

Phage Therapy: Future Inquiries

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Abstract

Western scientists have steadily been gaining interest in phage therapy since the mid-1980's due to the rising problem of antibiotic resistance. Its introduction in the 20th century by Felix d'Herelle marked the beginning for the uses of bacteriophages as antibacterial agents. However, a lack in understanding phage biology, as well as the arrival of broad-spectrum antibiotics deprioritized using phage therapy to treat bacterial infections in the West. With the advent of molecular biology, we are now better able to understand the predator-prey relationships with which phage co-evolve with their hosts as well as the specificity of phage-host interactions which could lend itself into personalized treatments for infection. These discoveries give us greater insights on how to most effectively use bacteriophage as potential therapeutic agents. It is encouraging to note that bacteriophages are used as food additives in the U.S., suggesting that the FDA acknowledges the positive potential of bacteriophages for human applications. Unfortunately, there are only a few examples to date of bacteriophages used on humans in controlled clinical trials. Rigorous studies *in-vitro* and especially *in-vivo* are critically important to avoid the mishaps of our predecessors. Phage biologists must strive to meet regulatory standards and to design thorough, rugged studies in order to establish a substantiated need for phage therapy in health care.

Phage Therapy: The Pre-Antibiotic Era

Bacteriophages (or phages) are bacterial viruses. They are only capable of attacking prokaryotic cells like bacteria and they cannot attack eukaryotic cells such as those of humans. First discovered in the early 1900's, bacteriophages were thought to be bacteriolytic agents capable of killing bacterial cultures. Felix d'Herelle was the first to consider using phage suspensions to treat bacterial infections such as dysentery, which at the time did not have any other consistently effective treatments. His success led to a widespread period of enthusiasm in the field (Abedon *et al.* 2011), which stimulated numerous studies including those of phage therapy on wounds. The application of phages to treat locally infected sites such as carbuncles, abscesses and other superficial wounds showed their potential as antibacterial agents, although results were not always successful or reproducible. For a review on phage therapy of wounds and related purulent infections see Loc-Carrillo *et al.* 2012.

Among the earliest phage therapy studies was a 1923 article by McKinley. McKinley reported four clinical cases presenting with open wound infections where *Staphylococcus aureus* was claimed to be responsible. In these cases, filtered *Staphylococcus*-specific phage were injected either directly into the wound, subcutaneously, or both. The results exhibited a decrease in discharge and eventual improvement of patient condition. McKinley suggested that the phage treatment might not have been the cause for improvement in two of the cases, as he speculated that factors such as pus disturbance and protein in the filtrate had a greater effect on wound healing. Despite this, he found his results to be encouraging and concluded the article with his optimistic vision of phage therapy and its "*enormous potential possibilities*" (McKinley 1923). However, in 1934 Eaton and Bayne-Jones published a rigorous review of more than 100 phage therapy papers, including reports of phages applied to wounds by the then-popular methods of wet dressing or direct injection (Eaton & Bayne-Jones 1934a, b, c). Their evaluations criticized the lack of scientific rigor

undertaken to conduct the clinical trials. They suggested an extreme disparity between the successes reported by over 90% of cases and the disappointing results published by the more critically conducted laboratory experiments. These reviewers also reflected on the unremarkable speed of recovery in most cases, the self-limiting nature of certain wounds, as well as the practice of usual surgical intervention, all of which they believed could have played a role on the patient's recovery rather than from the use of phage therapy.

Although Eaton and Bayne-Jones incorrectly assumed that phages were inanimate protein, the leverages of their review along with a second negative review by Krueger and Scribner (Krueger & Scribner 1941) quickly halted the enthusiasm with which research in phage therapy was pursued in Western medicine for the remainder of the 20th century. In the intervening years after World War II, the discovery and widespread availability of antibiotics shifted the use of bacteriophages to model genetic systems for research in molecular biology (Stent 1968; Summers 2005).

