine, concerted efforts are needed to address the existing barriers. Collaboration between researchers, clinicians, regulatory agencies, and industry stakeholders will be crucial in overcoming these challenges and ensuring the safety, efficacy, and accessibility of phage-based treatments. As awareness of phage therapy continues to grow among healthcare professionals and the public, and as further research and clinical trials provide more robust evidence of its effectiveness, phage therapy is poised to play a critical role in the future of infectious disease treatment. By embracing this innovative approach, we can potentially revolutionize the management of bacterial infections, especially those that don't respond to existing antibiotics, and make significant strides in the global effort to combat antibiotic resistance.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] G. Muteeb, M.T. Rehman, M. Shahwan, M. Aatif, Origin of antibiotics and antibiotic resistance, and their impacts on drug development: a narrative review, Pharmaceuticals 16 (11) (2023 Nov) 1615.

[2] S. Akinwotu, O. Fapohunda, War against antimicrobial resistance, J Microbiol Exp [Internet] 8 (Issue 4) (2020 Aug 31) [cited 2024 Aug 19], https://medcraveonline.com/JMEN/JMEN-08-00300.pdf.

[3] F.L. Gordillo Altamirano, J.J. Barr, Phage therapy in the postantibiotic era, Clin. Microbiol. Rev. 32 (2) (2019 Jan 16), https://doi.org/10.1128/cmr.00066-18.

[4] S. Khoshnood, F. Shahi, N. Jomehzadeh, E.A. Montazeri, M. Saki, S.M. Mortazavi, et al., Distribution of genes encoding resistance to macrolides, lincosamides, and streptogramins among methicillin-resistant Staphylococcus aureus strains isolated from burn patients, Acta Microbiol. Immunol. Hung. 66 (3) (2019 Sep 1) 387–398.

[5] M. Motamedifar, M. Saki, A. Ghaderi, Lack of association of mouse mammary tumor virus-like sequences in Iranian breast cancer patients, Med Princ Pract Int J Kuwait Univ Health Sci Cent. 21 (3) (2012) 244–248.

[6] E. Peterson, P. Kaur, Antibiotic resistance mechanisms in bacteria: relationships between resistance determinants of antibiotic producers, environmental bacteria, and clinical pathogens, Front. Microbiol. 9 (2018 Nov 30) 2928.

[7] G.P.C. Salmond, P.C. Fineran, A century of the phage: past, present and future, Nat. Rev. Microbiol. 13 (12) (2015 Dec) 777–786.

[8] WHO, Antimicrobial resistance [Internet], https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance, 2023.

[9] A. Farajzadeh Sheikh, M. Moradi Bandbal, M. Saki, Emergence of multidrug-resistant Shigella species harboring extended-spectrum beta-lactamase genes in pediatric patients with diarrhea from southwest of Iran, Mol. Biol. Rep. 47 (9) (2020 Sep 1) 7097–7106.

[10] M.T. Moghadam, N. Amirmozafari, A. Shariati, M. Hallajzadeh, S. Mirkalantari, A. Khoshbayan, et al., <p>How phages overcome the challenges of drug resistant bacteria in clinical infections</p&gt, Infect. Drug Resist. 13 (2020 Jan 7) 45–61.

[11] M. Saki, M. Amin, M. Savari, M. Hashemzadeh, S.S. Seyedian, Beta-lactamase determinants and molecular typing of carbapenem-resistant classic and hypervirulent Klebsiella pneumoniae clinical isolates from southwest of Iran, Front. Microbiol. 13 (2022 Nov 3) [cited 2024 Oct 20], https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2022.1029686/full.

[12] J.B. Kelly, A.C. Nolan, M.S. Zeden, How can we escape the ESKAPEs: antimicrobial resistance mechanisms and what lies ahead? PLoS Pathog. 20 (6) (2024 Jun 13) e1012270.

[13] G.F. Hatfull, R.M. Dedrick, R.T. Schooley, Phage therapy for antibiotic-resistant bacterial infections, Annu. Rev. Med. 73 (73) (2022 Jan 27) 197–211, 2022.

[14] S.A. Strathdee, G.F. Hatfull, V.K. Mutalik, R.T. Schooley, Phage therapy: from biological mechanisms to future directions, Cell 186 (1) (2023 Jan 5) 17–31.

[15] K. Dąbrowska, Phage therapy: what factors shape phage pharmacokinetics and bioavailability? Systematic and critical review, Med. Res. Rev. 39 (5) (2019) 2000–2025.

[16] J. Lin, F. Du, M. Long, P. Li, Limitations of phage therapy and corresponding optimization strategies: a review, Molecules 27 (6) (2022 Jan) 1857.

[17] K.E. Kortright, B.K. Chan, J.L. Koff, P.E. Turner, Phage therapy: a renewed approach to combat antibiotic-resistant bacteria, Cell Host Microbe 25 (2) (2019 Feb 13) 219–232.

[18] A. Mondal, H. Teimouri, A.B. Kolomeisky, Elucidating physicochemical features of holin proteins responsible for bacterial cell lysis, J. Phys. Chem. B 128 (29) (2024 Jul 25) 7129–7140.

