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BACTERIOPHAGE THERAPY IN HOSPITALS: UNVEILING THE POTENTIAL OF RIVER GANGA BACTERIOPHAGES

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Abstract- Bacteriophages are viruses that consume bacteria; these viruses proliferate in Ganga water and have been proven to be more efficacious in treating both acute and chronic human infections in the hospitals settings and also in certain ongoing studies. The goal of the research is to isolate new bacteriophages, which could be the most effective alternative to the antibiotics. The antibiotics have lost their effectiveness in treating bloodstream infections, urinary tract infections, burns, surgical site infections, pneumonia, bed sores, and diabetic foot ulcers etc. The Ganga River is recognized to be a major source of bacteriophages. It contains a variety of bacteriophages. Numerous research institutes in India and elsewhere studied Ganga water samples taken from various ghats or sites. They discovered that one of the bacteriophages in the river Ganga has the ability to fight drug-resistant diseases in humans brought on by Pseudomonas aeruginosa. Numerous studies conducted in the last few years have shown that antibiotics, such as ceftazidime, imipenem, and amikacin, are inefficient at curing infections i.e. bacteria are becoming resistant to antibiotics, known as antimicrobial resistance AMR, presently a huge global concern. Also, the presence of MDR, Amp-C traits and ESBL bacteria are confirmed in the water of Ganges. Therefore, there will be high chances to find bacteriophages against these resistant bacteria's. As it presents a problem with fewer antibiotic alternatives and increased treatment costs. Certain bacterial infections have a high death and morbidity rate and are frequently persistent. Some persons with diabetes develop chronic skin sores, necessitating the amputation of affected body parts. The WHO has classified bacteriophage as a priority pathogen as well. This suggests that the development of new antimicrobial medicines needs to be given top priority. According to a review of the literature, as compared to other antibiotic medications that destroy good gut microbiota, bacteriophages in ganga water have not been shown to be side-effects.

Keywords- Bacteriophages, Alternatives of antibiotics, Phage therapy, Phage cocktail, Multidrug resistant, Bacterial infection

Introduction

Antibiotic resistance in bacteria has increased as a result of widespread use of antibiotics to treat bacterial infections. Antibiotic-resistant microorganisms are not a novel issue in the medical field. In actuality, the 1940s [1] saw the first example of Staphylococcus aureus developing resistance to penicillin. An immune-compromised patient may be affected by the gram-negative bacteria Pseudomonas aeruginosa. When a bacteria develops resistance to an antibiotic or an antifungal treatment that it was previously sensitive to, this phenomenon is known as antimicrobial resistance (AMR). After this, the recommended course of therapy for that specific infection is no longer effective, which causes the infection to continue. According to WHO estimates, antibiotic resistance in bacteria could be responsible for over 1.3 million deaths in 2023. Given that one of the largest dangers to world health, food security, and development is antibiotic resistance, consider the potential benefits of using bacteriophages isolated from Ganga water as a phage therapy alternative to antibiotic treatment [2]. Also, the 40 percent of bacteria present in Ganga showed resistance to semisynthetic drugs like ampicillin and amoxicillin, etc. The presence of multi-drug resistant (MDR), Amp-C traits, and ESBL (extended-spectrum beta-lactamase) bacteria were also examined in the river Ganga [2,3]**.** Therefore, the chances of isolating bacteriophages that will efficiently kill the antibiotic resistance bacteria are high. These ganga water bacteriophages do not pose a threat to humans, animals, or plants; rather, they only target bacteria. The natural enemies of bacteria are called bacteriophages, which essentially transform into "bacteria eaters." Bacteriophages can also be discovered in sewage, soil, and other bacterial habitats. In nature, these viruses aid in controlling the growth of microorganisms. Bacteriophages cause bacteria to rupture or lyse in order to kill them during phage therapy. This occurs when a virus attaches itself to a bacterium and injects its genes (DNA or RNA) into the organism.

