Open Access Contents
Int. J. Res. Pharm & Allied Sci
| January - March 2023 | Vol. 1 | Issue 1 |

Full Length Original Research Paper

Antibiotics Resistance and Bacteriophage Therapy

www.ijrpas.co

Harshvardhan Purane *,
Sham Andhale,
Mahesh Kshirsagar,
Vishal Rasve,
Sanjay Garje,
Lad S.D.

* SAJVPM'S College of Pharmaceutical and Science Research Center, Kada

Corresponding Authors:

Harshvardhan Purane
Email:

Abstract:
Once the clinical trials are done, the drug is approved and released in the market, lacking the knowledge of rare and chronic effects. Here comes the Pharmacovigilance or say Post Marketing Surveillance which study the rare and chronic effects of the drugs. About a 100 years ago we found the fungi that produce chemical compounds which kills bacteria (Penicillin) we named it Antibiotics. We started using Antibiotics more and more for less serious causes but Bacteria are living things, they evolved and started to become immune, until we have created superbugs (Bacteria immune to everything we have). After many case studies and Surveillance, we found about the resistance and now we realized that it's going at rapid rates. Antibiotics resistance happens when germs like bacteria and fungi develop the ability to defeat the drugs designed to kill them. As we are relying more on antibiotics, bacteria growing more immune to it. Also due to overuse we have created some superbugs like MRSA, VRE, CRE, ESBL making shortage of treatment options. This problem fuelled the development of alternate options and mainly bacteriophage therapy. It's effective, quick but difficult, specific and maybe sometimes fatal if not carried correctly. Hence currently it's only in clinical trials or used as Final option for the dieing person. As we discuss further about pros and cons of phage therapy we'll also see about D'Herelle's history in bacteriophage research, treatment challenges and moral aspects.

Keywords:. *Antibiotics, Bacteriophage, Superbugs, Surveillance, MRSA, VRE, CRE, ESBL*.

Introduction

Pharmacovigilance or say Post Marketing Surveillance is so necessary that previously approved drugs might show the problem which might be bigger than the solution like in the case of Rofecoxib(*Vioxx*) Recall in 2004 by the Merck company. Rofecoxib prescribed as painkiller in arthritis is prescribed to nearly 20 million people which later found responsible for increased risk of heart attack and stroke. Reports suggest about 140000 people May have suffered and company facing massive financial damage. As by the Post Market Surveillance and reports suggesting the increased use of antibiotics causing the huge resistance resulting failing of antibiotics treatment. Answer to that the bacteriophage therapy or simply Phage Therapy was tried causing the revolution in the field of antibiotics Resistance treatment, but the concept of Phage Therapy is quite old idea and performed before also[1].

They are unique to a particular bacterium or possibly some of its very close relatives. Phages are so specialized that humans are immune to them. Antibiotics kill both good and bad bacteria, whereas phages kill only their target bacteria. For example, phage therapy has been successfully tested many times. One of them is a man suffering from a Pseudomonas aeruginosa infection in the pleural space because thousands of phages were introduced into the pleural space along with antibiotics that the bacterium had previously been immunized with. After a few weeks, the infection has completely disappeared[2].

By the 1920s, bacteriophages were known as bacterial epidemics and were almost immediately used for antibacterial therapy and prophylaxis. However, early studies of bacteriophage therapy against infectious diseases were flawed because the biology of bacteriophages was poorly understood. The early literature reviewed here indicates that there is good reason to believe that phage therapy may be effective in certain circumstances. Combined with the "Soviet contamination", this meant that phage therapy was not rigorously evaluated until recently[3].

What is Pharmacovigilance?

Pharmakon (Greek) = Medicinal Substances

Vigilia (Latin) = To keep watch

- WHO defines Pharmacovigilance (PV) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. Pharmacovigilance is also known as drug safety and it focuses on ADR (Adverse drug reaction). The main aim of Pharmacovigilance is to monitor approved drugs and Investigational new drugs.
- Pharmacovigilance is all about minimizing the risk to the patient by collecting and assessing data for products in the market and products under clinical trial
- Pharmacovigilance is more than spontaneous reporting alone, and the evaluation of marketed medicines is more than just pharmacovigilance. The positioning of a drug usually takes place during the years following introduction, when worldwide experience has accumulated. Originally a modest appendix of drug regulation.
- Pharmacovigilance has become a major activity. The provision of the information needed for the evaluation of the benefits and risks of drugs is in the first place a scientific challenge. In addition, there are important ethical, logistical, legal, financial and commercial constraints. Good pharmacovigilance practice needs to be developed to ensure that data are collected and used in the right way and for the right purpose.
- Pharmacovigilance, and more generally the study of the benefits and risks of drugs, plays a major role in pharmacotherapeutic decision-making, be it individual, regional, national or international. In addition, pharmacovigilance is becoming a scientific discipline in its own right.

