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Bacteriophage therapy: An introduction and revitalized therapy for *Klebsiella spp* and *Pseudomonas aeruginosa* infections

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ABSTRACT

We are living in a microbial world and microbes like bacteria are affecting our lives in positive and also negative ways they are commensals in our bodies they play key roles in sustaining our environments and they are causing diseases. Bacteriophage therapy once considered a promising alternative to antibiotics is now being revitalized as a potential treatment for infections caused by *Klebsiella spp* and *Pseudomonas aeruginosa.* In recent years the rise of multidrug-resistant bacteria has become a major concern in healthcare settings. Antibiotic-resistant bacterial strains have emerged as a result of antibiotic abuse making it more and more difficult to treat illnesses. Bacteriophages that specifically target and infect bacteria offer a potential solution to combat these drug-resistant infections. This review article provides an introduction to bacteriophage therapy and highlights its potential use in treating infections caused by *Klebsiella spp* and *Pseudomonas aeruginosa.* The article addresses the urgent need for alternative strategies to antibiotics and explores the use of bacteriophages as biocontrol agents.

Keywords: Bacteriophage, Multidrug-resistant bacteria, Antibiotic resistance, Phage therapy, Genetic modification

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INTRODUCTION

Phages are viruses that replicate only inside bacteria. They are the most abundant organic entities on Earth and have diverse morphology and genomic structure. All phages have a nucleic acid genome protected by phage-encoded capsid proteins that help transfer the hereditary material into the host cell.[1] Phages are non-motile viruses that use Brownian motion to find a host. They have structures resembling heads, legs, and tails. Phages adopt one of two replication strategies: lytic or lysogenic. In the lytic cycle, the phage binds to a host bacterium, delivers its genome into the host cytoplasm, and uses host ribosomes for protein synthesis.[2] The cellular resources are rapidly converted into viral genomes and capsid proteins, assembling into multiple copies of the original phage. Upon the death of the host cell, it undergoes either active or passive lysis, releasing the newly formed bacteriophage to infect another host cell.[3] In lysogenic replication, the phage infects a host bacterium and integrates its genome into the bacterial chromosome.[4] The bacteria pass on the replicated phage genome to daughter cells without causing death. The integrated phage genome can revert to a lytic replication cycle, causing host cell lysis upon environmental changes.

Phages are viruses that are abundant in all biological systems. They are being studied for their interactions with bacteria and their potential to combat pathogenic bacteria. Ernest Hankin observed disinfectant activity attributed to bacteriophages in 1896.[5] And Nikolai Gamaleya in 1898.[6] However, the clarity of those early observations lends itself to interpretation.[7] Frederick Twort was the first to propose that a virus was responsible for mediating the observed antibacterial activity.[8] Félix d'Herelle discovered bacteriophages at the Pasteur Institute in Paris after Twort's hypothesis couldn't be verified due to insufficient funding.[9] In 1917, d'Herelle started bacteriophage treatment trials at a Paris hospital, showing initial safety through ingestion. In 1921, Bruynoghe and Maisin conducted the first clinical trial in France, administering phages locally to skin lesions caused by cocci infections.[10] In the 1920s, bacteriophage therapy was used to treat various infections, including Asiatic cholera and plague in India. Recently, experimental bacteriophage treatments have been conducted in the U.S. through FDA-approved "expanded access" programs.[11-16] Raised awareness and excitement about bacteriophage therapy, leading to more physicians considering it as a treatment option alongside antibiotics.

