Medical Principles and Practice

Systematic Review

Med Princ Pract 2024;33:1–9
DOI: 10.1159/000534717

Received: June 19, 2023
Accepted: October 19, 2023
Published online: October 25, 2023

The Potential of Bacteriophage Therapy as an Alternative Treatment Approach for Antibiotic-Resistant Infections

Nike Walter[a, b] Mohammadali Khan Mirzaei[c, d] Li Deng[d, e] Christian Willy[e] Volker Alt[a] Markus Rupp[a]

[a]Department of Trauma Surgery, University Hospital Regensburg, Regensburg, Germany; [b]Department for Psychosomatic Medicine, University Hospital Regensburg, Regensburg, Germany; [c]Helmholtz Centre Munich, German Research Center for Environmental Health, Institute of Virology, Munich, Germany; [d]Institute of Virology, Technical University of Munich, Munich, Germany; [e]Department Trauma and Orthopedic Surgery, Septic and Reconstructive Surgery, Research and Treatment Center Septic Defect Wounds, Federal Armed Forces of Germany, Military Academic Hospital Berlin, Berlin, Germany

Highlights of the Study

- Phage therapy has gained increasing interest over the years.
- Identified indications included bacterial diarrhea, urinary tract infections, infected burn wounds, chronic otitis, chronic venous leg ulcers, and chronic rhinosinusitis.
- Randomized-controlled trials (RCTs) on different indications suggest the safety of phage therapy.
- Future trials should consider issues such as the quality of phage preparation, sensitivity testing, titer and dosages.

Keywords
Bacteriophages · Phage therapy · Randomized-controlled trials

Abstract
Objective: This study aimed to provide a comprehensive overview of the current state of the literature on the therapeutical application of bacteriophages. ***Methods:*** First, a bibliometric analysis was performed using the database Web of Science to determine annual number of publications and citations. Second, a systematic literature review was conducted on randomized-controlled trials (RCTs) of phage therapy in PubMed. ***Results:*** Over the past decade, the number of publications on bacteriophage therapy increased more than fourfold with 212 articles in 2011 and 739 in 2022. The systematic search in PubMed yielded 7 RCTs eligible for inclusion, reporting on a total of 418 participants. Identified indications in this study included bacterial diarrhea, urinary tract infections, infected burn wounds, chronic otitis, chronic venous leg ulcers, and chronic rhinosinusitis. In three studies, mild to moderate adverse events were reported in 10/195 participants (5.1%). Three of the studies reported a statistically significant difference in outcomes comparing phage therapy with standard of care or placebo. ***Conclusion:*** Phage therapy has gained increasing interest over the years.

karger@karger.com
www.karger.com/mpp

Correspondence to:
Markus Rupp, markus.rupp@ukr.de

RCTs on different indications suggest the safety of phage therapy; however, reasons why phage therapy is not yet well accepted are limitations in the study designs. For a successful translation into clinical practice researchers and clinicians should learn from the earlier experiences and consider issues such as the quality of phage preparation, sensitivity testing, titer and dosages, as well as access to the infection site and stability for standardized protocols and future trials.

Introduction

Bacteriophages, also known as phages, are abundant biological entities found ubiquitously in the environment [1]. Phages are viruses with the ability to infect, replicate in, and finally kill bacteria, exhibiting specificity in the lytic phase. Compared to antibiotics, phages have narrower host ranges, making them a promising supplement and, in certain cases, an alternative to antibiotic therapy. This becomes especially crucial when antibiotic effectiveness is severely compromised due to the prevalence of multiple drug-resistant (MDR) bacterial infections [2]. It is worth noting that bacteriophage therapy is not a recent discovery. Felix d'Herelle recognized the possibility of bacterial lysis, previously described by the British bacteriologist Frederick W. Twort in 1915 [3]. The former Soviet Union had continuously employed bacteriophages to treat various infections, such as gastrointestinal infections and gas gangrene in soldiers [4]. However, in the Western world, especially after World War II, this treatment approach has been increasingly forgotten due to the discovery of penicillin [5]. As a consequence of the excessive use of antibiotics in clinical settings, agriculture, and animal husbandry during the "golden era" of antibiotics, the rise of MDR bacteria has become an urgent global issue [6]. Presently, MDR bacteria are responsible for 1.27 million annual deaths worldwide [7]. Estimates predict an increase to 10 million deaths per year after 2050 [8]. A revival of phages, bacteria's natural predators can provide a solution to this major global public health concern, while conventional antibiotics are losing their effectiveness [9].

However, despite their wide application in the past, not many papers have been published on bacteriophage therapy. As a result, the existing evidence on the safety and efficacy of phage therapy relies mainly on case reports, preclinical studies, and initial randomized-controlled trials (RCTs) with limitations [10].

This bibliometric analysis aimed at providing a comprehensive overview of the current state of the literature on the therapeutical application of bacteriophages. Additionally, this analysis sought to outline ongoing efforts to establish a high level of evidence through RCT, while also evaluating the potentials and pitfalls of this new but old therapy approach.

