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Review Article

"BACTERIOPHAGE THERAPY" AN EMERGING CURE FOR BACTERIAL DISEASE

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ABSTRACT

Bacteriophages are viruses that infect bacterial cells and have been explored for their potential in treating bacterial infections. This review discusses the taxonomy of bacteriophages and the safety concerns in phage therapy. Although bacteriophages were initially considered safe for humans and animals, recent research indicates potential interactions with eukaryotic cells, raising questions about safety. Nevertheless, successful phage therapy cases have been reported, showing promising results in treating biofilm-based and multidrug-resistant infections. The use of bacteriophages has demonstrated minimal side effects and appears to be a viable alternative to traditional antibiotics. However, more research and controlled clinical trials are needed to fully understand the efficacy and safety of phage therapy in various clinical settings.

Keywords: Bacteriophages, Viruses, Life cycle, Bacterial parasites, Phage therapy, Transcytosis, Phage therapy, Phage resistance, Phage delivery, Superhost immune response

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INTRODUCTION

Bacteriophages are a set of viruses extensively distributed in nature whose life cycle is strictly related to the bacterial cell. They are referred to as bacterial parasites due to the fact they lack the cell structure and enzyme systems vital for food uptake, protein synthesis, or production of new particles, and incomplete organisms cannot replicate in a live cell. Bacteriophages have been discovered as unidentified molecules that inhibit bacterial growth by Twort (1915), however, in1917 D'Herelle become the first to isolate and categorize phages, and he additionally developed the primary phage therapy towards fowl typhoid induced by *Salmonella Gallinarum* in chickens. Positive results of the usage of bacteriophages in fighting bacterial infections have contributed to the development of research on the potential use of viruses that destroy bacteria in the treatment of diseases in both humans and animals.

Given the apparently low toxicity of phages and the minimum side effects of phage therapy as practiced, phage therapy can be successful as long as phages can reach the targeted bacteria insufficiently excessive numbers and adsorb, after which kill those bacteria. Greater awareness of what barriers to this achievement typically or in particular can exist, as documented in this review, need to resource within side the further improvement of phage therapy toward wider use [1].

Taxonomy of bacteriophage

The criterion of the taxonomy of bacteriophages implemented through the ICTV (International Committee on Taxonomy of Viruses, Hungary, August 2016) is primarily based totally in particular on genome type and virion morphology. The ICTV report, based ongenomic and proteomic-based methods, was utilized by the BAVS to classify phages into 873 species, 204 genera, and 14 subfamilies in the 2015 taxonomy release. The basic classification of the viruses, It needs to be emphasized that the huge majority (~ 96%) of known phages belong to the Myoviridae, Podoviridae, and Siphoviridae. Their fundamental characteristic is the presence of 1 type of nucleic acid as a carrier of genetic information and a capsid constructed from structural proteins. In terms of DNA structure, phages can be divided into 3 groups: the ones containing dsDNA, those with a single strand of DNA, and phages containing RNA. Most known bacteriophages have a genome that includes double-stranded DNA. There are two types of bacteriophages distinguished on the basis of capsid symmetry: isometric (polyhedral) and helical (spiral).

Safety trouble in phage therapy

Bacteriophages are viruses infecting bacterial cells. Since there's a lack of specific receptors for bacteriophages on eukaryotic cells, those viruses have been for long term taken into consideration to be neutral to animals and humans. However, research in the latest years supplied clear proof that bacteriophages can engage with eukaryotic cells, significantly influencing the functions of tissues, organs, and systems of mammals, including humans [2]. Furthermore, the current literature lacks strongly documented significant adverse effects related to phage administration, and phage therapy is broadly regarded as safe. However, there are additional controversies concerning each the efficacy and protection of this therapeutic method [3]. Both older and recent papers indicated that interactions among bacteriophages and eukaryotic cells are possible, affecting both biochemical and physiological processes. Therefore, one may also be surprised whether or not such interactions are really safe, considering that regardless of a lack of acute reactions, a few milder effects is probably nevertheless deleterious for patients or animal subjected to phage therapy procedures [2]. If the human body is treated as an ecological niche, bacteriophages can occur not only within side the gastrointestinal tract, which is obvious because of the intestine bacteria present there, but additionally in the blood, urine, or cerebrospinal fluid, which could already theoretically pose potential risks [4]. For example, it becomes recommended that circulating phages may also effectively engage with the host immune system. However, this effect is still being investigated and discussed. Studies on the mouse model of the usage of theT4 bacteriophage did not verify its immunomodulatory properties [5].

