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Expert Opinion Article

Bacteriophage Therapy As An Alternative To Antibiotics: A Meta-Analysis

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Abstract

Background: The rise of antimicrobial resistance has driven the search for alternative therapies. Bacteriophage (phage) therapy, which employs viruses to target specific bacterial pathogens, is regaining attention as a promising solution for multidrug-resistant (MDR) infections.

Objective: This meta-analysis aims to evaluate the clinical efficacy, safety, and treatment outcomes associated with phage therapy in managing MDR bacterial infections.

Methods: A systematic review and meta-analysis were conducted using data from observational studies and case reports published between 2000 and early 2025. Eligible studies included human subjects treated with phage therapy for laboratory-confirmed MDR infections. Data were extracted on clinical outcomes, adverse events, phage characteristics, and concurrent antibiotic use. Risk of bias was assessed using the ROBINS-I tool for observational studies and the Joanna Briggs Institute (JBI) checklist for case reports. A random-effects model was used to calculate pooled cure rates and assess heterogeneity.

Results: Eight studies involving 196 patients were included in the meta-analysis. The pooled clinical cure rate was 71% (95% CI: 0.59–0.81), with moderate heterogeneity (I^2 = 44.4%). The highest efficacy was observed in studies targeting complex infections like prosthetic joint infections and osteomyelitis. Adverse events were rare and generally mild. Case reports also showed a favorable safety profile and microbiological clearance in 8 out of 9 patients.

Conclusion: Bacteriophage therapy demonstrates substantial clinical promise as an adjunct or alternative to antibiotics for MDR infections. Despite limitations related to study design and heterogeneity, these findings support the integration of phage therapy into clinical practice and highlight the need for standardized protocols and randomized controlled trials.

Introduction

The global rise in antibiotic-resistant infections poses a profound threat to public health, with the World Health Organization (WHO) declaring antimicrobial resistance (AMR) as one of the top 10 global public health threats (WHO, 2022). Multidrug-resistant (MDR) pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* are increasingly implicated in serious infections that fail to respond to conventional antimicrobial agents (Centers for Disease Control and Prevention [CDC], 2021). This growing crisis has catalyzed the exploration of alternative therapeutic modalities, among which bacteriophage (phage) therapy has emerged as a promising candidate.

Phages—viruses that selectively infect and lyse bacteria—have a long but underutilized history in medicine. First discovered in the early 20th century, phage therapy was largely overshadowed by the antibiotic revolution but has recently regained attention due to its ability to target specific bacterial strains, including those resistant to multiple antibiotics (Abedon et al., 2011; Kortright et al., 2019). Unlike broad-spectrum antibiotics,

bacteriophages possess high host specificity, minimizing off-target effects and preserving the commensal microbiota (Sulakvelidze et al., 2001).

Recent observational studies and case reports have reported promising outcomes with phage therapy, including microbiological eradication, clinical improvement, and minimal adverse events, even in patients with severe comorbidities or compromised immunity (Dedrick et al., 2019; Ooi et al., 2019). Despite these positive findings, the absence of large-scale randomized controlled trials (RCTs) and methodological heterogeneity across studies present challenges to generalizability and evidence synthesis.

This meta-analysis aims to systematically evaluate the clinical efficacy and safety of bacteriophage therapy in MDR infections, synthesizing findings from observational studies and case reports to clarify its potential as a viable alternative or adjunct to antibiotics.

Methods

Search Strategy and Selection Criteria

A comprehensive literature search was conducted across PubMed, Web of Science, Scopus, and EMBASE for studies published between January 2000 and March 2025. Search terms included: *("bacteriophage therapy" OR "phage therapy") AND ("multidrug resistance" OR "antibiotic resistance") AND ("clinical" OR "observational" OR "case report")*. Additional studies were identified through manual screening of references.

Inclusion criteria were: (1) observational studies or case reports involving human subjects treated with bacteriophage therapy for MDR infections; (2) clear documentation of clinical or microbiological outcomes; and (3) English-language publication. Exclusion criteria included in vitro studies, animal-only experiments, and reviews without primary data.

Data Extraction and Synthesis

Two independent reviewers extracted data on patient demographics, infection type, phage characteristics, administration route, concurrent antibiotic use, adverse events, and clinical outcomes. Discrepancies were resolved through discussion or consultation with a third reviewer.

