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A systematic review of phage therapy applied to bone and joint infections: an analysis of success rates, treatment modalities and safety

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- Bone and joint infections are difficult to treat, and increasing antibiotic resistance has only made them more challenging. This has led to renewed interest in phage therapy (PT). The aim of this systematic review was to determine success rate, current treatment modalities and safety of PT in bone and joint infections.
- A systematic search of PubMed, EMBASE and Cochrane databases as well as the journal *PHAGE* for literature published between January 2000 and April 2021 was conducted according to PRISMA guidelines to identify all human studies assessing bacteriophages as therapy for bone and joint infections. All study designs and patient populations were eligible. The review's primary outcome was success rate.
- Twenty records describing a total of 51 patients and 52 treatment episodes were included. No randomized controlled studies were identified. The overall success rate was 71% (n = 37/52). Topical administration alone was the most frequent administration route (85%, n = 44/52). Antibiotics were administered concomitantly with PT in the majority of treatments (79%, n = 41/52), and surgery was performed for 87% (n = 45/52) of treatment episodes. Four minor adverse events related to PT were reported, representing 8% (n = 4/52) of treatment episodes.
- PT for bone and joint infections has not been evaluated in any randomized controlled clinical study, and current administration modalities are highly variable between case reports and case series. While publications included here show potential benefit and few adverse effects, clinical trials are warranted to assess the efficacy of PT for bone and joint infections and determine optimal treatment modalities.

Keywords: bacteriophages; bone and joint infection; orthopaedics; osteomyelitis; periprosthetic joint infection; phage therapy; systematic review

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Introduction

Bone and joint infections include any infection of the bone (osteomyelitis), joint (septic arthritis) or implants related to these structures (periprosthetic joint infections [PJI], fracture-related infections [FRI] involving plates, screws, or intramedullary nails). Despite a trend towards single-stage treatments,[1–3] a large number of patients require complex treatment protocols involving prolonged antimicrobial therapy and multiple surgeries,[4,5] thus exposing patients to increased probability of multidrug-resistant organism (MDRO) carriage and operative risks. Treatment failure of PJIs and FRIs is encountered in 10–20%[6,7] of cases, and even higher treatment failures of 28% haven been reported amongst patients with foot osteomyelitis.[8] Mortality remains high: surgical revisions of infected joint arthroplasties are associated with a fivefold increase in mortality compared to aseptic revisions.[9] In cases of treatment failure, there are few therapeutic options and amputation is not uncommon.[10] Bacteriophage therapy, also known as phage therapy (PT), has brought fresh hope in curing these patients.

Phages are viruses that specifically infect bacteria.[11] They have an entirely different mechanism of action than antibiotics, and rather than acting on many types

of bacteria, phages are specific to the species, and sometimes strain of pathogen. Being viruses, they infect bacterial cells by adhering to specific cell surface receptors and inserting their genetic material into their hosts.[12] Phages then take over cell metabolism and replicate, ultimately culminating in bacterial lysis at the end of the lytic cycle. The phage progeny are finally released into the surroundings and new bacteria in the vicinity can be infected.[13] As a result of this particular mode of action, phages do not share the same resistance mechanisms as antibiotics, and can thus be effective against certain antibiotic-resistant bacteria.[14] Of particular benefit to bone and joint infections is the ability of phages to multiply at the infection site, making them especially appealing in biofilms where high concentrations of antimicrobials are necessary in order to reach the bacteria that are embedded in a mesh of extracellular proteins.[13] Lastly, some phages seem to be able to infect cells in low metabolic states, such as persister cells in biofilms, and lyse them when metabolic activity is restored.[15]