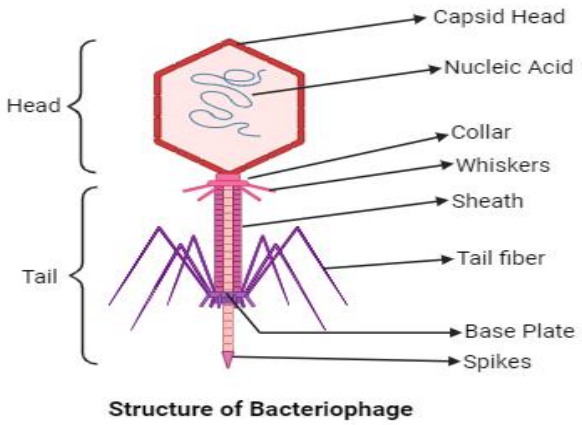


Fig.1 Structure of a typical bacteriophage.

Within bacteria, the phage virus replicates, producing up to 1000 new viruses per bacteria. At last, the virus ruptures the bacteria, allowing the newly formed bacteriophages to escape. These viruses that consume bacteria can only proliferate when they are within the host cell. The significance of Ganga water bacteriophages as an antibacterial and substitute for antibiotics will be covered in this review.

Medicinal and Antibacterial effects of Ganga river water

The Ganga, often called "maa" ganga, is revered as a holy river in Hinduism. Ganga water is popularly termed “Ganga Jal”. Ganga formed from the virgin snow high in the western Himalayas flows to Bangladesh, one of the mightiest rivers in the world. Ganga is a giver of life to one of the most diversified ecosystems on the globe, the most sacred river on earth running over 2500 km across the

heart of India [3]. With its rich waters, the Ganga nurtures one of the world's most densely inhabited regions, providing almost 600 million people with a lifeline akin to that of a mother. Ganga and its people have always had a timeless bond that dates back many generations. Indians believe that Ganga water possesses healing and self-cleaning properties and that it is more than just a river. By having bactericidal properties, ganga water can kill microorganisms or bacteria. Additionally, even if the complete answer to this puzzle is yet unknown, it seems to be related to bacteriophages. The intriguing and completely unproven claims made by numerous scientific research regarding the self-cleaning and healing abilities of ganga water are noteworthy. In addition, even in contaminated areas, ganga water possesses antimicrobial qualities and offers a high concentration of dissolved oxygen. British bacteriologist Ernest Hankins conducted research on Ganga water in 1896 with a focus on its antibacterial or bactericidal activity. He obtained cholera bacterial colonies that had survived in tap water but had promptly perished in Ganga water [3,4]. Using Ganges water that had been heated and filtered, he repeated his experiment. He was taken aback by the findings that boiling water lost its antibacterial effect whereas filtered water retained it. The results show unequivocally that the heat-labile but non-filterable component that gave water its bactericidal activity was unrelated to the porcelain Pasteur filters Hankin utilised in his experiment. Twenty years later, a Canadian microbiologist solved the puzzle by discovering elements that support ganga water's antibacterial activity. Felix d'Herelle discovered phages at the Institute Pasteur in Paris as early as 1917 [4]. Phages consist of proteins and genetic material, which can be either DNA or RNA. Their characteristics include being heat-labile and difficult to filter; they match the results of a scientific analysis of Hankin's findings in Ganga water. This asserts Ganga has a large phage population. Because phages are highly strain-specific, they may be harmful to humans [5]. Phage treatments for bacterial infections, either alone or in conjunction with antibiotics, are the subject of numerous investigations.

Fig.2 A man gathers water from the Ganges River at Lakshman Jhula, Rishikesh

Phage treatments have not yet received complete approval, but they may be more effective than antibiotics in preventing opportunistic infections and replicating in vivo, requiring fewer doses. Since Phage will only infect and destroy bacteria that are compatible with its strain, its great specificity can occasionally be a concern [6]. Using a cocktail of phages rather than a single phage may help to lessen

this issue. Phage cocktail is the term for this tactic [7]. Numerous scientific studies have been conducted in the past several years to assess the efficacy of phage cocktails in treating burn injuries caused by *Pseudomonas aeruginosa* and *Escherichia coli*. Because there are still a lot of unanswered questions regarding the commercial use of phages to treat bacterial infections in people, regulatory authorities have not yet been granted approval. This analysis assessed the numerous research publications on bacteriophages as an alternative treatment for bacterial infections, particularly the use of bacteriophage cocktails, that were available online as well as research projects that were not published in any journals. Because there are still a lot of unanswered questions regarding the commercial use of phages to treat bacterial infections in people, regulatory authorities have not yet been approved. This analysis assessed the numerous research publications on bacteriophages as an alternative treatment for bacterial infections, particularly the use of bacteriophage cocktails, that were available online as well as research projects that were not published in any journals.

