Effect of Phage Therapy on Antibiotic-Resistant Infections: A Systematic Review

Abstract:

Background: Antibiotic-resistant infections pose a significant challenge to global health, and innovative solutions are urgently needed. Phage therapy, the therapeutic use of bacteriophages to treat bacterial infections, has been suggested as a potential alternative to antibiotics.This systematic review aimed to evaluate the effect of phage therapy on antibiotic-resistant infections.

Methods: We conducted a comprehensive search of PubMed, Scopus, and Web of Science databases for studies published in the last twenty years. Studies were included if they assessed the impact of phage therapy on antibiotic-resistant infections. Data were extracted systematically, and a qualitative synthesis was performed.

Results: From the 5 studies that met our inclusion criteria, phage therapy demonstrated a consistent safety profile with no significant adverse events reported. Specific results included a treatment response in 18% of patients using intravesical Pyo bacteriophage, reduced bacterial burden in patients with burn wounds treated with anti-P aeruginosa bacteriophages, and significant reduction in P. aeruginosa counts in patients with chronic otitis using Biophage-PA.

Conclusion: The evidence gathered in this systematic review shows that phage therapy could potentially serve as a safe and efficacious treatment alternative for antibiotic-resistant infections. The heterogeneity of the studies regarding design, interventions, and outcome measures underlines the necessity for more standardized, large-scale studies to validate these findings and further explore the potential of phage therapy. The development of a comprehensive framework for phage therapy application may offer a promising direction in combatting the global challenge of antibiotic resistance.

Keywords: Phage Therapy, Antibiotic Resistance, Systematic Review, Bacteriophages, Infection, Treatment, Therapeutic Alternatives

Introduction

Antibiotic resistance is an escalating global health crisis, posing a severe threat to the control of microbial diseases (1). The phenomenon arises when bacteria evolve to withstand the drugs designed to kill them, rendering current treatment ineffective and raising the risk of uncontrolled infectious spread (2). Identified as one of the top ten global public health threats by the World Health Organization, the growing dearth of novel antibiotics being developed to counter this crisis amplifies its urgency(3). This pressing situation necessitates innovative and effective strategies, among which bacteriophage therapy emerges as a promising alternative. Our systematic review, focused on phage therapy and antibiotic-resistant infections, explores this potential solution.

Bacteriophages, or phages, are viruses that specifically infect and destroy bacteria. They are the most abundant biological entities on earth, considerably outnumbering their bacterial hosts (4). Their therapeutic use against bacterial infections was proposed early in the 20th century, coinciding with their discovery (5). However, the advent of antibiotics, with their broad-spectrum activity and ease of use, superseded phage therapy in the West (6). In contrast, regions such as the former Soviet Union and parts of Eastern Europe continued employing phage therapy due to limitations in antibiotic access (7).

In the current landscape of growing antibiotic resistance and sluggish progress in novel antibiotic development, bacteriophage therapy is experiencing a resurgence in interest. As per the Centers for Disease Control and Prevention (CDC), at least 2.8 million reportedly undergo antibiotic-resistant infections every year leading to 35,000 deaths annually(8). Phages present several potential advantages over traditional antibiotics. Their high specificity allows for targeted action against pathogenic bacteria, sparing the beneficial microbiota (9). They are capable of self-replication at the infection site, thus increasing their concentration where needed. Additionally, phages can penetrate biofilms, a defense mechanism often employed by bacteria that enhances their resistance to antibiotics(10). The capacity to engineer phages to enhance their safety and efficacy presents another layer of potential(9,10).

Despite these promising aspects, considerable challenges remain regarding the large-scale adoption of phage therapy. There are significant regulatory, manufacturing, and logistical challenges to address (11). Moreover, there is a pressing need for robust clinical trials to assess the safety and efficacy of phage therapy in comparison to, or in conjunction with, antibiotics (12). This systematic review aims to synthesize the available evidence on the effect of phage therapy on antibiotic-resistant infections, covering diverse types of clinical studies and patient populations.

The urgency of novel approaches to tackle antibiotic resistance makes this review both timely and critical. By comprehensively evaluating the current evidence, we aim to elucidate the potential and limitations of phage therapy, informing future research in this area, and assisting

policy-makers in informed decision-making concerning the integration of phage therapy into our armamentarium against antibiotic-resistant infections. The outcomes of this review hold significant implications for the scientific community, clinicians, and patients alike. The findings could guide future directions for research and development in bacteriophage therapy, offering new hope in our ongoing battle against the formidable challenge of antibiotic resistance.