Phages were first employed in humans in 1919 and were largely used thereafter until the widespread use of antibiotics in the 1940s, after which they were mostly abandoned in Western medicine.[16] Today, PT is gaining a renewed interest to treat infections against which antibiotics have failed, an increasingly frequent problem with the rise of MDROs. In countries where phages are not authorized medicines, phage treatments are carried out under Article 37 of the Helsinki Declaration or under national regulatory frameworks for treating individual patients with unauthorized treatments.[17] Phage therapy treatments are being increasingly reported in case reports, as well as the mainstream media, and the US Food and Drug Administration (FDA) recently approved the first randomized controlled trial (RCT) using phages for the treatment of PJIs.[18] The aim of this systematic review was to identify recent clinical records published on the use of PT to treat bone and joint infections in order to determine the success rate of this therapy, analyse treatment modalities and evaluate safety. The Population, Intervention, Comparator and Outcome (PICO) inclusion criteria are summarized in Fig. 1.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[19] were followed for this systematic review; no review protocol is available. The Cochrane, PubMed and EMBASE databases were searched for records published from 1 January 2000 to 23 April 2021 with the keywords “phage”, “osteoarticular”, and “infection” along with their synonyms (see Appendix I in Supplemental Material for search formulae with MeSH terms). The journal *PHAGE* published by Mary Ann Liebert, Inc. (not indexed in any of the aforementioned databases at the time of the review) was searched separately due to the journal’s focus on PT. Although PT dates back over a century, a 20-year time frame was chosen in order to reflect publications pertaining to the recent renewed interest in PT and relevant treatment and reporting standards.

Eligibility criteria

Inclusion criteria for this review are described in Fig. 1. Briefly, records reporting studies of any design and any patient population were eligible; animal studies and in vitro experimental models were excluded, as were records of conferences. There were no language restrictions; articles not in English or French were translated using DeepL or Google Translate™. Records were excluded if they did not report, explicitly or implicitly, the complete treatment regimen (i.e. whether antibiotics and surgical procedures were concomitantly employed) and the route of phage administration, in relation to the outcome. Reporting of the full treatment regimen was deemed necessary in order to interpret the success of PT in the light of the two current treatments of bone and joint infections, which are antibiotics and surgery. Records in which the specific outcome of osteoarticular patients could not be distinguished from that of other patients were excluded.

Deduplication of records was performed using EndNote™. Screening of titles and abstracts, as well as full-text assessment, was performed independently by two reviewers (JG and SM). Screening was inclusive, meaning that a record needed to be identified only by one reviewer in order to make it to the next step. In records describing more than one patient, care was taken to include only patients fulfilling entry criteria. Any disagreements in the screening or data extraction processes were resolved by discussion between both reviewers; a third reviewer (DS) was consulted if no consensus was reached. Authors were contacted only in situations of great ambiguity. Finally, the reference lists of selected records were screened and reviewed by one reviewer (JG) for any relevant literature not already included using the same methodology, and any other literature answering entry criteria known to the authors but not identified in the database search was included. Any records published after the systematic search were also included. No risk-of-bias assessments were conducted due to the fact that all but one record were case reports and series, whose inherent risk of bias is well established to be high.[20]

Data concerning records (publication year, country), patient characteristics (gender, age) and treatment

PICO entry criteria

Population: Human patients of both genders and all ages with a bone and/or joint infection. Bone and joint infections were defined as any bacterial infection of the bone, joint, or prostheses/implants of the previously mentioned anatomical structures.

Intervention: Phage therapy as defined by the use of bacteriophages to treat an infection. Bacteriophage application used solely for prophylaxis is not included in this definition. No limitations were set regarding administration route, dose, frequency, duration, or the presence of any concomitant therapies. All types of phages and/or combinations were included.

Comparator: Any anti-infective treatment. An absence of comparator was admitted in records that did not have a control group.

Outcome: Rated as success (A) or failure (B–E, depending on the underlying cause).

- **Success**
  A – Clinical, microbiological and radiological resolution of infection and absence of infection relapse after administration of a PT treatment episode. Not all three parameters had to be reported, but all parameters that were reported had to indicate infection resolution.
- **Failure**
  B – No microbiological and/or radiological evidence of infection, clinical signs of infection still present (B1, infection resolution after additional interventions or therapies; B2, persistence of infection).
  C – No clinical, microbiological and/or radiological evidence of infection, but reinfection with a different bacterial strain or species (C1, infection resolution after additional interventions or therapies; C2, persistence of infection).
  D – No clinical, microbiological and/or radiological resolution of infection, or relapse with same bacterial strain (D1, infection resolution after additional interventions or therapies; D2, persistence of infection).
  E – Final outcome affected by a comorbidity.