Highlights

- These days, one of the biggest risks to world health is bacterial multidrug resistance (MDR) to antibiotic therapy.
- Bacteriophages are a desirable therapeutic agent due of their high specificity and lack of toxicity to humans, plants, or animals.
- Only a small percentage of the clinical trials conducted to date have been randomized and controlled, and even those have had partially negative results.
- Problems with formulation preparation for clinical and standardized usage in bacterial control reduce the likelihood that bacterial resistance may evolve and need to be addressed.
- Phage therapy cannot be implemented in clinical practice unless cocktail formulations for various bacterial illnesses are optimized and immunological responses to various phage therapies are closely studied and overcome.
- Given the promising data thus far and the progress made in biotechnology, we anticipate that bacteriophages, either by themselves or in conjunction with antibiotics, will be utilised in clinical practice worldwide in ten years to treat all chronic infections that will either be totally resistant to all antibiotics currently in use.

Review of Literature

Methodology

Research work done on Bacteriophages as an alternative therapy for bacterial infections were reviewed by independent reviewers (SMA) using electronic databases. Studied some of the important research articles published in PubMed and google scholar and some unpublished data on the internet related to the topic. Search terms used for this purpose included Bacteriophages, alternatives to antibiotics, phage therapy, phage cocktail, bacteriophages as an alternative to antibiotics.

Exclusion Criteria

All published literature with an English abstract and some unpublished data were included in the search. There were no more exclusion selection standards used.

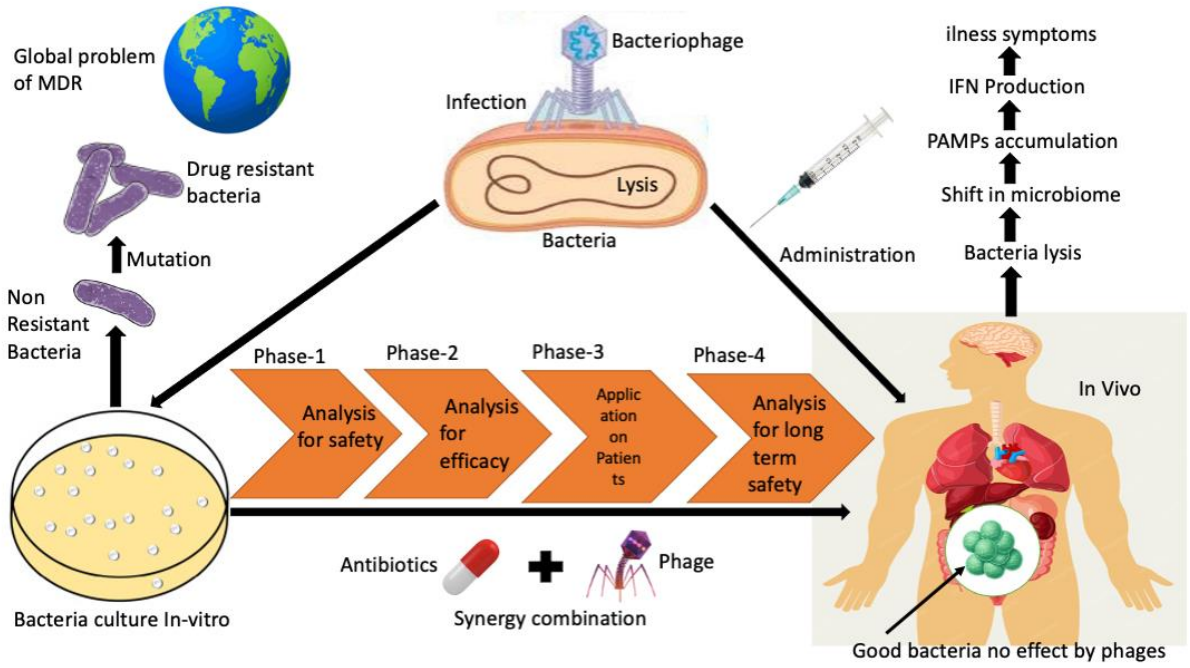
Study Selection

A total of 70 studies were initially identified and considered potentially relevant. Of these, 40 studies did not meet the inclusion criteria. Twenty nine studies were evaluated in detail. Seventeen studies meeting the selection criteria were considered for the current review and analysis [8].

