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Review Article

Could Phage Therapy be the Protector of Humankind?

Nicholas A Kerna[1,2]*, John V Flores[3,4], Hilary M Holets[3,4], Lawrence U Akabike[5], Mark H Chen[6], Emmaneulla Olubumni Solomon[7], Kevin D Pruitt[8], Uzoamaka Nwokorie[9] and Shain Waugh[10]

[1]*SMC–Medical Research, Thailand*

[2]*First InterHealth Group, Thailand*

[3]*Beverly Hills Wellness Surgical Institute, USA*

[4]*Orange Partners Surgicenter, USA*

[5]*Larrico Enterprises, LLC, USA*

[6]*For Your Health, LLC, USA*

[7]*Obafemi Awolowo University, Nigeria*

[8]*Kemet Medical Consultants, USA*

[9]*University of Washington, USA*

[10]*Fettle Path, USA*

***Corresponding Author:** Nicholas A Kerna, (mailing address) POB47 Phatphong, Suriwongse Road, Bangkok, Thailand 10500. Contact: medpublab+drkerna@gmail.com.

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Abstract

In some scientific circles, the current time is referred to as the "post-antibiotic era" due to several multidrug-resistant bacterial infections. Thus, there is an immediate need for novel medicines and alternative therapies. Phages are the most abundant and ubiquitous organisms in the ecosystem. Phage therapy has shown promise as a therapeutic approach for managing antibiotic-resistant bacterial infections. Several studies have investigated phage therapy for systemic bacterial infections, highlighting the efficacy of phage therapy alone or with antibiotics to treat such bacterial infections. Research has also posited a rationale for phage therapy in managing local disorders, including burn wounds, otitis media, and urinary tract infections. Although prophylactic treatment with phage particles has shown potential in gastrointestinal infections, some researchers have suggested that preventive therapy is improbable.

In addition to chronic persistent diarrhea, other potential indications for fecal microbiota transplantation (FMT) include inflammatory bowel disease (IBD), obesity, and specific psychiatric disorders. FMT changes both the bacteria and phage populations. In one study, cystic fibrosis in mice caused by *P. aeruginosa* was eradicated following intranasal administration of two doses of phage particles after infection. Thus, there is a renewed interest in FMT and phage therapy. Despite the promising results of FMT in chronic diarrhea, the U.S. Food and Drug Administration (FDA) has issued a safety alert regarding treatment with FMT after reporting six patients who contracted enteropathogenic *E. coli* and Shiga toxin-producing *E. coli* (two patients died) after FMT. The FDA's position is that FMT must meet investigational new drug administration standards for approval due to its theoretical safety concerns. As phages are biologicals and cannot satisfy the strict regulatory standards for approval of chemical drugs, such as antibiotics, obtaining regulatory approval is problematic.

Keywords: *Antibiotic Resistance; Bacteriophage; Biodivergence; Fecal Transplant; Microbiota; Post-Antibiotic Era*

Abbreviations

EPEC: Enteropathogenic *E. coli;* FDA: (U.S.) Food and Drug Administration; FMT: Fecal Microbiota Transplantation; IBD: Inflammatory Bowel Disease; IND: Investigational New Drug; ORS: Oral Rehydration Salt; STEC: Shiga Toxin-producing *E. coli*; T2D: Type 2 Diabetes

Introduction

Phage therapy has shown potential as a therapeutic approach for managing antibiotic-resistant bacterial infections [1]. The therapy has been used for nearly a century but is not yet approved in the United States and European Union. Its use has been justified by a lack of any reported adverse severe events following application in antibiotic-resistant bacterial infections [2]. Nevertheless, as phages are biologicals and do not meet the strict regulatory criteria for approval of chemical drugs, such as antibiotics, seeking regulatory approval for its use is complicated.

The present time is called by some the "post-antibiotic era" due to several multidrug-resistant bacterial infections [3]. The commonly identified multidrug-resistant bacteria are *Enterococcus faecium, Staphylococcus aureus*, *Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter species* [4]. Phage therapy has the potential to be exploited as an effective adjuvant to the currently preferred antibiotics in managing infections.

Discussion

History of phage therapy

Phages are the most abundant organisms in the ecosystem, with approximately 10^{31} phage particles present on Earth. They are found almost everywhere, from freshwater bodies to oceans, from air to the stratosphere, and even inside and outside other living organisms, including humans [5,6].

Félix d'Herelle, a self-taught scientist of Franco-Canadian background without any formal university education, published an article on "invisible antagonists". He isolated particles from stools of patients with dysentery, labelling them "bacteriophages". He was successful in using bacteriophages to destroy harmful bacteria [7].

d'Herelle's study used bacteriophages (phage culture) to treat avian typhoid in chickens, followed by their application in managing human diseases [7]. In 1921, oral application of phages cured children with toxic dysentery. A scientist successfully treated four patients with bubonic plague by injecting a phage preparation directly into the inflamed lymph nodes [8]. In 1927, phage therapy was employed for managing cholera outbreaks in India, reducing the mortality rate from 63% (in untreated patients) to 8% (in patients receiving phage therapy) [8].