Methods

Bibliometric Analysis

Data for this analysis were obtained from the Web of Science (WoS) electronic database, specifically from the SCI-Expanded sub-database. WoS encompasses an extensive collection of approximately 34,000 journals, comprising over 75 million records. It includes sub-databases such as Science Citation Index, Social Sciences Citation Index, Arts and Humanities Citation Index, Conference Proceedings Citation Index, Book Citation Index, and Emerging Sources Citation Index. Additionally, the Thomas Scientific impact factor is based on data sourced from the WoS database [11]. To conduct the search, we utilized the following keywords: "bacteriophage" OR "phage" AND "therapy" OR "application." The search encompassed articles published between January 1, 1965 and December 31, 2022, without any language restrictions. To ensure accuracy and relevance, two authors independently screened titles and abstracts, confirming their alignment with the topic.

Data were extracted in January 2023; the retrieved information was exported to plain text format and compiled in a tabulated manner. The extracted data included various aspects such as the year of publication, total number of citations, number of citations per year, institutional affiliations of authors, journal publications, subject areas, article types, and countries of origin.

Systematic Review

An additional search was conducted in PubMed, utilizing the filter "randomized controlled trial."| The same keywords, "bacteriophage" OR "phage" AND "therapy" OR "application," were used for the period spanning January 1, 1965–December 31, 2022. Only RCTs with articles written in English or German were included in this sub-analysis. For this specific sub-analysis, articles were considered eligible if they reported on the application of bacteriophages in humans regardless of the indication and incorporated either a placebo or standard of care control group. Studies involving protocols, animal experiments, or articles focusing on the therapeutic use of bacteriophage-derived products (e.g., lysins) were excluded from the analysis. Moreover, studies in which the same group of participants received both the phage application and a placebo at different randomized time points were also excluded. The extracted outcomes of interest comprised the author's details, publication year, origin of the study, indication for treatment, sample size, targeted pathogen, type of phages used, mode of application, efficacy results, and reported side effects. To ensure accuracy and relevance, two authors independently screened the full texts of the eligible articles, and discrepancies were discussed and resolved with a third author. This systematic

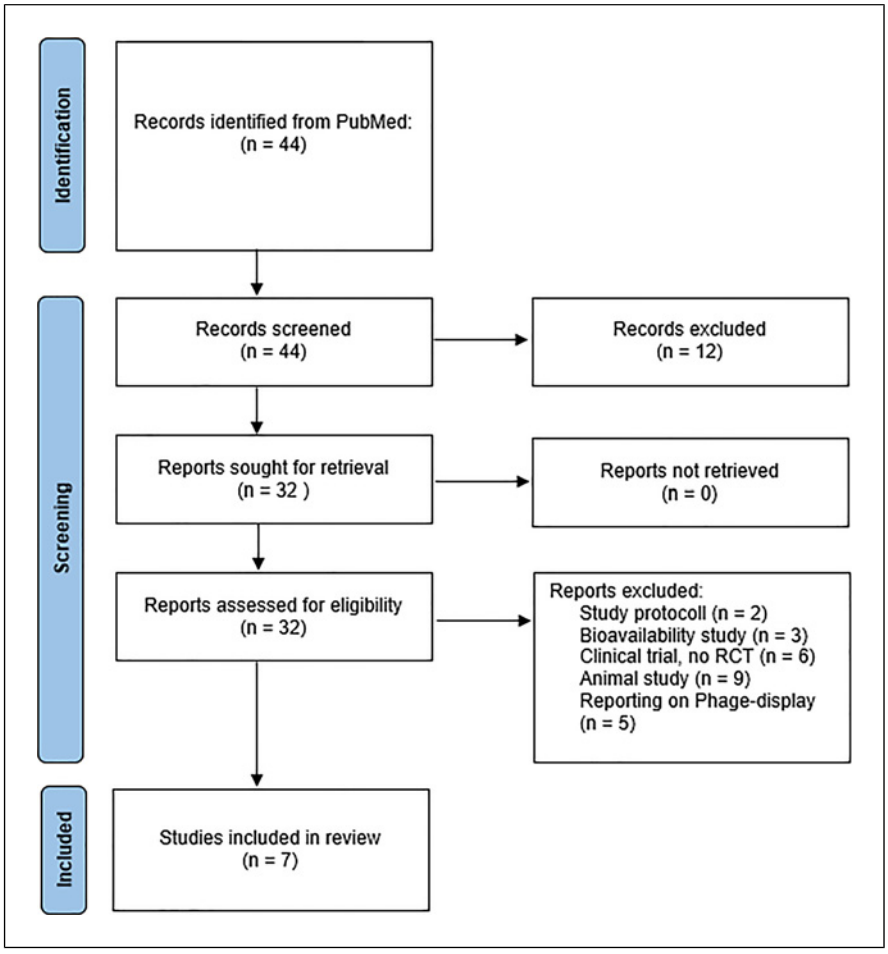

Fig. 1. PRISMA flow diagram showing the article selection process.

review of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Fig. 1) [12].