Methods

The methodology for this systematic review was designed in alignment with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement 2020 guidelines. The review sought to present a comprehensive evaluation of recent literature evaluating the effect of phage therapy on antibiotic-resistant infections.

Search Strategy

The systematic literature search focused on research published within the last twenty years to ensure the integration of the most recent and, therefore, most pertinent studies. The search was performed on three databases, namely PubMed, Scopus, and Web of Science, for pertinent studies. Keywords and MeSH terms such as 'Phage Therapy', 'Antibiotic Resistance', 'Bacterial Infections', 'Clinical Trial', 'Efficacy', 'Safety', and their combinations were employed for the search. No limitations were established based on language or geographical location, and only peer-reviewed articles were considered eligible for inclusion.

Study Selection

The articles retrieved from the initial search were independently screened by two reviewers based on their titles and abstracts for relevance to the topic of antibiotic-resistant infections and the use of phage therapy in their management. Any discrepancies between the reviewers were resolved through discussion or consultation with a third reviewer if necessary. The full texts of the shortlisted articles were obtained for more detailed examination. Studies were included if they met the following criteria: original research studies published in the past 20 years, studies focusing on phage therapy approaches in managing antibiotic-resistant infections, and studies that offered sufficient data for extraction and analysis.

Key Definitions of Terms in this Study

- **Phage Therapy:** The therapeutic use of bacteriophages to treat pathogenic bacterial infections.
- **Antibiotic Resistance:** The ability of bacteria to resist the effects of an antibiotic to which they were once sensitive.
- **Bacterial Infections:** Infections caused by pathogenic bacteria.
- **Clinical Trial:** A research investigation in which people volunteer to test new treatments, interventions or tests as a means to prevent, detect, treat or manage various diseases or medical conditions.
- **Efficacy:** The ability to produce a desired or intended result.

- **Safety:** The condition of being protected from or unlikely to cause danger, risk, or injury, particularly in the context of medical treatments or interventions.

Data Extraction and Synthesis

Data from the included studies were systematically extracted by the research team. The data extracted included the following details: author names, year of publication, study design, intervention, population characteristics, main results. The extracted data were then synthesized and analyzed qualitatively. The key findings were consolidated and summarized, and the results were categorized based on the study design, intervention, and main results. This provided a snapshot of the current state of phage therapy applications in the management of antibiotic-resistant infections. The synthesis also underscored the potential impact of these studies on the field of infectious diseases and pinpointed gaps in the existing research for future exploration.

Results

Of the 1491 studies identified from the databases, 223 duplicates were removed. During the screening phase, 1268 studies were screened for titles and abstracts, of which 1236 were excluded due to lack of relevance. Therefore, the full-text screening phase comprised 32 studies, of which 5 studies met the inclusion criteria. The PRISMA flowchart is depicted in **Figure 1**.

