

G57: Is there a role for bacteriophage therapy in treatment of orthopedic infections?

Gina A. Suh, Cecile Batailler, Laura E. Damioli, James B. Doub, Karan Goswami, Antonia Scobie, Roshan P. Shah, Kenneth Urish, Tristan Ferry

Response/Recommendation:

Yes. Phage therapy demonstrates a favorable safety profile and is a reasonable therapeutic consideration for patients with refractory bone and joint infections.

Strength of Recommendation: Moderate

Delegate Vote:

Rationale:

Bacteriophages (phages) are viruses that specifically infect bacteria and are being explored as a potential novel therapy for infections where antibiotics may fail, such as those involving multidrug resistance or biofilm formation. Over the past decade, there has been increasing interest in using phage therapy for bone and joint infections, with a growing body of human cases reported. In 2022, the World Health Organization classified phages as a key component of non-traditional antibacterial agents requiring urgent development, particularly for their efficacy against priority pathogens driving the global spread of antimicrobial resistance¹.

We reviewed all documented cases of bone and joint infections treated with phage therapy in English-language publications since 2010. Our analysis includes 30 publications: one clinical trial², five case series^{3,4 5,6} (including one involving 100 cases, 34 of which were bone and joint infections⁷), and multiple individual case reports. After removing duplicates and redundancies, the dataset encompasses 98 unique cases^{6,8-32}.

Phage therapy targeted a single bacterial species in 89 cases and multiple organisms in nine cases. The most commonly targeted organism was *Staphylococcus aureus* (48 cases, 49%), followed by *Pseudomonas aeruginosa* (22), coagulase-negative staphylococci (22), *Klebsiella pneumoniae* (6), *Enterococcus faecalis* (6), *Escherichia coli* (2), *Proteus mirabilis* (1), vancomycin-resistant *Enterococcus faecium* (1), *Acinetobacter baumannii* (1), and *Streptococcus agalactiae* (1). The most frequent indications for phage therapy were periprosthetic joint infection (57 cases), diabetic foot infection (11), fracture-related infection (8), osteomyelitis of the long bone (7), osteomyelitis of the pelvis (7), osteomyelitis of the foot/ankle (3), spinal infection (2), osteomyelitis of the head and neck (2), and septic polyarthritis (1).

Adverse events were not reported in three cases, while transient events occurred in 16 cases. These included transient increases in liver enzymes (8 cases)^{5,15,21}, transient fever (5)^{2,7,9,28}, localized erythema and pain at the delivery site (1)⁴, and nonspecific symptoms such as exhaustion and dizziness (1)³. All events resolved without lasting effects. No adverse events were noted in the remaining cases. Phage susceptibility testing was conducted in all cases. Of the 98 cases, 68 involved the use of mono-phage therapy. In two cases, single-phage therapy was used in a sequential manner. The remaining 30 cases employed multiple phages employed simultaneously, as in a cocktail. The routes of administration varied, with 69 patients receiving local delivery (11 intraoperative only, 18 local delivery outside the operating room (OR) only,

and 40 both intraoperative and outside the OR), 7 receiving systemic therapy, 21 receiving combined local and systemic delivery, and 1 patient receiving oral therapy¹². Conventional antibiotics were invariably given alongside phage in all cases.

Surgical intervention was common and varied by infection type. All patients with head and neck or spinal infections underwent surgery, as did 92% of those with periprosthetic joint infections (PJI), 88% with fracture-related infections, 71% with long bone osteomyelitis, and 57% with pelvic osteomyelitis. In contrast, only 33% of patients with foot or ankle osteomyelitis and none with diabetic foot infections (DFI) underwent concurrent surgery. Overall, 88 of 98 patients (88%) achieved clinical improvement or resolution, with nine patients experiencing worsening and one showing no change. Microbiological clearance was achieved in 54 cases, was not achieved in 18, and was not assessed in 26. It must be noted that microbiological clearance was not assessed mostly in patients who were doing well and for whom microbiological clearance would have required an invasive procedure. Clearance rates were higher among patients undergoing concurrent surgical intervention (64.9%) compared to those without surgery (25.0%). There was a wide range of durations of therapy (single-dose to one year); dosing intervals (daily to three-times daily); and dosing concentrations (10^5 PFU/mL to 10^{10} PFU/mL).

