

# Combination treatment of antibiotics and phages in biofilm-related infections

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## Summary:

The treatment of biofilm-related bacterial infections is challenging. Biofilm structure is an evasion mechanism for various bacterial pathogens, the treatment is complicated due to low antibiotic penetration and bacterial cell persistence with altered metabolism. Lytic bacteriophages are promising in biofilm-related infection treatment including multi-drug resistant infections. Phages produce enzymes such as depolymerases that can destroy biofilm matrix and increase antibiotic penetration. However antibiotic and phage combination may cause not only synergistic or additive, but also antagonistic effects. Host cell interaction with bacteriophage and antibiotic action mechanism determines bacterial response. These factors are crucial for decision making in biofilm-related multi-drug resistant infection treatment.

## Methods and materials:

We present two patient cases that were treated with bacteriophage-antibiotic combination and surgical intervention in complex biofilm-related osteomyelitis and left ventricular assistance device infection. Multi-drug resistant *Pseudomonas aeruginosa* strains were isolated from both patients. Bacterial strains were evaluated for their biofilm production properties. Biofilm production was determined using crystal-violet assay. Calgary device was used to detect phage, antibiotic and phage-antibiotic effects on biofilm producing and planktonic cells.

## Results:

Antibiotic-bacteriophage combination was safe and well tolerated in both cases. Addition of bacteriophages led to increased antibiotic effectiveness. Both multi-drug resistant *P. aeruginosa* strains were major biofilm producers. Combined treatment was most effective in biofilm prevention. Patient with osteomyelitis had infection relapse nine months after the treatment. Patient with left ventricular assistance device did not show any further signs of infection for one year follow-up and was accepted for heart transplantation waiting list.

## Conclusions:

Bacteriophages in combination with antibiotics have a great potential in biofilm-related infection treatment particularly in case of multi-drug resistant infections. Nevertheless, it is of great importance to choose appropriate antibiotic-phage combination to augment antimicrobial effect.