

CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Bacteriophage Therapy for Multi-Drug Resistant Bacterial Infections: Clinical Effectiveness and Guidelines

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Research Questions

1. What is the clinical effectiveness of phage therapy for multi-drug resistant bacterial infections in patients who have limited or failed antibiotic regimen?
2. What are the evidence-based guidelines regarding the use of phage therapy for multi-drug resistant bacterial infections?

Key Findings

One systematic review and two randomized controlled trials were identified regarding the clinical effectiveness of phage therapy for multi-drug resistant bacterial infections who have previously failed antibiotic treatment. No relevant evidence-based guidelines were identified.

Methods

A limited literature search was conducted on key resources including MEDLINE (via Ovid), the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and guidelines. An additional focused search with main concepts appeared in title only was conducted. For this focused search, no study design filters were applied. The search was also limited to English language documents published between January 1, 2014 and April 5, 2019. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with multi-drug resistant (MDR) bacterial infections who have limited or failed antibiotic regimen. (e.g., <i>Pseudomonas aeruginosa</i> peritonitis)
Intervention	Bacteriophage Therapy
Comparators	Q1: Any comparator; No comparator Q2: No comparator
Outcomes	Q1: Clinical effectiveness (e.g. mortality, disease progression), safety, harms Q2: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

One systematic review and two randomized controlled trials were identified regarding the effectiveness of phage therapy for patients with multi-drug resistant bacterial infections who have failed a previous antibiotic regimen. No relevant health technology assessments, non-randomized studies, or evidence-based guidelines were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

One systematic review¹ and two randomized controlled trials (RCTs),^{2,3} were identified regarding the effectiveness of phage therapy for patients with multi-drug resistant bacterial infections who have failed a previous antibiotic regimen.

The systematic review¹ assessed the effectiveness and safety of phage therapy against multi-drug resistant organisms in clinical practice. The authors identified 30 articles that met the inclusion criteria and determined that a majority of studies showed efficacy and safety in support of phage therapy.¹

The first RCT² aimed to compare the effectiveness and tolerability of phage therapy with standard of care in adults patients who had a burn wound clinically infected with *Pseudomonas aeruginosa*. Over a seven day period, patients were randomized to receive topical phage therapy plus standard care or standard care only. Overall, researchers concluded that standard of care was more effective in reaching the median time to sustained reduction in bacterial burden compared to the oral phage therapy.²

The second RCT³ examined whether oral phage therapy was effective and safe for treating 120 hospitalized children with acute diarrhea. Patients received one of the following oral treatments over a four day period: T4-like coliphages, a commercial Russia coliphage product, or a placebo. The researchers concluded there were no adverse events associated with oral phage therapy but it did not demonstrate clinical effectiveness by improving diarrhea outcomes due to insufficient phage coverage and the need for higher dosages.³

No evidence-based guidelines were identified; therefore, no summary can be provided.

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

1. El Haddad L, Harb CP, Gebara MA, Stibich MA, Chemaly RF. A systematic and critical review of bacteriophage therapy against multi-drug resistant ESKAPE Organisms in Humans. *Clin Infect Dis*. 2018 Nov 03. [Epub ahead of print].
[PubMed: PM30395179](#)

Randomized Controlled Trials

2. Jault P, Leclerc T, Jennes S, 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 Jan;19(1):35-45.
[PubMed: PM30292481](#)
3. Sarker SA, Sultana S, Reuteler G, et al. Oral phage therapy of acute bacterial diarrhea with two coliphage preparations: a randomized trial in children from Bangladesh. *EBioMedicine*. 2016 Feb;4:124-137.
[PubMed: PM26981577](#)

Non-Randomized Studies

No literature identified.

Guidelines and Recommendations

No literature identified.

Appendix — Further Information

Systematic Reviews and Meta-Analyses – Ongoing

4. Saperkin NV, Ruizendaal E, Kovalishena OV, Scholten RJPM. Bacteriophage therapy for the prevention or treatment of bacterial infections in humans (CRD42018100813). PROSPERO: International prospective register of systematic reviews. York (GB): University of York Centre for Reviews and Dissemination; 2018: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018100813. Accessed 2019 Apr 17.

