IJPSR (2023), Volume 14, Issue 8 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 December 2022; received in revised form, 21 February 2023; accepted 29 May 2023; published 01 August 2023

IMPACT OF PHAGE THERAPY ON ANTIBIOTIC RESISTANCE: CLINICAL TRIALS BASED APPROACH

Sutripto Ghosh [1], Tamalika Chakraborty [*1] and Jeenatara Begum [2]

Department of Biotechnology [1], Department of Pharmacy [2], Guru Nanak Institute of Pharmaceutical Science and Technology, Kolkata - 700114, West Bengal, India.

Keywords:

Antibiotic resistance, Phage therapy, Antibiotic-resistant pathogen, Clinical trials

Correspondence to Author:
Ms. Tamalika Chakraborty

Assistant Professor,
Department of Biotechnology,
Guru Nanak Institute of Pharmaceutical Science and Technology, Kolkata - 700114, West Bengal, India.

E-mail: tamalika.chakraborty@gnipst.ac.in

ABSTRACT: The advent of new diseases and the subsequent outbreak of the Covid-19 pandemic has resulted in a tremendous increase in both the production and consumption of antibiotics. While this has helped the economy expand, it has also led to the rise of a problem known as antibiotic resistance. Scientists and researchers worldwide are worried about the spread of antibiotic resistance among various bacterial species. Treating ailments brought on by bacteria resistant to antibiotics is possible through phage treatment. Although phage therapy has shown promise in treating several diseases, it is currently hindered by several obstacles that make widespread use of the technique problematic. We analyze an online survey's results to better understand the prevalence of antibiotic resistance and phage therapy in human practice and the benefits and downsides of utilizing phages to combat pathogenic microbes.

INTRODUCTION: The development of antibiotics and their bactericidal properties have encouraged progress in treating bacterial diseases. The overuse of antibiotics has led to the development of antibiotic resistance in many kinds of bacteria. Alexander Fleming, who developed penicillin, warned against its improper usage since it may cause bacteria to become immune to antibiotics [1]. Antibiotics have been misused, leading to widespread bacterial resistance to many different classes of drugs [2, 3]. Therefore, it is time to revert to the tried-and-true strategy of employing bacteriophage to change antibiotic-resistant bacteriophage. Bacteriophages are viruses capable of showing bactericidal effects against a specific bacterium.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(8).4086-94

This article can be accessed online on www.ijpsr.com

DOI link: http://doi.org/10.13040/IJPSR.0975-8232.14(8).4086-94

Bacteriophages can be classified into two groups based on their life cycles: virulent and temperate **Fig. 1** and **Fig. 2**. The virus, by hijacking the host cell's replication and packaging processes, lytic phages can then release clones of their viral particles. The lytic cycle continues when the virus's progeny infects new bacterial cells. Since temperate phages can transfer genetic information to the host cells, virulent phages are preferable for phage treatment. Also, the rate at which lytic phages produce offspring is much higher than temperate phages [4].

Another advantage of phage therapy is that the phages reproduce randomly upon contact with the infected region. This is helpful since it means that inconvenient diseases to treat can be cured with just one dosage of phage **Fig. 3** [5-7]. However, phages are highly selective for the bacteria they infect. Mixtures of phages, known as "phage cocktails," can potentially affect various bacteria. It's important to remember that bacteria and bacteriophages have shared the Earth's ecosystems

for a very long time. Because co-evolution makes treatments like phage therapy flexible, this will also happen when it is utilized as a therapeutic intervention. Therefore, using phage cocktails is more likely to prevent the spread of phage-resistant diseases than using individual phages [8, 9, 3].

It's also feasible that their immune system interactions will be unique. The effectiveness of these therapies will also depend on the specifics of the illness, such as its place, intensity, or the make-up of the bacterial cell.

