



# Case Report: Arthroscopic “Debridement Antibiotics and Implant Retention” With Local Injection of Personalized Phage Therapy to Salvage a Relapsing *Pseudomonas Aeruginosa* Prosthetic Knee Infection

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Bacteriophages are viruses that specifically target bacteria. They are considered to have a high potential in patients with prosthetic joint infection (PJI), as they have a synergistic anti-biofilm activity with antibiotics. We report here the case of an 88-year-old man (63 kg) with relapsing *Pseudomonas aeruginosa* prosthetic knee infection. The patient had severe alteration of the general status and was bedridden with congestive heart failure. As prosthesis explantation and/or exchange was not feasible, we proposed to this patient the use of phage therapy to try to control the disease in accordance with the local ethics committee and the French National Agency for Medicines and Health Products Safety (ANSM). Three phages, targeting *P. aeruginosa*, were selected based on their lytic activity on the patient’s strain (phagogram). Hospital pharmacist mixed extemporaneously the active phages (initial concentration 1 ml of  $1 \times 10^{10}$  PFU/ml for each phage) to obtain a cocktail of phages in a suspension form (final dilution  $1 \times 10^9$  PFU/ml for both phages). Conventional arthroscopy was performed and 30 cc of the magistral preparation was injected through the arthroscope (PhagoDAIR procedure). The patient received intravenous ceftazidime and then oral ciprofloxacin as suppressive antimicrobial therapy. Under this treatment, the patient rapidly improved with disappearance of signs of heart failure and pain of the left knee. During the follow-up of 1 year, the local status of the left knee was normal, and its motion and walking were unpainful. The present case

suggests that the PhagoDAIR procedure by arthroscopy has the potential to be used as salvage therapy for patients with *P. aeruginosa* relapsing PJI, in combination with suppressive antimicrobial therapy. A Phase II clinical study deserves to be performed to confirm this hypothesis.