Why the Initial Uses of Phage Therapy Misfired

Like many innovations that are discovered before they are understood, the use of bacteriophages as therapeutic agents had many problems due to the lack of knowledge in phage biology (Skurnik *et al.* 2007). Nevertheless, although d'Herelle did not understand the complete nature of bacteriophages, his scientific prowess helped him undertake rigorous procedures that encapsulated many of the important requirements necessary for phage therapy to have a chance of success. Kuhl and Mazure (2011) recently translated an important section within d'Herelle's book on "*Le Phenomene de la Guerison dans les maladies infectieuses*", describing the preparation of therapeutic bacteriophages. In it, d'Herelle emphasizes how crucial the preparation of therapeutic bacteriophages is towards being effective at treating bacterial infections. D'Herelle was so mindful of the

repercussions of having inactive phage preparations that he decided to set up a laboratory to study therapeutic phages. He wanted to share his results with any official laboratory interested in conducting phage therapy. He realized that each therapeutic phage needed to be well characterized and this would more than likely take years to investigate. To d'Herelle it was obvious that a commercial laboratory would not be able to tackle such a task and make a profit from it (Kuhl & Mazure 2011). One can postulate that this might have been an early attempt at personalized medicine.

We now know that there are a number of critical characteristics required of bacteriophage before being considered suitable candidates for therapeutic use. These include: only using obligately lytic bacteriophage incapable of transferring genes (specifically those encoding for toxins) from one bacterium to another; using appropriately lytic bacteriophage to the target bacterial infection (i.e., bacteriophages often have a narrow host range and will not infect all bacteria in a particular species); as well as being stable at relevant pH and temperatures over a significant period of time (e.g. ~2 -4 years) (Gill & Hyman, 2010).

Antibiotic Resistant Bacteria and Re-Thinking Phage Therapy

When penicillin was first used in the 1940's, it was thought to be a 'wonder drug'. However, delirious excitement and high expectations from physicians led to them being overused and abused before people understood the consequences and hence the development of antibiotic-resistant bacteria (Singh & Barrett 2006). As the crisis to antibiotic resistance escalated (Neu 1992), phage therapy increasingly gained re-interest by Western scientists (Alisky *et al.* 1998). Bacteriophages are very specific to bacterial species, and most known phage only infect and replicate in a limited number of host strains (Hyman & Abedon 2010). This specificity makes

bacteriophages harder to apply as blanket antibacterial agents; however, phage therapy offers its own set of advantages.

Although, the antagonistic co-evolution of bacteriophage and their host has allowed bacteria to develop mechanisms against phage infections such as: uptake blocks, restriction, and abortive infection, it has also allowed the phage population to become progressively more infective to a wider range of host populations through the acquisition of mutations which result in reduced specificity of their binding site (Buckling & Rainey 2002; Hyman & Abedon 2010). This co-evolution is speculated to be driven by directional selection (Buckling & Rainey 2002), as opposed to spontaneous mutations, which occurs as a random act (Drake 1991). Antibiotics have no such selection mechanism, and their indiscriminant targeting of bacteria is more likely to generate resistance. When a broad-spectrum antibiotic exerts selective pressure on every bacterium in the human body, each bacterium has a probability to be resistant. In addition, plasmid transfer has the potential to spread the resistance across an entire bacterial population. Highly specific bacteriophages exert selective pressure on a much smaller population of bacteria. By reducing the size of the population encountering the selective pressure, bacteriophages vastly decrease the probability of promoting the development of phage-resistant bacteria (Kerr *et al.* 2008).

Antibiotics have proven to be too good to be true, and antibiotic resistant bacterial infections have become an enormous problem to manage. Phage therapy is seen as a cure to antibiotic resistance, and a handful of early-phase clinical trials have had some promising results (Merabishvili *et al.* 2009; Rhoads *et al.* 2009; Wright *et al.* 2009); however, phage biologists should be cautioned not to make the same mistakes of overconfidence that the early advocates of antibiotics had.

Pros and Cons of Phages as Antimicrobials

Today when considering phage therapy as a means to combat pathogenic bacteria, there are a few issues that should be considered:

Phage Specificity

Phages recognize and bind to their hosts by taking advantage of the bacterial cell's surface receptors; therefore, the interactions between phage and bacteria tend to be very specific. Some are so specific, in fact, that they may target only a sub-group of a species, rather than the whole species of bacteria itself (Koskella & Meaden 2013). This characteristic of phage, called narrow-host range, can be a double-edged sword. As mentioned previously, the benefits of specific phage-bacteria interactions means that the beneficial bacterial microbiota of the body are minimally disturbed. In the area of infections and diseases, a healthy and un-altered human microbiome imparts a robust immunity to the host (Pflughoeft & Versalovic 2012), which may reduce the incidence of preventable diseases associated with a disrupted microbiota.

