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COMMENTARY

Bacteriophage Therapy: An Alternative Solution for Antibiotics

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Introduction

For the past 100 years, bacteriophage, or phage therapy, has greatly helped close the gap of resistance to antibiotics. This has been a great compliment to antibiotics and is slowly becoming an alternative to antibiotics. It was originally discovered in 1915 by Federick Twort and Felix d'Herelle in Great Britain, which started the beginning of molecular biology (1). D'Herelle coined the term bacteriophage meaning "bacteria eater" to describe the agent's bactericidal ability (2). Phage therapy goes way back to the times of World War II, when armies from Germany and Japan would practice phage therapy in their medical services to soldiers, and even today bacteriophage therapy still persists (3). Bacteriophages work by killing bacteria and create a form of therapy that regulates itself at the sites of the infection and decays once the bacteria is completely killed (4). The use of phages has been proposed since its inception as a therapy to treat acute and chronic infections with initial successes first described in the disciplines of dermatology, ophthalmology, urology, stomatology, pediatrics, otolaryngology, and surgery (3). According to the United Kingdom government's 2016 Review on Antimicrobial Resistance, an estimated 700,000 people die each year globally from resistant infections with a projected cost of $100 trillion and a death toll of 10 million by 2050 (5). Bacteriophage endolysins, enzymes that degrade the bacterial peptidoglycan (PG), have gained an increasing interest as alternative agents, due to their ability to kill antibiotic resistant pathogens efficiently when applied externally as purified proteins (6). They are ubiquitous in the environment and are recognized as the most abundant biological agent on earth. They are extremely diverse in size, morphology, and genomic organization (7). In this review, the information below will serve to explain the concept of phage therapy, from the pros and cons of phage therapy to the amount of availability that bacteriophage therapy can reach.

What is a Bacteriophage?

Bacteriophages, also referred to as phages or bacteria viruses are any type of viruses that infect bacteria. Like many viruses, phages are simple

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organisms that have a core of nucleic acid surrounded by a protein capsid. Phages are classified in a variety of virus families, which include: Inoviridae, Microviridae, Rudivirade, and Tectiviridae (8). The nucleic acid that surrounds the core consists of DNA or RNA and can be double stranded or single stranded. Bacteriophage has three basic structural forms such as an icosahedral head with a tail, and a flamentus form (see Figure 1). In the process of an infection, a phage attaches to a bacterium and inserts its genetic material into the cell. Furthermore, a phage usually follows one of two life cycles, which is either lytic (virulent) or lysogenic (temperate) bacteriophage (8). The lysogenic cycle is when the DNA is only replicated, not transformed into proteins. The lytic cycle is when a virus hijacks a host cell, uses its components to make more of the virus, and then destroys and exits the cell and continues to infect other cells bacteriophage (8).

Under certain circumstances, lysogenic phages can be induced to follow a lytic cycle. Understanding the structure of a bacteriophage allows us as researchers to make better decisions when it comes to treatment as well as understand how it reacts with the patient's body (9).

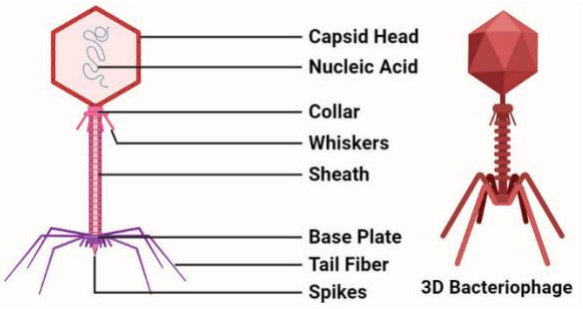

Figure 1

Why Do We Need Bacteriophages?

The need for bacteriophages, or an alternative medication for antibiotics, has been increasing, and although research on them has been going on for the past 100 years, the reliance on antibiotics has sabotaged further research on the topic (10). With the reintroduction, launched in early 2011 by Alexander Sulakvelidze, he released the new *Bacteriophage* journal where he discusses bacteriophages and how "they play a significant role in maintaining the microbial balance of the planet." From this came a new spark in the research of these phages, and a resurgence in the practical use of these medications (3). First, we need these viruses to combat bacteria because of a process known as the antibiotic treadmill or resistance treadmill. This is the process of bacteria becoming resistant to most types of antibiotics after their usage because of mutations. Strains of bacteria adapt to become resistant towards different types of antibiotics resulting in increased dosages, using multiple antibiotics, and overall, not being able to efficiently treat bacterial infections. Secondly, many of these strains have a pattern of arising in nosocomial disease, a disease that is contracted from the hospital. This means that patients who are already being treated for a disease could be contracting potentially a strain of bacteria that is highly resistant to antibiotics which causes a decrease in their chances of survival. One example of this is with a critically ill patient with a multidrug- resistant bacteria *Acinetobacter Baumannii* infection, who was also combatting COVID-19 at the time. (11) This patient essentially had a slim to none chance of survival and his condition worsened even with the antibiotics that the bacteria strain seemed susceptible to. However, through bacteriophage therapy the patient's condition improved greatly and he made a recovery (11). Therefore, because of the effectiveness of this treatment, there needs to be more access to this treatment and more rigorous clinical trials in order to get this therapy available for widespread use across Texas and The Rio Grande Valley.