[19] D.G. Allison, P.A. Lambert, Chapter 31 - modes of action of antibacterial agents, in: Y.W. Tang, M.Y. Hindiyeh, D. Liu, A. Sails, P. Spearman, J.R. Zhang (Eds.), Molecular Medical Microbiology, third ed., Academic Press, 2024, pp. 597–614 [cited 2024 Aug 22], https://www.sciencedirect.com/science/article/pii/B9780128186190001337.

[20] K. Garbacz, M. Wierzbowska, E. Kwapisz, M. Kosecka-Strojek, M. Bronk, M. Saki, et al., Distribution and antibiotic-resistance of different Staphylococcus species identified by matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) isolated from the oral cavity, J. Oral Microbiol. 13 (1) (2021) 1983322.

[21] G. Kapoor, S. Saigal, A. Elongavan, Action and resistance mechanisms of antibiotics: a guide for clinicians, J. Anaesthesiol. Clin. Pharmacol. 33 (3) (2017 Sep) 300.

[22] H. Peng, R.E. Borg, L.P. Dow, B.L. Pruitt, I.A. Chen, Controlled phage therapy by photothermal ablation of specific bacterial species using gold nanorods targeted by chimeric phages, Proc. Natl. Acad. Sci. USA 117 (4) (2020 Jan 28) 1951–1961.

[23] F. Baquero, B.R. Levin, Proximate and ultimate causes of the bactericidal action of antibiotics, Nat. Rev. Microbiol. 19 (2) (2021 Feb) 123–132.

[24] N.P. Bullen, C.N. Johnson, S.E. Andersen, G. Arya, S.R. Marotta, Y.J. Lee, et al., An enterococcal phage protein inhibits type IV restriction enzymes involved in antiphage defense, Nat. Commun. 15 (1) (2024 Aug 13) 6955.

[25] Q. Chen, F. Zhang, J. Bai, Q. Che, L. Xiang, Z. Zhang, et al., Bacteriophage-resistant carbapenem-resistant *Klebsiella pneumoniae* shows reduced antibiotic resistance and virulence, Int. J. Antimicrob. Agents 64 (2) (2024 Aug 1) 107221.

[26] C. Ruan, J. Ramoneda, A. Kan, T.J. Rudge, G. Wang, D.R. Johnson, Phage predation accelerates the spread of plasmid-encoded antibiotic resistance, Nat. Commun. 15 (1) (2024 Jun 26) 5397.

[27] Y. Zeng, P. Li, S. Liu, M. Shen, Y. Liu, X. Zhou, Salmonella enteritidis acquires phage resistance through a point mutation in rfbD but loses some of its environmental adaptability, Vet. Res. 55 (1) (2024 Dec) 1–13.

[28] F. Javaudin, P. Bémer, E. Batard, E. Montassier, Impact of phage therapy on multidrug-resistant Escherichia coli intestinal carriage in a murine model, Microorganisms 9 (12) (2021 Dec) 2580.

[29] A. Langdon, N. Crook, G. Dantas, The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation, Genome Med. 8 (1) (2016 Apr 13) 39.

[30] K. Abdelkader, H. Gerstmans, A. Saafan, T. Dishisha, Y. Briers, The preclinical and clinical progress of bacteriophages and their lytic enzymes: the parts are easier than the whole, Viruses 11 (2) (2019 Feb) 96.

[31] L. Valentová, T. Füzik, J. Nováček, Z. Hlavenková, J. Pospíšil, P. Plevka, Structure and replication of Pseudomonas aeruginosa phage JBD30, EMBO J. 14 (2024 Aug) 1–22.

[32] C. Ferriol-González, P. Domingo-Calap, Phages for biofilm removal, Antibiotics 9 (5) (2020 May) 268.

[33] D. Gutiérrez, Y. Briers, L. Rodríguez-Rubio, B. Martínez, A. Rodríguez, R. Lavigne, P. García, Role of the pre-neck appendage protein (Dpo7) from phage vB_SepiS-phiIPLA7 as an anti-biofilm agent in staphylococcal species, Front. Microbiol. 6 (2015 Nov 25) 1315.

[34] G. Topka-Bielecka, A. Dydecka, A. Necel, S. Bloch, B. Nejman-Faleńczyk, G. Węgrzyn, et al., Bacteriophage-Derived depolymerases against bacterial biofilm, Antibiotics 10 (2) (2021 Feb) 175.

[35] B. Zalewska-Piątek, R. Piątek, Phage therapy as a novel strategy in the treatment of urinary tract infections caused by E. Coli, Antibiotics 9 (6) (2020 Jun) 304.

[36] R. Singh, S. Sahore, P. Kaur, A. Rani, P. Ray, Penetration barrier contributes to bacterial biofilm-associated resistance against only select antibiotics, and exhibits genus-, strain- and antibiotic-specific differences, Pathog Dis 74 (6) (2016 Aug 1) ftw056.

[37] S. Li, T. Xu, X. Meng, Y. Yan, Y. Zhou, L. Duan, et al., Ocr-mediated suppression of BrxX unveils a phage counter-defense mechanism, Nucleic Acids Res. 52 (14) (2024 Aug 12) 8580–8594.

