BMC Infectious Diseases

RESEARCH Open Access

Proportion of patients with prosthetic joint infection eligible for adjuvant phage therapy: a French single-centre retrospective study

Ambroise Le Pogam[1], Fernanda Medina[1], Anna Belkacem[1], Alice Raffetin[1], Danielle Jaafar[1], Philippe Wodecki[2], Camille Corlouer[3], Alain Dublanchet[4], Pauline Caraux-Paz[1] and Kevin Diallo[5*]

Abstract

Background Bone and joint infections represent a major public health issue due to their increasing prevalence, their functional prognosis and their cost to society. Phage therapy has valuable anti-biofilm properties against prosthetic joint infections (PJI). The aim of this study was to establish the proportion of patients eligible for phage therapy and to assess their clinical outcome judged against all patients presenting with PJI.

Method . Patients admitted for periprosthetic joint infection (PJI) at a French general hospital between 2015 and 2019 were retrospectively included. Eligibility for phage therapy was determined based on French recommendations, with polymicrobial infections serving as exclusion criteria. Patients were categorized into two groups: those eligible and those ineligible for phage therapy. We analyzed their characteristics and outcomes, including severe adverse events, duration of intravenous antibiotic therapy, length of hospitalization, and relapse rates.

Results . In this study, 96 patients with PJI were considered in multidisciplinary medical meetings. Of these, 44% patients (42/96) were eligible for additional phage therapy. This group of patients had a longer duration of intravenous therapy (17 days vs. 10 days, $p=0.02$), more severe adverse events (11 vs. 3, $p=0.08$) and had a longer hospital stay (43 days vs. 18 days, $p<0.01$).

Conclusion . A large number of patients met eligibility criteria for phage therapy and treatment and follow-up is more complex. A larger epidemiological study would more accurately describe the prognosis of eligible patients.

Keywords Phage therapy, Bone and joint infection, Prosthesis

*Correspondence:
Kevin Diallo
kevin.diallo@chu-reunion.fr
[1]Department of Infective and Tropical Diseases, Intercommunal Hospital Centre of Villeneuve- Saint-Georges, Villeneuve-Saint-Georges 94190, France
[2]Department of Orthopaedic surgery, Intercommunal Hospital Centre of Villeneuve-Saint- Georges, Villeneuve-Saint-Georges 94190, France
[3]Department of Bacteriology, Intercommunal Hospital Centre of Villeneuve-Saint-Georges, Villeneuve-Saint-Georges 94190, France
[4]46 rue Céline Robert, Vincennes 94300, France
[5]Department of Infective and Tropical Diseases and Dermatology, University Hospital of La Reunion, Saint-Pierre 97448, France

Introduction

Bone and joint infections (BJI) are severe infections that can impact functional joint prognosis. Incidence is rising due to the increase in joint replacement surgeries using prostheses, itself the result of the aging and comorbidity of the general population. Their increasing incidence, complexity of management, associated complications and economic cost to society make BJIs a major public health issue [1, 2]. In France between 2014 and 2019, there were 28,365 BJI. Of these, 11,298 were due to prosthetic joint infections (PJI), 67% of which were considered complex [3].

In France, referral centers for complex BJI (CRIOAc) were created in 2008 with the objective of improving management, education and clinical research and benefit from multidisciplinary team (MDT) expertise including an infectiologist, an orthopaedic surgeon and a microbiologist [4].

French criteria defines complex BJI as: host specificity (severe comorbidities impacting the therapeutic strategy, severe allergy to an antibiotic), causative microorganisms (multi-resistant bacteria, mycobacteria, anaerobic bacteria, polymicrobial infection), surgical criteria (BJI requiring bone resection or complex skin or soft tissue reconstruction), and BJI relapse [5].

These criteria can identify a BJI at risk of complication and therapeutic failure, which could potentially benefit from complementary therapies. Despite improvements and standardization in surgical and medical management protocols over time, therapeutic innovations for IBD remain scarce. Of the various complementary therapies for BJI infections, phage therapy is gaining popularity.

Phage therapy consists of using a bacteriophage virus (virus infecting bacteria) to treat an infection. Since its first use in 1919 by Félix d'Hérelle [6] and despite frequent use, especially in Eastern Europe, phage therapy was supplanted by antibiotics, whose efficacy revolutionized the treatment of infections from the Second World War to the present day [7]. Nevertheless, the almost exclusive use of antibiotics in the treatment of bacterial infections has led to the growing incidence of antibiotic resistance in the absence of therapeutic alternatives [8]. Phage therapy has unique properties that give it a key role in the post-antibiotic era therapeutic arsenal. Its specificity of action on one bacterial species [9], its antibiofilm action via phage-derived enzymes [10], a continued efficacy against multi-resistant bacteria due to a different mechanism of action to that of antibiotics [11] and its synergistic action with antibiotics [12]. Although several publications have reported on the clinical success of phage therapy in cases where antibiotics alone have been inadequate [13], particularly endocarditis, pulmonary infection in cystic fibrosis and BJI, phage therapy is still struggling to find its place in medical therapeutics.