Fig. 1 PICO entry criteria.
Note. PICO, Population, Intervention, Comparator and Outcome; PT, phage therapy.

episodes (infection site, orthopaedic diagnosis, surgery, microbiology, phage characteristics, phage administration modality, phage administration duration and frequency, concomitant antibiotics, suppressive antimicrobial therapy) were extracted from each record and inserted into a Microsoft® Excel table. The outcome of each treatment episode was assessed using our classification of success and failure (Fig. 1). Success was defined as clinical, microbiological and radiological resolution of infection and absence of infection relapse after administration of a PT treatment episode. Information about the occurrence of any adverse events (AEs) linked to PT was recorded separately. Adverse events included unfavourable events that occurred after the administration of PT; they were considered minor if they did not pose a serious threat to the patient's health. In addition, each record was classified based on its level of evidence (case report, case series or cohort study). Categorical variables were described by counts and percentages, while mean and standard deviations were used to summarize continuous variables.

Results

Record retrieval for screening yielded a total of 695 records published between 2000 and 2021, 20 of which met all eligibility criteria (Fig. 2). Most records were case reports ($n = 13$) or case series ($n = 6$), and only $n = 1$ record was a cohort study (Table 1). Publications described experiences in the USA ($n = 7$), France ($n = 6$), Russia ($n = 2$), Germany ($n = 2$), Georgia ($n = 1$), Belgium ($n = 1$) and Israel ($n = 1$) (Supplemental Table 2). The 20 publications represented 51 patients and 52 treatment episodes (one patient received two separate rounds of PT). The mean age of reported patients was 63.0 (standard deviation 24.8) years, and the gender distribution was equal