Results

Bibliometric Analysis

A total of 6,355 articles were included. Overall, these were cited 215,209 times (157,789 without self-citations), yielding 33.9 citations on average per item and an H-index of 178. Over the past decade, the number of publications on bacteriophage therapy increased more than threefold with 212 articles in 2011 and 739 in 2022 (Fig. 2). Articles were mostly written in English (98.9%), followed by French (0.3%), and German (0.2%). Most articles were original (4,886, 76.8%), 1,187 (18.7%) were reviews, and 131 (2.1%) editorials. The remaining ones included meeting abstracts, proceeding papers, book chapters, and letters to the editor. Articles were published in 923 different journals (Table 1). In total, 24,005 different authors were identified and were in the USA (28.2%), followed by China (16.0%), the UK (7.8%), Germany (7.5%), and Poland (5.1%) (Fig. 3). The most cited articles are shown in Table 2.

Systematic Review

The systematic search in PubMed with the filter "randomized controlled trial" yielded 44 articles sought for retrieval. Only 7 articles were found eligible for inclusion (Table 3). These reported on a total of 418 participants. In three studies, mild to moderate adverse events were reported as being associated with phage therapy in 10/195 participants (5.1%). Phages were tested in healthy participants in one study. Treatment indications included bacterial diarrhea, urinary tract infections, infected burn wound, chronic otitis, chronic venous leg ulcers, and chronic rhinosinusitis. Three of the studies reported a statistically significant difference in outcomes comparing a single-phage therapy with standard of care or placebo (Table 3).

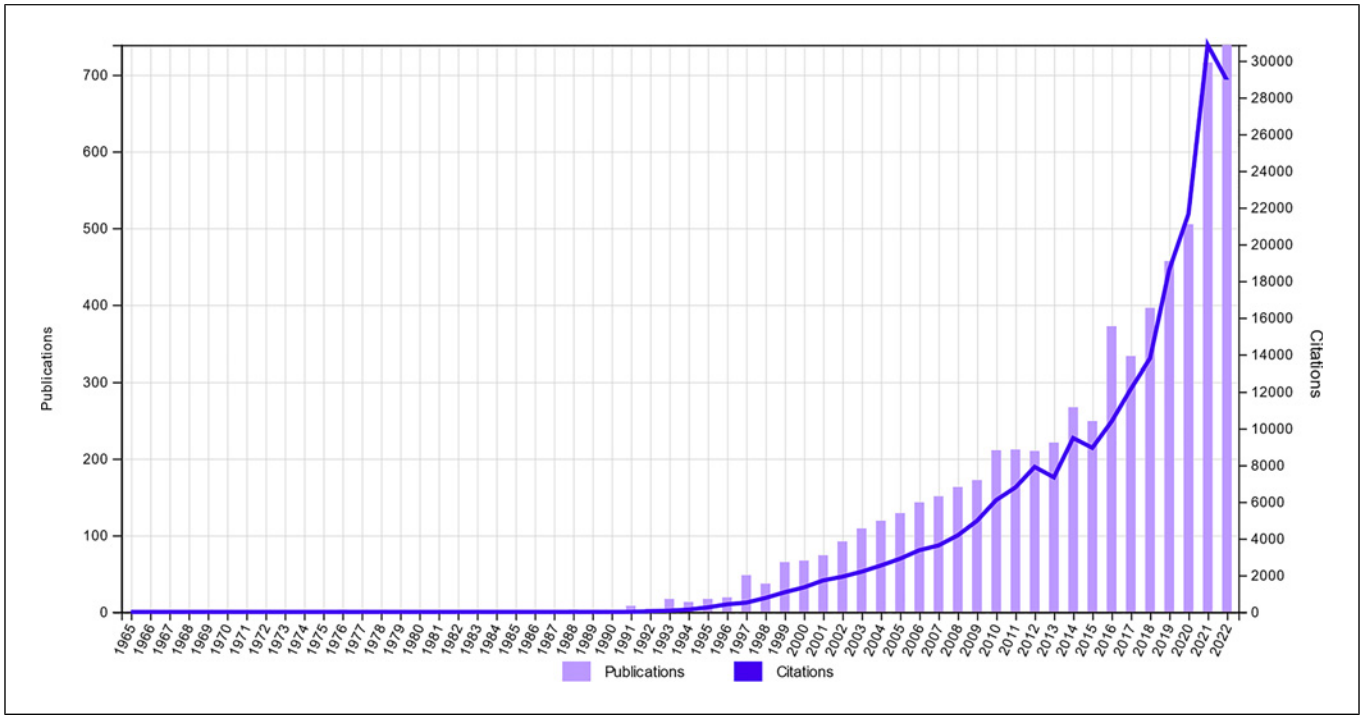

Fig. 2. Annual number of publications and citations between 1965 and 2022 identified through a systematic search in WoS with the keywords: "bacteriophage" OR "phage" AND "therapy" OR "application."

