**QUESTION 5:** Do bacteriophages have a role in treating multidrug-resistant periprosthetic joint infection (PJI)?

**RESPONSE:** Unknown. Although some preclinical and clinical studies have demonstrated a good safety profile as well as promising therapeutic effects using bacteriophages for treating bone and joint infections, further clinical research using bacteriophage therapy in patients with multidrug-resistant PJI is required.

There are known obstacles to bacteriophage therapy, including the fact that bacteriophages are neutralized in serum and relevant pathogens contain Clustered Regularly Interspaced Short Palindromic Repeats - associated protein-9 nuclease (CRISPR/cas9) immunity against bacteriophage. Phages are usually bacterial strain specific; thus, a cocktail of different bacteriophage lineages may be necessary to effectively treat biofilm-mediated infections.

**LEVEL OF EVIDENCE:** Consensus

**DELEGATE VOTE:** Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

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**PRE-MEETING RATIONALE**

PJI represent serious issues for patients worldwide. The surfaces of orthopaedic implants are all susceptible to colonization by biofilm-forming bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* (*P. aeruginosa*) and numerous other organisms, whose presence has been reported to play a key role in the occurrence of PJI, thus leading to antibiotic resistance [1–4]. To overcome these problems novel treatment strategies focusing on disrupting biofilms are being developed [5]. Utilization of lytic bacteriophages to eradicate bacteria causing biofilms is one of the promising emerging technologies [2,6].

Bacteriophages are natural viruses that infect bacteria. They are one of the most abundant organisms in the biosphere. Each bacteriophage is specific to a particular microbial species. Like all viruses, phages are only able to replicate inside their host cells. Lytic phages inject their genetic material into the host bacterial cell, cause bacterial cell lysis that liberates subsequent new phage particles. These new particles allow successive infection of additional bacteria in a rapid and exponential pattern, facilitating the complete eradication of the bacteria. The French microbiologist Felix d’Herelle first described bacteriophages in 1917 [7]. By their nature, bacteriophages are good candidates for antibacterial therapy. Indeed, they target a bacterium specifically, as long as the corresponding host bacteria is present. In comparison with antibiotics, this phenomenon is unique as it is exponential and self-sustained after a single or a few administrations. Moreover, lytic bacteriophages do not affect eukaryotic cells and not impact the gut microbiota when administered locally.

Bacteriophage technology is particularly promising in patients with multidrug-resistant PJI as: (i) multidrug-resistant PJI are becoming more and more frequent [8,9]; (ii) the rate of relapse is particularly high in patients with PJI caused by multidrug-resistant pathogen [9-11]; (iii) bacteriophages and antibiotics are synergistic [12,13]; (iv) there is no cross-resistance between antibiotic resistance and bacteriophage resistance [6-12]; (v) some in vitro and animal models demonstrated that bacteriophages could have an antibiofilm activity [6,13,14]; and (vi) recent human and animal trials using phage therapy have not shown any local tissue toxicity or any adverse effects to the host [15-20].

Bacteriophages were used in the 1970s in France [21] and remained a popular treatment throughout the 20th century in Eastern Europe (Poland) and the former Soviet Union (Georgia, Russia) in patients with relapsing osteomyelitis. Few case series have been published in the literature, including patients with pyogenic native joint infection, chronic osteomyelitis, suppuration after bone fracture and diabetic foot osteomyelitis [22-26].

In preclinical studies using animal models for PJI bacteriophages were found to prevent bacterial adhesion and also effectively disrupt the formation of biofilm [13,27]. Animal studies also have proven synergism between antibiotics and bacteriophages [13]. In another animal study, Kishor et al. [26] studied the efficacy of several phages used in conjunction as a treatment modality for chronic osteomyelitis caused by MRSA in rabbits. The study showed that the combination of specific phages selected based on their virulence against various clinical MRSA strains was effective in eradicating the infection, thus suggesting that a “tailor-made cocktail” of phages can alone be effective in targeting specific bacteria in the setting of a chronic infection. Some of the issues with current PJI animal models are that they don’t replicate mechanical stresses occurring in clinical settings and, therefore, may not be fully representative of clinical situations.