Phage Therapy

Phage treatment is the application or use of bacteriophages as a therapeutic in the removal of bacterial infections. Twort and d'Herelle made the initial discovery of this use in 1915 and 1917. Bacteriophages are viruses that feed on bacteria and have a very basic structure, with DNA encased in a capsid coat for protection. Phages are similar to other viruses in that they can infect bacteria by

attaching themselves to their cell surface receptors, inserting their own genetic material (DNA or RNA) that the bacteria then use for replication, causing the bacteria to lyse and release other similar bacteria into the surrounding area, and ultimately ending the infection. Phage therapy may also be a good option for treating immunocompromised bacterial infections in synergy combination with antibiotics in shown below in **Figure 3.**



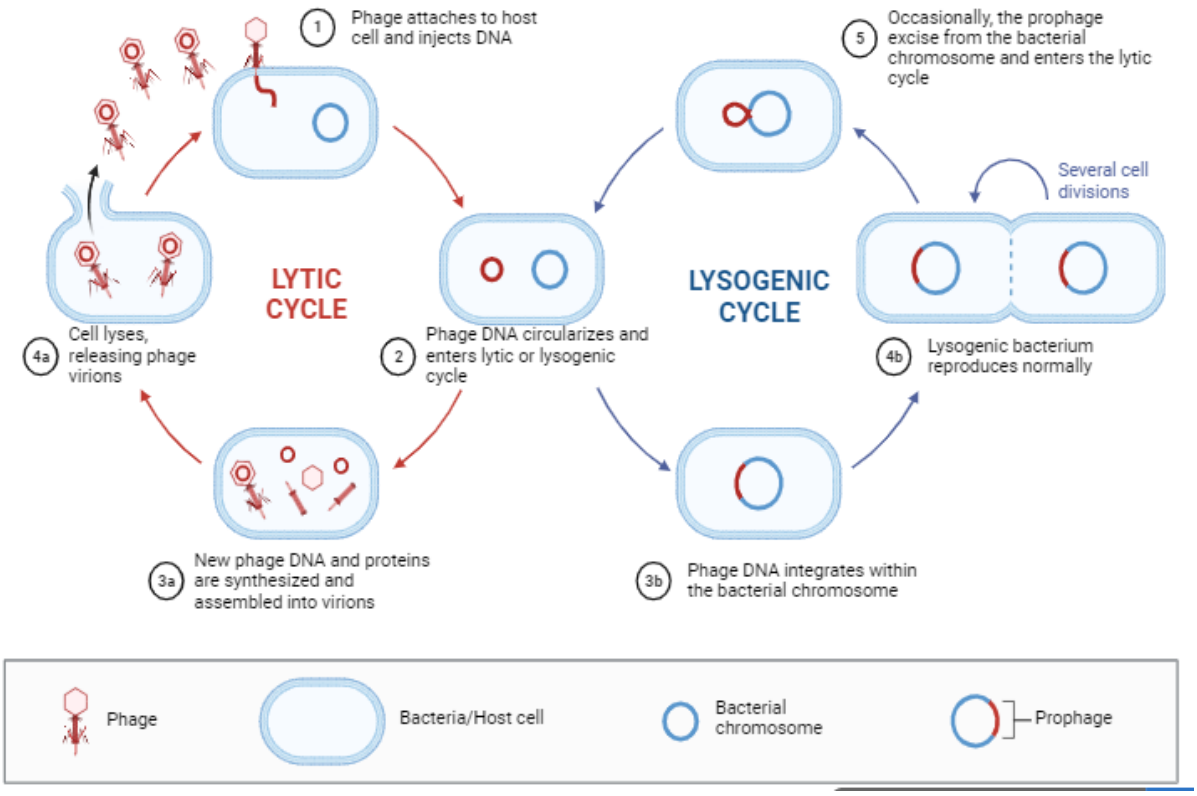
The lytic cycle, which occurs when bacterial cells lyse and become integrated into bacterial chromosomes to replicate and pass on to their progeny without harm, can occur quickly after the replication of viral DNA inside bacterial cells or gradually. However, the lytic cycle will eventually become active when bacterial cells deteriorate, most likely due to nutrient depletion [9, 10].