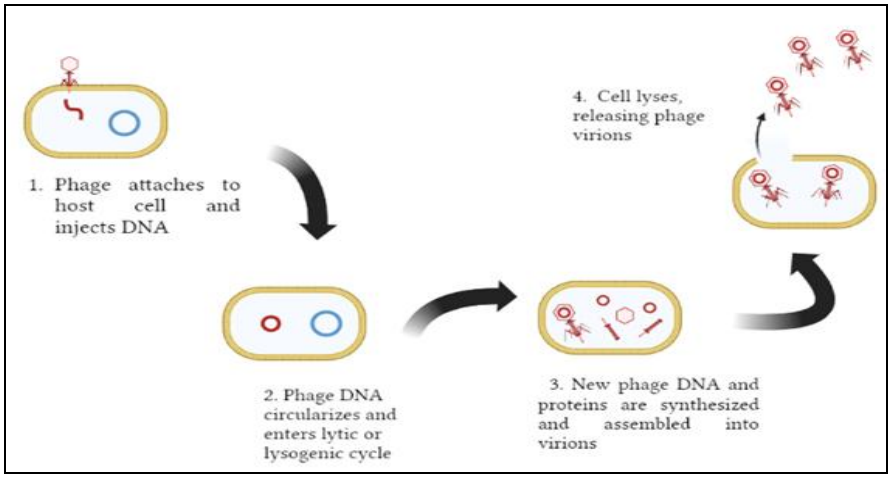

FIG. 1: LYTIC CYCLE OF BACTERIOPHAGES

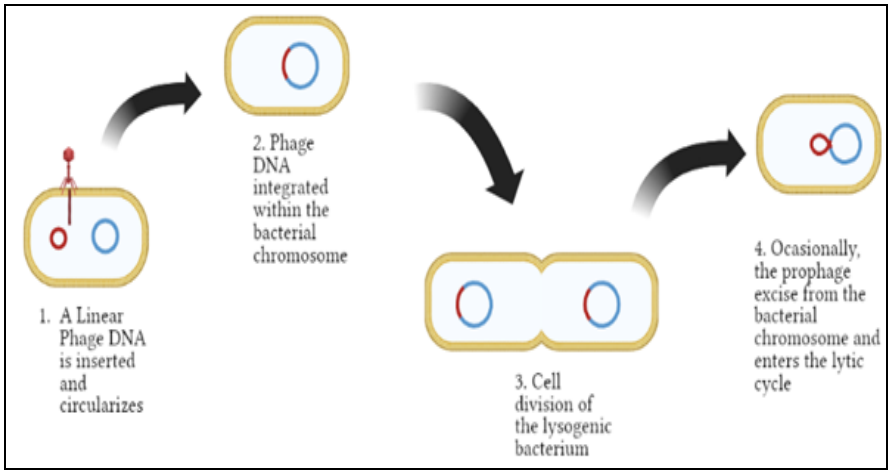

FIG. 2: LYSOGENIC CYCLE OF BACTERIOPHAGES

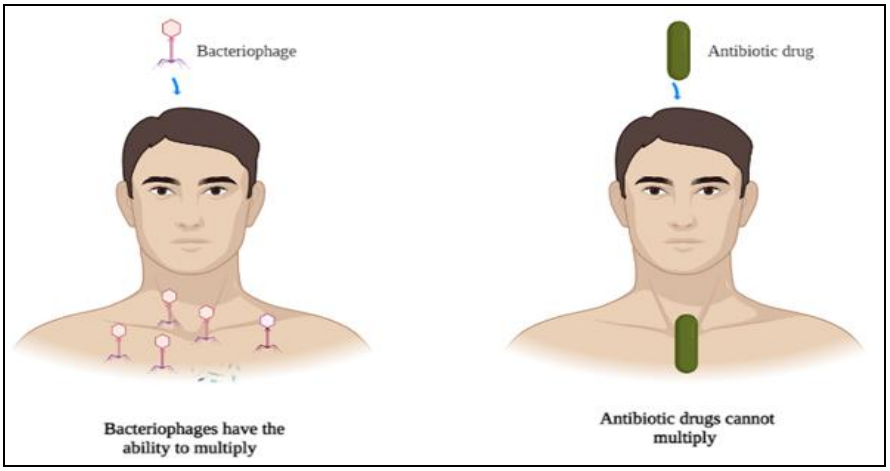

FIG. 3: COMPARISON BETWEEN BACTERIOPHAGES AND ANTIBIOTICS AS THERAPEUTIC INTERVENTION

Before we go any further, it's important to review the history of how bacteriophages have been used in the past for medical purposes. River waters have the power to cure many bacterial illnesses from the beginning. The prophet Elisha treated Naaman's sickness by bathing in river water, according to "The Book of Kings" [10]. Sir Ernest Hankin discovered in 1896 that the Ganga and Yamuna River waters in India were capable of treating Cholera disease in people caused by *Vibrio cholerae* infection[11]. Further, in 1918, Felix d' Herelle recognized Bacteriophages as the cause of bacterial colony death, which he demonstrated by seeing spherical zones of no growth, which he called plaques [12]. Seven years later, he cured dysentery in a 12-year-old boy in Paris by ingesting bacteriophage in his body. He reported that the bacterial infection completely ceased after a single dose of bacteriophage. Thus, he proved that bacteriophages were efficient enough to control the growth of bacteria responsible for diseases [13].