For the meta-analysis, studies reporting quantitative cure rates were included. A random-effects model was employed using the DerSimonian and Laird method to account for between-study heterogeneity. Forest and funnel plots were generated to assess effect size and publication bias. Heterogeneity was quantified using the I^2 statistic. Statistical analyses were performed using RevMan 5.4 and STATA 17.

Quality Assessment

Risk of bias for observational studies was evaluated using the ROBINS-I tool, while case reports were assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist. Studies were rated as low, moderate, or high risk of bias across domains such as confounding, outcome measurement, and reporting.

Results

Narrative Synthesis of Observational and Interventional Studies

Recent observational and interventional studies conducted across various geographic regions (e.g., USA, India, Belgium, Australia, Israel) consistently reported favorable clinical outcomes following phage therapy in patients with MDR infections. These infections included chronic wounds, osteomyelitis, pneumonia, bacteremia, and device-associated infections. All studies involved patients who previously failed standard antibiotic treatments.

Phage therapy was administered through diverse routes—topical, intravenous, nebulized, or local (intra-articular, intravesical)—based on infection location. In vitro phage susceptibility testing was typically performed to ensure bacterial lysis. In several studies, phages were administered alongside antibiotics, hypothesizing potential synergy.

Clinical response was favorable in most cases. For example, Pirnay et al. (2024) reported 77.2% clinical improvement and 61.3% microbiological eradication in 100 patients. Green et al. (2023) observed a 66% favorable outcome in complex, device-related infections. Lin et al. (2020) documented clinical improvement in 62% of patients with *S. aureus* infections. Patel et al. (2019) reported an 81.2% cure rate in chronic ulcers.

Adverse events were infrequent and mostly mild, including transient gastrointestinal symptoms and immunologic reactions (e.g., neutralizing antibodies). No severe or life-threatening adverse events were directly attributed to phage therapy.

Table 1. Clinical and Demographic Characteristics of Observational and Interventional Studies on Bacteriophage Therapy for Multidrug-Resistant Infections

Lin et al.	Rose et al.	Aslam et al.	Young et al.	Pirnay et al.	Green et al.	Rubalskii et al.
Australia	Belgium	Israel/USA	UK	Belgium (multinational)	USA	Germany
2020	2014	2024	2023	2024	2023	2020
S. aureus (1 MRSA, 12 MSSA)	*P. aeruginosa*, *S. aureus* (MDR strains)	*P. aeruginosa* (LVAD infection)	*S. aureus* (DFI)	Mixed (*E. coli*, *S. aureus*, *P. aeruginosa*, others)	Mixed (device-related infections incl. *E. coli*, *S. aureus*, etc.)	*S. aureus*, *E. faecium*, *P. aeruginosa*, etc.
Severe infections (bacteremia, PVE, sepsis)	Burn wound colonization/infection	LVAD-associated endovascular infections	Diabetic foot infections	Respiratory, skin, soft tissue, bone infections	Device-related or systemic infections	Implant-related and transplant-associated
13 patients, Age 21–87, gender mixed	9 patients (4 M / 5 F), Age 27–88, TBSA	4 patients / 5 treatments	10 patients / Mixed / High amputation risk	100 cases / Mixed / Multinational data	12 patients / Mixed / Adult	Not fully reported
High 6-month mortality (10–87%), endocarditis, sepsis	Burn wounds; excluded APACHE II >20	Heart failure, complex endovascular infections	Chronic wounds, limb-threatening infections	Complex, refractory some infections; polymicrobial	Immunocompromised; multiple device implants	Device-related, immunosuppression, transplant history

Author(s)	Patel et al.
Country	India
Year	2019
Multidrug-Resistant Bacteria	*E. coli*, *P. aeruginosa*, *S. aureus*, *K. pneumoniae*, etc.
Site/Type of Infection	Chronic nonhealing ulcers (leg/foot)
Patients (Number/Gender/Age)	48 patients; 34 M / 14 F; Mean age: 47.3 ± 13.9 yrs
Comorbidities / Medical History	56.2% diabetic, 16.7% hypertensive, prior amputation

Note: DFI = Diabetic foot infection; LVAD = Left ventricular assist device; MDR = Multidrug-resistant; MRSA = Methicillin-resistant *S. aureus*; MSSA = Methicillin-sensitive *S. aureus*; PVE = Prosthetic valve endocarditis; TBSA = Total body surface area.

