

Systematic Review

# Bacteriophages in Hip and Knee Periprosthetic Joint Infections: A Promising Tool in the Era of Antibiotic Resistance

Filippo Migliorini <sup>1,2,3,4,\*</sup>, Luise Schäfer <sup>4</sup>, Raju Vaishya <sup>5</sup>, Jörg Eschweiler <sup>1,6</sup>, Francesco Oliva <sup>7</sup>, Arne Driessen <sup>8</sup>, Gennaro Pipino <sup>9</sup> and Nicola Maffulli <sup>10,11,12</sup>

<sup>1</sup> Department of Trauma and Reconstructive Surgery, University Hospital of Halle, Martin-Luther University Halle-Wittenberg, 06097 Halle (Saale), Germany; joerg.eschweiler@uk-halle.de

<sup>2</sup> Department of Orthopaedic and Trauma Surgery, Academic Hospital of Bolzano (SABES-ASDAA), 39100 Bolzano, Italy

<sup>3</sup> Department of Life Sciences, Health, and Health Professions, Link Campus University, 00165 Rome, Italy

<sup>4</sup> Department of Orthopaedic and Trauma Surgery, Eifelklinik St. Brigida, Kammerbruchstr. 8, 52152 Simmerath, Germany; luiseschaefer83@gmail.com

<sup>5</sup> Department of Orthopaedics and Joint Replacement Surgery, Indraprastha Apollo Hospital, Sarita Vihar, New Delhi 110076, India; raju.vaishya@gmail.com

<sup>6</sup> Department of Trauma and Reconstructive Surgery, BG Klinikum Bergmannstrost Halle GmbH, 06112 Halle (Saale), Germany

<sup>7</sup> Department of Sports Traumatology, Università Telematica San Raffaele, 00166 Rome, Italy; olivafrancesco@hotmail.com

<sup>8</sup> Department of Orthopaedic and Trauma Surgery, Luisenhospital, 52064 Aachen, Germany; arne.driessen@luisenhospital.de

<sup>9</sup> Department of Orthopaedics, Villa Erbosa Hospital, IRCCS Ospedale S. Raffaele, 40119 Milano, Italy; dottgennaropipino@yahoo.it

<sup>10</sup> Department of Trauma and Orthopaedic Surgery, Faculty of Medicine and Psychology, University La Sapienza, 00185 Roma, Italy; n.maffulli@qmul.ac.uk

<sup>11</sup> School of Pharmacy and Bioengineering, Faculty of Medicine, Keele University, Stoke on Trent ST4 7QB, UK

<sup>12</sup> Centre for Sports and Exercise Medicine, Barts and the London School of Medicine and Dentistry, Mile End Hospital, Queen Mary University of London, London E1 4DG, UK

\* Correspondence: filippo.migliorini@uk-halle.de

## Abstract

**Background:** Periprosthetic joint infections (PJIs) of the hip and knee are one of the most severe complications in arthroplasty, often requiring prolonged antibiotic therapy and multiple revision surgeries. The increasing prevalence of multidrug-resistant organisms and biofilm-associated PJIs has renewed interest in bacteriophage therapy as a targeted, adjunctive treatment option in refractory cases. This investigation systematically reviews and discusses the current evidence regarding the application, outcomes, and safety profile of bacteriophage therapy in the management of PJIs. **Methods:** This systematic review was conducted in accordance with the 2020 PRISMA statement. PubMed, Google Scholar, EMBASE, and Web of Science were accessed in August 2025. No time constraints were used for the search. All clinical studies investigating bacteriophage therapy for bacterial PJIs were considered for eligibility. **Results:** A total of 18 clinical studies, comprising 53 patients treated with bacteriophage therapy for PJI, were included. The mean follow-up was approximately 13.6 months. *Staphylococcus aureus* was the most frequent pathogen (18 cases); phage cocktails were used in 33 patients and monophage preparations in 9, all combined with suppressive antibiotic therapy. Persistent or resistant joint pain was reported in only two patients (3.8%), while signs of ongoing infection despite phage therapy were observed in four patients (7.5%). Adverse events following BT were inconsistently reported.

**Conclusions:** Bacteriophage therapy shows promise as an adjunctive treatment for hip and knee PJIs, especially in refractory or multidrug-resistant cases. Current evidence is limited and methodologically weak, underscoring the need for well-designed clinical trials to clarify efficacy, safety, and optimal integration into existing orthopaedic infection protocols.



Academic Editor: Giuliana Banche

Received: 19 November 2025

Revised: 16 December 2025

Accepted: 18 December 2025

Published: 25 December 2025

**Copyright:** © 2025 by the authors.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\) license](#).

**Keywords:** biofilm; suppressive antibiotic therapy; personalised phage preparation; chronic infection; relapse; *Staphylococcus aureus*; therapy

## 1. Introduction

Total hip and knee arthroplasties are among the most effective procedures in orthopaedic surgery, offering substantial improvements in mobility [1,2], pain reduction, and quality of life for patients suffering from advanced degenerative joint diseases [3,4]. With ageing populations, expanding surgical indications, and evolving implant technology, the number of hip and knee replacements continues to rise globally [5,6]. Despite their clinical success, these interventions are not without complications [7–13]. Periprosthetic joint infection (PJI) remains one of the most serious and challenging complications after total joint arthroplasty, with reported incidence ranging from 0.5% to 2% in primary implant settings and up to 10% in revision settings [14–17]. The clinical management of PJI typically requires prolonged antimicrobial therapy in combination with surgical intervention [18,19], including debridement and implant retention in selected acute cases or explantation and staged reconstruction in chronic or relapsing infections [20,21]. However, treatment failure rates remain significant, particularly among patients with impaired host defences, compromised soft tissues, or infections caused by biofilm-forming or multidrug-resistant bacteria, such as *Staphylococcus aureus* (*S. aureus*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Enterococcus faecalis* (*E. faecalis*) [22,23]. Moreover, current antimicrobial strategies are often limited by poor biofilm penetration, systemic toxicity, and increasing antibiotic resistance, all of which contribute to high recurrence rates and a substantial economic and functional burden [24–26]. Within this complex therapeutic landscape, bacteriophage therapy (BT) has re-emerged as a promising adjunct or salvage option for the treatment of difficult PJIs involving the hip and knee [27,28]. Bacteriophages, or phages, are viruses that selectively infect and lyse specific bacterial targets while preserving the host microbiota and surrounding tissues [29,30]. Their natural ability to penetrate biofilms and replicate at the site of infection offers a distinct theoretical advantage in the management of PJIs, particularly when standard therapies have failed or are contraindicated [31–34]. Although the clinical application of phage therapy has historically been restricted to certain regions, such as Eastern Europe, recent advances in microbiology, genomics, and phage purification have made personalised phage preparations increasingly accessible and safer [35–41]. Case reports and small series have described favourable outcomes following intra-articular, intravenous, or local phage administration in patients with hip and knee PJIs, including those with multiple prior revisions or limited surgical options [42–54]. However, the evidence remains sparse, heterogeneous, and largely anecdotal, with variations in phage selection, delivery protocols, and outcome definitions. This investigation systematically reviews and discusses the current evidence regarding the application, outcomes, and safety profile of BT in the management of PJIs.

## 2. Methods

### 2.1. Eligibility Criteria

All clinical studies investigating BT for PJIs were considered for eligibility. Articles published in English, German, French, Italian, or Spanish were included. Only studies corresponding to Levels I to IV of evidence, as defined by the Oxford Centre for Evidence-Based Medicine [55], were eligible. Reviews, editorials, opinion papers, or letters were excluded, as were studies involving animal models, in vitro experiments, cadaveric speci-

mens, computational simulations, or biomechanical analyses. Furthermore, studies lacking quantitative outcome data relevant to this analysis were excluded from the final analysis.

## 2.2. Search Strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [56]. This systematic review has not been registered. To guide the search and ensure methodological transparency, a structured framework was established as follows:

- Problem: PJIs;
- Intervention: bacteriophage therapy;
- Outcomes: clinical results and complications.

A comprehensive electronic literature search was conducted on 26 August 2025 using the PubMed, Web of Science, Google Scholar, and Embase databases, with no publication date restrictions. For PubMed, medical subject headings (MeSH) terms were combined with free-text keywords. For Web of Science, EMBASE, and Google Scholar, keyword-based searches adapted to the syntax of each database were used. All records were exported to EndNote (v 20.6; Clarivate Analytics, Philadelphia, PA, USA), where duplicate records were removed both automatically and manually. Grey literature and trial registries (ClinicalTrials.gov, WHO ICTRP) were screened using exact keywords; however, no additional studies were identified. The full database-specific search strings are reported in Table 1.