Table 1 shows a variety of patient cases in which bacteriophages were utilized to treat individuals with various bacterial disorders.

TABLE 1: DETAILS ABOUT SEVERAL INCIDENCES OF ANTIBIOTIC RESISTANCE AND THEIR TREATMENT USING PHAGE THERAPY USAGE

	Disease Reported	Disease conditions	Antibiotics used	Resistance to Antibiotics/known allergies	Bacteriophage Dosage	Duration	Result
1	Craniectomy followed by Acinetobacter baumanii [14]	Brain Injury followed by craniectomy	Combination of colistin with rifampin, azithromycin, and chloramphenicol separately	Resistant to Rifampin, chloramphenicol as well as azithromycin	98 doses: 2 x 1010 PFU every 2 hours for 8 days, 12 days after hospitalization	8 days of phage administration, a total of 98 doses	Signs of improvement of the patient after phage therapy
2	Urinary tract infection due to Pseudomonas aeruginosa [15]	Intra-abdominal resurrection, pelvic irradiation adenocarcinom, stent placement	Gentamicin, ceftazidime, ciprofloxacin, meropenem	None	2 x 107 PFU into the urinary bladder every 12 hours	20 ml phage every 12 hours for 10 days, colistin (Days 6-10), and meropenem (Days 6-30)	Analyzed urine samples sterile after phage treatment, discharged after 10 days, 30 days course of meropenem
3	Aortic graft infected with *Pseudomonas aeruginosa* [16]	Replacement of aortic arch followed by infection of *Pseudomonas aeruginosa* of aortic graft	Ceftazidime and ciprofloxacin	Resistance towards ciprofloxacin	1 x 10^7 PFU per ml injected into the fistula in the chest	One minimum dosage to remove biofilm for antibiotic resistance	The condition of the patient successively improved
4	Infection of *Pseudomonas aeruginosa*, sepsis [17]	DiGeorge symptoms, several congenital heart disorders	Meropenem, tobramycin, aztreonam, colistin, polymyxin B	Cephalosporins, fluoroquinolones and later to meropenem, tobramycin, aztreonam and colistin	3.5 x 10^6PFU for every 6 hours	6 doses phage for 6 hours: 36 hours,restarted on 12th days	During phage therapy, the blood was sterile, but after treatment was discontinue, infection was detected
5	Acinetobacter	Pancreatitis due to the	Tigecycline,	Resistance	Phage cocktail	59 days of	Signs of

	baumanii infection of the pseudocyst, pancreatitis [18]	presence of gall stones, presence of pseudocysts	vancomycin, colistin, meropenem	against antibiotics such as ciprofloxacin, gentamycin, sulfamethoxazole, tetracycline, cephalosporins, meropenem, and amikacin.	of 109 PFU from the 109th day per 6 to 12 hours, another phage cocktail of 109 PFU per 12 hours for the 112th to 114th day and then at 2 hours frequency, and another phage cocktail 109 PFU for the remaining days.	phage administration	improvement of patient's condition
6	Total joint arthroplasty, periprosthetic joint infection due to Staphylococcu sepidermidi, followed by a number of different bacterial infections [19]	Right Total Knee Arthroplasty followed by an infection due to *Staphylococcus epidermidis*, followed by an infection of *Enterococcus faecalis* at the surgical site, then an infection of *Klebsiella pneumoniae* from abscessa year later	Daptomycin, penicillin, linezolid, meropenem as well as cefadroxil	Oxacillin	40 Intravenous injection doses of 6.3 x 10^{10} Phages mixed in 50 ml of saline water combined with minocycline	57 days of phage administration	Reduced CRP levels in patient's blood after completing phage therapy, reduced infection, redness, and swelling of the skin
7	Cystic fibrosis followed by infection of Mycobacterium abscesses [20]	Patients with cystic fibrosis underwent lung transplantation but soon after the surgery, and around a week after stopping intravenous therapy, Mycobacterium abscesses were detected from the surgery sites. Soon painful lesions appeared at various sites on the skin	Clofazimine, Bedaquiline, along with rituximab injections to cure the painful lesions on the skin	None	Cocktail of 3 phages each 1 x 10^9 PFU each dose, in 12 h intervals of time	8 months	Patient's condition gradually improved with appetite getting better. Painful skin blisters begin to cure along with the wounds from surgery