Table 1. List of the top 10 journals of published articles on bacteriophage therapy

Journal	Record counts	Impact factor in 2022 (Clarivate), open access (yes/no)
Frontiers in Microbiology	201	6.06, yes
Viruses Basel	174	5.82, yes
Antibiotics Basel	107	5.22, yes
Applied and Environmental Microbiology	73	4.79, yes
Antimicrobials Agents and Chemotherapy	69	5.94, yes
PLOS One	66	3.24, yes
Scientific Reports	50	4.99, yes
Microorganisms	40	4.93, yes
Journal of Applied Microbiology	37	4.06, yes
Journal of Virology	33	4.50, yes

Discussion

The aim of this bibliometric analysis was to provide an overview of the current state of the literature on the therapeutic application of bacteriophages. Our analysis revealed an upward trend in citations on this topic, indicating that phage therapy has garnered significant attention within the research community.

The most highly cited paper in our analysis was published in 2001; it reviewed studies conducted in Poland and the former Soviet Union and compared phages to antibiotics and proposed solutions to challenges encountered in early therapeutic phage research, paving the way for future advancements in therapeutic application of phage therapy [13]. The potential of phages was further explored in the second and third most cited publications identified. In particular, the study by Lu and

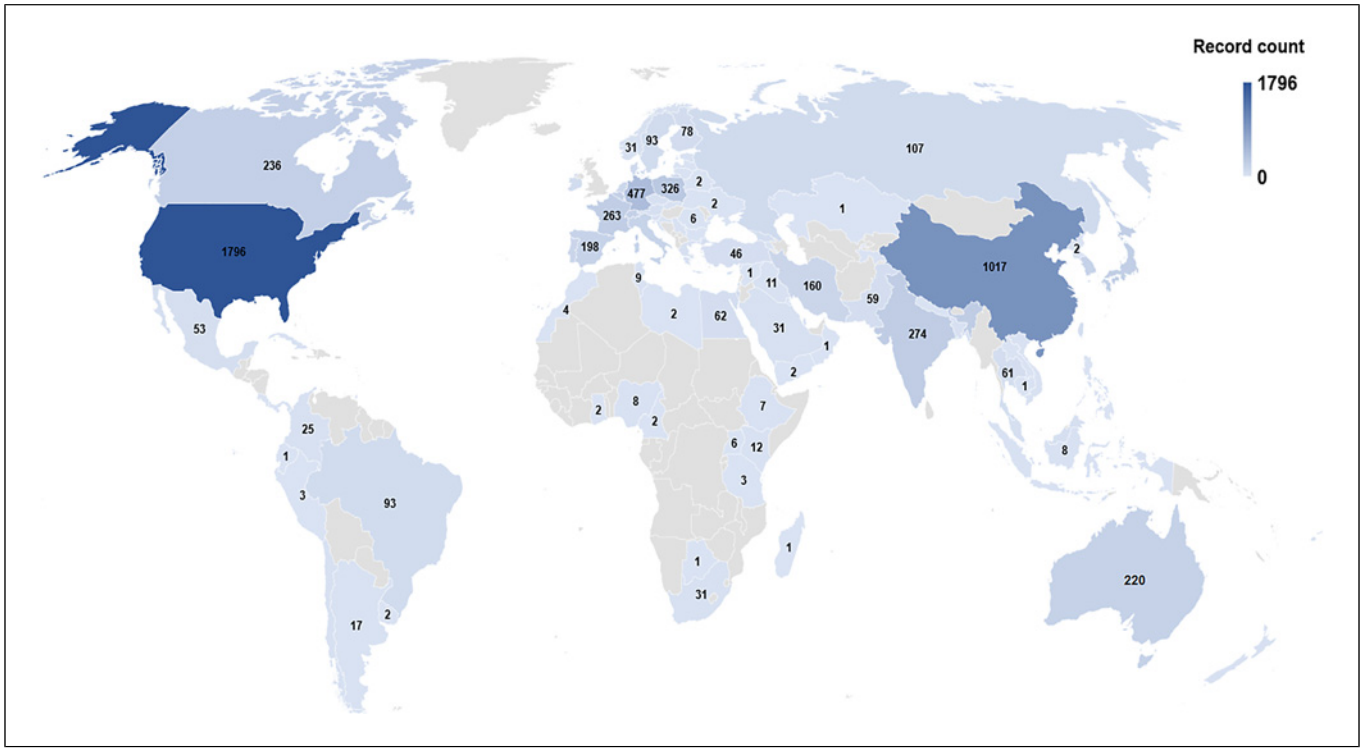

Fig. 3. Global distribution of articles from 1965 through 2022 identified with the keywords "bacteriophage" OR "phage" AND "therapy" OR "application" in a WoS search.