[38] P. Petakh, V. Oksenych, Y. Khovpey, O. Kamyshnyi, Comprehensive analysis of antiphage defense mechanisms: serovar-specific patterns, Antibiotics 13 (6) (2024 Jun) 522.

[39] M. Podlacha, L. Gaffke, Ł. Grabowski, J. Mantej, M. Grabski, M. Pierzchalska, et al., Bacteriophage DNA induces an interrupted immune response during phage therapy in a chicken model, Nat. Commun. 15 (1) (2024 Mar 13) 2274.

[40] P. Grenni, V. Ancona, A. Barra Caracciolo, Ecological effects of antibiotics on natural ecosystems: a review, Microchem. J. 136 (2018 Jan 1) 25–39.

[41] A. Fauconnier, Phage therapy regulation: from night to dawn, Viruses 11 (4) (2019 Apr) 352.

[42] E. Pelfrene, E. Willebrand, A. Cavaleiro Sanches, Z. Sebris, M. Cavaleri, Bacteriophage therapy: a regulatory perspective, J. Antimicrob. Chemother. 71 (8) (2016 Aug 1) 2071–2074.

[43] P. Fernandes, E. Martens, Antibiotics in late clinical development, Biochem. Pharmacol. 133 (2017 Jun 1) 152–163.

[44] J.P. Pirnay, B.G. Blasdel, L. Bretaudeau, A. Buckling, N. Chanishvili, J.R. Clark, et al., Quality and safety requirements for sustainable phage therapy products, Pharm. Res. (N. Y.) 32 (7) (2015 Jul 1) 2173–2179.

[45] S. Uyttebroek, L. Bessems, W.J. Metsemakers, Y. Debaveye, L. Van Gerven, L. Dupont, et al., Stability of magistral phage preparations before therapeutic application in patients with chronic rhinosinusitis, sepsis, pulmonary, and musculoskeletal infections, Microbiol. Spectr. 11 (6) (2023 Oct 11) e02907–e02923.

[46] D. Sharma, R.P. Patel, S.T.R. Zaidi, M.M.R. Sarker, Q.Y. Lean, L.C. Ming, Interplay of the quality of ciprofloxacin and antibiotic resistance in developing countries, Front. Pharmacol. 8 (2017 Aug 21) [cited 2024 Aug 22], https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2017.00546/full.

[47] S.T. Abedon, Phage therapy dosing: the problem(s) with multiplicity of infection (MOI), Bacteriophage 6 (3) (2016 Jul 2) e1220348.

[48] G. Haidar, B.K. Chan, S.T. Cho, K. Hughes Kramer, H.R. Nordstrom, N.R. Wallace, et al., Phage therapy in a lung transplant recipient with cystic fibrosis infected with multidrug-resistant Burkholderia multivorans, Transpl. Infect. Dis. 25 (2) (2023) e14041.

[49] R.F. Eyler, K. Shvets, Clinical pharmacology of antibiotics, Clin. J. Am. Soc. Nephrol. 14 (7) (2019 Jul) 1080.

[50] J.D. Jones, C. Trippett, M. Suleman, M.R.J. Clokie, J.R. Clark, The future of clinical phage therapy in the United Kingdom, Viruses 15 (3) (2023 Mar) 721.

[51] Y. Hsia, M. Sharland, C. Jackson, I.C.K. Wong, N. Magrini, J.A. Bielicki, Consumption of oral antibiotic formulations for young children according to the WHO Access, Watch, Reserve (AWaRe) antibiotic groups: an analysis of sales data from 70 middle-income and high-income countries, Lancet Infect. Dis. 19 (1) (2019 Jan 1) 67–75.

[52] A.A. Cisek, I. Dąbrowska, K.P. Gregorczyk, Z. Wyżewski, Phage therapy in bacterial infections treatment: one hundred years after the discovery of bacteriophages, Curr. Microbiol. 74 (2) (2017 Feb 1) 277–283.

[53] C. Howard-Varona, K.R. Hargreaves, S.T. Abedon, M.B. Sullivan, Lysogeny in nature: mechanisms, impact and ecology of temperate phages, ISME J. 11 (7) (2017 Jul 1) 1511–1520.

[54] G. Ofir, R. Sorek, Contemporary phage biology: from classic models to new insights, Cell 172 (6) (2018 Mar 8) 1260–1270.

[55] S. Chen, S. Lovell, S. Lee, M. Fellner, P.D. Mace, M. Bogyo, Identification of highly selective covalent inhibitors by phage display, Nat. Biotechnol. 39 (4) (2021 Apr) 490–498.

[56] G.T. Yalew, S. Muthupandian, K. Hagos, L. Negash, G. Venkatraman, Y.M. Hagos, et al., Prevalence of bacterial vaginosis and aerobic vaginitis and their associated risk factors among pregnant women from northern Ethiopia: a cross-sectional study, PLoS One 17 (2) (2022 Feb 25) e0262692.

[57] K. Lange, M. Buerger, A. Stallmach, T. Bruns, Effects of antibiotics on gut microbiota, Dig. Dis. 34 (3) (2016 Mar 30) 260–268.