**Table 1.** Medical subject headings (MeSH) and keyword-based searches used as strings for each database.

Database	Search Strategy (MeSH Terms and Keywords)
PubMed	((“Bacteriophages” [MeSH Terms]) OR (“phage therapy”) OR (“bacteriophage therapy”) OR (“phage treatment”)) AND (“Prosthesis-Related Infections” [MeSH Terms]) OR (“Joint Prosthesis Infection”) OR (“Periprosthetic Joint Infection”))
Web of Science	TS = (“bacteriophage therapy” OR “phage therapy” OR “phage treatment”) AND TS = (“periprosthetic joint infection” OR “prosthetic joint infection”)
Google Scholar	“bacteriophage therapy” AND (“periprosthetic joint infection” OR “prosthetic joint infection”)
Embase	(‘bacteriophage therapy’/exp OR ‘phage therapy’ OR ‘phage treatment’) AND (‘joint prosthesis infection’/exp OR ‘orthopedic infection’)

## 2.3. Selection and Data Collection

Two authors (J.E. and L.S.) conducted a systematic search across the selected databases. Titles were manually screened for thematic relevance, followed by a thorough evaluation of abstracts from potentially eligible publications. When inclusion appeared likely, full texts were obtained and assessed accordingly. The reference lists of all included full-text articles were also systematically reviewed to capture any additional studies not identified during the initial search. Discrepancies between the reviewers were resolved through discussion and, if necessary, adjudicated by a third senior author (J.E.).

## 2.4. Data Items

Two reviewers (J.E. and L.S.) independently performed data extraction. The following data were systematically retrieved: first author and year of publication; journal name; study design; follow-up duration; number of included patients; mean age; sex distribution; type

and duration of BT; key clinical outcomes; and treatment-related complications. Infection control was defined as the absence of clinical signs of infection with or without ongoing suppressive antibiotic therapy, eradication as sustained clinical remission combined with negative microbiological findings after treatment completion, and recurrence as the reappearance of clinical and or microbiological evidence of infection during follow-up.

### 2.5. Assessment of the Risk of Bias and Quality of the Recommendations

The risk of bias was assessed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [57]. Two reviewers (G.P. and L.S.) independently evaluated the included studies. Case reports were appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports [58], which covers eight domains: patient demographics, medical history (as a timeline), clinical presentation, diagnostic workup, treatment, post-treatment condition, adverse events, and clinical takeaways. Each domain was rated as “Yes”, “No”, “Unclear”, or “Not applicable”. No overall score was generated. Case series were assessed using the JBI Checklist for Case Series [59], which comprises 10 domains covering inclusion criteria, diagnostic reliability, participant selection, reporting of demographics and outcomes, and statistical methods. Non-randomised controlled trials (non-RCTs) were evaluated using the ROBINS-I tool [60], which assesses seven domains of bias: confounding, selection, classification of interventions, deviations from intended treatment, missing data, outcome measurement, and selective reporting. ROBINS-I results were visualised using Robvis software (Risk-of-Bias Visualisation web application; Bristol, UK; available at <https://www.riskofbias.info>, accessed 3 September 2025) [61].

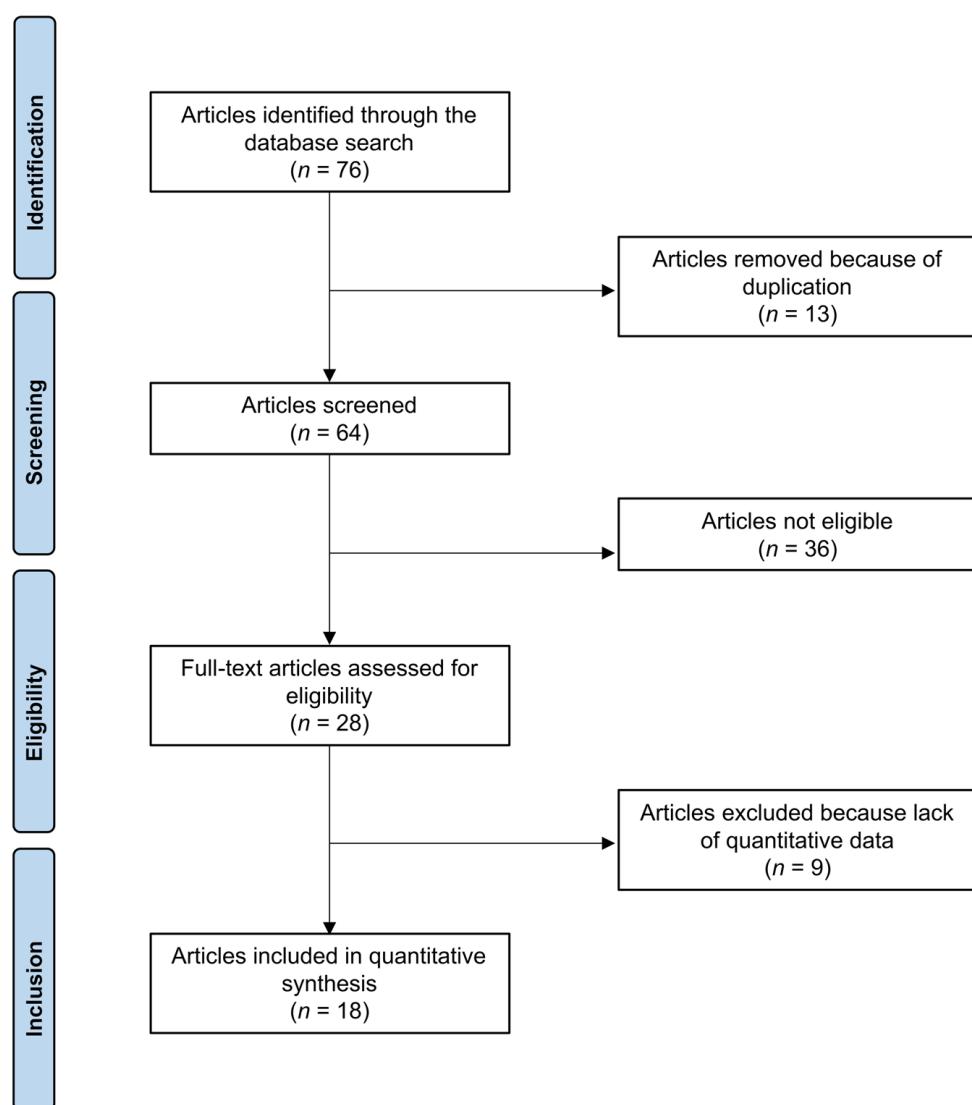
### 2.6. Synthesis Methods

The statistical analysis was performed by the main author (F.M.) using IBM SPSS Statistics (version 25.0; IBM Corp., Armonk, NY, USA). The approach was based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [57]. Descriptive statistics were used to summarise the extracted data. Continuous variables were reported as arithmetic means and standard deviations. Dichotomous variables were presented as absolute frequencies (events/observations).

## 3. Results

### 3.1. Study Selection

The literature search resulted in 76 articles concerning the topic of interest. All search results were extracted and checked for relevance. Of these, 13 were discarded because they were duplicates. Following the defined inclusion criteria, abstracts of 64 articles were reviewed, and 36 studies were excluded because they did not fulfil the eligibility criteria. The reasons that led to exclusion were, in detail: study design ( $N = 6$ ), improper level of evidence ( $N = 6$ ), not evaluating PJI of hip or knee ( $N = 13$ ), Insufficient reporting of therapeutic protocol ( $N = 7$ ) and language limitations ( $N = 4$ ). An additional nine articles were excluded because they did not offer quantitative data on the outcomes of interest. Finally, 18 investigations were included in the present analysis. Of them, 17 were case reports or series, and one had a prospective design. The results of the literature search are shown in Figure 1.



**Figure 1.** PRISMA flow chart of the literature search.

### 3.2. Methodological Quality Assessment

The overall methodological quality of the included case reports was high. Most studies provided clear and consistent information regarding patient demographics, clinical presentation, therapeutic procedures, post-treatment course, and reported complications. Follow-up data (Q7) were adequately described in 10 of the 13 case reports, whereas in three reports [42,45,54] follow-up information was either incomplete or not explicitly stated. Despite these minor limitations, the available data in most reports were sufficient to allow critical appraisal and meaningful clinical interpretation. The results of the quality assessment for all case reports are summarised in Table 2.

