Investigating the Effectiveness of Bacteriophage therapy on antibiotic resistant bacterial infections

Abstract

In recent years, antibiotic resistant pathogens have been labeled as a paramount threat to public health and safety. As a result, alternative antimicrobials such as bacteriophages have gained attention. Bacteriophages are bacteria-specific viruses that infect and destroy their host bacteria. This study investigates bacteriophage therapy and its effectiveness in treating drug-resistant bacterial infections. The objective of this study is to determine whether bacteriophages are effective in the inhibition of bacterial infections. Data was collected through meta-analysis Data was collected in tables and phage treatment groups were compared to untreated control groups using a risk difference analysis. Data obtained indicated that the use of bacteriophage therapy results in greater bacterial inhibition of drug-resistant bacterial infections compared to untreated groups. Bacteriophage therapy was on average 90.6% more effective at treating resistant S. aureus infections ($p<0.001$) and 60.3% more effective at treating resistant E. coli infections ($p<0.001$) than untreated control groups using a fixed effects model. During a time of growing antibiotic resistance, bacteriophage therapy is a promising alternative antimicrobial option.

Introduction

On September 21, 2016, the United Nations General Assembly convened to discuss the problem of antibiotic resistance and deemed it "the greatest and most urgent global risk". Antibiotic resistant bacteria are a major problem in today's medical field. The Center for Disease Control (CDC) estimate antibiotic-resistant infections result in 2 million illnesses and at least 23,000 deaths a year; deaths from complications by antibiotic resistant infections cost the United States $55 billion annually. This created interest into alternative antimicrobials, notably bacteriophage therapy. Bacteriophage therapy involves using bacteriophages, which are viruses that target specific species types of bacteria and cause lysis of the cell membrane. Due to the epidemic of antibiotic resistant bacteria, there is a rekindled interest in bacteriophage therapy. Bacteriophages have several advantages over conventional antibiotics, including host-specificity, minimal disruption of local flora, low toxicity, and a lack of cross-resistance to antibiotics. The goal of this study is to determine the effectiveness of administering specific bacteriophages in the treatment of antibiotic resistant bacterial infections.

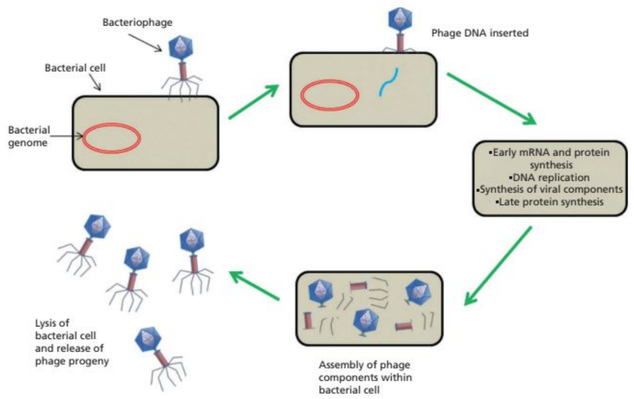

Figure 1. Label in 16pt Calibri.

Methods and Materials

Research was conducted through meta-analysis. Data was obtained from other researchers' published peer-reviewed articles. Literature related to bacteriophage therapy through databases such as EBSCOhost, California State University of Channel Islands' library databases, PLOS Journal, Google Scholar, ScienceDirect, ResearchGate, American Society for Microbiology, and National Center for Biotechnology Information (NCBI). Studies were included in the meta-analysis if they involved the treatment of antibiotic-resistant bacteria using specific phages. Studies were narrowed down into two categories based on the host bacteria: *S. aureus* and *E. coli.* Data collection included the animal infected with the host bacteria, infection type, initial bacterial concentration measured in colony forming units (CFU), initial phage concentration used in treatment measured in plaque forming units (PFU), phage type, and bacterial inhibition. For each experiment, the data from the corresponding control group was collected. Control groups were administered equal concentration of CFU but did not receive phage treatment. Bacterial inhibition of treated animals was compared between phage treatment groups and control groups using a risk difference analysis.