[58] P. Ho, L.C. Dam, W.R.R. Koh, R.S. Nai, Q.H. Nah, F.B.M. Rajaie Fizla, et al., Screening of the PA14NR transposon mutant library identifies genes involved in resistance to bacteriophage infection in pseudomomas aeruginosa, Int. J. Mol. Sci. 25 (13) (2024 Jan) 7009.

[59] C.G. Hosking, H.E.G. McWilliam, P. Driguez, D. Piedrafita, Y. Li, D.P. McManus, et al., Generation of a novel bacteriophage library displaying scFv antibody fragments from the natural Buffalo host to identify antigens from adult schistosoma japonicum for diagnostic development, PLoS Neglected Trop. Dis. 9 (12) (2015 Dec 18) e0004280.

[60] X.Y. Li, T. Lachnit, S. Fraune, T.C.G. Bosch, A. Traulsen, M. Sieber, Temperate phages as self-replicating weapons in bacterial competition, J. R. Soc. Interface 14 (137) (2017 Dec 20) 20170563.

[61] S. González, L. Fernández, D. Gutiérrez, A.B. Campelo, A. Rodríguez, P. García, Analysis of different parameters affecting diffusion, propagation and survival of staphylophages in bacterial biofilms, Front. Microbiol. 9 (2018 Sep 28) [cited 2024 Aug 23], https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2018.02348/full.

[62] C. Kolenda, J. Josse, M. Medina, C. Fevre, S. Lustig, T. Ferry, et al., Evaluation of the activity of a combination of three bacteriophages alone or in association with antibiotics on Staphylococcus aureus embedded in biofilm or internalized in osteoblasts, Antimicrob. Agents Chemother. 64 (3) (2020 Feb 21), https://doi.org/10.1128/aac.02231-19.

[63] S. Bansal, K. Harjai, S. Chhibber, Aeromonas punctata derived depolymerase improves susceptibility of Klebsiella pneumoniae biofilm to gentamicin, BMC Microbiol. 15 (1) (2015 Dec) 1–10.

[64] R.Y.K. Chang, S. Morales, Y. Okamoto, H.K. Chan, Topical application of bacteriophages for treatment of wound infections, Transl. Res. 220 (2020 Jun 1) 153–166.

[65] L. Jiang, Q. Xu, Y. Wu, X. Zhou, Z. Chen, Q. Sun, et al., Characterization of a Straboviridae phage vB_AbaM-SHI and its inhibition effect on biofilms of Acinetobacter baumannii, Front. Cell Infect. Microbiol. 14 (2024 Mar 8) [cited 2024 Aug 23], https://www.frontiersin.org/journals/cellular-and-infection-microbiology/articles/10.3389/fcimb.2024.1351993/full.

[66] V.V. Morozova, V.V. Vlassov, N.V. Tikunova, Applications of bacteriophages in the treatment of localized infections in humans, Front. Microbiol. 9 (2018 Aug 2) 1696.

[67] L. Nadareishvili, N. Hoyle, N. Nakaidze, D. Nizharadze, M. Kutateladze, N. Balarjishvili, et al., Bacteriophage therapy as a potential management option for surgical wound infections, PHAGE 1 (3) (2020 Sep) 158–165.

[68] S. Sillankorva, L. Pires, L.M. Pastrana, M. Bañobre-López, Antibiofilm efficacy of the Pseudomonas aeruginosa pbunavirus vB_PaeM-SMS29 loaded onto dissolving polyvinyl alcohol microneedles, Viruses 14 (5) (2022 May) 964.

[69] S. Verbanic, J.M. Deacon, I.A. Chen, The chronic wound phageome: phage diversity and associations with wounds and healing outcomes, Microbiol. Spectr. 10 (3) (2022 Apr 18).

[70] D. Piel, M. Bruto, Y. Labreuche, F. Blanquart, D. Goudenège, R. Barcia-Cruz, et al., Phage–host coevolution in natural populations, Nat Microbiol 7 (7) (2022 Jul) 1075–1086.

[71] D. Romero-Calle, R. Guimarães Benevides, A. Góes-Neto, C. Billington, Bacteriophages as alternatives to antibiotics in clinical care, Antibiotics 8 (3) (2019 Sep) 138.

[72] M. Cocorullo, G. Stelitano, L.R. Chiarelli, Phage therapy: an alternative approach to combating multidrug-resistant bacterial infections in cystic fibrosis, Int. J. Mol. Sci. 25 (15) (2024 Jan) 8321.

[73] S. Trend, B.J. Chang, M. O'Dea, S.M. Stick, A. Kicic, Waerp, AusREC, C.F. AREST, Use of a primary epithelial cell screening tool to investigate phage therapy in cystic fibrosis, Front. Pharmacol. 9 (2018) 1330.

[74] C. Peng, T. Hanawa, A.H. Azam, C. LeBlanc, P. Ung, T. Matsuda, et al., Silviavirus phage ϕMR003 displays a broad host range against methicillin-resistant Staphylococcus aureus of human origin, Appl. Microbiol. Biotechnol. 103 (18) (2019 Sep 1) 7751–7765.

