Comparison of Antibiotic and Bacteriophage Therapies in *Pseudomonas aeruginosa* Infections in Cystic Fibrosis Patients

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Abstract

Cystic fibrosis (CF) is a genetic disorder that causes abnormally thick secretions. CF patients tend to be overwhelmed with chronic pulmonary infections that lead to lung damage. Pulmonary damage due to bacterial infections, most commonly *Pseudomonas aeruginosa*, is the leading cause of death for CF patients. Current treatments for these infections are antibiotics, but due to growing antibacterial resistance, new alternatives are being investigated. This research analyzes whether bacteriophage therapy compares to antibiotic therapy in eradicating *Pseudomonas aeruginosa* infections and improving health outcomes in cystic fibrosis patients. Research consisted of peer reviewed research articles, case studies of patients, clinical trials, review articles, and articles by professional organizations and was compiled to create a comprehensive look at *Pseudomonas aeruginosa* infections and treatments for CF patients. The ELITE clinical trial (Ratjen et al., 2009) was designed to investigate the optimal therapeutic drug regimen, 28 days and 56 days, for the eradication of *P. aeruginosa* infections of tobramycin inhaled solution (TIS) and to keep the patient clear of this pathogen for as long as possible. The clinical case study by Law et al. (2019) evaluated the efficacy of bacteriophages in combination with antibiotics to clear an multi-drug resistant *P. aeruginosa* infection. Antibiotics are an effective treatment as long as the patient does not have a resistant isolate of the pathogen. In the case of clinical resistance, bacteriophages would pose a good alternative for treatment, especially in combination with antibiotics.

Introduction

The current recommended treatment for pulmonary infections with *Pseudomonas aeruginosa* are rigorous antibiotics, but do not include prophylaxis. Prophylactic antibiotic treatment is not recommended to prevent the initial colonization of *P. aeruginosa*, as it did not reduce the risk of *P. aeruginosa* infections in pediatric populations (Doring et al., 2012). The goal of antibiotics after the initial or early infection of the pathogen is to eradicate the infection and keep the patient's respiratory tract free of the pathogen for as long as possible. The delivery systems for antibiotics are oral, intravenous, and inhaled (Cystic Fibrosis Foundation, n.d.), including penicillins, cephalosporins, aminoglycosides, macrolides, quinolones, carbapenems, aztreonam, and colistimethate. Most patients will receive inhaled or oral antibiotics with the addition of intravenous antibiotics. Antibiotic resistance has become a major problem in the healthcare industry. This can provide many issues when it comes to treating CF patients with pulmonary infections, especially chronic infections. CF patients potentially will be on an antibiotic regimen for most of their life, which can lead to antibiotic resistance. This resistance has led to a growing need for alternative treatments to infections. One alternative is bacteriophage therapy, which is a treatment that utilizes viruses that only infect and kill specific bacterial species. Advantages of this treatment is that they leave human cells alone and do not infect normal flora required for a healthy microbiome. Bacteriophages have the potential to become a potent and effective treatment to *P. aeruginosa* infections in cystic fibrosis patients. The question is whether bacteriophage therapy compares to antibiotic therapy in eradicating *Pseudomonas aeruginosa* infections and improving health outcomes in cystic fibrosis patients.

Methods

The research was compiled to create a comprehensive look at *Pseudomonas aeruginosa* infections and treatments for cystic fibrosis patients. The review consisted of peer reviewed research articles, case studies of patients, clinical trials, review articles, and articles by professional organizations. These were used to understand the relevance of the problem and current and past treatments for *Pseudomonas aeruginosa* infections in cystic fibrosis patients. The case studies and clinical trial articles of bacteriophage therapy and antibiotics were used to compare these two approaches of treatments for *Pseudomonas aeruginosa* infections. Research articles were included based off reliability of source, production year, and usefulness of the information.

Results

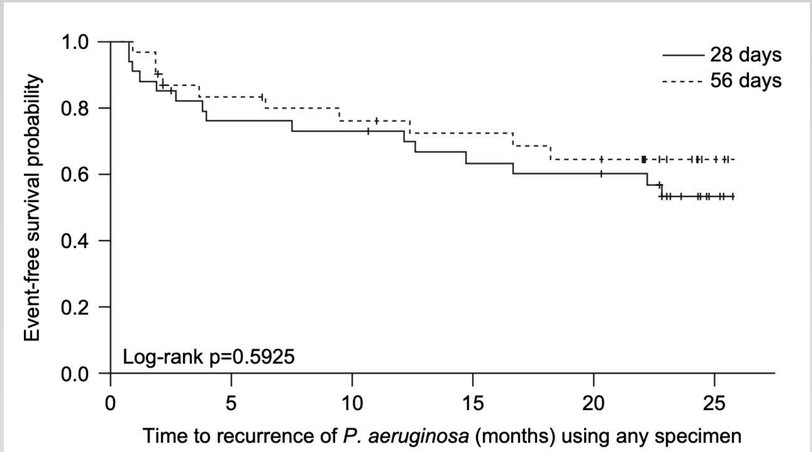

Figure 1. Kaplan-Meier plot of time that shows probability of the time of recurrence of *Pseudomonas aeruginosa* infections in cystic fibrosis patients when treated with tobramycin inhalation solution twice daily for the 28 and 56 day treatment groups.
From F. Ratjen, et al. (2010). Treatment of early *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: the ELITE trial. *Thorax*, 65, pp. 286-291.