Antibiotics

Antibiotics or antibacterial are a type of antimicrobial agents used specifically against bacteria and are often used in medical treatment of bacterial infections and certain parasitic infections. Antibiotics do not fight infections caused by viruses or fungi or fungal infections of the skin. There are various antibiotics available in the market with different brand names.

Antibiotics are usually grouped together based on their action. Each type of antibiotic only works against certain types of bacteria or parasites. This is why different antibiotics are used to treat different types of infection[4].

The main types of antibiotics include:

- Penicillin's
- Cephalosporins
- Tetracyclines
- Aminoglycosides
- Macrolides
- Quinolones etc.

Antibiotics works on two mechanisms.

Some antibiotics works by killing germs. This is often done by interfering with the structure of the cell wall of the bacterium or

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 36-47

parasite. Those are called Bactericidal antibiotics.

Examples of Bactericidal antibiotics:

- Penicillins
- Cephalosporins
- Fluoroquinolones (Ciprofloxacin)
- Glycopeptides (Vancomycin)
- Monobactams
- Carbapenems

Some antibiotics works by inhibiting the growth of organisms. Those are called Bacteriostatics.

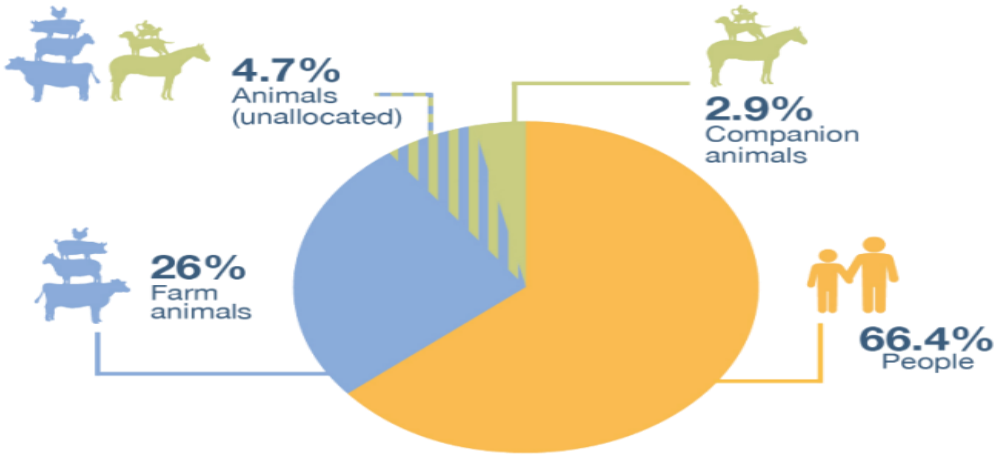

Figure 1 Fields of antibiotics use

Examples of Bacteriostatics:.

- Tetracyclines
- Spectinomycin
- Sulphonamides
- Macrolides
- Chloramphenicol
- Trimethoprim.

Fields of Antibiotics Use

- Farm animals (26%)
- Unlocated animals (4.7%)
- Companion animals (2.9%)
- Humans (66.4%)

Most Used antibiotics

1. Amoxicillin-Clavulnate (27%)
2. Amoxicillin (8%)
3. Cefovecine (8%)
4. Enrofloxacin (8%)
5. Cefalexin (7%)
6. Spiramycin metronidazole (7%) etc[5].

What is Antibiotics Resistance?

"Antibiotic resistance", which can also be called "antibacterial resistance", refers specifically to the ability of bacteria to resist the effects of antibiotics. As a result, the antibiotics no longer kill the bacteria, and bacterial growth is not stopped. This means that standard antibiotic treatments become ineffective and infections persist, increasing the risk of severe consequences to the person and spread to others. Antimicrobial resistance (AMR) is the ability of a microorganism to resist the effects of an antimicrobial medicine.

An Antimicrobial medicines include antibiotics, antivirals, antimalarials and antifungals, which are used to treat microbial infections caused by: Bacteria, Viruses, Parasites, Fungi, etc[6].