Wright et al. conducted a randomized, double-blind clinical trial using bacteriophages in humans [28]. They studied the effect of the combination cocktail of six phages targeting *P. aeruginosa* in the treatment of antibiotic-resistant chronic otitis media infection. The authors achieved measurable therapeutic effects with minimal dosing, thus suggesting a promising role for phage therapy in treating antibiotic-resistant infections.

No case series including patients with PJI has been published (we retrieved only two cases from a French series of bone and joint infection treated with bacteriophages) [6]. In the Georgian practice, specific phages mixtures are used, such as the “pyophage” cocktail that contains phages against *S. aureus, Streptococcus, Proteus, P. aeruginosa* and *Escherichia coli* (*E. coli*) or specific bacteriophages targeting specifically staphylococci, as the Sb1 phage (that could be imported in the USA), the bacteriophage K or the bacteriophage ISP [22]. In Poland, phage(s) are selected from a bank based on their activity on the patient’s strain to adapt the treatment (personal medicine) and to ensure antibacterial activity of phages used [23,24]. All these bacteriophages are classically prepared with a bacterial inoculum, in vitro infection with the bacteriophage and purification of the preparation in aliquots at 10^7 to 10^8 PFU/mL. These preparations are approved by local authorities but do not respect European “good manufacturing practice” (GMP) standards for conducting clinical trials and targeting Market Authorizations (MA). Indeed, the final product requires total elimination of bacterial components that are
generated during the production process, such as toxins, in order to limit pyrogenicity and adverse events that may arise during phase administration/use, especially when the phase is administered intravenously or directly in a joint cavity. As a consequence, bacteriophages are currently not injected directly into the joint in patients with PJI but locally throughout the fistula and/or orally in patients with chronic osteomyelitis [23–25].

Recently, an European multicentric clinical trial evaluating phage therapy of burn wound infections has been done using P. aeruginosa and E. coli bacteriophages from a GMP French bioproduction process that was implemented according to European Medicine Agency standards (ClinicalTrials.gov Identifier: NCT02116010). The French team from the Lyon bone joint infection (BJI) study group (also called CRIOAc Lyon, a regional reference center for the treatment of complex bone and joint infection in France; http://www.crioaclyon.fr) has treated as salvage therapy, under the supervision of the French health authorities, three patients with chronic bone and joint infection (one osteomyelitis due to extensively drug-resistant S. aureus, and two S. aureus PJI) with bacteriophages that follows the same process of production. For all the patients, the cocktail was personalized and selected based on the bacteriophage susceptibility of the clinical isolates (phage-gram; similar principle as antibiotic but with bacteriophages) that was isolated after a joint puncture before the surgery. The two patients with PJI had chronic infection with purulent discharge and were treated with debridement antibiotics and implant retention (DAIR) supplemented with a direct administration of the bacteriophage S. aureus cocktail in the joint cavity at the end of the procedure. Both patients are doing well during the follow-up of 12 months and 3 months, respectively (unpublished data). A randomized clinical trial called PHAGOS will start soon in France, to evaluate the addition of S. aureus bacteriophage in patients with relapsing S. aureus PJI. The availability of P. aeruginosa, E. coli and S. aureus with GMP standard in France is a great opportunity to evaluate the phage therapy as an additive treatment in patients with PJI, especially in patients with multidrug-resistant PJI.

Although phage treatment looks promising and safe, further research is needed to understand immunogenicity and answer the remaining questions related to treatment by phage such as timing, duration, methods of delivery and route of administration. Limitations of present studies include the reduced spectrum of bacteria tested, which are limited to MRSA and P. aeruginosa, without considering coagulase-negative staphylococci (CoNS), which substantially contribute to PJI onset [29]. In addition to these there is a concern with regards to the immunogenicity of phages and resulting diminished therapeutic efficacy [30].

REFERENCES