The five included case series [62–66] were assessed using the JBI Checklist for Case Series, covering ten methodological domains (Q1–Q10). Overall, the methodological quality was moderate, with some variation across studies. Strengths commonly observed included clear inclusion criteria (Q2), transparent reporting of patient demographics (Q3), description of clinical conditions (Q5), and consistent reporting of outcomes (Q7, Q8). Limitations were most frequently noted in the consecutive inclusion of participants (Q1), the level of detail regarding intervention descriptions (Q4), and the completeness of follow-up (Q9). Statistical analyses (Q10) were often not reported or insufficiently described. Only one case series [66] met all ten methodological criteria, reflecting exemplary reporting quality. The remaining

series demonstrated generally acceptable methodological standards, but with isolated unclear or missing items. A detailed summary of the quality assessment is presented in Table 3.

**Table 2.** JBI quality assessment of the included case reports (Q1–Q8). “Y” = Yes; “U” = Unclear.

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Aslam et al., 2020 [42]	Y	Y	Y	Y	Y	Y	U	Y
Cano et al., 2021 [43]	Y	Y	Y	Y	Y	Y	Y	Y
Cesta et al., 2023 [44]	Y	Y	Y	Y	Y	Y	Y	Y
Doub et al., 2020 [45]	Y	Y	Y	Y	Y	Y	U	Y
Doub et al., 2021 [46]	Y	Y	Y	Y	Y	Y	Y	Y
Ferry et al., 2018 [47]	Y	Y	Y	Y	Y	Y	Y	Y
Ferry et al., 2020 [48]	Y	Y	Y	Y	Y	Y	Y	Y
Ferry et al., 2021 [49]	Y	Y	Y	Y	Y	Y	Y	Y
Neuts et al., 2021 [50]	Y	Y	Y	Y	Y	Y	Y	Y
Ramirez-Sanchez et al., 2021 [51]	Y	Y	Y	Y	Y	Y	Y	Y
Schoeffel et al., 2022 [52]	Y	Y	Y	Y	Y	Y	Y	Y
Tkhilaishvili et al., 2020 [53]	Y	Y	Y	Y	Y	Y	Y	Y
Wahl et al., 2025 [54]	Y	Y	Y	Y	Y	Y	U	Y

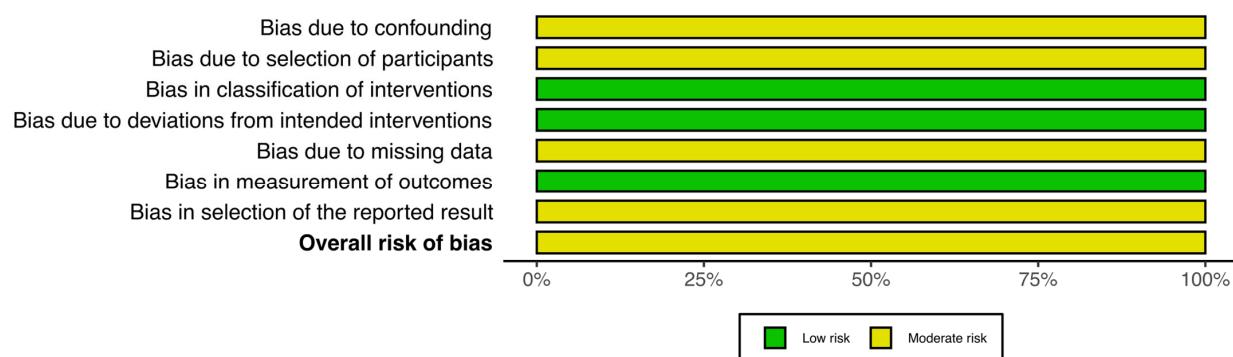
(Q1: Was the study question or objective clearly stated? Q2: Was the study population clearly and fully described, including a case definition? Q3: Were the cases consecutive? Q4: Were the subjects comparable? Q5: Was the intervention clearly described? Q6: Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? Q7: Was the length of follow-up well-described?).

**Table 3.** JBI quality assessment of the included case reports (Q1–Q10). Y: Yes; U: Unclear; N: No.

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Doub et al., 2023 [67]	Y	Y	Y	U	U	Y	Y	Y	N	N
Ferry et al., 2020 [66]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Munteanu et al., 2024 [64]	Y	Y	Y	N	Y	Y	Y	Y	Y	N
Patey et al., 2019 [65]	N	Y	Y	N	N	Y	Y	U	U	N

Q1: Were patient’s demographic characteristics clearly described? Q2: Was the patient’s history clearly described and presented as a timeline? Q3: Was the current clinical condition of the patient on presentation clearly described? Q4: Were diagnostic tests or assessment methods and the results clearly described? Q5: Was the intervention(s) or treatment procedures(s) clearly described? Q6: Was the post-intervention clinical condition clearly described? Q7: Were adverse events (harms) or unanticipated events identified and described? Q8: Does the case report provide takeaway lessons?

Applying the ROBINS-I tool, the study by Fedorov et al. [68] was judged to have an overall moderate risk of bias. Confounding was rated moderate because important baseline factors and potential confounders, such as infection characteristics, causative organisms, and surgical procedures, were documented, but no statistical adjustment was carried out. Selection bias was considered moderate, reflecting the prospective recruitment of the treatment group and use of a historical comparator. The risk related to intervention classification and protocol deviations was low, as treatment allocation was clearly defined and implemented as intended. Missing data introduced a moderate risk, given the incomplete follow-up in some participants. Outcome measurement and reporting were judged to be at low risk of bias. The detailed risk of bias assessment is presented in Figure 2.



**Figure 2.** The ROBINS-I of non-RCTs.

### 3.3. Study Characteristics and Results of Individual Studies

Data from 53 patients were included in the present analysis. The mean age was  $72.5 \pm 11.6$  years. The general characteristics, patient characteristics, and main results of the included studies are presented in Table 4. Persistent or resistant joint pain was reported in only two patients (3.8%), while signs of ongoing infection despite phage therapy were observed in 4 patients (7.5%). Adverse events following BT were inconsistently reported. Mild systemic reactions, such as fever or chills, after the first administration were reported in 5 of 53 patients (9.4%). Transient elevations in liver enzymes were documented in 9 patients (17%). Overall, non-specific side effects of any kind were reported in 16 patients, accounting for approximately 30% of the total cohort.

**Table 4.** Generalities, patient characteristics, and main results of the included studies.

Author, Year	Journal	LoE	Follow-Up (Months)	Patients (n)	Women (n)	Age (Mean)	Joint	DAIR (y/n)	Pathogen	Bacteriophage
Aslam et al., 2020 [42]	Open Forum Infect Dis	IV	-	1	1	61.0	Knee	Y	<i>S. aureus</i>	AB-SA01, SaGR51Φ1
Cano et al., 2021 [43]	Clin Infect Dis	IV	7.8	1	0	62.0	Knee	N	<i>K. pneumoniae</i>	Φ2 (KpJH46Φ2)
Cesta et al., 2023 [44]	Open Forum Infect Dis	IV	12	1	1	62.0	Hip	Y	<i>P. aeruginosa</i>	Pa53
Doub et al., 2020 [45]	Antibiotics (Basel)	IV	NR	1	0	72.0	Knee	N	MRSA	SaGR51Φ1
Doub et al., 2021 [46]	Pharmaceuticals (Basel)	IV	5	1	1	79.0	Knee	Y	<i>S. epidermidis</i>	PM448
Doub et al., 2023 [67]	Clin Infect Dis	IV	14	5	NR	NR	Knee, hip	Y N	<i>E. faecalis</i> , <i>S. epidermidis</i> , <i>S. lugdunensis</i> , MRSA	EF-1, PM448, Mallokai, SaWIQ0488Φ1, SaGR51Φ1
Fedorov et al., 2023 [68]	Viruses	II	12	23	NR	56.0	Hip	N	MSSE, MRSE, MSSA, MRSA	H143, H178, H182, H184
Ferry et al., 2018 [47]	Open Forum Infect Dis	IV	18	1	1	80.0	Hip	Y	MSSA	1493, 1815, 1957
Ferry et al., 2020 [48]	Front Med (Lausanne)	IV	12	1	0	49.0	Knee	Y	<i>S. aureus</i>	PP1493, PP1815
Ferry et al., 2020 [66]	Front Med (Lausanne)	IV	30	3	1	82.3	Knee	Y	<i>S. aureus</i>	PP1493, PP1815, PP1957
Ferry et al., 2021 [49]	Front Med (Lausanne)	IV	12	1	0	88.0	Knee	Y	<i>P. aeruginosa</i>	PP1450, PP1777, PP1792
Munteanu et al., 2024 [64]	Antibiotics (Basel)	IV	9	1	NR	84.0	Hip	Y	MSSA, <i>P. aeruginosa</i>	ISP (Myovirus)
				1	NR	71.0	Hip	N	<i>K. pneumoniae</i> , MSSA, <i>C. striatum</i>	ISP + SCM (Klebsiella phage)
				1	NR	77.0	Knee	N	<i>S. epidermidis</i>	COP-80B ( <i>S. epidermidis</i> )