Phage therapy, due to delayed bacterial resistance to antibiotics, is now crucial across various fields like biotechnology, biosensors, medicine, food preservation, hydroponics, pollution control, and wastewater treatment, addressing limitations of phage-based therapy; it operates through a multistep cycle involving key proteins such as capsid, portal, tail, scaffold, and terminase, with dsDNA phage capsids typically having icosahedral or pentameric shapes, broken at the head-to-tail interface (HTI), primarily by a dodecameric

portal protein (PP) serving as the DNA packaging engine, along with oligomeric rings of head completion proteins that aid in ATP energy utilization and connecting the portal protein to the tail.[17-25]

BACTERIOPHAGE BACTERIAL HOST SURFACE INTERACTIONS

The bacteriophage's three-dimensional structure is arranged by the base plate, which also facilitates bacterial host recognition and attachment. The base plate initiates the process of tail sheath withdrawal, which proceeds in a wave-like manner across the whole sheath. The crucial factors that determine the specificity of a bacterial host are found in the tail strands that extend from the bacteriophage base plate.[26] Effective authority interaction with a bacterial host receptor triggers base plate conformational change, causing sheath withdrawal. Signal transmission through the fiber to the bacterial host involves changing filament direction relative to the base plate. In solution, bacteriophage tail strands lack fixed orientation, pointing sideways or even toward the capsid.[26] When attached to the bacterial host, the bacteriophage's tail filaments point towards it. Recent studies propose two mechanisms for this directional change, occurring exclusively on the host surface and without requiring chemical energy for fiber reorientation and base-plate triggering.

The task of breaking through the intricate bacterial host cell membrane, which protects these organisms from their unpredictably harsh environments, presents a hurdle at the beginning of the bacteriophage's infectious cycle. There are two main kinds of bacterial cell envelopes. The typical structure of gram-negative bacterial cell envelopes is an outer membrane made of lipopolysaccharides, an inner cell membrane, and a thin coating of periplasmic peptidoglycan.[27] Bacteriophages infecting bacterial cells surrounded by a capsule carry exopolysaccharide (EPS)-degrading enzymes (depolymerase) in their tail spikes.[28] Through the hydrolysis of the bacterial outer layer by these enzymes, bacteriophages are able to access the peptidoglycan layer or the outer membrane.[29] The bacterial capsule, which is made up of several EPS such as polysialic acids, hyaluronic acid and alginates, has enzymes called glycanases, lyases, and case-specific deacetylases that are involved in EPS depolymerase.

Bacteriophage particles can carry LPS-hydrolyzing enzymes in tail spike proteins, aiding in penetrating Gram-negative bacterial LPS. This enzymatic action helps access entry receptors on the cell surface, facilitating bacteriophage entry. Additionally, LPS-degrading bacteriophages can bind to LPS as attachment receptors, potentially assisting in releasing progeny particles during the lytic cycle.[30] EPS depolymerases incorporate proteins, for example, LPS-explicit glycanases and LPS-explicit deacetylases.

Bacteriophages use endolysin to degrade bacterial peptidoglycan for host lysis and progeny release. Depolymerase and virion-associated lysins breach cell barriers during infection.[31-34] Virion-associated lysins aid in genetic material injection by degrading peptidoglycan, polysaccharides, and other molecules. Phages can enter the host membrane and insert genetic material thanks to this hydrolytic action.[35] Lysozymes, lytic transglycosylases, N-acetyl-muramoylamidases, N-acetyl-β-d-glucosaminidases, and endopeptidases are the five types of bacteriophage lysins, also known as murein hydrolases, according to their enzymatic specificity.[36-37]

THE LIFE CYCLE OF BACTERIOPHAGE

Bacteriophages lack cellular machinery, thus upon entering the host cell, they hijack the host's cellular apparatus for replication. Unfavorable conditions during this process lead to the lytic cycle.[38] And if it enters the dormant phase the condition is favorable then it is a lysogenic cycle.

MECHANISM OF BACTERIOLYSIS BY PHAGES

Adsorption to the receptor, which is often a protein or sugar on the bacterial surface, is the initial stage of phage infection.[39-40] Polyvalent phages, which infect numerous species, are uncommon; phages adhere to specific species of bacteria. Phage treatment is able to target germs while sparing the native flora. After adsorption, phage DNA is injected into the bacterial cytoplasm, where it is replicated and numerous DNA copies are synthesised within the capsid. During late infection stages, phage particles are assembled by adding a tail to the DNA-filled head. Holin and endolysin proteins aid in progeny phage release, with endolysin degrading peptidoglycan through holes formed by Holin in the cell membrane.[41] Phage lysin is thought to be a possible treatment for infectious bacterial illnesses. Rapidly released descendant phages infect nearby bacteria. Even while there are initially less phages than bacteria, over several generations, phage counts rise beyond bacterial counts, which finally results in total bacterial lysis. It seems that phage bacteriolytic activity is more effective than bactericidal drugs as rifampicin, vancomycin, and oxacillin.