TABLE 2: DETAILS ABOUT CLINICAL TRIALS ON PHAGE THERAPY FOR DIFFERENT DISEASES

S. no.	Disease and pathogen involved	Brief of trial	Group of people undergoing phage therapy	Group of people receiving placebo	Bacteriophage dosage	Results
1	Otitis caused due to *Pseudomonas putida* infection [21]	Placebo-controlled, double-blinded trial	12 people with the phage cocktail	12 people received a single dosage of glycerol-PBS	Single dosage of 105 PFU	Three people who received phage had a considerate reduction in bacterium count (>80%)
2	Diarrhea caused due to *Escherichia coli* [22]	Placebo controlled	Phage cocktail T was administered to thirty-nine patients; phage cocktail M was administered to forty patients	Placebo (oral rehydration salts supplemented with zinc) administered to forty-one patients	Phage cocktail M: 1.4 x 109 PFU, three times per day for four days. Phage cocktail T: 3.6 x 108 PFU, three times per	No significant differences in results among the three treatment groups were observed

3	Urinary tract infections in patients undergoing transurethral resurrection of the prostate gland [23]	Placebo-controlled, double-blind trial	The pyophage cocktail was administered to 37 different patients above 18 years of age	Placebo was given to 38 patients above 18 years of age	day for four days 10^4 PFUto 107PFU bacteriophages were administered to 37 different patients, two times a day for seven days.	No significant difference in results was observed among the three different treatment groups, most of the patients were free from UTI infections with satisfactory results after 7 days
4	Burn wounds infected with *Pseudomonas aeruginosa* [24]	Placebo controlled double-blinded trial	12 individuals received bacteriophage	13 individuals received a placebo (1% sulfadiazine silver topically)	1 x 10^6 PFU for seven days (expected) BUT 1 x 10^2 PFU administered	The trial stopped midway due to the low efficacy of the treatment

DISCUSSION:

Cases of Antibiotic Resistance and Phage Therapy: Case 1: LaVergne (2018) reported *Acinetobacter baumanii* infections in a patient after craniectomy surgery. Several antibiotic combinations began to be used, but the bacterial strain soon developed resistance against all the drugs except colistin. The patient did opt for phage therapy and received 98 doses for eight days and the condition of the patient increased after the phage treatment [14].

Phage therapy Case 2: According to the study Khawaldeh *et al.* (2011), after getting treatment for carcinoma, the elderly patient became infected with *Pseudomonas aeruginosa*. Soon, a wide range of antibiotics was prescribed, and the patient later chose phage therapy. For ten days, the patient received a mix of multiple bacteriophages specific to several microorganisms obtained from the Eliava Institute, which were injected into his urinary bladder every twelve hours[15].

Phages were given for 5 days, and then phages were given combined with meropenem and colistin from the sixth day. From the sixth to the tenth day, colistin was used, whereas meropenem was used until the 30th day. A dedicated five-day phage treatment resulted in a ten-fold reduction of bacteria in urine. The following two days of antibiotic treatment resulted in a further reduction of *Pseudomonas* bacteria, which was below detection limits. After the 30th day, the stents were removed and replaced, and the urine was sterile for the next year [15].

Phage therapy Case 3: Using a graft to treat an aortic aneurysm led to infection with Pseudomonas aeruginosa, resulting in the formation of a fistula that discharged puss[16]. The replacement of the infected transplant was rated high risk by doctors and heart surgeons. As a result, the focus has turned to antibiotics, specifically ceftazidime and ciprofloxacin. However, due to bacterial resistance to ciprofloxacin and recurring recurrence of infection over the next three years, this treatment was deemed a complete failure and the attention was switched to phage therapy [16]. Endotoxins from the phage OMKO1 were filtered since they posed a health risk and ceftazidime was delivered straight into the fistula. Due to bleeding from the location, the patient underwent a small graft excision four weeks later; no *Pseudomonas aeruginosa* was found at that time; thus, ceftazidime was withdrawn, and the patient did not report any recurrence of infection even two years after the treatment [16].