**Table 4.** *Cont.*

Author, Year	Journal	LoE	Follow-Up (Months)	Patients (n)	Women (n)	Age (Mean)	Joint	DAIR (y/n)	Pathogen	Bacteriophage
Neuts et al., 2021 [50]	<i>Acta Orthop</i>	IV	24	1	0	76.0	Hip	N	<i>E. faecalis</i>	Pyophages and IntestiPhages in 10 mL vials as an oral suspension
Patey et al., 2019 [65]	<i>Viruses</i>	IV	NR	1	1	80.0	Knee	N	<i>P. aeruginosa</i>	Commercial broad spectrum multi-bacteriophage suspension
			NR	1	1	72.0	Knee	Y	<i>Staphylococcus</i> sp.	Commercial anti- <i>S. aureus</i> suspension
Ramirez-Sanchez et al., 2021 [51]	<i>Viruses</i>	IV	20	1	1	61.0	Knee	N	MSSA	AB-SA01, J-Sa36, Sa83, Sa87, SaGR51ø1
Schoeffel et al., 2022 [52]	<i>Pharmaceuticals (Basel)</i>	IV	11	1	1	64.0	Hip	N	MRSA	SaWIQ0488ø1
Tkhilaishvili et al., 2020 [53]	<i>Antimicrob Agents Chemother</i>	IV	10	1	1	80.0	Knee	Y	<i>P. aeruginosa</i>	Both <i>P. aeruginosa</i> isolates were tested against the phage collection at the George Eliava Institute (Tbilisi, Georgia)
Wahl et al., 2025 [54]	<i>Front Med (Lausanne)</i>	IV	NR	1	1	94.0	Hip	N	MRSA	ISP phage (from Queen Astrid Military Hospital)

(PJI: periprosthetic joint infection; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-sensitive *Staphylococcus aureus*; MSSE: methicillin-sensitive *Staphylococcus epidermidis*; MRSE: methicillin-resistant *Staphylococcus epidermidis*; LoE: level of evidence; NR: not reported; DAIR: debridement, antibiotics, and implant retention; ISP, SCM: phage identifiers as reported in the original studies).

#### 4. Discussion

This systematic review highlights the emerging potential of BT as an adjunctive or salvage strategy in the management of PJI. Across the included studies, phages were often administered in complex clinical scenarios in which conventional treatments had failed or were deemed infeasible. While encouraging results were observed for infection control and tolerability, the overall strength of the evidence remains limited. Most of the included studies were case reports or small series, with substantial heterogeneity in patient selection, phage preparation, administration protocols, and outcome reporting. Methodological limitations, including a lack of control groups, incomplete follow-up, and inconsistent documentation of adverse events, restrict the generalisability of the findings and preclude firm conclusions. Nonetheless, the accumulated evidence provides a foundation for further clinical investigation and supports the rationale for developing controlled trials to better define the role of bacteriophages in PJs.

Beyond the individual case narratives, several consistent cross-study patterns can be identified. Across heterogeneous clinical settings, bacteriophage therapy was almost invariably administered in combination with surgery and prolonged systemic antibiotics, reinforcing its role as an adjunct rather than an independent antimicrobial strategy. A recurrent distinction also emerges between acute PJs managed with DAIR and chronic scenarios treated with staged revisions or salvage procedures, with phage application shifting from supportive to purely rescue-oriented as biological conditions deteriorate. Moreover, PJs caused by highly biofilm-adaptive pathogens, particularly staphylococci and *Pseudomonas* species, appear to represent the most frequent targets for phage intervention. These converging features, despite protocol variability, suggest that the clinical relevance of bacteriophage therapy is shaped less by technical delivery differences and more by the underlying host-pathogen context in which it is deployed. Rather than being viewed as a stand-alone antimicrobial alternative, bacteriophage therapy should currently be interpreted within a rescue-oriented conceptual framework for catastrophic PJs. The available evidence consistently places phages in scenarios characterised by compromised host biology, biofilm-dominant and multidrug-resistant pathogens, and repeated failure of standard surgical and antibiotic strategies, in which the remaining alternative would otherwise be implant sacrifice or amputation. In this setting, bacteriophages may act as a biologically targeted adjunct capable of reducing local bacterial burden and enhancing antibiotic susceptibility within hostile microenvironments, rather than as a definitive curative therapy [69–73].

The management of PJI involves a range of surgical and non-surgical strategies, adapted to the duration of infection, pathogen characteristics, implant stability, and patient comorbidities [74–79]. Debridement, antibiotics, and implant retention (DAIR) are typically indicated for acute PJs with a symptom duration of less than four weeks [80–83]. Ideal candidates have a well-fixed implant, intact soft tissues, an identifiable and susceptible pathogen, and no sinus tract or severe immunosuppression [83–86]. Aslam et al. [42] treated a persistent methicillin-resistant *Staphylococcus aureus* (MRSA) knee PJI with DAIR followed by BT, resulting in complete resolution. A similar outcome was observed by Cesta et al. [44] in a chronic *P. aeruginosa* hip PJI, with sustained eradication during follow-up. Doub et al. [46,62] contributed multiple cases involving *Staphylococcus epidermidis* (*S. epidermidis*) and *E. faecalis* PJs treated with DAIR and BT, with satisfactory infection control. Ferry et al. [47–49] included chronic relapsing hip and knee PJs, frequently involving *S. aureus* or *P. aeruginosa*, which were treated using DAIR and BT with infection resolution [47–49]. Ferry et al. [66] reported that one patient underwent amputation one year post-treatment because of prosthesis exposure after a myocardial infarction; the infection itself remained, however, controlled. Patey et al. [65] performed DAIR, closure of several

draining fistulae, and BT in a chronic knee PJI. The infection stabilised, but complete eradication was not documented [65]. Several studies performed BT following multiple procedures, ranging from conservative management to revision procedures with implant removal. In most patients, BT represents the last resort. Infection control was achieved in most patients; however, a few remained on suppressive antibiotics, and in some cases, the infection was stabilised rather than eradicated. One-stage revision was reported in several series, including all 23 patients in Fedorov et al. [68], where chronic hip and knee PJIs were managed by implant removal, debridement, and immediate reimplantation. BT was administered intraoperatively via cement and postoperatively through drains [68]. At follow-up, infection control was achieved in most patients, and no recurrences were reported [68]. Patients with more extensive infection or compromised soft-tissue envelopes were managed with a two-stage revision strategy. Ramirez-Sanchez et al. [51] described a persistent methicillin-sensitive *Staphylococcus aureus* (MSSA) knee PJI treated with explantation, cement spacer, intraarticular phage administration, and delayed reimplantation, resulting in infection eradication at 20 months. In Doub et al. [45], a chronic MRSA knee PJI with severe bone loss underwent explantation and static spacer placement; intra-articular and intravenous phages were administered, with negative cultures at reimplantation and no recurrence. Where infection persisted, or local conditions were unfavourable, more complex revision strategies were implemented, ranging from repeated spacer exchanges to a Girdlestone excision arthroplasty. Schoeffel et al. [52] reported a recalcitrant MRSA infection of the hip and knee after multiple failed revisions, managed by sequential single-stage exchange of a hip spacer and knee temporary prosthesis with intra-articular BT, achieving infection eradication at 11 months. Patey et al. [65] described a chronic *P. aeruginosa* knee PJI not suitable for complete revision; partial hardware removal with local phage injection controlled the *P. aeruginosa*, but an *Enterococcus* infection subsequently emerged. Few patients received BT without any revision surgery. In each instance, surgery was deemed high-risk or technically unfeasible because of severe comorbidities, poor bone and soft-tissue conditions, or multiple prior failed revisions. A patient with chronic *K. pneumoniae* knee PJI with multiple previous revision surgeries was treated using intravenous phages with oral minocycline suppression, with resolution of clinical symptoms and improved function [43]. Neuts et al. [50] reported a chronic relapsing *E. faecalis* hip PJI after failed revisions, managed with oral BT and antibiotics, achieving infection control. A patient with chronic MRSA hip PJI with secondary knee involvement was treated with intravenous and local phages in combination with suppressive antibiotics [54]. The infection was controlled until the patient's death from unrelated causes [54].