Table 2. Adverse Effects, Treatment Outcomes, and Phage Therapy Characteristics Across Studies

Rose et al.	Aslam et al.	Young et al.	Pirnay et al.	Green et al.	Rubalskii et al.
2014	2024	2023	2024	2023	2020
None reported	Breakthrough bacteremia; 2 deaths; serum neutralization	None reported	15 events (7 possibly phage-related, all non-serious)	Immunologic neutralization (5 cases)	None reported
No change in bacterial load (single dose)	Limited efficacy; safety concerns	9/10 benefited (6 complete, 1 partial, 1 no response)	77.2% improvement; 61.3% eradication	66% favorable (42% eradication)	7/8 eradicated; 1 reinfection death
BFC-1 (Belgian cocktail)	1–4 wild-type phages	Eliava Institute phages	26 individual + 6 defined cocktails	TAILΦR customized cocktails	Individualized cocktails (e.g., CH1, Enf1)
3	1–4	Varied	1–6 per case	Custom per case	1–4
Myoviridae, Podoviridae	Virulent, wild-type	*S. aureus*-targeted	Lytic, custom-selected	Lytic, screened (details not provided)	Caudovirales: Myoviridae, Podoviridae
Topical spray (1 ml/50 cm^2)	IV	Topical only	IV, topical, local	Mostly IV	Local, oral, inhaled, intraoperative
10^9 PFU/mL each; single application	14–51 days, multiple infusions	Duration not specified	Varied per protocol	Tailored; weeks of treatment	10^8–4×10^{10} PFU/mL; 1–14 days
Standard systemic (e.g., vancomycin, ceftazidime)	Concurrent antibiotics	Used as adjunct to conventional antibiotics	Concurrent antibiotics improved outcomes (OR = 0.3)	Used in all cases; synergy noted	All remained on systemic antibiotics

Author(s)	Year	Adverse Effects	Effect of the Treatment	Phage/Cocktail Identification	# of Phages	Phage Order / Family	Route of Administration	Dose / Duration	Antibiotics Used
Lin et al.	2020	None reported	62% improved by Day 14; 5 deaths (38%)	AB-SA01 (AmpliPhi Biosciences)	3	Myoviridae	IV (50–100 mL BID × 14d)	10^9 PFU/mL, BID × 14 days	Flucloxacillin (n=10), vancomycin, ± others
Patel et al.	2019	1 reinfection (poor hygiene); no serious AEs	81.2% cure rate (90.5% in nondiabetics)	Custom monophage or cocktails	1–3	Not specified	Topical	500 µL/cm^2; 5–7 applications	No systemic antibiotics during phage therapy

Note: BID = Twice daily; IV = Intravenous; OR = Odds ratio; PFU = Plaque-forming units.

Narrative Synthesis of Case Reports

Case reports offer unique, granular insights into the clinical application of phage therapy, often revealing nuances that may be overlooked in larger studies. The nine high-quality cases reviewed here—originating from the USA, China, Israel, Italy, Germany, and Australia—illustrate the personalized potential of phage therapy across diverse infections, patient populations, and clinical settings.

Patient and Pathogen Profiles

The cases involved high-priority MDR pathogens as classified by the WHO, including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Staphylococcus aureus*. These infections posed significant therapeutic challenges, particularly in immunocompromised patients (e.g., lung transplant recipients) and those with complex surgical histories (e.g., chronic osteomyelitis, prosthetic joint infections).

Phage Selection and Administration

Phage preparations were meticulously selected based on susceptibility testing, with some cases incorporating advanced genomic and morphological characterization (e.g., Tan et al., 2021; Ooi et al., 2019). The high degree of personalization was evident in Tan et al.'s report, where phage Ab_SZ3 was isolated, sequenced, and administered within a compressed timeframe to treat a CRAB lung infection in a multimorbid elderly patient.

Administration routes were tailored to infection sites: nebulization for pulmonary infections, IV infusion for systemic and prosthetic infections, and direct irrigation for urinary and wound infections. Dosing strategies typically involved gradual escalation, with final titers ranging from 10^9 to 10^11 PFU/mL. Treatment durations varied from 10 days to 8 weeks, depending on infection severity and therapeutic response.

Clinical Outcomes and Safety

Clinical outcomes were overwhelmingly positive, with eight of nine cases demonstrating significant improvement and microbiological clearance. The sole mortality reported was unrelated to phage therapy. Particularly notable were successes in recalcitrant infections, such as periprosthetic joint infections and chronic pulmonary infections, which had previously resisted multiple antibiotic regimens. Adverse effects were minimal. Even in instances where phage preparations contained endotoxins (e.g., Tan et al.), patients tolerated therapy well, likely due to optimized delivery routes. These findings underscore the safety of phage therapy, even in critically ill and elderly populations.