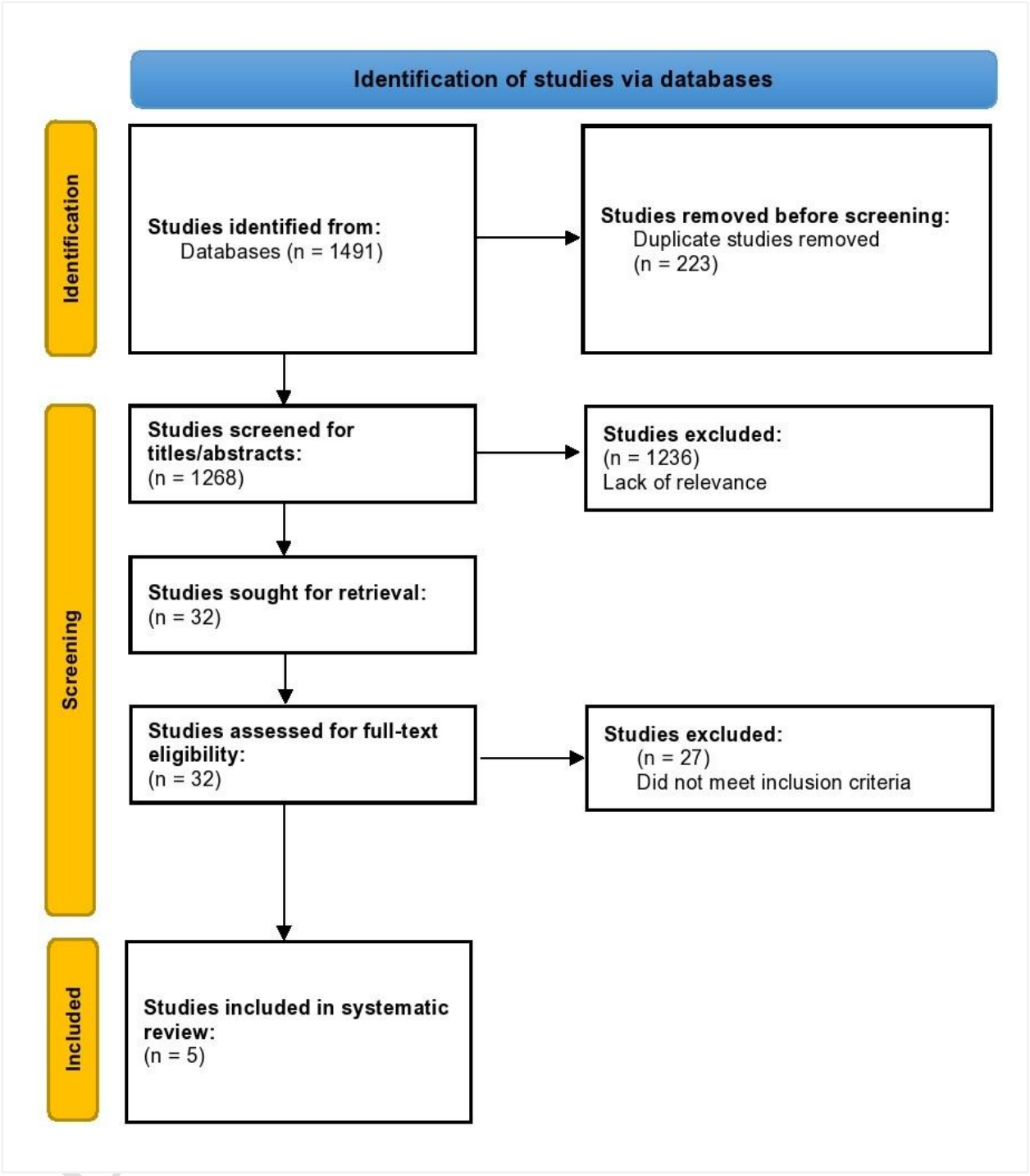

Figure 1. PRISMA flowchart depicting the study selection process.

In the systematic review, five studies were presented. They are tabulated in **Table 1**.

Author, Year	Title	Study Type	Inclusion Criteria	Outcome Measures	Population Characteristics	Intervention	Main Results
Leitner, 2021(13)	Intravesical bacteriophages for treating urinary tract infections in patients undergoing transurethral resection of the prostate: a randomised, placebo-controlled, double-blind clinical trial	Randomized, placebo-controlled, clinical trial	Men older than 18 years, scheduled for TURP, with complicated UTI or recurrent uncomplicated UTI but no signs of systemic infection	Microbiological treatment response after 7 days of treatment, measured by urine culture; secondary outcomes included clinical and safety parameters during the treatment period	Men with UTIs undergoing TURP	Intravesical Pyo bacteriophage (20 mL) twice daily for 7 days, or intravesical placebo solution (20 mL), or systemically applied antibiotics	Normalisation of urine culture achieved in 18% (Pyophage), 28% (placebo), and 35% (antibiotics). OR for adverse events: 0.36 (95% CI=0.11-1.17) for Pyophage vs placebo; 0.66 (95% CI=0.21-2.07) for Pyophage vs antibiotics
Leo, 2021(14)	Effects of antibiotic duration on the intestinal microbiota and resistome: The PIRATE RESISTANCE project, a cohort study nested within a randomized trial	Nested prospective cohort study	Adult patients hospitalized for gram-negative bacteremia and controls without antibiotic therapy	ARG abundance at day 30; secondary outcomes included microbiota-species composition and clustering over time	Hospitalized adults treated for gram-negative bacteremia	Shortened antibiotic courses (7 versus 14 days)	No significant difference in ARG abundance at day 30 between 7-day (median counts/million [mCPM]: 96) and 14-day groups (mCPM: 71; P=0.38). No significant difference in total ARG content by day 30 between both groups and controls (P=0.24 and 0.19, respectively)
Jault, 2019(15)	Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by Pseudomonas aeruginosa (PhagoBurn): a randomised, controlled,	Randomized phase 1/2 trial	Patients aged 18 years or older with a burn wound clinically infected with P aeruginosa	Median time to sustained reduction in bacterial burden by at least two quadrants, assessed by use of daily swabs	Patients with burn wounds infected with P aeruginosa	A cocktail of 12 natural lytic anti-P aeruginosa bacteriophages (PP1131; 1 × 106 PFU per mL) or standard of care (1% sulfadiazine silver emulsion cream)	Median time to sustained reduction in bacterial burden: 144 hours (PP1131) vs 47 hours (standard of care); hazard ratio 0.29 (95% CI=0.10-