The therapeutic use of phage therapy in BJI has been noted in numerous publications [14, 15] as yet without formal evidence of its efficacy [16–18]. Phage therapy represents a potentially new therapeutic treatment for BJI where the functional articular prognosis is severe and where therapeutic options are limited. Some phase III studies are in progress, such as PhagoDAIR in France [19], focusing on PJI.

In France, eligibility for phage therapy is incorporated into the eligibility criteria for complementary therapies. This encompasses the presence of a complex BJI and the validation of the indication by a MDT, without including specific criteria that take into account the distinctive properties and limitations of phage therapy, such as the necessity of a monobacterial infection with disponible phage cocktail (i.e. in France *Pseudomonas aerugenosa*, *Staphylococcus spp.*, *E. coli*).

Although few adverse events have been so far reported [20], the lack of homogenized therapeutic protocols and the absence of precise indications for phage use limits this treatment to salvage therapy in exceptional cases rather than its broader theoretical indication.

In this study, we analyzed the characteristics and outcomes of patients eligible for phage therapy according to the French BJI recommendation compared with ineligible patients, both of whom received standard of care treatment without phage therapy. The aim of this study is to evaluate the suitability of the existing eligibility criteria for phage therapy and to propose potential improvements for future randomized controlled trials.

Method

We retrospectively included all patients hospitalized for PJI between January 2015 and December 2019 in Villeneuve-Saint-Georges general hospital, a referral BJI center in France. MDT including microbiologists, infectious diseases specialists and orthopedic surgeons were held to discuss the patients' medical situations. Patients included in this study had a PJI proven by a culture-based method, such as joint fluid culture in the case of joint infection or bone biopsy in the case of osteitis, and antibiotic susceptibility testing with antibiogram.

The aim was to assess the indication for phage therapy and compare patient out-comes with or without indication for complementary treatment. For this, patients were divided into two groups: patients eligible as per the French criteria of complex BJI (similar for PJI), and ineligible patients.

The eligibility criteria fulfilled the definition of complex BJI according to French national recommendation [5], namely one of the following criteria:

- Severe allergy to at least one antibiotic class in the antibiogram of the causative germ leading to suboptimal antibiotherapy.
- Major comorbidities limiting treatment, specifically, any two of the following: cardiac insufficiency NYHA ≥ II, respiratory insufficiency, chronic renal failure with Glomerular Filtration Rate (GFR) < 30 mL/min, immunodeficiency, hypoalbuminemia < 30 g/L, grade II obesity (Body Mass Index (BMI) > 35 kg/m2) and hepato-cellular insufficiency.
- Multi-resistant bacterial infection (MRSA, ESBL) or unusual (mycobacteria, Gram Positive anaerobic bacteria such as *Clostridioides* spp.)
- Complex surgical criteria declared by a specialist in osteoarticular infections.
- "Infection relapse, defined as recurrence of the infection at the same joint, caused by the same pathogen, after a period of clinical remission, despite optimal treatment".

The only exclusion criterion were a polymicrobial infection or absence of bacterial documentation.

From December 2012 to December 2019, data were collected from patients' health records by two trained physicians. These researchers used a standardized protocol to ensure consistency and accuracy, including. The extracted data were then cross-checked by the second physicians. The data extraction process entailed the retrieval of the following characteristics information : infection site (knee, hip, long bone, ankle and shoulder prosthesis), early (less than 4 weeks) or late (more than 4 weeks) occurrence after surgery, acute (less than 3 months) or chronic (more than 3 months) infection, microbiological results (including bacterial identification, number of samples and resistance (especially MRSA, MDR, fluoroquinolone and rifampicin resistance).

The outcomes of the study were also retrospectively collected. Primary outcome was the occurrence of a relapse, defined as a recurrence of the infection at the same joint, caused by the same pathogen, after a period of clinical (no discharge, no inflammation) and biological remission (CRP < 5 mg/L, no bacterial documentation) of at least 1 month.

Secondary outcomes were the duration of antibiotic therapy and the duration of all intravenous therapy, time from diagnosis to surgery, treatment-related side effects and length of hospital stay.

Duration of antibiotic therapy were calculated from the first day of antibiotic administration to the last one, including the initial and any subsequent changes in the antibiotic regimen based on patient response and microbiological findings.

All adverse events were recorded including allergic reaction, gastrointestinal disturbances, acute kidney injury, cutaneous eruption. Adverse events were assessed according to the according to NCI CTCAE terminology, serious adverse effects being considered grade > 2, indicating a need for prolonged hospitalization or the limitation of self-care activities of daily living (grade 3), or life-threatening (grade 4) or fatal (grade 5) events.