**Keywords:** bacteriophages, phage therapy, prosthetic-joint infection, *P. aeruginosa*, phagotherapy

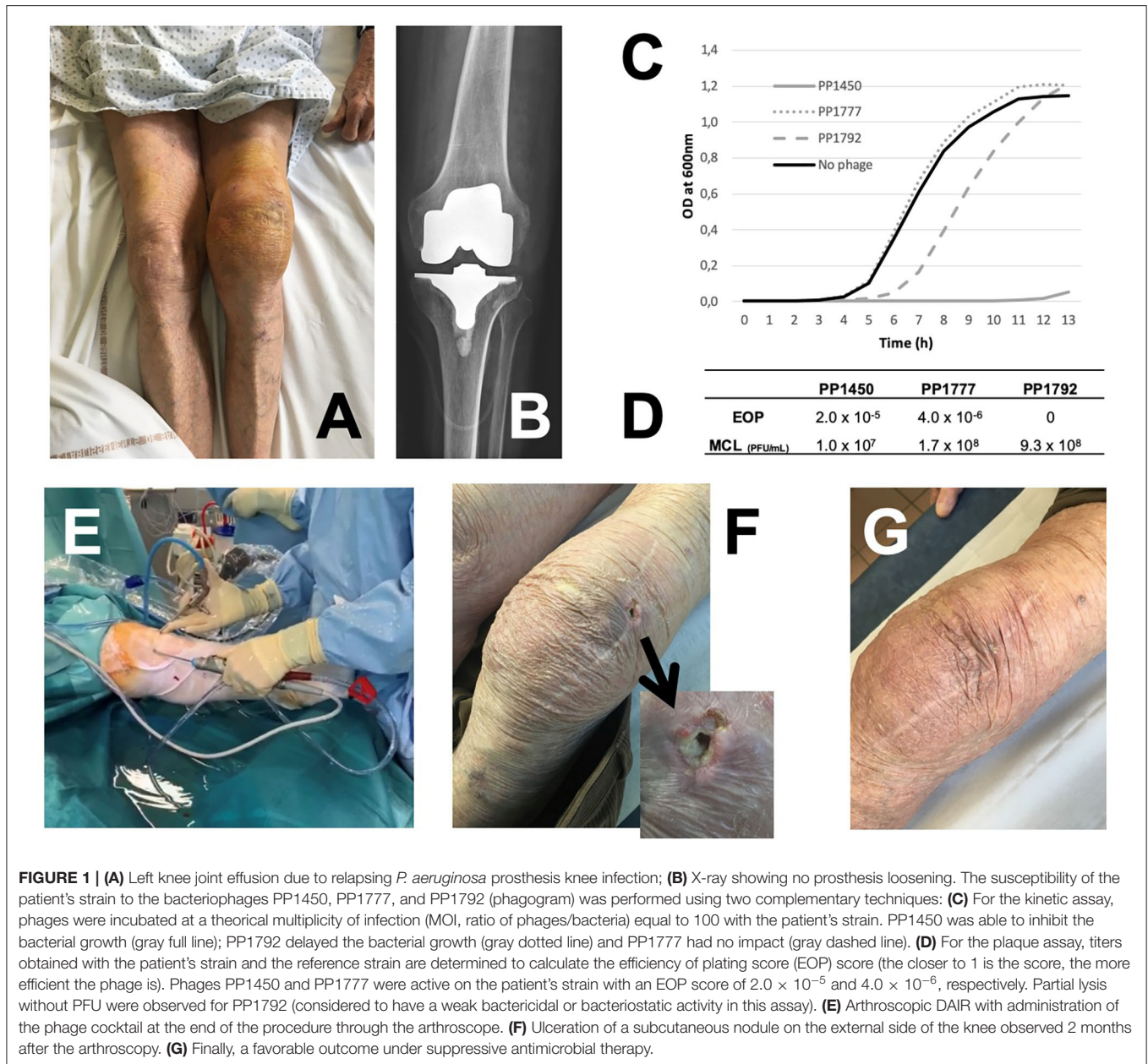
## CASE REPORT

An 88-year-old man (63 kg) had a past history of arrhythmia with severe cardiomyopathy and bilateral arthroplasties several years ago. A colonoscopy was performed and was followed a few days later by clinical signs of septic arthritis of the left knee. The patient did not have fever, but CRP was ~200 mg/L. Echocardiography disclosed no signs of endocarditis. Analysis of joint puncture showed infiltration by polymorphonuclear cells ( $57,000/\text{mm}^3$ ) and *Pseudomonas aeruginosa* susceptible to ceftazidime and ciprofloxacin grew in culture. Open (i.e., by arthrotomy) Debridement Antibiotics and Implant Retention (DAIR) procedure was performed (1), followed by treatment with intravenous ceftazidime 6 g/day plus oral ciprofloxacin (500 mg bid). Three weeks after the surgery, the outcome seemed to be favorable, ceftazidime was stopped, and ciprofloxacin was prolonged for a total duration of 12 weeks. Six months later, the patient experienced a relapse of the joint knee effusion (Figure 1A), with heart failure. CRP was ~100 mg/L. X-ray disclosed no loosening of the prosthesis (Figure 1B). A knee joint puncture showed *P. aeruginosa* persistence, with the same antimicrobial susceptibility profile. The patient was totally bedridden with severe alteration of the general status. As general anesthesia was contraindicated to explant the prosthesis or to perform a new open DAIR, we proposed to this patient the use of phage therapy to try to control the disease. After multidisciplinary meetings in our reference center (which is certified by the French ministry of health for the management of complex bone and joint infection), (2) and in accordance with the local ethics committee, this case was individually discussed with the French National Agency for Medicines and Health Products Safety (ANSM), to validate that no other options could be proposed without excessive risk of death. Phages, targeting *P. aeruginosa*, were selected from the Pherecydes Pharma library based on their lytic activity on the patient's strain (3). The phages have been produced in a non-GMP facility but have undergone a thorough quality evaluation with multiple quality control tests. Phagograms were performed using kinetic assay and the plaque assay, to calculate the efficiency of plating score (EOP) as previously described (Figures 1C,D) (4). Three bacteriophages (PP1450, PP1777, and PP1792) were selected, as they were totally or partially active for at least one technique. PP1450 and PP1777 belong to the *Myoviridae* family, and their closest relative in public database (Genbank) belong to the *Pbunavirus* genus (ICTV 2018). PP1792 belongs to the *Podoviridae* family and *Bruynoghevirus* genus. The patient signed a written consent, explaining the procedure and the risk/benefit ratio. Hospital pharmacist mixed extemporaneously the active phages [initial concentrations 1 ml of  $1 \times 10^5$  (5) PFU/ml for