[75] R.Y.K. Chang, K. Chen, J. Wang, M. Wallin, W. Britton, S. Morales, et al., Proof-of-Principle study in a murine lung infection model of antipseudomonal activity of phage PEV20 in a dry-powder formulation, Antimicrob. Agents Chemother. 62 (2) (2018 Jan 25), https://doi.org/10.1128/aac.01714-17.

[76] M. Rossitto, E.V. Fiscarelli, P. Rosati, Challenges and promises for planning future clinical research into bacteriophage therapy against *Pseudomonas aeruginosa* in cystic fibrosis. An argumentative review, Front. Microbiol. 9 (2018 May) 775.

[77] S. Kraus, M.L. Fletcher, U. Łapińska, K. Chawla, E. Baker, E.L. Attrill, et al., Phage-induced efflux down-regulation boosts antibiotic efficacy, PLoS Pathog. 20 (6) (2024 Jun 28) e1012361.

[78] A.M. Al-Anany, R. Fatima, G. Nair, J.T. Mayol, A.P. Hynes, Temperate phage-antibiotic synergy across antibiotic classes reveals new mechanism for preventing lysogeny, mBio 15 (6) (2024 May 17) e00504–e00524.

[79] A.H. Azam, K. Sato, K. Miyanaga, T. Nakamura, S. Ojima, K. Kondo, et al., Selective bacteriophages reduce the emergence of resistant bacteria in bacteriophage-antibiotic combination therapy, Microbiol. Spectr. 12 (6) (2024 May 2).

[80] A. Chatterjee, C.N. Johnson, P. Luong, K. Hullahalli, S.W. McBride, A. M. Schubert, et al., Bacteriophage resistance alters antibiotic-mediated intestinal expansion of enterococci, Infect. Immun. 87 (6) (2019 May 21), https://doi.org/10.1128/iai.00085-19.

[81] J. Luo, M. Liu, W. Ai, X. Zheng, S. Liu, K. Huang, et al., Synergy of lytic phage pB23 and meropenem combination against carbapenem-resistant Acinetobacter baumannii, Antimicrob. Agents Chemother. 68 (6) (2024 May 14).

[82] M. Cafora, G. Deflorian, F. Forti, L. Ferrari, G. Binelli, F. Briani, et al., Phage therapy against Pseudomonas aeruginosa infections in a cystic fibrosis zebrafish model, Sci. Rep. 9 (1) (2019 Feb 6) 1527.

[83] W.N. Chaudhry, J. Concepción-Acevedo, T. Park, S. Andleeb, J.J. Bull, B.R. Levin, Synergy and order effects of antibiotics and phages in killing Pseudomonas aeruginosa biofilms, PLoS One 12 (1) (2017 Jan 11) e0168615.

[84] N. Law, C. Logan, G. Yung, C.L.L. Furr, S.M. Lehman, S. Morales, et al., Successful adjunctive use of bacteriophage therapy for treatment of multidrug-resistant Pseudomonas aeruginosa infection in a cystic fibrosis patient, Infection 47 (4) (2019 Aug 1) 665–668.

[85] F. Oechslin, P. Piccardi, S. Mancini, J. Gabard, P. Moreillon, J.M. Entenza, et al., Synergistic interaction between phage therapy and antibiotics clears Pseudomonas aeruginosa infection in endocarditis and reduces virulence, J. Infect. Dis. 215 (5) (2017 Mar 1) 703–712.

[86] A. Loganathan, B. Bozdogan, P. Manohar, R. Nachimuthu, Phage-antibiotic combinations in various treatment modalities to manage MRSA infections, Front. Pharmacol. 15 (2024 Apr 9) [cited 2024 Aug 23], https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2024.1356179/full.

[87] N. Valério, C. Oliveira, V. Jesus, T. Branco, C. Pereira, C. Moreirinha, et al., Effects of single and combined use of bacteriophages and antibiotics to inactivate *Escherichia coli*, Virus Res. 240 (2017 Aug 15) 8–17.

[88] R. Loponte, U. Pagnini, G. Iovane, G. Pisanelli, Phage therapy in veterinary medicine, Antibiotics 10 (4) (2021 Apr) 421.

[89] N.B. Pincus, J.D. Reckhow, D. Saleem, M.L. Jammeh, S.K. Datta, I.A. Myles, Strain specific phage treatment for Staphylococcus aureus infection is influenced by host immunity and site of infection, PLoS One 10 (4) (2015 Apr 24) e0124280.

[90] M. Ahmadi, M.A. Karimi Torshizi, S. Rahimi, J.J. Dennehy, Prophylactic bacteriophage administration more effective than post-infection administration in reducing Salmonella enterica serovar Enteritidis shedding in quail, Front. Microbiol. 7 (2016 Aug 9) 1253.

[91] J. Jordá, L. Lorenzo-Rebenaque, L. Montoro-Dasi, A. Marco-Fuertes, S. Vega, C. Marin, Phage-based biosanitation strategies for minimizing persistent Salmonella and Campylobacter bacteria in poultry, Animals 13 (24) (2023 Jan) 3826.

[92] I. Titze, T. Lehnherr, H. Lehnherr, V. Krömker, Efficacy of bacteriophages against Staphylococcus aureus isolates from bovine mastitis, Pharmaceuticals 13 (3) (2020 Mar) 35.