The emergence of pathogenic bacterial resistant to most, if not all, currently available antimicrobial agents has become a critical problem in modern medicine, particularly because of the concomitant increase in immunosuppressed patients. The concern that

humankind is reentering the preantibiotics era has become very real, and the development of alternative antiinfection modalities has become one of the highest priorities of modern medicine and biotechnology[7]. Prior to the discovery and dissemination of antibiotics, it was hypothesized that administration of bacteriophage could prevent and / or treat bacterial infections. Early clinical trials of bacteriophage were not vigorous in the United States and Western Europe, but phages continued to be used in the former Soviet Union and Eastern Europe. The results of these studies were widely published in non-English (mainly Russian, Georgian, Polish) journals and were not readily available to the western scientific community. This mini-review briefly describes the history of bacteriophage discovery and early clinical trials with phage, and reviews recent literature focusing on studies in Poland and the former Soviet Union. We will also discuss why clinical use of bacteriophage is not widespread in the West and share our thoughts on the future prospects of phage therapy research[8].

Figure 2 Antibiotics Resistance

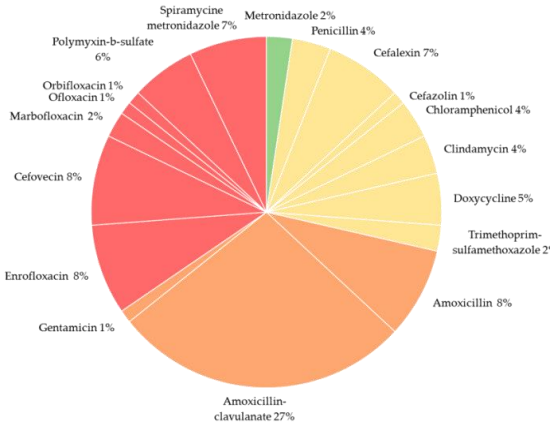

Figure 3 Most use antibiotics

The emergence of pathogenic bacterial resistant to most, if not all, currently available antimicrobial agents has become a critical problem in modern medicine, particularly because of the concomitant increase in immunosuppressed patients. The concern that humankind is reentering the preantibiotics era has become very real, and the development of alternative antiinfection modalities has become one of the highest priorities of modern medicine and biotechnology[7].

Prior to the discovery and dissemination of antibiotics, it was hypothesized that administration of bacteriophage could prevent and / or treat bacterial infections. Early clinical trials of bacteriophage were not vigorous in the United States and Western Europe, but phages continued to be used in the former Soviet Union and Eastern Europe. The results of these studies were widely published in non-English (mainly Russian, Georgian, Polish) journals and were not readily available to the western scientific community. This mini-review briefly describes the history of bacteriophage discovery and early clinical trials with phage, and reviews recent literature focusing on studies in Poland and the former Soviet Union. We will also discuss why clinical use of bacteriophage is not widespread

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 36-47

in the West and share our thoughts on the future prospects of phage therapy research[8].

How do bacteria become resistant to antibiotics?

Antibiotic resistance is not a new phenomenon. Although reported only since the 1940s, resistance has existed in nature for thousands of years. It has evolved as bacteria, fungi and parasites spontaneously produce antibacterial, ant parasitic and antifungal substances in order to survive in competition with these other species. In fact, this is how many of the antibiotics used today — for instance penicillin — were discovered. However, over the last 50 years, an increasing number of bacterial species have developed resistance to antibiotics. Moreover, genetic analysis has revealed that certain resistance genes have recently emerged as a consequence of over-use and misuse of antibiotics in medical and veterinary settings.

As the global consumption of antibiotics as well as international travel continue to rise, bacteria are mutating and exchanging their resistance genes at an unprecedented pace. Bacteria have the natural ability to multiply and change their genetic material (which we call “mutate”) very quickly, which can be seen as a survival mechanism that allows them to adapt to new environments. Every time we take antibiotics or use them in animals we create a selection pressure on resistant bacteria to survive and give them an opportunity to adapt to antibiotics[9].

Once bacteria have acquired the genetic mutations needed to survive in the presence of antibiotics (i.e. resistance to antibiotics), they spread their resistance to other bacteria through two main mechanisms called vertical or horizontal gene transfer. In fact, some bacteria can transfer resistance genes amongst one another very easily.

Resistance Mechanisms

There are mainly four different pathways of forming the antibiotics resistance.

- Impermeable barrier: the bacterial cell membrane develops an impermeable barrier which blocks antibiotics.

- Target modification: modification of components of the bacteria which are targeted by the antibiotic, meaning the antibiotic can no longer bind properly to its target in order to destroy the bacteria.