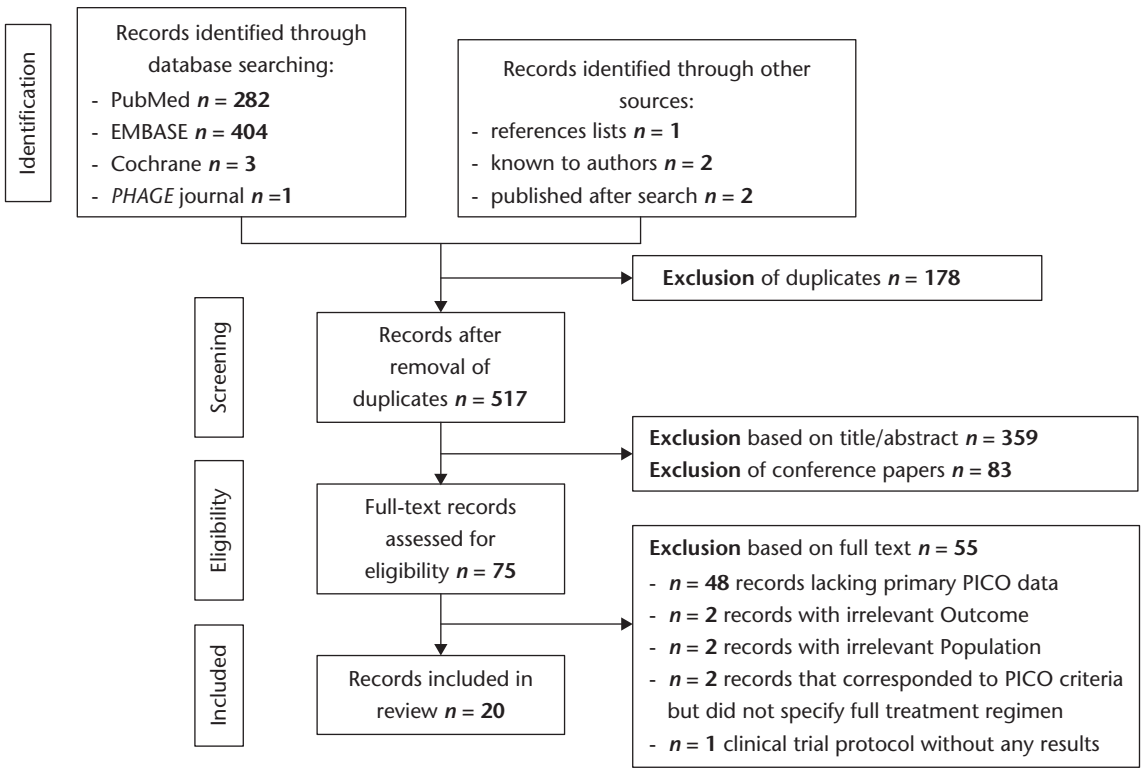

Fig. 2 Flowchart of record selection.

Table 1. Level of evidence of each record

Ref.	Number of patients included	Level of evidence
Ramirez-Sanchez et al[26]	1	Case report
Ferry et al[27]	1	Case report
Doub et al[24]	1	Case report
Ferry et al[28]	3	Case series
Nadareishvili et al[29]	3	Case series
Ferry et al[30]	1	Case report
Cano et al[31]	1	Case report
Doub et al[25]	1	Case report
Tkhilaishvili et al[32]	1	Case report
Onsea et al[33]	4	Case series
Nir-Paz et al[34]	1	Case report
Patey et al[35]	9	Case series
Ferry et al[36]	1	Case report
Fish et al[37]	1	Case report
Ferry et al[38]	1	Case report
Fish et al[39]	5	Case series
Efremov et al[40]	1	Case report
Vogt et al[41]	1	Case report
Samokhin et al[42]	12	Cohort study
Fish et al[43]	2	Case series

(50% males, *n* = 23) among the 46 patients for whom this information was reported. Almost all patients suffered from an infection located in the lower limbs, with the hip (27%, *n* = 14/52), knee (27%, *n* = 14/52) and toes (15%, *n* = 8/52) being the most common infection sites. Over half of patients (54%, *n* = 28/52) had a PJI, while the remainder (46%, *n* = 24/52) had osteomyelitis (including FRIs). The organisms targeted by PT were mostly *Staphylococcus aureus* (58%, *n* = 30/52), *Staphylococcus epidermidis* (25%, *n* = 13/52) and *Pseudomonas aeruginosa* (17%, *n* = 9/52). Phages were tested for specificity to the targeted bacteria in 83% (*n* = 43/52) of cases. PT was used to target one pathogen in the majority of treatment episodes (87%, *n* = 45/52) and targeted a maximum of two pathogens in seven cases (13%).

Concerning our primary outcome, 71% (*n* = 37/52) of treatment episodes satisfied our definition of success, relating to a clinical, microbiological and radiological resolution of infection and absence of infection relapse after administration of a PT treatment episode (Table 2). The success per indication was 57% for PJI (*n* = 16/28) and 88% for osteomyelitis (*n* = 21/24). In the situations considered as failures (29%, *n* = 15/52; categories B–E), 4% (*n* = 2/52) of treatment episodes still showed clinical signs of infection after PT without microbiological evidence of infection, 13% (*n* = 7/52) of treatment episodes were followed by a secondary infection with a different bacterial strain or species, 4% (*n* = 2/52) of treatment episodes did not result in any bacteriological and/or radiological resolution or were followed by a relapse with the same bacterial strain, and 8% (*n* = 4/52) of treatment episodes were negatively affected by a comorbidity. In failed cases, infection resolution was obtained for six cases after additional interventions and/or