Conversely, the logistics of using bacteriophages on a mass scale must be considered. If the use of phages in medical intervention were to be approved by the US Food and Drug Administration, then it is likely that stringent protocols would be necessary for ensuring the safety of phages as drugs; the implication given would be a rise in production costs. This begs the questions: how much would production costs be raised by, and would this increase be truly significant compared to the cost of antibiotic production or "small molecule" therapy (Projan 2004)? Another point to consider in logistics is the challenge a narrow-host range may present to industry for preparing 'personalized' phage formulations within a timely manner (Skurnik *et al.* 2007). All of these issues should be taken into account, whether for reviewing the practicality of implementing phage therapy or for purposes of proposing smarter ways of manufacturing phage formulations in the future. Regardless,

both phage proponents and opponents alike should balance their views with verifiable evidence.

Phage-Bacteria Interaction

Phages are natural predators of bacteria, and the interaction of bacteriophages with their environments i.e., phage ecology, is now a well-studied field. 'Wild' phage have long co-existed and co-evolved with bacteria in the environment without one out-competing the other due to the help of factors including complex or heterogenous spatial surroundings like those in soil or biofilm (Heilmann *et al.* 2010). The conventional wisdom of phage biologists hold that in homogenous mixtures such as liquid cultures, locally-adapted lytic phage that are introduced at a sufficiently high infection ratio can lyse bacterial cells until the host population is below the proliferation density threshold (Payne & Jensen 2003). Obligately lytic phages accomplish this by injecting their genetic material and using the host to replicate before bursting (hence killing) the bacteria cell. This self-replicating effect is a much-touted advantage, as it implies that phages are self-sustainable as long as bacteria are present (Payne & Jansen 2000).

Three concerns arise regarding the phage-bacteria interaction: 1) The unmanageable lysis of bacteria that can cause release of endotoxins from Gram negatives (Rietschel *et al.* 1994), which are responsible for sepsis; however, new ways of overcoming this problem by using phages that do not lyse cells have been investigated (Matsuda *et al.* 2005); 2) As the phage population increases, they exert a higher selective pressure for their targeted host to evolve resistance. Bacteria can evolve resistance through mutations that delineate changes to receptors on the cell surface (Bohannon & Lenski 2000); however, bacterial resistance to phage is often associated with reduced fitness (Brockhurst *et al.*, 2004), which could implicate increased vulnerability to immune defenses. In addition, phages are continuously evolving to gain advantage over

potential bacterial hosts; 3) The timing and inoculation size is critically important for obtaining satisfactory outcomes (Payne & Jansen 2003); although, it is currently unclear whether these factors apply for all phages or only for specific types of phages. When dealing with the treatment of human infections, an additional factor that would affect the rate of success would be the stage of the infection being treated, where more established infections i.e., chronically infected wounds, would be harder to treat due to the presence of biofilms.

Phages on Biofilms

It is estimated that at least half of all hospital-associated infections are biofilm-related (Potera 1999). Biofilms are communities of bacteria contained in complex three-dimensional matrices, which create heterogeneous environments within themselves. Tight-packing of cells contribute to coordination and communication amongst the population through cell-to-cell signaling, and heterogeneity in the biofilm cause bacteria at different levels of the biofilm to locally specialize their metabolic activities (Hall-Stoodley & Stoodley 2009). Bacteria in biofilms are also found in altered growth rates and transcribe genes that planktonic cells do not (Donlan & Costerton 2002). These characteristics of a biofilm are vastly different from standard flask cultures. Importantly, biofilms tend to have a general resistance to antibiotics that is likely due to low oxygen limitations that restricts bacterial metabolic activity rather than restricted penetration from the presence of the extracellular matrix (Walters *et al.* 2003; Pozo & Patel 2007). Slow-growing bacterial cells deep within the biofilm, known as persister cells, can survive many antimicrobial treatments even after a large majority of susceptible cells are eradicated, due to their altered growth rate. These persisters can then reconstitute the biofilm after the antimicrobial pressure has been removed (Pozo & Patel 2007).

