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PERSPECTIVES

Potential Use of Adjuvant Bacteriophage Therapy With Debridement, Antibiotics, and Implant Retention Surgery to Treat Chronic Prosthetic Joint Infections

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The number of arthroplasties conducted annually continues to increase; however, approximately 1%–2% of all knee and hip arthroplasties will become infected. These prosthetic joint infections are costly, difficult to treat, and cause significant morbidity and mortality as a direct result of conventional surgical and medical managements. In this perspective, we discuss factors that make these infections arduous to treat as well as the potential use of adjuvant bacteriophage therapy with debridement, antibiotics, and implant retention surgery to cure these infections without removing the infected prosthesis. We also provide rationale as to why future clinical trials evaluating this novel therapeutic will need to be designed as noninferiority trials, and we compare this approach to 2-stage revision surgery. If bacteriophage therapy continues to show effectiveness, this could revolutionize the treatment of prosthetic joint infections and pioneer new treatments for similar infections.

Keywords. arthroplasty; bacteriophage therapy; biofilm; DAIR; prosthetic joint infection.

The number of arthroplasties performed annually continues to increase with over 1 million conducted in the United States in 2019 [1]. Arthroplasties improve underlying conditions that severely debilitate patients' lives, allowing for increased mobility and enhanced functionality. Despite strict infection control measures, approximately 1%–2% of all arthroplasties will become infected [1]. This has devastating impacts on healthcare systems, costing the United States more than 1.6 billion dollars annually to treat prosthetic joint infections (PJIs) [2]. Beyond the financial ramifications, patients also have increased morbidity and mortality secondary to conventional surgical and medical managements. In some PJI cohorts, the 5-year mortality is 20%, which is comparable to some cancers [3]. When PJIs occur more than 90 days from the index arthroplasty, they are deemed chronic PJIs and are more onerous to treat than acute PJIs. The gold standard treatment of chronic PJIs is with either a 1- or 2-stage revision surgery in which removal of the prosthesis is required to eradicate the infection. These aggressive surgeries are invasive and burdensome to the patient, but failure rates in eradicating these infections are approximately 10% [4]. It is unfortunate that, even with numerous novel approaches, revision surgery outcomes have not significantly changed over the past several decades [4].

The lack of optimal treatments for PJIs are theorized to be secondary to microbial biofilms on prostheses and devitalized tissues that conventional antibiotics are unable to eradicate. This occurs because the concentrations of antibiotics needed to eradicate biofilm infections can be 1000 times the concentrations required to cure planktonic infections [5]. The spatial location of biofilm infections also complicates treatment whereby biofilms typically reside on poorly vascularized prosthetic surfaces [5]. In addition, immune cells have reduced activity to biofilm bacteria due to limited penetration into restrictive biofilm matrices [5]. Therefore, current chronic PJI treatments require surgical interventions with prosthesis removal in combination with antimicrobial agents to achieve adequate outcomes [6].

Although biofilms likely contribute immensely to PJIs, other factors are additional obstacles in treating PJIs. These include the following: (1) persister cells, (2) small colony variants, (3) abilities of some bacteria to reside inside osteoblasts and endothelial cells, (4) infection of cortical canaliculi, and (5) plasma protein bound bacterial aggregates in synovial fluid [5, 7, 8]. These additional factors complicate PJI treatments that require more sophisticated approaches beyond mere anti-biofilm agents. So far, no novel therapeutic has been the "magic bullet". However, bacteriophage therapy might be a potential adjuvant therapeutic to

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cure PJIs without necessitating prosthesis removal and thereby reduce morbidity and healthcare costs.

Bacteriophages are viruses that only infect bacteria and can be either lytic or lysogenic. Lytic bacteriophages are the most promising therapeutics in PJIs secondary to their robust bactericidal abilities. In nature, bacteria reside mostly in sessile communities closely resembling in vivo biofilms. As a result, evolutionary pressures have caused bacteriophages to develop innate abilities to lyse biofilm bacteria. Some of these abilities occur secondary to enzymes that degrade the extracellular polymeric substances and allow for increased attachment and then infection of biofilm bacteria [9–11]. Bacteriophages also can infect and subsequently kill metabolically inert bacteria such as persister cells and small colony variants [9]. They also have a unique ability to self-amplify their concentrations in the presence of bacterial hosts [9–11]. These factors allow bacteriophages to act synergistically with antimicrobials to degrade chronic PJI biofilm infections in a stepwise fashion [10, 11]. This is demonstrated in a murine experiment in which an implanted methicillin-resistant *Staphylococcus aureus* biofilm infection was significantly reduced with combined bacteriophage therapy and intravenous antibiotics [12].

