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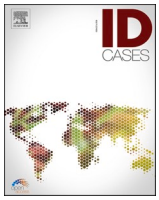

Case report

Salphage: Salvage bacteriophage therapy for a chronic *Enterococcus faecalis* prosthetic joint infection

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ABSTRACT

Chronic prosthetic joint infections are difficult to treat without conducting revision surgery because conventional antibiotics cannot eradicate bacteria that reside in biofilms. Consequently, novel therapeutics are needed to help treat prosthetic joint infections with one being bacteriophage therapy given its innate biofilm activity. Herein a sixty-nine-year-old man with a recalcitrant *Enterococcus faecalis* prosthetic joint infection is discussed. The patient was successfully treated with personalized bacteriophage therapy and after two years of follow up he has not had a clinical recurrence. Overall, this case report supports that bacteriophage therapy for prosthetic joint infections has promise to reduce the morbidity that is associated with current treatments. However, more research is needed to assess whether this therapeutic is helping eradicate infections or if it is making bacteria less pathogenic. This is an important point which will need to be evaluated as this therapeutic continues to be developed for all infections.

Introduction

Prosthetic joint infections (PJIs) are difficult to cure in part because conventional antibiotics have limited ability to eradicate sessile bacterial states such as biofilms [1–3]. Therefore, to attempt definitive cure, removal of prosthetics with revision surgery is required, but these surgical interventions are associated with significant morbidity and immense financial ramifications [1]. When periprosthetic fractures or traumatic injuries require additional orthopedic hardware to be inserted in proximity or in connection to the infected prosthetics this complicates traditional PJI treatments. This occurs because the extra hardware can serve as additional niduses that harbor more biofilms. Moreover, the removal of these additional prosthetic material is not always feasible. Therefore, novel therapeutics that have biofilm activity are drastically needed to help cure complex PJIs to reduce morbidity and mortality. Based on case reports bacteriophage therapy has promise to be such an agent [4]. However limited cases studies have been reported on the use of bacteriophage therapy in *Enterococcus spp.* PJI [5]. Consequently, herein we discuss a case of a patient who had a complex *Enterococcus faecalis* knee PJI that was successfully treated with personalized adjuvant bacteriophage therapy.

Case

A 69-year-old male with a past medical history of atrial fibrillation, diabetes and hypertension had an extensive motor vehicle accident in 2019. This resulted in an open book pelvis fracture, open left tibia fracture, bilateral comminuted ankle fractures and right femur fracture. Extensive trauma instrumentation was conducted on bilateral lower extremities with left lower extremity hardware seen in Fig. 1. Complicating his initial course, he had a polymicrobial soft tissue infection that caused a left knee PJI with *Pseudomonas aeruginosa*, *E. faecalis* and *Stenotrophomonas maltophila*. This was treated with conventional surgical and medical management but given the extensive trauma he had significant destruction of the soft tissues over the prosthesis requiring soft tissue reconstruction with his gastrocnemius soft tissues.

One year later, he started to have worsening left knee pain and drainage. These symptoms progressed prompting medical evaluation in which a draining sinus tract was observed. Subsequent arthrocentesis culture grew *E. faecalis*. Given his precarious soft tissue envelope over his prosthetic and extensive adjacent trauma hardware, revision surgery was deemed to be unlikely to be successful and he underwent debridement and implant retention surgery (DAIR). Since his past PJI was

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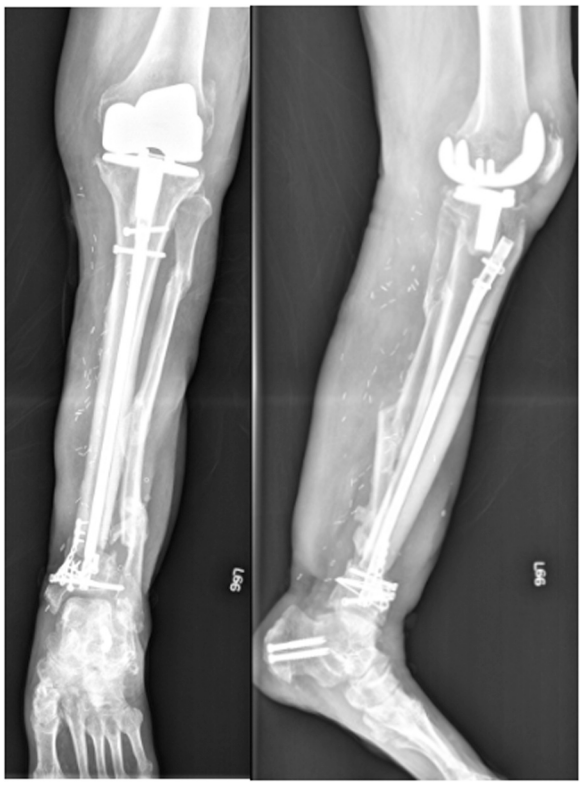

Fig. 1. X-ray of knee, tibia and fibula showing extensive orthopedic hardware.

polymicrobial, it was assumed that he had another polymicrobial infection and he was started on piperacillin/tazobactam and levofloxacin. However, operating room cultures only grew *E. faecalis* and next genomic sequencing only had *E. faecalis* nucleic acid present. Consequently, his antibiotics were changed to only intravenous ampicillin. The patient also expressed interest in alternative agents to salvage his limb since revision surgery was not an option in his case. Consideration for adjuvant bacteriophage therapy was discussed and the patient expressed desire to attempt to find a bacteriophage that had activity to his *E. faecalis* isolate.