Intriguingly, phages have been validated to be able to enter mammary epithelial cells via endocytosis or even reach nuclei. Such a mechanism of phage penetration may also facilitate the transportation of bacteriophages via epithelial cell layers. Indeed, the transcytosis process has been proposed to be liable for this phenomenon [6]. Another report demonstrated that phages can internalize neuroblastoma cells through endocytosis and possibly also enter the nucleus. In this light, the modulation of expression of a few eukaryotic genes through bacteriophages is probably considered likely [7].

Successful treatment through phage therapy

Recent interest in bacteriophage therapy has made it viable to treat some biofilm-based infections, in addition to the ones caused by

multidrug-resistant pathogens, successfully while traditional antibiotic therapy has failed. A 61 y old woman who was successfully treated after the second cycle of bacteriophage therapy administered at the time of a two-stage exchange procedure for a chronic methicillin-sensitive *Staphylococcus aureus* (MSSA) prosthetic knee-joint infection. The protection and efficacy of both intravenous and intra-articular inoculations of bacteriophage therapy, a successful result with a single lytic phage, and the development of serum neutralization with extended treatment [8].

A study by Łukasz Grabowski on the effects of phage therapy and antibiotic therapy onimmunological responses of chickens inoculated with Salmonella enterica serovar Typhimurium provided that the phage cocktail provided to the Salmonella enterica serovar Typhimurium-infected chickens discovered anti-inflammatory effects whilst administered either1 d after inoculation or 2 d after. S. Typhimurium detection in feces, as measured through inhibition of the growth in levels of inflammatory response markers (IL-1β, IL-6, IFN-γ, IL-8, and IL-12). This was additionally confirmed through elevated levels of cytokines that exert an anti-inflammatory action (IL-10 and IL-4) following phage therapy. Moreover, phages did now no longer cause a negative effect on the number and activity of lymphocytes' subpopulations vital for regular immune system function. These outcomes imply for the first time that phagetherapy now no longer only is effective but additionally may be utilized in veterinary medicinal drugs without disturbing immune homeostasis [9].

Another look at Phage therapy was mentioned by Pikria Zhvania for the treatment of serious staphylococcal infections and allergic reactions to multiple antibiotics on a 16 y old boy struggling with Netherton syndrome (NS) a rare autosomal recessive disorder. The family sought to help at the Eliava Phage Therapy Center while all different treatment alternatives had been failing. Treatment with several antistaphylococcal bacteriophage preparations led to substantial development within 7 d and substantial changes in his symptoms and quality of life after treatment for six months, including return visits to the Eliava Phage Therapy Center after three and six months of ongoing use of phage at home [10].

Antibiotic-resistant Pseudomonas aeruginosa (*P. aeruginosa*) is one of the most pathogenic in wound infections, inflicting excessive mortality and morbidity in extreme cases. However, bacteriophage therapy is a probable candidate to antibiotics against *P. aeruginosa*. The morphometric and genomic analyses found that ZCPA1 belongs to the Siphoviridae family and can infect 58% of the examined antibiotic-resistant *P. aeruginosa* clinical isolates it displayed substantial lytic activity and biofilm elimination against *P. aeruginosa* by completely reducing bacterial growth at a multiplicity of infection (MOI) of 100 and inhibiting bacterial growth *in vitro* in a dose-dependent way. In addition, *P. aeruginosa*-infected wounds treated with phages displayed 100% wound closure with an excessive quality of regenerated skin in comparison to the untreated and gentamicin-treated groups because of the complete elimination of bacterial infection. Therefore, some of these properties make phage ZCPA1 a promising therapeutic agent against *P. aeruginosa* skin wound infections. However, more research is needed on the phage formulations for use topically on wound infections and tested in clinical trials [11].

A case reported by Apurva Virmani Johri on treating a patient with Chronic Bacterial Prostatitis (CPS) is an inflammatory condition caused by a persistent bacterial infection of the prostate gland and its surrounding regions in the male pelvic region provided information on bacteriophage preparations from the Eliava Institute had been used to treat the patient after setting up phage sensitivity to the pathogenic bacteria. The patient noticed a substantial improvement in symptoms and positive vitals in bacterial titers and ultrasound command after the phage remedy. The defeat of antibiotic therapy and the eventual success of bacteriophage therapy in treating persistent bacterial prostatitis indicates the effectiveness of bacteriophages in controlling chronic infections in regions of low vascularity and anatomical complexity [12].