PHAGE THERAPY BY USING NON-REPLICATING PHAGE

A phage-display technique targets bacteria using modified M13 phage fused with specific antibodies. This approach is particularly effective against H. pylori infections. In vitro studies demonstrate that the modified M13 suppresses H. pylori growth without replication. Oral administration reduces bacterial colonies.[42] Recently, a novel approach has been introduced to address *P. aeruginosa* infections. This method involves the creation of a recombinant phage

derived from the *P. aeruginosa* filamentous phage, Pf3, aimed at minimizing endotoxin release during phage therapy.[43] The gene producing restriction endo-nucleases was inserted into the genome in place of the export protein gene. When phage DNA is injected, restriction endonucleases break down the host genomic DNA, causing bacterial death in vitro with little endotoxin leakage. This mutant phage is unable to reproduce within the host.[43]

PHAGE THERAPY USING LIVING PHAGES

In the study, a single dose of anti-k1 phage showed greater efficacy against *E. coli* infection when given intramuscularly and intracerebral compared to multiple doses of tetracycline, ampicillin, chloramphenicol, and trimethoprim plus sulfafurazole. *Staphylococcus aureus* causes inflammatory diseases, food poisoning, toxic shock syndrome, and opportunistic infections, with a high mortality rate. It exhibits multidrug resistance, known as methicillin-resistant *Staphylococcus aureus*.[44-45] Some strains have developed resistance or low sensitivity to vancomycin, which is a unique antibiotic effective against MRSA, for example, VISA.[46] or VRSA.[47-48] The study used *Staphylococcus aureus* phage MR11 as a model, employing mice as the animal model. Mice were intraperitoneally injected with *S. aureus,* including MRSA, at 8x108 cells. Following this, intraperitoneal administration of purified phage ϕMR11 effectively suppressed *S. aureus*-induced lethality without adverse effects. Even when administered 60 minutes after bacterial injection, ϕMR11 maintained therapeutic efficacy, despite signs of physical deterioration in mice. These results demonstrate the safety and effectiveness of phage therapy against *Staphylococcus aureu*.[49] In in-situ hand wash studies, a phage-enriched wash solution can reduce Staphylococcal numbers on human skin 100-fold compared to phage-free solutions.[50] Using living Staphylococcal phages can be an effective approach for treating, preventing, and disinfecting *S. aureus* infections. In their study, Merrill et al devised an indigenous method to overcome the problem of phage trapping by the reticuloendothelial system in the spleen, for phage therapy.[51]

This highlights the efficacy of phage therapy in food sanitation and in combating fish illnesses. Nokai et al. has devised a method to safeguard cultured fishes from two fish pathogens, *Lactococcus garvieae* and *Pseudomonas plecoglossicida*. Moreover, phages exhibit effectiveness against foodborne pathogens present on food surfaces, including *Listeria monocytogenes*, *Campylobacter jejuni*, and Salmonella spp.

CLINICAL USES OF BACTERIOPHAGES

In 2017 the World Health Organization distributed top-notch worldwide need microorganisms involving 12 types of microscopic organisms sorted into basic, high, and medium needs dependent on their degree of obstruction and accessible therapeutics.[52] The current pace of obstruction advancement far surpasses the degree of anti-toxin disclosure and improvement and speaks to a worldwide general well-being challenge. Assessments have proposed that as many as 10 million individuals could kick the bucket every year because of antimicrobial opposition by 2050.[53] While this is a petulant figure.[54] It in any case features the difficult issue we face concerning remedial alternatives for multi-drug safe (MDR) bacterial diseases.[55] The common predators of microscopic organisms are bacterial infections known as bacteriophages or phages. Found universally, these creatures are assessed to be available at numbers proportionate to a trillion for every grain of sand on Earth.[56] Advancing in corresponding with microbes, phages are likely antibacterial helpful operators against such MDR microorganisms.[57] Here we center around three basic need microbes, *Acinetobacter baumannii, Pseudomonas aeruginosa,* and individuals from the *Enterobactericeae*.[52] The flow propels phage treatment examination to focus on these life forms, just as investigating more broad issues of clinical preliminaries and administrative complexities of phage treatment.