Statistical analyses were performed using Jupyter Notebook software. Quantitative variables were represented by mean and standard deviation with a 95% confidence interval (CI) and were compared by analysis of variance using the Student test (ANOVA). Categorical variables were represented by numerical values and percentages and were compared using the Chi2 test (or Fisher test when the conditions for the Chi2 test were not met). A p-value < 0.05 was considered significant.

This study received approval from the Research Committee of the University Hospital of Bordeaux, reference CER-BDX 2024−120. As the data collected were retrospective, Jarde law was not appliable and no consent was requested.

Results

A total of 96 patients with PJI were presented to the hospital BJI multidisciplinary team between January 2015 and December 2019. Of these 96 patients, 36 (37%) patients did not meet the eligibility criteria for phage therapy (Group 1) and 42 (44%) met the eligibility criteria for phage therapy (Group 2); 18 (19%) patients meeting the eligibility criteria were excluded from the study due to polymicrobial infection. Of the 42 eligible patients (Group 2), 39 had two major comorbidities, 32 had complex surgical criteria, 8 had a MDR bacteria (6 MRSA and 2 ESBL), 4 patients had a PJI relapse and 2 patients had severe allergy (anaphylaxis) to beta-lactam antibiotics. The 3 eligible patients without the 2 major comorbidities criterion had complex surgical criteria (2 patients) or MRSA infection (1 patient).

The 18 excluded patients presented at least one of the eligible criteria (16 had two major comorbidities, 12 had complex surgical criteria, 3 had relapse) and also a polymicrobial infection: 5 patients had co-infection with 2 strains of staphylococci (3 coagulase-negative *Staphylococcus* co-infections, and 2 with co-infection by a *Staphylococcus aureus* and a coagulase-negative *Staphylococcus*) and the remaining 13 had co-infection with different types of bacteria including *Staphylococcus*, *Streptococcus* (*S. agalactiae*, *S. oralis* and *S. anginosus*), *Enterococcus* (*E. faecalis* and *E. faecium*), anaerobic bacteria (*Bacteroides fragilis*, *Clostridium perfringens* and *Cutibacterium acnes*) and a *Candida glabrata*.

Of the initial characteristics of the population (Table 1), the mean age was significantly higher in Group 2 (eligible)

Table 1 Baseline characteristics of patients and PJI according to eligibility for phage therapy

	Group 1 Ineligible	Group 2 Eligible	*p*-value
Total (N)	36	42	
Age (mean in years)	60.2 ± 18.2	71.1 ± 13.7	0.005
BMI (mean in kg/m2)*	27.8 ± 5.9	30.3 ± 7.8	-
Female Sex (%)*	16 (44.4)	18 (42.6)	0.93
Albumin level (mean in g/L)*	35.1 ± 8.6	30.6 ± 6.4	-
Allergy (n, %)*	3 (8.3)	6 (14.3)	-
Diabetic (n, %)	3 (8.3)	11 (26.2)	0.008
GFR < 30 mL/min (n, %)*	0 (0)	2 (4.7)	-
Hepatocellular insufficiency (n, %)*	2 (5.6)	3 (7.1)	-
Cardiopathy (n, %)*	7 (19.4)	22 (52.3)	-
Immunocompromised (n, %)*	1 (2.8)	9 (21.4)	-
At least one major medical comorbidity (n, %)*	22 (61.1)	39 (92.9)	-
Late infection (n, %)	18 (50.0)	28 (66.6)	0.2
Chronic infection (n, %)	10 (27.8)	22 (52.4)	0.049
Material withdrawal (n, %)	21 (58.3)	21 (50.0)	0.45
***Staphylococcus aureus*(n, %)**	20 (55.6)	19 (45.2)	0.56
Negative Coagulase*Staphylococcus*(n, %)	10 (27.8)	6 (14.3)	0.27
Enterobacteria (n, %)	2 (5.6)	7 (16.7)	0.22
***Pseudomonas aeruginosa*(n, %)**	1 (2.7)	3 (7.1)	0.7
More than one bacteria (n, %)*	8 (22.2)	0 (0)	-
MRSA (n, %)*	0 (0)	6 (14.3)	-
ESBL (n, %)*	0 (0)	2 (4.8)	-
Fluoroquinolone resistance (n, %)*	3 (8.3)	6 (14.3)	-
Rifampicine resistance (n, %)	0 (0)	0 (0)	
MDR bacteria (n, %)*	0 (0)	8 (19.0)	-

Plus-minus values are means +/- SD. Abbreviations: BMI: Body Mass Index, GFR: Glomerular Filtration Rate, MRSA: Methicillin Resistant *Staphylococcus aureus*, ESBL: Extended Spectrum Beta-Lactamases, MDR : Multi-Drug Resistant

* Statistical analysis was not performed on characteristics corresponding to eligibility or exclusion criteria.