The Process of Bacteriophage Therapy

As before mentioned, a large reason bacteriophage are needed is because of a process known as the resistance treadmill. Approximately 100 years ago, antibiotics became the gold standard for treating bacterial infections. However, a new crisis has occurred where bacteria have become highly resistant to multiple antibiotic treatments, and not all antibiotics react well to everyone's body (7).

Because of this we need to outpace the bacteria to solve the antibiotic resistance crisis. The rapid increase in AMRB (antimicrobial resistance bacteria) led researchers to look for alternative treatments, and currently one of the most promising ones are bacteriophages. Current research is being done on the use of phages and lytic proteins, mainly against drug resistant bacterial infections, and potentially as an alternative for antibiotic treatments (14). The reason bacteriophages are more efficient than antibiotics is because super bacteria have yet to become resistant to bacteriophages. There are also many more advantages to bacteriophages over antibiotics, such as the high therapeutic index and having fewer side effects, and their specialty and other safety for the host organism, including the intestinal microbiota (14).

To put it simply, bacteriophages are the predators for bacteria. While this seems very broad, that is what they do. Whether it is a urinary tract infection, or a strain of *E. Coli*, phage therapy has been proven to effectively treat these infections with no major side effects reported (12). Although there are yet to be more rigorous clinical trials on the treatment, there are many benefits to be considered. There are different routes of administration depending on the area of infection on the human body. One option is oral treatment that can be given three times a day. This is done by first neutralizing the gastric acid so the phages can thrive and spread, achieved by giving the patient sodium bicarbonate or bicarbonate mineral water (baking soda) (12). The second way it is administered is locally by applying a moist bandage with the phages onto an open wound to allow the phages to enter the body (12). It can also be administered using drops on the eyes, or in the mucous membrane, through intravenous drip, or by nebulization (12). The goal of all of these methods is to allow the phages to enter the body without being destroyed by our body's defenses, stomach acid, the skin, and our eyelashes/ nose hairs (12). By doing this the phages are allowed to safely enter the body and kill the strains of bacteria causing the infection. Once inside the body, the bacteriophages work through a process named lysis. The virus infiltrates the bacteria's cell membrane by injecting its own DNA and RNA. It then creates up to 1,000 copies of itself and causes the bacteria to lyse or burst (1). Then, once the bacteria is gone it will stop multiplying and remain dormant until more bacteria enters the body. Furthermore, the phages will not attack human cells because they have high specificity, meaning they only attack the bacteria (13). The therapy lasts about 1-16 weeks and is highly effective.

Overall, the process of bacteriophage therapy is very simple and takes a short time period with mild side effects reported.

Advantages on Bacteriophage Therapy

The use of bacteriophages as antimicrobial agents is one possible replacement option for antibiotics (15). Lytic Bacteriophages are able to kill antibiotic-resistant bacteria at the end of the phage infection cycle. Thus, the development of phage therapy is potentially a way to improve the treatment of bacterial infections (16). While not common in South Texas, but talked about for future resources, phage therapy is an important alternative to antibiotics in the current era of drug-resistant pathogens. Another reason this type of therapy is beneficial is because these phages cannot infect human cells (17). Phage therapy is a natural and secure form of antibiotics working to treat infections and to use the bacteria to replicate themselves which results in a cycle of killing bacteria while also producing more copies to keep destroying. Because of these bactericidal agents, bacteria get infected and do not regain their viability, meaning once it is killed it remains dead whilst other antibiotics are bacteriostatic, meaning they only stop the growth of bacteria contributing further to its resistance. Another advantage is the auto "dosing" factor of bacteriophages, it has been proven to reproduce in areas where the host is located making them even more effective in curing an infection (17). Some other advantages include non-toxicity, phages are made of proteins and nucleic acids that are nontoxic (something a lot of antibiotics cannot claim), and although they can cause harmful responses from the immune system, they can be prevented by using purified phage preparations to prevent anaphylactic reactions (the immune system releases a flood of chemicals resulting in the body going into shock) (17). Minimal shock to normal flora, unlike most antibiotics that are broad spectrum, bacteriophages do not harm the microbiome that is found inside of our bodies whilst antibiotics tend to harm or kill the "good" bacteria within us that maintain balance. Lack of cross resistance, since super bacteria only have resistance mechanisms made for antibiotics, the difference of the attack system of phages allows the phages to kill these types of bacteria more effectively, (think of it as a surprise attack). Bacteriophage may have single dose potential, because of their auto-dosing, there is potential for the phages to be applied only once and allow them to multiply and kill. Although culturing the bacteria can be expensive for testing, phage purification prices are declining due to improvements in the technology and compared to prices of pharmaceuticals is relatively low (17).