About two years earlier, Frederick Twort, a British bacteriologist, identified a specific "bacteriolytic agent" in bacterial cultures [9]. Ernest Hankin, also a British bacteriologist, identified agents from the Jamuna river in India that displayed antibacterial properties. He reported that *Vibrio cholera* treatment with the river water killed the bacteria, but the effect was lost when the water was boiled [10]. Although the conclusions were a matter of contention, the finding favored phage particles' bactericidal effects [11].

In 2005, Curtis Suttle proved there exists an abundance of phages in the ocean water ecosystem. He did so by using fluorescent DNA staining and electron microscopy [12,13]. Recent studies have demonstrated numerous new phage species in the ocean ecosystem that affect the carbon, sulfur, and nitrogen cycles [14,15].

Specific studies revealed that animal dung's efficacy for treating infections could be attributed to phage activity. Fecal matter contains 1010 phages per gram of its dry weight [16,17].

Phage cocktails, which are combinations of different phage species, are available for use in certain countries, such as Russia [18]. In Georgia's republic, the Eliava Phage Therapy Center, founded by d'Herelle and George Eliava, offers phage therapy for antibiotic-resistant infections.

In 1939, phage therapy was used to treat about 6000 Soviet soldiers (fighting in the Winter War with Finland) with open wound *Streptococcal* or *Staphylococcal* infections. The cocktail phage therapy comprised several phage species used against harmful bacteria, such as *Staphylococci, Streptococci, Shigella,* and *Salmonella* [19]. The treatment reduced mortality and the need for amputation from gangrene [19].

Several pharmaceutical companies, such as Eli Lilly, produced commercial phage preparations. In 1928, the era of antibiotics began and large-scale use of antibiotics occurred during World War II—phage therapy and research was esentially abandoned [20].

Antibiotic resistance and phage therapy

The discovery of penicillin in 1928 by Alexander Fleming sparked the widespread use of antibiotics in the Western world, gradually extending to other parts of the globe. Notably, Fleming warned against the possible emergence of antibiotic-resistant bacteria with the indiscriminate, widespread use of antibiotics [21]. An early documented report of antibiotic resistance was *Mycobacterium tuberculosis* against streptomycin [22].

The discovery and manufacturing of several new antibiotics classes continued through many decades, but it decreased in the latter half of the 20th century. From the 1980s to 2018, only three new antibiotics classes have been discovered [23–25]. The lack of new-generation antibiotics and the emergence of bacterial antibiotic resistance at an excelerating pace have signalled the end of the "golden era of antibiotics".

Modification in the structure of existing antibiotics has extended their spectrum to a certain extent; however, it has increased the risk of the emergence of cross-resistance. There has been considerable increase in the cross-resistance among different antibiotics of the same group [26]. Thus, there is a critical need to discover new alternative therapies.

Phage therapy has regained popularity in this regard. The use of the state-of-the-art bioengineering techniques to produce phages and that phages are biodivergent in nature, have renewed the promise of phage therapy as an alternative or adjuvant therapy to antibiotics [27,28].

Systemic bacterial infections

Several studies have investigated the efficacy of phage therapy for systemic bacterial infections. Watanabe., *et al*. (2007) explored phage therapy's effectiveness in a gut-derived murine model of *P. aeruginosa* sepsis. The researchers found that 67% of the infected mice survived after oral administration of phage therapy within a day of infection [29].

Capparelli., *et al*. (2007) reported that phage therapy protected against systemic staphylococcal infection in a dose-dependent manner [30]. In a similar study, Biswas., *et al*. (2002) demonstrated the dose-dependent efficacy of phage therapy against bacteremia caused by vancomycin-resistant *Enterococcus faecium* in mice [31]. Cerveny., *et al*. (2002) found that a combination of antibiotics and phage therapy successfully combated systemic infection with Vibrio vulnificus in an animal model [32].

Overall, these findings highlighted the efficacy of phage therapy alone or with antibiotic therapy to treat systemic bacterial infections. However, several factors are involved in determining the success or failure of the specific treatment. Thus, more *in vivo* and human studies evaluating these factors in phage therapy's efficacy are needed for gaining approval for their application in humans.

Local bacterial infections

Research has also established a rationale for phage therapy in managing local infections, such as burn wounds, otitis media, and urinary tract infections.