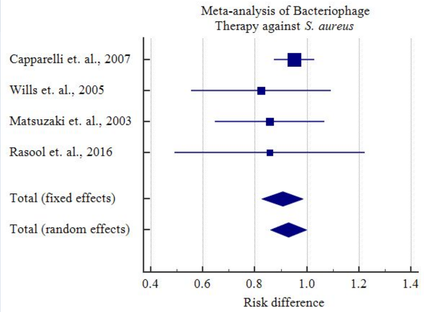

Figure 2: Risk difference analysis for data collected on *S. aureus* infections. Risk difference using a fixed effects model was 0.906 ($p<0.001$), while risk difference using a random effects model was 0.929 ($p<0.001$).

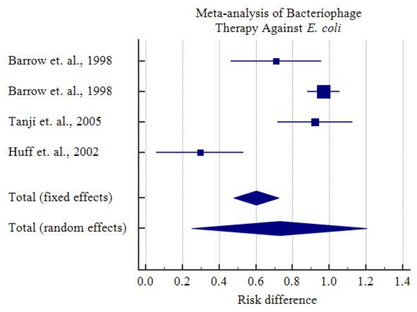

Figure 3: Risk difference analysis for data collected on *E. coli* infections. Risk difference using a fixed effects model was 0.603 ($p<0.001$) while risk difference using a random effects model was 0.728 ($p=0.003$).

Results

The potential efficacy of specific phages to inhibit drug-resistant strains of S. aureus was evaluated by analyzing survival rates of infected animals that were administered phage treatment. Four trials of phage therapy were analyzed. Bacterial inhibition was much higher for groups that received phage treatment. The average bacterial inhibition of the phage therapy trials was 96.07%, while the average bacterial inhibition of the control groups was 0.019%.

Four trials concerning antibiotic resistant strains of E. coli were also analyzed to determine the efficacy of phage therapy. Two trials of phage therapy were taken from Barrow et al., one from Tanji et al., and one from Huff et al. The average bacterial inhibition of phage treatment was 83.3%, while the average bacterial inhibition of the control groups was 21.2%.

Table 1. Average Bacterial Inhibition of treated and control groups for *S. aureus* and *E. coli* infections

	Phage Treated *S. aureus*	*S. aureus* control group	Phage Treated *E. coli*	*E. coli* control group
Average Bacterial Inhibition (%)	96.07	0.019	83.3	21.2

Discussion

The present study shows the effectiveness of bacteriophage therapy in treating antibiotic resistant *S. aureus* infections and *E. coli* infections. Review of four trials indicates that the average bacterial inhibition of *S. aureus* was 96.07%, compared to the control group inhibition of 0.019%. According to the risk difference analysis, phage therapy was 90.6% more effective at treating drug resistant *S. aureus* infections when compared to untreated control groups in a fixed effects model ($p<0.001$) and 92.9% more effective using a random effects model ($p<0.001$). The average bacterial inhibition of drug resistant E. coli was 83.3%, compared to the control group with an average bacterial inhibition of 21.2%. According to the risk difference analysis, the application of E. coli specific phages was 60.03% more effective at treating antibiotic resistant strains of E. coli when compared to untreated control groups using a fixed effects model ($p<0.001$), and 72.8% more effective using a random effects model ($p=0.003$). Therefore, it can be concluded that phage therapy is effective in treating antibiotic resistant *S. aureus* and *E. coli* infections.

Conclusions

Phages have several advantages over conventional antibiotics, including host-specificity, concentration at the site of infection, low toxicity, and a lack of cross-resistance with antibiotics. Phage therapy has large room for improvement through the isolation and amplification of new lytic phages and development of phage encapsulation to improve delivery methods. The development of phage preparations may prove to be one of the most potent methods of treating bacterial infections in both animals and humans in the future.

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