Table 2 Evolution characteristics of patients according to eligibility for phage therapy after management of PJI

	Group 1 Ineligible	Group 2 Eligible	*p*-value
Time from diagnosis to surgery (mean in days)	13.6 ± 42.8	8.7 ± 12.1	0.52
Antibiotherapy duration (mean in days)	56.7 ± 20.3	61.1 ± 24.0	0.39
Intravenous therapy (mean in days)	9.6 ± 7.4	17.2 ± 7.5	0.02
Serious adverse events (n, %)	3 (8.3)	11 (26.2)	0.08
Hospitalization length (mean in days)	18.3 ± 15.3	42.5 ± 32.0	< 0.001
Relapse (n, %)	5 (13.9)	9 (21.4)	0.23

Plus-minus values are means +/- SD

than in Group 1 patients (ineligible) (71.1 vs. 60.2 years, $p<0.01$) and diabetes was more frequent (26.2% vs. 8.3%, $p=0.008$).

The removal of the device occurred in 58% and 50% of patients in Group 1 and 2 respectively and time from prosthesis installation to infection was 641 days (Group 1) and 747 days (Group 2), with no significant difference. There were significantly more chronic infections (>3 months) in the eligible group than the non-eligible group (52.4% vs. 27.8% respectively).

S. aureus was the most frequently causative bacteria, responsible for 45% of infections in Group 2 and 55% in Group 1. Presence of resistant bacteria was an eligibility criterion for phage therapy: 14% of MRSA were found in Group 2, 4% of ESBL and a total of 18% of MDR bacteria.

No significant difference in primary outcome was observed: successful treatment without relapse occurred in 78.6% of cases in the eligible group (Group 2) compared to 86.1% in the non-eligible group (Group 1) ($p=0.23$) (Table 2).

The duration of intravenous antibiotic therapy was longer in the eligible group (17.2 days versus 9.6 days, $p=0.02$). The incidence of serious adverse events was higher in the eligible group than in the ineligible group, although this difference was not statistically significant (11 vs. 3, respectively; $p=0.08$). The serious adverse events experienced by the eligible group included severe

cutaneous reactions ($n=3$), acute kidney injuries ($n=3$), *Clostridioides difficile* infection ($n=2$), tendon rupture ($n=2$) and hepatic insufficiency ($n=1$). In the ineligible group, three serious adverse effects were observed: one case of hepatic insufficiency, one case of *Clostridioides difficile* infection, and one case of acute kidney injury. Time from diagnosis to surgery and duration of antibiotic therapy did not have any significant differences.

Finally, the length of hospitalization was significantly longer in the eligible group (42.5 days versus 18.3 days, $p<0.001$).

Discussion

Our study provides important insights into the potential application of phage therapy in the treatment of BJI, particularly PJI. We identified that 42 out of 96 (44%) patients were eligible for phage therapy, while 36 (37%) were not, indicating that a substantial proportion of patients could potentially benefit from this treatment modality, especially those with resistant pathogens or significant comorbidities at high risk of complications under standard protocols. The sole categorical exclusion criterion was polymicrobial infections, which affected 18 out of 96 (19%) patients, highlighting the critical need for precise patient selection criteria. Also, material withdrawal occurred at a comparable rate (58% vs. 50%, $p=0.45$) between the two groups. However, a more precise definition of the population eligible for phage therapy could increase the use of DAIR (Debridement, Antibiotherapy, Implant Retention) procedures, which are less aggressive and costly, while still maintaining success in infection control due to the adjunctive use of phage therapy.

Furthermore, our analysis revealed that eligible patients experienced longer intravenous treatment and hospitalization times, as well as more frequent adverse events, all of which increased the risk of severe complications, particularly in patients with numerous co-morbidities. Future randomized controlled trials should include these outcomes to provide a comprehensive assessment of the effectiveness of phage therapy.

These findings underscore the necessity of redefining eligibility and exclusion criteria specific to phage therapy to ensure the identification of the most appropriate patient population for this complementary therapy. Our study sets the stage for future research to refine these criteria and optimize treatment protocols, ultimately enhancing patient outcomes and addressing the growing challenge of managing PJI in an ageing population with rising antibiotic resistance.

Eligibility criteria

The eligibility criteria used in this study are based on the French complex BJI criteria, which are broad and define a population at risk of complication and therapeutic failure, but without prejudging the therapy to be initiated. The criteria should be improved and provide a better prediction of patients specifically eligible for phage therapy.

The combination of major comorbidities making a patient eligible for complementary therapy dominates all other criteria since they are present in almost all eligible patients (39/42). The intrinsic heterogeneity of this composite criterion is also a limitation, since the respective weight of each component on the risk of intraoperative and postoperative complications is unknown. Assigning a weight to each of the patient's comorbidities would allow the risks of postoperative complications to be more accurately gauged and would determine the value of complementary therapies such as phage therapy. Furthermore, comorbidities such as immunosuppression must be more accurately categorized as they do not reflect the vast heterogeneity of immunosuppressed patients. This criterion, which is highly sensitive, deserves to be re-evaluated in the light of epidemiological BJI data.