McVay., *et al*. (2007) demonstrated that phage therapy in mouse models of burn wounds infected with *P. aeruginosa* improved survival from 6% (untreated group) to 88% (treated group) [33]. The researchers found that intraperitoneal administration led to 88% success compared to 22% and 28% with subcutaneous and intramuscular administration, respectively. Pharmacokinetic studies revealed that intraperitoneal delivery of phages, compared to subcutaneous and intramuscular delivery routes, led to persistently high levels of phages in the liver, spleen, and blood [33].

Dufour., *et al*. (2016) explored phage therapy's role in managing urinary tract infections [34]. They found a 100-fold reduction in the bacterial load (*Escherichia coli*) in the kidneys following intraperitoneal phage administration 24h after the bacterial challenge [34]. Moreover, the same phage therapy caused a significant decrease in the *E. coli* load in a pneumonia model, but not in a sepsis model.

In an insect model of *Clostridium difficile* colonization, prophylactic phage therapy administered 2h before the bacterial challenge led to 100% survival of infected mice. In contrast, concomitant use of antibacterial and phage therapy led to a 72% survival rate. However, phage therapy in the same model administered 2h after the bacterial challenge led to a survival rate of only 30.5% [35].

Yen., *et al*. (2017) observed that prophylactic administration of phage cocktail (3–6h before the bacterial challenge) led to reduced colonization of *V. cholerae* in the small intestine of infant mice [36]. However, after the study period, phage-resistant mutant bacteria were identified from the mice's intestines. The efficacy of the phage therapy was reduced when administered 6h before the bacterial challenge. The dose of *V. cholera* was higher [36].

Although prophylactic treatment with phage particles has shown potential in gastrointestinal infections, more studies exploring the efficacy of phage therapy after bacterial infection are needed. As pointed out by Galtier., *et al*. (2017), prophylactic treatment is not possible [37].

Studies have investigated phage therapy's role in recurrent lung infections (in most cases caused by multidrug-resistant bacteria) typically observed in patients with cystic fibrosis. Waters., *et al*. (2017) demonstrated complete eradication of *P. aeruginosa* in a cystic fibrosis mouse model following intranasal administration of two doses of phage particles after infection [38]. The researchers observed complete eradication of the condition in 70% of mice and a significantly reduced bacterial load in 30% of mice [38].

In another cystic fibrosis murine model, phage therapy significantly improved animals' survival rate following intranasal administration of phage particles [39]. Moreover, a high dose of phage therapy 4 days before a bacterial infection led to complete protection, suggesting the possible role of prophylactic phage therapy in preventing cystic fibrosis [39].

Semler., *et al*. (2014) explored a different administration route in a respiratory infection murine model with *Burkholderia cepacia* complex [40]. The researchers found that the bacterial load was reduced by 100% following the administration of phage particles via nebulization compared to intraperitoneal administration, suggesting the role of phage therapy in preventing and treating a respiratory infection, especially when administered locally [40].

Only a few studies have compared the efficacy of phage therapy alone or in combination with antibiotic treatment.

Huff., *et al*. (2004) investigated the efficacy of bacteriophage or enrofloxacin alone and in combination to treat colibacillosis infection in chickens [41]. The standard antibiotic enrofloxacin reduced mortality rate to 3% in treated chickens compared to 68% in the untreated

group, whereas phage therapy alone reduced mortality to 15%. Interestingly, the combination of phage therapy and antibiotic treatment led to no deaths [41].

Similarly, Oechslin., *et al*. (2017) found that phage therapy with concomitant administration of antibiotics (ciprofloxacin) led to a 10,000-fold reduction in the bacterial load in a rat model of experimental endocarditis following *P. aeruginosa* infection [42]. They also found that the phage and ciprofloxacin combination exerted a synergistic bactericidal action on *P. aeruginosa in vivo* and *in vitro* [42].

Nevertheless, further studies are required to better understand the potential synergistic bactericidal effect of a combination therapy of phage and antibiotics both *in vitro* and *in vivo*.

Phage therapy: fecal microbiota transplantation (FMT)

Fecal microbiota transplantation (FMT) has renewed the interest in phage therapy. In 2008, a female patient presented to the Institute of Microbiology, Zurich, with a history of chronic diarrhea due to *C. difficile* infection following antibiotic therapy for a mandibular infection. Two years later, she received FMT from a donor (sister) under standard laboratory conditions, becoming one of the world's first patients to receive this treatment. The patient recovered completely in a few days after FMT [43]. Her intestinal phage population (in months) and bacterial population (within 4 years) achieved a profile similar to those of the donor [44,45].

FMT changes both the bacteria and phage populations. Still, it should be considered a phage therapy due to the abundance of phages compared to bacteria in human fecal matter. The first recorded use of FMT dates back to the 4th century in China, wherein stool diluted with water ("yellow soup") was used to manage diarrhea and food poisoning [46].