Collins (2007) demonstrated the efficacy of engineered phages in biofilm removal, showcasing the practicality of synthetic biology in manipulating these viruses [14]. Further, Schooley and colleagues described methods for the design of therapeutic cocktails and the development of personalized phage therapy for diabetic patients with necrotizing pancreatitis complicated by an MDR *Acinetobacter baumannii* infection [35].

The implementation of phage therapy has been impeded by the limited availability of clinical data on its safety and efficacy. In this study, out of an initial pool of 6,355 articles, only 7 RCTs were identified, involving a total of 418 participants. Consequently, the majority of the evidence originates from case studies, with over 2,200 applications in challenging-to-treat infections being published [35]. This disparity can be attributed to the regulatory framework surrounding phage therapy, which necessitates adherence to Article 37 of the Declaration of Helsinki of the World Medical Association as phage therapy remains categorized as an unapproved medical product. Additionally, the personalized approach to phage adaptation and the difficulty in accessing effective phages may have contributed to the limited clinical data available [36]. Moreover, issues pertaining to protection of intellectual property rights and the lack of interest among pharmaceutical companies have further hindered the advancement of phage therapy [37]. To address these challenges, it is advisable for governmental sectors to intervene and create a more enticing investment environment for pharmaceutical companies or provide more support to research sectors. By fostering collaboration and incentivizing further exploration, such measures could accelerate the progress of phage therapy and facilitate its integration into mainstream medical practices.

While it appears that the safety of phage therapy can be concluded with only a few adverse events being reported, results on its efficacy have been mixed. Among the RCT included in this study, 57.1% did not demonstrate a statistically significant improved outcome compared to standard of care or placebo [21–23, 25]. This might be attributable to specific clinical and microbiological challenges. For instance, it is of uttermost importance to have in vitro or in vivo efficacy demonstrated before starting phage therapy. This was not the case in one study which found phage resistant bacteria in three of the ten participants in the experimental group [23]. Sarker and colleagues [21] tested a phage cocktail against *E.coli* and suggested that persistence of diarrhea was attributable to streptococci species they identified in the stool microbiota. Further, the quantity of

Table 2. List of the fifteen most cited articles on bacteriophage therapy

Rank	Title	Author, year	Journal	Total citations	Average citation per year	OA	Type of article
1 [13]	Bacteriophage therapy	Sulakvelidze, Alavidze, Morris, 2001	Antimicrob Agents Chemother	999	45.41	Yes	Review
2 [14]	Dispersing biofilms with engineered enzymatic bacteriophage	Lu, Collins., 2007	Proc Natl Acad Sci U S A	524	32.75	Yes	Original, in vitro
3 [15]	Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails to Treat a Patient with a Disseminated Resistant *Acinetobacter baumannii* Infection	Schooley et al., 2017	Antimicrob Agents Chemother	508	84.67	Yes	Original, case report
4 [16]	Phage cocktails and the future of phage therapy	Chan, Abedon, Loc-Crrillo, 2013	Future Microbiol	459	45.9	Yes	Review
5 [17]	Phage Therapy in Clinical Practice: Treatment of Human Infections	Kutter et al., 2010	Curr Pharm Biotechnol	410	31.54	Yes	Review
6 [18]	Human volunteers receiving *Escherichia coli* phage T4 orally: a safety test of phage therapy	Bruttin, Brüssow, 2005	Antimicrob Agents Chemother	378	21	Yes	Original, clinical trial
7 [19]	Bacteriophage therapy rescues mice bacteremic from a clinical isolate of vancomycin-resistant *Enterococcus faecium*	Biswas et al., 2002	Infect Immun	347	16.52	Yes	Original, in vivo
8 [20]	Bacteriophage therapy	Summers, 2001	Annu Rev Microbiol	326	14.82	Yes	Review
9 [21]	Population and evolutionary dynamics of phage therapy	Levin, Bull, 2004	Nat Rev Microbiol	314	16.53	Yes	Review
10 [22]	Quality-Controlled Small-Scale Production of a Well-Defined Bacteriophage Cocktail for Use in Human Clinical Trials	Merabishvili et al., 2009	PLOS One	310	22.14	Yes	Original, in vitro
11 [23]	Bacteriophages as potential new therapeutics to replace or supplement antibiotics	Kutateladze, Adamia, 2010	Trends Biotechnol	293	22.54	Yes	Review
12 [24]	Phage Therapy in the Postantibiotic Era	Gordillo Altamirano, Barr, 2019	Clin Microbiol Rev	274	68.5	Yes	Review
13 [25]	Phage selection restores antibiotic sensitivity in MDR *Pseudomonas aeruginosa*	Chan BK, et al., 2016	Sci Rep	272	38.86	Yes	Original, in vitro
14 [26]	Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease	Duan et al., 2019	Nature	267	66.75	Yes	Original, in vivo
15 [27]	A historical overview of bacteriophage therapy as an alternative to antibiotics for the treatment of bacterial pathogens	Wittebole, De Roock, Opal, 2014	Virulence	263	29.22	Yes	Review

OA, open access.