A case 68-year-old diabetic patient with necrotizing pancreatitis complicated by an MDR A. baumannii infection received a bacteriophage therapy that saved his life. The patient's condition was grave when bacteriophage therapy was first initiated with a cocktail ΦPC. Over the 36 h, his clinical situation was stable; however, he remained comatose, intubated, and on 3 pressors with worsening renal and hepatic function. Over the following three weeks, the course remained complex; however, the patient generally established ongoing improvement on all fronts. His mental status continued to improve, and he turned absolutely conversant and lucid. He was weaned off the ventilator, his pressors had been gradually weaned and discontinued, and his renal function gradually improved. Bacteriophage therapy was continued for an extra eight weeks, during which period he confirmed continued clinical improvement. All drains were eliminated and he was discharged home on day 245. He has subsequently returned to work [13].

A report by Kevin Paul through a case of vancomycin-resistant *Enterococcus faecium* abdominal infection in a one-year-old, severely ill, and 3 times liver transplanted girl, was treated intravenously with magistral preparation containing two Enterococcus phages (twice per day for 20 d). Covering three hundred and sixty-five days of follow-up, they provide further evidence for the feasibility of bacteriophage therapy, which can function as a foundation for urgently needed controlled clinical trials [14].

A 62-year-old diabetic guy with a record of right total knee arthroplasty eleven years earlier who had suffered multiple episodes of prosthetic knee infection in spite of several surgical procedures and extended courses of antibiotics, with progressive clinical worsening and development of severe allergic reactions to antibiotics, were presented limb amputation for persistent right prosthetic knee infection because of Klebsiella pneumoniae complex. Intravenous phage therapy was initiated as a limb-salvaging intervention. Phage therapy resulted in the resolution of local signs and symptoms of infection and recovery of function. The patient did now no longer experience treatment-associated negative consequences and remained asymptomatic 34 w after finishing the therapy while still receiving minocycline. The addition of phage was associated with satisfactory final results in this case of an intractable biofilm-associated prosthetic knee infection [15].

Even during the COVID-19 pandemic, secondary infections were treated with phage therapy. A case reported through Nannan Wu from Fudan University, Shanghai on four patients hospitalized with critical COVID-19 and pulmonary Carbapenem-resistant Acinetobacter baumannii (CRAB)infections were treared with phage therapy (at 2 successive doses of 109 plaque-forming unit phages). Treatment with 2 successive doses of a pre-optimized 2-phage cocktail was associated with decreased CRAB burdens and may have contributed to the clinical improvement of the patients. At the end of this treatment, Patient 1 and Patient 2 had been weaned from ECMO and ultimately discharged from the hospital; Patient four's illness severity improved, and he was discharged from ICU, unfortunately due to complication in the respiratory tract he could not survive. Patient 3's CRAB was removed however an un-subdued Carbapenem-resistant Klebsiella Pneumoniae (CRKP) infection was observed and he died of respiratory failure 10days after phage therapy [16].

DISCUSSION

Today, bacteria that are multidrug-resistant pose a severe threat to public health. Drug resistance in these bacteria is further increased by the continued use of broad-spectrum antibiotics. There is a significant amount of research being done to create alternative treatments for infections brought on by these microorganisms. Phage therapy seems to be an effective solution to this issue. Bacterial viruses called bacteriophages attack bacterial cells. Despite what we have learned over the years of research, not all viruses are harmful to living things. Bacteriophages are viruses, and bacteriophage-derived phage treatment is crucial in the management of lethalbacterial infections, including chronic bacterial prostatitis and Netherton syndrome. In addition to this, some secondary illnesses may also be treated, as was the case with the Covid-19 pandemic when the original therapy of phage therapy was rejected. The use of bacteriophages has no negative side effects. Bacteriophage therapy has received less analysis overall; we would like to see more research on it.

CONCLUSION

Due to the growing demand for alternative or complementary anti-infectives to traditional antibiotics, phage therapy has reemerged as a viable treatment for refractory infections in recent years. Numerous uncontrolled case studies document productive clinical outcomes. However, clinical failures are probably underreported, and the few randomized controlled trials that have been carried out have not been successful in demonstrating benefit. The efficacy of phage therapy and potential causes of failure, such as dosing, frequency of dosing, duration of therapy, routes of administration, interactions with antibiotics, interactions with other phages, emergence of phage resistance, inadequate phage delivery, and superhost immune response, to name a few, are not well understood. As a result, no recommendation can be made to support the routine clinical use of phage therapy under any circumstances.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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