Case Studies

5. Nir-Paz R, Gelman D, Khouri A, et al. Successful treatment of antibiotic resistant polymicrobial bone infection with bacteriophages and antibiotics combination. *Clin Infect Dis*. 2019 Mar 14. [Epub ahead of print].
[PubMed: PM30869755](https://pubmed.ncbi.nlm.nih.gov/30869755/)
6. Duplessis C, Biswas B, Hanisch B, et al. Refractory Pseudomonas bacteremia in a 2-year-old sterilized by bacteriophage therapy. *J Pediatric Infect Dis Soc*. 2018 Aug 17;7(3):253-256.
[PubMed: PM28992111](https://pubmed.ncbi.nlm.nih.gov/28992111/)
7. Hoyle N, Zhvaniya P, Balarjishvili N, et al. Phage therapy against Achromobacter xylooxidans lung infection in a patient with cystic fibrosis: a case report. *Res Microbiol*. 2018 Nov;169(9):540-542.
[PubMed: PM29777836](https://pubmed.ncbi.nlm.nih.gov/29777836/)
8. LaVergne S, Hamilton T, Biswas B, Kumaraswamy M, Schooley RT, Wooten D. Phage therapy for a multidrug-resistant Acinetobacter baumannii craniectomy site infection. *Open forum infect*. 2018 Apr;5(4):ofy064.
[PubMed: PM29687015](https://pubmed.ncbi.nlm.nih.gov/29687015/)
9. Schooley RT, Biswas B, Gill JJ, 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 10;61(10):10.
[PubMed: PM28807909](https://pubmed.ncbi.nlm.nih.gov/28807909/)
10. Fadlallah A, Chelala E, Legeais JM. Corneal Infection therapy with topical bacteriophage administration. *Open Ophthalmol J*. 2015;9:167-168.
[PubMed: PM26862360](https://pubmed.ncbi.nlm.nih.gov/26862360/)

In Vitro/Vivo Studies

11. Dickey J, Perrot V. Adjunct phage treatment enhances the effectiveness of low antibiotic concentration against Staphylococcus aureus biofilms in vitro. *PLoS ONE*. 2019;14(1):e0209390.
[PubMed: PM30650088](https://pubmed.ncbi.nlm.nih.gov/30650088/)

12. Cha K, Oh HK, Jang JY, et al. Characterization of two novel bacteriophages Infecting Multidrug-Resistant (MDR) *Acinetobacter baumannii* and evaluation of their therapeutic efficacy in vivo. *Front Microbiol.* 2018;9:696.
[PubMed: PM29755420](#)
13. Gelman D, Beyth S, Lerer V, et al. Combined bacteriophages and antibiotics as an efficient therapy against VRE *Enterococcus faecalis* in a mouse model. *Res Microbiol.* 2018 Nov;169(9):531-539.
[PubMed: PM29777835](#)
14. Lopes A, Pereira C, Almeida A. Sequential combined effect of phages and antibiotics on the inactivation of *Escherichia coli*. *Microorganisms.* 2018 Dec 05;6(4):05.
[PubMed: PM30563133](#)
15. Wang JL, Kuo CF, Yeh CM, Chen JR, Cheng MF, Hung CH. Efficacy of phikm18p phage therapy in a murine model of extensively drug-resistant *Acinetobacter baumannii* infection. *Infect.* 2018;11:2301-2310.
[PubMed: PM30532563](#)
16. Jung LS, Ding T, Ahn J. Evaluation of lytic bacteriophages for control of multidrug-resistant *Salmonella Typhimurium*. *Ann Clin Microbiol Antimicrob.* 2017 Sep 22;16(1):66.
[PubMed: PM28938899](#)
17. Oechslin F, Piccardi P, Mancini S, et al. Synergistic interaction between phage therapy and antibiotics clears *Pseudomonas aeruginosa* infection in endocarditis and reduces Virulence. *J Infect Dis.* 2017 03 01;215(5):703-712.
[PubMed: PM28007922](#)
18. Aleshkin AV, Ershova ON, Volozhantsev NV, et al. Phagebiotics in treatment and prophylaxis of healthcare-associated infections. *Bacteriophage.* 2016;6(4):e1251379.
[PubMed: PM28090384](#)
19. Oduor JM, Onkoba N, Maloba F, Arodi WO, Nyachieo A. Efficacy of lytic *Staphylococcus aureus* bacteriophage against multidrug-resistant *Staphylococcus aureus* in mice. *J.* 2016 Nov 24;10(11):1208-1213.
[PubMed: PM27886033](#)
20. Rahmani R, Zarrini G, Sheikhzadeh F, Aghamohammadzadeh N. Effective phages as green antimicrobial agents against antibiotic-resistant hospital *Escherichia coli*. *Jundishapur j.* 2015 Feb;8(2):e17744.
[PubMed: PM25834712](#)