In 2013, the U.S. Food and Drug Administration (FDA) stated that FMT must meet investigational new drug (IND) administration criteria for approval [47], restricting its use. The FDA released the statement due to its theoretical safety concerns associated with the procedure and disease transmission risk and lack of standardized protocols.

However, within a month, following strong opposition from patients with recurrent *C. difficile* infections who were left with no other treatment options, the FDA stated that FMT could be used for *C. difficile* infections that have failed to respond to standard therapy. Nevertheless, the regulatory authority would exercise enforcement discretion under limited conditions. The FDA would require the treating physician to obtain consent from patients or their legal representatives [47].

Potential adverse effect of FMT-therapy in bacterial infections

Despite the promising results of FMT in chronic diarrhea, the FDA has issued a safety alert regarding FMT treatment. The FDA reported on six patients who were infected with enteropathogenic *E. coli* (EPEC) (two patients) and Shiga toxin-producing *E. coli* (STEC) (four patients) following therapy with FMT. Among the six patients, two died of the STEC infection [48].

The encouraging application of FMT in IBD, T2D, and obesity

In addition to chronic persistent diarrhea, other potential indications for FMT include inflammatory bowel disease (IBD), obesity, and specific psychiatric disorders [49].

Microbiological studies investigating the effects of FMT typically concentrate on the change in the bacterial population; however, it is highly likely that in cases of successful FMTs, phages also play a vital role. It has also been found that FMT can ameliorate or eliminate *C. difficile* infection even if the bacteria from the donor's stool are removed by filtration [50].

However, confirmatory studies are needed for these findings. Thus, the benefits of phagebiota in the success of FMT underscore the potential of phage therapy in diseases with altered microbiota, including IBD, type 2 diabetes (T2D), and obesity. Research has revealed significant alterations in patients' phagebiota with IBD [43] and T2D [51]. Moreover, phages attached to the intestinal wall supposedly protect against other infections and control local inflammation [52]. Again, these and similar findings highlight the potential of phage therapy in other diseases.

Ridaura., *et al*. (2017) found that obese mice that were fed feces of lean mice (caged together) exhibited weight loss [53]. Notably, the intestinal microbiota of obese mice is less complicated and lacks diversity. The results could have been influenced by the rich nutritional status, facilitating the overgrowth of specific microbes [54,55]. The ingestion of fecal matter of lean mice introduces diversity in obese mice. Less diverse microbiota can predispose humans to gain weight [56,57], although further studies are needed to confirm such a conclusion.

Phage therapy: clinical

There have been several documented clinical trials of phage therapy in humans.

Wright., *et al*. (2009) conducted a randomized controlled clinical trial consisting of patients with chronic otitis due to antibiotic-resistant *P. aeruginosa* treated with bacteriophage preparations [56]. In the phase 1/2 clinical trial, 24 patients with chronic otitis, aged between 2 and 58, were included. At the start of the trial, the patients had an ear infection from antibiotic-resistant *P. aeruginosa* strain sensitive to one or more of the six phages of Biophage-PA. The patients were randomized into two groups of 12 each; one group received a single dose of Biophage-PA, and the other group received a placebo. All patients were checked by the same otologist (blinded) at 7, 21, and 42 days after treatment. Compared to the placebo group, the phage-treated group demonstrated significant improvement in clinical parameters, patient-reported improvement, and microbiological parameters (significant reduction in *P. aeruginosa* count) [56].

Sarker., *et al*. (2016) performed a randomized clinical trial assessing phage therapy's safety in healthy and diarrhea-affected children in Bangladesh [57]. One group of children received phage therapy (one or two distinct cocktails of the phage) in oral rehydration salt (ORS) solution, while the other group received only ORS solution. No adverse events were reported in the phage-treated group [57].

Jault., *et al*. (2019) carried out a randomized, double-blind, phase 1/2 clinical trial to evaluate a bacteriophage cocktail's efficacy and tolerability in treating burn wounds infected with *P. aeruginosa* [58]. The researchers found that, at a considerably low concentration, the lytic anti-*P. aeruginosa* bacteriophages decreased the bacterial burden at the wound site in patients receiving phage therapy slower than those receiving the standard of care. Hence, the researchers suggested further studies with higher phage concentrations to establish phage therapy's efficacy [58].

Conclusion

The emergence of antibiotic resistance has renewed interest in phage therapy. Moreover, the development and application of phage therapy in several countries, such as Poland, Russia, and Georgia, has piqued the interests of researchers and the medical community worldwide. Phage therapy is proving beneficial and cost-effective. However, adverse effects, contraindications, and protocols need to be further investigated and established. Clinical trials to evaluate the efficacy and safety of phage therapy under diverse clinical conditions are ongoing. Phage therapy has the potential to treat not only bacterial infections but also other pathological conditions, such as IBD, T2D, and obesity.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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