Steps of Phage therapy-

1- Bacteriophage attaches to bacterial cell surface
2- Bacteriophage injects genetic material
3- Biosynthesis, phage DNA replicates and phage protein coat are made using bacterial cell machinery
4- Maturation, new phage particles are assembled, packing genetic material inside protein coat
5- Lysis, cell breaks open releasing newly formed phages

Bacteriophage Life Cycle

A phage genome is integrated into the bacterial genome when lytic phages attach to and infect a bacterial cell. This process, known as the lysogenic cycle, causes the phages to multiply and the cell host to lyse. Bacteriophage life cycle is shown below in **Figure 4.** The use of phage therapy was authorised in the early 1930s [11].



The Eli Lilly Company subsequently created seven phage products, and phage therapy was put to use commercially in the early 1940s [12]. However, phage therapy was only used on a small scale in Russia and Poland after the introduction of antibiotics, and it was discontinued in the rest of the world [13]. Here is a quick discussion of several significant studies that were conducted by various researchers employing phage cocktail therapy and various bacteriophages:

Discussion

Studies Using Animals

Smith et al back in 1980 have done a crucial study to evaluate the effectiveness of bacteriophage to treat an bacterial infection. He did his work on the efficacy of specific *E.coli* bacteriophages in acute diarrhea in the mice. He got very interesting and encouraging results. He was identified that six strains of pathogenic *E.coli* were degraded by single dose of pool of six bacteriophages specific for pathogenic *E.coli* [14]. After one year same researchers were evaluated efficacy of specific phage therapy in treating the diarrheal infection of experimental *E.coli* in calves, piglets and lambs and got similar outcomes as they obtained in case of treating acute diarrhea in mice [15,16]. According to a study performed in 1991 and 1992, phage therapy is not required repeated dose of administration as that is required antibiotics for several weeks [17,18]. Many scientists was encourages this success and experiments, them to further experiments towards use of bacteriophages in bacterial infections. One of study was conducted in 1992, in this study induced infection in mice with experimental *Acinetobacter baumanii*, *P. aeruginosa*, and *S. aureus* pathogens can be controlled by specific bacteriophages [19]. After two years later Soothill, et al. did a another study, that study showed bacteriophage can be effective in guinea pigs after skin graft that were susceptible to infection by *Pseudomonas aeruginosa* [20]. Many latest studies claims after the treatment of bacteriophage in food producing animals are less likely to be susceptible to the contamination of food by bacteria during processing. Although, in other side this type of studies favoured the use of phage therapy to reduce Campylobacter spread in humans from chickens. Phage therapy are play crucial to treat respiratory infections of animals for example in 2010 Hawkins, et al. investigated treatment of chronic, refractory *P. aeruginosa* otitis media in ten dogs using specific bacteriophages. He introduced a single pool dose of each of 6 bacteriophages, specific for these pathogens, directly into

the auditory canal of one ear. He had done evaluation of a clinical score based on 5 indicators for conditions of the ear and did measurement of bacteriophage and *P. aeruginosa* concentrations. Results was claimed bacteriophage therapy are very effective and safe as pathogens mean counts decreased by 67%, accompanied by a significant increase in bacteriophage counts, showing significant viral replication. Furthermore this therapy didn't provide any cause other adverse effects. Additionally, the combination of aerosol spray and bacteriophages are responsible for mortality reduction of broiler chickens with E. coli respiratory infection and limited the mice infection by *P. aeruginosa, Klebsiella pneumoniae or Burkholderia cenocepacia*. In back few years, phage cocktails or polyphagia therapy is play a key role behind the use and increases as the results of using single phage preparation is not quite good in some cases. The purpose behind use of polyphagia or phage therapy do not the replacement of single phage preparation but instead to broaden spectrum of treatment of bacterial infection [21,22]. Kelly, et al. introduced a cocktail therapy in the reference of previously resistant strains of *S.aureus*, based on *Staphylococcus* phage K. Cocktail has six of the most potent phage derivatives, along with the original phage K. This cocktail outcomes in broadening the spectrum of activity compared with *Staphylococcus* phage K used as a single phage preparation. Same as Kelly was develop a phage cocktail preparation using three phages, tested for efficacy against pathogenic *Klebsiella pneumoniae* infection in mice. A single dose of cocktail preparation administered intraperitoneally 1 h after *Klebsiella pneumoniae* inoculum resulted in 100% recovery.