each phage] to obtain a cocktail of phages in a suspension form [final concentration of  $1 \times 10^6$  (6) PFU/ml for both phages]. Conventional arthroscopy was performed (Figure 1E) using anteromedial and anterolateral entry points and washing of joint with saline. After drainage of the arthroscopic liquid, 30 cc of the phage suspension was injected through the arthroscope. Then, entry points were closed to be waterproof. No other bacteria grew in culture. The patient received again 3 weeks of intravenous ceftazidime (6 g/day) and oral ciprofloxacin (500 mg bid). The patient rapidly improved with disappearance of signs of heart failure and pain of the left knee (Supplementary Video 1). The CRP reached normal values quickly. A subcutaneous nodule that has spontaneously ulcerated appeared on the external side of the knee (Figure 1F), without discharge or any communication with the joint, and then disappeared spontaneously. At 6 months, the local status of the left knee was normal (Figure 1G) and its motion and walking were unproblematic (Supplementary Videos 2, 3). The dose of ciprofloxacin was reduced to 250 mg bid as suppressive antimicrobial therapy to prolong the remission of symptoms (7). One year after the phage administration, the patient unfortunately died from lithiasic pancreatitis, without any clinical signs of prosthetic joint infection (PJI).

Bacteriophages are viruses that specifically target bacteria. They are considered to have a high potential in patients with PJI, as they have a synergistic anti-biofilm activity with antibiotics (8, 9). In several patients with relapsing chronic PJI due to *S. aureus* for whom explantation was not possible, we already performed open DAIR and used selected bacteriophages that were injected into the joint (PhagoDAIR procedure) with a good clinical response (6, 10). Moreover, recent data from animal models provided further support for phage therapy as effective adjunctive treatment for PJI (5). In the present case, arthroscopic DAIR was the only possible surgery, to limit the risk of perioperative death, whereas this procedure is considered to have no place in the management of PJI due to (i) an incomplete debridement (peroperative dislocation is not feasible), (ii) an inability to exchange the polyethylene part of the prosthesis, and (iii) an extremely low success rate. In counterpart, it is easy to inject into the joint the bacteriophages preparation during arthroscopy, and the joint remained perfectly tight (6). The opportunity to target the biofilm is a potential key determinant in such patients if the prosthesis cannot be explanted. By using personalized phage therapy as adjuvant therapy, the aim is to act locally on bacteria embedded in biofilm stucked on the implant surface into the joint cavity, as demonstrated recently in animal and *in vitro* models (11).

This case report leads to question the intrinsic capacity of the phage therapy to improve the outcome of the patient, as



he was also managed with surgery and antibiotics. However, as the patient presented relapsing PJI after previous standard of care treatments, the expected success rate of iterative DAIR procedure performed by arthroscopy and followed by suppressive antimicrobial therapy was very limited if the bacteriophages had no effect on the biofilm. Indeed, arthroscopic DAIR is usually contraindicated in patients with PJI, as (i) the risk of relapse is particularly high if the polyethylene part cannot be changed, likely because such plastic surface promotes biofilm formation; (ii) the reduction of the bacterial load is significantly lower in comparison with open DAIR; and (iii) the evidence and guidelines discourage its use as too much worse outcomes were reported (1, 7, 11–16). Finally here, we hypothesized that the

phage administration has helped the suppressive antimicrobial therapy to succeed in the control of the infection, i.e., to prolong the remission (15, 16).

The present data suggest that the PhagoDAIR procedure by arthroscopy has the potential to be used as salvage therapy for patients with *P. aeruginosa* relapsing PJI, in combination with suppressive antimicrobial therapy. A Phase II clinical study deserves to be performed to confirm this hypothesis.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hospices Civils de Lyon Ethic Committee. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

TF managed the patients and coordinated the treatment procedure. TF wrote the draft of the manuscript. CB, RG, and SL participated to the patient care. CK, C-AG, CF, and CP participated to the microbiological work. GL prepared the phage mix. All authors contributed to the article and approved the submitted version.

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The patient was treated under the routine care in our regional reference center. The patients were treated under the supervision of the French Health ministry. Pherecydes Pharma provided the bacteriophages.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmed.2021.569159/full#supplementary-material>