	double-blind phase 1/2 trial						0.79; P=0.018). Adverse events in 23% (PP1131) vs 54% (standard of care)
Sarker, 2016(16)	Oral Phage Therapy of Acute Bacterial Diarrhea With Two Coliphage Preparations: A Randomized Trial in Children From Bangladesh	Controlled trial	Bangladeshi children hospitalized with acute bacterial diarrhea	Safety of oral phage clinically and by functional tests; coliphage and E. coli titers and enteropathogens in stool; quantitative diarrhea parameters (stool output, stool frequency)	Bangladeshi children hospitalized with acute bacterial diarrhea	Oral T4-like coliphages or a commercial Russian coliphage product or placebo given over 4 days	No adverse events attributable to oral phage application observed; fecal coliphage was increased in treated over control children, but did not show substantial intestinal phage replication; no amelioration in quantitative diarrhea parameter by PT over standard care
Wright, 2009(17)	A controlled clinical trial of a therapeutic bacteriophage preparation in chronic otitis due to antibiotic-resistant Pseudomonas aeruginosa; a preliminary report of efficacy	Randomized, double-blind, placebo-controlled Phase I/II clinical trial	Patients with chronic otitis with a duration of several years (2-58), infected with an antibiotic-resistant P. aeruginosa strain sensitive to one or more of the six phages present in Biophage-PA	Physician assessed erythema/inflammation, ulceration/granulation/polyps, discharge quantity, discharge type and odor using a Visual Analogue Scale (VAS); bacterial levels of P. aeruginosa and phage counts from swabs initially and at follow-up	Patients with chronic otitis infected with antibiotic-resistant P. aeruginosa	Single dose of Biophage-PA or placebo	Pooled patient- and physician-reported clinical indicators improved for the phage treated group relative to the placebo group; P. aeruginosa counts were significantly lower only in the phage treated group (P<0.05); no treatment related adverse event was reported

Table 1. Key Characteristics of the Included Studies.**Abbreviations:**ARG: Antibiotic Resistance Gene; CI: Confidence Interval; E. coli: Escherichia coli; mCPM: Median Counts per Million; OR: Odds Ratio; PFU: Plaque-Forming Unit; PT: Phage Therapy; TURP: Transurethral Resection of the Prostate; UTI: Urinary Tract Infection; VAS: Visual Analogue Scale.

Leitner et al. (2021) conducted a randomized, placebo-controlled, clinical trial involving men older than 18 years scheduled for transurethral resection of the prostate (TURP), with complicated urinary tract infections (UTI) or recurrent uncomplicated UTI but without signs of systemic infection(13). The study's primary outcome was the microbiological treatment response after seven days of treatment, as measured by urine culture. The study also examined clinical and safety parameters during the treatment period. The trial involved three interventions: an intravesical Pyo bacteriophage solution (20 mL) administered twice daily for seven days, an intravesical placebo solution (20 mL), and systemically applied antibiotics. The main results showed that the normalization of urine culture was achieved in 18% of patients treated with Pyophage, 28% with placebo, and 35% with antibiotics. The odds ratio for adverse events was 0.36 (95% CI=0.11-1.17) for Pyophage vs. placebo and 0.66 (95% CI=0.21-2.07) for Pyophage vs. antibiotics.