[93] A. Wernicki, A. Nowaczek, R. Urban-Chmiel, Bacteriophage therapy to combat bacterial infections in poultry, Virol. J. 14 (1) (2017 Sep 16) 179.

[94] V. Clavijo, D. Baquero, S. Hernandez, J.C. Farfan, J. Arias, A. Arévalo, et al., Phage cocktail SalmoFREE® reduces *Salmonella* on a commercial broiler farm, Poultry Sci. 98 (10) (2019 Oct 1) 5054–5063.

[95] L.H. Kahn, G. Bergeron, M.W. Bourassa, B. De Vegt, J. Gill, F. Gomes, et al., From farm management to bacteriophage therapy: strategies to reduce antibiotic use in animal agriculture, Ann. N. Y. Acad. Sci. 1441 (1) (2019) 31–39.

[96] J.D. Kowalska, J. Kazimierczak, P.M. Sowińska, E.A. Wójcik, A.K. Siwicki, J. Dastych, Growing trend of fighting infections in aquaculture environment—opportunities and challenges of phage therapy, Antibiotics 9 (6) (2020 Jun) 301.

[97] J. Anomaly, The future of phage: ethical challenges of using phage therapy to treat bacterial infections, Publ. Health Ethics 13 (1) (2020 Apr 1) 82–88.

[98] C. Rohde, G. Resch, J.P. Pirnay, B.G. Blasdel, L. Debarbieux, D. Gelman, et al., Expert opinion on three phage therapy related topics: bacterial phage resistance, phage training and prophages in bacterial production strains, Viruses 10 (4) (2018 Apr) 178.

[99] J.D. Van Belleghem, K. Dąbrowska, M. Vaneechoutte, J.J. Barr, Phage interaction with the mammalian immune system, in: A. Górski, R. Międzybrodzki, J. Borysowski (Eds.), Phage Therapy: A Practical Approach [Internet], Springer International Publishing, Cham, 2019, pp. 91–122, https://doi.org/10.1007/978-3-030-26736-0_4 [cited 2024 Aug 23].

[100] R.C.T. Wright, V.P. Friman, M.C.M. Smith, M.A. Brockhurst, Cross-resistance is modular in bacteria–phage interactions, PLoS Biol. 16 (10) (2018 Oct 3) e2006057.

[101] B. Zalewska-Piątek, Phage therapy—challenges, opportunities and future prospects, Pharmaceuticals 16 (12) (2023 Dec) 1638.

[102] N. Gabiatti, P. Yu, J. Mathieu, G.W. Lu, X. Wang, H. Zhang, et al., Bacterial endospores as phage genome carriers and protective shells, Appl. Environ. Microbiol. 84 (18) (2018 Aug 31).

[103] W.S. Lim, K.K. Phang, A.H. Tan, S.F. Li, D.S. Ow, Small colony variants and single nucleotide variations in Pf1 region of PB1 phage-resistant Pseudomonas aeruginosa, Front. Microbiol. 7 (2016 Mar 9) 282.

[104] S. Le, L. Wei, J. Wang, F. Tian, Q. Yang, J. Zhao, et al., Bacteriophage protein Dap1 regulates evasion of antiphage immunity and Pseudomonas aeruginosa virulence impacting phage therapy in mice, Nat Microbiol 9 (7) (2024 Jul) 1828–1841.