Studies Using Human

Extensive research is ongoing to investigate the efficacy of bacteriophages to treat bacterial infections in humans; most of this research is focused on topical use of bacteriophages to treat skin infections [23,24]. Different scientists have shown the beneficial effects of bacteriophages on topical applications in case of burns, wounds, diabetic foot ulcer during and after the second world war. Reported in the 1990's that infection caused by multidrug resistant *P. aeruginosa* in burns can be cured by the use of specific bacteriophages, and 18 out of 30 adult patients in whom he used this therapy allowed successful skin grafting [24,25]. Recent works done by researchers like from 2009 to 2018 also confirmed the beneficial effects of bacteriophages in the treatment of local topical infections for instance treatment of numbers of diabetic foot infections, which previously show resistance to antibiotic therapy. But all these research on topical infections were not randomized. The only randomized clinical trials on bacteriophage efficacy in topical infections were carried out in 2018. He used a cocktail preparation of 12 phages but unfortunately his results were very disappointing that sulfadiazine cream showed more efficacy than the cocktail preparation [26,27]. In 1993 proposed that use of bacteriophages orally is effective in treating cholera, but yet no randomized, placebo controlled trials have been done in patients with this disease. Similarly, the studied carried out proposed that the use of a two phage cocktail is effective in the treatment of diarrheal infection caused by *E.coli*, but the results of later randomized and placebo controlled clinical trials carried out were disappointing, where the two phage cocktail preparation did not show very positive results [28,29]. Some *in vitro* studies also suggested that use of bacteriophage cocktail therapy can be effective in treating patients with cystic fibrosis. But yet no randomized and placebo controlled clinical trials done on patients enrolling with cystic fibrosis [30]. Though some cases have shown the efficacy of bacteriophages when administered with aerosol, but we cannot draw a definitive conclusion about the relevance of bacteriophage with cystic fibrosis treatment. The **Figure.5** given below demonstrates the timeline of some of the important events that occur during the studies of Phage therapy and antibiotics.

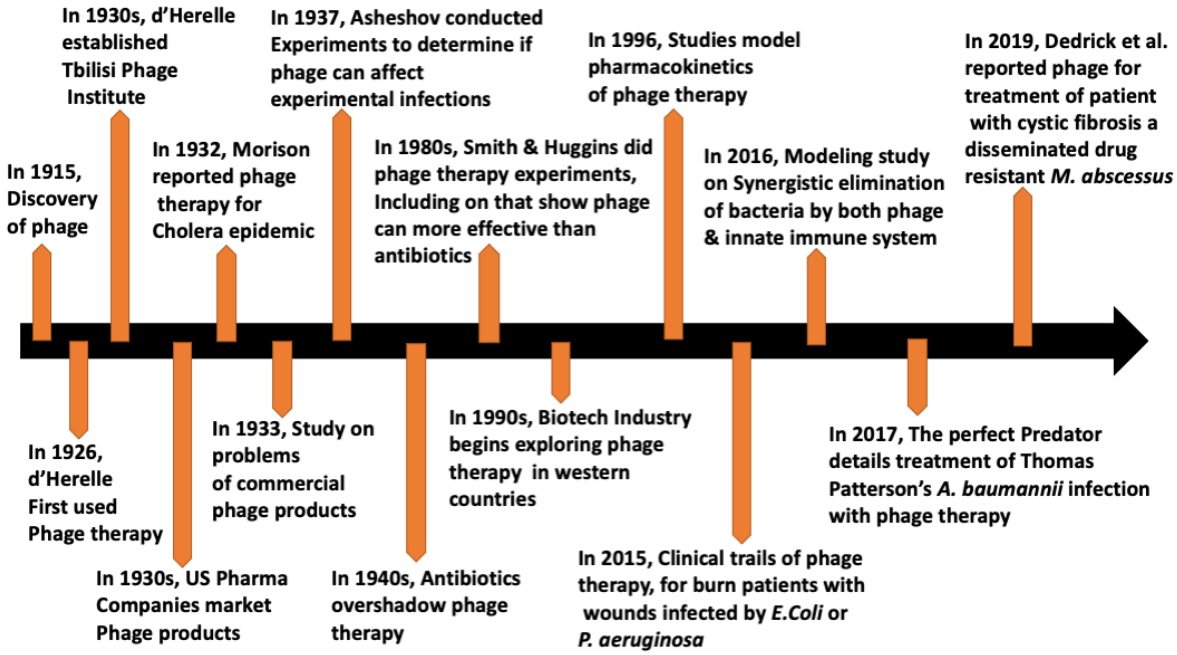


Figure 5: Highlights in the development of phage as a potential therapeutic agent for bacterial infections.