This review has several limitations that must be acknowledged when interpreting the findings. Foremost, the overall low quality of the included studies, with the majority consisting of single-patient case reports and a small number of case series. According to the JBI critical appraisal tools, although most reports adequately described the clinical presentation, intervention, and follow-up, several domains were incompletely addressed, particularly the systematic documentation of adverse events and the clarity of the diagnostic workup. Although a minority of case series demonstrated reasonable methodological standards, only one study fulfilled all ten JBI quality domains, and none included comparator groups or predefined clinical endpoints. The clinical heterogeneity among the reported cases further limits the ability to synthesise results. The spectrum of included patients ranged from those undergoing DAIR procedures for acute infection to others treated after multiple failed revision surgeries, some of whom had severe soft tissue compromise or were considered inoperable. The pathogens involved also varied widely, including methicillin-sensitive and methicillin-resistant *S. aureus*, *P. aeruginosa*, *Klebsiella pneumoniae* (*K. pneumoniae*), *E. faecalis*, and *Corynebacterium striatum*, each of which differs in biofilm formation, phage suscepti-

bility, and clinical course [87–89]. Moreover, the phage preparations and administration strategies were highly inconsistent. Some patients received intravenously administered purified commercial cocktails, while others were treated with personalised phages selected *in vitro* and delivered locally, orally, or via drainage systems. The duration and frequency of therapy also varied substantially, and the combination with systemic antibiotics was not uniform. Given these heterogeneities, the reported results cannot be generalised. In addition, the evidence base is likely affected by substantial publication bias. Unsuccessful or inconclusive applications of bacteriophage therapy are less likely to be reported, potentially leading to an overestimation of treatment effectiveness in the available literature. While the overall infection control rate appears encouraging and the safety profile acceptable, these data must be interpreted as preliminary and exploratory rather than definitive. It is also important to note that none of the included studies employed randomisation or blinded assessment of outcomes, and in several cases, treatment success was defined clinically or radiographically without microbiological confirmation. Given the substantial heterogeneity in phage preparations, administration routes, dosing regimens, and concurrent antibiotic strategies, any meaningful subgroup analysis or comparative evaluation across studies was not feasible. These methodological inconsistencies further limited the ability to explore dose–response relationships or to identify protocol-dependent outcome patterns. Future studies should prioritise the design of controlled clinical trials that incorporate microbiological endpoints, standardised definitions of treatment success, and rigorous monitoring of adverse events. Additionally, the development of regulatory pathways for phage preparation, characterisation, and quality control will be essential to support broader clinical application. Despite these limitations, the growing body of clinical experience and the urgent need for alternative strategies for managing refractory PJs suggest that BT holds considerable promise. Its integration into well-designed translational studies may help define specific indications, optimise administration routes, and clarify its role in combination with surgical and antibiotic treatment. Until such evidence becomes available, current findings should be viewed as hypothesis-generating and supportive of further prospective investigation rather than as a basis for widespread implementation.

## 5. Conclusions

Bacteriophage therapy shows promise as an adjunctive treatment for hip and knee PJs, especially in refractory or multidrug-resistant cases. Current evidence is limited and methodologically weak, underscoring the need for well-designed clinical trials to clarify efficacy and safety, and to determine the optimal integration into existing orthopaedic infection protocols.

**Author Contributions:** F.M.: conception and design, statistical analysis, drafting (original and revision); L.S. and J.E.: literature search, study selection and data extraction; L.S. and G.P.: risk of bias assessment; A.D. and R.V.: drafting (original), supervision; N.M. and F.O.: drafting (revision). All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

**Conflicts of Interest:** The authors declare no conflicts of interest.

## References

1. Macken, A.A.; Prkic, A.; Koenraadt-van Oost, I.; Buijze, G.A.; The, B.; Eygendaal, D. Can a single question replace patient-reported outcomes in the follow-up of elbow arthroplasty? A validation study. *J. Orthop. Traumatol.* **2024**, *25*, 49. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Zhang, X.; Shen, X.; Zhang, R.; Chen, M.; Ma, R.; Zhang, Z.; Zhang, H.; Yang, B.; Zhu, C. Radiographic evaluation of robot-assisted versus manual total hip arthroplasty: A multicenter randomized controlled trial. *J. Orthop. Traumatol.* **2024**, *25*, 33. [\[CrossRef\]](#)
3. Migliorini, F.; Biagini, M.; Rath, B.; Meisen, N.; Tingart, M.; Eschweiler, J. Total hip arthroplasty: Minimally invasive surgery or not? Meta-analysis of clinical trials. *Int. Orthop.* **2019**, *43*, 1573–1582. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Migliorini, F.; Eschweiler, J.; Niewiera, M.; El Mansy, Y.; Tingart, M.; Rath, B. Better outcomes with patellar resurfacing during primary total knee arthroplasty: A meta-analysis study. *Arch. Orthop. Trauma Surg.* **2019**, *139*, 1445–1454. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Migliorini, F.; Maffulli, N.; Cuozzo, F.; Elsner, K.; Hildebrand, F.; Eschweiler, J.; Driessens, A. Mobile Bearing versus Fixed Bearing for Unicompartmental Arthroplasty in Monocompartmental Osteoarthritis of the Knee: A Meta-Analysis. *J. Clin. Med.* **2022**, *11*, 2837. [\[CrossRef\]](#)
6. Migliorini, F.; Maffulli, N.; Knobe, M.; Eschweiler, J.; Tingart, M.; Baroncini, A. Arthroscopic labral repair for femoroacetabular impingement: A systematic review. *Surgeon* **2022**, *20*, e225–e230. [\[CrossRef\]](#)
7. Migliorini, F.; Maffulli, N.; Velaj, E.; Bell, A.; Kammer, D.; Hildebrand, F.; Hofmann, U.K.; Eschweiler, J. Antithrombotic prophylaxis following total hip arthroplasty: A level I Bayesian network meta-analysis. *J. Orthop. Traumatol.* **2024**, *25*, 1. [\[CrossRef\]](#)
8. Migliorini, F.; Driessens, A.; Colarossi, G.; El Mansy, Y.; Gatz, M.; Tingart, M.; Eschweiler, J. Short stems for total hip replacement among middle-aged patients. *Int. Orthop.* **2020**, *44*, 847–855. [\[CrossRef\]](#)
9. Axenhus, M.; Mukka, S.; Magneli, M.; Skoldenberg, O. Comparative outcomes of uncemented and cemented stem revision in managing periprosthetic femoral fractures: A retrospective cohort study. *J. Orthop. Traumatol.* **2024**, *25*, 35. [\[CrossRef\]](#)
10. Migliorini, F.; Maffulli, N.; Pilone, M.; Kammer, D.; Hofmann, U.K.; Nobili, A.; Velaj, E.; Bell, A. Subsidence of the Corail stem in total hip arthroplasty: No influence of bony contact. *J. Orthop. Traumatol.* **2024**, *25*, 53. [\[CrossRef\]](#)
11. Pagano, S.; Plate, J.F.; Kappenschneider, T.; Reinhard, J.; Scharf, M.; Maderbacher, G. Polyethylene liner dissociation in total hip arthroplasty: A retrospective case-control study on a single implant design. *J. Orthop. Traumatol.* **2024**, *25*, 38. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Dewidar, A.A.; Mesregah, M.K.; Mesriga, M.M.; El-Behiry, A.M. Autogenous structural bone graft reconstruction of  $\geq 10$ -mm-deep uncontaminated medial proximal tibial defects in primary total knee arthroplasty. *J. Orthop. Traumatol.* **2024**, *25*, 22. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Moret, C.S.; Masri, S.E.; Schelker, B.L.; Friederich, N.F.; Hirschmann, M.T. Unexpected early loosening of rectangular straight femoral Zweymuller stems with an alumina-reduced surface after total hip arthroplasty—A prospective, double-blind, randomized controlled trial. *J. Orthop. Traumatol.* **2024**, *25*, 12. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Ascione, T.; Balato, G.; Pagliano, P. Upcoming evidence in clinical practice of two-stage revision arthroplasty for prosthetic joint infection. *J. Orthop. Traumatol.* **2024**, *25*, 26. [\[CrossRef\]](#)
15. Hamoudi, C.; Hamon, M.; Reiter-Schatz, A.; Debordes, P.A.; Gaudias, J.; Ronde-Oustau, C.; Jenny, J.Y. Cement loaded with high-dose gentamicin and clindamycin does not reduce the risk of subsequent infection after aseptic total hip or knee revision arthroplasty: A preliminary study. *J. Orthop. Traumatol.* **2024**, *25*, 37. [\[CrossRef\]](#)
16. Lee, W.S.; Park, K.K.; Cho, B.W.; Park, J.Y.; Kim, I.; Kwon, H.M. Risk factors for early septic failure after two-stage exchange total knee arthroplasty for treatment of periprosthetic joint infection. *J. Orthop. Traumatol.* **2024**, *25*, 6. [\[CrossRef\]](#)
17. Puetzler, J.; Hofschneider, M.; Gosheger, G.; Theil, C.; Schulze, M.; Schwarze, J.; Koch, R.; Moellenbeck, B. Evaluation of time to reimplantation as a risk factor in two-stage revision with static spacers for periprosthetic knee joint infection. *J. Orthop. Traumatol.* **2024**, *25*, 15. [\[CrossRef\]](#)
18. Hofmann, U.K.; Eleftherakis, G.; Migliorini, F.; Fink, B.; Mederake, M. Diagnostic and prognostic relevance of plain radiographs for periprosthetic joint infections of the hip: A literature review. *Eur. J. Med. Res.* **2024**, *29*, 314. [\[CrossRef\]](#)
19. Migliorini, F.; Hofmann, U.K. Editorial on the validity of plain radiographs in low-grade periprosthetic hip infections. *Ann. Med.* **2024**, *56*, 2352590. [\[CrossRef\]](#)
20. Wang, D.; Li, H.; Zhang, W.; Li, H.; Xu, C.; Liu, W.; Li, J. Efficacy and safety of modular versus monoblock stems in revision total hip arthroplasty: A systematic review and meta-analysis. *J. Orthop. Traumatol.* **2023**, *24*, 50. [\[CrossRef\]](#)
21. Descamps, J.; Teissier, V.; Graff, W.; Mouton, A.; Bouche, P.A.; Marmor, S. Managing early complications in total hip arthroplasty: The safety of immediate revision. *J. Orthop. Traumatol.* **2023**, *24*, 38. [\[CrossRef\]](#)
22. Migliorini, F.; Weber, C.D.; Bell, A.; Betsch, M.; Maffulli, N.; Poth, V.; Hofmann, U.K.; Hildebrand, F.; Driessens, A. Bacterial pathogens and in-hospital mortality in revision surgery for periprosthetic joint infection of the hip and knee: Analysis of 346 patients. *Eur. J. Med. Res.* **2023**, *28*, 177. [\[CrossRef\]](#) [\[PubMed\]](#)