Table 2. Summary of patient characteristics and treatment episodes

Age (years), mean (*SD*)	63.0 (24.8) [of 47 patients]
Sex male, *n* (%)	23/46 (50) [of 46 patients]
Localization (per treatment episode), *n*[a] (%)	
- Hip	14/52 (27)
- Knee	14/52 (27)
- Toes	8/52 (15)
- Femur	5/52 (10)
- Tibia	5/52 (10)
- Pelvis	3/52 (6)
- Foot	2/52 (4)
- Other*	3/52 (6)
Pathogens (per treatment episode), *n*[a] (%)	
- *Staphylococcus aureus*	30/52 (58)
- *Staphylococcus epidermidis*	13/52 (25)
- *Pseudomonas aeruginosa*	9/52 (17)
- Staphylococci other than *S. aureus* and *S. epidermidis***	2/52 (4)
- Other***	5/52 (10)
Diagnostics (per treatment episode) [b]	
- PJI	28/52 (54)
- Osteomyelitis (including FRI)	24/52 (46)
Phage specificity testing (per treatment episode)[c]	43/52 (83)
Administration route (per treatment episode), *n* (%)	
- **Topical only**	**44/52 (85)**
- **IV only**	**2/52 (4)**
- **Topical and IV**	**3/52 (6)**
- **Topical and PO**	**3/52 (6)**
- *Topical IOIA*	*39/52 (75)*
- *Topical sup.*	*11/52 (21)*
Combined surgery before or during PT (per treatment episode), *n* (%)	**45/52 (87)**
Combined antibiotics with PT (per treatment episode), *n* (%)	**41/52 (79)**
Combined surgery and antibiotics with PT (per treatment episode), *n* (%)	**39/52 (75)**
Outcome (per treatment episode), *n* (%)	
- **A**	**37/52 (71)**
- **B**	**2/52 (4)**
- **C**	**7/52 (13)**
- **D**	**2/52 (4)**
- **E**	**4/52 (8)**
- *1 (B1, C1 and D1)*	*6/52 (12)*
- *2 (B2, C2 and D2)*	*5/52 (10)*
Success (per treatment episode), *n* (%)	**37/52 (71)**
Failure (per treatment episode), *n* (%)	**15/52 (29)**
Positive outcome A + 1 (per treatment episode), *n* (%)	**43/52 (83)**
Follow-up (per treatment episode) time (months), mean (*SD*), range	11.9 (9.4) 1.5–41.0 [of 39 treatment episodes]
Reports of AE linked to PT (per treatment episode), *n* (%)	4/52 (8)
Patients with SAT initiated during or after PT (per treatment episode), *n* (%)	8/36 (22) [of 36 treatment episodes]

Notes. IV, intravenous; PO, *per os*; PT, phage therapy; SD, standard deviation; AE, adverse events; SAT, suppressive antibiotics; FRI, fracture-related infection; PJI, periprosthetic joint infection; IOIA, intraoperative and/or intraarticular; sup., superficial (on wound or into surrounding tissue).

*Including: jaw (*n* = 1), sternum (*n* = 1), multiple fractures not specified (*n* = 1).

***Staphylococcus* sp. (*n* = 1), *Staphylococcus lugdunensis* (*n* = 1).

***Including: *Klebsiella pneumoniae* (*n* = 2), *Enterococcus faecalis* (*n* = 2), *Acinetobacter baumannii* (*n* = 1).

[a]Total number of pathogens detected (*n* = 59) is greater than the number of treatment episodes (*n* = 52) due to some patients who presented an infection at more than one site or due to polymicrobial infections. Similarly, some infections concerned more than one localization.

[b]If PJI was associated with a diagnosis of osteomyelitis, PJI was retained as the diagnosis (Supplemental Table 2: P13).

[c]On two occasions (Supplemental Table 2: P14, P28) not all phages used were tested for specificity prior to treatment.

therapies (12%); the final outcome remained unfavourable in five patient cases (10%), and was negatively affected by a comorbidity in four cases (8%). Ultimately, 83% (*n* = 43/52) of treatment episodes resulted in an eventual positive outcome. The median follow-up time was 11.9 months (range 1.5–41.0 months) in the 39 treatment episodes for which this information was provided.

