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Controversy in Virology: Bacteriophage Therapy versus Antibiotics

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Since their emergence into conventional medicine, antibiotics have dominated as remedies for bacterial infections. Doctors prescribe an antibiotic or combinations of them to treat diseases from tuberculosis to botulism, often with outstanding results. Because of their widespread use and pervasiveness in society, a new problem has arisen: antibiotic resistance. Antibiotic resistance has become a grave medical problem throughout the world because bacteria have the ability to adapt and evolve to changing environmental conditions (Lorch, 1999). The growing resistance of bacteria to antimicrobial agents threatens to make the revolutionary achievements of modern medicine obsolete, posing a concern of re-entering the "preantibiotics" era. The development of alternative anti-infection methods is paramount in both modern medicine and biotechnology (Morris, Sulakvelidze, Alavidze, 2001). A promising alternative approach uses bacteriophages to cure bacterial diseases and infections. Bacteriophage therapy has many advantages that may make it the new standard treatment.

Antibiotics are generally substances derived from microorganisms, but chemically derived synthetic antibiotics have also been produced. Antibiotics control the growth of or kill bacteria cells. Sir Alexander Fleming set the stage for modern antibiotics with his discovery in 1928 of the lysozyme and arguably the most famous antibiotic substance, penicillin. When it was first discovered, penicillin was a very effective agent in the treatment of syphilis, gangrene, and tuberculosis (Hani, 2010). Penicillin is a bactericidal antibiotic, meaning it kills bacteria by interfering with the bacterium's cell wall or its other organelles. Since the bacteria are killed, they can no longer attack the body, preventing any further damage.

There are two categories of antibiotics, bactericidal and bacteriostatic. Bactericidal antibiotics are typically administered when the host's immune defenses are especially low and actually kill bacteria directly. Bacteriotstatic antibiotics, on the other hand, stop bacteria from multiplying by disrupting the cell's protein production, DNA replication, or other parts of bacterial cellular metabolism. Bacteriostatic antibiotics give time for the immune system to create its own means of defense by preventing nutrients from reaching the bacteria and hampering the proliferation of cells (Fisher, 2012). Because human cells and bacterial cells are very different, particularly in their cell walls, antibiotics are only activated and attracted by the components on bacteria cell walls. Furthermore, antibiotics are only effective on living cells, which is why they are useless against other invading microbes like viruses (Marshall, 2001).

Despite all the great advancements and successes with antibiotics, they do have drawbacks. Although they are a powerful weapon against bacterial infections and disease, side effects can often occur in subjected patients. For example, stomach discomfort, loose stools, and nausea are just a few common side effects in children. In addition, allergies to penicillin and other antibiotics can also occur, causing symptoms like breathing problems and skin rashes (Fisher, 2010).

Antibiotics can also kill the normal, useful bacteria found throughout the human body. This healthy bacterium is beneficial for processes like detoxification, or the elimination of undesired wastes, and the cleansing of the blood and liver. Furthermore, antibiotics do not always effectively concentrate at the site of an infection and are readily metabolized and eliminated from the body. They are also quite complicated to produce, due to their complex

nature. The research and production of a new antibiotic is very time consuming and can take several years (Morris, Sulakvelidze, Alavidze, 2001).

Despite some drawbacks, the main problem and disadvantage of antibiotic use is the evolution of resistant bacteria. Antibiotics become ineffective over time because bacteria reproduce so quickly that the probability of a resistant mutation is very high (Marshall 2001). Bacterial resistance is aided by both the overuse and insufficiency of antibiotic doses. When overused, antibiotics are very prevalent in communities and therefore have a greater opportunity to develop a resistant mutation. Insufficient dosage can leave surviving bacteria cells which have been exposed to a specific antibiotic and can then develop resistance. Antibiotics may kill millions of bacteria cells, but if just one has a resistant mutation, it can reproduce and spread quickly. Bacteria are developing widespread resistance to a plethora of antibiotics in industrialized countries. Antje Lorch, a writer for *Biotechnology and Development Monitor,* explains, "without the protection against bacterial infections, for instance, large- scale operations and treatments that weaken the patient's immune system, such as chemotherapy or organ transplantation, would not be possible"(1999).

A study done by a group of researchers investigated the prevalence of resistant bacteria to antibiotics in India, Pakistan, and the United Kingdom. Bacteria isolates were studied from two major cities in India and multiple cities in the United Kingdom and Pakistan. The antibiotic susceptibilities were assessed using polymerase chain reaction, or PCR, which is a technology that generates millions of copies of a particular DNA sequence. This DNA was further analyzed using gel electrophoresis (Kumarasamv, Toleman, et al. 2010). The researchers found multiple cases of antibiotic resistance among *Escgerichia coli* and *Klebsiella pneumonia* bacteria. These bacteria were highly resistant to all antibiotics except tigecycline and colistin. In the United Kingdom alone, resistant isolates increased slightly in both 2008 and 2009. All of this evidence proves that antibiotic resistant bacteria are a worldwide health concern (Kumarasamv, Toleman, et al. 2010).

Another study conducted by a group of doctors researched the prevalence of antimicrobial resistance among uropathogens. The results of the study were shocking; "the data demonstrated a significant increase in the prevalence of resistance to several commonly used antimicrobial agents among a large group of isolates from women with well- defined episodes of acute uncomplicated cystitis"(Kalpana, et al. 1999). Clearly, these results are worrisome and further exemplify the need for an alternative treatment of ailments caused by bacteria.