23. Su, X.; Zhu, B.; Qin, L.; Yang, J.; Wei, L.; Xu, Z.; Wei, K.; Wang, J.; Chen, L.; Zhao, C.; et al. Joint fluid interleukin-6 combined with the neutral polymorphonuclear leukocyte ratio (PMN%) as a diagnostic index for chronic periprostheses infection after arthroplasty. *J. Orthop. Traumatol.* **2023**, *24*, 34. [CrossRef] [PubMed]

24. Chen, Z.; Lin, J.J.; Liu, W.G.; Zhou, Z.K.; Shen, B.; Yang, J.; Kang, P.D.; Pei, F.X. Distribution and drug resistance of pathogens causing periprosthetic infections after hip and knee arthroplasty. *Zhongguo Gu Shang* **2020**, *33*, 1032–1036. [CrossRef] [PubMed]

25. Chang, C.Y.; Chien, W.C.; Chung, C.H.; Tsao, C.H.; Lin, F.H.; Chang, F.Y.; Shang, S.T.; Wang, Y.C. Protective effect of N-acetylcysteine in prosthetic joint infection: A nationwide population-based cohort study. *J. Microbiol. Immunol. Infect.* **2020**, *53*, 225–233. [CrossRef]

26. Shoji, M.M.; Chen, A.F. Biofilms in Periprosthetic Joint Infections: A Review of Diagnostic Modalities, Current Treatments, and Future Directions. *J. Knee Surg.* **2020**, *33*, 119–131. [CrossRef]

27. Van Belleghem, J.D.; Manasherob, R.; Miedzybrodzki, R.; Rogoz, P.; Gorski, A.; Suh, G.A.; Bollyky, P.L.; Amanatullah, D.F. The Rationale for Using Bacteriophage to Treat and Prevent Periprosthetic Joint Infections. *Front. Microbiol.* **2020**, *11*, 591021. [CrossRef]

28. Sosa, B.R.; Niu, Y.; Turajane, K.; Staats, K.; Suhardi, V.; Carli, A.; Fischetti, V.; Bostrom, M.; Yang, X. 2020 John Charnley Award: The antimicrobial potential of bacteriophage-derived lysin in a murine debridement, antibiotics, and implant retention model of prosthetic joint infection. *Bone Jt. J.* **2020**, *102*, 3–10. [CrossRef]

29. Faruk, O.; Jewel, Z.A.; Bairagi, S.; Rasheduzzaman, M.; Bagchi, H.; Tuha, A.S.M.; Hossain, I.; Bala, A.; Ali, S. Phage treatment of multidrug-resistant bacterial infections in humans, animals, and plants: The current status and future prospects. *Infect. Med.* **2025**, *4*, 100168. [CrossRef]

30. Abedi, A.O.; Abedi, A.A.; Ferry, T.; Citak, M. Current Applications and the Future of Phage Therapy for Periprosthetic Joint Infections. *Antibiotics* **2025**, *14*, 581. [CrossRef]

31. Mehta, N.; Nguyen, A.T.; Rodriguez, E.K.; Young, J. Smart Phages: Leveraging Artificial Intelligence to Tackle Prosthetic Joint Infections. *Antibiotics* **2025**, *14*, 949. [CrossRef]

32. Parmar, K.; Chaudhry, W.; Fackler, J.R.; Sowers, J.M.; Vadlamudi, A.; Greenwood-Quaintance, K.; Patel, R. In vitro activity of phages against periprosthetic joint infection-associated staphylococcal biofilms. *Sci. Rep.* **2025**, *15*, 22199. [CrossRef] [PubMed]

33. Chen, B.; Chitto, M.; Tao, S.; Wagemans, J.; Lavigne, R.; Richards, R.G.; Metsemakers, W.J.; Moriarty, T.F. Isolation and Antibiofilm Activity of Bacteriophages against *Cutibacterium acnes* from Patients with Periprosthetic Joint Infection. *Viruses* **2024**, *16*, 1592. [CrossRef] [PubMed]

34. Doub, J.B.; Fogel, J.; Urich, K.L. The stability of Staphylococcal bacteriophages with commonly used prosthetic joint infection lavage solutions. *J. Orthop. Res.* **2024**, *42*, 555–559. [CrossRef] [PubMed]

35. Rupp, M.; Ferry, T.; Khan Mirzaei, M.; Alt, V.; Deng, L.; Walter, N. Bacteriophages for the treatment of musculoskeletal infections—An overview of clinical use, open questions, and legal framework. *Orthopadie* **2025**, *54*, 904–912. [CrossRef]

36. Paranos, P.; Vourli, S.; Pournaras, S.; Meletiadis, J. In Vitro Interactions Between Bacteriophages and Antibacterial Agents of Various Classes Against Multidrug-Resistant Metallo-beta-Lactamase-Producing *Pseudomonas aeruginosa* Clinical Isolates. *Pharmaceuticals* **2025**, *18*, 343. [CrossRef]

37. Osman, A.H.; Darkwah, S.; Kotey, F.C.N.; Asante-Poku, A.; Donkor, E.S. Lytic bacteriophages as alternative to overcoming antibiotic-resistant biofilms formed by clinically significant bacteria. *Ther. Adv. Infect. Dis.* **2025**, *12*, 20499361251356057. [CrossRef]

38. Shirzad-Aski, H.; Yazdi, M.; Mohebbi, A.; Rafiee, M.; Soleimani-Delfan, A.; Tabarraei, A.; Ghaemi, E.A. Isolation, characterization, and genomic analysis of three novel *Herelleviridae* family lytic bacteriophages against uropathogenic isolates of *Staphylococcus saprophyticus*. *Virol. J.* **2025**, *22*, 87. [CrossRef]

39. Kim, S.G. Targeting bacterial persistence with bacteriophages: A next-generation antimicrobial strategy. *Virology* **2025**, *611*, 110649. [CrossRef]

40. Lukasiak, A.; Wesolowski, W.; Neumann, J.; Lewandowska, N.; Weglinska, E.; Bloch, S.; Wegrzyn, G.; Nejman-Falenczyk, B. Groundwork for phage therapy: Multi-faceted comparative analysis of lytic bacteriophages infecting uropathogenic *Escherichia coli*. *Virology* **2025**, *615*, 110738. [CrossRef]