The criterion of complex surgery assesses the feasibility and risks of arthroplasty for patients. This operation frequently gives rise to complications in elderly patients with comorbidities. This composite criterion is assessed by an orthopedic surgeon with expertise in BJI and determined by the site of infection, the clinico-radiological characteristics of the infection, the patient's comorbidities and the technical complexity of the surgical procedure. This is an important criterion that encourages, faced with a very high risk of pre-operative and postoperative complications, conservative management of the joint in certain situations, as in the DAIR protocol, which may be associated with phage therapy.

Although relevant and common in this cohort, complex surgery was the sole eligibility criterion in only two patients. This can be explained by the fact that patients with numerous comorbidities or who had already relapsed are considered as complex by the surgeon, making this criterion redundant with the other eligibility criteria based on patients' comorbidities.

Phage therapy is also the preferred option in cases of suboptimal antibiotic treatment, such as allergy or MDR bacteria. However, it cannot be used as a substitute for antibiotic therapy at this time: optimal and conventional antibiotic therapy should always be used even when additional treatment is initiated. Severe allergy to one of the antibiotics recommended for the optimal management of PJI occurred in 2 patients, but was never the sole criterion for eligibility.

MDR bacteria were found in 8/42 patients and were the only eligibility criterion in one patient (MRSA infection). MDR bacteria are a major global health problem [21], making the need for alternative or complementary antibiotic therapy vital. Furthermore, antibiotic resistance

in Staphylococcus strains (the bacteria most commonly implicated in the BJI and in this cohort) is complex; a single antibiogram is of limited use due to the coexistence of multiple colonies with different resistance profiles, the small colony variants (SCVs) [22]. Phage therapy bypasses antibiotic resistance and is effective even against MDR or SCV [23], making it extremely valuable in such cases.

Relapses are a robust indication as the optimal medical-surgical treatment has already been proven to be insufficient. In this situation, phage therapy requires a new antibiogram to ascertain that the relapse is attributable to the same bacteria, to confirm the absence of co-infection and the sensitivity of the strain to antibiotics and phage cocktails. In case reports such as Patey et al. [15], Ferry et al. [24] or more recently Doub et al. [25], patients underwent several courses of antibiotic or surgical treatments unsuccessfully before undergoing phage therapy. Nevertheless, phage therapy should not be limited to salvage unsuccessful complex multitreated BJI and could find a role in first-line curative treatment in selected patients at risk of unfavorable outcome. A promising concept would be the creation of a weighted clinical score assessing the vital, functional and relapse prognosis of patients managed for BJI in order to better select patients for complementary phage therapy.

Exclusion criteria

In the absence of known contraindications and in the absence of adverse effects related to phage therapy [20], the sole exclusion criterion retained in this study was polymicrobial infection, in which the narrow spectrum activity of phage therapy would have been impaired. However, it is not excluded that phage therapy may still retain its efficacy in cases of polymicrobial infection, either by combining phage cocktails [26], or by the action of phage lysins on the biofilm, indirectly improving the diffusion of the antibiotic to the bacterial strains without direct lytic action. In our cohort, of the 18 polymicrobial infections, 5 were due to two strains of *Staphylococcus*, common in polymicrobial PJI infections. If the bacteria are sensitive to the anti-*Staphylococcus* phage cocktail, administration of a single anti-*Staphylococcus* phage cocktail may be beneficial. Nevertheless, in the absence of compelling evidence supporting the efficacy or safety of phage therapy, it is prudent to initially reserve its use for conventional monomicrobial infections, thereby avoiding the potential for confounding factors to contribute to treatment failure.

Current randomized controlled studies in France have stricter indications than this study. The PhagoDAIR study [19] focuses exclusively on *Staphylococcus aureus* PJI, where phage administration takes place during the DAIR (Displacement Antibiotic Implant Retention). It specifies many other exclusion criteria in addition to polymicrobial infection. Among these, sensitivity of the identified bacterial strain to the phage cocktail, proven by phagogram, is a key criterion. However, criteria such as cytolysis and renal failure (defined respectively in PhagoDAIR as ALT or AST > 5 x ULN and creatinine > 1.53 mg/dL in men or > 1.24 mg/dL in women), sepsis or septic shock and an ASA score ≥ 4 were not retained as exclusion criteria in our study due to lack of evidence for potential hepatotoxicity, nephrotoxicity or other toxicity of phage therapy. In addition, the study excluded early *S. aureus* infections (< 3 months), which have a better prognosis than chronic infections and for which the benefit of additional treatment is unclear. Rigorous recruitment in therapeutic phage therapy trials in PJI is essential to homogenize the patients and to provide formal scientific proof of the value of phage therapy in specific indications, and finally to expand the use of phage therapy from mere salvage therapy. Conversely, the poor prognosis of patients with complex BJI and the theoretical safety of phage therapy would encourage its wider use once proof of efficacy is obtained.

