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Phage Therapy to Tackle Difficult-To-Treat Bacterial Infections - What's The Future?

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INTRODUCTION

As quoted in the Bhagwat Gita,the life of one living being depends on the life of another living being *"(जीवो जीवस्य जीवनम्)"*. The relationship between two living beings can range from symbiotic to commensal to parasitic. In a parasitic relationship, one of the partners derives the benefit (parasite) from the other partner (Host), even, at the cost of the host's life. One such relationship exists between the viruses that can infect Bacteria. These viruses are known as phage viruses. This activity of viruses was taken advantage of to use them as potential antibacterial agents [1]. Universal increase in antibiotic resistance and decline in newer antibiotic discovery led to renewed interest in using phage viruses as antibacterial agents.

What are Phage Viruses?
Bacteriophages, or simply phage viruses, are viruses that infect bacteria. Most phage viruses are non-enveloped, with an icosahedral capsid head protecting a double-stranded DNA and a tail. The virus attaches to the surface of specific bacterial species with the help of receptors, injects its nucleic acid into the cytoplasm of the bacterial cell. The Vial nucleic acid hijacks the bacterial cell protein synthetic machinery to synthesize many progeny viruses. The progeny viruses are released out of the bacterial cell by destroying the bacterial cell. The newly released viruses are now ready to infect more bacteria and destroy them. This bactericidal activity of phage viruses can be used as a therapeutic bactericidal drug, especially to treat chronic and/or multi-drug resistant bacterial infections.

Phage use in other non-medical areas:
Historically, phage viruses have been known for their antibacterial activity for over a century. The use of phage treatment in the medical field is not widely accepted. For several decades since the discovery of antibiotics in 1940, newer antibiotic discoveries have helped to tackle the slowly increasing antimicrobial resistance. Maybe because of this reason, phage therapy was not actively embraced by most of the clinicians. Bringing the in-vitro bactericidal activity to the bedside had many hurdles. It was essential to study the potential side effects of phage therapy as they contained proteins. Further studies were needed to decide the therapeutic dosage, route of administration, and other Pharmaco-kinetics and pharmaco-dynamics of phage viruses. The phage viruses have different pharmacokinetics as they are self-amplifying drugs.

With ever-increasing antimicrobial resistance in hospitals, judicious use of antibiotics was given importance. Besides overuse in humans, antimicrobial resistance was attributed to their use in other fields like veterinary, plants, poultry, food industry, and in protection of crops. One way to reduce antibacterial usage in other fields was by using phage viruses instead of antibiotics.

Phage viruses have been used in veterinary clinics to treat bacterial infections. Phages have been used as biological control agents to reduce the harmful bacterial (e.g., Listeria monocytogenes) loads in food processing [2]; Phages were also used in food processing to reduce the bacterial loads of zoonotic pathogens [3]. Also, in treating crops against bacterial plant pathogens [4].

Potential therapeutic use of phage in human infections

Phage use in the medical field is still limited, with anecdotal success stories. With so many pharma companies researching newer antibacterial agents in combination with beta-lactamase inhibitors, phage therapy is still not getting the required appreciation.

Phage activity is targeted towards a specific bacteria strain. Phage isolation, characterization, animal experiments, and their outcomes are the primary requirements for successful therapeutic use of phage viruses.

There are countries like Georgia, Poland, and Russia where phage therapy has been in clinical use for many years [5,6].

Sources of Phage viruses:

Mattila et al. studied the environmental sources of phage viruses. They found that phage viruses isolated from municipal sewage had the best results for Pseudomonas *aeruginosa*, Salmonella, and the extended-spectrum B-lactamase-producing E.coli and Klebsiella pneumoniae. This procedure was less efficient for Vancomycin-resistant Enterococcus and Acinetobacter *baumanii*and isolation of new phages against Methicillin-resistant Staphylococcus aureus (MRSA) was difficult. Wang et al. found that pig fecal sewage is a better source for phages against MRSA.

Host range and Animal experiment: Many preclinical studies include the characterization of phages and their host range. The animal experiments included treatment of MRSA, MDR Acinetobacter baumanii, Pseudomonas aeruginosa, and many drug-resistant bacterial pathogens. A phage mixture (Phage cocktail) was used to tackle the biofilm formation.

Use of Phage in Human infections:

Before the therapeutic use of phage, it is very important to develop an adequately robust pipeline for proving the efficacy of the therapy and to get permission from the regulatory authorities. Currently, phage therapy is used relatively widely in only three countries: Georgia, Poland, and Russia [7].

A significant problem exists in the administration of phage viruses. The usual routes, like oral, cannot be used as the stomach's acid may destroy the phage viruses. Local delivery of phage viruses at the infection site is best.

Since phage viruses have a very narrow spectrum of activity, most of the time, to treat polymicrobial infection, a mixed population of phage viruses is used (Phage cocktail). The phage cocktail is effectively used in treating biofilm formation as the proteolytic enzyme present in phage viruses helps destroy the polysaccharides in the biofilm [8,9].

Pre-clinical and in-vitro evidence: In a study on immunocompromised patients, phage therapy reduced bacterial load in patients undergoing bone marrow transplant procedures. It has also been proven effective in eradicating MDR osteoarticular infection [10,11].

Many clinical studies have shown the efficacy of phage therapy in various orthopedic infections, non-healing wounds, and diabetic wounds causing osteomyelitis. Phages were used for different organisms like Staphylococcus aureus, Enterococci, especially VRE, Pseudomonas aeruginosa, Acinetobacter baumanii, etc., in these infections.

Limitations of bacteriophage therapy

1. It needs to be proved before therapy that the infective isolate is susceptible to the phage used for the treatment.
2. The bacterial strain is likely to produce resistance against the phage
3. Prolonged treatment can lead to an immune response against the viral proteins, rendering the virus less effective when used subsequently.
4. Preparation of phage product for administration

Future Prospects: Phage therapy requires more pre-clinical studies. The studies should be done about the infective agents and the phage as single or cocktail preparations. There is also a need to form less immunogenic phages so that prolonged therapy will have a minimum immune response.

Conclusion: Looking at the dreadful scenario of drug-resistant organisms taking a toll every day in hospitals around the world. Imminent lurking peril of pandemic of MDR organisms. With the ever-increasing burden of resistant bacterial strains and increasing susceptible immuno-compromised population, phage viruses have a strong potential to be the only weapon left to kill these pathogens.

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