41. Huang, Y.; Huang, Y.; Wu, Z.; Fan, Z.; Zheng, F.; Liu, Y.; Xu, X. Characterization and genomic insights into bacteriophages Kpph1 and Kpph9 against hypervirulent carbapenem-resistant *Klebsiella pneumoniae*. *Virulence* **2025**, *16*, 2450462. [CrossRef] [PubMed]

42. Aslam, S.; Lampley, E.; Wooten, D.; Karris, M.; Benson, C.; Strathdee, S.; Schooley, R.T. Lessons Learned From the First 10 Consecutive Cases of Intravenous Bacteriophage Therapy to Treat Multidrug-Resistant Bacterial Infections at a Single Center in the United States. *Open Forum Infect. Dis.* **2020**, *7*, ofaa389. [CrossRef] [PubMed]

43. Cano, E.J.; Caflisch, K.M.; Bollyky, P.L.; Van Belleghem, J.D.; Patel, R.; Fackler, J.; Brownstein, M.J.; Horne, B.; Biswas, B.; Henry, M.; et al. Phage Therapy for Limb-threatening Prosthetic Knee *Klebsiella pneumoniae* Infection: Case Report and In Vitro Characterization of Anti-biofilm Activity. *Clin. Infect. Dis.* **2021**, *73*, e144–e151. [CrossRef] [PubMed]

44. Cesta, N.; Pini, M.; Mulas, T.; Materazzi, A.; Ippolito, E.; Wagemans, J.; Kutateladze, M.; Fontana, C.; Sarmati, L.; Tavanti, A.; 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.* **2023**, *10*, ofad051. [CrossRef]

45. Doub, J.B.; Ng, V.Y.; Johnson, A.J.; Slomka, M.; Fackler, J.; Horne, B.; Brownstein, M.J.; Henry, M.; Malagon, F.; Biswas, B. Salvage Bacteriophage Therapy for a Chronic MRSA Prosthetic Joint Infection. *Antibiotics* **2020**, *9*, 241. [CrossRef]

46. Doub, J.B.; Ng, V.Y.; Wilson, E.; Corsini, L.; Chan, B.K. Successful Treatment of a Recalcitrant *Staphylococcus epidermidis* Prosthetic Knee Infection with Intraoperative Bacteriophage Therapy. *Pharmaceutics* **2021**, *14*, 231. [CrossRef]

47. Ferry, T.; Boucher, F.; Fevre, C.; Perpoint, T.; Chateau, J.; Petitjean, C.; Josse, J.; Chidiac, C.; L'Hostis, G.; Leboucher, G.; 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*, 2901–2903. [CrossRef]

48. Ferry, T.; Batailler, C.; Petitjean, C.; Chateau, J.; Fevre, C.; Forestier, E.; Brosset, S.; Leboucher, G.; Kolenda, C.; Laurent, F.; et al. The Potential Innovative Use of Bacteriophages Within the DAC((R)) Hydrogel to Treat Patients With Knee Megaprosthesis Infection Requiring “Debridement Antibiotics and Implant Retention” and Soft Tissue Coverage as Salvage Therapy. *Front. Med.* **2020**, *7*, 342. [CrossRef]

49. Ferry, T.; Kolenda, C.; Batailler, C.; Gaillard, R.; Gustave, C.A.; Lustig, S.; Fevre, C.; Petitjean, C.; Leboucher, G.; Laurent, F.; 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.* **2021**, *8*, 569159. [CrossRef]

50. Neuts, A.S.; Berkhout, H.J.; Hartog, A.; Goosen, J.H.M. Bacteriophage therapy cures a recurrent *Enterococcus faecalis* infected total hip arthroplasty? A case report. *Acta Orthop.* **2021**, *92*, 678–680. [CrossRef]

51. Ramirez-Sanchez, C.; Gonzales, F.; Buckley, M.; Biswas, B.; Henry, M.; Deschenes, M.V.; Horne, B.; Fackler, J.; Brownstein, M.J.; Schooley, R.T.; et al. Successful Treatment of *Staphylococcus aureus* Prosthetic Joint Infection with Bacteriophage Therapy. *Viruses* **2021**, *13*, 1182. [CrossRef] [PubMed]

52. Schoeffel, J.; Wang, E.W.; Gill, D.; Frackler, J.; Horne, B.; Manson, T.; Doub, J.B. Successful Use of Salvage Bacteriophage Therapy for a Recalcitrant MRSA Knee and Hip Prosthetic Joint Infection. *Pharmaceutics* **2022**, *15*, 177. [CrossRef] [PubMed]

53. Tkhilaishvili, 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*. *Antimicrob. Agents Chemother.* **2019**, *64*, 10–1128. [CrossRef] [PubMed]

54. Wahl, P.; Schlappi, M.; Loganathan, A.; Uckay, I.; Hodel, S.; Fritz, B.; Scheidegger, J.; Djebara, S.; Leitner, L.; McCallin, S. Bacteriophage therapy created the necessary conditions for successful antibiotic suppression in a periprosthetic hip joint infection: A Case Report. *Front. Med.* **2025**, *12*, 1564369. [CrossRef]

55. Howick, J.C.I.; Glasziou, P.; Greenhalgh, T.; Heneghan, C.; Liberati, A.; Moschetti, I.; Phillips, B.; Thornton, H.; Goddard, O.; Hodgkinson, M. *The 2011 Oxford CEBM Levels of Evidence*; Oxford Centre for Evidence-Based Medicine: Oxford, UK, 2011; Available online: <https://www.cebm.net/index.aspx?o=5653> (accessed on 30 August 2025).

56. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [CrossRef]

57. Higgins, J.P.T.; Thomas, J.; Chandler, J.; Cumpston, M.; Li, T.; Page, M.J.; Welch, V.A. (Eds.) *Cochrane Handbook for Systematic Reviews of Interventions Version 6.3*; Cochrane: London, UK, 2022; Available online: [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook) (accessed on 30 August 2025).

58. Moola, S.; Munn, Z.; Tufanaru, C.; Aromataris, E.; Sears, K.; Sfetcu, R.; Currie, M.; Qureshi, R.; Mattis, P.; Lisy, K. Systematic reviews of etiology and risk. *Joanna Briggs Inst. Rev. Man.* **2017**, *5*, 217–269.

59. Munn, Z.; Barker, T.H.; Moola, S.; Tufanaru, C.; Stern, C.; McArthur, A.; Stephenson, M.; Aromataris, E. Methodological quality of case series studies: An introduction to the JBI critical appraisal tool. *JBI Evid. Synth.* **2020**, *18*, 2127–2133. [CrossRef]

60. Sterne, J.A.; Hernan, M.A.; Reeves, B.C.; Savovic, J.; Berkman, N.D.; Viswanathan, M.; Henry, D.; Altman, D.G.; Ansari, M.T.; Boutron, I.; et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* **2016**, *355*, i4919. [CrossRef]

61. McGuinness, L.A.; Higgins, J.P.T. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Res. Synth. Methods* **2020**, *12*, 55–61. [CrossRef]

62. Doub, J.B.; Johnson, A.J.; Nandi, S.; Ng, V.; Manson, T.; Lee, M.; Chan, B. Experience Using Adjuvant Bacteriophage Therapy for the Treatment of 10 Recalcitrant Periprosthetic Joint Infections: A Case Series. *Clin. Infect. Dis.* **2023**, *76*, e1463–e1466. [CrossRef]

63. Miedzybrodzki, R.; Fortuna, W.; Weber-Dabrowska, B.; Górska, A. A retrospective analysis of changes in inflammatory markers in patients treated with bacterial viruses. *Clin. Exp. Med.* **2009**, *9*, 303–312. [CrossRef] [PubMed]

64. Munteanu, D.I.; Dunn, J.; Apjok, G.; Kintses, B.; Griselain, J.; Steurs, G.; Cochez, C.; Djebara, S.; Merabishvili, M.; Pirnay, J.P.; et al. Phage Therapy for Orthopaedic Infections: The First Three Cases from the United Kingdom. *Antibiotics* **2025**, *14*, 114. [CrossRef] [PubMed]

65. 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*, 18. [[CrossRef](#)] [[PubMed](#)]

66. Ferry, T.; Kolenda, C.; Batailler, C.; Gustave, C.A.; Lustig, S.; Malatray, M.; Fevre, C.; Josse, J.; Petitjean, C.; Chidiac, C.; 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*, 570572. [[CrossRef](#)]