Strength and limitations

Although this study is the first to our knowledge to explore the impact of phage therapy eligibility criteria in patients with PJI, it suffers from several limitations. Firstly, the monocentric recruitment limited the number of patients to be analyzed and the strength of the study. Although eligible patients were more comorbid and had longer hospital stays than patients not eligible for phage therapy, this study did not find any significant difference in terms of adverse events or relapse. This may be explained by the lack of power of the monocentric recruitment and its limited follow-up. A nationwide study would be necessary to provide a better evaluation of the need for complementary therapy and the potential socio-economic impact. Also, some of the results, such as the differences between the two groups in terms of comorbidity and hospitalization length, are inherent to the eligibility criteria and can be explained by the selection of older patients with more comorbidities in the eligible group. Finally, the generalizability of study is a significant point. This study's methodology for defining eligibility criteria is essentially based on the French BJI complex criteria adapted to phage therapy. Although these criteria are not internationally validated, they are based on generally accepted arguments regarding the risk of complications (comorbidity, surgical complexity, multi-drug resistant bacteria and relapse), to which the need for a monomicrobial infection has been added. The criterion of availability of phage cocktails was not included in our study due to international differences. For example in France, three phage cocktails are available for use in accordance with the European Good

Manufacturing Process, while other phage cocktails are already available in other country (e.g. against *Acinetobacter baumanii* in the United State [27] and others will probably be developed in the next few years.

Perspectives for phage therapy in PJI for clinical practice, research and policy makers

The advantages of phage therapy are numerous and offer new opportunities in PJI, an increasingly common condition for which therapeutic innovation is rare. Although specific indications and eligibility criteria for phage therapy have yet to be defined, other variables must be taken into consideration. Parameters remaining to be clarified to determine optimal use of phage therapy include its method of administration, composition, pharmacodynamics and accessibility of phage cocktails. Phage therapy does not follow the same rules as conventional drugs, in part due to the capacity of phages to multiply and thus increase their concentration at the site of infection without further administration. Furthermore, eligible patients who already have a longer length of stay, there may be concerns that the addition of phage therapy could further extend hospitalization. However, some protocols, such as those used in the PHAGODAIR study, propose a single intraoperative administration at the end of the DAIR procedure, which would not be expected to prolong the length of hospital stay or impair the usual PJI care. New tools are being developed [28] to predict the optimal timing of administration and amount of phage to administer in order to achieve an effective concentration of phage at the site of infection after administration.

The route of administration and bioavailability of the phage cocktail is also a determining factor in its clinical efficacy [29]. While current studies favor intraarticular administration, it is possible that intravenous administration may lead, to a lesser extent, to diffusion of phages in the joint. Indeed, intraarticular use during a DAIR procedure with prosthesis maintenance ensures maximum exposure of the joint to the phage cocktail but is limited to a single use, while intravenous administration allows several administrations. Phages are cleared by the immune system and phage proteins are rapidly degraded by enzymes [30], making the development of new phage delivery options essential to protect them as they travel through the bloodstream to the target. Encapsulation in nanovesicles, as pegylated liposomes, appears to be a promising solution to increase phage diffusion via the bloodstream to the infection site, and would allow oral administration of the phages [31].

The manipulation of phage cocktails also requires special hospital infrastructure, in particular a high security biological laboratory, which is currently not the case in many health care facilities. To overcome this problem, a promising new therapeutic approach is the exclusive use of phage derived-enzymes, simplifying manipulation of phage-derived products [32] and providing greater accessibility to phage therapy. There are two classes of phage-derived enzymes: lysines, which hydrolyze bacterial peptidoglycan layers, and polysaccharide depolymerases which target extracellular polysaccharides, an essential component of biofilm and bacterial capsules [33].

Finally, new challenges will also have to be overcome, such as supply: there are few pharmaceutical companies producing phages to current Good Manufacturing Practice regulations (GMP) in Europe and is currently not sufficient to meet demand [34] other than salvage therapy.

Conclusions

To our knowledge, this is the first study to examine the eligibility criteria for phage therapy in PJI, which has a promising therapeutic potential but requires a more precise definition of patients most likely to benefit from phage therapy as well as optimal delivery protocols of phage cocktails. This study showed that many patients with PJI are eligible for phage therapy according to French recommendation and presented a worse outcome in terms of hospitalization and intravenous treatment duration than non-eligible patients. We recommend that future randomized controlled trials consider these outcomes as valuable and pertinent in addition to clinical success, in order to assess the effectiveness of phage therapy.

A larger study could clarify the importance of further research on complementary therapies, especially phage therapy, to improve individual prognoses and the associated socio-economic benefits.