  Antibiotic modification: the cell produces substances (usually a protein called an enzyme) that inactivate the antibiotic before it can harm the bacteria.

- Efflux pump mechanism: the antibiotic is actively pumped out of the bacteria so that it cannot harm the bacteria[10]

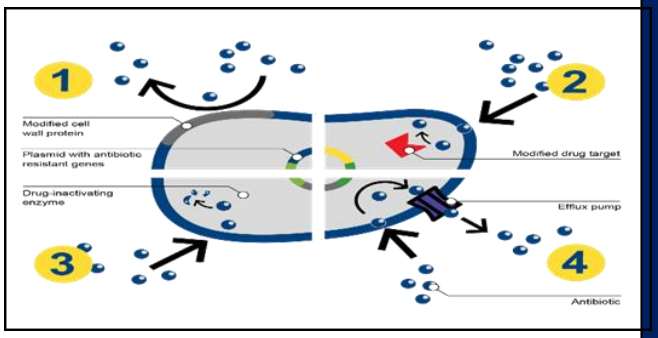

Figure 4 Resistance Mechanisms

Bacteriophages

Although found everywhere and there are so many bacteriophage types of all shapes and sizes, they are all categorized into one of the two replication methods; lytic and lysogenic. It is important to understand the differentiation of the two as that plays a crucial rule in regards to how phages may interact with

us; as one happens to always play on our side, whilst the other has its interests aligned with its survival, which may go against us.

Virulent bacteriophages Lytic cycle (cytoplasmic viral replication)

Virulent bacteriophages happen to be those that play in our interest, as well as theirs. This bacteriophage type uses the lytic cycle for replication. Lysis or lytic cycle is a cytoplasmic viral replication process in which the bacteriophage injects its genetic material into a host cell, which allows this genetic material to replica, producing many new phages. Once the host cell is filled with new bacteriophages, the host cell raptures from within, releasing the newly formed phages.

- Temperate bacteriophages Lysogenic cycle[11]

Temperate bacteriophages are the bacteriophage type that use the lysogenic cycle for replication. The lysogenic cycle is one where a phage infuses its generic material into a host, but instead of rapidly replicating, this generic material finds its way to the hosts genetic material and infuses itself with it, becoming a prophage. It becomes part of the hosts genetic material and when the host cell divides, the temperate phage genetic material also undergoes a replication process. It is important to note that the bacteriophages that are used for phage products and phage therapy are all virulent phages[12].

Bacteriophage types

Current known breakdown of bacteriophages. Since phages are still being studied and there is a lot that has not be discovered, the following information may be seen as incomplete.

- Order - Caudovirales.
- Family - Ackermannviridae, Myoviridae, Siphoviridae and Podoviridae.
- Sub family - Peduovirinae. Genera Hpuna like virus & P_2like virus.
- Sub family - Spounavirinae. Genera Spouna like virus & Twort like virus.
- Sub family - Tevenvirinae. Genera T_4virus & Schizot4virus.
- Sub family - Eucampyvirinae. Genera Cp220likevirus & Cp8unalikevirus.
- *Unassigned family*. Genera Bcep78likevirus, Bcepmu like virus, Felixouna like virus, Hapuna like virus, I3likevirus, Mu like virus, Pbuna like virus, Phicd119 like virus, Phih like virus, Phikz like virus, Puna like virus & Viuna like virus.
- Order - Ligamenvirales.
- Family- Lipothrixviridae and Rudiviridae.
- Order- Unassigned.
- Family -Ampullaviridae, Bicaudaviridae, Clavaviridae, Corticoviridae, Cystoviridae, Fuselloviridae, Globuloviridae, Guttaviridae, Inoviridae, Leviviridae, Microviridae, Plasmaviridae, Pleolipoviridae, Portogloboviridae, Sphaerolipoviridae, Spiraviridae, Tectiviridae, Tristromaviridae & Turriviridae[13].

Bacteriophage Therapy

Initial stages of phage therapy research

Bacteriophages or phages are bacterial viruses that invade bacterial cells and, in the case of lytic phages, disrupt bacterial metabolism and cause the bacterium to lyse. The history of bacteriophage discovery has been the subject of lengthy debates, including a controversy over claims for priority. Ernest Hankin, a British bacteriologist, reported in 1896 on the presence of marked antibacterial activity (against Vibrio cholerae) which he observed in the waters of the Ganges and Jumna rivers, and he suggested that an unidentified substance

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 36-47

(which passed through fine porcelain filters and was heat labile) was responsible for this phenomenon and for limiting the spread of cholera epidemics. Two years later, the Russian bacteriologist Gamaleya observed a similar phenomenon while working with Bacillus subtilis, and the observations of several other investigators are also thought to have been related to the bacteriophage phenomenon. However, none of these investigators further explored their findings until Frederick Twort, a medically trained bacteriologist from England, reintroduced the subject almost 20 years after Hankin's observation by reporting a similar phenomenon and advancing the hypothesis that it may have been due to, among other possibilities, a virus. However, for various reasons including financial difficulties, Twort did not pursue this finding, and it was another 2 years before bacteriophages were "officially" discovered by Felix d'Herelle, a French-Canadian microbiologist at the Pasteur Institute in Paris[14].