Control or Storage Measures

21. Jamal M, Bukhari S, Andleeb S, et al. Bacteriophages: an overview of the control strategies against multiple bacterial infections in different fields. *J Basic Microbiol.* 2019 Feb;59(2):123-133.
[PubMed: PM30485461](#)

22. Cortes P, Cano-Sarabia M, Colom J, Otero J, Maspoch D, Llagostera M. Nano/micro formulations for bacteriophage delivery. *Methods Mol Biol.* 2018;1693:271-283.
[PubMed: PM29119446](#)
23. Hathaway H, Milo S, Sutton JM, Jenkins TA. Recent advances in therapeutic delivery systems of bacteriophage and bacteriophage-encoded endolysins. *Ther Deliv.* 2017 07;8(7):543-556.
[PubMed: PM28633592](#)
24. Hathaway H, Milo S, Sutton JM, Jenkins TA. Recent advances in therapeutic delivery systems of bacteriophage and bacteriophage-encoded endolysins. *Ther Deliv.* 2017 Jul;8(7):543-556.
[PubMed: PM28633592](#)

EMA and FDA Regulatory Measures

25. Bacteriophage therapy: scientific and regulatory issues. Public workshop; 2017 Jul 10. Transcript of proceedings. Silver Spring (MD): U.S. Food and Drug Administration; 2017:
<https://www.fda.gov/downloads/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/UCM579441.pdf>. Accessed 2019 Apr 17.
26. Workshop on the therapeutic use of bacteriophages. Amsterdam: European Medicines Agency; 2015:
<https://www.ema.europa.eu/en/events/workshop-therapeutic-use-bacteriophages>. Accessed 2019 Apr 17.
27. Debarbieux L, Pirnay JP, Verbeken G, et al. A bacteriophage journey at the European Medicines Agency. *FEMS Microbiol Lett.* 2016 Jan;363(2):fnv225.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5812529/>. Accessed 2019 Apr 17.

Dosage Forms

28. Brown TL, Petrovski S, Chan HT, Angove MJ, Tucci J. Semi-solid and solid dosage forms for the delivery of phage therapy to epithelia. *Pharmaceuticals.* 2018 Feb 26;11(1):26.
[PubMed: PM29495355](#)
29. Morozova VV, Vlassov VV, Tikunova NV. Applications of bacteriophages in the treatment of localized infections in humans. *Front Microbiol.* 2018;9:1696.
[PubMed: PM30116226](#)
30. Chang RY, Wong J, Mathai A, et al. Production of highly stable spray dried phage formulations for treatment of *Pseudomonas aeruginosa* lung infection. *Eur J Pharm Biopharm.* 2017 Dec;121:1-13.
[PubMed: PM28890220](#)
31. Leung SS, Parumasivam T, Gao FG, et al. Production of inhalation phage powders using spray freeze drying and spray drying techniques for treatment of respiratory Infections. *Pharm Res.* 2016 06;33(6):1486-1496.
[PubMed: PM26928668](#)