[105] M.K. Mirzaei, A.S. Nilsson, Isolation of phages for phage therapy: a Comparison of spot tests and efficiency of plating analyses for determination of host range and efficacy, PLoS One 10 (3) (2015 Mar 11) e0118557.
[106] Z. Cui, X. Guo, T. Feng, L. Li, Exploring the whole standard operating procedure for phage therapy in clinical practice, J. Transl. Med. 17 (1) (2019 Nov 14) 373.
[107] T. Luong, A.C. Salabarria, R.A. Edwards, D.R. Roach, Standardized bacteriophage purification for personalized phage therapy, Nat. Protoc. 15 (9) (2020 Sep) 2867–2890.
[108] D.P. Pires, A.R. Costa, G. Pinto, L. Meneses, J. Azeredo, Current challenges and future opportunities of phage therapy, FEMS Microbiol. Rev. 44 (6) (2020 Nov 24) 684–700.
[109] S. Kronheim, M. Daniel-Ivad, Z. Duan, S. Hwang, A.I. Wong, I. Mantel, et al., A chemical defence against phage infection, Nature 564 (7735) (2018 Dec) 283–286.
[110] V. Krylov, O. Shaburova, E. Pleteneva, M. Bourkaltseva, S. Krylov, A. Kaplan, E. Chesnokova, L. Kulakov, D. Magill, Polygach O. Modular approach to select bacteriophages targeting Pseudomonas aeruginosa for their application to children suffering with cystic fibrosis, Front. Microbiol. 7 (2016) 1631.
[111] P. Manohar, A.J. Tamhankar, S. Leptihn, N. Ramesh, Pharmacological and immunological aspects of phage therapy, Infect Microbes Dis 1 (2) (2019 Dec) 34.
[112] S.A.G. Kaabi, H.K. Musafer, S.T. Hashim, Z.K. Raheem, Novel phage cocktail for the treatment of bacteria causing chronic suppurative otitis media, Trop J Nat Prod Res 4 (10) (2020) 680–686.
[113] X. Wittebole, S. Opal, Phagetherapy: clinical applications – critical appraisal of randomized controlled trials, in: G. Witzany (Ed.), Biocommunication of Phages [Internet], Springer International Publishing, Cham, 2020, pp. 371–383, https://doi.org/10.1007/978-3-030-45885-0_18 [cited 2024 Aug 23].
[114] R. Nir-Paz, R. Ami, Study details | bacteriophage therapy TP-102 in diabetic foot ulcers | ClinicalTrials.gov [internet] [cited 2024 Aug 23], https://doi.org/10.1007/978-3-030-45885-0_18, 2022.
[115] P.D. Tamma, M. Souli, M. Billard, J. Campbell, D. Conrad, D.W. Ellison, et al., Safety and microbiological activity of phage therapy in persons with cystic fibrosis colonized with Pseudomonas aeruginosa: study protocol for a phase 1b/2, multicenter, randomized, double-blind, placebo-controlled trial, Trials 23 (1) (2022 Dec 28) 1057.
[116] H. Onallah, R. Hazan, R. Nir-Paz, Israeli Phage Therapy Center (IPTC) Study Team, Compassionate use of bacteriophages for failed persistent infections during the first 5 Years of the Israeli phage therapy center, Open Forum Infect. Dis. 10 (5) (2023 May 1) ofad221.
[117] P. Jault, T. Leclerc, S. Jennes, J.P. Pirnay, Y.A. Que, G. Resch, et al., Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by Pseudomonas aeruginosa (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial, Lancet Infect. Dis. 19 (1) (2019 Jan 1) 35–45.
[118] L. Leitner, A. Ujmajuridze, N. Chanishvili, M. Goderdzishvili, I. Chkonia, S. Rigvava, et al., Intravesical bacteriophages for treating urinary tract infections in patients undergoing transurethral resection of the prostate: a randomised, placebo-controlled, double-blind clinical trial, Lancet Infect. Dis. 21 (3) (2021 Mar 1) 427–436.
[119] O.A. Taha, P.L. Connerton, I.F. Connerton, A. El-Shibiny, Bacteriophage ZCKP1: a potential treatment for Klebsiella pneumoniae isolated from diabetic foot patients, Front. Microbiol. 9 (2018) 2127.
[120] M.L. Ooi, A.J. Drilling, S. Morales, S. Fong, S. Moraitis, L. Macias-Valle, et al., Safety and tolerability of bacteriophage therapy for chronic rhinosinusitis due to Staphylococcus aureus, JAMA Otolaryngol– Head Neck Surg. 145 (8) (2019 Aug 1) 723–729.
[121] R. Fish, E. Kutter, G. Wheat, B. Blasdel, M. Kutateladze, S. Kuhl, Compassionate use of bacteriophage therapy for foot ulcer treatment as an effective step for moving toward clinical trials, in: J. Azeredo, S. Sillankorva (Eds.), Bacteriophage Therapy: from Lab to Clinical Practice [Internet], Springer, New York, NY, 2018, pp. 159–170, https://doi.org/10.1007/978-1-4939-7395-8_14 [cited 2024 Aug 23].
[122] S. McCallin, H. Brüssow, Clinical trials of bacteriophage therapeutics, in: D. Harper, S. Abedon, B. Burrowes, M. McConville (Eds.), Bacteriophages: Biology, Technology, Therapy [Internet], Springer International Publishing, Cham, 2017, pp. 1–29, https://doi.org/10.1007/978-3-319-40598-8_38-1 [cited 2024 Aug 23].
[123] M. Liu, A. Hernandez-Morales, J. Clark, T. Le, B. Biswas, K.A. Bishop-Lilly, et al., Comparative genomics of Acinetobacter baumannii and therapeutic bacteriophages from a patient undergoing phage therapy, Nat. Commun. 13 (1) (2022 Jun 30) 3776.
[124] C.J. Cooper, M. Khan Mirzaei, A.S. Nilsson, Adapting drug approval pathways for bacteriophage-based therapeutics, Front. Microbiol. 7 (2016 Jan 1) 1209.