Although d'Herelle apparently first observed the bacteriophage phenomenon in 1910 while studying microbiologic means of controlling an epizootic of locusts in Mexico. Several soldiers were hospitalized, and d'Herelle was assigned to conduct an investigation of the outbreak. During these studies, he made bacterium-free filtrates of the patients' fecal samples and mixed and incubated them with Shigella strains isolated from the patients. A portion of the mixtures was inoculated into experimental animals (as part of d'Herelle's studies on developing a vaccine against bacterial dysentery), and a portion was spread on agar medium in order to observe the growth of the bacteria. It was on these agar cultures that d'Herelle observed the appearance of small, clear areas, which he initially called taches, then taches vierges, and, later, plaques. D'Herelle's findings were presented during the September 1917 meeting of the Academy of Sciences, and they were subsequently published in the meeting's proceedings. In contrast to Hankin and Twort, d'Herelle had little doubt about the nature of the phenomenon, and he proposed that it was caused by a virus capable of parasitizing bacteria. The name "bacteriophage" was also proposed by d'Herelle, who, according to his recollections, decided on this name together with his wife Marie on 18 October 1916 the day before their youngest daughter's birthday (d'Herelle apparently first isolated bacteriophages in the summer of 1916, approximately 1 year after the Maisons-Laffitte outbreak). The name was formed from bacteria and phagein (to eat or devour, in Greek), and was meant to imply that phages "eat" or devour bacteria[15].

D'Herelle, who considered himself to be the discoverer of bacteriophages, was made aware of the prior discovery of Twort but maintained that the phenomenon described by Twort was distinct from his discovery. In the meantime, in contrast to Twort, d'Herelle actively pursued studies of bacteriophages and strongly promoted the idea that phages were live viruses and not "enzymes" as many of his fellow researchers thought. The priority dispute ceased eventually, and many scientists accepted the independent discovery of bacteriophages and simply referred to it as the "Twort-d'Herelle phenomenon" and, later, the "bacteriophage phenomeno[16].

Early studies of phage therapy. Not long after his discovery, d'Herelle used phages to treat dysentery, in what was probably the first attempt to use bacteriophages therapeutically. The studies were conducted at the Hospital des Enfants-Malades in Paris in 1919 under the clinical supervision of Professor Victor-Henri Hutinel, the hospital's Chief of Pediatrics. The

phage preparation was ingested by d'Herelle, Hutinel, and several hospital interns in order to confirm its safety before administering it the next day to a 12-year-old boy with severe dysentery. The patient's symptoms ceased after a single administration of d'Herelle's antidysentery phage, and the boy fully recovered within a few days. The efficacy of the phage preparation was "confirmed" shortly afterwards, when three additional patients having bacterial dysentery and treated with one dose of the preparation started to recover within 24 h of treatment. However, the results of these studies were not immediately published and, therefore, the first reported application of phages to treat infectious diseases of humans came in 1921 from Richard Bruynoghe and Joseph Maisin, who used bacteriophages to treat staphylococcal skin disease. The bacteriophages were injected into and around surgically opened lesions, and the authors reported regression of the infections within 24 to 48 h. Several similarly promising studies followed, and encouraged by these early results, d'Herelle and others continued studies of the therapeutic use of phages (e.g., d'Herelle used various phage preparations to treat thousands of people having cholera and/or bubonic plague in India). In addition, several companies began active commerical production of phages against various bacterial pathogens[17].

Prevention and treatment of bacterial infections

The international literature contains hundreds of reports on human phage therapy, with most of the recent publications coming from researchers in Eastern Europe and the former Soviet Union, with few reports from other countries. Not. Recently, several reviews on phage therapy have been published in the English literature. Additionally, extensive information on the discovery of bacteriophages and the history of phage therapy was recently published by Yale University Press. Of course, it is impossible to summarize all these publications in this mini-review. Therefore, we focused our mini-review primarily on articles published in non-English literature that are not widely available in the international scientific community. In total, we reviewed over 100 publications on phage therapy in the Georgian, Russian, and English literature, including Ph.D. Papers and conference talks from the former Soviet Union. However, these and conference presentations (all in favor of phage therapy) are not discussed here and are primarily focused on reports published in peer-reviewed journals[18].