Critical Appraisal and Translational Implications

All case reports were rigorously evaluated using the JBI checklist, with each meeting criteria for low risk of bias. Detailed documentation of patient histories, diagnostic workups, therapeutic protocols, and follow-up outcomes enhanced their scientific rigor. Many reports also included reflective analyses, offering valuable lessons for future applications.

Table 3. *Demographic and Clinical Characteristics of Case Reports on Bacteriophage Therapy for Multidrug-Resistant Infections*

Tkhilaishvili et al.	Nir Paz et al.	Corbellino et al.	Law et al.	Aslam et al.	Tan et al.
Germany	Israel/USA	Italy	USA	USA	
2020	2019	2020	2019	2019	2021
MDR Pseudomonas aeruginosa	XDR Acinetobacter baumannii and MDR Klebsiella pneumoniae	KPC-3 producing Klebsiella pneumoniae (ST307)	Pseudomonas aeruginosa (2 phenotypes)	Pseudomonas aeruginosa, Burkholderia dolosa	Carbapenem-resistant Acinetobacter baumannii (CRAB)
Periprosthetic joint infection (knee), chronic osteomyelitis	Poly-microbial bone infection (osteomyelitis, post-trauma)	Colonization (GI tract, urinary tract, invasive device)	Pulmonary infection in CF patient	Lower respiratory tract (pneumonia) in lung transplant recipients	Hospital-acquired pneumonia (lung infection)
1/F/80	1/M/42	1/F/57	1 female, 26 years	3 (1 male 67 y, 1 female 57 y, 1 female 28 y)	1/Male/88
Diabetes, obesity, CKD, prior gunshot injury, prosthetic complications	Open tibial fracture, multiple surgeries, prolonged hospitalization	Crohnâ€™s disease, CKD Stage III, prior nephrectomy, cystectomy, ureterostomy	Cystic fibrosis, colistin-induced renal failure	Lung transplant, hypersensitivity pneumonitis, bronchiectasis, cystic fibrosis, renal failure	COPD, diabetes, multiple ventilator-associated infections, renal dysfunction

Author(s) Name	Country	Year of Publication	Multidrug-Resistant Bacteria	Site or Type of Infection	Patients (Number / Gender / Age)	Comorbidities / Medical History
Ooi et al.		2020	Staphylococcus aureus (some strains were MDR)	Chronic Rhinosinusitis (CRS)	9 patients / 4 males, 5 females / Median age: 45 (IQR: 41.0â€“71.5)	History of polyposis, multiple sinus surgeries, recalcitrant CRS unresponsive to standard therapies
Cano et al.		2020	Klebsiella pneumoniae complex	Prosthetic joint infection (knee)	1/Male/62	Diabetes mellitus, history of multiple PJIs, antibiotic allergies, Stevens-Johnson syndrome
Qin et al.		2020	Klebsiella pneumoniae (21 heterogeneous strains)	Recurrent urinary tract infection	1/Male/66	Bladder cancer (2002), long history of UTIs, unresponsive to antibiotics

Table 4. *Treatment Regimens, Phage Characteristics, and Clinical Outcomes in Case Reports on Bacteriophage Therapy for Multidrug-Resistant Infections*