Therefore the *E. faecalis* clinical isolate was then sent to Dr. Benjamin Chan and a bacteriophage with lytic activity to his clinical isolate was found (EF phage 1). This bacteriophage was then propagated on his clinical isolate and amplified to create tiers of 1×10^{10} PFU/mL. This therapeutic was also purified to have zero endotoxins per mL and sterility testing showed no bacterial or fungal growth with USP-71 testing. Consequently, an individual FDA IND 27513 was obtained as was IRB approval (HP-00096598) from the University of Maryland, Baltimore.

Since his soft tissue coverage was so precious repeat DAIR with intraoperative phage was not conducted because of concern for wound healing. Rather the patient received 1×10^{10} PFU/mL of bacteriophage diluted in 10 mL of normal saline directly injected into his knee with the use of an arthrocentesis for two days. This was followed by Intravenous bacteriophage therapy for 4 days in which 1×10^{10} PFU/mL were diluted in 50 mL of normal saline and then infused over 30 min. The patient did not have any adverse reactions and daily labs did not show any derangement of liver function with the bacteriophage therapy. While the patient was receiving bacteriophage therapy ampicillin was stopped and daily intravenous daptomycin 1 g daily was started for 7 days and then transitioned to oral amoxicillin 500 mg every 12 h.

Six months later, his course was complicated by methicillin resistant Staphylococcus aureus (MRSA) bacteremia and MRSA right ankle hardware infection. This was treated with hardware removal and intravenous vancomycin therapy for 6 weeks and then indefinite oral minocycline 100 mg twice a day. Unfortunately, his right MRSA ankle infection and MRSA bacteremia recurred requiring below the knee amputation. Given his MRSA right leg infection and recurrent bacteremia, he has remained on chronic oral antibiotic suppression therapy. Twenty-four months since receiving bacteriophage therapy he is without clinical signs of left knee PJI recurrence, and a PET/CT 20 months since receiving bacteriophage therapy had no increased uptake on his left knee prosthetic.

Discussion

In nature bacteria live mostly in sessile sates and therefore bacteriophages have evolved the ability to degrade the EPS of the biofilm and infect biofilm bacteria [6,7]. However, bacteriophages are not motile but rather interact with bacteria through chance encounters. Therefore, the confined environments of biofilms allow for theoretically enhanced ability of bacteriophages to find susceptible bacteria. These attributes make bacteriophage therapy attract adjuvant agents in the treatment of PJIs. As seen here, adjuvant bacteriophage therapy has promise to cure PJIs without prosthesis removal, which would revolutionize PJI treatments [6].

Yet bacteriophage therapies are not like conventional antibiotics, rather bacteriophage therapeutics can have a very narrow spectrum of activity to only certain strains of a bacterial species [8]. Therefore, we had to ensure no other pathogens were present besides *E. faecalis* given his past polymicrobial infection. Consequently, we did not use bacteriophage therapy with surgical intervention as we have discussed is likely the most useful route [5]. Rather the patient underwent DAIR and five weeks of IV antibiotics therapy and then intraarticular and intravenous bacteriophage therapy. We would have liked to administer bacteriophage with debridement surgery to directly engage bacteriophages into a manually debrided biofilm [6,9]. However, his precarious soft tissue envelope over the prosthesis made further surgeries high risk for poor wound healing. Therefore, we choose to use a personalized protocol with IA bacteriophage therapy via an arthrocentesis and intravenous bacteriophage therapy. This allowed for bacteriophage therapy to be directly instilled into the site of infection thereby creating a very high theoretical multiplicity of infection in the joint. The subsequent intravenous dosing also allowed for bacteriophages to reach distant areas not reached with repeated IA administration [6].

However, combining surgical interventions with bacteriophage therapy does cloud the effectiveness of bacteriophage therapy in individual cases. In this case given the chronicity and extent of retained infected hardware, it was unlikely that conventional treatments would have cured his infection and it does seem that bacteriophage therapy has prevented PJI recurrence and improved his quality of life. This is reinforced by no recurrence of his PJI at two years and a PET/CT that did not show any metabolic activity on his left knee arthroplasty, but a statement of definitive cure cannot be made.

Rather another plausible reason that he has not had clinical recurrence is that after bacteriophage therapy exposure the virulence of his *E. faecalis* may have been altered resulting in a more indolent or easier to control infections as discussed with another case [10]. To assess this pathogenicity assays with *C. elegans* assay could be conducted comparing clinical bacterial isolates before and after phage therapy to assess virulence. This would require an additional arthrocentesis to evaluate which outside a clinical trial is ethically unsettling if patients do not have clinical signs of recurrence. Nonetheless this would be important to evaluate in clinical trials and in the development of bacteriophages therapeutics moving forward. If full eradication of bacterial infections are not occurring then this therapeutic will need to be viewed more as an powerful suppressive antimicrobial and not a curative one, which would drastically reduce its alure amongst pharmaceutical companies. However, it wouldn't reduce the ability to improve PJI morbidity as clinicians could still use this therapeutic in patients who are unable to undergo revision surgery. Regardless, only well-designed clinical trials will be able to determine bacteriophage therapy efficacy

and its role in PJI treatments.

In conclusion, this case further reinforces the potential benefit of using bacteriophage therapy for complex recalcitrant PJI infections and hardware infections. It also adds to the limited data on clinical uses of bacteriophage therapy for *Enterococcus spp.* infections. Overall while bacteriophage therapy has promise much more translational research and proof of concept trials are needed before efficacy trials are to be conducted to thereby create effective and reproducible bacteriophage therapeutics.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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None.

CRediT authorship contribution statement

J.B.D: Conceptualization, investigation, data curation, writing – original draft preparation. **B.C.:** Conceptualization, supervision, writing-reviewing, and editing. **A.J.:** Investigation, writing – review & editing.

Declarations of Competing Interest

None.

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