There is a renewed interest in phage therapy in response to the threat of antibiotic resistance and the need for personalized treatment. Despite gaps in knowledge, rapid scientific advances are refining therapeutic indications and the modalities of therapy, leading to randomized controlled trials. The use of phage therapy in PJI has the potential to prove its safety and efficacy and provide a much-needed alternative to antibiotics in the therapeutic arsenal against bacterial infection.

Abbreviations

BJI	Bone and Joint Infections
PJI	Periprosthetic Joint Infection
MDT	Multidisciplinary Team
GFR	Glomerular Filtration Rate
BMI	Body Mass Index
MRSA	Methicillin Resistant Staphylococcus aureus
ESBL	Extended Spectrum Beta-Lactamase
MDR	Multi-Drug Resistant
CRP	C-Reactive Protein
CI	Confidence Interval
SD	Standard Deviation
DAIR	Debridement, Antibiotherapy, Implant Retention
SCV	Small Colony Variant
GMP	Good Manufacturing Practice

Acknowledgements
The authors would like to thank Andrew Hobson or his careful reading of the manuscript in English and the late Dr. Olivier Patey for pioneering the use of phages in the Infectious Diseases Department of Villeneuve-Saint-Georges.

Author contributions
Conceptualization, A.L. and K.D.; methodology, A.L. and K.D.; writing—review and editing, A.L., F.M., A.B., A.R., D. J., P.W., C.C., A.D., P.C.P. and K.D.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
This study received approval from the Research Committee of the University Hospital of Bordeaux, reference CER-BDX 2024 – 120. As the data collected were retrospective, Jarde law was not appliable and no consent was requested.

Clinical trial number
Not applicable.

Consent for publication
All authors have read and agreed to the published version of the manuscript.

Competing interests
The authors declare no competing interests.

Received: 16 June 2024 / Accepted: 27 August 2024
Published online: 05 September 2024