Review Articles

32. Kakasis A, Panitsa G. Bacteriophage therapy as an alternative treatment for human infections. A comprehensive review. *Int J Antimicrob Agents*. 2019 Jan;53(1):16-21. [PubMed: PM30236954](#)
33. Saha D, Mukherjee R. Ameliorating the antimicrobial resistance crisis: phage therapy. *IUBMB Life*. 2019 Jan 23. [Epub ahead of print]. [PubMed: PM30674079](#)
34. Wienhold SM, Lienau J, Witzentrath M. Towards inhaled phage therapy in Western Europe. *Viruses*. 2019 Mar 23;11(3):23. [PubMed: PM30909579](#)
35. McCallin S, Sarker SA, Sultana S, Oechslein F, Brussow H. Metagenome analysis of Russian and Georgian Pyophage cocktails and a placebo-controlled safety trial of single phage versus phage cocktail in healthy *Staphylococcus aureus* carriers. *Environ Microbiol*. 2018 Sep;20(9):3278-3293. [PubMed: PM30051571](#)
36. Chang RYK, Wallin M, Lin Y, et al. Phage therapy for respiratory infections. *Adv Drug Deliv Rev*. 2018 Aug;133:76-86. [PubMed: PM30096336](#)
37. Expert round table on a re-implementation of bacteriophage therapy, Sybesma W, Rhode C, et al. Silk route to the acceptance and re-implementation of bacteriophage therapy-Part II. *Antibiotics (Basel)*. 2018 Apr 23;7(2):23. [PubMed: PM29690620](#)
38. Furfaro LL, Payne MS, Chang BJ. Bacteriophage therapy: clinical trials and regulatory hurdles. *Front*. 2018;8:376. [PubMed: PM30406049](#)
39. Trend S, Fonceca AM, Ditcham WG, Kicic A, Cf A. The potential of phage therapy in cystic fibrosis: Essential human-bacterial-phage interactions and delivery considerations for use in *Pseudomonas aeruginosa*-infected airways. *J Cyst Fibros*. 2017 Nov;16(6):663-670. [PubMed: PM28720345](#)
40. Zelasko S, Gorski A, Dabrowska K. Delivering phage therapy per os: benefits and barriers. *Expert Review of Antiinfective Therapy*. 2017 02;15(2):167-179. [PubMed: PM27885865](#)
41. Pelfrene E, Willebrand E, Cavaleiro Sanches A, Sebris Z, Cavaleri M. Bacteriophage therapy: a regulatory perspective. *J Antimicrob Chemother*. 2016 08;71(8):2071-2074. [PubMed: PM27068400](#)

Additional References

42. Djebara S, Maussen C, De Vos D, et al. Processing phage therapy requests in a Brussels military hospital: lessons identified. *Viruses*. 2019 Mar 17;11(3):17.
[PubMed: PM30884879](#)
43. Gordillo Altamirano FL, Barr JJ. Phage therapy in the postantibiotic era. *Clin Microbiol Rev*. 2019 04;32(2):04.
[PubMed: PM30651225](#)
44. Hoggarth A, Weaver A, Pu Q, et al. Mechanistic research holds promise for bacterial vaccines and phage therapies for *Pseudomonas aeruginosa*. *Drug Des Devel Ther*. 2019;13:909-924.
[PubMed: PM30936684](#)
45. Kortright KE, Chan BK, Koff JL, Turner PE. Phage therapy: a renewed approach to combat antibiotic-resistant bacteria. *Cell Host Microbe*. 2019 Feb 13;25(2):219-232.
[PubMed: PM30763536](#)
46. Fish R, Kutter E, Wheat G, Blasdel B, Kutateladze M, Kuhl S. Compassionate use of bacteriophage therapy for foot ulcer treatment as an effective step for moving toward clinical trials. *Methods Mol Biol*. 2018;1693:159-170.
[PubMed: PM29119440](#)
47. Patey O, McCallin S, Mazure H, Liddle M, Smithyman A, Dublanchet A. Clinical indications and compassionate use of phage therapy: personal experience and literature review with a focus on osteoarticular infections. *Viruses*. 2018 Dec 28;11(1):28.
[PubMed: PM30597868](#)