Table 3. Identified RCTs

Author, year, origin	Sample size	Indication	Pathogen	Type of phages	Mode of application	Results	Side effects
Sarker et al. [28] 2016, Bangladesh	$n = 40$ phage cocktail 1 $n = 39$ phage cocktail 2 $n = 41$ placebo	Children with acute bacterial diarrhea	*E. coli*	(1) ColiProteus phage cocktail (Microgen, Russia) (2) T4-like coliphages (Nestlé, Switzerland)	Orally for 4 days, concentration not given	No improved diarrhea outcome	No adverse events
Leitner et al. [29] 2021, Georgia	$n = 28$ intervention $n = 32$ placebo $n = 37$ antibiotics	Patients undergoing transurethral resection of the prostate with urinary tract infections	Enterococcus spp, *E.coli, Proteus mirabilis, P. aeruginosa,* Staphylococcus spp, and Streptococcus spp	Pyo bacteriophage cocktail (Eliava BioPreparations, Georgia)	Intravesical 20 mL, 10^4–10^5 PFU/mL	Treatment success rates did not differ between groups	Adverse events occurred in 6 (21%) patients, most were sudden onset of fever
Jault et al. [30] 2019, France, Belgium, Switzerland	$n = 13$ intervention $n = 14$ SOC	Infected burn wound	*P. aeruginosa*	Natural lytic anti-*P. aeruginosa* bacteriophages PP1131 (Pherecydes Pharm, France)	Locally, 10^6 PFU/mL, daily for 7 days	The trial was stopped on Jan 2, 2017 because of insufficient efficacy of PP1131	Three (23%) of 13 analyzable participants had adverse events
Wright et al. [31] 2009, UK	$n = 12$ intervention $n = 12$ placebo	Chronic otitis	*P. aeruginosa*	Biophage-PA (not specified)	Locally 10^6 PFU/mL, one time 200 µL	Physician-reported and patient-reported outcomes improved	No adverse events
Rhoads et al. [32] 2009, USA	$n = 20$ intervention $n = 22$ control	Chronic venous leg ulcers	*E. coli, S. aureus, P. aeruginosa*	WPP-201 cocktail (Intralytix, USA)	Locally 10^9/mL, 4 mL dripped on the wound	No significant difference ($p > 0.05$) between the test and control groups for frequency of adverse events, rate of healing, or frequency of healing	No adverse events
Dobretsov et al. [33] 2021, Russia	$n = 20$ intervention $n = 20$ placebo	Chronic rhinosinusitis with nasal polyps	Streptococci, Enterobacteriaceae, Staphylococci	Bacteriophages mixture (Otofag, Micromir, Russia)	Intranasal gel twice a day for 10 weeks	Significant bacterial reduction, significant reduced interleukin-1β activity	Not reported
Grubb et al. [34] 2020, USA	$n = 23$ intervention $n = 21$ placebo $n = 24$ SOC	Healthy adults	*E. coli*	LH01-Myoviridae, LL5-Siphoviridae, T4D-Myoviridae, and LL12-Myoviridae (PreforPro, Deerland Enzymes, Kennesaw, GA, USA)	Orally, 10^6 PFU in one capsula daily for 28 days	Within-group improvements in gastrointestinal inflammation ($p = 0.01$) only in the phage group	Constipation, bloating, flatulence, fatigue/lack of energy, or other in 4.5% of the intervention group

SOC, Standard of care; PFU, Plaque-forming units.

phages administered has to be sufficient. In the identified studies, titers of 10^4–10^6 PFU/mL were used with variations regarding application methods and frequency. For instance, in the clinical trial performed by Leitner and coworkers [22] with patients suffering from urinary tract infection, phage therapy did not appear to be superior to the placebo group receiving sterile bacteriology solution or to the antibiotic treatment group. The patients in the study group received 20 mL of the Georgian Pyo phage cocktail intravesical with a concentration of 10^4–10^5 PFU/mL. The authors postulated that the concentration of the phages delivered to the infection site may have been inadequate [22]. Jault and colleagues [30] observed that the concentration of the phage cocktail has decreased during the time of trial due to instability issues; initially, the designed cocktail comprising 12 anti-*P. aeruginosa* phages had a concentration of 10^6 PFU/mL, which decreased to 10^2 PFU/mL at the time of treatment [30]. To design successful clinical trials, various factors such as the quality of phage preparation, sensitivity testing, titers and dosages, access to the infection site, and stability must be thoroughly evaluated [10]. Moreover, the establishment of optimal treatment protocols is urgently needed, given the high variety of the modes of application used in the studies. Further, a better understanding of phage pharmacology is imperative as it fundamentally differs from the concepts developed for chemotherapeutics, contributing to some instances of unsuccessful application [38]. In addition, while phages can be effective by themselves, researchers have been exploring the potential synergistic effects of combining phages and antibiotics to enhance their antibacterial capability. The combined approach shows enhanced bacterial suppression, improved penetration into biofilms, and reduced likelihood of emergence of phage resistance, making it a promising strategy [39, 40]. Thus, for successful translation of phage therapy, researchers and clinicians should learn from earlier experiences as insufficient or questionable data of RCT may disarm this potential weapon in combating the MDR challenge.

