Abstract

Have you ever heard of bacteriophages? They are tiny viruses that can infect and kill bacteria, including the harmful bacteria that make us sick! Scientists discovered bacteriophages (phages) over a century ago. And they are actually all around us! Researchers have found phages in sewage, soil, and even in our bodies. What if we used this natural enemy of bacteria to our advantage? Can phages protect us against bacterial diseases? Researchers have used phage to treat disease in the past. But were they successful? We reviewed clinical reports of phage therapy for the last 15 years. Our research showed that phages can be quite helpful and phage therapy was successful against bacterial infections. This is really important, because antibiotic resistance has become a major threat to our health.

Introduction

Did you know that some experimental treatments against dangerous bacterial infections come from soil or sewage water? There are viruses, called bacteriophages, or phages, that “hunt” and kill bacteria (Figure 1). Once the phage gets inside the bacterial cell, it takes over and forces it to make more viruses, and then finally kills the bacteria (see Figure 2 on the next page). This includes the bacteria that make people sick!

For many years doctors overlooked phage therapy since antibiotics were so effective. Another microbiologist, Alexander Fleming, discovered the first antibiotic (penicillin) in 1928. Since then, scientists have discovered and produced many more types of antibiotics to cure illnesses like pneumonia, tuberculosis, and meningitis. Sadly, because of evolution, some bacteria have learned to resist antibiotics so they don’t work as well. Nowadays, antibiotic-resistant bacteria are a huge threat. Some pathogens have even become resistant to multiple antibiotics! This makes it more and more difficult for doctors to prescribe the right medication.

A microbiologist named Félix d’Hérelle, along with other scientists, discovered phages in the early 20th century.
And the good news is phages are everywhere! Scientists have found them in sewage water, rivers, soil – wherever there are bacteria. Then they purify (clean) the phages in the lab so there are no other substances. After that, scientists replicate (multiply) the phages on bacterial cells and purify them once again. Then these tiny viruses are ready to treat dangerous bacterial infections!

So now scientists and physicians are once again looking at phage therapy. Can viruses actually come to the rescue? Does this therapy help people? Are there any problems with it? These are the questions we wanted to answer.

Methods

We looked through case reports and research articles published between 2005 and 2020 about phage therapy. Here’s what we wanted to know:

- Did the patient’s health improve? We call this a “clinical outcome.”
- What bacteria did the researchers want to target?
- How were the phages given to patients? Did the patients receive an injection?
- Were there any side effects?
- Did the bacteria develop resistance against the phages?
- Did the researchers use both phage therapy and antibiotic therapy?

There were some aspects of phage therapy that we wanted to understand better:

- How to choose the right phage or mix of phages.
- How to administer it – where, how often, and how much.
Results

Phage therapy shows promising results. In many of the cases we reviewed, phages helped the patients without the bacteria becoming resistant to the phages. Moreover, phage therapy has helped not only humans, but also pets! A 5-year-old St. Bernard dog received phages to treat a bad ear infection. Only 27 hours later the ear condition improved, leading to the dog’s full recovery in a few months.

However, in most cases, we found that doctors used a combination of phages and antibiotics. This made it harder to figure out if the phages alone were helpful.

A big advantage of phages is that they do very well against bacterial biofilms, something antibiotics don’t fight well against. Furthermore, they work well against a variety of bacteria! (Figure 3)

Unfortunately, in several cases, there were negative side effects. Some side effects (like stomach ache or toothache) were mild. Others (like serious allergic reactions) were life-threatening.

Based on the data we reviewed, choosing the right phages can be difficult. For example, if the phages infect a wide range of bacteria, there is a risk they can change a patient’s microbiome. It can also be hard for doctors to decide how many phages a person needs since phages are not chemicals like antibiotics. They replicate (reproduce) in the cells by themselves.

1. **Eye** - Successful against one species of bacteria.
2. **Ear** - Successful against one species of bacteria.
3. **Nose** - Successful against one species of bacteria.
4. **Heart** - Successful against four species of bacteria.
5. **The entire body** - Successful against two species of bacteria.
6. **Gut** - Successful against one species of bacteria. Unsuccessful against one species of bacteria.
7. **Prostate** - Successful against one species of bacteria.
8. **Skin** - Successful against two species of bacteria. Unsuccessful against two species of bacteria.
10. **Bone** - Successful against seven species of bacteria.
11. **Urinary tract** - Successful against six species of bacteria.
12. **Lungs** - Successful against six species of bacteria.

**Figure 3:**
Summary of phage therapy against different infections of the body. Was it successful or not?

Image: Roach Lab, SDSU
Discussion

Antibiotic resistance is a serious problem. Eventually, we may run out of reliable antibiotics, so it’s very important to find an alternative. Phages – a natural enemy of bacteria – are an excellent option. The data we reviewed proved they can be very beneficial. A combination of antibiotic and phage therapy showed the most promising results. These treatments used together seem to help each other, because:

1. Sometimes the drugs help the phages to replicate faster.
2. Phages can sometimes affect bacterial resistance, making the bacteria respond better to the medicine.

Still, there are several things to consider. Phage resistance is also a problem. Out of 12 phage therapy clinical studies, phage resistance happened in 7 cases. But it’s important to note that most of the researchers in other cases didn’t test for phage resistance. This is most likely because the therapy was successful. Side effects can be not only unpleasant, but life-threatening. More clinical trials are necessary to determine the best formulas and methods to apply phage therapy. And hopefully, we can develop another shield against infectious diseases.

Conclusion

One reason for antibiotic-resistant bacteria is the incorrect use of antibiotics. This is why it’s very important to take your drugs exactly as your doctor has prescribed. Don’t stop taking them early, even if you feel better! The very best prevention though is to avoid infection:

- Wash your hands regularly with soap.
- Prepare your food with care.
- Check your vaccination calendar regularly and make sure you are up to date.

Glossary of Key Terms

**Antibiotic** – a type of medicine that will search out and destroy bacteria that make people sick.

**Antibiotic resistance** – this happens when bacteria change and cannot be killed by antibiotics. Bacteria (not humans or animals) become antibiotic-resistant.

**Bacteriophages (phages)** – viruses that infect bacteria. Usually, after they enter the bacterial cell, the cell creates more viruses and dies.

**Biofilm** – a group of bacteria (or other microorganisms) that stick to the surface of a cell. These sticky cells create a slimy layer of protection against things like antibiotics.

**Dysentery** – a bacterial infection of the intestines, causes diarrhea and blood in the stool (poop).

**Microbiome** – the collection of microorganisms that live on us. They live on the skin, in the saliva and mouth, in the eyes, and in the gut and the rest of the gastrointestinal tract. These microorganisms can either be helpful, neutral or harmful.

**Pathogen** – a virus, fungus, bacteria or other microorganism that can cause disease. For example, HIV is the virus that causes AIDS.

**Phage therapy** – using phages to treat bacterial infections.

**Replication (viral)** – the creation of new viruses during infection.

**Acknowledgment:** This article’s adaptation was supported by the US Embassy in Bulgaria.
Check your understanding

1. What is antibiotic resistance and why is it a problem?

2. What are some similarities and differences between antibiotic therapy and phage therapy?

3. If you get COVID-19, do you think your doctor will prescribe antibiotics?

4. Can you think of a situation where phages might be harmful?

REFERENCES


UC San Diego School of Medicine: Center for Innovative Phage Applications and Therapeutics http://ipath.ucsd.edu/


NPR: Can A 100-Year-Old Treatment Help Save Us From Superbugs? https://www.npr.org/transcripts/796743684