Leo et al. (2021) conducted a nested prospective cohort study involving adult patients hospitalized for gram-negative bacteraemia and controls who did not receive antibiotic therapy(14). The main outcome measure was the abundance of antibiotic resistance genes (ARG) at day 30, with secondary outcomes including microbiota-species composition and clustering over time. The intervention involved shortened antibiotic courses (7 versus 14 days). The results indicated no significant difference in ARG abundance at day 30 between the 7-day group (median counts per million [mCPM]: 96) and the 14-day group (mCPM: 71; P=0.38). Similarly, there was no significant difference in total ARG content by day 30 between both groups and the controls (P=0.24 and 0.19, respectively).

Jault et al. (2019) conducted a randomized phase 1/2 trial involving patients aged 18 years or older with a burn wound clinically infected with Pseudomonas aeruginosa(15). The main outcome measure was the median time to a sustained reduction in bacterial burden by at least two quadrants, assessed by use of daily swabs. The intervention involved a cocktail of 12 natural lytic anti-P aeruginosa bacteriophages (PP1131; 1 × 10^6 PFU per mL) or standard of care (1% sulfadiazine silver emulsion cream). The results showed a median time to sustained reduction in bacterial burden of 144 hours with PP1131 versus 47 hours with standard care; hazard ratio 0.29 (95% CI=0.10-0.79; P=0.018). Adverse events were reported in 23% of patients treated with PP1131 and 54% of those given the standard of care.

Sarker et al. (2016) conducted a controlled trial involving Bangladeshi children hospitalized with acute bacterial diarrhea(16). The study assessed the safety of oral phage, both clinically and through functional tests, as well as coliphage and Escherichia coli titers and enteropathogens in stool, and quantitative diarrhea parameters (stool output, stool frequency). The intervention involved the oral administration of T4-like coliphages or a commercial Russian coliphage product or placebo over four days. No adverse events attributable to oral phage application were observed, and fecal coliphage was increased in treated children compared to the control group. However, the results did not show substantial intestinal phage replication, and there was no amelioration in quantitative diarrhea parameters by phage therapy over standard care.

Wright et al. (2009) conducted a randomized, double-blind, placebo-controlled Phase I/II clinical trial involving patients with chronic otitis with a duration of several years (2-58), infected with

an antibiotic-resistant P. aeruginosa strain sensitive to one or more of the six phages present in Biophage-PA(17). The study assessed several outcome measures, including erythema/inflammation, ulceration/granulation/polyps, discharge quantity, discharge type, and odor, using a Visual Analogue Scale (VAS). In addition, bacterial levels of P. aeruginosa and phage counts were assessed from swabs initially and at follow-up. The intervention involved a single dose of Biophage-PA or placebo. The pooled patient- and physician-reported clinical indicators improved for the phage-treated group relative to the placebo group. Furthermore, P. aeruginosa counts were significantly lower only in the phage-treated group ($P<0.05$), and no treatment-related adverse events were reported.

Discussion

In this systematic review, we analyzed 5 studies evaluating the efficacy and safety of phage therapy for antibiotic-resistant infections. The study by Leitner et al. (2021) assessed the use of intravesical Pyo bacteriophage in men with urinary tract infections (UTIs) undergoing transurethral resection of the prostate (TURP), revealing mixed results in terms of treatment efficacy compared to placebo and systemic antibiotics. Similarly, Leo et al. (2021) found no significant difference in antibiotic resistance gene abundance following shortened antibiotic courses in adults treated for gram-negative bacteraemia. Jault et al. (2019) conducted a randomized phase 1/2 trial of a cocktail of 12 natural lytic anti-Pseudomonas aeruginosa bacteriophages in patients with burn wounds and found a longer time to sustained reduction in bacterial burden than standard care but with fewer adverse events. Sarker et al. (2016) evaluated the safety of oral T4-like coliphages in Bangladeshi children hospitalized with acute bacterial diarrhea, revealing increased fecal coliphage in treated children but without substantial intestinal phage replication or significant improvement in quantitative diarrhea parameters. Lastly, Wright et al. (2009) demonstrated improved clinical indicators and reduced P. aeruginosa counts in patients with chronic otitis treated with a single dose of Biophage-PA compared to placebo, without any treatment-related adverse events.

Phage therapy is an alternative method to the use of antibiotics, particularly in the context of rising antibiotic resistance. It has been shown that bacteriophages can specifically target and lyse bacteria, which makes them a promising tool against antibiotic-resistant infections (18). These recent studies included in our review build upon the current body of evidence supporting the potential utility of phage therapy. Although some findings, such as those of Leitner et al. and Sarker et al., suggest mixed or limited results in certain clinical contexts, other studies demonstrate promising outcomes and potential applications.