Of the 10 unfavorable clinical outcomes, five occurred in osteomyelitis (three of the pelvis^{7,32} and two of the foot or ankle⁷), four occurred in PJI^{2,3,7,19}, and one in DFI⁷. Of note, 30% of all clinical failures occurred in infections involving the foot or ankle. Among Gram-positive infections, 89.4% achieved clinical improvement, while Gram-negative infections achieved 95.2% improvement. Polymicrobial infections, defined here as infections where more than one bacterial species was targeted by phage, demonstrated favorable outcomes, achieving 100% clinical improvement, likely reflecting the relatively small sample size (N=9) rather than a definitive trend. Generalizations could not be made regarding route of administration, dose, dosing interval, or duration of therapy due to heterogeneity and multiple confounding contributors for each case.

The promising outcomes reported must be interpreted cautiously due to several limitations. Variations in phage selection, preparation, and administration methods complicate comparisons and generalizations. The reliance on retrospective case reports and small-scale studies introduces potential publication bias, with successful cases more likely to be reported. Inconsistent microbiological and clinical outcome measures hinder accurate assessment of phage therapy's efficacy. The effects of adjunctive therapies, such as antibiotics and surgical interventions, cannot be isolated from those of phage therapy. Technical and logistical challenges also exist. Phage susceptibility testing is labor-intensive and not universally accessible. Regulatory hurdles and the need for individualized preparations further challenge scalability. Additionally, the risk of bacterial resistance to phages, while less well-documented than antibiotic resistance, may be of concern. Patient-specific factors, such as immune responses and comorbid conditions, may affect outcomes³³.

In conclusion, phage therapy, particularly when combined with surgical intervention, appears to be a promising adjunctive treatment for refractory bone and joint infections. Surgical debridement and biofilm disruption, when given with conventional antibiotics, likely enhance

phage efficacy. Furthermore, available evidence strongly supports the safety of phage therapy, with minimal adverse events reported across studies. This underscores the low risk associated with its use, making it a viable consideration from a safety standpoint. While the high clinical success rates are encouraging, they must be interpreted in light of potential publication bias and other limitations. Large-scale, well-designed clinical trials are needed to validate these findings and standardize protocols. Understanding the specific contributions of phage therapy, distinct from adjunctive treatments, will be critical in optimizing its role in managing complex infections^{34,35}.

References:

1. Organization WH. *2023 Antibacterial agents in clinical and preclinical development: an overview and analysis*. 2024. Licence: CC BY-NC-SA 3.0 IGO.
2. Fedorov E, Samokhin A, Kozlova Y, et al. Short-Term Outcomes of Phage-Antibiotic Combination Treatment in Adult Patients with Periprosthetic Hip Joint Infection. *Viruses*. Feb 10 2023;15(2)doi:10.3390/v15020499
3. Onallah H, Hazan R, Nir-Paz R, et al. Refractory *Pseudomonas aeruginosa* infections treated with phage PASA16: A compassionate use case series. *Med*. Sep 8 2023;4(9):600-611.e4. doi:10.1016/j.medj.2023.07.002
4. Onsea J, Soentjens P, Djebara S, et al. Bacteriophage Application for Difficult-to-treat Musculoskeletal Infections: Development of a Standardized Multidisciplinary Treatment Protocol. *Viruses*. 2019;11(10)doi:<https://dx.doi.org/10.3390/v11100891>
5. Doub JB, Johnson AJ, Nandi S, et al. Experience Using Adjuvant Bacteriophage Therapy for the Treatment of 10 Recalcitrant Periprosthetic Joint Infections: A Case Series. *Clin Infect Dis*. Feb 8 2023;76(3):e1463-e1466. doi:10.1093/cid/ciac694
6. Ferry T, Kolenda C, Batailler C, et al. Phage Therapy as Adjuvant to Conservative Surgery and Antibiotics to Salvage Patients With Relapsing *S. aureus* Prosthetic Knee Infection. *Frontiers in Medicine*. 2020;7doi:10.3389/fmed.2020.570572
7. Pirnay JP, Djebara S, Steurs G, et al. Personalized bacteriophage therapy outcomes for 100 consecutive cases: a multicentre, multinational, retrospective observational study. *Nat Microbiol*. Jun 2024;9(6):1434-1453. doi:10.1038/s41564-024-01705-x
8. Doub JB, Chan B, Johnson AJ. Salphage: Salvage bacteriophage therapy for a chronic *Enterococcus faecalis* prosthetic joint infection. *IDCases*. 2023;33:e01854. doi:10.1016/j.idcr.2023.e01854
9. Cesta N, Pini M, Mulas T, et al. Application of Phage Therapy in a Case of a Chronic Hip-Prosthetic Joint Infection due to *Pseudomonas aeruginosa*: An Italian Real-Life Experience and In Vitro Analysis. *Open Forum Infect Dis*. Feb 2023;10(2):ofad051. doi:10.1093/ofid/ofad051
10. Doub JB, Shishido A, Srikumaran U, et al. Salphage: salvage bacteriophage therapy for a recalcitrant *Klebsiella pneumoniae* prosthetic shoulder infection - a case report. *Acta Orthop*. Sep 20 2022;93:756-759. doi:10.2340/17453674.2022.4579
11. Doub JB, Ng VY, Lee M, et al. Salphage: Salvage Bacteriophage Therapy for Recalcitrant MRSA Prosthetic Joint Infection. *Antibiotics (Basel)*. May 4 2022;11(5)doi:10.3390/antibiotics11050616
12. Neuts AS, Berkhout HJ, Hartog A, Goosen JHM. Bacteriophage therapy cures a recurrent *Enterococcus faecalis* infected total hip arthroplasty? A case report. *Acta Orthop*. Dec 2021;92(6):678-680. doi:10.1080/17453674.2021.1968714
13. Ramirez-Sanchez C, Gonzales F, Buckley M, et al. Successful Treatment of *Staphylococcus aureus* Prosthetic Joint Infection with Bacteriophage Therapy. *Viruses*. Jun 21 2021;13(6)doi:10.3390/v13061182
14. Ferry T, Kolenda C, Batailler C, et al. Case Report: Arthroscopic "Debridement Antibiotics and Implant Retention" With Local Injection of Personalized Phage Therapy to Salvage a Relapsing *Pseudomonas Aeruginosa* Prosthetic Knee Infection. *Front Med (Lausanne)*. 2021;8:569159. doi:10.3389/fmed.2021.569159