Phage therapy Case 4: Duplessis (2017) reported a toddler suffering from multiple heart disorders got an infection of *Pseudomonas aeruginosa,* for which antibiotics were administered [17]. But due to allergies against a maximum of the prescribed antibiotics **Table 1**, this treatment method was deemed useless. Thus, the focus was shifted to phage therapy, informing and taking consent from the child's parents. A cocktail of two different bacteriophages, obtained from the U.S. Navy was used now to control the proliferation of *Pseudomonas aeruginosa,* administered every 6 hours. Blood cultures assayed after four to five days of starting phage therapy were completely sterile. But phage therapy was ceased due to a decompensation contributing to heart failure, which

coincided with phage therapy. After cessation of phage therapy, blood cultures again turned positive [17]. Lastly, due to the total lack of other treatment options, the therapy was resumed eleven days after ceasing. The blood cultures were reported to be negative within just one day of resuming phage therapy. But the patient passed due to a severe cardiac arrest. Thus, the use of phage therapy, in this case, resulted in blood cultures becoming negative but reverting to positive once phage therapy was stopped [17].

Phage therapy Case 5: Schooley (2017) reported a man in his mid-sixties developed pancreatitis along with *Acinetobacter baumanii* infection due to the presence of a pseudocystSeveral antibiotics were prescribed for the treatment of the infection, but the bacterium has developed broad resistance to several of the medications specified **Table 1**, resulting in antibiotic failure[18]. After 109 days, their focus was turned to phage therapy. The initial phage mixtures were given intracavitary at the cyst's location. Another phage cocktail was given intravenously the next day. However, the bacteria's resistance to the two phage cocktails led to administering a third phage virus cocktail, which was subsequently injected at the site of *Acinetobacter baumanii* infection. Meropenem was also given, along with minocycline, to treat the bacterial infection, which was eventually terminated. As reported by (Schooley 2017), the therapy was continued for 59 days, during which time the patient's condition improved significantly, and the infection was healed [18].

Phage therapy Case 6: Cano *et al.* (2021) reported that following a complete knee arthroplasty, the patient developed an infection caused by *Staphylococcus epidermidis.* Different antibiotics were prescribed to the patient **Table 1** [19]. Moreover, the patient showed antibiotic resistance towards Oxacillin. He then developed persistent bacterial infections and eventually turned to phage therapy to heal himself. *Klebsiella pneumoniae*-specific phages were injected and administered for 57 days in 40 doses of 6.3 x 10^{10} mixed with 50 cc of saline solution and minocycline. After phage-induced therapy, the CRP level in the patients' blood was found to be quite low. Following that, the patient was in good health and reported no difficulties after 57 days of phage treatment. The knee's redness and swelling at the operation site were minimised [19]. Phage therapy Case 7: The presence of cystic fibrosis in a 15-year-old patient with diabetes, liver illness, gastrotomy, and other symptoms were reported [20]. The patient had lung transplants, but after ceasing intravenous medication for a week, he developed drug-resistant *Mycobacterium abscesses* at the surgical sites **Table 1**. Painful sores appeared on the victims' skin soon after. Rituximab was given to the patient as a treatment for painful skin sores. A cocktail of three lytic phages was given every 12 hours for eight months. Within 9 days, the patient's condition began to improve, and after a month, the lesions began to improve, and the phage treatment was continued for nearly six months. With improved lung and liver function, the patient's condition improved, and his appetite improved as well [20]. Trials of phage therapy have been conducted in several parts of the world to combat the issue of antibiotic resistance with patients having different disease conditions. A list of different clinical trials has been mentioned in **Table 2.**

Trials Conducted to Check the Efficacy of Phage Therapy:

Clinical Trial 1: In the clinical trial conducted by Wright (2009) to understand the efficacy of phage therapy for otitis caused by *Pseudomonas aeruginosa,* 24 patients consisting of males and females with *Pseudomonas aeruginosa* caused otitis were screened [21]. Out of them, twelve patients received a single dosage of phage cocktail while the other twelve received a Glycerol-PBS placebo. All the patients from the two groups regularly attended follow-up check-ups. No significant improvement was observed in patients administered with a placebo. However, among all the people administered with the phage cocktail, no *Pseudomonas aeruginosa* pathogen was observed in three people after the 42nd day [21]. Patients when they visited the clinic for follow-up on the 21st day, and no significant phages were isolated from them. Since, *Pseudomonas aeruginosa* was not detected in the patients after the 42nd day, and the phages were not detected after the 21st day, there might be chances of the bacterium developing resistance against the phages [21].