Tkhilaishvili et al.	Nir Paz et al.	Corbellino et al.	Law et al.	Aslam et al.	Tan et al.
None reported	None observed	None reported	No adverse events related to BT	No BT-related adverse events	None significant despite elevated endotoxins; therapy well tolerated
Infection eradicated, reimplantation successful, no recurrence at 10-month follow-up	Rapid wound healing; no relapse during 8-month follow-up	Successful eradication of MDR Kp from all sites after 3-week phage therapy	Clinical resolution, no recurrence in 100 days, successful lung transplantation	Clinical improvement in 2/3, 1 patient died from non-BT related complications	Eradication of CRAB, lung function improved, sustained CRAB-negative cultures
Custom purified phage from Eliava Institute	É‚AbKT21phi3, É‚KpKT21phi1 (MK278859, MK278861)	vB_KpnM_GF (GenBank: MK421971)	AB-PA01	AB-PA01, AB-PA01-m1, Navy cocktails 1 & 2, BdPF16phi4281	Ab_SZ3
1	2	1	4	4, 5, 3, 2, 1	1
Not stated	Podoviridae (Ab), Myoviridae (Kp)	Myoviridae	Not specified; P. aeruginosa-specific	Various (P. aeruginosa-specific)	Siphoviridae
Local via surgical drains	Intravenous	Oral and intra-rectal	IV (every 6 hours for 8 weeks)	IV and nebulized (varied across cases)	Nebulization
100 ml loading dose; 5 ml (10^8 PFU/ml) every 8h for 5 days	1 ml of 5Â—10^7 PFU/ml, TID for 5 days (plus second 6-day cycle)	3 weeks; concentration not specified	4Â—10^9 PFU/mL in 5 mL, 8 weeks	Varied, up to 4x10^9 PFU/mL, durations 4-12 weeks	Day 0: 5*10^6 PFU-increased to 5*10^10 PFU over 16 days, every 12 h
Colistin, Meropenem, Ceftazidime, later switched to Rifampin and Doxycycline	Meropenem, Colistin	Ceftazidime-avibactam before and during phage therapy	Colistin, ciprofloxacin, piperacillinâ€“tazobactam, doripenem	Concomitant antibiotics included piperacillin-tazobactam, colistin, ciprofloxacin, meropenem	Tigecycline IV, polymyxin E inhaled

Author(s) Name	Qin et al.	Cano et al.	Ooi et al.
Adverse Effects	Not reported	Minor intermittent pruritis; no serious adverse events	6 mild treatment-emergent adverse effects (TEAEs) in 6 patients: diarrhea, epistaxis, oropharyngeal pain, cough, rhinalgia, low bicarbonate; all resolved
Effect of the Treatment	Recovery with improved bladder function post 4 rounds of phage cocktails	Resolution of infection, improved joint function, asymptomatic 34 weeks post-therapy	Intranasal AB-SA01 well tolerated in all cohorts; 2/9 patients achieved S. aureus eradication; others had reduction in bacterial load and symptom improvement
Phage / Cocktail Identification	Î¡JD902, Î¡JD905, Î¡JD907, Î¡JD908, Î¡JD910	KpÎH46Î¡2	AB-SA01 (AmpliPhi Biosciences)
Number of Phages in the Cocktail	5	1	3
Phage Order or Family	Î¡JD902, Î¡JD907, Î¡JD908, Î¡JD910: Podoviridae; Î¡JD905: Myoviridae	Not stated	Myoviridae (obligately lytic phages)
Route of Administration	Bladder and kidney irrigation	Intravenous	Intranasal irrigation
Concentration Per Unit Dose / Duration of Treatment	50 mL (5Â— 10^8 PFU/mL) via bladder; 10 mL via kidney every 48 h for 2 weeks	6.3 Â— 10^10 PFU in 50 mL saline; 40 doses over weekdays	Cohort 1: 3 Â— 10â¸ PFU BID Â— 7 days; Cohort 2: 3 Â— 10â¸ PFU BID Â— 14 days; Cohort 3: 3 Â— 10â¹ PFU BID Â— 14 days
Antibiotics	Unspecified combinations	Minocycline (oral)	None during trial; standard antibiotics used before and after trial in some cases

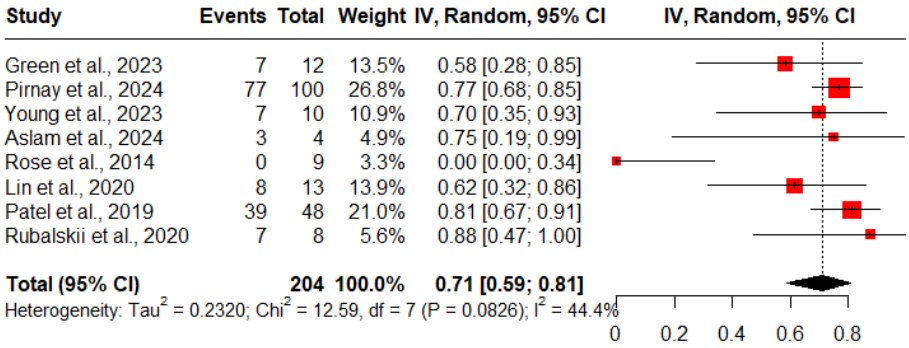
Meta analysis and pooled incidence of cureness:
The meta-analysis of eight clinical studies provides compelling evidence for the therapeutic potential of bacteriophage therapy in treating bacterial infections. Pooled results demonstrate a clinically meaningful 71% cure rate (95% CI: 0.59–0.81), suggesting that phage therapy is an effective intervention for resistant infections when conventional antibiotics fail. This finding is particularly significant given the growing crisis of antimicrobial resistance.