In terms of treatment modality, topical administration was the most frequent route of administration (ROA), either alone or in combination with additional routes. Topical administration was defined as an administration of phages either during surgery (intraoperative) or into the articulation (intraarticular), which was the case in 75% (*n* = 39/52) of treatment episodes, or a superficial application of phages on the wound or into surrounding tissue, which occurred in 21% (*n* = 11/52) of treatments. Administration was exclusively topical in 85% (*n* = 44/52) of cases, topical and *per os* in 6% (*n* = 3/52) of cases, topical and intravenous (IV) in 6% (*n* = 3/52) of cases, and exclusively IV in 4% (*n* = 2/52) of cases. Administration frequency and duration varied greatly, ranging from one intraoperative application to 40 days of IV therapy (Supplemental Table 2). Concomitant antibiotics were given in 79% of cases (*n* = 41/52). Surgery was performed in 87% of cases (*n* = 45/52). All three treatment modalities (antibiotics, surgery and PT) were employed concomitantly in 75% of cases (*n* = 39/52). Of successful treatments, 73% (*n* = 27/37) involved some form of concomitant or suppressive antimicrobial therapy and 84% (*n* = 31/37) involved surgical procedures; 70% (*n* = 26/37) involved both.

Data concerning the occurrence of any adverse events considered to be linked to PT are summarized in Table 3. Adverse reactions were reported during only 8% (*n* = 4/52) of treatment episodes, all of which were minor: elevation of liver function tests (*n* = 2), mild pruritus associated with an elevation of Tumour Necrosis Factor alpha (TNF-alpha) (*n* = 1), or redness and pain (*n* = 1) (Table 3). Suppressive antimicrobial treatment (SAT) was initiated during or after PT in 22% (*n* = 8) of treatment episodes (of the 36 treatment episodes for which this information was reported).

Discussion

Infection resolution, both microbiological and clinical, can be very challenging for bone and joint infections. Current therapies, namely antibiotics and surgery, result in 10–20% of failures.[6,7] In these situations, orthopaedic surgeons and infectious disease specialists are left with few therapeutic options and new strategies need to be developed. PT is emerging as a promising therapy, and the goal of this systematic review of current literature was to evaluate its potential for the treatment of bone and joint infections.

Table 3. Adverse events (AEs)

Ref.	Number of treatment episodes	Reports of AEs considered to be linked to PT and therapeutic consequence if applicable	Reports of other AEs or comorbidities
Ferry et al[27]	1	–	Death due to lithiasic pancreatitis after 1 year ($n = 1$)
Doub et al[24]	1	Elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) the day following topical PT → IV PT not administered ($n = 1$)	–
Ferry et al[30]	1	–	Myocardial infarction, uncontrolled bleeding ($n = 1$)
Cano et al[31]	1	Minor and intermittent pruritus of the right lower extremity 2 weeks into the course of therapy and slight elevation of TNF-alpha after PT ($n = 1$)	–
Doub et al[25]	1	Elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) after third IV dose → IV PT discontinued ($n = 1$)	–
Onsea et al [33]	4	Local redness and pain during rinsing procedure after 7 days of treatment ($n = 1$)	–
Ferry et al[38]	1	–	Death due to oncological comorbidity ($n = 1$)
Vogt et al[41]	1	–	Stiffening of two large joints of a leg with corresponding functional deficit ($n = 1$)

Notes. Ref., reference; AE, adverse events; PT, phage therapy; –, not reported; IV, intravenous.

The success rate for the use of PT in the treatment of bone and joint infections determined here from 52 treatment episodes from 20 included publications was 71%. We applied a more conservative definition of success, requiring evidence of microbiological, clinical and radiological resolution of infection in order to promote a realistic expectation of PT. Being more specific and having lower pharmaco-distribution profiles than conventional antibiotics, it is important to contextualize PT in terms of additional antimicrobial treatment and surgeries required to obtain positive clinical outcomes. Concomitant treatments make it difficult to determine the contribution of PT to successful outcomes. Indeed, no correlation could be made between the treatment modalities of PT and the outcome in this review, given the small number of patients and level of evidence of available publications.