67. Doub, J.B.; Urish, K.; Chan, B. Bacteriophage therapy for periprosthetic joint infections: Current limitations and research needed to advance this therapeutic. *J. Orthop. Res.* **2023**, *41*, 1097–1104. [[CrossRef](#)]

68. Fedorov, E.; Samokhin, A.; Kozlova, Y.; Kretien, S.; Sheraliev, T.; Morozova, V.; Tikunova, N.; Kiselev, A.; Pavlov, V. Short-Term Outcomes of Phage-Antibiotic Combination Treatment in Adult Patients with Periprosthetic Hip Joint Infection. *Viruses* **2023**, *15*, 499. [[CrossRef](#)]

69. Akturk, E.; Melo, L.D.R.; Oliveira, H.; Crabbe, A.; Coenye, T.; Azeredo, J. Combining phages and antibiotic to enhance antibiofilm efficacy against an in vitro dual species wound biofilm. *Biofilm* **2023**, *6*, 100147. [[CrossRef](#)]

70. Al-Mustapha, A.I.; Raufu, I.A.; Ogundijo, O.A.; Odetokun, I.A.; Tiwari, A.; Brouwer, M.S.M.; Adetunji, V.; Heikinheimo, A. Antibiotic resistance genes, mobile elements, virulence genes, and phages in cultivated ESBL-producing *Escherichia coli* of poultry origin in Kwara State, North Central Nigeria. *Int. J. Food Microbiol.* **2023**, *389*, 110086. [[CrossRef](#)]

71. Xiao, S.; Xie, L.; Gao, Y.; Wang, M.; Geng, W.; Wu, X.; Rodriguez, R.D.; Cheng, L.; Qiu, L.; Cheng, C. Artificial Phages with Biocatalytic Spikes for Synergistically Eradicating Antibiotic-Resistant Biofilms. *Adv. Mater.* **2024**, *36*, e2404411. [[CrossRef](#)]

72. Wang, Y.; Zhang, Z.; Kang, J.; Chen, B.; Hong, W.; Lv, B.; Wang, T.; Qian, H. Phages in different habitats and their ability to carry antibiotic resistance genes. *J. Hazard. Mater.* **2024**, *469*, 133941. [[CrossRef](#)]

73. Fletcher, J.; Manley, R.; Fitch, C.; Bugert, C.; Moore, K.; Farbos, A.; Michelsen, M.; Alathari, S.; Senior, N.; Mills, A.; et al. The Citizen Phage Library: Rapid Isolation of Phages for the Treatment of Antibiotic Resistant Infections in the UK. *Microorganisms* **2024**, *12*, 253. [[CrossRef](#)] [[PubMed](#)]

74. Nazligul, A.S.; Guven, S.; Erdogan, Y.; Firat, A.; Dogan, M.; Akkaya, M. Periprosthetic Joint Infection in Unicompartimental vs. Total Knee Arthroplasty: Microbiological Spectrum and Management Outcomes. *Antibiotics* **2025**, *14*, 585. [[CrossRef](#)] [[PubMed](#)]

75. Taylor Iv, W.L.; Bergstein, V.; Weinblatt, A.; Long, W.J. The financial burden of vancomycin as an alternative to cefazolin for periprosthetic joint infection prophylaxis in total knee arthroplasty. *Arch. Orthop. Trauma Surg.* **2025**, *145*, 272. [[CrossRef](#)] [[PubMed](#)]

76. Werner, A.; Werkmeister, M.; Neumann, J.; Linke, P. Diagnostic value of preoperative joint aspiration for periprosthetic shoulder infection: Analysis of microbiological aspects and preoperative ICM minor criteria. *Arch. Orthop. Trauma Surg.* **2025**, *145*, 413. [[CrossRef](#)]

77. Abdelnasser, M.K.; Bakhet, A.; Hosni, A.; Kamal, D.T.; Osman, O.B.; Abdelhameed, M.A.; Moustafa, M.M. Alpha defensin immunoassay is more effective for ruling out rather than diagnosing periprosthetic joint infection (PJI): A prospective cohort study. *Arthroplasty* **2025**, *7*, 52. [[CrossRef](#)]

78. Lin, J.; Li, H.; Chen, Y.; Ding, H.; Wang, Q.; Lv, J.; Li, W.; Zhang, W.; Fang, X. Prosthetic articulating spacers as a preferred option for two-stage revision arthroplasty in chronic periprosthetic joint infection. *Arthroplasty* **2025**, *7*, 4. [[CrossRef](#)]

79. Mu, W.; Lizcano, J.D.; Xu, B.; Guo, W.; Aimaiti, A.; Zhang, X.; Parvizi, J.; Cao, L. Monitoring the hematologic markers in patients undergoing single-stage exchange arthroplasty for periprosthetic joint infection. *Arthroplasty* **2025**, *7*, 46. [[CrossRef](#)]

80. Bouhadana, A.; Steinberg, A. DAIR to Be Different: Successful Use of DAIR Regimen, a Novel Treatment Combination for EBV-induced HLH. *Clin. Hematol. Int.* **2025**, *7*, 21–26. [[CrossRef](#)]

81. Zellner, A.A.; Watzlawik, N.; Roos, J.; Hischebeth, G.T.R.; Molitor, E.; Franz, A.; Froschen, F.S. Microbiological Profiles of Patients with Acute Periprosthetic Joint Infection Undergoing Debridement, Antibiotics, Irrigation and Implant Retention (DAIR). *Antibiotics* **2025**, *14*, 873. [[CrossRef](#)]

82. McPherson, E.J.; Jones, R.M.; Sorial, R.M.; Chowdhry, M. We need a new acronym supplementing DAIR: Introducing DECRA. *Arthroplasty* **2025**, *7*, 43. [[CrossRef](#)]

83. Zellner, A.A.; Watzlawik, N.; Roos, J.; Hischebeth, G.T.R.; Prangenber, C.; Franz, A.; Froschen, F.S. Mid-term results after DAIR for patients with acute periprosthetic joint infections of the hip or knee. *J. Orthop. Surg. Res.* **2025**, *20*, 676. [[CrossRef](#)] [[PubMed](#)]

84. Izzo, A.; Carbone, C.; Matteo, V.; Lintz, F.; Festa, E.; Balato, G.; Bernasconi, A. Eradication rate after debridement, antibiotics, and implant retention (DAIR), 1.5-stage revision or 2-stage revision in periprosthetic ankle joint infection: A systematic review. *Foot Ankle Surg.* **2025**, *31*, 695–702. [[CrossRef](#)] [[PubMed](#)]

85. Sigmund, I.K.; Ferry, T.; Sousa, R.; Soriano, A.; Metsemakers, W.J.; Clauss, M.; Trebse, R.; Wouthuizen-Bakker, M. Debridement, antimicrobial therapy, and implant retention (DAIR) as curative strategy for acute periprosthetic hip and knee infections: A position paper of the European Bone & Joint Infection Society (EBJIS). *J. Bone Jt. Infect.* **2025**, *10*, 101–138. [[CrossRef](#)] [[PubMed](#)]

86. Sigmund, I.K.; Wouthuyzen-Bakker, M.; Ferry, T.; Metsemakers, W.J.; Clauss, M.; Soriano, A.; Trebse, R.; Sousa, R. Debridement, antimicrobial therapy, and implant retention (DAIR) as curative surgical strategy for acute periprosthetic hip and knee infections: A summary of the position paper from the European Bone & Joint Infection Society (EBJIS). *J. Bone Jt. Infect.* **2025**, *10*, 139–142. [[CrossRef](#)]
87. Chandler, C.C.; Graham, S.D.; Hietpas, K.T.; Fehring, T.K.; Otero, J.E. Trends in Antibiotic-Resistant Bacteria in Surgically Treated Periprosthetic Joint Infection: A Decade of Experience at a Regional Referral Center. *J. Arthroplast.* **2025**, *in press..* [[CrossRef](#)]
88. Gomez-Junyent, J.; Lora-Tamayo, J.; Sorli, L.; Murillo, O. Challenges and strategies in the treatment of periprosthetic joint infection caused by multidrug-resistant Gram-negative bacteria: A narrative review. *Clin. Microbiol. Infect.* **2025**, *31*, 1458–1466. [[CrossRef](#)]
89. Koepf, U.S.; Scheidt, S.; Hischebeth, G.T.R.; Strassburg, C.P.; Wirtz, D.C.; Randau, T.M.; Lutz, P. Increased rate of enteric bacteria as cause of periprosthetic joint infections in patients with liver cirrhosis. *BMC Infect. Dis.* **2022**, *22*, 389. [[CrossRef](#)]

**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.