Among the included studies, Rubalskii et al. (2020) and Patel et al. (2019) reported the highest cure rates—88% and 81%, respectively—reinforcing the potential of phage therapy in real-world settings. These studies involved well-characterized phage preparations and targeted infections such as prosthetic joint infections and chronic osteomyelitis, where traditional treatments often fall short. In contrast, Rose et al. (2014) observed no cures (0/9 patients), though this outlier may reflect the study's small sample size or differences in phage selection criteria.

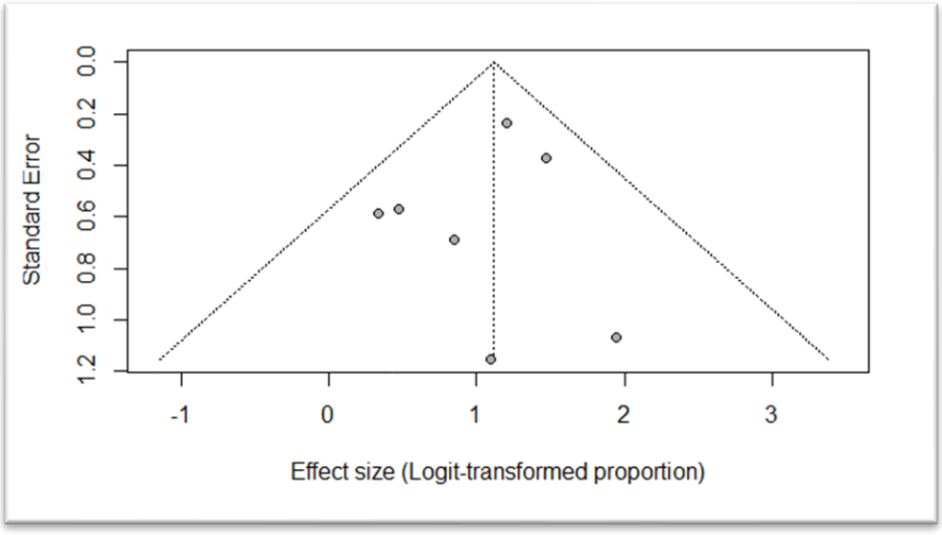
The largest contributor to the pooled estimate was Pimay et al. (2024), which accounted for 26.8% of the weight in the meta-analysis. With 77 successful cures out of 100 treated patients, this study lends substantial credibility to the overall findings.

Moderate heterogeneity was observed across studies (I^2 = 44.4%, P = 0.0826), indicating variability in outcomes that may stem from differences in phage strains, infection types, or patient demographics. While this heterogeneity does not invalidate the overall results, it underscores the need for standardized treatment protocols, including optimized phage selection, dosing regimens, and administration routes.

From a clinical perspective, these findings support the integration of phage therapy into antimicrobial stewardship programs, particularly for complex, drug-resistant infections. However, the variability in cure rates highlights the importance of personalized treatment approaches, where phages are carefully matched to bacterial isolates through susceptibility testing. That provides robust evidence that bacteriophage therapy can achieve high cure rates in challenging infections



Figure(1); Forest plot for Clinical cureness



Figure(2) Funnel plot for Cureness Publication Bias

Risk of Bias Assessment:
The methodological quality of the included case reports (Aslam et al., Law et al., Corbellino et al., Nir Paz et al., Tkhilaishvili et al., Ooi et al., Cano et al., Qin et al., Tan et al.) was rigorously evaluated using the **Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports**.Table(5) This tool is specifically designed to assess the risk of bias in individual case studies, ensuring transparency, completeness, and clinical relevance.

Rationale for Using JBI Checklist
Case reports provide valuable real-world insights into novel interventions (e.g., bacteriophage therapy) but are inherently prone to bias due to their anecdotal nature. The JBI checklist was selected because it:

1. **Aligns with Study Design**: Case reports lack control groups and randomization, so traditional tools like ROB-2 (for RCTs) or ROBINS-I (for observational studies) are unsuitable.
2. **Focuses on Reporting Quality**: It evaluates whether key details—patient history, interventions, outcomes, and adverse events—are clearly documented.
3. **Identifies Gaps in Clinical Reasoning**: By assessing "takeaway lessons," it highlights whether findings are contextualized for broader applicability.