Compared to a systematic review recently published by Clarke et al on the use of PT in bone and joint infections, our success rate was lower than the 93% of successful outcomes for the 277 patients reported by these authors.[21] This difference may be accounted for by the types of literature included, with our review including only recent publications and only cases for which the full treatment regimen of patients was specified. Interestingly, PJIs accounted for a minority (1.8%, $n = 5/277$) of the Clarke et al cohort, while they represented over half (54%, $n = 28/52$) of the cases included in this review. While there is value in examining the long-standing experience of phage therapy through historical publications, they are less reflective of modern standards, both for phage products and clinical evaluation, as well as for clinical practice.

Standards of care for the treatment of bone and joint infections vary between hospitals and practitioners, which has further impact on the treatment modalities used for phage application. In all but two cases reviewed here, PT was administered via the topical route, either by application of phages during/at the end of surgery directly or as an antimicrobial coating on prosthetic material, or postoperatively by injections or via an instilled drain for prolonged administration. The close contact of phage(s) with the pathogen at the site of infection likely contributed to the relatively high success rate found in this review and may be an important factor for the utility PT. A phase II RCT that evaluated the efficacy of PT to treat paediatric *Escherichia coli* diarrhoea failed to demonstrate a superiority of PT over the standard treatment protocol.[22] This contrasts with a successful phase II RCT that used PT to treat chronic *Pseudomonas aeruginosa* otitis.[23] In the former study, phages were administered *per os*, whilst in the latter, phages were administered via a topical route. Topical administration reduces concerns linked to pharmaco-distribution, in particular the concentration of phages at the infection site. In certain orthopaedic infections, topical administration can be carried out in an intraoperative or intraarticular fashion, ensuring an optimal delivery of phages at the infection site.

In terms of safety, only 8% of treatment episodes reported minor adverse events linked to PT. This included patients treated both locally and systemically with a variety of different phages, compositions, and posology. In two cases where elevated liver enzymes in response to PT were reported, this resulted in a cessation of IV therapy, although both cases ultimately resulted in a successful outcome.[24,25] Safety remains the utmost priority for phage applications, and the analysis presented here further corroborates the numerous publications reporting phage treatments as safe.[21,23]

Ultimately, the only way for PT to become a recognized and validated treatment is for it to be tested through

well-designed and sufficiently powered clinical trials. No RCTs were available for inclusion in this systematic review. The records identified were all case reports and series except for one cohort study composed of 12 patients. Case reports and series are categorically considered as poor evidence due to the strong publication bias for reporting successful rather than failed cases. Indeed, the outcome was described as successful in some of the included literature, despite events such as reinfections and/or amputations. This is indicative of the inherent bias of case reports and series to present the outcomes in a favourable light, as well as the fact that in many cases PT was administered as a last resort to patients with complex infection histories or with short follow-up times for bone and joint infections. As no centralized reporting, either prospective or retrospective, currently exists for PT cases, there is a lack of negative-outcome reporting. The success rate found in this review, although promising, is thus likely an overestimate of what can be expected of PT for the treatment of bone and joint infections.

What is encouraging, however, is that all of the case reports and case series identified were published in the last five years. This is telling of an increase in interest and experience of PT in orthopaedics. The experience and careful analysis of these case reports should enable the conception of well-planned clinical trials, which are ultimately needed to provide evidence on the actual clinical utility of PT and how it should be used in relation to standard-of-care. Currently, one active RCT aimed at determining the efficacy of PT in bone and joint infections is registered on clinicaltrials.gov (NCT04787250), which will evaluate PT administered with concomitant antibiotics to prevent the need for surgery in hip and knee PJIs.[18] The results of this trial, and others like it that are sure to follow, will be a decisive factor in determining the future of PT for the treatment of bone and joint infections. In the meantime, all clinical experiences, both positive and negative, should be published and made available in order to create a realistic expectation of PT.

Conclusion

According to this systematic review, PT, alone or associated with antibiotics and/or surgery, appears to be effective and safe in treating bone and joint infections, with a success rate of 71%. However, care must be taken in interpreting this estimate, which is based on an aggregation mostly of case reports and case series, given the publication bias inherent to this type of literature. Clinical trials are the next step required to confirm the efficacy of PT in bone and joint infections and to define to what extent they are indicated in situations of therapeutic failure.

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