Given the hardness of biofilms, the idea of attempting to treat them using bacteriophages seems insurmountable; however, *in-vitro* experiments have shown varying degrees of success — some have demonstrated clinically significant reductions of bacterial load of over $\text{Log}_{10} 3$ (Hughes *et al.* 1998b; Lu & Collins 2007; Rhaman *et al.* 2011) while others have been able to reduce bacterial load by more modest amounts e.g. under $\text{Log}_{10} 2$ (Hanlon *et al.* 2001; Bedi *et al.* 2009; Pires *et al.* 2011) or not at all (Sharma *et al.* 2005). Of-course it is important to note that the differences in results between these studies may be influenced by the concentration of phage used and the method used to grow the biofilm (e.g. under static or dynamic conditions), which affect the biofilm structure and hypothetically its susceptibility. In general, it appears that phage therapy against biofilms can work, but under specific conditions. Naturally-occurring lytic phages have been found to possess biofilm-attacking properties using polysaccharide depolymerizing enzymes (Hughes *et al.* 1998a). However, not all phages are efficiently adapted to targeting biofilm, and some may require genetic manipulation to express an enzyme that can degrade extracellular polymeric substances (EPS) that help maintain the biofilm structure (Lu & Collins 2007); this could be attainable over time as the production costs in biosynthesis become more feasible, allowing for faster and cheaper preparation of biofilm-eradicating phages. As previously mentioned in the *Phage Specificity* section, the logistics of mass production by industry must also be accounted for.

Phages have been found to prevent the formation of biofilms (Liao *et al.* 2012), although the advantages of phage used against already formed biofilms has only been tentatively explored. In addition, a number of those studies investigating the efficacy of phages against biofilms have used 24-hour biofilms with treatments usually lasting no more than 24 hours. These types of studies should ideally involve increased treatment

durations as well as a diversification of biofilm age, condition, and starting titers to better reflect the relevant clinical regimens encountered.

Phages in Combination Therapy

One of the avenues, which some phage proponents believe has great promise, is the use of phages in combination therapies, particularly phages and antibiotics. Phages have been shown to work synergistically with common antibiotics such as amoxicillin, enrofloxacin, azithromycin, vancomycin, and rifampicin (Huff *et al.* 2004; Bedi *et al.* 2009; Rahman *et al.* 2011). The use of this combination therapy has shown greater antibacterial properties when compared to either phage or antibiotic treatments alone (Hagens *et al.* 2006). Surprisingly however, the combination of phage and azithromycin (a bacteriostatic antibiotic) resulted in killing more cells in a biofilm after 24 hours than the combination of phage and vancomycin (a bactericidal antibiotic) (Rahman *et al.* 2011). This is the first time where the co-treatment of phage and a bacteriostatic antibiotic (i.e. killing 90-99% of the inoculum) has been shown to be an effective treatment, since it has been speculated that the use of a bacteriostatic antibiotic with phage would be detrimental to the efficacy of the phage infecting and killing bacterial population under such conditions, particularly since bacteriostatic antibiotics are known to interfere with bacterial protein production, DNA replication, and other aspects of bacterial metabolism (Pankey & Sabath 2004), which are required for phage production.

Although there are only a few published studies investigating the co-treatment of infections with phage and antibiotics, scientists at the Eliava Institute observed this phenomenon as early as the 1970's. A review by Kutateladze & Adamia (2010) summarize some findings from clinical trials carried out in the Soviet Union using combination therapy of phages and antibiotics. Up to 78% of patients were reported to fully recover from three types of

staphylococcal infections (i.e., sepsis, lung infection, or osteomyelitis), compared to 23% of those in the control group who were treated with antibacterial remedies only (Kutateladze & Adamia 2010).

In addition to some of the advantages and disadvantages mentioned above, there are a number of other pros and cons associated with phage therapy (Loc-Carrillo & Abedon 2011). Table 1 summarizes the major pros and cons generally considered when attempting to use phages as antimicrobials.

Table 1. Major pros and cons associated with using bacteriophages as antimicrobials.