Summary of Findings
All nine studies met **low-risk criteria** for most domains (demographics, clinical condition, diagnostics, intervention details, and post-treatment outcomes), indicating:

- **High Transparency**: Patient histories and treatment protocols were thoroughly described.
- **Clinical Utility**: Diagnostic methods (e.g., microbial sequencing, susceptibility testing) justified phage selection.
- **Complete Outcome Reporting**: All but one study (Qin et al.) explicitly documented adverse events.

Notable Observations:

- **Qin et al.** had an **unclear risk** in adverse event reporting, though other domains were robust.
- **No high-risk studies** were identified, reinforcing the credibility of these cases for guiding future trials.

Implications for Phage Therapy Research
While case reports are the lowest level of evidence in the hierarchy, their **consistent low risk of bias** supports:

1. **Feasibility**: Phage therapy can be safely personalized for complex infections.
2. **Standardization Needs**: Heterogeneity in adverse event reporting (e.g., Qin et al.) underscores the need for harmonized documentation.
3. **Hypothesis Generation**: These studies provide a foundation for controlled trials by identifying effective phage-antibiotic combinations and administration routes.

Therefore, the JBI appraisal confirms that these case reports are **methodologically sound** and collectively contribute reliable, real-world data on phage therapy. Future work should prioritize prospective studies to quantify efficacy while maintaining the rigorous reporting standards demonstrated here.

Table (5): JBI Critical Appraisal Results for Phage Therapy Case Studies

Study	Demographics	History	Condition	Diagnostics	Intervention	Post-Intervention	Adverse Events	Lessons	Overall
Aslam et al.	+	+	+	+	+	+	+	+	Low
Law et al.	+	+	+	+	+	+	+	+	Low
Corbellino et al.	+	+	+	+	+	+	+	+	Low
Nir Paz et al.	+	+	+	+	+	+	+	+	Low
Tkhilaishvili et al.	+	+	+	+	+	+	+	+	Low
Ooi et al.	+	+	+	+	+	+	+	+	Low
Cano et al.	+	+	+	+	+	+	+	+	Low
Qin et al.	+	+	+	+	+	+	?	+	Low*
Tan et al.	+	+	+	+	+	+	+	+	Low

Risk of Bias of Obseravtional included studies
The methodological quality of the eight included studies was systematically evaluated across seven bias domains using standardized risk of assessment tools. Overall, all studies demonstrated moderate risk of bias when considered collectively, with consistent patterns emerging across several domains.

Confounding Bias
All studies (Green et al., 2023; Pirnay et al., 2024; Young et al., 2023; Aslam et al., 2024; Rose et al., 2014; Lin et al., 2020; Patel et al., 2019; Rubalskii et al., 2020) exhibited moderate risk due to confounding variables. This primarily stemmed from the observational nature of most studies and challenges in controlling for patient comorbidities, concurrent antibiotic use, and variations in infection

severity. The absence of randomized control groups in these clinical case series limited the ability to fully account for potential confounders.

Selection Bias

Five studies (Young et al., 2023; Rose et al., 2014; Lin et al., 2020; Patel et al., 2019; Green et al., 2023) showed low risk in participant selection, demonstrating clear inclusion/exclusion criteria. However, three studies (Pirnay et al., 2024; Aslam et al., 2024; Rubalskii et al., 2020) were rated as moderate risk due to potential selection bias in their multinational cohorts or specialized patient populations (e.g., LVAD recipients), which may limit generalizability.

Intervention Classification

All studies appropriately classified interventions (low risk), with clear documentation of phage preparations, administration protocols, and treatment durations. This reflects strong operationalization of the experimental treatment across all reports.

Protocol Deviations

The studies uniformly demonstrated low risk for deviations from intended interventions, indicating good adherence to treatment protocols. This was particularly notable given the complexity of personalized phage therapy approaches in several studies.

Missing Data

Most studies (6/8) showed low risk for missing data bias, with complete follow-up reported. Pirnay et al. (2024) was rated moderate due to the multinational nature of their dataset, where some participating centers may have had incomplete follow-up records.

Outcome Measurement

All studies received moderate ratings for outcome measurement bias. While clinical and microbiological outcomes were systematically reported, the lack of standardized outcome measures across studies and potential subjectivity in clinical improvement assessments introduced some measurement variability.