Clinical Trial 2: Another clinical trial Sarker et al. (2016) reported on *Escherichia coli* induced

diarrhea among children in Dhaka, Bangladesh[22]. The trial divided the children into three groups. Among them one such group of 39 were administered T4 phage cocktail orally through oral rehydration salts, another group of 40 children was administered a Microgen phage cocktail. In contrast, the last group of 41 headcounts was administered only a placebo (oral rehydration salts). All three groups were given three dosages daily for four days, a total of twelve doses per group [22]. However, no satisfactory result difference between the three treatment groups was observed. As Sarker *et al.* (2016) listed, most *Escherichia coli* were not specific to the bacteriophages utilized, and phages were supplied orally; therefore most of them would not have been able to tolerate the low pH acidic environment of the stomach [22].

Clinical Trial 3: Ninety-seven people were divided into three groups in trials reported by Leitner *et al.* (2021) for the treatment of urinary tract infections using bacteriophage: the first group of thirty-seven people received Pyophage cocktail (specific to several different bacteria responsible for *Escherichia coli*), the next thirty-eight patients were treated with antibiotics, and the last thirty-eight people were treated with placebo [23]. All three groups of participants (Pyophage 18%, placebo 28%, and antibiotic 35%) demonstrated nearly identical improvements in their diseases, with very little difference in their rates between them. According to Leitner *et al.* (2021), bladder irrigation to lower the bacterial burden may have resulted in similar findings [23].

Clinical Trial 4: Jault *et al.* (2018) reported a clinical trial where bacteriophage specific for *Pseudomonas aeruginosa* was used to cure burn wounds infected with *Pseudomonas aeruginosa* [24]. Here the total people were divided into two groups such that in one group, twelve were administered phage at a concentration of 1×10^6 PFU, and a control (placebo) was used consisting of 1% of sulfadiazine applied topically. The trial was hauled due to the less efficacy of the mediated treatment. This was because the number of phages administered was much lower than the expected amount (1×10^2 PFU per ml). Thus, using such a low concentration of phages has led to the decreasing treatment efficacy; *Pseudomonas aeruginosa* was present in the burn wounds even after the end of the seventh day [24]. Numerous cases of antibiotic resistance and phage therapy as a potential remedy are seen along with the several clinical trials conducted to establish phage therapy as a potential remedy for antibiotic-resistant bacteria. Phage therapy possesses numerous advantages but along with several disadvantages.

The advantages are as follows:

1. Based on the above occurrences of phage therapy, it is clear that phages have a bactericidal impact against bacteria resistant to antibiotics. As a result, they can be used instead of antibiotics to treat infections caused by antibiotic-resistant organisms.

2. Bacteriophages can replicate on their own when specific bacterial cells are present. Thus, using a little number of phages or plaque forming units can yield beneficial effects [25].

3. The formation of biofilms by various bacterial species has resulted in resistance to various antibiotics, which is currently a major source of concern. Phages have the capacity to remove biofilms while also lowering antibiotic resistance in bacterial populations.

4. From the above online study of various phage therapy cases, it is obvious that phages can be administered in a variety of methods, including orally, intravenously, topically and so on.

5. Because phages can multiply on themselves and expand in number to modify the bacterial population, they can be given in a single dose, making phage therapy extremely convenient. Chan *et al.* (2018) used a single dose of phages to cure *Pseudomonas aeruginosa* infection of an aortic transplant [16].

6. Because phages are highly selective and particular for their host bacterium, they can be utilized to treat illnesses caused by bacterial expansion without disturbing the body's normal flora.

Thus, phage therapy offers some advantages over antibiotics or other illness therapies. Still, today it also has several drawbacks that prevent it from being utilized effectively as a substitute for

antibiotics or other similar medications. The following are some of the drawbacks of phage therapy:

1. Lytic phages are those that are thought to be good for phage therapy. Temperate phages generate virulence factors in the host bacteria, making it resistant to the phage in consideration, resulting in the development of superinfection immunity [19].

2. Phages have a limited host range; they are specific for specific host bacterial cells, a drawback of phage therapy.

3. Because phages may reproduce and multiply independently, administering low concentrations of phages is a significant benefit of phage therapy. However, when Jault *et al*. (2018) utilized phages at lower concentrations than expected, believing that phages may reproduce and multiply on their own, no satisfying results with bacterial cell killing were obtained, and the study was discontinued midway due to the low efficacy of therapy [17].

4. Phages were used in conjunction with antibiotics in all of the investigations presented. As a result, more research is needed to see if phages can be employed as the sole therapeutic agent.