Pros	Cons
Bactericidal agents – once infected by an obligately lytic phage, bacteria will not regain their viability (Kropinski 2006).	Problems with narrow host range – due to their highly specific nature, it is more than likely that more than one phage (i.e. phage cocktail) will be needed to treat a particular bacterial infection (Chan <i>et al.</i> 2013). This is most probable when treating chronic infections, which more commonly harbor polymicrobial populations.
Auto ‘dosing’ – a phage can use the bacterial cell to produce more phages (Abedon 2011).	
Minimal disruption to microbiota – due to their highly specific nature, phages are target specific predators and will not affect the population of health protecting bacteria present the body.	Temperate phages – some phages carry toxin-coding genes and are capable of transducing those genes to benign bacteria (Brussow <i>et al.</i> 2004). In addition, these phages can convert phage-sensitive bacteria into insensitive ones (i.e., superinfection immunity).
Narrower potential for inducing resistance – the selective pressure for specific phage-resistance mechanisms will only occur in a small population size within a microbiota, if at all. Some phages use receptors that are essential for survival in the infected hosts (Linberg 1973; Rakhuba <i>et al.</i> 2010).	Host immunity – Some phage have shown immunomodulatory activity and the development of anti-phage neutralizing antibodies (Gorski <i>et al.</i> 2012). Evidence suggests that >90% of phage may be cleared from circulation by the reticuloendothelial system and spleen (Merril <i>et al.</i> 1996).
Lack of cross-resistance with antibiotics – the mechanisms phage use to infect bacteria differs from the mechanisms involved in antibiotic resistance (O’Flaherty <i>et al.</i> 2005; Burrowes <i>et al.</i> 2011).	Poor penetration – phages cannot penetrate tissues without the need of genetic engineering (Poul & Marks 1999).
Rapid discovery – there is an abundance of phage present in sewage and elsewhere. Improving the odds of finding the ‘right’ phage is dependent of using an appropriate host (Gill & Hyman 2010).	Unfamiliarity as potential pharmaceuticals – currently there are no phage-based pharmaceutical products in the Western market (Verbeken <i>et al.</i> 2012). A handful of clinical safety trials have been conducted in Europe and the U.S. and only one clinical trial has shown some efficacy (Parracho <i>et al.</i> 2012).
Formulation and application versatility – phages have been blended with creams, impregnated into solids, and applied as liquid preparations (Ryan <i>et al.</i> 2011).	

Meeting Regulatory Standards

Although phage therapy has been extensively used in the Soviet Union and Eastern Europe to treat bacterial infections in humans, the lack of

English-written scientific publications outlining the composition and characteristics of the phage preparations, as well as a disregard for undertaking controlled clinical trials have made

it almost impossible to include that research in evaluating the efficacy of phage therapy by today's standards. For a comprehensive look at some of that work, readers are referred to read the book by Chanishvili & Sharp (2009). This book reviews phage therapy research published in Russian, Georgian and Ukrainian articles, reports and books dating back as far as 1926 – making this early research more accessible to Western scientists.

The current regulatory framework in both Europe (Verbeken *et al.* 2012) and the U.S. hinder rather than facilitate the clinical use of phage therapy. This is because there is no specific categorization that is amenable to using bacteriophages as therapeutic agents (Pirnay *et al.* 2011). There are two approaches to using phage therapy. The first is to manufacture a cocktail of bacteriophages that have been developed to treat a broad spectrum of bacterial infections. This approach works with the regulatory agencies as it mimics the processes developed for the annual flu vaccine. The flu vaccine is an evolving product that is updated every 1-2 years based on data investigating the adaptation of the flu strain(s) likely to appear in the coming season. This approach works for industry since it is possible to obtain intellectual property (IP) rights from such well-characterized phages and techniques of administration, as well as manufacturing processes. However, many phage therapy researchers believe this is not the best approach for phage therapy. Favoring a more 'personalized medicine' approach, which requires the bacterial strain(s) causing the infection to be cross-referenced with a panel of phages, identifying the most effective phage for treatment and resulting in a higher rate of successfully treated infections. This personalized approach would require frequent testing of the patient's infecting strain in order to reduce the likelihood of the development of phage-resistance. Alternatively, the bacteriophages could be allowed to evolve *in-vitro* against patient strain(s). With this personalized approach it would be less likely for

industry to 'make money' since it would be too costly to characterize so many bacteriophages and claim IP rights to them. Testing the efficacy of so many bacteriophages would also leave industry with an almost impossible task.