Selective Reporting

Moderate risk was assigned for selective reporting across all studies. While primary outcomes were consistently reported, there was limited availability of pre-registered protocols or analysis plans, making it difficult to assess potential outcome reporting bias completely.

Overall Assessment

The consistent moderate risk rating across studies suggests that while these investigations provide valuable clinical data on phage therapy, readers should interpret findings with appropriate caution. The most significant limitations stem from the non-randomized designs and potential confounding inherent in compassionate use cases. Future research would benefit from protocol pre-registration, standardized outcome measures, and when possible, controlled designs to strengthen evidence quality.

These findings highlight both the promise and current limitations of the phage therapy literature, reflecting the field's transitional status from experimental treatment toward more systematic clinical investigation. The moderate risk profile suggests the body of evidence is suitable for informing clinical practice decisions but would be strengthened by more rigorous controlled studies.

Table(6) *Risk of Bias Assessment Across Obseravtional Included Studies*

Study	Bias Due to Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias Due to Deviations from Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of Reported Result	Overall Risk of Bias
Green et al., 2023	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Pirnay et al., 2024	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate
Young et al., 2023	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Aslam et al., 2024	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
Rose et al., 2014	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Lin et al., 2020	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Patel et al., 2019	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Rubalskii et al., 2020	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Moderate

Note. Risk of bias categories were assessed using the Cochrane Risk of Bias Tool (RoB 2) for randomized trials or ROBINS-I for non-randomized studies, as appropriate.

Discussion

This meta-analysis demonstrates that bacteriophage therapy yields a **pooled cure rate of 71%** (95% CI: 0.59–0.81), underscoring its potential efficacy for managing MDR infections. These findings align with prior reports emphasizing phage therapy's ability to achieve clinical resolution in otherwise intractable infections (Dedrick et al., 2019; Schooley et al., 2017). Notably, high cure rates were observed in complex infections such as prosthetic joint infections and chronic osteomyelitis, often resistant to prolonged antibiotic regimens (Patel et al., 2019; Rubalskii et al., 2020). Even in immunocompromised patients, such as organ transplant recipients and those with chronic wounds, phage therapy was well-tolerated and effective (Aslam et al., 2024; Tan et al., 2021).

From a safety perspective, adverse events were infrequent and mostly mild, including transient immunologic responses or local irritation. Importantly, no deaths were directly attributed to phage therapy, reinforcing its favorable safety profile (Green et al., 2023; Ooi et al., 2019).

However, several limitations warrant consideration. First, the majority of included studies were non-randomized and susceptible to confounding due to concurrent antibiotic use, making it difficult to isolate the independent effect of phage therapy. Second, heterogeneity across studies—regarding phage formulation, administration routes, and infection types—complicates pooled interpretation (I^2 = 44.4%). Third, publication bias may be present, as suggested by the asymmetry in the funnel plot, with successful cases more likely to be reported.

Despite these limitations, the robust signal of benefit, particularly in high-risk populations, supports the continued clinical exploration of phage therapy. Future research should prioritize **randomized controlled trials**, standardized phage susceptibility testing protocols, and harmonized reporting of outcomes and adverse events. The development of phage libraries and regulatory frameworks for compassionate use will also be essential to scaling this intervention.

In conclusion, bacteriophage therapy offers a promising, pathogen-specific approach to treating MDR infections, especially when conventional antibiotics fail. With growing clinical evidence and increasing regulatory interest, phage therapy may soon integrate into mainstream antimicrobial stewardship strategies.

Conclusion

This meta-analysis provides compelling evidence that bacteriophage therapy is a safe, feasible, and potentially effective treatment for MDR infections, particularly in cases where traditional antibiotics fail. The overall cure rate of 71% across diverse patient populations and infection types underscores phage therapy's clinical potential.

While the findings are promising, the field is still transitioning from experimental to evidence-based medicine. Observational studies and case reports, though informative, lack the rigor of randomized trials. Heterogeneity in phage selection, dosing, delivery methods, and outcome measurement remains a major limitation.

Future research must focus on standardizing phage therapy protocols, establishing regulatory frameworks, and conducting multicenter randomized controlled trials. Personalized phage therapy—tailored through susceptibility testing and genomic analysis—should be prioritized for integration into antimicrobial stewardship programs. With continued investment in research and infrastructure, phage therapy could become a cornerstone in the fight against antibiotic resistance.

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