15. Doub JB, Ng VY, Wilson E, Corsini L, Chan BK. Successful Treatment of a Recalcitrant Staphylococcus epidermidis Prosthetic Knee Infection with Intraoperative Bacteriophage Therapy. *Pharmaceuticals (Basel)*. Mar 8 2021;14(3)doi:10.3390/ph14030231
16. Alt V, Gessner A, Merabishvili M, et al. Case report: Local bacteriophage therapy for fracture-related infection with polymicrobial multi-resistant bacteria: hydrogel application and postoperative phage analysis through metagenomic sequencing. *Front Med (Lausanne)*. 2024;11:1428432. doi:10.3389/fmed.2024.1428432
17. Ferry T, Onsea J, Roussel-Gaillard T, Batailler C, Moriarty TF, Metsemakers WJ. Bacteriophage therapy in musculoskeletal infections: from basic science to clinical application. *EFORT Open Rev*. May 10 2024;9(5):339-348. doi:10.1530/EOR-24-0042
18. Ferry T, Kolenda C, Laurent F, et al. Personalized bacteriophage therapy to treat pandrug-resistant spinal Pseudomonas aeruginosa infection. *Nat Commun*. Jul 22 2022;13(1):4239. doi:10.1038/s41467-022-31837-9
19. Ferry T, Batailler C, Petitjean C, et al. The Potential Innovative Use of Bacteriophages Within the DAC® Hydrogel to Treat Patients With Knee Megaprosthesis Infection Requiring “Debridement Antibiotics and Implant Retention” and Soft Tissue Coverage as Salvage Therapy. *Frontiers in Medicine*. 2020;7doi:10.3389/fmed.2020.00342
20. Cano EJ, Caflisch KM, Bollyky PL, et al. Phage Therapy for Limb-threatening Prosthetic Knee Klebsiella pneumoniae Infection: Case Report and In Vitro Characterization of Anti-biofilm Activity. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2020;doi:10.1093/cid/ciaa705
21. Doub JB, Ng VY, Johnson AJ, et al. Salvage Bacteriophage Therapy for a Chronic MRSA Prosthetic Joint Infection. *Antibiotics (Basel)*. May 9 2020;9(5)doi:10.3390/antibiotics9050241
22. Tkilaishvili T, Winkler T, Muller M, Perka C, Trampuz A. Bacteriophages as Adjuvant to Antibiotics for the Treatment of Periprosthetic Joint Infection Caused by Multidrug-Resistant Pseudomonas aeruginosa. *Antimicrobial agents and chemotherapy*. 2019;64(1)doi:<https://dx.doi.org/10.1128/AAC.00924-19>
23. Ferry T, Leboucher G, Fevre C, et al. Salvage debridement, antibiotics and implant retention (“dair”) with local injection of a selected cocktail of bacteriophages: Is it an option for an elderly patient with relapsing staphylococcus aureus prosthetic-joint infection? *Open Forum Infectious Diseases*. 2018;5(11)doi:10.1093/ofid/ofy269
24. Ferry T, Boucher F, Fevre C, et al. Innovations for the treatment of a complex bone and joint infection due to XDR Pseudomonas aeruginosa including local application of a selected cocktail of bacteriophages. *The Journal of antimicrobial chemotherapy*. 2018;73(10):2901-2903. doi:<https://dx.doi.org/10.1093/jac/dky263>
25. Schoeffel J, Wang EW, Gill D, et al. Successful Use of Salvage Bacteriophage Therapy for a Recalcitrant MRSA Knee and Hip Prosthetic Joint Infection. *Pharmaceuticals (Basel)*. Jan 31 2022;15(2)doi:10.3390/ph15020177
26. Eskenazi A, Lood C, Wubbolts J, et al. Combination of pre-adapted bacteriophage therapy and antibiotics for treatment of fracture-related infection due to pandrug-resistant Klebsiella pneumoniae. *Nat Commun*. Jan 18 2022;13(1):302. doi:10.1038/s41467-021-27656-z
27. Fish R, Kutter E, Wheat G, Blasdel B, Kutateladze M, Kuhl S. Compassionate Use of Bacteriophage Therapy for Foot Ulcer Treatment as an Effective Step for Moving Toward Clinical Trials. *Methods in molecular biology (Clifton, NJ)*. 2018;1693:159-170. doi:https://dx.doi.org/10.1007/978-1-4939-7395-8_14