Disadvantages of Bacteriophage Therapy

Concerns about using phages as antibacterial agents can be distinguished into four categories: (1) phage selection, (2) phage host-range limitations, (3) the "uniqueness" of phages as pharmaceuticals, and (4) unfamiliarity with phages (17). When dealing with bacteriophage therapy, one of the most common disadvantages is that researchers must choose one specific phage and weigh whether the benefits of phage therapy outweigh the risks. Each bacteriophage is unique in its own way which could be a disadvantage because it is harder to have concrete research on each of them. The most common and also biggest disadvantage is the limited knowledge about the effectiveness of phage therapy. Having limited

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information makes it harder to do research and have a positive outcome when it comes to experimenting with phages, and phage therapy. And even though it is classified as GRAS (Generally Regarded as Safe) by the FDA, the general public regards these phages as equivalent to an antigen (an organism that causes disease) instead of as a cure. However, so far people have not been resistant to this treatment because it is known as a "phage" rather than a virus. Some other disadvantages to consider, these are live organisms that can trigger the human immune system to respond and can carry endotoxins, which are normally cleared in the phage preparation stage. There is also a narrow host range, or only a small range of bacteria can be targeted by phages, however this can be solved by mixing phages (otherwise known as phage cocktails) and can create a broader spectrum for this therapy (17).

Availability of Bacteriophage Therapy

Recent studies of bacteriophage therapy have been successful, which helps increase the probability of the therapy to become more common in all regions. As phage therapy is considered safe, this leads to possible use in the future for patients who have drug resistant infections. One reason why phage therapy hasn't been approved yet is because antibiotics prescribed are more available to the public and are considered to be safer by the FDA. Currently there is ongoing research on the best way to use phages and phage therapy on pathogens, and how to make it more available to the public in the near future. Since phage therapy has not been approved in the US or Europe, there have only been rare cases where it was used. Our hope is that more research and more trials can be done on this topic to make the treatment more available to the public.

One such study was performed at DHR Health in 2021 (11). While not commonly heard of in the Rio Grande Valley, there have been a few exceptional cases in which bacteriophage therapy was used experimentally. Currently, there is not a standard of care regimen for phage therapy as it is still in the experimental phase. Some research indicates about 1-16 weeks for the therapy, and because of auto-dosing, a single dose can be effective enough to treat the whole infection (13, 17). Phages are currently undergoing study and experimental use for future and safer use on humans.

Target Age Groups

When working with bacteriophage therapy target age groups are not specified. It has been experimented on people of all different ages who have the issue of not being able to intake antibiotics. Any person who is not able to utilize antibiotics because they have no function on them are considered for this experimental phase. They are known to be used for people of all ages above five to fight off multidrug resistant bacteria (18).

Conclusion

This treatment would benefit RGV patients in several ways. One reason is that using bacteriophage therapy has no major side effects. Secondly, it can be administered in several ways such as eye drops, in the mucous membrane, applied locally to an open wound, can be given intravenously or even through nebulization. Antibiotics can be replaced with the use of bacteriophages as antimicrobial agents. Using a bacteriophage is a way to end the infection cycle, and as mentioned earlier, it is a safer method to eliminate drug resistant pathogens. Bacteriophages, being a natural bacteria predator, have become a greatly used alternative or even a supplement to reduce the need for antibiotics because bacteria can develop resistance to conventional antibiotics.

In general, it can be said that phage therapy, long overshadowed by chemical antibiotics, is gathering renewed interest in western medicine. This stems from the rise in frequency of multidrug-resistant bacterial infections in humans (19). According to Lin et al., "The available literature on the use of phages and phage-derived proteins for combating bacterial infections, specifically those of multidrug-resistant bacteria, increasingly shows promise for the prospect of phage therapy as either an alternative or a supplement to antibiotics" (5). Bacteriophage therapy is an opportunity to help cure patients in the RGV with multi-drug resistant infections.

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