Several complex, recalcitrant PJI case reports have also documented potential beneficial outcomes when bacteriophage therapy is used as an adjuvant with debridement, antibiotics, and implant retention (DAIR) surgery [11, 13–15]. The benefits of using DAIR with bacteriophage therapy are as follows: (1) removal of planktonic infection, (2) ensuring prosthetic is salvageable, (3) removal of the synovial fluid that harbors plasma protein-bacterial aggregates, (4) manually debridement of the prosthesis that harbors biofilm, and (5) direct instilment of bacteriophage therapy to debrided biofilm. As such, using adjuvant bacteriophage therapy with DAIR for chronic PJIs may allow for eradication of these infections, whereas retaining the prosthesis and success rates might rival that of 2-stage revision surgery [13]. If this can be proven, it would transform the treatment of PJIs by curing these infections without prosthesis removal and therefore reduce morbidity, mortality, and the financial ramifications associated with PJIs.

However, DAIR is not routinely used for chronic PJIs because this surgical procedure has limited rates of success of approximately 50% [6]. Therefore, DAIR is usually only preformed in chronic PJIs that have well fixed prosthetics and either symptoms of PJIs for less than 3 weeks or in patients that have comorbidities that severely limit the ability to conduct 2-stage revision surgery [6]. Given the historical limited success of DAIR in chronic PJIs, testing a standardized bacteriophage therapeutic regimen with DAIR will first need to be conducted in small proof-of-concept trials with primary outcomes assessing safety, tolerability, and rates of infection recurrence at 1 and 2 years after DAIR. We believe that intraoperative application of bacteriophage therapy directly to the manually debrided biofilm, as has been used in case reports [11, 13–15], will be required to cure these infections. However, given the immobility of bacteriophages, the use of only intraoperative doses limits bacteriophage to only 1 infected implant interface, which may miss deep-seated infections on the bone-implant interface. Therefore, a short course of intravenous bacteriophage therapy for 4 days may be needed to reach other areas with adequate blood flow. Longer durations of intravenous bacteriophage therapy can be associated with resistance development and neutralizing antibody production potentially limiting any added benefit from these prolonged treatments [11, 16]. In correlation, assurance of in vitro lytic activity is vital, and, consequently, an arthrocentesis culture would need to be obtained in advance to match a clinical isolate to specific bacteriophage therapeutics. Although premanufactured cocktails of bacteriophages may potentially simplify therapeutic selection, a previous clinical trial has shown that assuring in vitro sensitivity is paramount [17]. Therefore, a single bacteriophage or a collection of 2 or 3 bacteriophages with proven in vitro activity against a clinical isolate should be used. Finally, because the effectiveness of bacteriophage monotherapy remains unproven, standard-of-care conventional antibiotics should continue to be used with bacteriophage therapeutics for synergistic activity [11, 12, 16].

If these proof-of-concept trials can show potential effectiveness similar to revision surgeries, larger efficacy trails could then follow to establish the noninferiority of DAIR and adjuvant bacteriophage therapy to standard-of-care, 2-stage, revision surgery. It is unfortunate that, at this nascent stage, there is a paucity of data supporting bacteriophage therapy use in the treatment of PJIs without combined surgical interventions [11, 13]. This stems from one of the central dogmas of treating PJIs, in which surgery is paramount to achieve infection source control.

Although bacteriophage therapy is a promising therapeutic in PJIs, there are still significant hurdles. One of the main hurdles is the narrow spectrum of activity of bacteriophages, which limits the ability to devise wide-ranging PJI therapeutics. This can be partially overcome by matching clinical isolates to a library of bacteriophages or using either cocktails of bacteriophages or genetically engineered bacteriophages that have wider spectrums of activity [13]. However, as stated previously, assurance of in vitro activity of a specific bacteriophage therapeutic to a clinical isolate must be confirmed with bacterial growth inhibition and lytic activity assay [11, 17]. Further complicating bacteriophage therapy use is the enigma of bacteriophage pharmacokinetics that may obstinately differ between various bacteriophages secondary to unique surface proteins and

other parameters [16]. Although these are hindrances in treating acute infections, those treating chronic PJIs have ample time to determine a clinical pathogen by arthrocentesis and ensure in vitro bacteriophage activity. In addition, when using bacteriophage therapy as an adjuvant with DAIR, this therapeutic can be directly applied to the infected joint, potentially circumventing the poorly understood bacteriophage pharmacokinetics and relying instead on the innate ability of bacteriophages to self-replicate and penetrate biofilms.

CONCLUSIONS

In summary, PJIs are complex infections that desperately need more effective therapeutics. Early research suggests that adjuvant bacteriophage therapy with DAIR may cure chronic PJIs without needing to remove the prosthesis. Testing this novel approach should be first conducted in small proof-of-concept trials. If safety and effectiveness can be proven, larger noninferiority trials could follow, comparing this novel approach to 2-stage revision surgery, and, if efficacious, it would revolutionize the treatment of PJIs and expand therapeutic options for similar biofilm infections, such as spinal hardware infections and fracture-related infections.

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