Limitations

Bibliometric analysis can serve as a valuable tool for evaluating research impact, influence, and identifying trends. However, it is essential to recognize its limitations, which should be taken into consideration. First, this analysis relies on published studies, potentially leading to an incomplete representation of the entire research activity in the field of phage therapy. Unpublished or gray literature, such as conference proceedings, may not be accounted for in the analysis. Additionally, the search process in WoS focuses on citation, abstract, and keyword identifiers, potentially overlooking articles that mention the keywords of interest solely in their methods sections, which could impact the completeness of the identified list of articles on phage therapy. Moreover, the analysis solely relies on citation counts, neglecting the consideration of research quality. Various factors, such as the age of the study, the journal of publication, and open-access availability, can influence citation counts, and thus, the presented results might not fully reflect the actual quality of the research. It is important to note that a study with a smaller number of citations might possess higher quality compared to one with a larger number of citations.

Conclusions

In conclusion, phage therapy has garnered increasing interest as a potential complement to antibiotics over the years. While RCTs on various indications suggest the safety of phage therapy, its limited evidence of in vivo efficiency remains a significant barrier to widespread acceptance. These limitations are often attributed to issues with study design. Additionally, a more comprehensive understanding of phage pharmacology is necessary as it frequently hampers their successful application in clinical settings. To ensure successful translation into clinical practice, researchers and clinicians should draw lessons from earlier experiences and address crucial aspects, such as the quality of phage preparation, sensitivity testing, titer and dosages, as well as access to the infection site and stability, rigorously in future trials. Establishing standardized treatment protocols is also crucial in optimizing the efficacy of phage therapy.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on the published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received for this study.

Author Contributions

Conceptualization: Nike Walter and Markus Rupp. Methodology, formal analysis, and preparation of original draft: Nike Walter. Validation: Markus Rupp. Review and editing:

Mohammadali Khan Mirzaei, Li Deng, Christian Willy, Volker Alt, and Markus Rupp. Project administration: Volker Alt. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