**Supplementary Video 1** | Video showing the patient walking without any pain 3 weeks after the surgery.

**Supplementary Video 2** | Video showing the motion of the left knee without any pain 3 months after the surgery.

**Supplementary Video 3** | Video showing the patient walking without any pain 3 months after the surgery.

## REFERENCES

- Byren I, Bejon P, Atkins BL, Angus B, Masters S, McLardy-Smith P, et al. One hundred and twelve infected arthroplasties treated with “DAIR” (debridement, antibiotics and implant retention): antibiotic duration and outcome. *J Antimicro Chem.* (2009) 63:1264–71. doi: 10.1093/jac/dkp107
- Ferry T, Seng P, Mainard D, Jenny JY, Laurent F, Senneville E, et al. The CRIOAc healthcare network in France: a nationwide health ministry program to improve the management of bone and joint infection. *Orthop Traumatol Surg Res.* (2019) 105:185–90. doi: 10.1016/j.otsr.2018.09.016
- Jault P, Leclerc T, Jennes S, Pirnay JP, Que YA, Resch G, et al. Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial. *Lancet Infect Dis.* (2019) 19:35–45. doi: 10.1016/S1473-3099(18)30482-1
- Ferry T, Boucher F, Fevre C, Perpoint T, Chateau J, Petitjean 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. *J Antimicrob Chemother.* (2018) 73:2901–3. doi: 10.1093/jac/dky263
- Morris JL, Letson HL, Elliott L, Grant AL, Wilkinson M, Hazratwala K, et al. Evaluation of bacteriophage as an adjunct therapy for treatment of peri-prosthetic joint infection caused by *Staphylococcus aureus*. *PLoS ONE.* (2019) 14:e0226574. doi: 10.1371/journal.pone.0226574
- Ferry T, Kolenda C, Batailler C, Gustave CA, Lustig S, Malatray M, et al. Phage therapy as adjuvant to conservative surgery and antibiotics to salvage patients with relapsing *S. Aureus* prosthetic knee infection. *Front Med.* (2020) 7:570–2. doi: 10.3389/fmed.2020.570572
- Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the infectious diseases society of America. *Clin Infect Dis.* (2013) 56:e1–25. doi: 10.1093/cid/cis966
- Kolenda C, Josse J, Medina M, Fevre C, Lustig S, Ferry T, et al. Evaluation of the activity of a combination of three bacteriophages alone or in association with antibiotics on staphylococcus aureus embedded in biofilm or internalized in osteoblasts. *Antimicrob Agents Chemother.* (2020) 64:e02231-19. doi: 10.1128/AAC.02231-19
- Chegini Z, Khoshbayan A, Taati Moghadam M, Farahani I, Jazireian P, Shariati A. Bacteriophage therapy against *Pseudomonas aeruginosa* biofilms: a review. *Ann Clin Microbiol Antimicrob.* (2020) 19:45. doi: 10.1186/s12941-020-00389-5
- Ferry T, Leboucher G, Fevre C, Herry Y, Conrad A, Josse J, 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 Infect Dis.* (2018) 5:ofy269. doi: 10.1093/ofid/ofy269
- Abouljoud MM, Backstein D, Battenberg A, Dietz M, Erice A, Freiberg AA, et al. Hip and knee section, treatment, surgical technique: proceedings of international consensus on orthopedic infections. *J Arthroplasty.* (2019) 34(Suppl. 2):S445–51. doi: 10.1016/j.arth.2019.02.063
- Ariza J, Cobo J, Baraia-Etxaburu J, de Benito N, Bori G, Cabo J, et al. Executive summary of management of prosthetic joint infections. Clinical

- practice guidelines by the Spanish society of infectious diseases and clinical microbiology (SEIMC). *Enferm Infecc Microbiol Clin.* (2017) 35:189–95. doi: 10.1016/j.eimce.2017.02.013
13. Malhotra R, Dhawan B, Garg B, Shankar V, Nag TC. A comparison of bacterial adhesion and biofilm formation on commonly used orthopaedic metal implant materials: an *in vitro* study. *Indian J Orthop.* (2019) 53:148–53. doi: 10.4103/ortho.IJOrtho\_66\_18
  14. Waldman BJ, Hostin E, Mont MA, Hungerford DS. Infected total knee arthroplasty treated by arthroscopic irrigation and debridement. *J Arthroplasty.* (2000) 15:430–6. doi: 10.1054/arth.2000.4637
  15. Escudero-Sanchez R, Senneville E, Digumber M, Soriano A, Del Toro MD, Bahamonde A, et al. Suppressing antibiotic therapy in prosthetic joint infections: a multicentre cohort study. *Clin Microbiol Infect.* (2020) 26:499–505. doi: 10.1016/j.cmi.2019.09.007
  16. Pradier M, Robineau O, Boucher A, Titecat M, Blondiaux N, Valette M, et al. Suppressing antibiotic therapy with oral tetracyclines for prosthetic joint infections: a retrospective study of 78 patients. *Infection.* (2018) 46:39–47. doi: 10.1007/s15010-017-1077-1

**Conflict of Interest:** CF and CP are employed by Pherecydes Pharma.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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