

# Chronic Suppression of a Multidrug-Resistant *Pseudomonas aeruginosa* in Prosthetic Joint Infection Using Personalized Bacteriophage Treatment

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**INTRODUCTION:** Multidrug-resistant (MDR) bacterial infections are a critical public health concern. Periprosthetic joint infection (PJI) caused by MDR organisms, often associated with biofilm formation, present a life-threatening challenge when surgical removal of hardware is not feasible and conventional antibiotics fail. Bacteriophages (phages) offer targeted anti-biofilm activity and potential virulence modulation but have mostly been studied as adjuncts to antibiotics. In this study, we assessed whether personalized phage therapy, deployed as a salvage stand-alone therapeutic without antibiotics, could achieve long term clinical suppression of an otherwise intractable MDR *P. aeruginosa* PJI.

**METHODS:** A nonagenarian with intractable MDR knee and hip *P. aeruginosa* PJI refractory to multiple surgeries and antibiotic regimens was the subject of the study. To validate the effectiveness of phage therapy in treating the infection, we employed a combination of clinical, microbiological, and genomic methodologies. Two lytic phages with high planktonic and biofilm activity against the isolate tested were selected. Under FDA expanded access, the patient received intra-articular and intravenous phage therapy intermittently every 1–6 months. The patient was monitored over a two-year period, with clinical assessments used to evaluate symptom resolution and infection control. Serial cultures were obtained to monitor microbial persistence. Biofilm disruption was assessed indirectly through clinical response and failure of infection recurrence. Whole genome sequencing (WGS) of bacterial isolates was performed to detect genetic changes, assess phage integration, and confirm the sustained presence of phages without incorporation into the bacterial genome. Phage susceptibility testing and virulence factor analysis were also utilized to understand bacterial adaptation.

**RESULTS:** Over the two-year period, intermittent bacteriophage therapy led to clinical resolution of the MDR *P. aeruginosa* PJI and was well tolerated with only mild, transient transaminitis noted. At the nine-month mark, effusion and pain had resolved and inflammatory markers normalized despite persistent culture positivity. Genomic analysis confirmed the persistent presence of bacteriophage during treatment without evidence of integration into the bacterial genome. Clinical improvement was associated with disrupted biofilm and altered bacterial virulence. While neutralizing antibodies were noted in serum and synovial fluid, phage efficacy was not diminished.

**DISCUSSION:** Bacteriophage monotherapy achieved durable clinical suppression of an otherwise untreatable MDR *P. aeruginosa* PJI, despite host antibody responses and ongoing culture positivity. Further controlled studies to define optimal protocols and long-term outcomes are warranted.

**SIGNIFICANCE/CLINICAL RELEVANCE:** Bacteriophage therapy represents a viable salvage option for the management of MDR PJI, especially where conventional antibiotics fail and redo surgeries are not a suitable option.

## IMAGES AND TABLES:

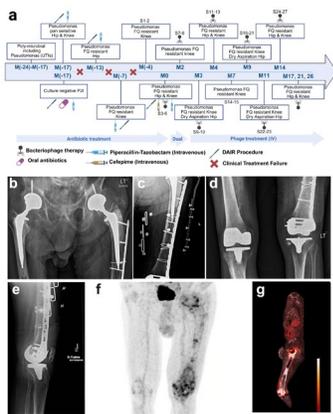


Figure 1: Clinical Timeline and Imaging. a. Clinical timeline of PJI course by months, b-e. Radiographs demonstrate complexity of implants and hardware, f-g. PET imaging of the pelvis and upper leg.

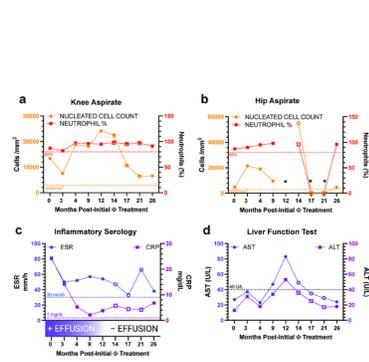


Figure 2. Clinical laboratory values measured at different time points (in months) following the initiation of phage therapy. a. Knee aspirate data, b. Hip aspirate data, c. Inflammatory serology, d. liver function tests (transaminases).

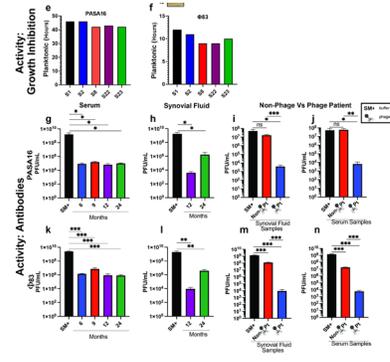


Figure 3: Phage lytic activity on pre-, mid- and late-term treatment samples, e-f. Phage activity in serum and synovial fluid samples from different time points, g-n. phage activity and development of antibodies over time (months).