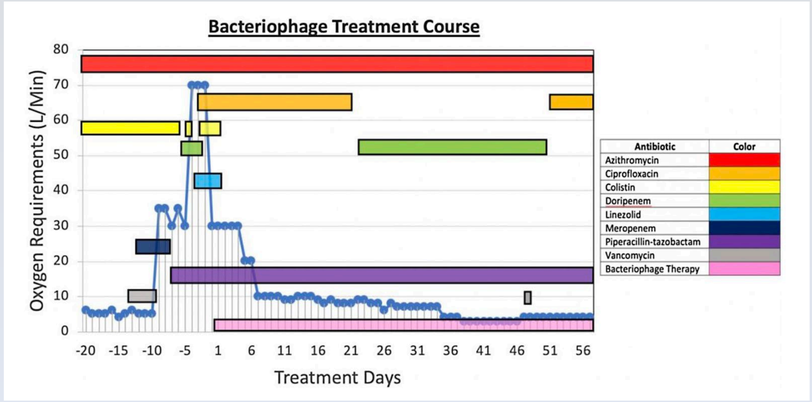

Figure 2. Oxygen saturation, antibacterial, and bacteriophage use during the clinical course of a patient from a case study. Oxygen saturation is used to show the oxygen requirements in L/minute of the patient to represent the patient's health during the treatment course.
From N. Law, et al. (2019). Successful adjunctive use of bacteriophage therapy for treatment of multidrug-resistant *Pseudomonas aeruginosa* infection in a cystic fibrosis patient. *Infection*, 47, pp. 665-668.

Discussion

Antibiotics are the current treatment of choice for *P. aeruginosa* infections for cystic fibrosis patients, but there are many different options for what antibiotics to use and how the treatment is delivered. The ELITE clinical trial (Ratjen et al., 2009) was designed to investigate the optimal therapeutic drug regimen for the eradication of *P. aeruginosa* infections of inhaled tobramycin solution (TIS). Figure 1 depicts the proportion of patients free of P. aeruginosa at day 28, which is the last day of treatment, and 1 month (56 days) after the end of the TIS treatment. This shows the efficacy of TIS to meet the two major goals of antibiotic therapy, which are to clear P. aeruginosa infections and keep the patient's pathogen free for as long as possible. Ratjen et al. recommended that inhaled antibiotics be combined with oral or IV antibiotics to increase the chance of infection eradication, because inhaled antibiotics don't reach all parts of the lungs due to the mucus plugs obstructing airways.

Antibiotic resistance has increasingly become a problem for treating infections thus making alternative treatments necessary to investigate for treating resistant or multi-drug resistant (MDR) bacterial infections. Figure 2 illustrates the treatment course for a patient in one clinical case study. This CF patient had a MDR *P. aeruginosa* infection and was given a variety of treatments over the 76 day period. Day 1 represents the first day of bacteriophage therapy given to the patient. The antibiotics given were azithromycin, ciprofloxacin, colistin, doripenem, linezolid, meropenem, pipreracillan-tozobactam, and vancomycin. The patient's health was depicted by the oxygen saturation and requirements of supplemental oxygen. As the patient is given different combinations of antibiotics that do not improve their infection, their oxygen requirements continue to increase which depicts their declining lung function. Once the bacteriophage therapy has started, the patient's lung function and health begins to improve. This therapy was a cocktail of different bacteriophages to increase the chance of eradication by targeting multiple isolates of the pathogen (Law et al., 2019). This case study demonstrates the potential for bacteriophage therapy to aid in the eradication of *Pseudomonas aeruginosa* infections in CF patients when antibiotics fail due to resistance.

Conclusion

Antibiotics are an effective treatment if the pathogen is not resistant. In the case of clinical resistance, bacteriophages would pose a good alternative for treatment, especially in combination with antibiotics. Bacteriophages are currently in the clinical trial phase for some medical applications in the U.S. and are used as antimicrobials in other countries. As they are a living organism as opposed to a chemical, bacteriophages have more FDA regulations in the U.S. that they must meet than a typical antimicrobial.

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