5. Phages are protein-based biological agents that can disrupt the immune system and cause a variety of allergic immunological responses that are harmful to the body [27, 28].

CONCLUSION: Phage therapy has come a long way and offers several benefits. However, numerous scientists and experts believe this kind of therapy still has several limitations. This is why phage therapy is not being employed broadly to treat diseases caused by antibiotic-resistant organisms. Because phages have a narrow host range, careful selection of phages is required for phage therapy, as is the adequate formulation for phage administration. However, we are currently unsure how to provide phage therapy to bacteria that can develop both antibiotic and phage resistance. Furthermore, we still don't know how to use phages that target many bacteria in the body, as this could affect the bacterial ecology of other body parts. People in possibly primitive places may also refuse to undertake phage therapy, mistaking bacteriophages for viruses that can cause health problems. Nonetheless, we still don't know the answers to several of these concerns, and more studies and large-scale clinical studies based on risk and benefit are needed to understand them better.

ACKNOWLEDGEMENT: We would like to extend our gratitude to the Guru Nanak Institute of Pharmaceutical Science and Technology for providing us with the necessary support during this work.

CONFLICTS OF INTEREST: The authors declare no conflicts of interest.

REFERENCE:

1. Penicillin's finder assays its future; sir Alexander Fleming says improved dosage method is needed to extend use other scientists praised self-medication decried (1945) The New York Times. The New York Times. Available at: https://www.nytimes.com/1945/06/26/archives/penicillins-finder-assays-its-future-sir-alexander-fleming-says.html (Accessed: December 22, 2022).
2. Al-Bahry SN, Mahmoud IY, Al-Khaifi A, Elshafie AE and Al-Harthy A: Viability of multiple antibiotic resistant bacteria in distribution lines of treated sewage effluent used for irrigation. Water Science and Technology 2009; 60(11): 2939–48.
3. Patra B, Chakraborty T and Ghosh S: Prevalence and Transmission of Multi Drug Resistance Gene in *Staphylococcus aureus*, Current Biotechnology 2022; 11(3): 196-211. https://dx.doi.org/10.2174/2211550112666221117091252.
4. Monteiro R, Pires DP, Costa AR and Azeredo J: Phage Therapy: Going Temperate?. Trends in Microbiology 2019; 27(4): 368–378.
5. Payne RJ, Phil D and Jansen VA: Phage Therapy: The Peculiar Kinetics of Self-Replicating Pharmaceuticals. Clin Pharmacol Ther 2000; 68: 225–230.
6. Squires R: Bacteriophage Therapy for Management of Bacterial Infections in Veterinary Practice: What Was Once Old Is New Again. N Z Vet J 2018; 66: 229–235.
7. Melo LD, Veiga P, Cerca N, Kropinski AM, Almeida C, Azeredo J and Sillankorva S: Development of a Phage Cocktail to Control Proteus mirabilis Catheter-associated Urinary Tract Infections. Front Microbiol 2016; 7: 1024. doi: 10.3389/fmicb.2016.01024.
8. Green SI, Kaelber JT, Ma L, Trautner BW, Ramig RF and Maresso AW: Bacteriophages from ExPEC Reservoirs Kill Pandemic Multidrug-Resistant Strains of Clonal Group ST131 in Animal Models of Bacteremia. Sci Rep 2017; 7: 46151. doi: 10.1038/srep46151.
9. Domingo-Calap P and Delgado-Martínez J: Bacteriophages: Protagonists of a Post-Antibiotic Era. Antibiotics (Basel) 2018; 7(3): 66. doi: 10.3390/antibiotics7030066.
10. Keen EC: Felix d'Herelle and our microbial future. Future Microbiology 2012; 7(12): 1337–1339.