References

1. Singh JA, Yu S, Chen L, Cleveland JD. Rates of total joint replacement in the United States: future projections to 2020–2040 using the National Inpatient Sample. J Rhuematol. 2019;46(9):1134–40.
2. Nelson SB, Pinkney JA, Chen AF, Tande AJ. Periprosthetic Joint infection: current clinical challenges. Clin Infect Dis. 2023;77(7):e34–45.
3. Lemaignen A, Bernard L, Marmor S, Ferry T, Grammatico-Guillon L, Astagneau P. Epidemiology of complex bone and joint infections in France using a national registry: the CRIOAc network. J Infect. 2021;82(2):199–206.
4. 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. Orthopaedics & Traumatology: Surgery & Research. 2019;105(1):185–90.
5. Légifrance - Droit national en vigueur. - Circulaires et instructions - INSTRUCTION N°DGOS/PF2/2010/466 du 27 décembre 2010 relative au dispositif de prise en charge des infections ostéo-articulaires complexes [Internet]. [cited 2024 Jul 20]. https://www.legifrance.gouv.fr/download/pdf/circ?id=32322
6. Hérelle F. D'. Le bactériophage Et son comportement. Masson; 1926. p. 568.
7. Chanishvili N. Bacteriophages as therapeutic and prophylactic means: Summary of the Soviet and Post Soviet experiences. Curr Drug Deliv. 2016;13(3):309–23.
8. Coignard B. Antibiorésistance: la situation en France et dans le monde. Bull De l'Académie Nationale De Médecine. 2019;203(3–4):159–69.
9. Olszak T, Latka A, Roszniowski B, Valvano MA, Drulis-Kawa Z. Phage life cycles behind bacterial biodiversity. Curr Med Chem. 2017;24(36):3987–4001.
10. Chan B, Abedon S. Bacteriophages and their enzymes in Biofilm Control. CPD. 2014;21(1):85–99.
11. Ferry T, Kolenda C, Laurent F, Leboucher G, Merabischvilli M, Djebara S, et al. Personalized bacteriophage therapy to treat pandrug-resistant spinal Pseudomonas aeruginosa infection. Nat Commun. 2022;13(1):4239.
12. Diallo K, Dublanchet A. Benefits of combined phage–antibiotic therapy for the control of antibiotic-resistant Bacteria: a Literature Review. Antibiotics. 2022;11(7):839.
13. Stacey HJ, De Soir S, Jones JD. The Safety and Efficacy of Phage Therapy: a systematic review of Clinical and Safety trials. Antibiot (Basel). 2022;11(10):1340.
14. Fedorov E, Samokhin A, Kozlova Y, Kretien S, Sheraliev T, Morozova V, et al. Short-term outcomes of phage-antibiotic combination treatment in adult patients with periprosthetic hip joint infection. Viruses. 2023;15(2):499.
15. Patey O, McCallin S, Mazure H, Liddle M, Smithyman A, Dublanchet A. Clinical indications and compassionate use of phage therapy: personal experience and literature review with a focus on Osteoarticular infections. Viruses. 2018;11(1):18.
16. Abedon ST, Danis-Wlodarczyk KM, Alves DR. Phage therapy in the 21st Century: is there modern, clinical evidence of phage-mediated efficacy? Pharmaceuticals. 2021;14(11):1157.
17. Ferry T, Kolenda C, Gustave CA, Lustig S, Josse J, Batailler C, et al. Phage therapy in bone and joint infection: history, scientific basis, feasibility and perspectives in France. Virologie. 2018;24(1):49–56.
18. Khalifa AA, Hussien SM. The promising role of bacteriophage therapy in managing total hip and knee arthroplasty related periprosthetic joint infection, a systematic review. J Experimental Orthop. 2023;10(1):18.
19. Pherecydes Pharma A, Pilot M, Randomized N-C. Double-Blind Study of Phage Therapy in Patients With Hip or Knee Prosthetic Joint Infection Due to Staphylococcus Aureus Treated With DAIR and Antibiotic Therapy. [Internet]. clinicaltrials.gov; 2022 Jun [cited 2023 Mar 16]. Report No.: NCT05369104. https://clinicaltrials.gov/ct2/show/NCT05369104
20. Geneviève J, McCallin S, Huttner A, Pham TT, Suva D. A systematic review of phage therapy applied to bone and joint infections: an analysis of success rates, treatment modalities and safety. EFORT Open Reviews. 2021;6(12):1148–56.
21. The burden of bacterial antimicrobial resistance in the WHO European region in. 2019: a cross-country systematic analysis - The Lancet Public Health [Internet]. [cited 2024 Jul 20]. https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(22)00225-0/fulltext
22. Loss G, Simões PM, Valour F, Cortês MF, Gonzaga L, Bergot M et al. Staphylococcus aureus Small Colony Variants (SCVs): News From a Chronic Prosthetic Joint Infection. Frontiers in Cellular and Infection Microbiology [Internet]. 2019 [cited 2023 Apr 8];9. https://www.frontiersin.org/articles/https://doi.org/10.3389/fcimb.2019.00363
23. Totten KMC, Patel R. Phage activity against Planktonic and Biofilm Staphylococcus aureus Periprosthetic Joint infection isolates. Antimicrob Agents Chemother. 2022;66(1):e0187921.
24. 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 (Lausanne). 2020;7:570572.
25. Doub JB, Johnson AJ, Nandi S, Ng V, Manson T, Lee M, et al. Experience using adjuvant bacteriophage therapy for the treatment of 10 recalcitrant Periprosthetic Joint infections: a Case Series. Clin Infect Dis. 2023;76(3):e1463–6.
26. Nir-Paz R, Gelman D, Khouri A, Sisson BM, Fackler J, Alkalay-Oren S, et al. Successful treatment of Antibiotic-resistant, poly-microbial bone infection with bacteriophages and antibiotics Combination. Clin Infect Dis. 2019;69(11):2015–8.
27. Schooley RT, Biswas B, Gill JJ, Hernandez-Morales A, Lancaster J, Lessor L, et al. Development and Use of Personalized bacteriophage-based therapeutic cocktails to treat a patient with a disseminated resistant Acinetobacter baumannii infection. Antimicrob Agents Chemother. 2017;61(10):e00954–17.
28. Abedon ST. Further considerations on how to improve phage Therapy Experimentation, Practice, and reporting: Pharmacodynamics perspectives. Phage (New Rochelle). 2022;3(2):98–111.
29. Durr HA, Leipzig ND. Advancements in bacteriophage therapies and delivery for bacterial infection. Mater Adv 4(5):1249–57.
30. Totten KMC, Cunningham SA, Gades NM, Etzioni A, Patel R. Pharmacokinetic Assessment of Staphylococcal Phage K Following Parenteral and Intra-articular Administration in Rabbits. Frontiers in Pharmacology [Internet]. 2022 [cited 2023 Apr 4];13. https://www.frontiersin.org/articles/https://doi.org/10.3389/fphar.2022.840165
31. Loh B, Gondil VS, Manohar P, Khan FM, Yang H, Leptihn S. Encapsulation and Delivery of Therapeutic Phages. Appl Environ Microbiol. 2021;87(5):e01979-20, AEM.01979-20.
32. Murray E, Draper LA, Ross RP, Hill C. The advantages and challenges of using endolysins in a clinical setting. Viruses. 2021;13(4):680.
33. Danis-Wlodarczyk KM, Wozniak DJ, Abedon ST. Treating bacterial infections with bacteriophage-based enzybiotics: in Vitro, in vivo and clinical application. Antibiot (Basel). 2021;10(12):1497.

34. Ferry T, Kolenda C, Briot T, Souche A, Lustig S, Josse J, et al. Past and future of phage therapy and phage-derived proteins in patients with bone and joint infection. Viruses. 2021;13(12):2414.

Publisher's note