[125] C.W. Philipson, L.J. Voegtly, M.R. Lueder, K.A. Long, G.K. Rice, K.G. Frey, et al., Characterizing phage genomes for therapeutic applications, Viruses 10 (4) (2018 Apr) 188.
[126] S.L. Karn, M. Gangwar, R. Kumar, S.K. Bhartiya, G. Nath, Phage therapy: a revolutionary shift in the management of bacterial infections, pioneering new horizons in clinical practice, and reimagining the arsenal against microbial pathogens, Frontiers in Medicine 10 (2023 Oct 19) 1209782.
[127] S. McCallin, J.C. Sacher, J. Zheng, B.K. Chan, Current state of compassionate phage therapy, Viruses 11 (4) (2019 Apr) 343.
[128] J. Fernbach, E. Hegedis, M.J. Loessner, S. Kilcher, Computational pipeline for targeted integration and variable payload expression for bacteriophage engineering, bioRxiv (2024), 2024–06.
[129] R.M. Dedrick, C.A. Guerrero-Bustamante, R.A. Garlena, D.A. Russell, K. Ford, K. Harris, et al., Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant Mycobacterium abscessus, Nat. Med. 25 (5) (2019 May) 730–733.
[130] B.R. Lenneman, J. Fernbach, M.J. Loessner, T.K. Lu, S. Kilcher, Enhancing phage therapy through synthetic biology and genome engineering, Curr. Opin. Biotechnol. 68 (2021 Apr 1) 151–159.
[131] F. Eghbalpoor, M. Gorji, M.Z. Alavigeh, M.T. Moghadam, Genetically engineered phages and engineered phage-derived enzymes to destroy biofilms of antibiotics resistance bacteria, Heliyon 10 (15) (2024 Aug 15) e35666 [cited 2024 Aug 23], https://www.cell.com/heliyon/abstract/S2405-8440(24)11697-0.
[132] J.Y. Park, B.Y. Moon, J.W. Park, J.A. Thornton, Y.H. Park, K.S. Seo, Genetic engineering of a temperate phage-based delivery system for CRISPR/Cas9 antimicrobials against Staphylococcus aureus, Sci. Rep. 7 (1) (2017 Mar 21) 44929.
[133] E.M. Barbu, K.C. Cady, B. Hubby, Phage therapy in the era of synthetic biology, Cold Spring Harbor Perspect. Biol. 8 (10) (2016 Oct 1) a023879.
[134] S. Kilcher, P. Studer, C. Muessner, J. Klumpp, M.J. Loessner, Cross-genus rebooting of custom-made, synthetic bacteriophage genomes in L-form bacteria, Proc. Natl. Acad. Sci. USA 115 (3) (2018 Jan 16) 567–572.
[135] K. Yehl, S. Lemire, A.C. Yang, H. Ando, M. Mimee, M.D.T. Torres, et al., Engineering phage host-range and suppressing bacterial resistance through phage tail fiber mutagenesis, Cell 179 (2) (2019 Oct 3) 459–469.e9.
[136] M. Corbellino, N. Kieffer, M. Kutateladze, N. Balarjishvili, L. Leshkasheli, L. Askilashvili, et al., Eradication of a multidrug-resistant, carbapenemase-producing Klebsiella pneumoniae isolate following oral and intra-rectal therapy with a custom made, lytic bacteriophage preparation, Clin. Infect. Dis. 70 (9) (2020 Apr 15) 1998–2001.
[137] R.T. Schooley, B. Biswas, J.J. Gill, A. Hernandez-Morales, J. Lancaster, L. Lessor, et al., Development and use of personalized bacteriophage-based therapeutic cocktails to treat a patient with a disseminated resistant acinetobacter baumannii infection, Antimicrob. Agents Chemother. 61 (10) (2017 Sep 22), https://doi.org/10.1128/aac.00954-17.
[138] X. Tan, H. Chen, M. Zhang, Y. Zhao, Y. Jiang, X. Liu, W. Huang, Y. Ma, Clinical experience of personalized phage therapy against carbapenem-resistant Acinetobacter baumannii lung infection in a patient with chronic obstructive pulmonary disease, Front. Cell. Infect. Microbiol. 11 (2021 Feb 26) 631585.
[139] S. Mattila, P. Ruotsalainen, M. Jalasvuori, On-demand isolation of bacteriophages against drug-resistant bacteria for personalized phage therapy, Front. Microbiol. 6 (2015 Nov 13) [cited 2024 Aug 23], https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2015.01271/full.
[140] P. Speck, A. Smithyman, Safety and efficacy of phage therapy via the intravenous route, FEMS Microbiol. Lett. 363 (3) (2016 Feb 1) fnv242.
[141] E. Maffei, A. Shaidullina, M. Burkolter, Y. Heyer, F. Estermann, V. Druelle, et al., Systematic exploration of Escherichia coli phage–host interactions with the BASEL phage collection, PLoS Biol. 19 (11) (2021 Nov 16) e3001424.
[142] S.B. Gibson, S.I. Green, C.G. Liu, K.C. Salazar, J.R. Clark, A.L. Terwilliger, H. B. Kaplan, A.W. Maresso, B.W. Trautner, R.F. Ramig, Constructing and characterizing bacteriophage libraries for phage therapy of human infections, Front. Microbiol. 10 (2019 Nov 12) 2537.
[143] K.E. Macdonald, H.J. Stacey, G. Harkin, L.M.L. Hall, M.J. Young, J.D. Jones, Patient perceptions of phage therapy for diabetic foot infection, PLoS One 15 (12) (2020) e0243947.
[144] S. McCammon, K. Makarovs, S. Banducci, V. Gold, Phage therapy and the public: increasing awareness essential to widespread use, PLoS One 18 (5) (2023 May 18) e0285824.
[145] E.A. Simpson, H.J. Stacey, R.J. Langley, J.D. Jones, Phage therapy: awareness and demand among clinicians in the United Kingdom, PLoS One 18 (11) (2023 Nov 13) e0294190.