28. Khatami A, Lin RCY, Petrovic-Fabijan A, et al. Bacterial lysis, autophagy and innate immune responses during adjunctive phage therapy in a child. *EMBO Mol Med*. Sep 7 2021;13(9):e13936. doi:10.15252/emmm.202113936
29. Nir-Paz R, Gelman D, Khouri A, et al. Successful Treatment of Antibiotic-resistant, Polymicrobial Bone Infection With Bacteriophages and Antibiotics Combination. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2019;69(11):2015-2018. doi:<https://dx.doi.org/10.1093/cid/ciz222>
30. Racenis K, Rezevska D, Madelane M, et al. Use of Phage Cocktail BFC 1.10 in Combination With Ceftazidime-Avibactam in the Treatment of Multidrug-Resistant *Pseudomonas aeruginosa* Femur Osteomyelitis-A Case Report. *Front Med (Lausanne)*. 2022;9:851310. doi:10.3389/fmed.2022.851310
31. Simner PJ, Cherian J, Suh GA, et al. Combination of phage therapy and cefiderocol to successfully treat *Pseudomonas aeruginosa* cranial osteomyelitis. *JAC Antimicrob Resist*. Jun 2022;4(3):dlac046. doi:10.1093/jacamr/dlac046
32. Van Nieuwenhuysse B, Van der Linden D, Chatzis O, et al. Bacteriophage-antibiotic combination therapy against extensively drug-resistant *Pseudomonas aeruginosa* infection to allow liver transplantation in a toddler. *Nat Commun*. Sep 29 2022;13(1):5725. doi:10.1038/s41467-022-33294-w
33. Doub JB, Urish K, Chan B. Bacteriophage therapy for periprosthetic joint infections: Current limitations and research needed to advance this therapeutic. *J Orthop Res*. May 2023;41(5):1097-1104. doi:10.1002/jor.25432
34. Ferry T. A Review of Phage Therapy for Bone and Joint Infections. *Methods Mol Biol*. 2024;2734:207-235. doi:10.1007/978-1-0716-3523-0_14
35. Suh GA, Ferry T, Abdel MP. Phage Therapy as a Novel Therapeutic for the Treatment of Bone and Joint Infections. *Clin Infect Dis*. Nov 2 2023;77(Suppl 5):S407-S415. doi:10.1093/cid/ciad533