The figure represent a qualitative measure of the overall interest, research, and use of phage therapy and antibiotics, showing how the introduction of antibiotics and the critical review of the early phage therapy studies coincided to bring phage therapy research and development to an almost complete standstill around the 1940's.

Conclusion

In conclusion, several features of bacteriophages like high specificity toward infecting and lysing pathogenic bacteria only without causing any harm to humans, plants or animals make them an attractive therapeutic agent. The recent research also indicated that it is rational to think phage therapy against pathogenic bacterial infections as an alternative to conventional antibiotics treatment. However, the data obtained from the recent research is not enough to use bacteriophage therapy in humans. Of all the clinical trials done so far, very few trials are randomized and controlled and that too result in partially negative. Also the problem to prepare the formulations for standardized and clinical use in bacterial control, limiting the risk of emergence of bacterial resistance is not solved. In view of global health problems by increasing antibiotics resistance, desperate need of alternative strategies to treat bacterial infection and research data collected so far regarding phage therapy, further studies need to be carried out to solve the above mentioned problems that limit the use of bacteriophage therapy.

Future Perspective

Keeping in view the useful and encouraging data obtained so far by the researchers regarding phage therapy and the fact that bacterial resistance to antibiotics treatment has become a serious threat to global health, there is a need to start over all the clinical trials of bacteriophage therapy using modern biotechnology. This time these clinical trials must be randomized and placebo controlled. Currently, phage therapy is used only in Poland and Russia on a very small scale so it is much needed that the scientists and pharmaceutical companies in the western world must carry out more controlled research and must overcome all problems before finally using this for humans in the Western side and in America. The cocktail preparations for different bacterial infections must be optimized and also immune responses to different phage therapy must also be monitored closely and overcome so that phage therapy can be introduced into clinical practice. Seeing the encouraging data obtained so far

and the advancement of biotechnology, we can expect that within a decade, bacteriophages either alone or in combination with antibiotics will be used in clinical practice globally to treat all the chronic infections that will be either completely resistant to all available antibiotics.

Limitations with the use of Bacteriophages

Despite rigorous research on bacteriophages as an alternative to conventional antibiotic therapy in bacterial infection, still it is not approved by the FDA, because we don't have enough data regarding use of bacteriophage therapy in humans and also all the research done so far is not randomized or placebo controlled. Also, the preparations of bacteriophages for clinical use is difficult, and many problems related to the biology of the bacteriophages need to be solved first.

Some of the factors that limit the development of new phage preparations includes:

- Absence of specific activity in bacteriophage against certain bacterial strains is one of the limitations in the use of phage therapy.
- The genome of bacteriophage must be sequenced and free from integrate genes, antibiotic resistant genes, genes for phage-encoded toxins or genes for other bacterial virulence factors for the development of new phage preparations. Difficulty in the production of sequenced genomes of bacteriophage is another limiting factor.
- Another limiting factor in the development of new phage preparations is that formulation and stabilization of pharmaceutical preparations for clinical use undergo some problems, hence stabilization strategies should be optimized for each bacteriophage separately which can result in very costly clinical trials and is discouraging for pharmaceutical companies to carry out preparations for humans.
- Bacterial cell can adopt several mechanisms to prevent viral infections probably by change or loss of receptor, by inhibiting phage DNA injecting in the cell, or by blocking phage DNA replication and cell lysis. Because of these mechanisms, it is quite possible that bacteria can develop resistance against specific phage. This is another important factor that limits the use phage therapy.
- However this problem can be overcome by using phage cocktails that is a mixture of different phages to kill pathogenic bacteria.
- Another factor that limits the use of bacteriophage to treat bacterial infection commercially is that phages when following lysogenic infection cycle may integrate their DNA into bacterial chromosomes, causing exchange of genetic material. This transduction can result in the development of more resistant bacteria against antibiotics.
- Finally, reduced activity of bacteriophages as a result of response shown by the immune system toward bacteriophages also limits the development of new phage preparation against bacterial infection. This is because bacteriophages and their products are non-self-antigens and recognized by the immune system which then act by reducing the benefits resulting from bacteriophage administration.

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