References

1 Clokie MR, Millard AD, Letarov AV, Heaphy S. Phages in nature. Bacteriophage. 2011;1:31–45.
2 Romero-Calle D, Guimarães Benevides R, Góes-Neto A, Billington C Bacteriophages as alternatives to antibiotics in clinical care. Antibiotics. 2019;8(3):138.
3 Twort FW. An investigation on the nature of ultra-microscopic viruses. Lancet. 1915; 186(4814):1241–3.
4 Krestovnikova VA. Phage treatment and phage prophylactics and their approval in the works of the Soviet researchers: Springer; 1947. p. 56–65.
5 Bartlett JG, Gilbert DN, Spellberg B. Seven ways to preserve the miracle of antibiotics. Clin Infect Dis. 2013;56(10):1445–50.
6 Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P T. 2015;40(4):277–83.
7 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629–55.
8 de Kraker MEA, Stewardson AJ, Harbarth S. Will 10 million people die a year due to antimicrobial resistance by 2050? PLoS Med. 2016;13(11):e1002184.
9 Moelling K, Broecker F, Willy C. A wake-up call: we need phage therapy now. Viruses. 2018;10(12):688.
10 Górski A, Borysowski J, Międzybrodzki R. Phage therapy: towards a successful clinical trial. Antibiotics. 2020;9(11):827.
11 Birkle C, Pendlebury DA, Schnell J, Adams J. Web of Science as a data source for research on scientific and scholarly activity. Quan Sci Stud. 2020;1:363–76.
12 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
13 Sulakvelidze A, Alavidze Z, Morris JG. Bacteriophage therapy. Antimicrob Agents Chemother. 2001;45(3):649–59.
14 Lu TK, Collins JJ. Dispersing biofilms with engineered enzymatic bacteriophage. Proc Natl Acad Sci U S A. 2007;104(27):11197–202.
15 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.
16 Chan BK, Abedon ST, Loc-Carrillo C. Phage cocktails and the future of phage therapy. Future Microbiol. 2013;8(6):769–83.
17 Kutter E, De Vos D, Gvasalia G, Alavidze Z, Gogokhia L, Kuhl S, et al. Phage therapy in clinical practice: treatment of human infections. Curr Pharm Biotechnol. 2010;11(1):69–86.
18 Bruttin A, Brüssow H. Human volunteers receiving Escherichia coli phage T4 orally: a safety test of phage therapy. Antimicrob Agents Chemother. 2005;49(7):2874–8.
19 Biswas B, Adhya S, Washart P, Paul B, Trostel AN, Powell B, et al. Bacteriophage therapy rescues mice bacteremic from a clinical isolate of vancomycin-resistant Enterococcus faecium. Infect Immun. 2002;70(1):204–10.
20 Summers WC. Bacteriophage therapy. Annu Rev Microbiol. 2001;55:437–51.
21 Levin BR, Bull JJ. Population and evolutionary dynamics of phage therapy. Nat Rev Microbiol. 2004;2:166–73.
22 Merabishvili M, Pirnay J-P, Verbeken G, Chanishvili N, Tediashvili M, Lashkhi N, et al. Quality-controlled small-scale production of a well-defined bacteriophage cocktail for use in human clinical trials. PLoS One. 2009;4(3):e4944.
23 Kutateladze M, Adamia R. Bacteriophages as potential new therapeutics to replace or supplement antibiotics. Trends Biotechnol. 2010;28(12):591–5.
24 Gordillo Altamirano FL, Barr JJ. Phage therapy in the postantibiotic era. Clin Microbiol Rev. 2019;32(2):e00066-18.
25 Chan BK, Sistrom M, Wertz JE, Kortright KE, Narayan D, Turner PE. Phage selection restores antibiotic sensitivity in MDR Pseudomonas aeruginosa. Sci Rep. 2016;6:26717.
26 Duan Y, Llorente C, Lang S, Brandl K, Chu H, Jiang L, et al. Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease. Nature. 2019;575(7783):505–11.
27 Wittebole X, De Roock S, Opal SM. A historical overview of bacteriophage therapy as an alternative to antibiotics for the treatment of bacterial pathogens. Virulence. 2014;5(1):226–35.
28 Sarker SA, Sultana S, Reuteler G, Moine D, Descombes P, Charton F, et al. Oral phage therapy of acute bacterial diarrhea with two coliphage preparations: a randomized trial in children from Bangladesh. EBioMedicine. 2016;4:124–37.
29 Leitner L, Ujmajuridze A, Chanishvili N, Goderdzishvili M, Chkonia I, Rigvava S, et al. Intravesical bacteriophages for treating urinary tract infections in patients undergoing transurethral resection of the prostate: a randomised, placebo-controlled, double-blind clinical trial. Lancet Infect Dis. 2021; 21(3):427–36.
30 Jault P, Leclerc T, Jennes S, Pirnay JP, Que Y-A, Resch G, et al. Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by Pseudomonas aeruginosa (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial. Lancet Infect Dis. 2019;19(1):35–45.
31 Wright A, Hawkins CH, Anggård EE, Harper DR. A controlled clinical trial of a therapeutic bacteriophage preparation in chronic otitis due to antibiotic-resistant Pseudomonas aeruginosa; a preliminary report of efficacy. Clin Otolaryngol. 2009;34(4):349–57.
32 Rhoads DD, Wolcott RD, Kuskowski MA, Wolcott BM, Ward LS, Sulakvelidze A. Bacteriophage therapy of venous leg ulcers in humans: results of a phase I safety trial. J Wound Care. 2009;18(6):237–8.
33 Dobretsov KG, Kolenchukova O, Sipkin A, Bellussi LM, Ciprandi G, Passali D. A randomized, double-blind, placebo- -controlled study to investigate the use of bacteriophages in patients with chronic rhinosinusitis with nasal polyps. Otolaryngol Pol. 2021;75(6):33–7.
34 Grubb DS, Wrigley SD, Freedman KE, Wei Y, Vazquez AR, Trotter RE, et al. PHAGE-2 study: supplemental bacteriophages extend bifidobacterium animalis subsp. lactis BL04 benefits on gut health and microbiota in healthy adults. Nutrients. 2020;12(8):2474.
35 Uyttebroek S, Chen B, Onsea J, Ruythooren F, Debaveye Y, Devolder D, et al. Safety and efficacy of phage therapy in difficult-to-treat infections: a systematic review. Lancet Infect Dis. 2022;22(8):e208–20.
36 Pirnay J-P, Kutter E. Bacteriophages: it's a medicine, Jim, but not as we know it. Lancet Infect Dis. 2021;21(3):309–11.
37 MacLean MR, Harper DR. Intellectual property issues for bacteriophages. In: Harper DR, Abedon ST, Burrowes BH, McConville ML, editors. Bacteriophages. Cham: Springer International Publishing; 2021. p. 731–49.
38 Danis-Wlodarczyk K, Dąbrowska K, Abedon ST. Phage therapy: the pharmacology of antibacterial viruses. Curr Issues Mol Biol. 2021;40:81–164.
39 Łusiak-Szelachowska M, Międzybrodzki R, Drulis-Kawa Z, Cater K, Knežević P, Winogradow C, et al. Bacteriophages and antibiotic interactions in clinical practice: what we have learned so far. J Biomed Sci. 2022;29(1):23.
40 Tagliaferri TL, Jansen M, Horz H-P. Fighting pathogenic bacteria on two fronts: phages and antibiotics as combined strategy. Front Cell Infect Microbiol. 2019;9:22.