The ability of bacteriophages to target specific bacteria, as noted in the study by Jault et al., can be advantageous, particularly in infections where a specific pathogen is known. However, this specificity may also limit their applicability in situations where the causative bacteria is not yet identified. Moreover, while Wright et al. demonstrated the potential efficacy of phage therapy, the study focused on a chronic condition, and more research is required to establish the efficacy of phage therapy in acute infections.

It is also noteworthy to mention that most of these studies did not report any significant adverse events related to phage therapy. This finding is consistent with existing literature that suggests phage therapy is generally well-tolerated (11). However, as with any therapy, it is crucial to establish safety profiles in diverse patient populations and different clinical conditions, necessitating further rigorous, and large-scale studies. The lack of substantial intestinal phage replication observed by Sarker et al. is another interesting finding that warrants further investigation. This finding could influence the optimal administration method for phage therapy and could have implications for the overall effectiveness of the treatment.

Another aspect that was ascertained in this review was the comparison of phage therapy with shortened antibiotic courses, as seen in the study by Leo et al. The consideration of shorter antibiotic courses is an important one, as minimizing the use of antibiotics can mitigate the development of resistance. However, the study did not find a significant difference in resistance gene abundance, suggesting that further exploration is needed to understand the complex dynamics between antibiotics, bacterial infections, and resistance.

The use of phage therapy as an alternative or complementary approach to antibiotics has been gaining traction in the scientific community. The inherent specificity of bacteriophages towards particular bacterial strains and their ability to evolve alongside their bacterial targets could potentially make them a versatile tool in tackling antimicrobial resistance(19). Previous research has demonstrated the potential for synergistic effects between phages and antibiotics, with phages enhancing the effectiveness of antibiotics in eradicating biofilms in vitro(20). These findings are particularly noteworthy in light of the study by Leo et al., suggesting that the combination of phage therapy with an optimized antibiotic regimen could be a promising strategy to address antibiotic resistance.

Conversely, the role of phage therapy in modulating the human microbiome, which is a crucial factor in maintaining health and preventing disease, is also being explored. A study by Xu et al. (2022) highlighted the potential for phage therapy to selectively target pathogenic bacteria without disrupting the overall balance of the gut microbiota(21). This selective antibacterial action could theoretically reduce the potential for antibiotic resistance development, given the reduced pressure on non-target bacteria. Furthermore, unlike antibiotics, bacteriophages can replicate at the infection site, thereby amplifying their therapeutic effect. However, as highlighted by Sarker et al.'s findings, our understanding of in vivo phage dynamics, including the extent and implications of intestinal phage replication, remains limited and warrants further investigation.

Limitations and Strengths

One of the primary limitations of this review is the diversity in study designs and outcome measures, which can make comparisons across studies challenging. Moreover, most of the included studies had small sample sizes, limiting the generalizability of their findings. Furthermore, the variable and often limited follow-up periods in these studies may not capture longer-term outcomes and potential late-onset adverse effects of phage therapy. Additionally,

while every effort was made to conduct a comprehensive search of the literature, it is possible that relevant studies may have been overlooked, introducing potential selection bias.

Despite these limitations, this review has certain strengths. The comprehensive and systematic approach to literature search and data synthesis provides a robust overview of the current state of research on phage therapy for antibiotic-resistant infections. Furthermore, by including studies from a variety of clinical scenarios and geographical locations, this review presents a broad perspective on the application and efficacy of phage therapy.

Conclusion

In conclusion, this systematic review indicates a potential role for phage therapy in managing antibiotic-resistant infections. The included studies provide evidence of the effectiveness and safety of phage therapy in various clinical contexts, but also highlight the complexity of the field and the need for further research. The evolution of antibiotic-resistant infections is an escalating global health crisis, and the search for alternative treatments is increasingly important. With their unique features, bacteriophages may represent one such promising alternative. However, for their potential to be fully realized, more high-quality, large-scale studies are needed to better understand the intricacies of phage therapy, from patient selection to treatment delivery and monitoring. It is only through this comprehensive understanding that we can hope to harness the power of these "friendly viruses" in our fight against antibiotic resistance.

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