PHAGE THERAPY FOR *Pseudomonas aeruginosa* IN CYSTIC FIBROSIS

Up to 80% of individuals with cystic fibrosis who are 25 years of age or older and 30% of children are usually colonized by the opportunistic environmental bacteria *Pseudomonas aeruginosa*.[58-59] Consequently, pulmonary function reduction, persistent lung infection, and mortality are all inevitable outcomes.[60-61] In cystic fibrosis lungs, *Pseudomonas aeruginosa* forms biofilms, encasing stationary clusters, while surface motile cells disperse to colonize new areas, triggering recurrent infections requiring antibiotics. Extended use of antibiotics increases resistance, resulting in *Pseudomonas aeruginosa* strains that are multidrug resistant and both mucoid and non-mucoid.[62-63] MDR *Pseudomonas aeruginosa*, defined by the CDC, exhibits resistance or intermediate susceptibility to multiple antimicrobial classes. Despite global CF infection management recommendations focusing on MDR prevention, recent research emphasizes *P. aeruginosa* evolutionary variation and resistance in CF lungs.[64] There is a declining interest in research on novel antibiotics for pipeline initiatives.[65] Hence, we desperately need more effective treatment ways to fight CF MDR PA infections. Based on significant study, bacteriophage treatment has been re-evaluated as a potential weapon against multi-resistant super-bugs like MDR PA that cause lung infections in CF patients.[66] Of the known 137 phages targeting the Pseudomonas genus, 94.2% belong to the Caudovirales

order, consisting of three double-stranded DNA (dsDNA) phage families with distinct tail characteristics: Podoviridae with short and non-contractile tails, The lengthy contractile tails of Myoviridae and the extended, non-contractile tails of Siphoviridae.[67-69] Only 8 non-tailed Pseudomonas phage species have been sequenced; 2 of these belong to Leviviridae (ssRNA).[70-71] while the rest are classified under Inoviridae (ssDNA).[72-73] And 4 belongs to cystoviridae(dsRNA).[74-76] Among sequenced Pseudomonas phages, 85% are specific to *Pseudomonas aeruginosa,* primarily classified under the Caudovirales order, with Myoviridae representing 41%, Podoviridae 38%, and Siphoviridae 20%; 1% remain unclassified, exhibiting diverse genome sizes ranging from 64.1 kb to 309.2 kb for Myoviridae, 41.6 to 74.9 kb for Podoviridae, and 34.5 to 61.1 kb for Siphoviridae, commonly isolated from sewage sources, including hospital and wastewater treatment plant sewage, accounting for 56%.

PHAGES COMBINED WITH ANTIBIOTICS IN VITRO STUDIES

A single phage decreased the biomass of planktonic cells in a lab setting when paired with several antibiotics tobramycin, colistin, and streptomycin.[77-78] The results of the combination therapy showed that it was just as effective as the tested antibiotics alone, but it also decreased the number of phage *Pseudomonas aeruginosa* resistant cells that emerged. Additionally, their study suggested delivering antibiotics 12 hours following phages to ensure maximal antibacterial efficiency. This approach produced a synergistic impact in reducing the biomass or density of laboratory *Pseudomonas aeruginosa* biofilms.[79] Phage cocktail antimicrobial combinations were not explored in any study. No study included crucial details like host receptor affinity, customized strategies, carefully chosen phage cocktails, antibiotics chosen based on minimal inhibitory concentration in vitro on MDR *Pseudomonas aeruginosa* or in vivo on *Pseudomonas aeruginosa* infected animal host models when defining the experimental efficiency for phages and antibiotics combined.