Some of the most important human phage therapy studies carried out in Polish newspapers in Poland and the former Soviet Union. The most extensive English-language report on human phage therapy published a series of his six articles on the efficacy of phages against infections caused by several bacterial pathogens, including multidrug-resistant mutants. He is due to Slopek et al. His seventh paper in them summarizes the results of all these studies and is discussed in detail here. His 550 patients with bacterial sepsis from 1 week of age to his 86 years of age were treated in a total of 10 departments and hospitals in 3 different cities. In 518 patients, antibiotic treatment (no information was provided on the specific antibiotics used) was reported to be ineffective, leading to the decision to use phage therapy. Pathogens in the study by Slopek et al. are staphylococci, Pseudomonas, Escherichia, Klebsiella and Salmonella, and treatment was initiated after the pathogen was isolated and a specific highly potent phage was selected from a collection of over 250 lytic phages. rice field. Phages were administered as follows. (ii) Topically by applying a wet phage-containing

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 36-47

dressing directly to the wound and/or the thoracic and abdominal cavities. (iii) applying a few drops of the phage suspension to the eyes, middle ear, or nasal mucosa; During the course of phage treatment, pathogens were continuously monitored for phage susceptibility, and when phage resistance developed, phages were replaced by other bacteriophages that lyse against newly emerging phage-resistant bacterial mutants. Treatment duration ranged from 1 to 16 weeks, and in some cases he applied phages up to 14 days after obtaining negative cultures. Success rates (marking complete recovery associated with negative cultures) ranged from 75 to 100% (92% overall) and were even higher in 518 patients in whom antibiotic therapy was ineffective (94%). . A control group not treated with phage was not included in the study[19].

In other Polish publications (Table 1), phages were used to treat neonatal encephalomyelitis, skin infections caused by Pseudomonas, Staphylococcus, Klebsiella, Proteus, and Escherichia coli. reported to be useful [20], recurrent subdiaphragmatic and subhepatic abscesses, and various chronic bacterial diseases [21]. In addition to being effective in treating long-term pyogenic infections, a recent study showed that phage therapy reduced serum levels of tumor necrosis factor-alpha (TNF-α) and blood cell cultures of TNF-α and It was found to normalize the production of interleukin-6[22].

USSR document. In 1963-1964, one of the largest, if not the largest, studies evaluating the usefulness of therapeutic phages for the prevention of infectious diseases was conducted in Tbilisi, Georgia [23]. This was about a phage against shigellosis. A total of 30,769 children (6 months to 7 years old) participated in this study. Of these, children across the street (17,044 children) were orally administered Shigella phage (once every 7 days) and children across the street (13,725) did not receive the phage. Children in both groups were administered phage and visited her once a week to monitor their overall condition. Fecal samples from all children with gastrointestinal disease were tested for the presence of Shigella spp. Tested. and other unspecified diarrhea-causing bacteria. Based on clinical diagnosis, the incidence of dysentery was 3.8 times higher in the placebo group than in the phage-treated group during the 109-day study period (6.7 and 1.76 per 1,000 children, respectively). Based on culture-confirmed cases, the incidence of dysentery was 2.6 times higher in the placebo group than in the phage-treated group (1.82 and 0.7, respectively) (Fig. 1.1). The phage efficacy index (incidence of disease per 1,000 children in the placebo group divided by the corresponding number in the phage-treated group) was highest in children aged 6 months to 1 year, and highest in children aged 5 to 7 years. It was lowest in children. An interesting finding of this study was the overall reduction in unexplained diarrhea in phage-treated children (2.3-fold) compared to children in the placebo group. This may have been observed because some cases of dysentery were not so diagnosed (but prevented with Shigella phage preparations), or phage preparations were specifically against Shigella spp. Despite being designed, it was also active against some additional gastrointestinal pathogens[24].