Bacteriophages are viruses specialized to infect bacteria cells and are among the most abundant entities on earth. Their genetic material is in the form of DNA or RNA covered by a protein coat. The capsid, where the genetic material is stored, is attached to a tail that has fibers. Theses fibers respond to specific receptors on the surface of bacteria and attach themselves to the cell's surface.

Phages infect and propagate in two possible ways, a lytic life cycle and a lysogenic life cycle. Both cycles make use of the host's DNA machinery. The lytic life cycle occurs when phages kill their hosts by replicating separately from the host's genetic information. The lysogenic life cycle, on the other hand, is generally associated with temperate phages that can grow vegetatively and can integrate their genetic material into host chromosomes. Replication of the genome is carried out within the host for many generations and eventually an environmental stimulus causes the phage progeny to lyse out of the bacteria (Haq, et al 2012).

Felix d'Herelle, a French-Canadian microbiologist at the Institut Pasteur in Paris, is lauded for officially discovering bacteriophages in 1917. D'Herelle was assigned to conduct

research on the severe hemorrhagic dysentery that plagued many French soldiers. He made bacteria free filtrates of stool samples collected from the soldiers and incubated them with *Shigella* strains (a bacterium found in the intestines known for causing dysentery), also taken from the soldiers. D'Herrele spread the filtrates on agar plates and noticed small clear spots or plaques. He concluded that these areas where produced by viruses capable of parasitizing bacteria (Morris, Sulakvelidze, Alavidze, 2001). Research into the promising medicinal applications of bacteriophages may one day make d'Herrelle as commonly well known as Fleming.

By their very nature bacteriophages appear to be great alternatives for treating bacterial infections and diseases. Phages are highly specific to their bacterial counterparts, therefore a microbial imbalance in the body or secondary infections do not occur (Summers, 2001). Conversely to antibiotics, phages replicate exponentially as long as the specified bacteria is still abundant. They concentrate at the site of infection, which may require less frequent administration by a doctor as compared to antibiotic substances. As a particular bacteria population dwindles, the specified phages do as well and are eliminated from the patient.

Furthermore, no serious side-effects have been noted with phage therapy. Minor ones may occur due to the release of endotoxins in bacteria when lysed by phages (Morris, Sulakvelidze, Alavidze, 2001). Bacteria also have a limited resistance to phages. Since bacteria are constantly evolving they will invariably develop resistance to phages, however, bacteriophages have a higher mutation and adaptation rate that outcompetes that of bacteria, limiting their evolved resistance. Additionally, bacteria that have developed resistance to one or a number of phages are still susceptible to other phages with a similar target range (Lorch, 1999).

Doctors and researchers are also able to select new phages in a relatively rapid process in a matter of days or weeks whereas the development of new antibiotics is rather time consuming and can take several years (Morris, Sulakvelidze, Alavidze, 2001). Phages are also flexible; their genetic material can be modified to accommodate specific bacteria. Likewise, individual mechanisms of phages can also be used as antibiotics. For example, antibodies capable of causing the destruction of bacteria, also known as lysins, are a component of bacteriophages that can be incorporated in antibiotic substances (Hausler, 2007).

Like antibiotics, phage therapy also has its drawbacks. Despite being known for nearly a century, there is no credible evidence that proves the effectiveness of phage therapy in humans. The literature and research on phages until recently has been silent on the therapeutic applications of bacteriophages (Summers, 2001). Along with being an advantage, the tremendous specificity of phages can be burdensome when the exact species of bacteria is unknown or if there are multiple infections.

In addition, phages are larger than the chemical molecules of antibiotics and therefore the sites in the body that can be affected by phage must be specified. For this reason, it appears that phage therapy is most effective in treating wounds or other easily accessible sites of infection. Subsequently, infections whose agents are on the interior of human cells may also be inaccessible to phages (Hausler, 2007). Some phage that are injected directly into the bloodstream can be excreted because they are immediately recognized by the immune system and antibodies may be produced as an immune response. Phage are also more difficult to administer than antibiotics. Proper administration requires a physician with special training in order to prescribe and use phage therapy (Hausler, 2007).

Considering the evidence for both sides of the issue, bacteriophage therapy has the potential to effectively replace the use of all antibiotics. The impending crisis of antibiotic

resistant bacteria will undoubtedly lead to use of new treatment of bacterial diseases and infections. Bacteriophages are currently the most promising of any alternatives to antibiotics.

Bacteriophages are capable of killing bacteria as effectively as antibiotics and are far more flexible in their capabilities. The customization and versatility of phages allows them to be modified and specifically designed for individual cases. Bacteriophages are a useful threat to bacteria because they are both specific and modifiable. Another beneficial attribute of phage therapy is the limited side effects. Antibiotics can have fairly hazardous side effects, but phage therapy seems to be innocuous from a clinical standpoint.

Overall, bacteriophage therapy is a necessary alternative in the antibiotic-dominated world in which we live. With further research and experimentation, there is much confidence that bacteriophage therapy will one day be as effective and mainstream as popular antibiotics. For an entity that outnumbers all forms of life, it is certainly time to acknowledge the potentially rewarding future of bacteriophage therapy.

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