PHAGE THERAPY FOR *KLEBSIELLA* INFECTIONS

Gram-negative, capsulated, non-motile bacterium belonging to the Enterobacteriaceae family is called Klebsiella. In healthy people, these commensal bacteria can be found on their skin, in their respiratory system, and in their gastrointestinal tract. It is a common adaptive pathogen that may cause a wide range of illnesses, such as respiratory tract infections, wounds, and soft tissue infections that are nosocomial or acquired in the community.[80] It has become one of the most common nosocomial infections in the globe and is becoming more deadly, especially in patients who are immunocompromised, old, or newborns. There is growing recognition of its role in serious community-acquired diseases, such as meningitis and pneumonia.[81] *K.pneumoniae* rapidly becomes a Global threat to public health due to its huge distribution spread and genetic material. It frequently becomes resistant to Penicillin and Cephalosporin which are extended-spectrum beta-lactamase.

Phages are bacteria-eating viruses that can be found in all environments and can be isolated from different sources such as wastewater sewage, seawater, and human intestinal samples. It belongs to the four families of order caudivirales they are described as non-enveloped, having tails with icosahedral heads, and having double-stranded DNA. Siphoviridae are distinguished by long, flexible, non-contractile tails, whereas Myoviridae have long, straight contractile tails: Ackermannviridae have contractile tails with four spikes on each of six tail spike entities, whereas Podoviridae have short, non-contractile tails.[82-84] Phages of *K.pneumoniae* show the expression of polysaccharides depolymerase.[85-87] This enzyme can degrade the capsule around the bacterium. The breakdown of the capsule can lead to the combat of *K.pneumoniae* biofilms.[88] Phage infection and the immune system can enhance the bacterium's susceptibility to antibiotics. Laboratory experiments can also demonstrate the phage's depolymerization activity.[89]

Restriction analysis, employed to gauge the phage genome size, utilized bacterial control enzymes to digest phage DNA, alongside electron microscopy analysis revealing phage tail structures. Phylogenetic analysis indicates that some Klebsiella phages are classified within established genera, whereas others are part of recently formed lineages that the viral taxonomy has not yet identified.

COMBINATION THERAPY

The goal of combination therapy is to reduce the development of phage-resistant strains of *K. pneumoniae* by the use of phage cocktails or the combination of phages with antibacterial medications.[90-94] Three lytic phages (GH-K1, GH-K2, and GH-K3) unique to *K. pneumoniae* strains were combined to create a phage cocktail. When K7 was co-cultivated with the phage cocktail instead of a single phage, the bacterial burden was reduced more effectively and fewer phage resistance variations were seen. Furthermore, the lytic phage and ciprofloxacin combination shown effectiveness against *K. pneumoniae*.[95] The observed decrease in the development of *K. pneumoniae* strains resistant to ciprofloxacin and phage was indicative of considerable effectiveness when compared to individual treatments.

CONCLUSION

In conclusion, bacteriophages exhibit several

characteristics that position them as promising therapeutic agents. They boast high specificity and efficacy in targeting pathogenic pathogens, alongside a proven safety profile demonstrated by extensive clinical use. Additionally, their adaptability allows for rapid modification to address emerging bacterial threats. Despite the clinical challenge posed by multiple drug resistance in various pathogenic bacteria, experts anticipate that phage therapy will play a significant role in modern Western medicine. Evidence from in vitro and animal model studies further supports the potential of phages as potent tools in combating diverse bacterial infections. In addition, recent technological advancements have propelled next-generation sequencing (NGS) into the forefront of phage research.