Phages use for therapeutics

Mode of action. Despite numerous publications on phage therapy, few reports explain the pharmacokinetics of therapeutic phage preparations. Several publications (10, 11) available on this subject show that phages can enter the bloodstream of test animals in the internal organs (liver, spleen, kidneys, etc.) within 2-4 hours. (After a single oral

administration)). In about 10 hours. In addition, data on the persistence of administered phages indicate that the phages can survive for a relatively long period of time. H. It can remain in the human body for up to a few days[23]. However, additional studies are needed to obtain rigorous pharmacological data on lytic phage, including extensive toxicological studies, before lytic phage can be used therapeutically in the West. With respect to their bactericidal activity, therapeutic phage have been hypothesized to replicate within the host cell and kill their target bacteria by lysing the host cell (ie, via a lysis cycle)[25]. However, subsequent studies have shown that not all phages replicate in the same way, and that there are important differences in the replication cycles between lytic and lysogenic phages (Fig-2). In addition, a recent description of the complete sequence of T4 phage (GenBank Accession No. AF158101) and many years of sophisticated research on the mechanism of T4 phage replication are based on a complex process in which lysis of host bacteria by lytic phage consists of: Indicates that there is. Analysis of a series of events involving multiple structural and regulatory genes (figure. (Fig-3). Since the T4 phage is a typical lytic phage, many therapeutic phages may act through a similar cascade. However, it is possible that some therapeutic phages possess some unique, as yet unidentified genes or mechanisms involved in their ability to effectively lyse their target bacteria. For example, the EIBMV author group [26] identified and cloned an anti-Salmonella phage gene that is at least partially responsible for the phage's potent lethal activity against the host strain Salmonella serovar Typhimurium. Another study [27] describes a unique mechanism to protect phage DNA from restriction-modification defenses of S. aureus host strains. Further elucidation of this and related mechanisms will likely provide useful information for the genetic engineering of optimally effective therapeutic phage preparations[28].

Replication cycles of lytic and lysogenic phages. (A) Lytic phages: step 1, attachment; step 2, injection of phage DNA into the bacterial host; step 3, shutoff of synthesis of host components, replication of phage DNA, and production of new capsids;

The genomic map of T4 phage. The full sequence of T4 phage has been determined, and several genes responsible for its lytic properties have been identified. For example, the genes encoding tail fibers (e.g., gp37) and baseplate wedges (e.g., gp12) are ...

Conclusion

In summary, bacteriophages have several characteristics that make them potentially attractive therapeutic agents. They are highly specific and very effective in lysing targeted pathogenic bacteria, safe, as underscored by their extensive clinical use in Eastern Europe and the former Soviet Union and the commercial sale of phages in the 1940s in the United States, and rapidly modifiable to combat the emergence of newly arising bacterial threats. In addition, a large number of publications, some of which are reviewed in this mini review, suggest that phages may be effective therapeutic agents in selected clinical settings. Granted, many of these studies do not meet the current rigorous standards for clinical trials and there still remain many important questions that must be addressed before lytic phages can be widely endorsed for therapeutic use. However, we think that there is a sufficient body of data and a desperate enough need to find alternative treatment modalities against rapidly emerging, antibiotic-resistant bacteria—

to warrant further studies in the field of phage therapy.

Acknowledgement: The authors are thankful to the college management for providing necessary facilities.

Conflict of interest: There is no conflict of interest

References:

1. Levin B, Bull J J. Phage therapy revisited: the population biology of a bacterial infection and its treatment with bacteriophage and antibiotics. Am Naturalist. 1996;147:881–898.
2. Bruynoghe R, Maisin J. Essais de thérapeutique au moyen du bacteriophage. C R Soc Biol. 1921; 85:1120–1121.
3. Chernomordik A B. Bacteriophages and their therapeutic-prophylactic use. Med Sestra. 1989;6:44–47.
4. Proskurov V A. Use of staphylococcal bacteriophage for therapeutic and preventive purposes. Zh Mikrobiol Epidemiol Immunobiol. 1970;2:104–107.
5. Silver L L, Bostian K A. Discovery and development of new antibiotics: the problem of antibiotic resistance. Antimicrob Agents Chemother. 1993;37:377–383.
6. Kwarcinski W, Lazarkiewicz B, Weber-Dabrowska B, Rudnicki J, Kaminski K, Sciebura M. Bacteriophage therapy in the treatment of recurrent subphrenic and subhepatic abscess with jejunal fistula after stomach resection. Pol Tyg Lek. 1994;49:535.
7. Slopek S, Kucharewicz-Krukowska A, Weber-Dabrowska B, Dabrowski M. Results of bacteriophage treatment of suppurative bacterial infections. V. Evaluation of the results obtained in children. Arch Immunol Ther Exp. 1985; 33:241–259.
8. Chopra I, Hodgson J, Metcalf B, Poste G. The search for antimicrobial agents effective against bacteria resistant to multiple antibiotics. Antimicrob Agents Chemother. 1997;41:497–503
9. Ochs H D, Buckley R H, Kobayashi R H, Kobayashi A L, Sorensen R U, Douglas S D, Hamilton B L, Hershfield M S. Antibody responses to bacteriophage phi X174 in patients with adenosine deaminase deficiency. Blood. 1992;5:1163–1171.
10. Soothill J S. Bacteriophage prevents destruction of skin grafts by Pseudomonas aeruginosa. Burns. 1994;20:209–211.
11. Lang G, Kehr P, Mathevon H, Clavert J M, Sejourne P, Pointu J. Bacteriophage therapy of septic complications of orthopaedic surgery. Rev Chir Orthop Reparatrice Appar Mot. 1979;1:33–37.
12. Kochetkova V A, Mamontov A S, Moskovtseva R L, Erastova E I, Trofimov E I, Popov M I, Dzhubalieva S K. Phagotherapy of postoperative suppurative-inflammatory complications in patients with neoplasms. Sov Med. 1989;6:23–26.
13. Kutter E, Guttman B, Carlson K. The transition from host to phage metabolism after T4 infection. In: Karam J D, editor. Molecular biology of bacteriophage T4. Washington, D.C.: American Society for Microbiology; 1994. pp. 343–346.
14. D'Herelle F. Sur un microbe invisible antagoniste des bacilles dysentériques. C R Acad Sci (Paris) 1917;165:373–375.
15. Hankin E H. L'action bactericide des eaux de la Jumna et du Gange sur le vibrion du cholera. Ann Inst Pasteur. 1896;10:511.

16. Eaton M D, Bayne-Jones S. Bacteriophage therapy. Review of the principles and results of the use of bacteriophage in the treatment of infections. JAMA. 1934;23:1769–1939.
17. D'Herelle F. The bacteriophage and its clinical applications. Springfield, Ill: Charles C Thomas; 1930.
18. Krueger A P, Scribner E J. Bacteriophage therapy. II. The bacteriophage: its nature and its therapeutic use. JAMA. 1941;19:2160–2277.
19. Kaczkowski H, Weber-Dabrowska B, Dabrowski M, Zdrojewicz Z, Cwioro F. Use of bacteriophages in the treatment of chronic bacterial diseases. Wiad Lek. 1990;43:136–141.
20. Kucharewicz-Krukowska A, Slopek S. Immunogenic effect of bacteriophage in patients subjected to phage therapy. Arch Immunol Ther Exp. 1987;5:553–561.
21. Prins J M, Deventer S J, Kuijper E J, Speelman P. Clinical relevance of antibiotic-induced endotoxin release. Antimicrob Agents Chemother. 1994;38:1211–1218.
22. Stout B F. Bacteriophage therapy. Texas State J Med. 1933;29:205–209.
23. Cislo M, Dabrowski M, Weber-Dabrowska B, Woyton A. Bacteriophage treatment of suppurative skin infections. Arch Immunol Ther Exp. 1987;2:175–183.
24. Ioseliani G D, Meladze G D, Chkhetiia N S, Mebuke M G, Kiknadze N I. Use of bacteriophage and antibiotics for prevention of acute postoperative empyema in chronic suppurative lung diseases. Grudn Khir. 1980;6:63–67.
25. Bogovazova G G, Voroshilova N N, Bondarenko V M, Gorbatkova G A, Afanas'eva E V, Kazakova T B, Smirnov V D, Mamleeva A G, Glukharev I A, Erastova E I, Krylov I A, Ovcherenko T M, Baturo A P, Yalsyk G V, Arefyeva N A. Immunobiological properties and therapeutic effectiveness of preparations from Klebsiella bacteriophages. Zh Mikrobiol Epidemiol Immunobiol. 1992;3:30–33.
26. Bordet J, Ciuca M. Remarques sur l'historique de recherches concernant la lyse microbienne transmissible. Compt Rend Soc Biol. 1921;84:745–747.
27. Carlton R M. Phage therapy: past history and future prospects. Arch Immunol Ther Exp. 1999;5:267–274.
28. Kiknadze G P, Gadua M M, Tsereteli E V, Mchedlidze L S, Birkadze T V. Efficiency of preventive treatment by phage preparations of children's hospital salmonellosis. In: Kiknadze G P, editor. Intestinal infections. Tbilisi, Georgia: Sovetskaya Meditsina; 1986. pp. 41–44

Covered in & Embase, Elsevier **Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 36-47**