In Europe, phage therapy can be used under the Declaration of Helsinki which states; "*In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health, or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available*" (Merabishvili *et al.* 2009; Verbeken *et al.* 2012). In contrast, in the U.S. the FDA evaluates phage-based products on a case-by-case basis. The first FDA-approved phase I clinical trial was conducted by Rhoads and colleagues in 2009 (Rhoads *et al.* 2009). It is worth mentioning that a small number of phage-based products have been approved by the FDA. Under the GRAS (Generally Recognized As Safe) exemption, bacteriophages can be used as food additives for the decontamination of meat and poultry products to control *Listeria monocytogenes* and *E. coli* O157:H7. This is an indication that the regulatory agencies, although unfamiliar with bacteriophages as pharmaceuticals, are slowly becoming more amenable to allowing the use of bacteriophages for human applications.

The FDA sees the potential for using bacteriophages therapeutically, although they remain cautious and aware that certain requirements must be met. That includes the use of obligately lytic non-transducing phages that are derived from the natural environment (Brussow 2012). In addition, each phage must: a) be fully sequenced (to identify any known

virulence genes); b) have a characterized seed lot system and growth media (to minimize the contamination from prions); and c) pass toxicity testing *in-vivo*, as well as undergo sterility and stability tests. Controlled human clinical trials would still be required to demonstrate their safety and efficacy. A small number of human clinical trials, which meet these requirements, have evaluated the safety of phage therapy (Bruttin & Brussow 2005; Merabishvili *et al.* 2009; Rhoads *et al.* 2009; Sarker *et al.* 2012). However, to date only one human clinical trial has been set-up to evaluate the efficacy of phage therapy (Wright *et al.* 2009).

Is There a Future for Phage Therapy?

Since the advent of molecular biology, we have gained a better understanding of the biological properties of bacteriophages along with the mechanisms involved in phage-bacterial host interactions. However, despite our knowledge of their manipulations *in-vitro*, we have limited understanding of their behavior *in-vivo*, particularly through clinical trials. The number of *in-vivo* studies used to evaluate the efficacy of phage therapy has steadily been increasing exponentially since the mid 1980's (Burrowes & Harper 2012; Loc-Carrillo *et al.* 2012). Although many of these phage therapy studies were successful to some extent, not all have shown efficacy. Well-controlled, methodical experimental designs are imperative in order to adequately evaluate the use of bacteriophages as antibacterial agents. In addition, studies should cover all types of bacterial infections with variations in the phage formulation and delivery system. Bacteriophage preparations must also contain highly purified and well-characterized clones in order to minimize any confusion that might result from immune responses that are seen resulting from the presence of bacteriophage in the body, rather than because of lysed bacterial components (Gorski *et al.* 2012).

Many phage therapy researchers believe that phage therapy should fall under the personalized treatment regime. This would

allow the treatment to be specifically targeted towards the patient's infective strain. Since phages are known to be very specific to the bacterial strains they infect, and there are hundreds of known pathogenic bacterial species, a bank of thousands of well-characterized phages would be needed to support a personalized treatment. Pharmaceutical companies may be less inclined to invest on phage-based products for therapeutic uses since intellectual property cannot be obtained on a technique that has been previously used (Clark & March 2006; Parracho *et al.* 2012). This may leave the task to a collaboration of efforts by academic researchers and government entities such as the special groups in the armed forces to work together – as had occurred with the Soviets when they tried phage therapy on their soldiers during the Finnish Campaign and World War II (Chanishvili *et al.* 2009). However, it may be possible to commercialize phage-based products containing a combination of bacteriophages. These cocktails could be used to treat acute infections at their early stages while the appropriate personalized cocktail of phage is determined.

Many researchers interested in phage therapy are initially enamored by the concept of using a bacterial virus to target and kill a pathogen; however, rather than viewing phage therapy at the single cell level, it would be more realistic to think of it terms of population sizes involving a predator-prey relationship that has been in existence since the beginning of time. That is to say, there is a lot of history on the dynamic nature of phage-host interactions and our ability to manipulate phages in our battle against pathogens is not as simple as it initially looks. It is unlikely that phage therapy will be useful at treating all bacterial infections, and it will only be through methodical experimental designs and perseverance that we can find the right infections where phage therapy can prove to be the best approach.

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