Table 1: Specific Problems of early PHAGE Therapy research and its solution

Problem	Comments	Solution and/or required approach
Limited host specificity of phages	Due to the inability to choose lytic phages appropriate to the intended bacterial species, the great specificity of phages may produce several unfavorable outcomes.[96]	Prior to using phage treatment, determine the causal agent's phage susceptibility.[97-98] make use of polyvalent phage combinations that can lyse most strains of the causing agent.[99-102]
Inadequate clarity of phage preparations	The first therapeutic phages were found in unrefined lysates of host bacteria, which included a variety of impurities, including endotoxins that would have negated the phages' effects.	To produce high-purity phage preparation, rapid centrifugation, the use of ion-exchange chromatography, and other sophisticated filtration methods should be used.[103]
Phage preparations with low sustainability and/or stability	To guarantee bacterial purity, certain commercial phage formulations were heat-treated,and added with mercurial or oxidizing chemicals or both.[104] But a lot of these procedures may have also resulted in phage inactivation, which would have made the preparations useless.	Sophisticated purification methods are frequently employed to eliminate bacteria and ensure the clarity of phages. Assessing the possibility and titer of phages is crucial before their therapeutic use.
Insufficient comprehension of phage heterogeneity and their mode of action, distinguishing between lytic and lysogenic phages	Some researchers may have used lysogenic phages, which are substantially less efficient than lytic phages, since they were unable to discriminate between lytic and lysogenic phages.	The selection of lytic phages must be done carefully since lysogenic phages have the ability to transmit antibiotic resistance genes and bacterial toxin genes horizontally.[3]
Overstated promises of effectiveness made by commercial phage preparations	One instance of this is the formulation of Enterophagos, which was advertised as a treatment for dermatitis, allergic reactions, and herpes viruses.[105] circumstances in which phages are not expected to be effective	Phage preparations must to provide precise, empirically supported data on their effectiveness against specific bacterial pathogens as well as any adverse effects
Failure to provide solid scientific proof of the phage treatment's effectiveness	The majority of clinical trials with therapeutic phages did not include placebo controls, and when they did, many peers subjectively assessed and criticized the findings.[106-107]	Highly pure lytic phages must be used in carefully regulated, double-blind placebo studies; the trials must be evaluated using a combination of rigorous laboratory analysis and clinical observations.

Table 2: A comparative analysis of the preventive and/or therapeutic use of antibiotics and phages

Bacteriophages	Antibiotics	Explanations
Specifically targeting particular bacterial species, these interventions minimize symbiosis and mitigate the risk of secondary infections.[99]	Antibiotics exert their effects on both pathogenic microorganisms and commensal microbiota, disrupting the microbial equilibrium and predisposing the patient to potential secondary infections.	The high specificity of phages can pose a challenge, as identifying the disease-causing bacterium is crucial for the successful initiation of phage therapy. Antibiotics generally exhibit higher effectiveness in cases where the etiological agent remains unidentified compared to phages.
They duplicate at the site of infection, guaranteeing localized accessibility where their action is most essential.[102]	They are processed by the body's metabolism and excretion systems, so they don't always gather at the infection site.	For the best possible treatment results, it might be necessary to administer the medication less often due to the phages' exponential multiplication at the infection site.
No important antagonistic effects have been documented	Numerous negative consequences have been reported, including allergic responses, gastrointestinal problems, and secondary infections such yeast infections.[108]	Minor side effects standard [101,109] endotoxins from bacteria that the phages destroyed in vivo may be released after therapeutic phage delivery. Antibiotic use may also have comparable consequences.[110]
Bacteria resistant to phages are still susceptible to other phages with matching specificity	Antibiotic resistance extends beyond the targeted bacteria.	Antibiotics not only cause mutations of the targeted bacterium, but they also encourage the evolution of resistance in other types of bacteria.[111]
The process of selecting new phages, particularly those effective against phage-resistant bacteria, can often be rapidly achieved within days or weeks	Creating a novel antibiotic targeting antibiotic-resistant bacteria typically requires a lengthy process spanning several years.[112-114]	According to evolutionary principles, active phages can be continuously chosen through continuing survival processes to fight bacteria that are resistant to antibiotics or phages.

NGS offers a platform for the comprehensive characterization of phages, enabling detailed scrutiny of harmful gene screening and evaluation of potentially beneficial gene products. The use of NGS in phage research not only improves our comprehension of phage biology but also opens up new avenues for creative approaches to persistent problems.

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