11. Adhya S and Merril C: The road to phage therapy. Nature 2006; 443(7113): 754–5.
12. Duckworth DH: Who discovered bacteriophage? Bacteriol Rev 1976; 40: 793-802.
13. Setlow J, Randesi M, Adams J, Setlow B and Setlow P: Mutation and killing of Escherichia coli expressing a cloned *Bacillus subtilis* gene whose product alters DNA conformation. J Bacteriol 1992; 174: 2943-2950.
14. LaVergne S, Hamilton T, Biswas B, Kumaraswamy M, Schooley RT and Wooten D: Phage therapy for a multidrug-resistant Acinetobacter baumannii craniectomy site infection. Open Forum Infect. Dis 2018; 5: 064.
15. Khawaldeh A, Morales S, Dillon B, Alavidze Z, Ginn AN and Thomas L: Bacteriophage therapy for refractory *Pseudomonas aeruginosa* urinary tract infection. Journal of Medical Microbiology 2011; 60(11): 1697–700.
16. Chan BK, Turner PE, Kim S, Mojibian HR, Elefteriades JA and Narayan D: Phage treatment of an aortic graft infected with *Pseudomonas aeruginosa*. Evol Med Public Health 2018; 60–66.
17. Duplessis C, Biswas B, Hanisch B, Perkins M, Henry M and Quinones J: Refractory pseudomonas bacteremia in a 2-year-old sterilized by bacteriophage therapy. Journal of the Pediatric Infectious Diseases Society 2017; 7(3): 253–6.
18. Schooley RT, Biswas B, Gill JJ, Hernandez-Morales A, Lancaster J and Lessor L: Development and use of personalized bacteriophage-based therapeutic cocktails to treat a patient with a disseminated resistant Acinetobacter baumannii infection. Antimicrobial Agents and Chemotherapy 2017; 61(10).
19. Cano EJ, Caflisch KM, Bollyky PL, Van Belleghem JD, Patel R and Fackler J: Phage therapy for limb-threatening prosthetic knee *Klebsiella pneumoniae* infection: Case report and *in-vitro* characterization of anti-biofilm activity. Clinical Infectious Diseases 2020; 73(1).
20. Dedrick RM, Guerrero-Bustamante CA, Garlena RA, Russell DA, Ford K, Harris K, Gilmour KC, Soothill J, Jacobs-Sera D, Schooley RT, Hatfull GF and Spencer H: Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*. Nature medicine 2019; 25(5): 730–733.
21. Wright A, Hawkins CH, Anggård EE and Harper DR: A controlled clinical trial of a therapeutic bacteriophage preparation in chronic otitis due to antibiotic-resistant *Pseudomonas aeruginosa*; a preliminary report of efficacy. Clinical otolaryngology: official journal of ENT-UK; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2009; 34(4): 349–357.
22. Sarker SA, Sultana S, Reuteler G, Moine D, Descombes P, Charton F, Bourdin G, McCallin S, Ngom-Bru C, Neville T, Akter M, Huq S, Qadri F, Talukdar K, Kassam M, Delley M, Loiseau C, Deng Y, El Aidy S, Berger B and Brüssow H: Oral Phage Therapy of Acute Bacterial DiarrheaWith Two Coliphage Preparations: A Randomized Trial in Children From Bangladesh. EBioMedicine 2016; 4: 124–137.
23. Leitner L, Ujmajuridze A, Chanishvili N, Goderdzishvili M, Chkonia I, Rigvava S, Chkhotua A, Changashvili G, McCallin S, Schneider MP, Liechti MD, Mehnert U, Bachmann LM, Sybesma W and Kessler TM: Intravesical bacteriophages for treating urinary tract infections in patients undergoing transurethral resection of the prostate: a randomised, placebo-controlled, double-blind clinical trial. The Lancet Infectious Siseases 2021; 21(3): 427–436.
24. Jault, Jault P, Leclerc T, Jennes S, Pirnay JP, Que YA and Resch G: Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): A randomised, controlled, double-blind phase 1/2 trial. The Lancet Infectious Diseases 2019; 19(1): 35–45.
25. Kutter E, De Vos D, Gvasalia G, Alavidze Z, Gogokhia L and Kuhl S: Phage therapy in clinical practice: treatment of human infections. Curr Pharm Biotech 2010; 11: 69-86
26. Hyman P and Abedon ST: Bacteriophage host range and bacterial resistance. Advances in Applied Microbiology 2010; 70: 217–248.
27. Loc-Carrillo C and Abedon ST: Pros and cons of phage therapy. Bacteriophage 2011; 1(2): 111–114.
28. Ghosh S and Chakraborty T: Bacteriophage mediated modulation of gut microbiome responsible for colorectal cancer. Int J Pharm Sci & Res 2023; 14(2): 852-59. doi: 10.13040/IJPSR.0975-8232.14(2).852-59.

How to cite this article:
Ghosh S, Chakraborty T and Begum J: Impact of phage therapy on antibiotic resistance: clinical trials based approach. Int J Pharm Sci & Res 2023; 14(8): 4086-94. doi: 10.13040/IJPSR.0975-8232.14(8).4086-94.